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# Intramolecular C−N Bond Addition of Amides to Alkynes Using Platinum Catalyst

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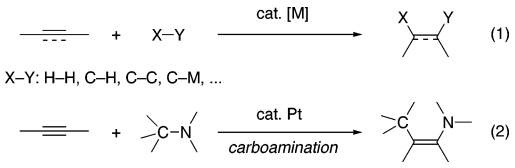
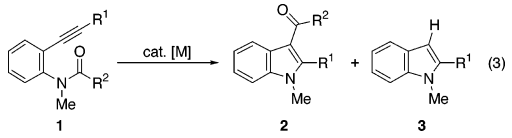
Catalytic additions of H−H, C−H, C−M, and H−X (X = N, O, halides and S, P...) to carbon−carbon unsaturated bonds have been well investigated as atom-economical transformations to construct carbon−carbon and −heteroatom bonds (eq 1).[1] However, the direct addition of a carbon−nitrogen bond (carboamination) to alkenes and alkynes is rare due to lack of reactivity and still considered as a challenging subject.[2,3] We report here that the C−N bond of *ortho*-alkynylanilides adds to the alkynyl bond intramolecularly in the presence of platinum catalyst (eq 2).




The transition metal-catalyzed reaction of the *ortho*-alkynyl amides **1** gave the 3-acylindoles **2** along with deacylated indoles **3** (eq 3).[4,5] First, the catalytic activity of metals was investigated using **1a** ($R^1$ = $^t$Bu, $R^2$ = Me) as a substrate (Table 1). Among various metals examined, $PtCl_2$ gave the best result and gave the products almost quantitatively (entry 1). The other Pt(II) catalysts, such as $PtCl_2(CH_3CN)_2$ and $PtBr_2$, gave the products in slightly lower yields (entries 2 and 3). Very interestingly, $Pt(PPh_3)_4$ did not give the products at all, even after a prolonged reaction time (entry 4), although $PtCl_4$ afforded the products in good yield in a very short time (entry 5). This reaction was strongly influenced by the solvents used. Among the solvents examined, aromatic solvents are suitable for this transformation, and an electron-donating substituent on the aromatic ring dramatically enhanced the reaction rate (entries 1 and 6−9).[6] Interestingly, only platinum complexes catalyzed the reaction efficiently, and other transition metals such as palladium complexes did not exhibit useful catalytic activity (entries 10 and 11).

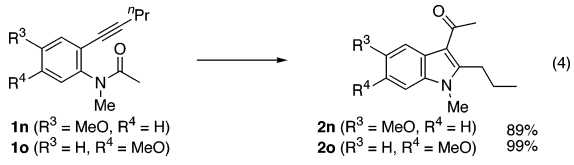



Next, we investigated the scope of this reaction using various substrates **1** (Table 2). The substrates **1b**,**c**, which had sterically less bulky groups, afforded the products within 1 h with high selectivities of **2** over **3** (entries 1 and 3), and the reaction also proceeded almost quantitatively even at room temperature (entry 2). However, the substrate having *tert*-butyl group **1a** proceeded sluggishly, and the ratio of **2**/**3** became lower (entry 4). The electron-donating groups of arylalkynes reduced the reaction rate, and methoxy substituent required slightly higher loadings of the catalyst compared to the other aryl derivatives (entries 5−7). On the other hand, the electron-withdrawing groups enhanced the rate and the reactions completed within 1 h (entries 8 and 9). The ratio of **2**/**3** was not affected by the electronic factor of the substituents of aryl group, giving a similar level of selectivity. Not only the methyl amides **1a**−**h** but also the other amides **1i**−**m** can be used. When the formamide **1i** was used, the formylindole **2i** was obtained in high yield (entry 10). The ratio of **2**/**3** was strongly influenced by the acyl moiety, and the benzamide **1j** gave **2j** in higher selectivity (entry 11). Phenylacetamide **1k** and trifluoroacetamide **1m** gave the acyl products **2k** and **2m**, respectively, as sole products (entries 12 and 14). Furthermore, phenyl-substituted amide **1l** also gave **2l** in good selectivity compared with the reaction using **1f** (entry 13). The reactions of the substrates **1n** and **1o**, which had a methoxy group at the 4 or 5 position of the aromatic ring, selectively produced the methoxyindole derivatives **2n** and **2o** in 89 and 99% yield, respectively (eq 4).

***Table 1.*** Catalyst Activity in the Intramolecular Aminoacylation of the Alkyne of *ortho*-Alkynylanilide **1a** ($R^1$ = $^t$Bu, $R^2$ = Me)[a]

| entry | catalyst | solvent | time, h | yield, %[b] | **2a**:**3a** |
|---|---|---|---|---|---|
| 1 | $PtCl_2$ | anisole | 3 | 94 | 2:1 |
| 2 | $PtCl_2(CH_3CN)_2$ | anisole | 8 | 80 | 2:1 |
| 3 | $PtBr_2$ | anisole | 5 | 79 | 2:1 |
| 4 | $Pt(PPh_3)_4$ | anisole | 12 | 0 | − |
| 5 | $PtCl_4$ | anisole | 1 | 80 | 2:1 |
| 6 | $PtCl_2$ | benzene | 24 | 33 | 2:1 |
| 7 | $PtCl_2$ | toluene | 14 | 99 | 3:1 |
| 8 | $PtCl_2$ | *p*-xylene | 7 | 92 | 2:1 |
| 9 | $PtCl_2$ | mesitylene | 14 | 93 | 2:1 |
| 10 | $Pd(PPh_3)_4$ | anisole | 12 | 0 | − |
| 11 | $PdCl_2$ | anisole | 12 | 18 | 1:7 |

[a] Reaction conditions: 0.5 mmol of substrate **1a**, 10 mol % catalyst, solvent (0.5 M), 80 °C. [b] Combined $^1$H NMR yields; dibromomethane was used as an internal standard.




A proposed mechanism is shown in Scheme 1. The coordination of the alkyne moiety of **1** to $PtCl_2$ gives the $\pi$-complex **A**. The intramolecular nucleophilic attack of the *ortho*-nitrogen atom to the electron-deficient alkyne leads to the zwitterionic intermediate **B**. An intramolecular [1,3]-migration of acyl moiety then yields the intermediate **C**, which produces **2** and $PtCl_2$. The substrates, bearing an acidic proton at the α-position of amide, gave the corresponding 3-deacylated indoles **3** as byproducts; presumably the deacylation takes place through protonolysis of the C−Pt bond of **B**, although it is highly speculative.

To confirm the proposed mechanism, we carried out the deuterium-labeling experiments. As shown in eq 5, the deuterium-



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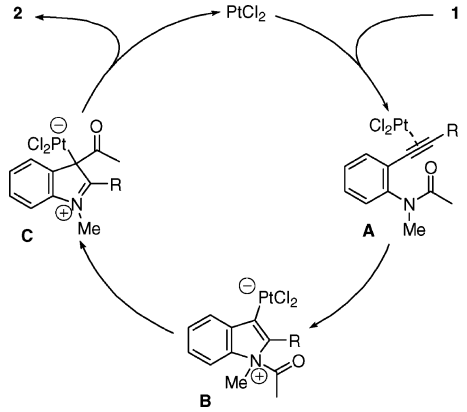
***Table 2.*** Platinum-Catalyzed Intramolecular Aminoacylation of Alkynes **1a**−**m**[a]

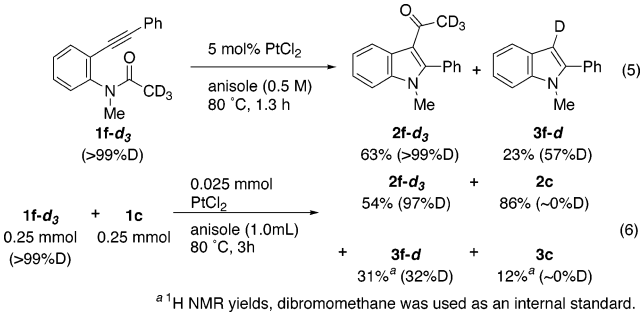
| entry | $R^1$ | $R^2$ | **1** | time, h | yield, %[b] | **2**:**3** |
|---|---|---|---|---|---|---|
| 1 | $^n$Pr | Me | **1b** | 0.3 | 96 | 9:1 |
| 2[c] | $^n$Pr | Me | **1b** | 10 | 93 | 8:1 |
| 3 | Cyclohexyl | Me | **1c** | 0.5 | 98 | 13:1 |
| 4[d] | $^t$Bu | Me | **1a** | 3 | 91 | 2:1 |
| 5[d] | 4-MeO−$C_6H_4$ | Me | **1d** | 0.3 | 81 | 3:1 |
| 6 | 4-Me-$C_6H_4$ | Me | **1e** | 3 | 97 | 2:1 |
| 7 | Ph | Me | **1f** | 1 | 94 | 3:1 |
| 8 | 4-F−$C_6H_4$ | Me | **1g** | 0.5 | 88 | 3:1 |
| 9 | 4-$CF_3$-$C_6H_4$ | Me | **1h** | 0.7 | 93 | 4:1 |
| 10[d,e] | $^n$Pr | H | **1i** | 24 | 74 | 5:1 |
| 11 | $^n$Pr | Ph | **1j** | 16 | 75 | 13:1 |
| 12 | $^n$Pr | Bn | **1k** | 0.5 | 99 | 1:−[f] |
| 13 | Ph | Bn | **1l** | 2 | 87 | 4:1 |
| 14 | $^n$Pr | $CF_3$ | **1m** | 3 | >99 | 1:−[g] |

[a] Reaction conditions: 0.5 mmol of substrate **1**, 5 mol % $PtCl_2$, anisole (0.5 M), 80 °C. [b] Combined isolated yields. [c] Reaction was performed at 30 °C. [d] 10 mol % of catalyst was used. [e] Reaction was achieved at 100 °C. [f] A trace amount of **3k** was detected (<1%). [g] **3m** was not detected.

***Scheme 1.*** Proposed Mechanism for the Intramolecular Aminoacylation of Alkynes **1**

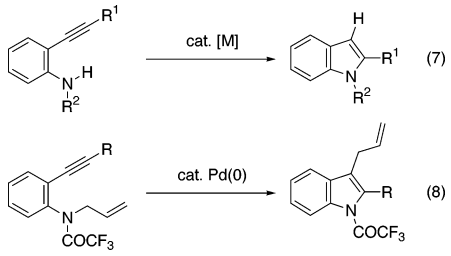



labeled substrate **1f**-$d_3$ gave the 3-deuterim-labeled indole **3f**-*d* along with the 3-acyl product **2f**-$d_3$. This observation indicates that the deuterium at the 3 position of **3f**-***d*** comes partially from $CD_3$ of the acylamide of **1f**-$d_3$. Next, we examined the reaction of an equimolar mixture of **1f**-$d_3$ and **1c** under similar conditions (eq 6). Interestingly, mixing of the acyl substituents did not occur at all.[8] This result definitely shows that the addition of the C−N bond of amides proceeds in an intramolecular fashion.




[a] $^1$H NMR yields, dibromomethane was used as an internal standard.

From synthetic point of view, the present reaction provides a useful procedure for synthesizing 2,3-disubstituted indoles directly from *ortho*-alkynylanilides. Until now, a mumber of synthetic procedures for indoles using *ortho*-alkynylaniline derivatives and transition metal catalysts have been reported, but most of them are useful for synthesizing 2-monosubsituted indoles (eq 7).[9−12] An exceptional example is the palladium-catalyzed allylamination by Cacchi and co-workers, although the trifluoroacetamide moiety is needed (eq 8).[2]




We are now in a position to synthesize 2,3-disubstituted indoles very easily from *ortho*-alkynylanilides. Further mechanistic investigation on the catalytic C−N bond addition is in progress.

**Supporting Information Available:** Spectroscopic and analytical data of synthesized compounds and information on procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Stoichiometric addition of an amide bond to alkynes was achieved by using a chromium complex. See: Rudler, H.; Parlier, A.; Bezennine-Lafollée, S.; Vaissermann, J. *Eur. J. Org. Chem.* **1999**, 2825−2833.

(5) Acylindoles are also produced catalytically through the three-component coupling reactions using carbon monoxide. See: (a) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803−11812. (b) Arcadi, A.; Cacchi, S.; Carnicellli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437−452.

(6) The precise role of the solvent is not clear. However, we presume that the zwitterionic intermediate would be stabilized in electron-rich aromatics.

(7) We confirmed that deacylation from *N*-methylacetanilide hardly occurred under the same conditions (90% recovery, 16 h). This result clearly indicates that indoles **3** were not generated through the catalytic cyclization of 2-alkynylanilines that might be yielded via the deprotection of the starting materials.

(8) We confirmed that the reactions from both of these substrates proceeded simultaneously by monitoring thin-layer chromatography (TLC) and gas chromatography (GC-MS) analyses.

(9) (a) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289−296. (b) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856−5966. (c) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255−1261. (d) See also ref 3f.

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(11) Recently, our group also reported catalytic constructions of highly substituted indoles. See: Kamijo, S.; Yamamoto. Y. *J. Org. Chem.* **2003**, *68*, 4764−4771 and references therein.

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