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Rhodium-catalyzed Oxidative Coupling of Benzylamines with Alkynes through Dehydrogenation and Dehydrogenative Cyclization

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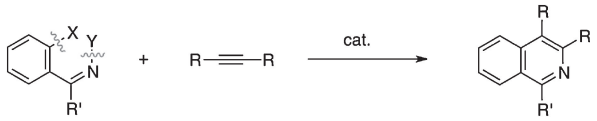
Oxidative coupling of benzylamines with internal alkynes accompanied by dehydrogenation and dehydrogenative cyclization proceeds efficiently under rhodium catalysis to selectively give the corresponding 3,4-substituted isoquinoline derivatives. The procedure is also applicable to the reactions of (1-naphthylmethyl)amine with diaryl- and dialkylacetylenes to construct benzo[*h*]isoquinoline and benzo[*e*]isoindole frameworks, respectively.

Nitrogen-containing fused heteroaromatic frameworks can be seen in a wide range of fine chemicals including medicines and organic functional materials.[1] Among them, isoquinoline derivatives are well-known to be utilized as anesthetic, antispasmodic, and antimicrobial reagents.[2] Therefore, the synthesis of isoquinolines from simple, readily available building blocks has attracted much attention.

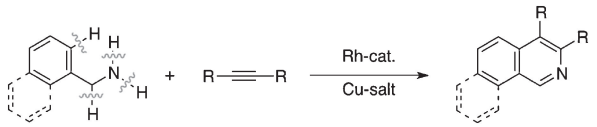
Among practical methods for constructing fused heterocyclic compounds is the transition-metal-catalyzed coupling of aromatic substrates with internal alkynes. Larock and coworkers developed an isoquinoline synthesis through the palladium-catalyzed coupling of *ortho*-halogenated benzaldimines with alkynes (Scheme 1, $X \neq H$, $Y \neq H$).[3] From the atom- and step-economical points of view, prefunctionalization of the aromatic substrates should be minimized. Recently, several groups have reported that halogen-free, *N*-substituted benzaldimines couple with alkynes under rhodium catalysis ($X = H$, $Y \neq H$).[4,5] As an example using more simple, *N*-unsubstituted imines ($X = Y = H$), we disclosed the rhodium-catalyzed oxidative coupling of benzophenone imine with alkynes to produce 3,4-substituted 1-phenylisoquinolines in good yields.[6] However, the substrate has so far been limited to only benzophenone imine. One of the reasons is that *N*-unsubstituted aldimines are labile under the oxidative coupling conditions.[7]

In the context of our further study of the rhodium-catalyzed oxidative coupling,[8] we have undertaken the coupling using readily available benzylamines and (1-naphthylmethyl)amine as stable building blocks in place of imines with alkynes. As a result, the catalytic coupling with arylalkynes has been found to proceed smoothly accompanied by dehydrogenation and dehydrogenative cyclization by employing a copper oxidant to produce isoquinoline and benzo[*h*]isoquinoline derivatives (Scheme 2). The new findings are described herein.

In an initial attempt, (1-naphthylmethyl)amine (**1a**) (1 mmol) was treated with diphenylacetylene (**2a**) (0.5 mmol) in the presence of $[Cp^*RhCl_2]_2$ (0.01 mmol, Cp^*: pentamethylcyclopentadienyl) and $Cu(OAc)_2 \cdot H_2O$ (2 mmol) as catalyst and oxidant, respectively, in *o*-xylene at 120 °C for 10 h under N_2. As a result, an oxidative coupling product, 3,4-diphenylbenzo[*h*]isoquinoline (**3a**), was obtained in 60% yield (Entry 1 in Table 1). Addition of DABCO (1 mmol, DABCO: 1,4-diazabicyclo[2.2.2]octane) improved the yield of **3a** up to 68% (Entry 2).[8a] Other additives, Na_2CO_3[8b,8d] and DBU, decreased the yield (Entries 3 and 4, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene). With a reduced amount of **1a** (0.5 mmol), the product yield somewhat decreased (Entry 5). The reaction was sluggish in DMF (Entry 6). Using $[RhCl(cod)]_2$ or $[Cp^*IrCl_2]_2$ as a catalyst in place of $[Cp^*RhCl_2]_2$, the reaction did not proceed at all (Entries 7 and 8). The reaction efficiency was found to be sensitive toward reaction temperature (Entries 9–11). At 130 °C, the highest yield was obtained (Entry 10).

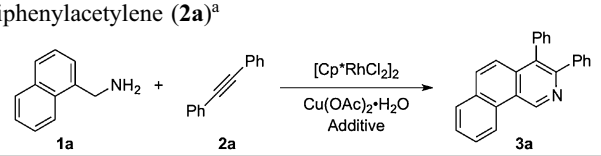


Scheme 1.



Scheme 2.

Table 1. Reaction of (1-naphthylmethyl)amine (**1a**) with diphenylacetylene (**2a**)[a]



Entry	Additive	Temp/°C	Time/h	Yield of **3a**[b]/%
1	—	120	10	60
2	DABCO	120	10	68
3	Na_2CO_3	120	6	35
4	DBU	120	6	31
5[c]	DABCO	120	10	55
6[d]	DABCO	120	6	16
7[e]	DABCO	120	6	0
8[f]	DABCO	120	6	0
9	DABCO	100	6	9
10	DABCO	130	10	72 (72)
11	DABCO	140	6	65

[a]Reaction conditions: **1a** (1 mmol), **2a** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), $Cu(OAc)_2 \cdot H_2O$ (2 mmol), additive (1 mmol), *o*-xylene (5 mL) under N_2. [b]GC yield based on the amount of **2a** used. Value in parentheses indicates yield after isolation. [c]**1a** (0.5 mmol) was used. [d]In DMF (2.5 mL). [e]$[RhCl(cod)]_2$ (0.01 mmol) was used in place of $[Cp^*RhCl_2]_2$. [f]$[Cp^*IrCl_2]_2$ (0.01 mmol) was used in place of $[Cp^*RhCl_2]_2$.

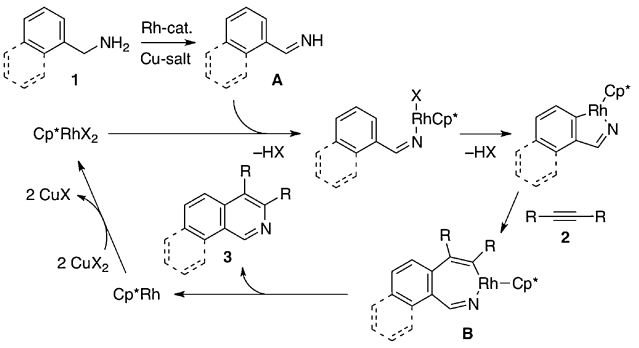
Table 2. Reaction of (arylmethyl)amines **1** with alkynes **2**[a]

Entry	1	2	Product(s), Yield[b]/%
1	**1a**	**2b**: X = Me	**3b**: X = H, 64
2		**2c**: X = OMe	**3c**: X = OMe, 73
3		**2d**: X = Cl	**3d**: X = Cl, 53
4	**1a**	**2e**: R = Me	**3e**: R = Me, 35 **3′e**: R = Me, 6
5		**2f**: R = *n*-Bu	**3f**: R = *n*-Bu, 44 **3′f**: R = *n*-Bu, 3
6[c]	**1b**: Y = H	**2a**	**3g**: Y = H, 60
7[c]	**1c**: Y = Me		**3h**: Y = Me, 58
8[c]	**1d**: Y = OMe		**3i**: Y = OMe, 50
9[c]	**1e**: Y = Cl		**3j**: Y = Cl, 18
10[c]	**1f**	**2a**	**3k**, 74

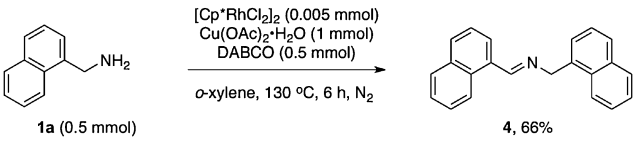
[a]Reaction conditions: **1** (1 mmol), **2** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), $Cu(OAc)_2 \cdot H_2O$ (2 mmol), DABCO (1 mmol), in *o*-xylene (5 mL) at 130 °C for 10 h under N_2. [b]Isolated yield based on the amount of **2** used. [c]**1** (1.5 mmol) was used.

Under the conditions employed for Entry 10 in Table 1, the couplings of **1a** with 4-methyl- (**2b**), 4-methoxy- (**2c**), and 4-chloro- (**2d**) substituted diphenylacetylenes provided the corresponding 3,4-diarylbenzo[*h*]isoquinoline **3b**–**3d** (Entries 1–3 in Table 2). 1-Phenylpropyne (**2e**) reacted with **1a** to give 4-methyl-3-phenylbenzo[*h*]isoquinoline (**3e**) predominantly, along with a minor amount of a separable regioisomer **3′e** (Entry 4). Similarly, from the reaction of 1-phenyl-1-hexyne (**2f**), 4-butyl-3-phenylbenzo[*h*]isoquinoline (**3f**) was obtained along with its regioisomer **3′f** (Entry 5). The reaction of benzylamine (**1b**) (1.5 mmol) with **2a** took place in a similar manner to give 3,4-diphenylisoquinoline (**3g**) selectively (Entry 6). A series of 4-substituted benzylamines **1c**–**1e** underwent coupling to form **3h**–**3j** (Entries 7–9). A sterically hindered amine, 2-methylbenzylamine (**1f**), also reacted with **2a** efficiently to afford 8-methyl-3,4-diphenylisoquinoline (**3k**) (Entry 10).

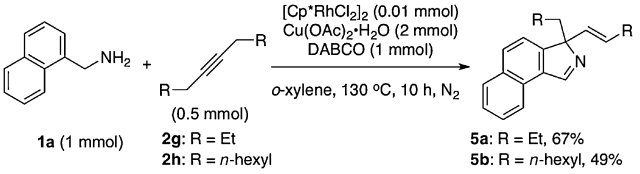
A plausible mechanism for the oxidative coupling of **1** with **2** through dehydrogenation and dehydrogenative cyclization is illustrated in Scheme 3, in which neutral ligands are omitted.



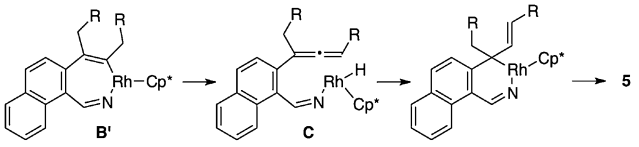
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

First, the dehydrogenation of **1** occurs to form the corresponding imine **A**.[9] Actually, treatment of **1a** with the $[Cp^*RhCl_2]_2$/$Cu(OAc)_2 \cdot H_2O$/DABCO system in the absence of **2** afforded (1-naphthyl)methanimine **A**, which immediately underwent condensation with another molecule of **1a** to produce **4** (Scheme 4).[7a,10] It was confirmed that the dehydrogenation did not proceed at all in the absence of the rhodium catalyst. In the absence of DABCO, on the other hand, the reaction took place, but the yield of **4** decreased to 45%. Therefore, DABCO seems to promote the dehydrogenation step in the oxidative coupling of **1** with **2** and enhance the yield of **3** (Entry 2 versus 1 in Table 1). The imine **A** may undergo oxidative coupling with **2** in a similar mechanism to that proposed for the reaction of benzophenone imine with **2**[6] through cyclorhodation, alkyne insertion, and reductive elimination to produce **3**.

In addition, the reactions of **1a** with dialkylacetylenes **2g** and **2h** were found to give 3*H*-benzo[*e*]isoindole derivatives **5a** and **5b**, respectively (Scheme 5). No benzo[*h*]isoquinoline type product could be detected.

In these reactions, the seven-membered intermediate **B′** is generated in a similar manner to that to **B** in Scheme 3 (Scheme 6). Since **B′** has a β-hydrogen, its elimination appears

to take place in preference to reductive elimination to form **C**.[8d] Then, **C** undergoes intramolecular allene insertion into the Rh–H bond and reductive elimination to produce **5**.

In summary, we have demonstrated that benzylamines and (1-naphthylmethyl)amine undergo oxidative coupling with alkynes under rhodium catalysis accompanied by dehydrogenation and dehydrogenative cyclization to afford isoquinoline and benzo[*h*]isoquinoline derivatives, respectively.[11]

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9 *N*-Unsubstituted imines similar to **A** also seem to be formed through the condensation of benzaldehydes with NH_4OAc as an ammonia equivalent: A. Winter, N. Risch, *Synthesis* **2003**, 2667. However, treatment of benzaldehyde (0.5 mmol) with NH_4OAc (0.5 mmol) and **2a** (0.5 mmol) in the presence of the $[Cp^*RhCl_2]_2/Cu(OAc)_2 \cdot H_2O$/DABCO system gave **3g** in only a low yield (5%).

10 However, it would be possible that other Rh-catalyzed reactions are involved for the formation of **4**.

11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

