ORGANIC LETTERS
2010
Vol. 12, No. 9
2068−2071

Rhodium-Catalyzed Oxidative Coupling/ Cyclization of 2-Phenylindoles with Alkynes via C−H and N−H Bond Cleavages with Air as the Oxidant

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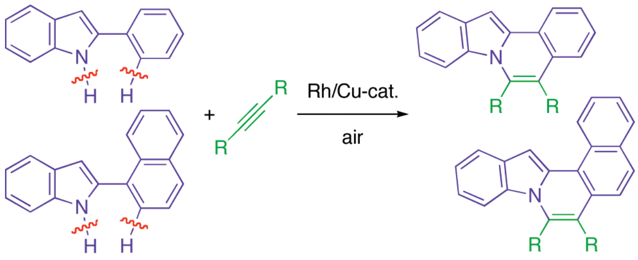
Received March 7, 2010

ABSTRACT



The straightforward and efficient synthesis of indolo[2,1-*a*]isoquinoline derivatives has been achieved by the rhodium-catalyzed aerobic oxidative coupling/cyclization of 2-phenylindoles with alkynes. Some of the polycyclic products exhibit solid-state fluorescence.

Nitrogen-containing polycyclic heteroarenes have attracted considerable attention because of their biological and photo- and electrochemical properties.[1] Their construction usually needs complicated multisteps with huge effort involving high-volume byproducts.[2] Recently, the oxidative coupling of aromatic substrates with internal alkynes by transition metal catalysis via regioselective C−H bond cleavage has been developed for preparing fused polycyclic molecules.[3] As such an example, we have reported the one-step synthesis of 5,6-diarylindolo[1,2-*a*]quinoline derivatives by the palladium-catalyzed oxidative coupling of 1-phenylindole-3-carboxylic acids with alkynes involving decarboxylation (Scheme 1).[4] The tetracyclic products have been found to exhibit intense fluorescence in the solid state.

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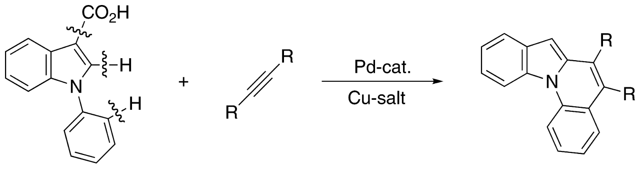
(2) Selected recent reviews: (a) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874. (b) Gil, C.; Bräse, S. *J. Comb. Chem.* **2009**, *11*, 175. (c) Vincze, Z.; Bíró, B.; Csékei, M.; Timári, G.; Kotschy, A. *Synthesis* **2006**, 1375.

(3) Selected recent reviews for C−H functionalization: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (e) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987. (f) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (g) Herrerias, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (h) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (i) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (j) Satoh, T.; Miura, M. *J. Synth. Org. Chem.* **2006**, *64*, 1199. (k) Conley, B. L.; Tenn, W. J., III.; Young, K. J. H.; Ganesh, S. K.; Meier, S. K.; Ziatdinov, V. R.; Mironov, O.; Oxgaard, J.; Gonzales, J.; Goddard, W. A., III.; Periana, R. A. *J. Mol. Catal. A* **2006**, *251*, 8. (l) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (m) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (n) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (o) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (p) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879.

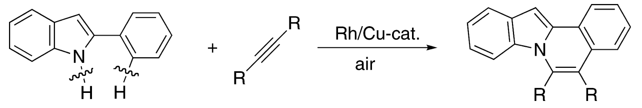
10.1021/ol100560k

Scheme 1



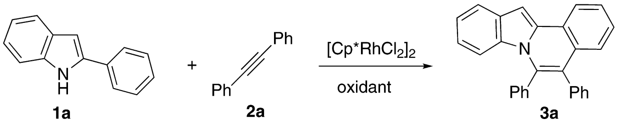
During our further study of fused heteroaromatic construction,[5] we have succeeded in building up an indolo[2,1-*a*]isoquinoline framework via the aerobic oxidative coupling of 2-phenylindoles with alkynes under rhodium catalysis, accompanied by C−H and N−H bond cleavages (Scheme 2).[6] Note that this reaction proceeds smoothly with air as terminal oxidant, in which no wastes are formed except for water. The tetracyclic framework can be seen in various natural products that exhibit a broad range of interesting biological activity.[7] Moreover, as are indolo[1,2-*a*]quinolines, some of the indolo[2,1-*a*]isoquinoline derivatives obtained have been found to show solid-state fluorescence. The results obtained for the coupling are described herein.

Scheme 2



In an initial attempt, 2-phenylindole (**1a**) (0.5 mmol) was treated with diphenylacetylene (**2a**) (0.5 mmol) in the presence of $[Cp^*RhCl_2]_2$ (0.01 mmol) and Ag_2CO_3 (0.5 mmol) as catalyst and oxidant, respectively, in *o*-xylene (3 mL) at 100 °C under N_2. As a result, 5,6-diphenylindolo[2,1-*a*]isoquinoline (**3a**) was formed in 44% yield after 6 h (entry 1 in Table 1, Cp* = pentamethylcyclopentadienyl). The product yield significantly increased to 80% by using AgOAc (1 mmol) as the oxidant in place of Ag_2CO_3 (entry 2). The addition of Na_2CO_3 (1 mmol) enabled **3a** to be produced quantitatively (entry 3). An inexpensive oxidant, $Cu(OAc)_2{\cdot}H_2O$, was also effective for the present reaction (entry 4). Furthermore, to our delight, a comparably good yield was obtained even when the reaction was conducted with a catalytic amount of $Cu(OAc)_2{\cdot}H_2O$ (0.05 mmol) under N_2−air (5:1) (entry 5).[8] Without the copper cocatalyst, the reaction was sluggish (entry 6).

Table 1. Reaction of 2-Phenylindole (**1a**) with Diphenylacetylene (**2a**)[a]



entry	oxidant (mmol)	yield of **3a**[b]
1[c]	Ag_2CO_3 (0.5)	44
2[c]	AgOAc (1)	80
3	AgOAc (1)	99 (96)
4	$Cu(OAc)_2{\cdot}H_2O$ (1)	92
5	$Cu(OAc)_2{\cdot}H_2O$ (0.05) + air[d]	96 (96)
6	air[d]	21

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), $[(Cp^*RhCl_2)_2]$ (0.01 mmol), Na_2CO_3 (1 mmol), *o*-xylene (3 mL) at 100 °C for 6 h under N_2. [b] GC yield based on the amount of **1a** used. The number in parentheses indicates yield after purification. [c] Without Na_2CO_3. [d] Under N_2−air (5:1, 900 mL).

Table 2 summarizes the results for the coupling of a series of 2-arylindoles **1b**−**h** with **2a** under conditions with air as terminal oxidant (entry 5 in Table 1). 2-(4-Substituted phenyl)indoles **1b**−**e** reacted with **2a** smoothly to form the corresponding 3-substituted 5,6-diphenylindolo[2,1-*a*]isoquinolines **3b**−**e** in good yields (entries 1−4). 5-Methoxy- and 5-chloro-2-phenylindoles, **1f** and **1g**, also underwent the reaction with **2a** to produce 10-substituted 5,6-diphenylindolo[2,1-*a*]isoquinoline derivatives **3f** and **3g**, respectively (entries 5 and 6). In the reaction of 2-(1-naphthyl)indole (**1h**) with **2a**, a pentacyclic product **3h** was selectively obtained in 74% yield (entry 7).

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(4) (a) Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7481. (b) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 2337.

(5) (a) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (b) Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3478. (c) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 2337. (d) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (e) Shimizu, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem. Asian J.* **2008**, *3*, 881. (f) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362. (g) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229.

(6) The heteroarene construction with transition metal catalysts has been developed: (a) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138. (b) Lötter, A. N. C.; Pathak, R.; Sello, T. S.; Fernandes, M. A.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2007**, *63*, 2263. (c) de Koning, C. B.; Michael, J. P.; Pathak, R.; van Otterlo, W. A. L. *Tetrahedron Lett.* **2004**, *45*, 1117.

(7) Selected examples: (a) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.—Eur. J.* **2004**, *10*, 4556. (b) Soldatenkov, A. T.; Soldatova, S. A.; Ryashentseva, M. A.; Ntaganda, Zh.; Zvolinskii, O. V.; Smirnova, E. N.; Kharlamova, M. D. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 2116. (c) Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. *Org. Lett.* **2000**, *2*, 1799. (d) Ambros, R.; Schneider, M. R.; von Angerer, S. *J. Med. Chem.* **1990**, *33*, 153. (e) Ewing, J.; Hughes, G. K.; Ritchie, E.; Taylor, W. C. *Nature* **1952**, *169*, 618.

(8) Under air (1 atm), the yield of **3a** slightly decreased to 78%.

(9) For related Cp*(1-pyrrolyl)Rh complexes, see: Jones, W. D.; Dong, L.; Myers, A. W. *Organometallics* **1995**, *14*, 855.

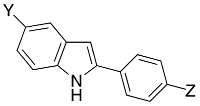
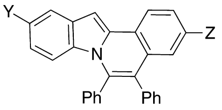
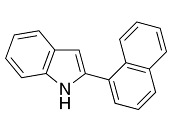
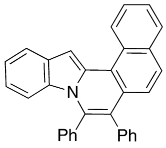
(10) Larock et al. reported copper-catalyzed addition of indole N−H to diphenylacetylene.[6a] However, in our blank experiment in the absence of the rhodium catalyst, any coupling products including 1-vinylindoles could not be detected.

(11) Another possible pathway via aminorhodation of **2a** by a indolylrhodium intermediate and subsequent cyclorhodation to form **B** cannot be excluded.

(12) (a) Terao, Y.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2004**, *69*, 6942. (b) Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236. (c) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407. (d) Eisenbraun, E. J.; Harms, W. M.; Palaniswamy, V. A.; Chen, H. H.; Porcaro, P. J.; Wood, T. F.; Chien, M. *J. Org. Chem.* **1982**, *47*, 342.

(13) It was confirmed that treatment of **4o** under similar conditions to those of entry 9 in Table 3 did not give **3o** at all.

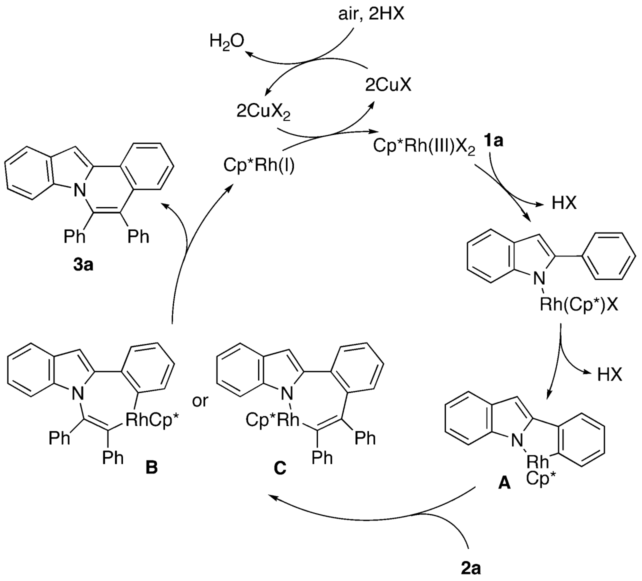
Table 2. Reaction of 2-Arylindoles **1** with Diphenylacetylene (**2a**)[a]

entry	1	product, % yield[b]
		
1	**1b**: Y = H, Z = Me	**3b**: Y = H, Z = Me, 90 (75)
2	**1c**: Y = H, Z = OMe	**3c**: Y = H, Z = OMe, (78)
3	**1d**: Y = H, Z = Cl	**3d**: Y = H, Z = Cl, 99 (84)
4[c]	**1e**: Y = H, Z = CO$_2$Me	**3e**: Y = H, Z = CO$_2$Me, (80)
5[d]	**1f**: Y = OMe, Z = H	**3f**: Y = OMe, Z = H, (73)
6[d]	**1g**: Y = Cl, Z = H	**3g**: Y = Cl, Z = H, 99 (93)
		
7	**1h**	**3h**, (74)

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), [(Cp*RhCl$_2$)$_2$] (0.01 mmol), Cu(OAc)$_2$•H$_2$O (0.05 mmol), Na$_2$CO$_3$ (1 mmol), *o*-xylene (3 mL) at 100 °C for 6 h under N$_2$−air (5:1, 900 mL). [b] GC yield based on the amount of **1** used. The number in parentheses indicates yield after purification. [c] For 10 h. [d] With **1** (0.25 mmol), **2a** (0.25 mmol), [(Cp*RhCl$_2$)$_2$] (0.005 mmol), Cu(OAc)$_2$•H$_2$O (0.025 mmol), Na$_2$CO$_3$ (0.5 mmol), and *o*-xylene (2 mL).

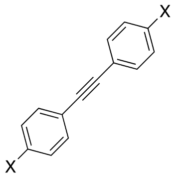
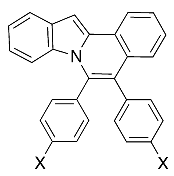
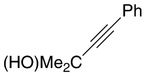
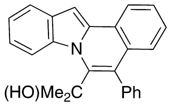
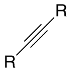
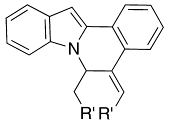
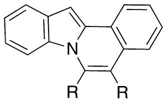
The oxidative coupling of **1a** with **2a** serves as an example in a possible mechanism illustrated in Scheme 3, in which neutral ligands are omitted. Initial coordination of the nitrogen atom of **1a** to Cp*Rh(III)X$_2$ species[9] and subsequent cyclorhodation gives a five-membered rhodacycle intermediate **A**.[10,11] Then, alkyne insertion into the N−Rh or C−Rh bond of **A** occurs to form seven-membered rhodacycle **B** or **C**, respectively. In either case, the final reductive elimination affords **3a**. The resulting Cp*Rh(I) species seems to be oxidized in the presence of the copper cocatalyst and air to regenerate Cp*Rh(III)X$_2$.

Scheme 3



The reactions of **1a** with various internal alkynes **2b**−**i** in place of **2a** were examined next. Methyl- (**2b**), *tert*-butyl- (**2c**), methoxy- (**2d**), chloro- (**2e**), and trifluoromethyl- (**2f**) substituted diphenylacetylenes underwent the coupling with **1a** to afford the corresponding 5,6-diarylindolo[2,1-*a*]isoquinolines **3i**−**m** in fair to good yields (entries 1−5 in Table 3). In the reaction of 2-methyl-4-phenyl-3-butyn-2-ol (**2g**) with **1a**, although the yield of the corresponding product **3n** was somewhat low, no other regioisomers were formed (entry 6). The yield of **3n** was significantly improved up to 94% by using a stoichiometric amount of AgOAc as the oxidant (entry 7). Note that the hydroxymethyl group can act as a leaving group for further fucntionalization.[12]

Table 3. Reaction of 2-Phenylindole (**1a**) with Alkynes **2**[a]

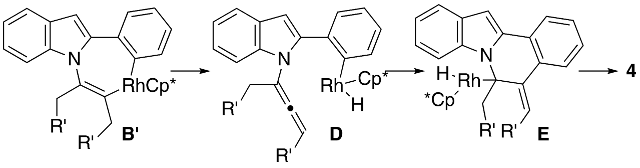
entry	2	product, % yield[b]	
			
1	**2b**: X = Me	**3i**: X = Me, 99 (94)	
2	**2c**: X = Bu^t	**3j**: X = Bu^t, 97 (90)	
3	**2d**: X = OMe	**3k**: X = OMe, (93)	
4	**2e**: X = Cl	**3l**: X = Cl, 86 (86)	
5	**2f**: X = CF$_3$	**3m**: X = CF$_3$, (64)	
			
6	**2g**	**3n**, 30	
7[c]	**2g**	**3n**, 94 (76)	
		 +	
8	**2h**: R = Pr	**4o**: R' = Et, 76	**3o**: R = Pr, 6
9[d]	**2h**: R = Pr	**4o**: R' = Et, 85 (75)	**3o**: R = Pr, 10 (9)
10	**2i**: R = C$_7$H$_{15}$	**4p**: R' = C$_6$H$_{13}$, 71 (62)	**3p**: R = C$_7$H$_{15}$, 23 (8)

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), [(Cp*RhCl$_2$)$_2$] (0.01 mmol), Cu(OAc)$_2$•H$_2$O (0.05 mmol), Na$_2$CO$_3$ (1 mmol), *o*-xylene (3 mL) at 100 °C for 6 h under N$_2$−air (5:1, 900 mL). [b] GC yield based on the amount of **1a** used. The number in parentheses indicates yield after purification. [c] Under N$_2$ with AgOAc (1 mmol) in place of Cu(OAc)$_2$•H$_2$O. [d] Under N$_2$ with Ag$_2$CO$_3$ (0.5 mmol) in place of Cu(OAc)$_2$•H$_2$O and Na$_2$CO$_3$.

Dialkylacetylenes such as 4-octyne (**2h**) and 8-octadecyne (**2i**) also reacted smoothly with **1a** under either aerobic conditions (entries 8 and 10) or conditions with a silver salt (entry 9) to efficiently afford the corresponding oxidative coupling products. The major product in each case was, unexpectedly, 6-alkyl-5-alkylidene-5,6-dihydroindolo[2,1-*a*]-isoquinoline **4o** or **4p**, anticipated 5,6-dialkylindolo[2,1-*a*]-isoquinoline **3o** or **3p** being produced in a minor amount.[13]

The product **4** seems to be constructed from **1a** and a dialkylacetylene through the steps depicted in Scheme 4. A seven-membered rhodacycle intermediate **B′** is generated in a similar manner to that to **B** in Scheme 3. Since **B′** has a β-hydrogen, its elimination appears to occur in preference to reductive elimination to form **D**.[14] Then, **D** undergoes intramolecular allene insertion into the C−Rh bond and reductive elimination to produce **4**.

Scheme 4



Some of the indolo[2,1-*a*]isoquinolines obtained above showed solid-state fluorescence in a range of 460−510 nm (see the Supporting Information). Notably, **3f** and **3j** exhibited relatively strong emissions compared to a typical emitter, coumarin 153, by factors of 3.5 and 3.1, respectively (λ_{emis} 470 (for **3f**; A) and 476 nm (for **3j**; B), Figure 1).

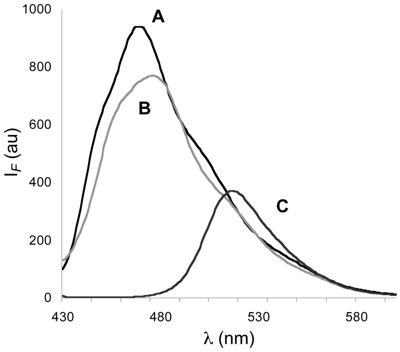


Figure 1. Fluorescence spectra of **3f** (A), **3j** (B), and coumarin 153 (C) in the solid state upon excitation at 422 nm.

In summary, we have demonstrated that the rhodium-catalyzed oxidative coupling of 2-phenylindoles with alkynes proceeds efficiently under aerobic conditions through C−H and N−H bond cleavages to give the corresponding indolo[2,1-*a*]isoquinoline derivatives, some of which exhibit solid-state fluorescence. Since 2-phenylindoles can be easily prepared via the palladium-catalyzed direct arylation of unsubstituted indole with arylboronic acids,[15] the sequence of the arylation and the present oxidative coupling provides a simple synthetic pathway of the nitrogen-containing polycyclic systems from readily available indole, arylboronic acids, and alkynes.

Acknowledgment. This work was partly supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan and the Kurata Memorial Hitachi Science and Technology Foundation.

Supporting Information Available: Standard experimental procedure and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] However, any byproducts possessing the allenyl moiety could not be detected in the reaction mixture.

[15] Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473.