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New Coupling Reaction of Secondary Amines, Aldehydes, and Alkynes Catalyzed by an Iridium Complex

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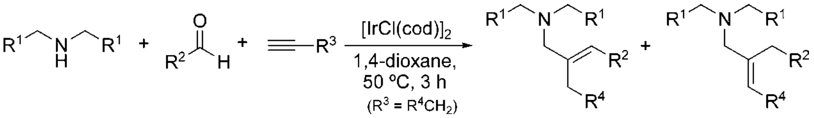
ABSTRACT



A new reductive coupling reaction of secondary amines, aldehydes, and alkynes using an iridium complex as catalyst has been developed. For example, dibutylamine was allowed to react with butyraldehyde and 1-octyne in 1,4-dioxane at 50 °C under the influence of a catalytic amount of [IrCl(cod)]$_2$ to give the corresponding allylamines such as *N,N*-dibutyl-2-butylideneoctylamine and *N,N*-2-tributyl-2-octenylamine in excellent yields.

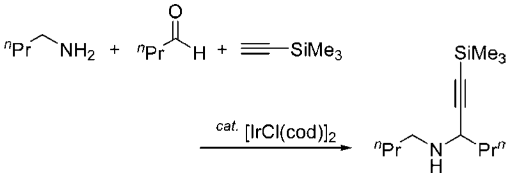
The transition-metal-catalyzed multicomponent coupling is a powerful synthetic tool because the reaction involving a new carbon−carbon bond formation gives complex compounds from simple precursors in one-pot.[1] Recently, it was reported that propargylic amines could be synthesized by a three-component coupling of amines, aldehydes, and alkynes (A^3-coupling) through activation of the C−H bond in the terminal alkynes catalyzed by a transition-metal complex.[2,3] For example, Li and co-workers showed that arylimines, which were readily prepared by in situ condensation of aniline with aldehydes, reacted with phenylacetylene catalyzed by Cu, Ag, or Au species to give the corresponding propargylic amines.[2] The reaction could be applied to the asymmetric synthesis of propargylic amines by the use of an appropriate chiral ligand such as bis(oxazolinyl)pyridines.[4]

The iridium-catalyzed A^3-coupling leading to propargylic amines has been independently developed by our[5] and Carreira's[6] groups (Scheme 1). Treatment of simple primary amines, aldehydes, and trimethylsilylacetylene in the presence of a catalytic amount of [IrCl(cod)]$_2$ afforded the corresponding propargylic amines in good yields. Later, the coupling of secondary amines, aldehydes, and trimethylsilylacetylene was also established by the same catalyst.[5b]

On the other hand, we have developed a new type of Ir-catalyzed three-component coupling reaction of primary amines, aldehydes, and 1-octyne (Scheme 2).[5a] This is the first example of the production of substituted allylimines via C−H bond activation adjacent to the nitrogen atom of imines by [IrCl(cod)]$_2$. Noteworthy is that two reactions of a different type leading to propargylic amines or allylimines have been thus achieved in the Ir-catalyzed A^3-coupling.

In the course of our studies on the three-component coupling reaction of amines, aldehydes, and alkynes, we have

Scheme 1. Iridium-Catalyzed A^3-Coupling Leading to Propargylic Amine



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[1] Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.−Eur. J.* **2000**, *6*, 3321.

[2] Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472 and references therein.

[3] (a) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* **2004**, *6*, 1001. (b) Park, S. B.; Alper, H. *Chem. Commun.* **2005**, 1315.

[4] (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

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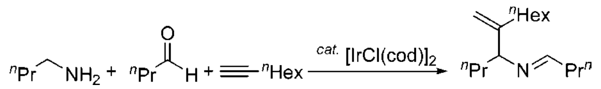
Scheme 2. Iridium-Catalyzed A^3-Coupling through C−H Bond Activation Adjacent to the Nitrogen Atom of Imine



found a third type of Ir-catalyzed A^3-coupling. The secondary amines coupled with aldehydes and terminal alkynes such as 1-octyne in the presence of a $[IrCl(cod)]_2$ catalyst lead to the corresponding allylamines. The reaction seems to proceed through a reductive A^3-coupling in which another amine molecule acts as a hydrogen donor. Here, we wish to describe the preparation of allylamines from the reductive A^3-coupling of secondary amines, aldehydes, and alkynes. Allylamines are versatile compounds, and their synthesis is an important industrial and synthetic goal.[7] The present methodology provides an alternative route to allylamines by an Ir-catalyzed A^3-coupling reaction involving a carbon−carbon bond formation.

The reaction of dibutylamine (**1a**), butyraldehyde (**2a**), and 1-octyne (**3a**) was selected as a model reaction and was examined under the influence of several Ir, Rh, and Ru catalysts (Scheme 3, Table 1). When **1a** was allowed to react with **2a** and **3a** (molar ratio of **1a**/**2a**/**3a** = 2:1:2) in 1,4-dioxane at 50 °C for 3 h in the presence of a catalytic amount of $[IrCl(cod)]_2$ (10 mol % with respect to **2a** used), *N*,*N*-dibutyl-2-butylideneoctylamine (**4a**) and *N*,*N*-2-tributyl-2-octenylamine (**5a**) were obtained in 72% and 20% yields, respectively, based on the amount of **2a** used (run 1). The reaction using 1:1:2 of **1a**, **2a**, and **3a** resulted in low yields (run 2). This may be due to the fact that the half amount of **1a** used acts as a hydrogen donor, as discussed later. The present A^3-coupling provides a new type of catalytic coupling of amines, aldehydes, and alkynes. Notably, no coupling reaction occurred by using other Ir, Rh, or Ru complexes such as $[IrCl(coe)_2]_2$, $[Ir(cod)_2]BF_4$, $[Cp^*IrCl_2]_2$, $IrCl_3$, $[RhCl(cod)]_2$, and $RuCl_2(cod)$ (runs 3−8). The choice of the ligand was a very important factor in obtaining the corresponding coupling products, thus only $[IrCl(cod)]_2$ has catalytic activity for the present reductive A^3-coupling. It is very interesting that when the reaction was carried out in the presence of $[IrCl(coe)_2]_2$ combined with 1,5-cyclooctadiene (cod) the corresponding products were obtained in excellent yields (run 9). Surprisingly, $IrCl_3$ also facilitated the present coupling by adding cod in the reaction medium (run 10). These results will be discussed later.

Scheme 3. Iridium-Catalyzed Reductive A^3-Coupling Leading to Allylamine

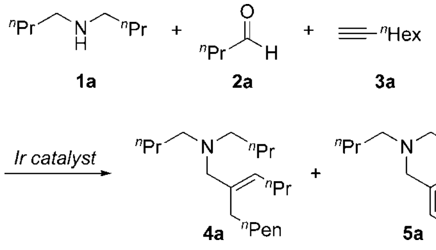
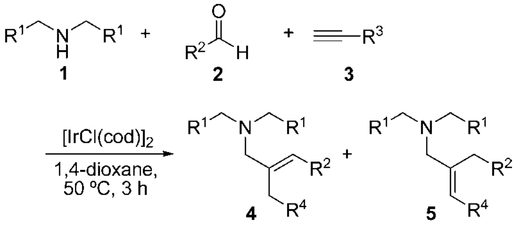


Table 1. Reductive Coupling of **1a** with **2a** and **3a** in the Presence of an Ir, Rh, or Ru Catalyst[a]

run	catalyst[b]	yield[c]/% (**4a**/**5a**)
1	$[IrCl(cod)]_2$	92 (78:22)
2[d]	$[IrCl(cod)]_2$	44 (75:25)
3	$[IrCl(coe)_2]_2$	nd
4	$[Ir(cod)_2]BF_4$	nd
5	$[Cp^*IrCl_2]_2$	nd
6	$IrCl_3$	nd
7	$[RhCl(cod)]_2$	nd
8	$RuCl_2(cod)$	nd
9[e]	$[IrCl(coe)_2]_2$	97 (62:38)
10[f]	$IrCl_3$	57 (67:33)

[a] **1a** (0.5 mmol) was allowed to react with **2a** (0.25 mmol) and **3a** (0.5 mmol) in the presence of a catalyst (0.025 mmol) in 1,4-dioxane (2 mL) at 50 °C for 3 h. [b] cod: 1,5-cyclooctadiene. coe: cyclooctene. Cp*: 1,2,3,4,5-pentamethylcyclopentadienyl. [c] Total yield of **4a** and **5a** based on the amount of **2a** used. Number in parentheses shows **4a**/**5a** ratio. nd: not determined. [d] Reaction was run using 0.25 mmol of **1a**. [e] Cod (0.1 mmol) was added. [f] $IrCl_3$ (0.05 mmol) and cod (0.3 mmol) were used.

Table 2. Ir-Catalyzed Reductive Coupling of Secondary Amines with Aldehydes and **3a**[a]



run	amine R^1−	aldehyde R^2−	alkyne R^3−	yield/% (**4**/**5**)
1	^{n}Pr− (**1a**)	^{n}Pr− (**2a**)	^{n}Hex− (**3a**)	92 (78:22)
2	Et− (**1b**)	Et− (**2b**)	**3a**	78 (74:26)
3	^{n}Pen− (**1c**)	^{n}Pen− (**2c**)	**3a**	80 (**4c** only)
4[b]	**1a**	**2a**	$PhCH_2$− (**3b**)	60 (77:23)

[a] **1** (0.5 mmol) was allowed to react with **2** (0.25 mmol) and **3** (0.5 mmol) in the presence of $[IrCl(cod)]_2$ catalyst (0.025 mmol) in 1,4-dioxane (2 mL) at 50 °C for 3 h; $R^3{-}{=}R^4CH_2{-}$. [b] **3b** (0.75 mmol), 1,4-dioxane (3 mL), 75 °C.

Table 2 summarizes the reductive coupling of several secondary amines with aldehydes and alkynes under the influence of the $[IrCl(cod)]_2$ catalyst. These reactions were performed using a 2:1:2 molar ratio of **1**/**2**/**3** to furnish the corresponding coupling products **4** and **5** in good yields. The

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(5) (a) Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2534. (b) Sakaguchi, S.; Mizuta, T.; Furuwan, M.; Kubo, T.; Ishii, Y. *Chem. Commun.* **2004**, 1638.

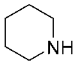
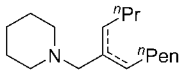
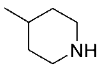
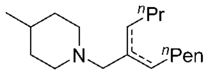
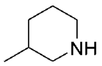
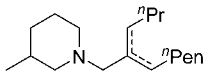
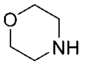
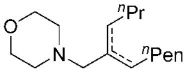
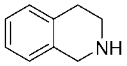
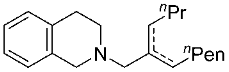
(6) (a) Fischer, C.; Carreria, E. M. *Org. Lett.* **2001**, *3*, 4319. (b) Fischer, C.; Carreria, E. M. *Synthesis* **2004**, 1497.

(7) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

reaction of dihexylamine (**1c**), hexylaldehyde (**2c**), and 1-octyne (**3a**) gave *N*,*N*-2-trihexyl-2-octenylamine (**4c**) (run 3). It is interesting to note in this reaction that the corresponding **5c** is the same as the product **4c**.

The present reductive A^3-coupling was applied to the reaction of cyclic amines, aldehydes, and alkynes. The representative results are shown in Table 3. Treatment of piperidine (**1d**) with **2a** and **3a** catalyzed by [IrCl(cod)]$_2$ in 1,4-dioxane at 100 °C for 2 h afforded allylamines, **4d** and **5d**, in total 55% yield (run 1). In this reaction, 28% of **1d** was recovered. After several examinations, it was found that the yield of the coupling products, **4d** and **5d**, was improved to 76% by adding a small amount of 1,5-cyclooctadiene (cod) as an additional ligand (run 1).

Table 3. Reductive Coupling of Cyclic Amines with **2a** and **3a**[a]

Run	Amine	Product	Yield / % (**4**/**5**)
1	 **1d**	 **4d + 5d**	55 (60/40) 76[b] (61/39)
2	 **1e**	 **4e+ 5e**	67 (66/34) 80[b] (51/49)
3	 **1f**	 **4f + 5f**	62[b] (52/48)
4	 **1g**	 **4g + 5g**	50 (72/28)
5	 **1h**	 **4h + 5h**	58[b] (81/19)

[a] **1** (0.5 mmol) was allowed to react with **2a** (0.25 mmol) and **3a** (0.5 mmol) in the presence of [IrCl(cod)]$_2$ catalyst (0.025 mmol) in 1,4-dioxane (2 mL) at 100 °C for 2 h. [b] 1,5-Cylooctadiene (cod) (0.05 mmol) was added.

Similarly, the coupling of 4-methylpiperidine (**1e**) with **2a** and **3a** was promoted by the use of the [IrCl(cod)]$_2$ catalyst combined with a small amount of cod to furnish the corresponding coupling product in 80% yield (run 2).

As shown in Table 1, the present reductive three-component coupling was catalyzed by [IrCl(cod)]$_2$ or [IrCl(coe)$_2$]$_2$ combined with cod. To obtain further information, ^{1}H NMR measurements of these complexes were performed (Figure 1). A signal around δ 4.2 in Figure 1a was assigned to protons of the sp^2 C−H bond of the cod ligand on [IrCl(cod)]$_2$. A signal at δ 3.4 in Figure 1b corresponds to protons of the sp^2 C−H bond of the coe ligand on [IrCl(coe)$_2$]$_2$. Figure 1c shows the ^{1}H NMR spectrum of a 1:2 mixture of [IrCl(coe)$_2$]$_2$ and cod, and it was found that signals around δ 4.2 and 5.5 were assigned to [IrCl(cod)]$_2$ and *free* coe, respectively. This indicated that the [IrCl(coe)$_2$]$_2$ complex easily reacted with cod to form [IrCl(cod)]$_2$. As a consequence, the combined catalytic system of [IrCl(coe)$_2$]$_2$ and cod promoted the present reductive coupling of amines, aldehydes, and alkynes, whereas no reaction occurred with [IrCl(coe)$_2$]$_2$ alone.

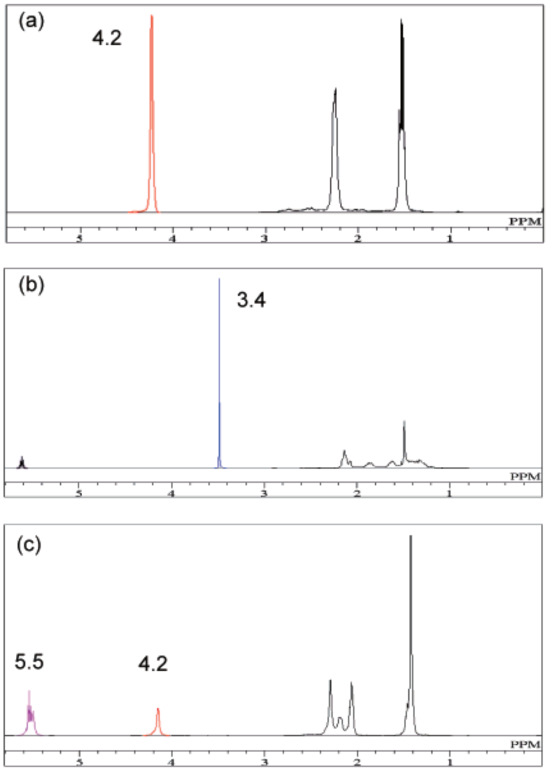


Figure 1. ^{1}H NMR spectra of (a) [IrCl(cod)]$_2$, (b) [IrCl(coe)$_2$]$_2$, and (c) a 1:2 mixture of [IrCl(coe)$_2$]$_2$ and cod.

To obtain further insight into the reaction pathway, the byproducts of the [IrCl(cod)]$_2$-catalyzed reaction of **1a**−**3a** were analyzed in detail. When the reaction of **1a** (0.5 mmol), **2a** (0.25 mmol), and **3** (0.5 mmol) was carried out under standard conditions, 0.18 mmol of **4a** and 0.05 mmol of **5a** were produced as shown in Table 1, entry 1. In this reaction, **6a** (0.12 mmol), **7a** (0.03 mmol), and **8** (0.08 mmol) were also found to be formed as side products (Scheme 4). The formation of **6a** was believed to result from dehydrogenation of **1a** that took place during the reaction. The **6a** thus formed reacted under these reaction conditions to afford **7a** and **8a**.[5a]

Furthermore, treatment of **1a** with a stoichiometric amount of [IrCl(cod)]$_2$ gave **6a** in 10% yield at 90% recovery of **1a** (Scheme 5). These results strongly indicated that **1a** was converted to **6a** through dehydrogenation under the influence of [IrCl(cod)]$_2$. Recently, Bäckvall and co-workers showed the dehydrogenation of amine to imine catalyzed by a Ru complex.[8]

Although it is difficult to show the reaction mechanism in detail at this stage, a possible pathway is suggested in

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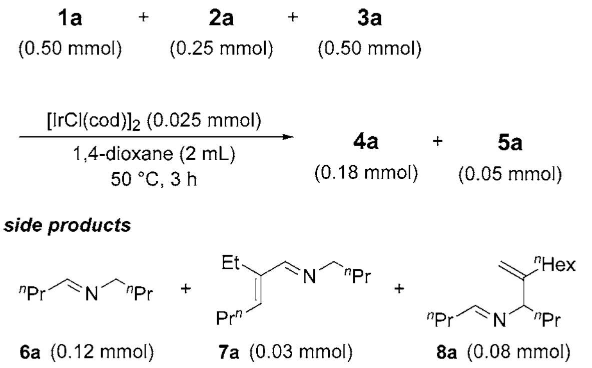
[8] (a) Éll, A. H.; Samec, J. S. M.; Brasse, C.; Bäckvall, J.-E. *Chem. Commun.* **2002**, 1144. (b) Samec, J. S. M.; Éll, A. H.; Bäckvall, J.-E. *Chem. Commun.* **2004**, 2748.

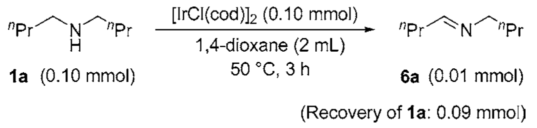
Scheme 4



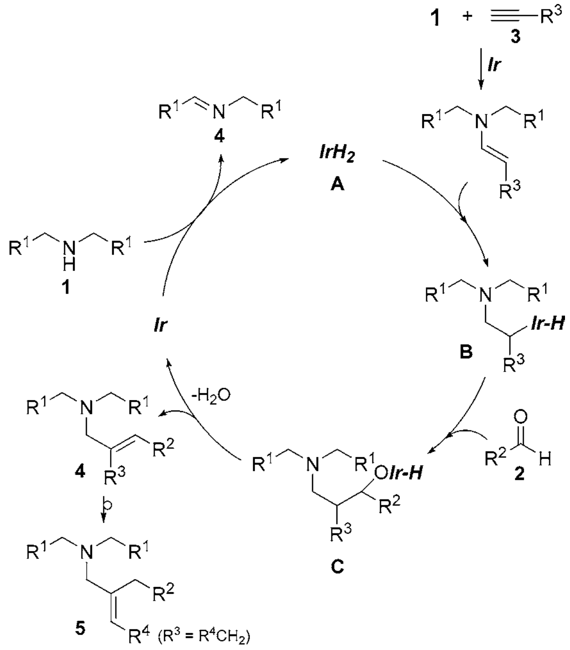
Scheme 6. The reaction is initiated by dehydrogenation of amine **1** to imine **4** by the action of an Ir complex to generate Ir dihydride **A** (or Ir hydride).[9] The addition of IrH_2 to enamine, derived from an anti-Markovnikov addition of amine **1** to alkyne **3** under the influence of an Ir catalyst, gives **B**. Subsequent insertion of aldehyde **2** to **B** forms the Ir complex **C**. The release of water from **C** would afford allylamine **4**, which partly may be isomerized to form **5**. Also, the regeneration of the low-valent Ir complex completes the catalytic cycle. It seems likely that the key step of the reaction is the dehydrogenation of amine to imine by $[IrCl(cod)]_2$. An independent experiment showed that no dehydrogenation of **2a** to **4a** took place by the use of $[IrCl(coe)_2]_2$ alone. Therefore, only $[IrCl(cod)]_2$ showed higher catalytic activity in the present reductive A^3-coupling reaction.

In summary, a new type of Ir-catalyzed reductive A^3-coupling has been developed. Thus, several allylamines were synthesized by the reaction of secondary amines, aldehydes, and alkynes through the carbon−carbon bond forming reaction.

Scheme 5



Scheme 6. Plausible Reaction Pathway for the Iridium-Catalyzed Reductive A^3-Coupling Leading to Allylamine



Acknowledgment. This work was supported by MEXT.KAKENHI (No.17750098).

Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Unfortunately, an attempt to observe the formation of the Ir dihydride (or the Ir hydride) by ^1H NMR measurements failed, probably because of the instability of the Ir hydride complex under these reaction conditions.