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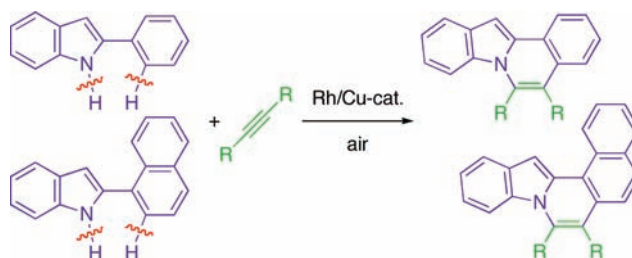
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ABSTRACT

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.

(1) Selected examples: (a) Abet, V.; Nuñez, A.; Menduti, F.; Burgos, C.; Alvarez-Builla, J. *J. Org. Chem.* **2008**, *73*, 8800. (b) Ahmed, E.; Briseno, A. L.; Xia, Y.; Jenekhe, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 1118. (c) Parenty, A. D. C.; Song, Y.-F.; Richmond, C. J.; Cronin, L. *Org. Lett.* **2007**, *9*, 2253. (d) Gondek, E.; Kityk, I. V.; Danel, A.; Wisla, A.; Sanetra, J. *Synth. Met.* **2006**, *156*, 1348. (e) Bersuker, I. B.; Bahceci, S.; Boggs, J. E.; Pearlman, R. S. *J. Comput.-Aided Mol. Des.* **1999**, *13*, 419. (f) Tomoda, H.; Hirano, T.; Saito, S.; Mutai, T.; Araki, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1327. (g) Barrio, J. R.; Sattsangi, P. D.; Gruber, B. A.; Dammann, L. G.; Leonard, N. J. *J. Am. Chem. Soc.* **1976**, *98*, 7408.

(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.

Scheme 1

Scheme 1
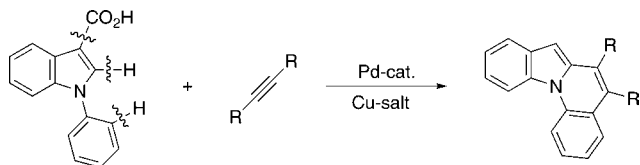
During our further study of fused heteroaromatic construction,[5] we have succeeded in building up an indolo[2,1-a]-isoquinoline framework via the aerobic oxidative coupling of 2-phenylindoles with alkynes under rhodium catalysis, accompanied by C–H and N–H bond cleavages (Scheme 2).[6] Note that this reaction proceeds smoothly with air as

Scheme 2

Scheme 2
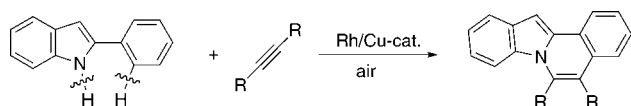
terminal oxidant, in which no wastes are formed except for water. The tetracyclic framework can be seen in various natural products that exhibit a broad range of interesting biological activity.[7] Moreover, as are indolo[1,2-a]quinolines, some of the indolo[2,1-a]isoquinoline derivatives obtained have been found to show solid-state fluorescence. The results obtained for the coupling are described herein.

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(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 indolyl-rhodium intermediate and subsequent cyclorhodation to form **B** cannot be excluded.

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$_2$CO$_3$ (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

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

entry	oxidant (mmol)	yield of **3a**[b]
1[c]	Ag$_2$CO$_3$ (0.5)	44
2[c]	AgOAc (1)	80
3	AgOAc (1)	99 (96)
4	Cu(OAc)$_2$·H$_2$O (1)	92
5	Cu(OAc)$_2$·H$_2$O (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$_2$CO$_3$ (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$_2$CO$_3$. [d] Under N$_2$–air (5:1, 900 mL).

product yield significantly increased to 80% by using AgOAc (1 mmol) as the oxidant in place of Ag$_2$CO$_3$ (entry 2). The addition of Na$_2$CO$_3$ (1 mmol) enabled **3a** to be produced quantitatively (entry 3). An inexpensive oxidant, Cu(OAc)$_2$·H$_2$O, 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)$_2$·H$_2$O (0.05 mmol) under N$_2$–air (5:1) (entry 5).[8] Without the copper cocatalyst, the reaction was sluggish (entry 6).

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*]iso-quinolines **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-diphenylin-dolo[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).

(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 = CO₂Me	**3e**: Y = H, Z = CO₂Me, (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)
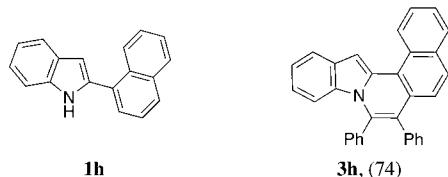
[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), [(Cp*RhCl₂)₂] (0.01 mmol), Cu(OAc)₂·H₂O (0.05 mmol), Na₂CO₃ (1 mmol), o-xylene (3 mL) at 100 °C for 6 h under N₂−air (5:1, 900 mL). [b] GC yield based on the amount of **1** used. The number in parentheses indicates yield after purification. [c] For 10 h. [d] With **1** (0.25 mmol), **2a** (0.25 mmol), [(Cp*RhCl₂)₂] (0.005 mmol), Cu(OAc)₂·H₂O (0.025 mmol), Na₂CO₃ (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

Scheme 3
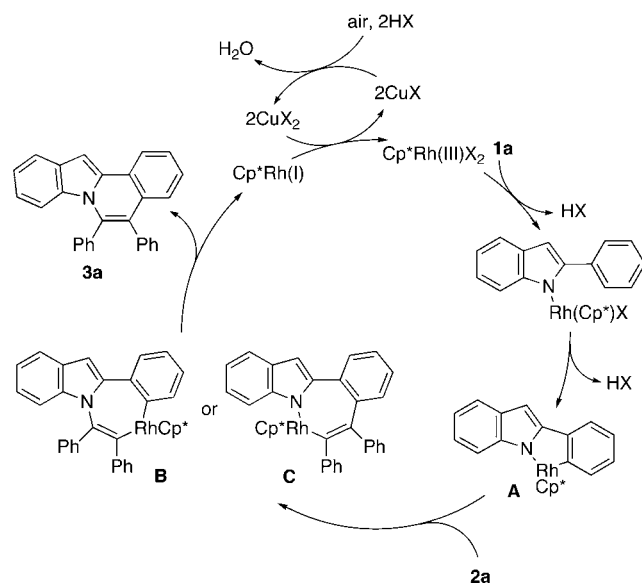
neutral ligands are omitted. Initial coordination of the nitrogen atom of **1a** to Cp*Rh(III)X₂ species[9] and subsequent cyclorhodation gives a five-membered rhodacycle intermediate **A**.[10,11] Then, alkyne insertion into the N−Rh or C−Rh

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)X₂.

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*]iso-quinolines **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**)

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 = Buᵗ	**3j**: X = Buᵗ, 97 (90)
3	**2d**: X = OMe	**3k**: X = OMe, (93)
4	**2e**: X = Cl	**3l**: X = Cl, 86 (86)
5	**2f**: X = CF₃	**3m**: X = CF₃, (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 = C₇H₁₅	**4p**: R' = C₆H₁₃, 71 (62)	**3p**: R = C₇H₁₅, 23 (8)

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), [(Cp*RhCl₂)₂] (0.01 mmol), Cu(OAc)₂·H₂O (0.05 mmol), Na₂CO₃ (1 mmol), o-xylene (3 mL) at 100 °C for 6 h under N₂−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 N₂ with AgOAc (1 mmol) in place of Cu(OAc)₂·H₂O. [d] Under N₂ with Ag₂CO₃ (0.5 mmol) in place of Cu(OAc)₂·H₂O and Na₂CO₃.

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]

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
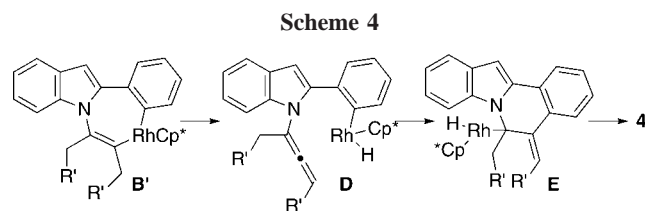
Scheme 4

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**.

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).

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

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(14) However, any byproducts possessing the allenyl moiety could not be detected in the reaction mixture.
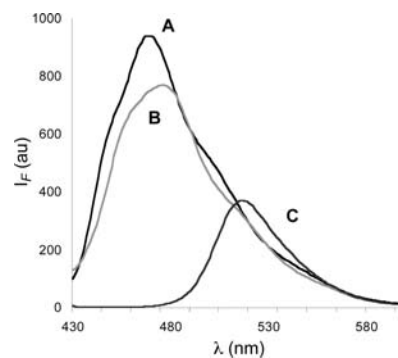
Figure 1. Fluorescence spectra of **3f** (A), **3j** (B), and coumarin 153 (C) in the solid state upon excitation at 422 nm.

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.

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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(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.