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Platinum-catalyzed consecutive C–N bond formation-[1,3] shift of carbamoyl and ester groups

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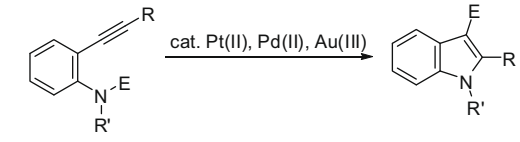
ABSTRACT

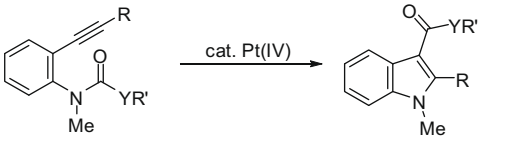
The reaction of *ortho*-alkynylphenylureas **1** having a carbamoyl group attached to the nitrogen atom proceeded in the presence of catalytic amounts of PtI_4, affording corresponding indole-3-carbamides **2** in moderate to high yields. In addition, the platinum-catalyzed cyclization of *ortho*-alkynylphenyl carbamates **3** afforded corresponding indole-3-carboxylates **4** in good yields. The present reaction proceeds through the intramolecular addition of carbon–nitrogen bonds to triple bonds, the so-called carboamination.

Polysubstituted indoles are widely used in the pharmaceutical field and in organic material science. Because of this, the efficient synthesis of these compounds is still a topic of interest in organic chemistry.[1] The catalytic cyclization of *ortho*-alkynylanilines is one of the most powerful methods for the synthesis of 3-nonsubstituted indoles.[2] Recently, several groups including ours have developed efficient protocols for the synthesis of polysubstituted indoles, which involve the cyclization of *ortho*-alkynylanilines having a migration group attached to the nitrogen atom in the presence of π-acidic transition metal catalysts (Eq. 1).[3–6] Not only strongly electrophilic functional groups, such as acyl groups, but also less electrophilic functional groups, such as allyl, methoxymethyl, and sulfonyl groups, have been employed as the migrating groups. These results encouraged us to explore other migrating groups that cannot be directly installed by Friedel–Crafts-type electrophilic substitution into the 3-position of the indole ring for this methodology. Herein, we report that the reaction of *ortho*-alkylphenylureas **1** in the presence of platinum catalysts proceeds via migration of the carbamoyl group, affording the corresponding indole-3-carbamides **2** in moderate to high yields (Eq. 2).[7] Moreover, we found that the platinum-catalyzed cyclization of *ortho*-alkynylanilines **3** having an ester group attached to the nitrogen atom produced the corresponding indole-3-carboxylates **4** in good yields. The present reaction proceeds through the addition of a carbon–nitrogen bond to a carbon–carbon triple bond, the so-called carboamination.



E: acyl, allyl, MOM, sulfonyl

(1)



YR' = NArMe (**1**) OR'(**3**)

YR' = NArMe (**2**) OR' (**4**)

(2)

We first optimized the conditions for the reaction of **1a**. The results are summarized in Table 1. The reaction of **1a** in the presence of 10 mol % of PtI_4 in ethyl acetate at 100 °C for 6 h gave **2a** in 55% yield along with corresponding 3-protonated product **5a** in 37% yield (entry 1).[8] The reaction at 80 °C took 24 h, affording **2a** in 52% yield along with 40% of **5a** (entry 2). $PtBr_4$ showed similar catalytic activity, while the use of $PtCl_4$ led to a lower chemical yield (entries 3 and 4). Divalent platinum salts, such as $PtBr_2$ and $PtCl_2$, were less effective and other metal salts, such as $AuBr_3$ and $InBr_3$, did not promote the present reaction at all (entries 5–8). The reaction using dimethoxyethane (DME), instead of ethyl acetate, gave a comparable result, whereas that using other solvents, such as 1,2-dichloroethane (DCE), toluene, and 1,4-dioxane, decreased the chemical yield (entries 9–12). Attempts to suppress the formation of protonated product **5a** by use of such additives as molecular sieves, bases, and radical scavengers failed (see Supplementary data).

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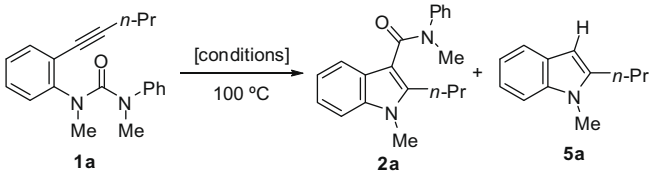
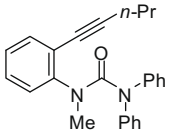
Table 1
Reaction development[a]



Entry	Catalyst	Solvent	Time (h)	Yield of **2a**[b] (%)	Yield of **5a**[b] (%)
1	PtI_4	EtOAc	6	55	37
2[c]	PtI_4	EtOAc	24	52	40
3	$PtBr_4$	EtOAc	4	46	46
4	$PtCl_4$	EtOAc	24	28	41
5	$PtBr_2$	EtOAc	24	16	9
6	$PtCl_2$	EtOAc	24	20	18
7	$AuBr_3$	EtOAc	24	0	0
8	$InBr_3$	EtOAc	25	0	0
9	PtI_4	DME	6	57	31
10	PtI_4	DCE	6	35	35
11	PtI_4	Toluene	24	49	14
12	PtI_4	1,4-Dioxane	20	25	39

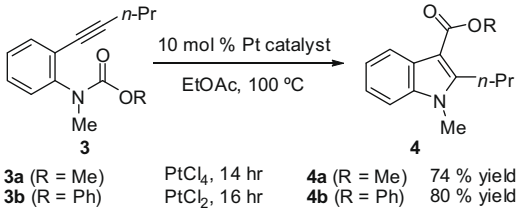
[a] The reaction of **1a** was carried out in the presence of 10 mol % of catalyst at 100 °C.
[b] The yield was determined by ^{1}H NMR using dibromomethane as an internal standard.
[c] At 80 °C.

We applied the optimal conditions (Table 1, entry 1) to various substrates **1** as summarized in Table 2. The reaction of **1b**, which had a weakly electron-withdrawing chloro group at the para position of the aromatic ring that is attached to the nitrogen atom of the migrating amide group, gave **2b** in good yield, while that of **1c** bearing a strongly electron-withdrawing trifluoromethyl group proceeded very slowly, affording **2c** in low yield (entries 1 and 2). Substrate **1d** having an anisyl group at R^2 was quickly converted into **2d** and **5a** in 46% and 53% yields, respectively (entry 3). The dimethylcarbamoyl group showed low migration ability (entry 4). The reaction of **1f** that had an alkyl chain at the alkynyl moiety proceeded smoothly, affording **2f** in good yield (entry 5). The reaction of **1g** having a cyclopropyl group afforded the desired product **2g**, while a phenyl group at the alkynyl terminus totally interrupted the desired reaction (entries 6 and 7). The reaction of terminal alkyne **1i** proceeded smoothly, affording **2i** in 83% yield (entry 8). The reaction of **1j** having a diphenylcarbamoyl group did not proceed at all.

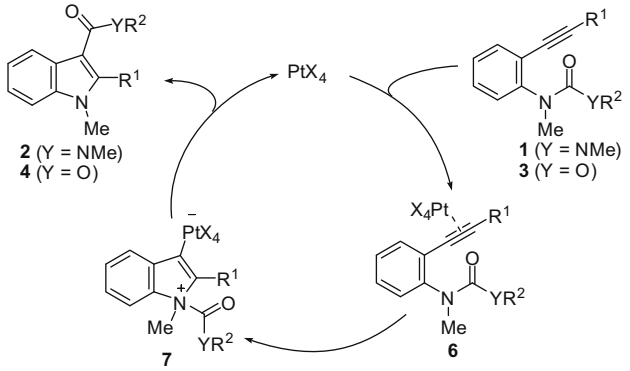


1j

We extended the present methodology to the migration of an ester group (Eq. 3). The reaction of *O*-methyl carbamate **3a** in the presence of 10 mol % of $PtCl_4$ afforded corresponding methyl ester **4a** in good yield.[9] Meanwhile, phenyl ester **4b** was obtained in good yield by using $PtCl_2$ as catalyst. Protonated product **5a** was not obtained at all in these reactions.

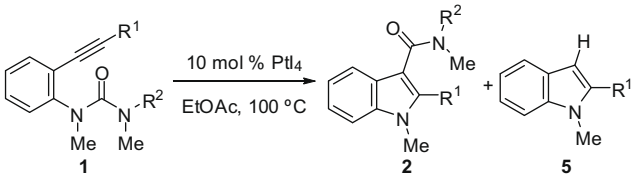


(3)



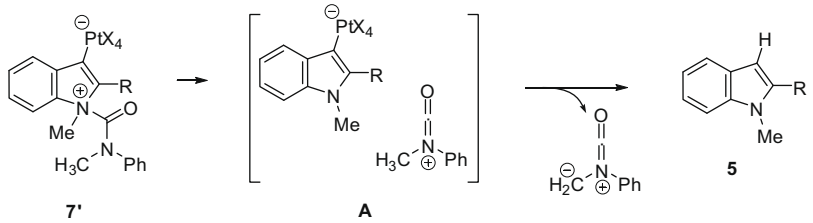
Scheme 1. Plausible mechanism.

Table 2
PtI_4-catalyzed cyclization of **1**[a]



Entry	**1**	R^1	R^2	Time (h)	Yield of **2**[b] (%)	Yield of **5**[b] (%)
1	**1b**	*n*-Pr	*p*-ClC_6H_4	4	**2b**, 61	**5a**, 36
2	**1c**	*n*-Pr	*p*-F_3C-C_6H_4	24	**2c**, 32	**5a**, 56
3	**1d**	*n*-Pr	*p*-Anisyl	2	**2d**, 46	**5a**, 53
4	**1e**	*n*-Pr	Me	4	**2e**, 23	**5a**, 48
5	**1f**	$(CH_2)_3Cl$	Ph	18	**2f**, 54 [c]	**5b**, 36
6	**1g**	Cyclopropyl	Ph	48	**2g**, 32	**5c**, 33
7	**1h**	Ph	Ph	24	trace [d]	**5d**, 31
8	**1i**	H	Ph	4	**2i**, 83 [c]	trace

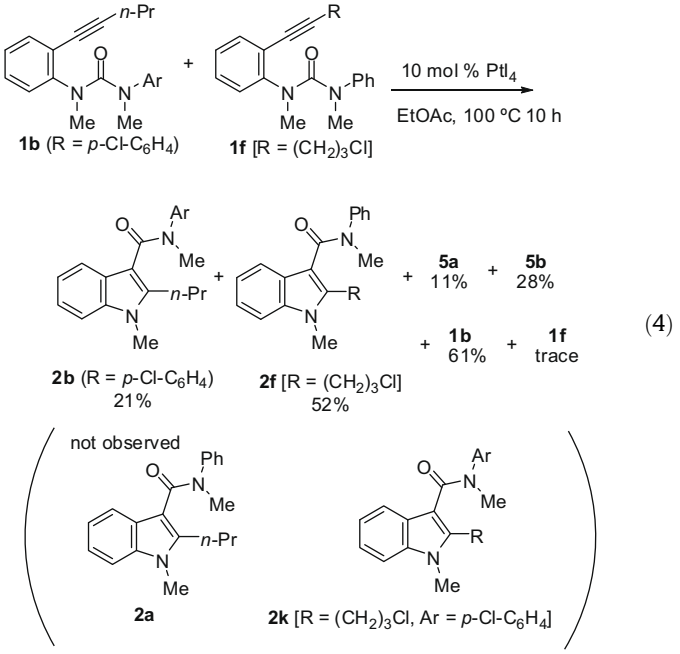
[a] The reaction of **1** (0.25 mmol) was carried out in the presence of 10 mol % of PtI_4 in ethyl acetate at 100 °C.
[b] The yield was determined by ^{1}H NMR using dibromomethane as an internal standard.
[c] Isolated yield.
[d] 49% of **1h** was recovered.



Scheme 2.

A plausible mechanism of the present reaction is illustrated in Scheme 1. The Lewis acidic platinum catalyst coordinates to the alkynyl moiety of substrate **1** or **3**. Intramolecular nucleophilic attack of the nitrogen atom on the triple bond yields cyclized intermediate **7**. [1,3] Migration of the carbamoyl or alkoxycarbonyl group followed by elimination of the platinum catalyst, the so-called carbodemetalation, gives product **2** or **4**.

To know if the reaction proceeds via intramolecular or intermolecular manner, we carried out a crossover experiment (Eq. 4). The reaction of a 1:1 mixture of **1b** and **1f** under the standard conditions afforded a mixture of **2b** and **2f**; no crossover products, such as **2a** and **2k,** were observed in GC–mass. This result indicates that the present reaction proceeds in an intramolecular manner.



(4)

In the reaction of *ortho*-alkynylphenylureas **1**, the formation of 3-protonated by-product **5** was observed (Tables 1 and 2). Because the formation of the protonated product **5** was not reduced by addition of drying agents, such as MS 4 Å, protodemetalation by a trace amount of water in the reaction system is less likely. Moreover, the reaction in deuterated solvents, such as toluene-d^8 and CD_2Cl_2 did not afford 3-deuterated indoles. Presumably, the formation of 3-protonated by-products is due to protodemetalation of the vinylplatinum moiety by a proton derived from the methyl moiety of the migrating carbamoyl group, which would be eliminated in the [1,3] carbamoyl migration step, as illustrated in Scheme 2. Further mechanistic investigations are currently ongoing in our laboratory.

In conclusion, we are now in a position to synthesize indole-3-carbamides and -carboxylates by the platinum-catalyzed cyclization of *ortho*-alkynylphenyl ureas and carbamates. As the present reaction proceeds through formal addition of a carbon–nitrogen bond to a carbon-carbon triple bond, the so-called carboamination, this methodology is useful to provide these molecules in an efficient and atom-economic manner.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and spectroscopic data of **1**, **2**, **3**, **4**, and **5c**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.108.

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8. *Representative procedure*: To a mixture of 10 mol % of PtI_4 and 0.25 mmol of **1** was added 1.0 mL of ethyl acetate in a pressure vial (Wheaton v-vial) at room temperature, and the mixture was stirred at 100 °C. After complete consumption of the starting material, which was monitored by TLC, the reaction mixture was cooled to room temperature. The reaction mixture was passed through a short pad of silica gel with ethyl acetate. After the solvents were removed in vacuo, the residue was purified by silica-gel column chromatography using ethyl acetate/hexane (1:5) as eluent. The obtained mixture of **2** and **5** was separated by gel permeation chromatography (Japan Analytical Industry Co. LC-918) to give product **2**.
9. The reaction of **3a** with lower catalyst loading (5 mol %) took 20 h, affording **4a** in 60% yield along with 21% of recovered **3a**.