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Iridium-catalyzed coupling of simple primary or secondary amines, aldehydes and trimethylsilylacetylene: preparation of propargylic amines

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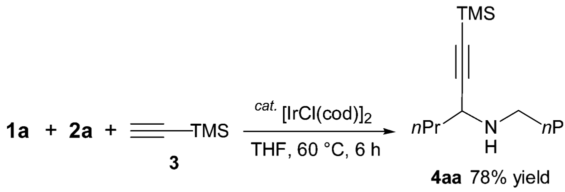
The coupling of amines, aldehydes and trimethylsilylacetylene was found to be promoted in the presence of a catalytic amount of $[IrCl(cod)]_2$; 1 : 1 : 1 or 1 : 2 : 2 coupling products were obtained by allowing primary amine to react with aldehyde and trimethylsilylacetylene.

The addition of terminal acetylenes to the C=N bond is an important reaction for the preparation of propargylic amines which act as synthetic intermediates of biologically active compounds.[1] Although many catalytic methods for the addition of alkynes to the C=O bond forming propargylic alcohols have been developed so far, work on the synthesis of propargylic amines by the reaction of terminal alkynes with the C=N bond through catalytic C–H activation of alkynes is still rare.[2] It has been reported that terminal acetylenes are coupled with nitrones in the presence of a catalytic amount of CuI or $Zn(OTf)_2$ to give 1-aza-1-buten-3-ynes or propargylic *N*-hydroxylamines, respectively.[3–5] However, few papers on the transition metal-catalyzed addition of terminal alkynes to simple imines have appeared. In 2001, Carreira and Fischer demonstrated the preparation of propargylic amines by the reaction of aldimines with trimethylsilylacetylene catalyzed by $[IrCl(cod)]_2$.[6] More recently, Li and Wei showed that the three-component coupling of amines, aldehydes and alkynes *via* C–H bond activation was facilitated by $AuBr_3$ or AgI catalyst in water to afford the corresponding propargylic amines.[7]

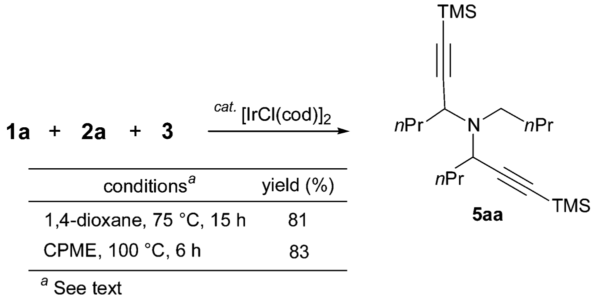
In the course of our studies on the development of iridium-catalyzed organic syntheses,[8] we have reported a new-type of C–H bond activation adjacent to the nitrogen atom of imines by $[IrCl(cod)]_2$, leading to three-component coupling products of amines, aldehydes and simple alkynes such as 1-octyne.[8a] We also briefly described that a propargylic amine was obtained by treatment of amine and aldehyde with trimethylsilylacetylene in place of 1-octyne in the presence of a catalytic amount of $[IrCl(cod)]_2$ [eqn. (1)].[9] Although we did not focus on the latter reaction of propargylic amines, the works of Carreira and Li prompted us to report our results on the study of the iridium-catalyzed reaction of amines, aldehydes and trimethylsilylacetylene. Here we wish to report a 1 : 1 : 1 or 1 : 2 : 2 coupling reaction of simple primary amines, aldehydes and trimethylsilylacetylene catalyzed by $[IrCl(cod)]_2$. Furthermore, propargylic amines could also be synthesized by the three-component coupling of secondary amines, aldehydes and TMS-acetylene.

The reaction of *n*-butylamine (**1a**) (0.25 mmol), *n*-butyraldehyde (**2a**) (0.25 mmol) and trimethylsilylacetylene (TMS-acetylene) (**3**) (0.25 mmol) in the presence of a catalytic amount of $[IrCl(cod)]_2$ (5 mol% with respect to **1a**) in THF at 60 °C for 6 h afforded butyl(1-propyl-3-trimethylsilyl-2-propynyl)amine (**4aa**) in 78% yield along with *N*-butylydene butylamine (15%) [eqn. (1)].



(1)

Interestingly, a trace amount of the 1 : 2 : 2 coupling product of **1a**, **2a** and **3**, *N,N*-bis(1-propyl-3-trimethylsilyl-2-propynyl)butylamine (**5aa**), was detected as a side product. As discussed later, it seems that **5aa** is produced through the formation of **4aa** as an intermediate. Thus, after optimization of the reaction conditions, **5aa** was found to be obtained in satisfactory yield. When **1a** (0.25 mmol), **2a** (1.5 mmol) and **3** (0.75 mmol) were allowed to react under the influence of $[IrCl(cod)]_2$ in 1,4-dioxane at 75 °C for 15 h, **5aa** was produced in 81% yield based on **1a** used [eqn. (2)].† By the use of cyclopentyl methyl ether (CPME) as a solvent, the reaction was completed within 6 h at 100 °C yielding **5aa** (83%). To the best of our knowledge, this is the first example of 1 : 2 : 2 multicomponent coupling reaction of simple amine, aldehyde and TMS-acetylene catalyzed by an iridium complex.



conditions[a]	yield (%)
1,4-dioxane, 75 °C, 15 h	81
CPME, 100 °C, 6 h	83

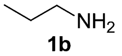
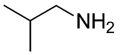
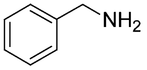
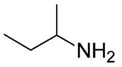
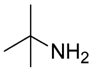
[a] See text

(2)

On the basis of these results, the coupling of several primary amines, aldehydes and **3** catalyzed by $[IrCl(cod)]_2$ was examined. The representative results are summarized in Table 1.

In a similar manner to the reaction of **1a**, **2a** and **3**, propylamine (**1b**), isobutylamine (**1c**) and benzylamine (**1d**) were reacted with **2a** or propionaldehyde (**2b**) and **3** under the influence of the iridium catalyst to produce the corresponding 1 : 2 : 2 coupling products, **5bb**, **5ca** and **5da**, in 75–83% yields, respectively (runs 1 to 3). Although the reaction of 2-aminobutane (**1e**) with **2a** and **3** at 60 °C for 6 h gave a 1 : 1 : 1 coupling product, propargyl amine **4ea**, in good yield (84%), it is difficult to obtain **5ea** as a major product in the reaction even at higher temperature (100 °C) probably due to the

Table 1 Results of the coupling reaction of primary amines, **2a** and **3** catalyzed by $[IrCl(cod)]_2$

Run	Amine	Method[a]	Product (Yield, %)	
1[b]	 **1b**	**B**	**4bb** (< 1)	**5bb** (83)
2		**B**	**4ca** (< 1)	**5ca** (75)
3		**B**	**4da** (5)	**5da** (75)
4		**A**	**4ea** (84)	**5ea** (< 1)
5	**1e**	**B**	**4ea** (34)	**5ea** (30)
6		**A**	**4fa** (82)	**5fa** (< 1)

[a] Method **A**: Amine (0.25 mmol), **2a** (0.25 mmol) and **3** (0.25 mmol) were allowed to react in the presence of a catalytic amount of $[IrCl(cod)]_2$ (0.025 mmol) in THF (2 mL) at 60 °C for 6 h; Method **B**: Amine (0.25 mmol), **2a** (1.5 mmol) and **3** (0.75 mmol) were allowed to react in the presence of a catalytic amount of $[IrCl(cod)]_2$ (0.025 mmol) in 1,4-dioxane (2 mL) at 75 °C for 15 h. [b] Propionaldehyde (**2b**) was used in place of **2a**.

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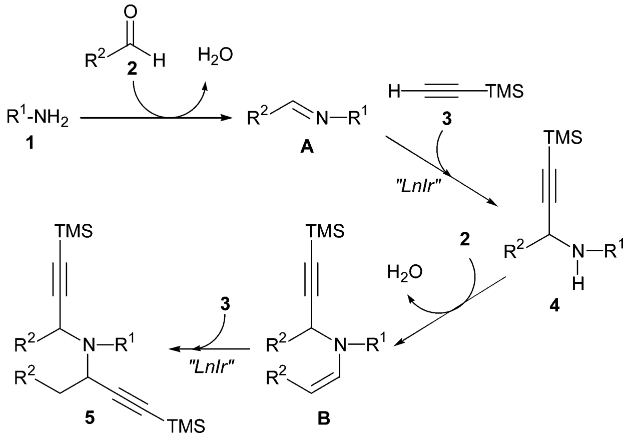
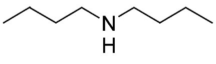
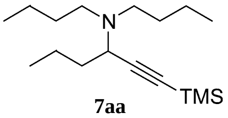
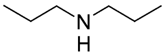
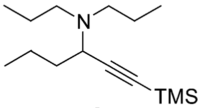
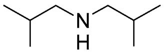
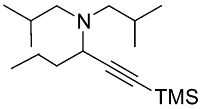
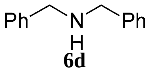
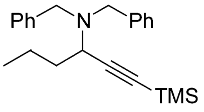
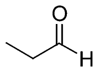
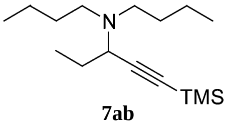
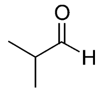
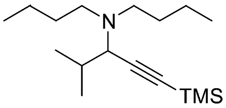
steric hindrance of **1e** (runs 4 and 5). Similarly, 2-amino-2-methylpropane (**1f**) coupled with **2a** and **3** to give a three-component coupling product **4fa** (82%) (run 6), but almost no 1 : 2 : 2 coupling product of **1f**, **2a** and **3** was formed even at 100 °C. Carreira reported the iridium-catalyzed synthesis of propargylic amines by employing aldimines and **3** as starting materials.[6] However, the reaction has been limited to the aldimines prepared independently by the reaction of benzylamine with aldehydes. Therefore, our results provide a simple procedure for the preparation of propargylic amines by the coupling of simple primary amines with aldehydes and TMS-acetylene.

Although it is difficult to clarify a detailed reaction mechanism of the present coupling, we would like to propose a plausible reaction pathway (Scheme 1). The coupling reaction of aldimine **A**, generated *in situ* from amine **1** and aldehyde **2**, with TMS-acetylene **3** under the influence of an iridium complex affords a 1 : 1 : 1 coupling product of **1**, **2** and **3**, propargylic amine **4**. **4** is then converted into enamine **B** by the reaction with aldehyde **2**. Subsequently, the enamine **B** couples with **3** in the presence of the Ir complex giving a 1 : 2 : 2 coupling product **5**.



Scheme 1 A plausible reaction pathway for the Ir-catalyzed coupling reaction of amine **1**, aldehyde **2** and TMS-acetylene **3**.

Table 2 Results of the coupling reaction of secondary amines, aldehydes and **3** catalyzed by $[IrCl(cod)]_2$[a]

Run	Amine	Aldehyde	Product	Yield (%)[b]
1	 **6a**	**2a**	 **7aa**	(97)[c]
2	 **6b**	**2a**	 **7ba**	(97)
3	 **6c**	**2a**	 **7ca**	(95)[c] (64)
4	 **6d**	**2a**	 **7da**	(99)
5	**6a**	 **2b**	 **7ab**	(90)
6	**6a**	 **2c**	 **7ac**	(86)

[a] Amine (1 mmol), aldehyde (6 mmol) and **3** (3 mmol) were allowed to react in the presence of a catalytic amount of $[IrCl(cod)]_2$ (0.1 mmol) in THF (8 mL) at 60 °C for 6 h. [b] Isolated yield. [c] GC yield.

According to the proposed reaction pathway, it is thought that the iridium-catalyzed coupling of secondary amines with aldehydes and **3** will produce the corresponding propargylic amines through the *in situ* generation of enamines. Recently, Knochel and co-workers reported the CuBr-catalyzed addition of terminal alkynes to enamines.[10] Thus, we next examined the three-component coupling reaction of secondary amines, aldehydes and **3** catalyzed by $[IrCl(cod)]_2$ (Table 2).

As expected, various secondary amines were found to react with aldehydes and **3** in the presence of a catalytic amount of $[IrCl(cod)]_2$ to give the corresponding propargylic amines in good to excellent yields. For example, the reaction of dibutylamine (**6a**) with **2a** and **3** (**6a** : **2a** : **3** = 1 : 6 : 3 molar ratio) catalyzed by $[IrCl(cod)]_2$ (10 mol%) in THF at 60 °C for 6 h produced dibutyl(1-propyl-3-trimethylsilyl-2-propynyl)amine (**7aa**) in 97% yield (run 1). The coupling of diisobutylamine (**6c**) with **2a** and **3** proceeded smoothly under these reaction conditions, but the isolated yield of the product **7ca** was somewhat low (run 3). This may be due to the instability of **7ca** during the isolation with column chromatography. In the CuBr-catalyzed synthesis of propargylic amine by the reaction of enamines with alkynes, the reaction was limited to *N*,*N*-diallyl or *N*,*N*-dibenzyl substituted enamines.[10] In the present iridium-catalyzed reaction, the simple secondary amines and aldehydes could be employed as the starting materials.

In conclusion, we have established an alternative synthetic route to propargylic amines by the reaction of amines, aldehydes and TMS-acetylene using an iridium complex as a catalyst.

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Notes and references

† Representative procedure: To a 1,4-dioxane solution (2.0 mL) of dichlorobis(1,5-cyclooctadiene)diiridium $[IrCl(cod)]_2$ (0.025 mmol) were added amine (0.25 mmol), aldehyde (1.5 mmol) and **3** (0.75 mmol) under Ar. Then, the reaction mixture was stirred at 75 °C for 15 h. The reaction was quenched with wet ether, and products were isolated by column chromatography (230–400 mesh Al_2O_3, hexane), and purified by distillation under reduced pressure. After the reaction, the GC and GC-MS analyses were performed. The yields of products were estimated from the peak areas based on the internal standard technique using GC.

1 M. A. Huffman, N. Yasuda, A. E. DeCamp and E. J. J. Grabowski, *J. Org. Chem.*, 1995, **60**, 1590–1594; M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. VanDuyne and J. Clardy, *J. Am. Chem. Soc.*, 1990, **112**, 3715–3716.
2 *Comprehensive Organic Transformations 2nd edn.*, R. C. Larock, ed., Wiley-VCH, New York, 1999, pp. 568–569.
3 M. Miura, M. Enna, K. Okuro and M. Nomura, *J. Org. Chem.*, 1995, **60**, 4999–5001.
4 D. E. Frantz, R. Fässler and E. M. Carreira, *J. Am. Chem. Soc.*, 1999, **121**, 11245–11246; R. Fässler, D. E. Frantz, J. Oetiker and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2002, **41**, 3054–3056.
5 S. Pinet, S. U. Pandya, P. Y. Chavant, A. Ayling and Y. Vallee, *Org. Lett.*, 2002, **4**, 1463–1466.
6 C. Fischer and E. M. Carreria, *Org. Lett.*, 2001, **3**, 4319–4321.
7 C. J. Li and C. Wei, *Chem. Commun.*, 2002, 268–269; C. Wei and C. J. Li, *J. Am. Chem. Soc.*, 2003, **125**, 9584–9585; C. Wei, Z. Li and C. J. Li, *Org. Lett.*, 2003, **5**, 4473–4475.
8 (*a*) S. Sakaguchi, T. Kubo and Y. Ishii, *Angew. Chem., Int. Ed.*, 2001, **40**, 2534–2536; (*b*) S. Sakaguchi, T. Yamaga and Y. Ishii, *J. Org. Chem.*, 2001, **66**, 4710–4712; (*c*) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 72–73.
9 We[8b] and Carreira[6] were independently reported the $[IrCl(cod)]_2$-catalyzed coupling reaction of amines, aldehydes (or aldimines) with trimethylsilylacetylene to give propargylic amines.
10 C. Koradin, K. Polborn and P. Knochel, *Angew. Chem., Int. Ed.*, 2002, **41**, 2535–2538; C. Koradin, N. Gommermann, K. Polborn and P. Knochel, *Chem. Eur. J.*, 2003, **9**, 2797–2811.