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Rhodium(III)-Catalyzed Synthesis of Cinnolinium Salts from Azobenzenes and Alkynes: Application to the Synthesis of Indoles and Cinnolines

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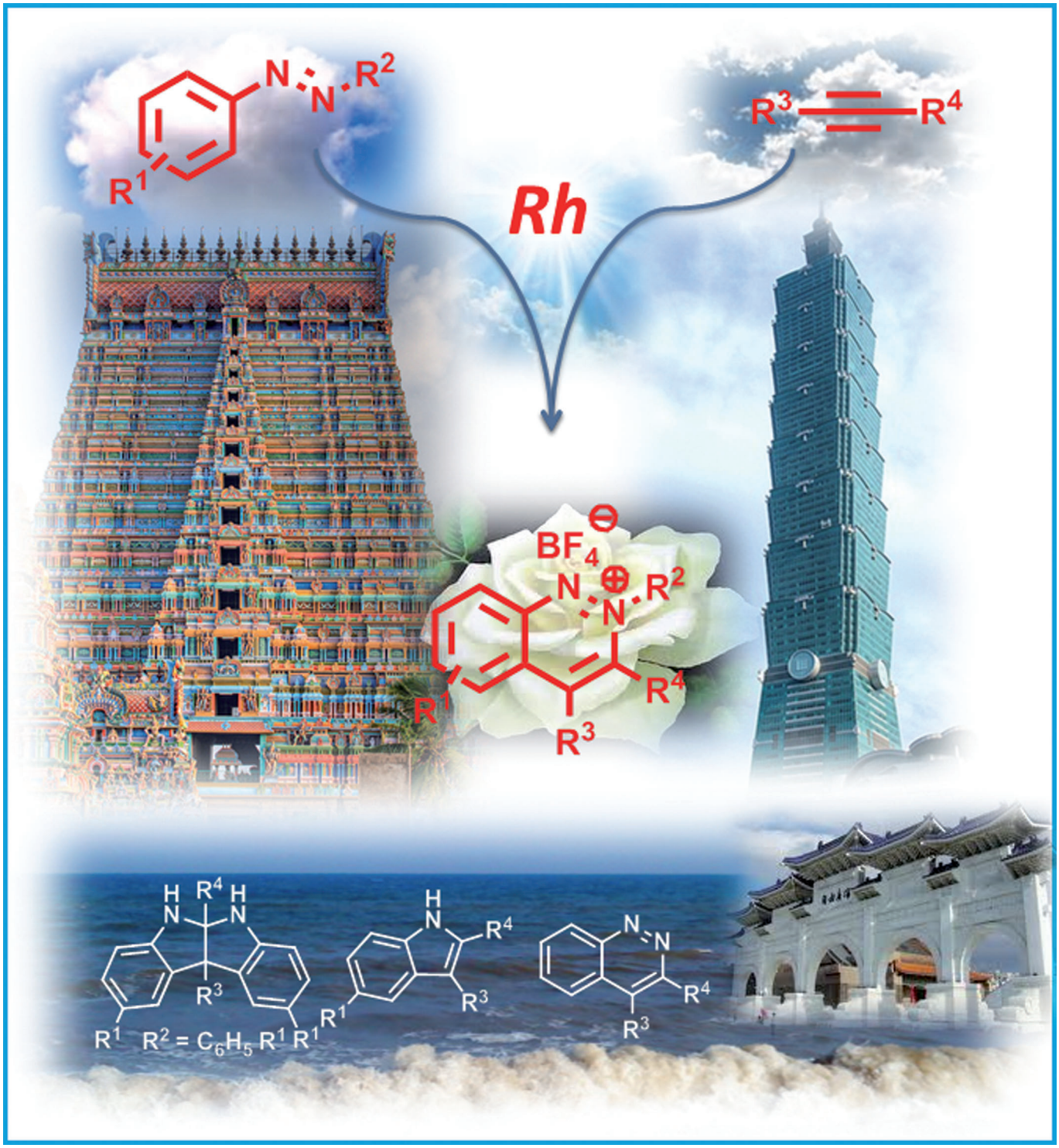
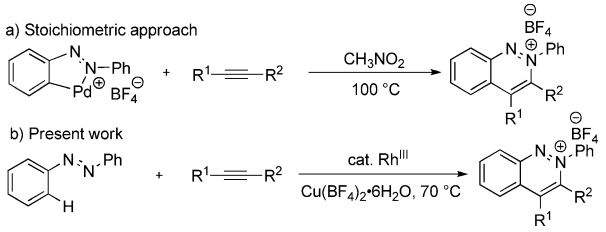


Substituted cinnolinium salts are flexible building blocks for many natural products, alkaloids, receptors, inhibitors, and pharmacologically active salts.[1] Consequently, great attention has been paid to the synthesis of heterocyclic compounds bearing a cinnoline moiety. Despite the high utility of cinnoline derivatives, only few synthetic routes for cinnolinium salts are available in the literature.[2a,b] Typical methods involve a direct alkylation of cinnolines to afford cinnolinium salts. The direct synthesis of cinnolinium salts from readily available starting materials in a one-pot manner was hardly demonstrated.[2c–g] Previously, Heck and co-workers described the stoichiometric annulation of cyclometalated azobenzenes with alkynes to give cinnolinium salts (Scheme 1).[3a–c] To the best of our knowledge, there is no



Scheme 1. Synthesis of cinnolinium salts.

report on the synthesis of cinnolinium salts catalyzed by metal complexes, despite the fact that a few reports are available for the synthesis of cinnolines and its related derivatives.[3d–g,4]

In recent years, transition-metal-catalyzed directed C–H functionalization offerd a great variety of useful transformations.[5] Extensive studies have been devoted towards Rh^{III}-catalyzed aromatic *ortho*-C–H bond activation[6] and annulation reactions involving nitrogen-containing directing groups to construct heterocyclic compounds.[7,8] In this context, Jones and co-workers described a stoichiometric reaction of *N*-benzylidenemethylamine, 2-phenylpyridine, and benzo[*h*]-quinoline with alkynes through C–H bond activation mediated by Rh^{III} complexes to give various nitrogen-containing salts.[9a]

Previously, we reported a nickel-catalyzed annulation of 2-halobenzaldimines[9b,c] or *ortho*-iodoketimines[9d] with alkynes to give isoquinolinium salts. Very recently we also succeeded in developing a rhodium- and ruthenium-catalyzed three-component reaction of aryl aldehydes, amines, and alkynes to afford isoquinolinium salts.[9e,f,10] Our continuous effort to develop synthetically versatile C–H activation reactions[11] prompted us to explore the metal-catalyzed C–H activation of azobenzenes and the subsequent reaction with alkynes. Herein, we report an RhCp*-catalyzed (Cp* = Me_5C_5) annulation of azobenzenes with alkynes to give biologically active cinnolinium salts. The reaction provides a mild, atom- and step-economical method for the synthesis of cinnolinium salts by using air as the co-oxidant.

The reaction of azobenzene (**1a**, 1.00 mmol) with diphenylacetylene (**2a**, 1.20 mmol) in the presence of $[(RhCp^*Cl_2)_2]$ (1.00 mol%), and $Cu(BF_4)_2{\cdot}6H_2O$ (0.50 mmol) in *t*BuOH under air at 70°C for 16 h gave cinnolinium salt **3a** in 91% isolated yield (Table 1, entry 1). The structure of **3a** was confirmed by its ^1H, ^{13}C, ^{19}F, and ^{11}B NMR spectra, as well as IR and mass data. Control experiments revealed that in the absence of either $Cu(BF_4)_2{\cdot}6H_2O$ or $[(RhCp^*Cl_2)_2]$ no product **3a** was formed. In addition to the above conditions, we also examined the reaction with various oxidants. Among them, the combination of $AgBF_4$ (1.00 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (1.00 mmol) gave the best result, affording **3a** in 96% yield. Using $AgBF_4$ (1.00 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.30 mmol) under air was also effective and gave **3a** in 94% isolated yield. It is worth noting that the present reaction requires two equivalents of the oxidant, such as Cu^{II} or Ag^+, and one equivalent of BF_4^- to reach completion. The solvent also plays a vital role for the reaction; the best solvent is *t*BuOH, affording **3a** in excellent yield. Other solvents, such as *t*-amylOH, MeOH, EtOH, 1,2-dichloroethane (DCE), THF, and acetic acid, are less effective for the catalytic reaction, giving **3a** in 65–86% yield (see the Supporting Information). Based on the results above, we choose $[(RhCp^*Cl_2)_2]$ (1.00 mol%), $Cu(BF_4)_2{\cdot}6H_2O$ (0.50 mmol), and *t*BuOH under air as the standard reaction conditions for most of the following studies; these conditions use less metal oxidant and are thus greener and less expensive.

Under the standard reaction conditions, various substituted azobenzenes **1b–k** reacted with diphenylacetylene (**2a**) to give the corresponding cinnolinium salts in good to excellent yields (Table 1, entries 2–11). Thus, azobenzenes **1b–e** with electron-rich 4,4′-diMe, 4-OMe, 4-*t*Bu, and 4-*n*Bu substituents afforded products **3b–e** in 89–94% yield (entries 2–5). Similarly, electron-withdrawing substituents, including F, Br, and CO_2Et, on the azobenzenes **1f–h** are also compatible, providing functionalized cinnolinium salts **3f–h** in slightly lower yields (74–79%, entries 6–8). To understand the steric effects on the reaction, *ortho*- and *meta*-substituted azobenzenes **1i–k** were examined. The reactions with **2a** gave products **3i–k** in 78–89% yield (entries 9–11). For (*E*)-1,2-bis(3,4-dimethoxyphenyl)diazene (**1j**), the annulation reaction gave single regioisomeric product **3j** in 80% yield (entry 10), although there are two possible C–H bond activation sites at C2 and C6. The C–H bond activation occurs only at C6, likely owing to the steric effect of the methoxy group at C3. On the other hand, **1k** and **l** with two different aromatic rings afforded isomeric product pairs **3k/k′** and **3l/l′** in a ratio of 58:42 and 63:37 with 89 and 82% combined yield, respectively (entries 11 and 12). The isomers **3k** or **l** with C–H bond activation and cyclization at the *p*-anisyl

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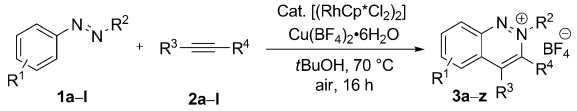
Table 1. Results of annulation of azobenzenes **1** with alkynes **2**.[a]



Entry	1	2	Product 3		Yield [%][b]
1	**1a**	**2a**		**3a**: R^1 = H	91
2	**1b**	**2a**		**3b**: R^1 = 4-Me	89
3	**1c**	**2a**		**3c**: R^1 = 4-OMe	93
4	**1d**	**2a**		**3d**: R^1 = 4-*t*Bu	94
5	**1e**	**2a**		**3e**: R^1 = 4-*n*Bu	90
6[c]	**1f**	**2a**		**3f**: R^1 = 4-F	79
7[c]	**1g**	**2a**		**3g**: R^1 = 4-Br	75
8[d]	**1h**	**2a**		**3h**: R^1 = 4-CO_2Et	74
9	**1i**	**2a**		**3i**	78
10	**1j**	**2a**		**3j**	80
11	**1k**	**2a**		**3k**	89 (58:42)[f]
12	**1l**	**2a**		**3l**	82 (63:37)[f]
13	**1a**	**2b**		**3m**: R^3 = 4-MeC_6H_4	80
14	**1a**	**2c**		**3n**: R^3 = 4-OMeC_6H_4	84
15	**1a**	**2d**		**3o**: R^3 = 4-BrC_6H_4	78
16	**1a**	**2e**		**3p**: R^3 = *n*Pr	81
17	**1a**	**2f**		**3q**: R^3 = CH_3	73
18	**1a**	**2g**		**3r**: R^3 = CH_2OMe	78
19[e]	**1a**	**2h**		**3s**: R^3 = Me	82 (96:4)
20[e]	**1a**	**2i**		**3t**: R^3 = Et	85 (99:1)
21[e]	**1a**	**2j**		**3u**: R^3 = CH_2OMe	78 (96:4)
22[e]	**1a**	**2k**		**3v**: R^3 = CO_2Et	86 (99:1)
23[e]	**1a**	**2l**		**3w**: R^3 = COMe	78 (92:8)
24	**1m**	**2a**		**3x**: R^2 = CH_3	83
25	**1n**	**2a**		**3y**: R^2 = *n*Pr	80
26	**1o**	**2a**		**3z**: R^2 = Cy	79

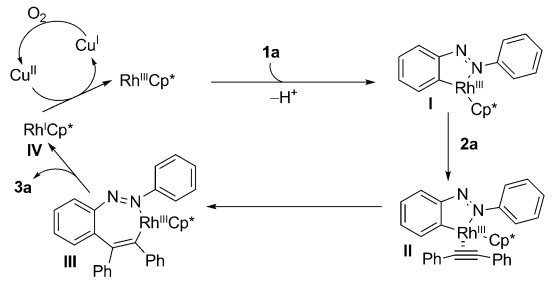
[a] Unless otherwise mentioned, all reactions were carried out by using azobenzene **1** (1.00 mmol), alkyne **2** (1.20 mmol), [(RhCp*Cl_2)$_2$] (1.0 mol%), Cu(BF_4)$_2$•6H_2O (0.50 mmol), and *t*BuOH (3 mL) at 70 °C for 16 h under air. [b] Isolated yields. [c] At 80 °C. [d] At 105 °C. [e] $AgBF_4$ (1.00 mmol) and Cu(OAc)$_2$•H_2O (0.30 mmol) under air were used. [f] Ratio of isomers **3k/k′** or **3l/l′**.

ring gave higher yields than the isomers **3k′** or **l′** in which the C–H bond activation occurs at the phenyl or *p*-fluorophenyl ring. It appears that the electron-rich *p*-methoxy group on the phenyl ring can stabilize the corresponding catalytic rhodacycle **I** better (an electrophilic Rh^{III} species, see Scheme 2 below), leading to higher yields of the corresponding isomeric products **3k** and **l** relative to **3k′** and **l′** after insertion of akyne **2a**.

In addition to **2a**, other symmetrical alkynes **2b–g** were tested (Table 1, entries 13–18). Thus, *p*-Me-, MeO-, and Br-substituted diphenylacetylenes **2b–d** reacted with **1a** to afford the corresponding salts **3m–o** in 78–84% yield (entries 13–15). The present catalytic reaction also proceeded smoothly with aliphatic alkynes, such as oct-4-yne (**2e**), but-2-yne (**2f**), and 1,4-dimethoxybut-2-yne (**2g**); treatment of these alkynes with **1a** afforded **3p–r** in 73–81% yield (entries 16–18).

To understand the regioselectivity of the present catalytic reaction with unsymmetrical alkynes, 1-phenyl-1-propyne (**2h**) was used in the reaction with **1a**. The catalytic reaction appears to be sensitive to the metal oxidant used. When only Cu(BF_4)$_2$•6H_2O (0.50 mmol) was employed, the reaction showed low regioselectivity with a regioisomeric ratio of 85:15 and a combined yield of 85%. Fortunately, when a combination of $AgBF_4$ and Cu(OAc)$_2$•H_2O was used, the regioselectivity greatly improved to 96:4. Under these conditions, other unsymmetrical alkynes PhC≡CR in which R = Et (**2i**), CH_2OMe (**2j**), CO_2Et (**2k**), and COMe (**2l**) also reacted in a highly regioselective manner with **1a** to afford products **3t–w** in good to excellent yields (entries 20–23). The regiochemistry of these products was confirmed by NOE experiments. The scope of the catalytic reaction can be further extended to various (phenylazo)alkanes **1m–o**.[12] The reaction of these substrates with **2a** afforded **3x–z** in 79–83% yield (entries 24–26).

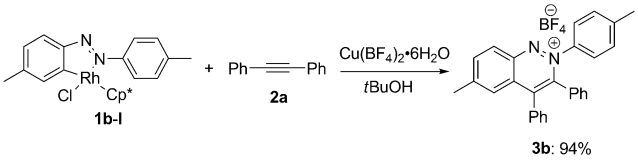
On the basis of known metal-catalyzed, directing-group-assisted C–H activation/C–C, C–N bond formation reactions,[5–8] a possible mechanism is proposed to account for the catalytic reaction (Scheme 2). The catalytic cycle starts with the coordination of azobenzene to the rhodium center, followed by *ortho*-C–H bond activation to form five-membered rhodacycle **I**. Coordination of alkyne **2a** to **I** gives intermediate **II**, and insertion of coordinated **2a** to the rhodium–carbon bond then leads to seven-membered rhodacycle **III**. Subsequent reductive elimination affords the final cinnolinium salt **3a** and Rh^{I}. The last was oxidized by Cu^{II} to regenerate the active Rh^{III} species for the next catalytic cycle. In the catalytic reaction, dioxygen acts as co-oxidant to oxidize Cu^{I} to Cu^{II}. There are two possible pathways for the insertion of a coordinated alkyne into rhodacycle **II**. One is the insertion into the rhodium–carbon bond of **II**, the other is the insertion into the rhodium–nitrogen bond. For most of the alkynes without an electron-withdrawing group (**2a–j**), the insertion occurs more likely into the Rh–C bond. However, for electron-deficient alkynes PhC≡CR in which R is an electron-



Scheme 2. A proposed mechanism for cinnolinium-salt formation.

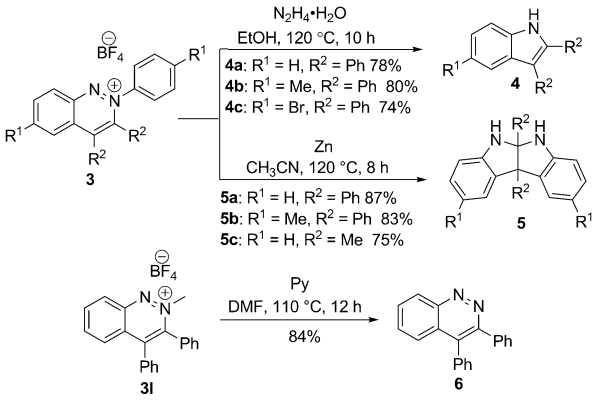
withdrawing group, such as CO_2Et (**2k**) or COMe (**2l**), insertion into the Rh–N bond likely becomes the major pathway in view of the observed regiochemistry of products **3v–w** (entries 22–23). In these products, the nitrogen group of azobenzene (**1a**) is bound to the β-carbon of the alkyne moiety.[13] It is worth noting that the insertion may be viewed as addition of the Rh–N bond to alkyne **2k** or **l** in a Michael-type addition, that is, the nitrogen atom adds to the β-carbon of alkyne **2k** or **l**. An opposite regiochemistry would be obtained if the insertion occurs though the metal–carbon bond of a metalacycle.[13a,c]

To shine light on the reaction mechanism, we prepared the assumed rhodium intermediate **I** from the reaction of **1b** with $[(RhCp^*Cl_2)_2]$ in *t*BuOH at 70 °C for 2 h, which afforded five-membered rhodacycle **1b-I** in 88 % yield (see the Supporting Information). This complex was characterized by its ^1H and ^{13}C NMR spectra, as well as single-crystal X-ray diffraction. The crystal structure revealed that the complex is an 18-electron system containing a Cp* moiety, a cyclometalated azobenzene and a chloro ligand. The reaction of **1b-I** (0.052 mmol) with **2a** (0.062 mmol) and $Cu(BF_4)_2{\cdot}6H_2O$ (0.026 mmol) in *t*BuOH at 70 °C for 0.5 h gave **3b** in 94 % yield (Scheme 3).



Scheme 3. Reaction of rhodium intermediate **1b-I** with diphenylacetylene (**2a**).

The importance of the present catalytic reaction was further established by its application to the synthesis of potentially bioactive indoles and cinnolines from cinnolinium-salt derivatives (Scheme 4).[14] Thus, heating **3a** with hydrazine in EtOH at 120 °C gave the corresponding 2,3-diphenylindole in good yield. Other substituted cinnolinium salts **3b** and **g** also reacted with hydrazine to give indoles **4b** and **c**. Surprisingly, in the presence of Zn, cinnolinium salts undergo skeletal rearrangement to give indoloindoles **5** in good yields. In addition, treatment of *N*-methylcinnolinium salt **3l** with pyridine in DMF afforded 3,4-diphenylcinnoline (**6**) in 84 % yield (see the Supporting Information).



Scheme 4. Synthesis of indoles, indoloindoles, and cinnolines.

In conclusion, we have developed a new rhodium-catalyzed, chelate-assisted C–H activation/annulation of azobenzenes with alkynes to give various substituted cinnolinium salts in good to excellent yields. The reaction is compatible with a wide substrate scope and highly atom- and step-economic. The proposed mechanism is strongly supported by the isolation of a five-membered rhodacycle. Finally, this protocol has been successfully applied to the synthesis of indole, indoloindole, and cinnoline derivatives. Further application of this methodology in natural product synthesis is in progress.

Acknowledgements

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Keywords: air · alkynes · azobenzenes · C–H activation · cinnolinium salts · rhodium

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Rhodium Catalysis

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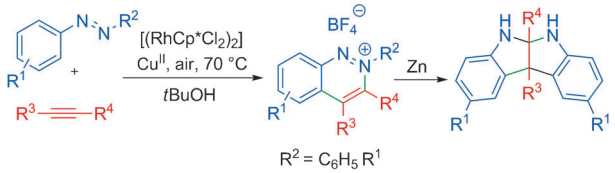
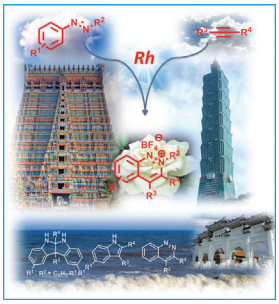
Rhodium(III)-Catalyzed Synthesis of Cinnolinium Salts from Azobenzenes and Alkynes: Application to the Synthesis of Indoles and Cinnolines



Versatile salts: A new rhodium-catalyzed synthesis of cinnolinium salts from various azobenzenes and alkynes under air is described. These salts readily transform into three important classes of products, including indoles, indoloindoles, and cinnolines (see scheme).



Rhodium Catalysis
An efficient RhCp*-catalyzed (Cp* = Me_5C_5) annulation of azobenzenes with alkynes to give cinnolinium salts is described. These salts are readily applied to the synthesis of three important classes of compounds: indole, indoloindoles, and cinnoline derivatives. The background picture is the Trichy Sri Ranganathaswamy Temple, India (left) and the Taipei 101 Tower and National Chiang Kai-Shek Memorial Hall, Taiwan (right).