Synthesis of 3,3-Disubstituted-2-Aminoindolenines by Palladium-Catalyzed Allylic Amidination with Isocyanide

Takeshi Nanjo, Chihiro Tsukano, Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Fax: +81(75)7534569; E-mail: takemoto@pharm.kyoto-u.ac.jp

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Abstract: Synthesis of 3,3-disubstituted-2-aminoindolenines was achieved by palladium-catalyzed allylic amidination with an isocyanide. It was found that isocyanides are effective building blocks in palladium-catalyzed allylic functionalizations, analogous to carbon monoxide. This approach enables the direct construction of the indolenine ring along with the formation of a quaternary carbon and the introduction of an amino substituent in one step under mild conditions.

Key words: palladium, isocyanide, allylic amidination, cyclization, indoles

3,3-Disubstituted indole skeletons are one of the most important structures in alkaloid chemistry and are present in a wide range of natural products and pharmaceuticals.[1] Among these derivatives, 3,3-disubstituted-2-aminoindolenines and 2-aminoindolines are substructures found in biologically active natural products such as flustramine C,[2] perophoramidine[3] and quinadoline B[4] (Figure 1). These compounds are structurally complex, and much effort has been put into the synthetic study toward them.[5] There are three key aspects in the synthesis of 3,3-disubstituted-2-aminoindolenines; (i) construction of the indole ring, (ii) formation of the quaternary carbon at the 3-position, and (iii) introduction of the amino substituent at the 2-position (Scheme 1). A direct, one-step method would be an efficient approach to these structures, but to date there have been no published reports on the direct construction of 3,3-disubstituted-2-aminoindolenines.

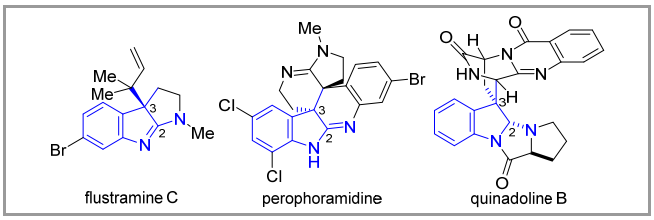
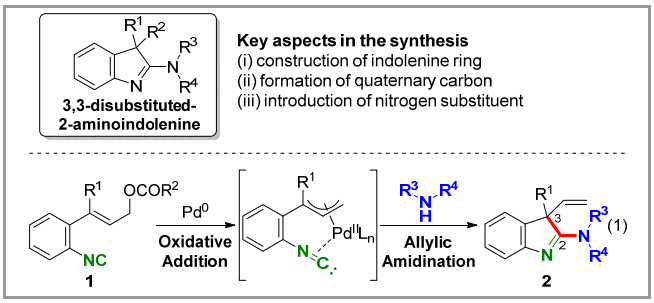


Figure 1 Bioactive 3,3-Disubstituted-2-Aminoindole Derivatives

Our group has previously developed a synthetic method for indole derivatives which involves the formation of a C2-C3 bond.[6] Based on this characteristic retrosynthetic analysis, the efficient construction of various 3,3-disubstituted indole derivatives was achieved. We also applied this strategy to the synthesis of 2-iminoindolines via SmI_2-mediated reductive cyclization of carbodiimides.[6b] Although this method is an effective approach for 3,3-disubstituted-2-aminoindolenine derivatives, stepwise introduction of the nitrogen unit and construction of the indolenine skeleton was required, meaning a one-step method was still needed. Herein we describe a direct and general approach for the construction of 3,3-disubstituted-2-aminoindolenines by palladium-catalyzed allylic amidination with an isocyanide (Scheme 1).



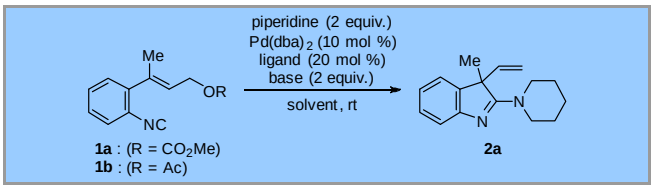
Scheme 1 Allylic Amidination for 3,3-Disubstituted-2-Aminoindolenine Derivatives

The reaction shown in Eq. (1) was designed to develop the direct method. Reaction of isocyanide **1** bearing an allyl ester moiety with an amine in the presence of a palladium catalyst would give 3,3-disubstituted-2-aminoindolenine **2** *via* oxidative addition and allylic amidination. Recent publications disclosed that isocyanides are useful building blocks for multicomponent reactions (e.g., Passerini and Ugi reactions) as well as for palladium-catalyzed reactions.[7-10] However, there are only a few reports of palladium-catalyzed allylic functionalization reactions with isocyanides, unlike the well-developed chemistry of carbon monoxide, which is isoelectronic with an isocyanide.[11] Usually, palladium-catalyzed allylic functionalization reactions occur at the less sterically hindered site.[11a,d] Our approach, however, would enable formation of a quaternary carbon at the more sterically hindered site under mild conditions, owing to intramolecular cyclization. This method would also enable the introduction of various amino substituents at the 2-position by using a range of amines.

To investigate the allylic amidination, we synthesized substrate **1a** bearing an isocyanide and an allyl carbonate moiety.[12] Treatment of **1a** with piperidine and 10 mol % of $Pd(PPh_3)_4$ in toluene at room temperature afforded 2-aminoindolenine **2a** in 18% yield (Table 1, entry 1). Using $Pd(dba)_2$ and PPh_3 instead of $Pd(PPh_3)_4$ increased the yield of **2a** to 35% (entry 2). Next, several ligands were screened. It was found that monodentate triarylphosphines were

effective, and P(2-furyl)$_3$ gave the best results in this reaction (entries 3-6), however, the yield of **2a** was still below 50%. We assumed that the low yields were caused by high reactivity of the allyl carbonate moiety in substrate **1a**, thus substrate **1b** bearing an allyl acetate moiety was used instead. As a result, the yield of the desired product **2a** increased to 55% (entry 7). When substrate **1a** was used, additional base was not necessary for this reaction, but the addition of two equivalents of Et$_3$N when using **1b** increased the yield of **2a** (entries 7, 8). Further optimization revealed that THF was the best solvent (entries 9-13). Although lowering the amount of catalyst slightly decreased the yield of **2a**, catalyst loadings as low as 2 mol % were sufficient for complete conversion (entries 14, 15).

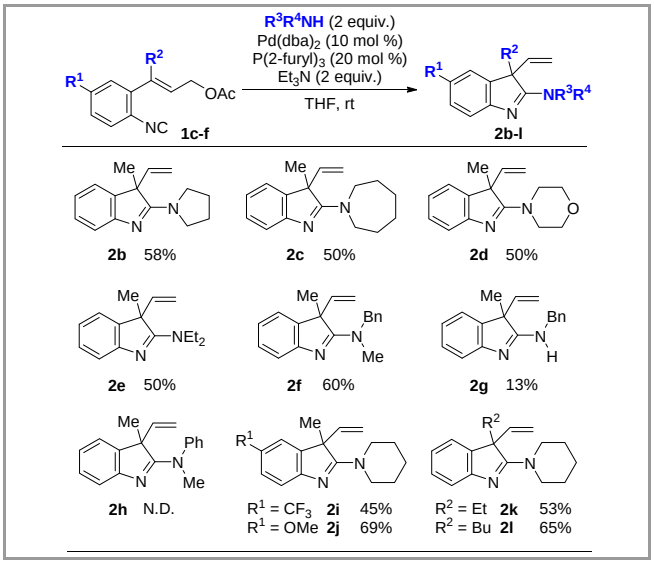
Table 1 Investigation of Reaction Conditions



Entry	R	Ligand	Base	Solvent	Yield[a]
1[b]	CO_2Me	None	none	toluene	18%
2	CO_2Me	PPh_3	none	toluene	35%
3	CO_2Me	DPPE[c]	none	toluene	15%
4	CO_2Me	BINAP[c]	none	toluene	20%
5	CO_2Me	P(*o*-tolyl)$_3$	none	toluene	36%
6	CO_2Me	P(2-furyl)$_3$	none	toluene	42%
7	Ac	P(2-furyl)$_3$	none	toluene	55%
8	Ac	P(2-furyl)$_3$	Et$_3$N	toluene	65%
9	Ac	P(2-furyl)$_3$	Et$_3$N	MeCN	19%
10	Ac	P(2-furyl)$_3$	Et$_3$N	DCE	16%
11	Ac	P(2-furyl)$_3$	Et$_3$N	DMF	30%
12	Ac	P(2-furyl)$_3$	Et$_3$N	1,4-dioxane	71%
13	Ac	P(2-furyl)$_3$	Et$_3$N	THF	73%
14[c,d]	Ac	P(2-furyl)$_3$	Et$_3$N	THF	64%
15[c,e]	Ac	P(2-furyl)$_3$	Et$_3$N	THF	63%

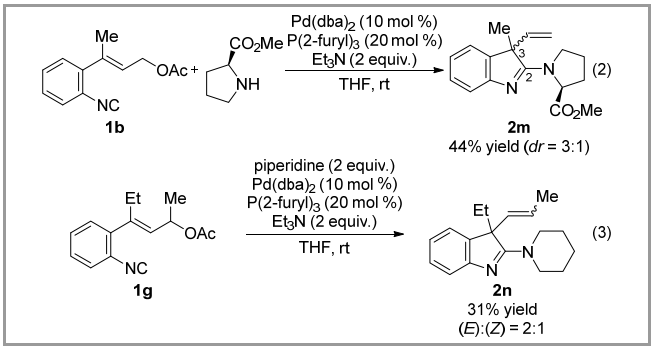
[a] Yield of isolated product.
[b] Pd(PPh$_3$)$_4$ was used instead of Pd(dba)$_2$.
[c] The reaction was performed at 50 °C.
[d] 5 mol % of Pd(dba)$_2$ and 10 mol % of P(2-furyl)$_3$ were used.
[e] 2 mol % of Pd(dba)$_2$ and 4 mol % of P(2-furyl)$_3$ were used.

Next we investigated the substrate scope of the reaction under the optimal conditions (Scheme 2).[13,14] Initially, a range of amines were examined as the nucleophile. The reactions of simple cyclic amines gave the desired products **2b** and **2c** in 58% and 50% yields respectively. Morpholine could also be used in this reaction (**2d**). The reaction of acyclic amines such as diethylamine and benzylmethylamine also gave good results (**2e**, **2f**). However, using a primary amine gave a low yield of the desired 2-aminoindolenine **2g**. When *N*-methylaniline was used, the desired product **2h** was not obtained, probably because of the weaker nucleophilicity. Next the reaction was performed using several isocyanides. The reactions of substrates bearing trifluoromethyl and methoxy groups at the *para* position of the aromatic ring gave the corresponding products **2i** and **2j** in 45% and 69% yields, respectively. An alkyl substituent on the olefin did not significantly influence the yield of the products (**2k**, **2l**).



Scheme 2 Investigation of Substrate Scope

Next we performed the reactions using a chiral amine and an allyl acetate **1g** derived from a secondary alcohol (Scheme 3). The optimal conditions were applied to the reaction using L-proline methyl ester as the nucleophile and interestingly, the desired product **2m** was obtained as a 3:1 mixture of diastereomers at the 3-position of the indolenine ring (Eq. 2). This result indicates that the configuration of the quaternary carbon was influenced by the steric effect of the nucleophile. When allyl acetate **1g** was used, the desired product **2n** was obtained as a 2:1 mixture of olefin geometric isomers (Eq. 3).



Scheme 3 Investigation Using L-Proline Methyl Ester and an Allyl Acetate **1g**

A plausible mechanism is shown in Figure 2. Firstly, oxidative addition of allyl acetate **1b** to Pd(0) generates allylpalladium complex **A**. There are two possibilities for the next step. One is that intramolecular isocyanide insertion proceeds to form

intermediate **B** and then C–N reductive elimination regenerates the Pd(0) species and affords the desired 2-aminoindolenine **2a** (Path A). The other possibility is that nucleophilic addition to the isocyanide activated by the Pd(II) occurs to give palladacycle **C** followed by C–C reductive elimination (Path B). Path B is analogous to the proposed catalytic cycle of the palladium-catalyzed decarboxylative cyclization reaction reported by Hayashi and co-workers.[11a] Considering the scope of this reaction and the nucleophilicity of the amine to isocyanide of intermediate **A**, we believe that Path B is dominant.[15]

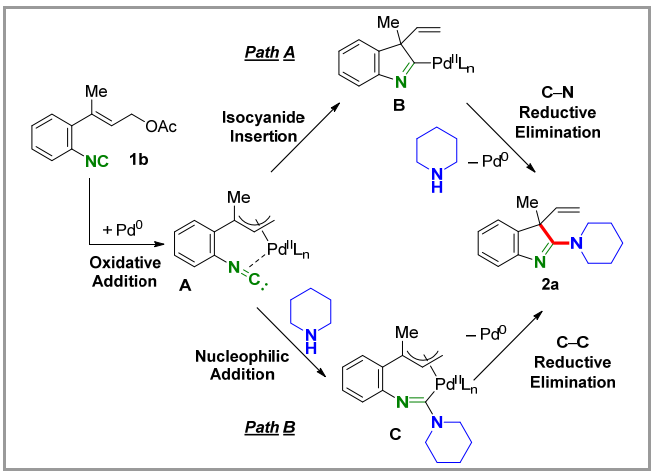


Figure 2 Plausible Mechanism of Allylic Amidination

In summary, we have developed the synthesis of 3,3-disubstituted-2-aminoindolenine derivatives by palladium-catalyzed allylic amidination of isocyanides. This approach enables the direct construction of an indolenine ring along with the formation of a quaternary carbon and introduction of an amino substituent under mild conditions. We are currently investigating the mechanistic detail of the reaction and extending the strategy to an asymmetric reaction.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgments

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(12) Substrates **1a** and **1b** were synthesized by Suzuki-coupling of *N*-formyl-2-iodoaniline with vinyl boronic esters followed by formation of the carbonate or ester and then the isocyanide. See Supporting Information for more details.

(13) **General Procedure for Synthesis of 3,3-Disubstituted-2-Aminoindolenines:** To a stirred solution of **1** (0.1 mmol), amine (0.2 mmol) and Et_3N (0.028 mL, 0.201 mmol) in THF (2 mL) were added $Pd(dba)_2$ (5.8 mg, 0.0101 mmol) and P(2-furyl)$_3$ (4.6 mg, 0.0198 mmol). After stirring for 12 h at room temperature, the reaction mixture was diluted with toluene and extracted with 2N aqueous HCl. The combined extracts were basified with 2N aqueous NaOH and extracted with EtOAc. The resultant organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to give **2**.

(14) **Analytical Data for 2a:** A colorless block, which was recrystallized from Et_2O: m.p. 83.0–86.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16–7.12 (m, 2H), 6.92 (d, 1H, J = 7.2 Hz), 6.86 (ddd, 1H, $J_1 = J_2$ = 6.6 Hz, J_3 = 1.7 Hz), 5.90 (dd, 1H, J_1 = 17.5 Hz, J_2 = 10.6 Hz), 5.35 (d, 1H, J = 17.5 Hz), 5.22 (d, 1H, J = 10.6 Hz), 3.71–3.63 (m, 4H), 1.67–1.58 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 154.7, 140.6, 138.9, 128.1, 121.2, 120.8, 115.7, 113.6, 55.6, 47.4, 26.0, 24.3, 20.7; IR (ATR) 2934, 1632, 1542, 1458, 1448 cm^{-1}; MS (FAB) m/z = 241 ([M+H]$^+$); HRMS (FAB$^+$) $C_{16}H_{21}N_2$: ([M+H]$^+$) 241.1705: Found 241.1708.

(15) As previous reports of the synthesis of amidines using palladium catalysis and isocyanides (ref. 9g, h), Path A is also possible. In this case, the diastereoselectivity of **2m** would be derived from a selective reaction of one enantiomer of racemic **B** and L-proline methyl ester (i.e. matched pair).

Synthesis of 3,3-Disubstituted-2-Aminoindolenines