Synthesis of 7-Phenylindole Derivatives through Rhodium-Catalyzed Dehydrogenative Coupling of 2-(Acetylamino)-1,1'-biphenyls with Alkynes

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FULL PAPER

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Dedication ((optional))

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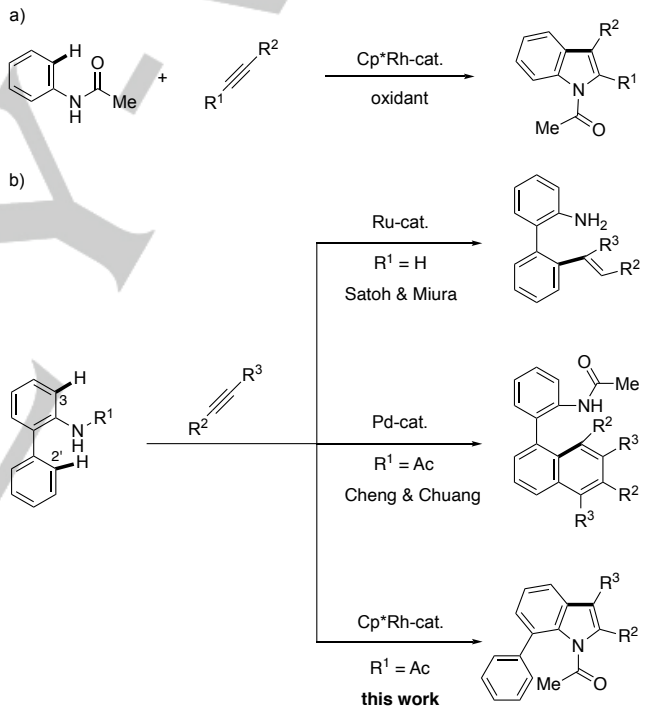
Abstract: The dehydrogenative coupling of 2-(acetylamino)-1,1'-biphenyls with internal alkynes proceeds regioselectively under rhodium catalysis to afford the corresponding 7-phenylindole derivatives. Combining with Suzuki-Miyaura coupling, the processes provide easy access to the 7-phenylindole structures from readily available starting materials.

Introduction

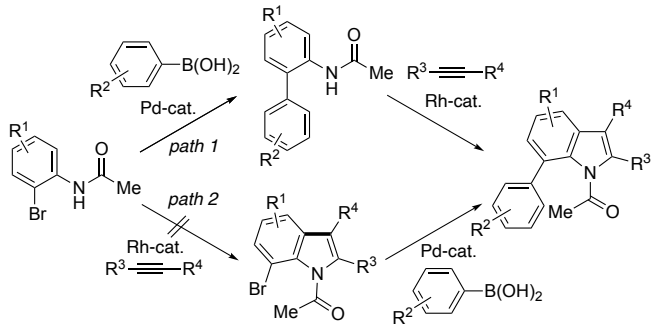
Indole frameworks can be widely seen in synthesized and naturally occurring bioactive compounds.[1] A variety of synthetic methods for preparing functionalized indoles have been developed.[2] Among such indoles, 7-phenylindole derivatives have attracted much attention because of their utility for anti-HIV,[3] anticancer,[4] and other bioactivities[5] as well as for fluorescent[6] and anion receptor abilities.[7]

Meanwhile, transition-metal-catalyzed C–H functionalization has been recognized as a powerful synthetic tool from the atom- and step-economical points of view.[8] Particularly, the dehydrogenative coupling of aromatic substrates possessing a heteroatom containing directing group with internal alkynes is a promising method for constructing fused heteroaromatic compounds.[9] For example, Fagnou and co-workers reported that acetanilides undergo dehydrogenative coupling with internal alkynes under rhodium catalysis to give 2,3-disubstituted *N*-acetylindoles (Scheme 1a).[10] We also continuously examined the transition-metal-catalyzed inter- and intramolecular coupling of 2-amino-1,1'-biphenyls and related compounds.[11] One of them is the ruthenium-catalyzed direct coupling of 2-aminobiphenyls with internal alkynes accompanied by C–H bond cleavage at the C2' position (Scheme 1b).[11e,12] Cheng, Chuang, and co-workers reported the palladium-catalyzed 1:2 dehydrogenative coupling of 2-(acetylamino)-1,1'-biphenyls with alkynes involving C2'–H bond cleavage.[12d] During our further study on the transformation of this type of substrates, we found that 2-(acetylamino)-1,1'-biphenyls couple with alkynes at the C3 position under rhodium catalysis to produce 7-phenylindole derivatives selectively (Scheme 1b, this work).[13]



Scheme 1. Coupling Reactions of a) Acetanilides and b) 2-Aminobiphenyls with Alkynes.

Taking account of the fact that 2-(acetylamino)-1,1'-biphenyls are readily available through the Suzuki-Miyaura coupling of 2-bromoacetanildes with phenylboronic acids, these processes provide a ready accessible two-step route toward 7-phenylindoles (Scheme 2, *path 1*). It has been confirmed that this route is superior to another route, composed of dehydrogenative coupling of 2-bromoacetanilides with alkynes and following Suzuki-Miyaura coupling (Scheme 2, *path 2*). Indeed, the coupling of 2-bromoacetanilide with diphenylacetylene did not proceed smoothly under standard conditions to give 7-bromoindoles in a low yield (<10%, vide infra).

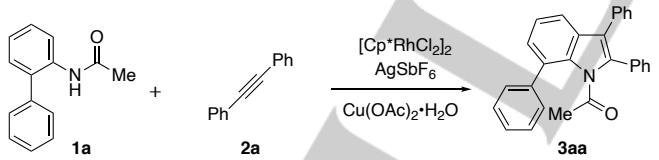


Scheme 2. Synthetic Strategies for 7-Phenylindoles.

Results and Discussion

As shown in Scheme 2, the reaction efficiency for the rhodium-catalyzed dehydrogenative coupling of 2-substituted acetanilides with alkynes was significantly affected by the identity of the substituent. Therefore, we first attempted to optimize reaction conditions for the reaction of 2-(acetylamino)-1,1'-biphenyl (**1a**). When **1a** (0.1 mmol) was treated with diphenylacetylene (**2a**) (0.1 mmol) using $[Cp^*RhCl_2]_2$ (0.0025 mmol), $AgSbF_6$ (0.01 mmol), and $Cu(OAc)_2•H_2O$ (0.1 mmol) as catalyst, cocatalyst, and oxidant, respectively, in *t*-AmOH under O_2 (1 atm) at 110 °C for 20 h, *N*-acetyl-2,3,7-triphenylindole (**3aa**) was obtained in 33% yield (Table 1, entry 1). No other coupling products were detected by TLC and GC-MS, considerable amounts of starting materials being recovered. Increasing the amount of $Cu(OAc)_2•H_2O$ to 0.22 mmol reduced the **3aa** yield (entry 2). The extension of reaction time to 67 h enhanced the yield up to 67% (entry 3). The reaction was found to proceed faster in diglyme. Thus, **3aa** was obtained in 70% yield within 5 h (entry 4). Increasing the reaction temperature to 130 °C slightly decreased the **3aa** yield in diglyme (entry 5) or in DCE (entry 6).

Table 1. Reaction of 2-(Acetylamino)-1,1'-biphenyl (**1a**) with Diphenylacetylene (**2a**).

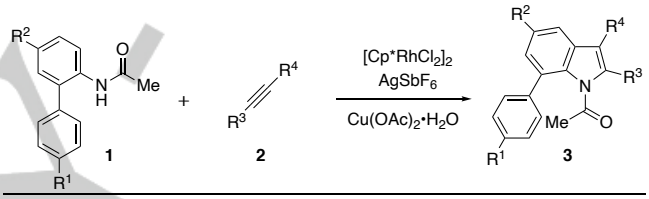


1a **2a** **3aa**

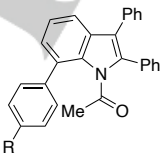
entry	Solvent	T [°C]	Time [h]	Yield [%][b]
1	*t*-AmOH	110	20	33
2[c]	*t*-AmOH	110	20	4
3	*t*-AmOH	110	67	67
4	diglyme	110	5	70
5	diglyme	130	5	60
6	DCE	130	20	65

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), $[Cp^*RhCl_2]_2$ (0.0025 mmol, 2.5 mol%), $AgSbF_6$ (0.01 mmol, 10 mol%), $Cu(OAc)_2•H_2O$ (0.1 mmol) in solvent (1 mL) under O_2 (1 atm), unless otherwise noted. [b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] With $Cu(OAc)_2•H_2O$ (0.22 mmol).

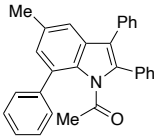
Under scaled-up conditions with the optimized reaction system (Table 1, entry 4), 2-(4-substituted phenyl)acetanilides **1b**-**g** reacted with **2a** to afford the corresponding 7-(4-substituted phenyl)indoles **3ba**-**3ga** (Scheme 3). 4-Methyl-2-phenylacetanilide (**1h**) also coupled with **2a** to produce **3ha** in a moderate yield. Next, we examined the reactions of **1a** with various alkynes **2**. 4-Methyl (**2b**), 4-methoxy (**2c**), and 4-chloro substituted diphenylacetylenes underwent the coupling with **1a** to produce **3ab**, **3ac**, and **3ad**, respectively, in 43-73% yields. Unsymmetrical alkylphenylacetylenes, 1-phenyl-1-propyne (**2e**) and 1-phenyl-1-pentyne (**2f**), also coupled with **1a** to give 3-alkyl-2,7-diphenylindoles **3ae** and **3af** selectively. In the present reaction, electron deficient methyl phenylpropionate (**2g**) was found to be applicable. Thus, methyl *N*-acetyl-2,7-diphenylindole-3-carboxylate (**3ag**) was obtained in 53% yield. Besides aromatic alkynes, dialkylacetylenes such as 4-octyne (**2h**) and 8-hexadecyne (**2i**) also underwent the reaction with **1a** to produce **3ah** and **3ai** in moderate yields.



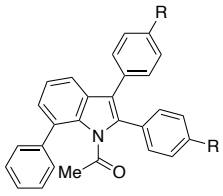
1 **2** **3**



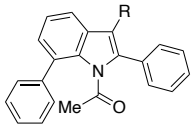
3aa: R = H, 64%
3ba: R = Me, 58%
3ca: R = OMe, 59%
3da: R = F, 35%
3ea: R = Cl, 56%
3fa: R = Br, 33%
3ga: R = CF_3, 21%



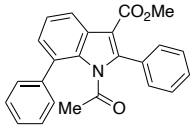
3ha, 38%



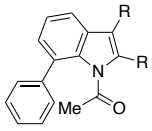
3ab: R = Me, 58%
3ac: R = OMe, 73%
3ad: R = Cl, 43%



3ae, R = Me, 47%
3af, R = *n*-Pr, 63%



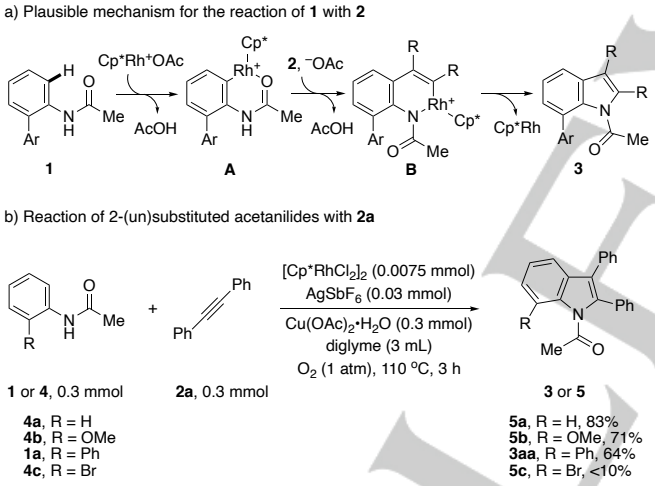
3ag, 53%



3ah, R = *n*-Pr, 39%
3ai, R = *n*-C_7H_{15}, 43%

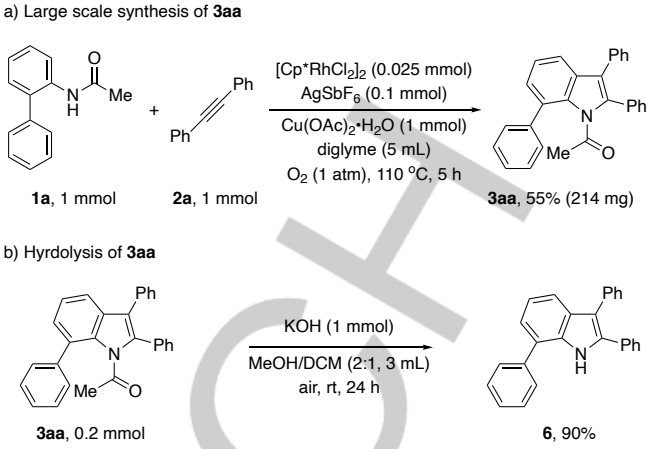
Scheme 3. Reaction Scope of 7-Phenylindoles and Alkynes. Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (0.0075 mmol), $AgSbF_6$ (0.03 mmol), $Cu(OAc)_2•H_2O$ (0.3 mmol) in diglyme (3 mL) under O_2 (1 atm) at 110 °C for 3 h. Yields after purification were listed.

The present dehydrogenative coupling of 2-(acetylamino)-1,1'-biphenyls **1** with alkynes **2** seems to proceed via a similar pathway to that proposed for Fagnou's indole synthesis from acetanilides.[10] Thus, coordination of the amide group in **1** to rhodium induces *ortho* C–H rhodation to form intermediate **A** (Scheme 4a). Then, alkyne insertion to form intermediate **B** and C–N reductive elimination may take place to give product **3**. A Rh(I) species liberated at the last step is reoxidized by a copper salt to regenerate an active Rh(III) species. 2-Unsubstituted (**4a**) and 2-methoxy- (**4b**) acetanilides underwent the coupling with **2a** more smoothly under our standard conditions to give *N*-acetyl-2,3-diphenylindole (**5a**) and *N*-acetyl-7-methoxy-2,3-diphenylindole (**5b**), respectively (Scheme 4b). A relatively bulkier phenyl substituent at the 2-position of **1** may retard the initial amide coordination step due to steric hindrance. As described above, the steric inhibition effect seems to be more significant in the case with 2-bromoacetanilide (**4c**). In this case, the reaction was sluggish and most of substrates were recovered. However, the details of the bromo substituent effect are obscure at the present stage.



Scheme 4. Large Scale Synthesis and Hydrolysis of **3aa**.

It was confirmed that the present dehydrogenative coupling could be further scaled up to a 1 mmol scale. Thus, the reaction of **1a** (1 mmol) with **2a** (1 mmol) gave **3aa** in a reasonable yield (214 mg, 55%) (Scheme 5a). In addition, **3aa** readily underwent hydrolysis upon treatment with KOH to give *N*-H 2,3,7-triphenylindole (**6**) (Scheme 5b).



Scheme 5. Large Scale Synthesis and Hydrolysis of **3aa**.

Finally, we conducted preliminary surveys on the optical properties of 7-phenylindoles. All indoles obtained by the present procedures showed fluorescence in $CHCl_3$ solutions in the visible region at 390-480 nm (see Figure S1 in the supporting information). As shown in Figure 1, significant red-shifts were observed for **3ca** and **3ac** possessing methoxy group(s), compared to **3aa** (Figure 1).

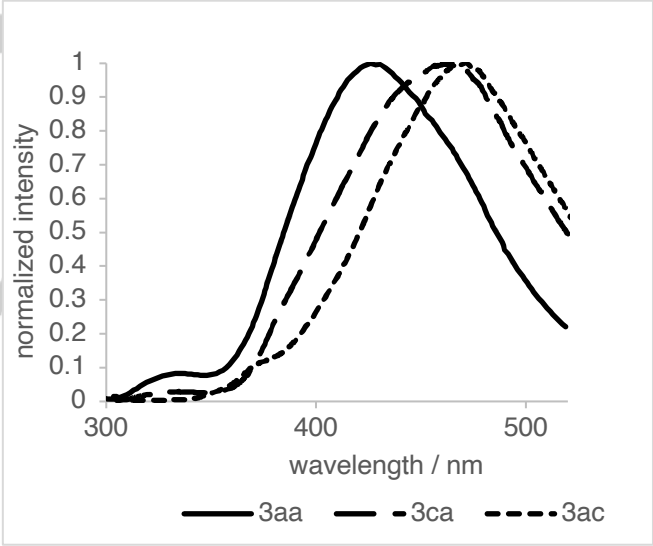


Figure 1. Normalized Fluorescence Emission Spectra of **3aa** (solid line, λ_{ex} = 315 nm), **3ca** (long dashed line, λ_{ex} = 270 nm), and **3ac** (short dashed line, λ_{ex} = 277 nm) in $CHCl_3$ solution (1.0×10^{-5} M).

Conclusion

We have demonstrated that variously substituted 7-phenylindole derivatives can be readily prepared by the rhodium-catalyzed dehydrogenative coupling of 2-(acetylamino)-1,1'-biphenyls with alkynes. Preliminary surveys on the optical properties of obtained 7-phenylindoles have also been conducted.

Experimental Section

Experimental Details: To a 20 mL two-necked flask with a reflux condenser, a balloon, and a rubber septum were added 2-(acetylamino)-1,1'-biphenyl **1** (0.3 mmol), alkyne **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (0.0075 mmol, 5 mg), $AgSbF_6$ (0.03 mmol, 10 mg), $Cu(OAc)_2•H_2O$ (0.3 mmol, 60 mg), diglyme (3 mL), and 1-methylnaphthalene (ca. 50 mg) as internal standard. The mixture was stirred under O_2 (1 atm) at 110 °C (bath temperature) for 3 h. The reaction mixture was diluted by ethyl acetate (60 mL). The organic layer was washed by water (60 mL, four times) and brine (60 mL, two times) and dried over Na_2SO_4. After evaporation of the solvents under vacuum, product **3** was isolated by column chromatography on silica gel using hexane−ethyl acetate as eluent. Further purification by GPC (gel permeation chromatography) was performed, if needed.

Acknowledgements

This work was partly supported by JSPS KAKENHI Grant Numbers 20H02745 and 18K19083 and OCU Strategic Research Grant 2020 for basic researches to T.S. and JSPS KAKENHI Grant Number JP18H04627 to Y.U.

Keywords: Annlation • C–C coupling • C–H activation • Homogeneous catalysis • Rhodium

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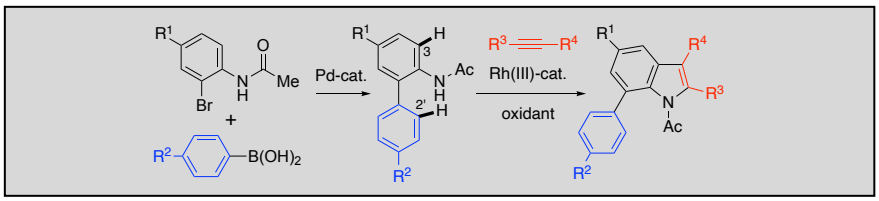

7-Phenylindole flameworks can be readily constructed through two steps, Suzuki-Miyaura coupling to form 2-(acetylamino)-1,1'-biphenyls and their dehydrogenative coupling with internal alkynes under rhodium catalysis. The 7-phenylindole derivatives have attracted much attention because of their bioactivities as well as their utilities as fluorescence agents and anion receptors.

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