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Synthesis of 1,2-dihydroisoquinolines via the reaction of *ortho*-alkynylarylimines with bis-π-allylpalladium

Manabu Ohtaka, Hiroyuki Nakamura[†] and Yoshinori Yamamoto[*]

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

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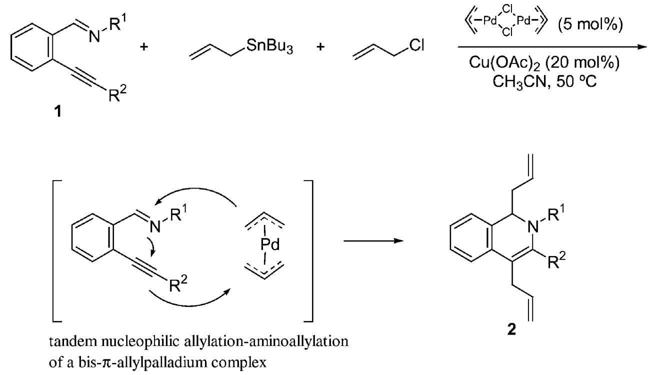
Abstract—The reaction of the *ortho*-alkynylarylimines **1** with allyltributylstannane and allyl chloride in the presence of allylpalladium chloride dimer (5 mol%) and $Cu(OAc)_2$ (20 mol%) in CH_3CN at 50 °C gave the 1,4-diallyl-1,2-dihydroisoquinolines **2** in good yields. Most probably, the reaction proceeds through tandem bis-allylation of the imine-alkyne functional groups with bis-π-allylpalladium.

Recently, much attention has been directed towards palladium-catalyzed annulations and electrophilic cyclizations of alkynes as a powerful method for construction of various heterocycles, such as indoles,[1–3] benzofurans,[4] isochromenes,[5] and isoquinolines,[6] under mild conditions. We recently found that a bis-π-allylpalladium complex acts as an amphiphilic reagent in the reaction with certain Michael acceptors to afford the corresponding bisallylation products.[7] A tandem nucleophilic allylation–alkoxyallylation of alkynylaldehydes proceeded under the catalytic amphiphilic bis-allylation conditions.[5b] In this paper, we report the synthesis of the 1,4-diallyl-1,2-dihydroisoquinolines **2** by the Pd(II)–$Cu(OAc)_2$ cocatalyzed tandem bis-allylation of the imine-alkyne functional groups of the *ortho*-alkynylarylimines **1** with bis-π-allylpalladium, generated in situ from allyltributylstannane and allyl chloride. Here also, the amphiphilic bis-π-allylpalladium species plays a key role in the bis-allylation (Eq. 1).



(1)

We first examined the allylation reaction of the alkynylimine **1a** (see Table 1) using a catalytic amount of π-allylpalladium chloride dimer (5 mol%) in THF. The reaction proceeded at 80 °C to give 1,4-diallyl-2-benzyl-3-phenyl-1,2-dihydroisoquinoline **2a** as the 6-*endo-dig* cyclized product in 32% yield. Very interestingly, the 5-*exo-dig* cyclized product was not obtained.[5b,8] Among various solvents examined, CH_3CN was most effective for this transformation and **2a** was obtained in 46% yield. Furthermore, the addition of $Cu(OAc)_2$ exerted a significant influence both on the product yield and on the reaction time.[9] The reaction of the alkynylimine **1a**, allyltributylstannane and allyl chloride in CH_3CN was complete within 20 min in the presence of π-allylpalladium chloride dimer (5 mol%) and $Cu(OAc)_2$ (20 mol%) at 50 °C to give **2a** in 69% yield (Table 1,

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Keywords: Palladium catalyst; Bis-π-allylpalladium; Amphiphilic reagent; 1,2-Dihydroisoquinoline; *ortho*-Alkynylarylimine; Copper catalyst; Bimetallic co-catalyst.

[*] Corresponding author. Tel.: +81 22 2176 581; fax: +81 22 2176 784; e-mail addresses: tl@yamamoto1.chem.tohoku.ac.jp; yoshi@yamamoto1.chem.tohoku.ac.jp

[†] Current address: Department of Chemistry, Faculty of Science, Gakushuin University, Tokyo, 171-8588, Japan.

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Table 1. The reaction of **1** with allyltributylstannane and allyl chloride in the presence of allylpalladium chloride dimer and copper(II) acetate catalysts

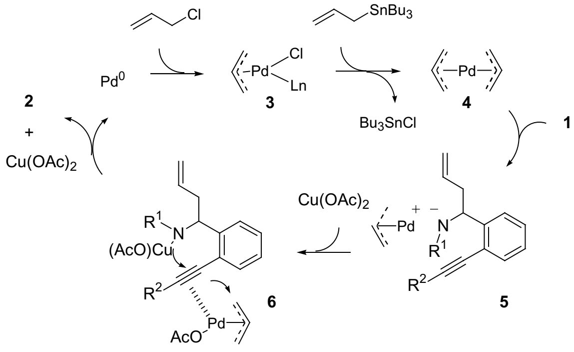
Entry		Alkynylimine **1**		Reaction time	Yields of **2** (%)[a]
		R^1	R^2		
1	**1a**	Bn	Ph	20 min	69
2	**1b**	Bn	4-$MeOC_6H_4$	5 min	76
3	**1c**	Bn	4-$CF_3C_6H_4$	1 h	12
4	**1d**	Allyl	Ph	30 min	60
5	**1e**	Allyl	4-$MeOC_6H_4$	40 min	70
6	**1f**	Allyl	4-$CF_3C_6H_4$	2 h	27
7	**1g**	Allyl	*n*-Bu	2 h	24
8	**1h**	*t*-Bu	Ph	14 h	58
9	**1i**	*t*-Bu	4-$MeOC_6H_4$	12 h	67
10	**1j**	*t*-Bu	4-$CF_3C_6H_4$	5 h	22
11	**1k**	*t*-Bu	*n*-Bu	24 h	10

[a] Isolated yields based on **1**.

entry 1). The alkynylimine **1b**, which has an electron-donating substituent at the *para*-position of the aromatic ring of the R^2 group, reacted more quickly and the 1,2-dihydroisoquinoline **2b** was obtained in 76% yield (entry 2). However, the alkynylimine **1c**, which has an electron-withdrawing substituent at the *para*-position of the aromatic ring of the R^2 group, reacted sluggishly and gave the corresponding 1,2-dihydroisoquinoline **2c** in a very low yield (entry 3). We next examined the reactions of alkynylimines **1d**–**g**, which were derived from the corresponding aldehydes and allylamine. Although the reactions of **1d** and **1e** proceeded smoothly to afford **2d** and **2e** in 60% and 70% yields, respectively (entries 4 and 5), the reactions of **1f** and **1g**, which have 4-$CF_3C_6H_4$ and *n*-butyl groups at the R^2 position, respectively, gave **2f** and **2g** in lower yields (27% and 24%, respectively) (entries 6 and 7). The alkynylimines **1h**–**k**, which were derived from the corresponding aldehydes and *t*-butylamine, were also examined and a similar tendency to that seen above was observed in the cases of the *t*-butylimines. The reactions of **1h** and **1i** afforded **2h** and **2i** in 58% and 67% yields (entries 8 and 9), whereas the reactions of **1j** and **1k** afforded **2j** and **2k** in low yields (entries 10 and 11).

A representative procedure is as follows. To a mixture of **1a** (0.2 mmol, 59 mg), allylpalladium chloride dimer (0.01 mmol, 3.7 mg) and copper(II) acetate (0.04 mmol, 7.2 mg) in CH_3CN (4 mL) were added allyl chloride (1.0 mmol, 0.12 μL) and allyltributylstannane (0.24 mmol, 80 mg) under Ar and the mixture was stirred at 50 °C. The reaction progress was monitored by TLC. After **1a** had been consumed, the reaction mixture was filtered through a short Al_2O_3 column with diethyl ether as eluent and the filtrate was concentrated. Purification by HPLC (Mightysil, NH_2-Si60, 250-20) with hexane gave 1,4-diallyl-2-benzyl-3-phenyl-1,2-dihydroisoquinoline **2a** as the sole product (52 mg, 69%).

A mechanistic rationale which accounts for the bis-allylation of the *ortho*-alkynylarylimines is shown in Scheme 1. The oxidative addition of Pd(0) to allyl chloride produces the π-allylpalladium chloride complex **3**. The transmetallation between **3** and allyltributylstannane gives the bis-π-allylpalladium complex **4**, which reacts with **1** in a nucleophilic manner to give the π-allylpalladium amide **5**. $Cu(OAc)_2$ assists cleavage of the Pd–N interaction and the formation of the Pd–alkyne complex **6**. Attack of the nitrogen atom to the alkyne followed by reductive coupling would give **2** and Pd(0) and $Cu(OAc)_2$ are regenerated.



Scheme 1. A possible mechanism.

In general, the construction of a 1,2-dihydroisoquinolines framework can be achieved by the nucleophilic addition to isoquinolines.[10] The current transformation provides an alternative method for the construction of 1,2-dihydroisoquinolines.

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