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Synthesis of Indolo[1,2-*a*][1,8]naphthyridines by Rhodium(III)-Catalyzed Dehydrogenative Coupling via Rollover Cyclometalation

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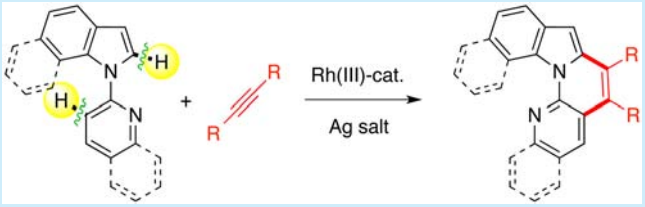
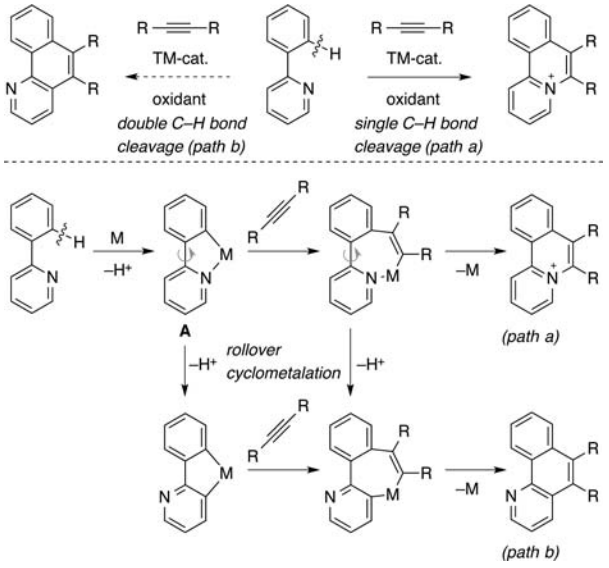
Supporting Information

ABSTRACT: The rhodium-catalyzed dehydrogenative coupling of *N*-pyridylindoles with alkynes proceeds smoothly through rollover cyclometalation to produce indolo[1,2-*a*][1,8]naphthyridine derivatives. A number of tetra-, penta-, and hexacyclic *N*-containing heteroaromatics can also be readily constructed in a similar manner. The L-shaped π-conjugated molecules exhibit intense solid-state fluorescence.



Fused polycyclic heteroarene compounds have been recognized as important frameworks in organic materials as well as pharmaceutical fields.[1] Therefore, simple and flexible procedures for constructing such π-conjugated molecules from readily available starting materials are strongly needed. One of the most promising strategies for such a synthetic purpose is the transition-metal-catalyzed dehydrogenative coupling of phenylheteroarenes or bisheteroarenes with alkynes via C−H bond cleavage.[2] For example, the rhodium(III)-mediated and -catalyzed annulation of 2-phenylpyridines with alkynes through successive C−C and C−N bond formations has been reported by Jones', Cheng's, and Huang's groups (Scheme 1, path a).[3] In this reaction, coordination of the nitrogen atom of the substrates to the metal center of the catalyst is the key to trigger the regioselective C−H bond cleavage/annulation at the neighboring positions. The other annulation that involves double C−H bond cleavages and two C−C bond formations (path b) also appears to be attractive because this enables us to construct a different neutral polycyclic system. The latter reaction proceeds through the rollover cyclometalation step[4] of a common metalacycle intermediate **A** before or after an alkyne insertion step. However, this type of annulation of pyridyl-(hetero)arenes rarely has been found,[5] probably due to the strong coordination of the pyridyl moiety to the metal center to render the rollover cyclometalation/annulation process less favorable. In the context of our studies on rhodium(III)-catalyzed fused (hetero)arene construction,[6] we succeeded in finding that *N*-(2-pyridyl)indoles undergo dehydrogenative coupling with alkynes via rollover cyclometalation to afford indolo[1,2-*a*][1,8]naphthyridine derivatives. This type of L-shaped π-extended molecules has attracted much attention because of their interesting fluorescent properties.[7] Expectedly, most of the thus obtained tetra-, penta-, and hexacyclic compounds exhibited intense fluorescence in the solid state. These new findings are described herein.

Scheme 1. Annulation of 2-Phenypyridine with Alkynes



In an initial attempt, *N*-(2-pyridyl)indole (**1a**) (0.2 mmol) was treated with diphenylacetylene (**2a**) (0.2 mmol) in the presence of $[Cp^*RhCl_2]_2$ (0.004 mmol, 2 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.4 mmol), and K_2CO_3 (0.4 mmol) as catalyst, oxidant, and additive, respectively, under N_2 in *o*-xylene at 120 °C for 6 h. As a result, small amounts of the desired rollover annulation product, 5,6-diphenylindolo[1,2-*a*][1,8]naphthyridine (**3aa**), and the C2-alkenylated product **4a** were formed (Table 1,

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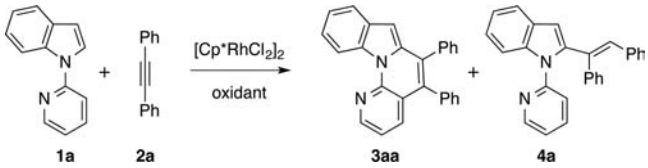
Table 1. Reaction of *N*-(2-Pyridyl)indole (1a) with Diphenylacetylene (2a)[a]



				yield[b] (%)	
entry	oxidant (mmol)	solvent	temp (°C)	**3aa**	**4a**
1[c]	$Cu(OAc)_2·H_2O$ (0.4)	*o*-xylene	120	11	4
2[c]	$Cu(OAc)_2·H_2O$ (0.4)	PhCl	120	18	12
3[c]	$Cu(OAc)_2·H_2O$ (0.4)	TCE	120	1	62
4[c]	AgOAc (0.4)	PhCl	120	20	tr
5	AgOAc (0.6)	PhCl	120	69	tr
6	AgOAc (0.6)	PhCl	140	77	tr
7[d]	AgOAc (0.6)	PhCl	140	>99 (91)	tr
8[e]	AgOAc (3)	PhCl	140	(84)	11
9	AgOAc (0.6)	DCE	100	5	95
10	$Cu(OAc)_2·H_2O$ (0.04)	TCE	100	tr	97
11	$Cu(OAc)_2·H_2O$ (0.04)	DCE	100	tr	>99 (91)

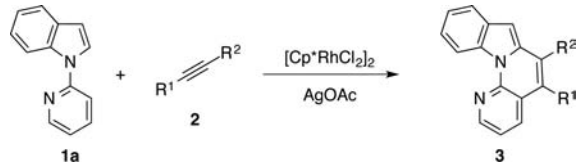
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.004 mmol) in solvent (2 mL) under N_2 for 6 h, unless otherwise noted. [b]GC yield based on the amount of **2a** used. Value in parentheses indicates yield after purification. [c]With K_2CO_3 (0.4 mmol). [d]With **1a** (0.3 mmol). [e]With **1a** (1.5 mmol), **2a** (1 mmol), and $[Cp^*RhCl_2]_2$ (0.02 mmol) in PhCl (10 mL).

entry 1).[8] The use of PhCl as solvent resulted in a slightly increased yield of **3aa** (entry 2). In contrast, the reaction in 1,1,2,2-tetrachloroethane (TCE) gave **4a** predominantly in 62% yield (entry 3). The use of AgOAc as oxidant suppressed the formation of **4a** almost completely to afford **3aa** in 20% yield (entry 4). Increasing in the amount of AgOAc to 0.6 mmol in the absence of K_2CO_3 improved the yield of **3aa** up to 69% (entry 5). Finally, **3aa** was obtained quantitatively at 140 °C with an increased amount of **1a** (0.3 mmol) (entry 7). The scale-up did not affect **3aa** yield significantly (entry 8). On the other hand, even with AgOAc as oxidant, **4a** was produced selectively when the reaction was conducted in 1,2-dichloroethane (DCE) (entry 9). Expectedly, the reaction in TCE or DCE using a catalytic amount of $Cu(OAc)_2·H_2O$ at 100 °C selectively gave **4a** in a high yield (entries 10 and 11).

Under the optimized conditions (Table 1, entry 7), the reactions of **1a** with bis(4-substituted phenyl) acetylenes **2b–h** proceeded efficiently to give the corresponding products **3ab–ah** in 61–94% yields (Table 2, entries 1–7). Di(2-naphthyl)- (**2i**) and di(2-thienyl)acetylenes (**2j**) could also be employed for the annulation (entries 8 and 9). The reaction with unsymmetric 1-phenyl-1-hexyne (**2k**) gave a mixture of regioisomers **3ak** and **3ak′** (entry 10).

Next, we examined the annulative coupling of various *N*-(2-pyridyl)indoles and related compounds **1** with **2a** (Table 3). The reactions of 3-, 5-, 6-, and 7-substituted *N*-(2-pyridyl)-indoles **1b–j** afforded the corresponding indolonaphthyridines **3ba–ja** in 60–93% yields. In the case of **1d**, an increase in the amount of the catalyst was needed to conduct the reaction comparably. 5-Substituted 2-pyridyl (**1k,l**) and 2-pyrazinyl

Table 2. Reaction of *N*-(2-Pyridyl)indole (1a) with Alkynes 2[a]



entry	**2**	product(s)	% yield[b]
1	**2b**: R = Me	**3ab**: R = Me	94
2	**2c**: R = Bu^t	**3ac**: R = Bu^t	85
3	**2d**: R = OMe	**3ad**: R = OMe	83
4	**2e**: R = F	**3ae**: R = F	85
5	**2f**: R = Cl	**3af**: R = Cl	93
6	**2g**: R = Br	**3ag**: R = Br	86
7	**2h**: R = CF_3	**3ah**: R = CF_3	61
8	**2i**	**3ai**	93
9	**2j**	**3aj**	51
10	**2k**	**3ak** + **3ak′**	71 (62:38)[c]

[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.004 mmol), AgOAc (0.6 mmol) in PhCl (2 mL) under N_2 for 6 h at 140 °C. [b]Isolated yield based on the amount of **2** used. [c]Determined by ^1H NMR.

(**1m**) groups were found to act as good directing groups to give **3ka–ma** selectively. *N*-(2-Pyridyl)benzimidazole (**1n**) also underwent coupling with **2a** to produce **3na** in 95% yield. Interestingly, *N*-(2-pyridyl)benzindole **1o**, *N*-(2-quinolinyl)-indoles **1p–r**, and *N*-(2-quinolinyl)benzindole **1s** coupled with **2a** smoothly to afford penta- and hexacyclic compounds **3oa–sa**.

A plausible mechanism for the reaction of **1a** with **2** is illustrated in Scheme 2. The reaction may involve pyridyl nitrogen-directed cyclorhodation to form intermediate **B** followed by alkyne insertion/rollover cyclorhodation via **C** or **D** and successive reductive elimination from resulting **E** to afford **3**. It was confirmed that the pyridyl nitrogen of **1a** is essential as the director for the present annulation. Thus, treatment of *N*-phenylindole (**5**) in place of **1a** together with **2a** did not give any coupling product (eq 1).

The protonation of intermediate **C** may take place preferably in TCE or DCE (Table 1, entries 8 and 9), rather than the

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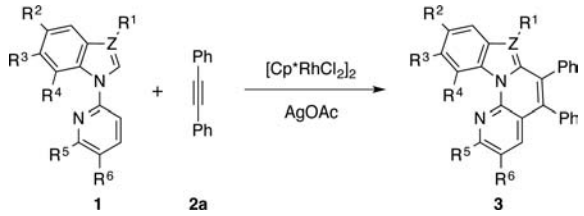
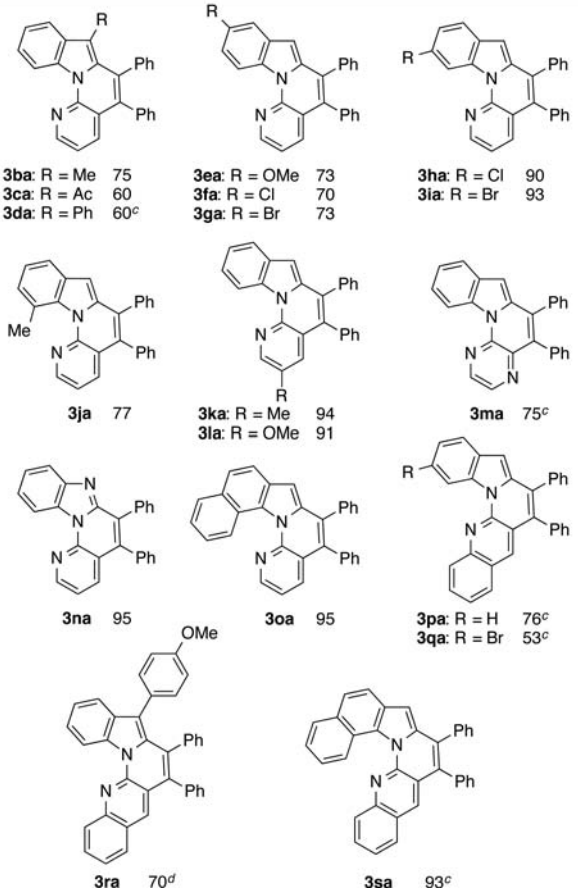
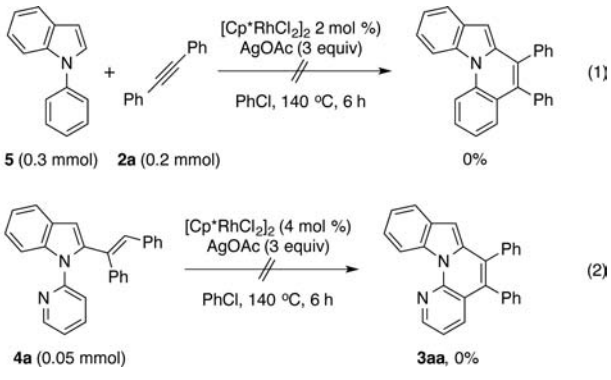
Table 3. Reaction of *N*-(2-Pyridyl)indoles 1 with Diphenylacetylene (2a)[a]



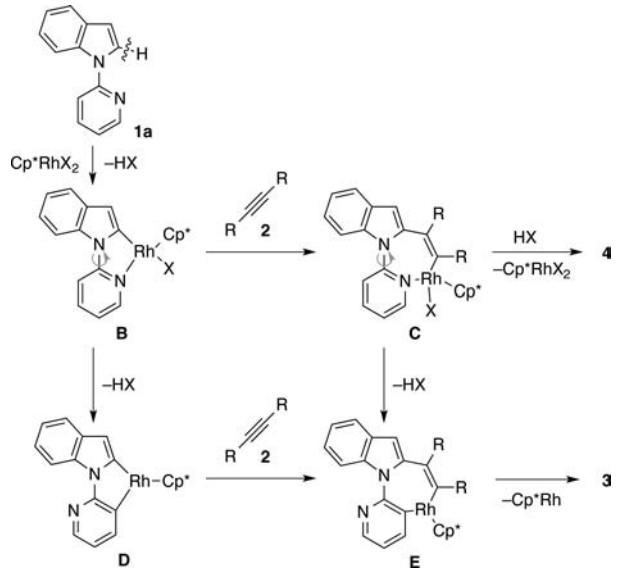
product % yield[b]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.004 mmol), AgOAc (0.6 mmol) in PhCl (2 mL) under N_2 for 6 h at 140 °C, unless otherwise noted. [b]Isolated yield based on the amount of **2a** used. [c]With $[Cp^*RhCl_2]_2$ (0.008 mmol). [d]With $[Cp^*RhCl_2]_2$ (0.016 mmol).



Scheme 2. Plausible Mechanism for the Reaction of 1a with 2



rollover cyclorhodation, to give **4** selectively. It was also confirmed that **4** is not an intermediate for the formation of **3**. Thus, **3aa** was not produced at all in the treatment of **4a** under the standard conditions (eq 2).

Most of the annulation products **3** described above showed solid-state fluorescence in a range of 430−550 nm, as was expected (see the Supporting Information). Notably, compounds **3ba** and **3na** exhibited relatively strong emissions compared with a typical emitter, tris(8-hydroxyquinolino)-aluminum (Alq_3), by factors of 3.4 and 8.1 (excited at 380 nm). The quantum efficiencies of the solid-state fluorescence of **3ba** and **3na** were measured at absolute values of 0.51 and 0.80, respectively.

In summary, we have demonstrated that indolo[1,2-*a*][1,8]-naphthyridine and related benzo-fused frameworks can be readily constructed by the rhodium-catalyzed dehydrogenative coupling of *N*-pyridylindoles with alkynes. This reaction involves rollover cyclometalation as a key step. Most of the annulation products exhibit intense fluorescence in the solid state.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, additional data for fluorescence, and characterization data of products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01452.

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Notes

The authors declare no competing financial interest.

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