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Platinum-Catalyzed Dehydroalkoxylation−Cyclization Cascade via N−O Bond Cleavage

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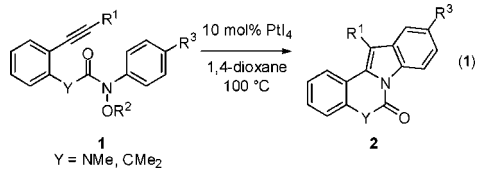
Carbophilic transition metal catalyzed reactions have attracted much attention to facilitate the construction of highly elaborate molecules in an efficient and atom-economic manner.[1] In general, the first step of these reactions involves a nucleophilic attack to the C−C triple bond, which possesses an enhanced electrophilicity due to its π-coordination with a transition metal (Scheme 1a). In many of these reactions, vinylmetal intermediate **A** is transformed into metal carbenoid intermediate **B** driven by the donation of electrons from the metal species. To date, various metal-carbenoid species bearing a net neutral functional group, such as furyl,[2] 1-acyloxyalkenyl,[3] imine,[4] carbonyl,[5] cyclopropyl,[6] and ylide groups,[7] have been employed as key intermediates. Accordingly, we envisioned that iminium-bound metal carbenoid species **C** would possess enhanced electrophilicity due to the cationic iminium group and may lead to favorable transformations. In this case, **C** can be generated via nucleophilic attack by an alkoxyamine onto a π-activated triple bond, followed by the elimination of the alkoxy group (Scheme 1b). Herein, we report the platinum-catalyzed dehydroalkoxylation−cyclization cascade of *ortho*-alkynylphenylureas and -acetamides **1**, bearing an alkoxy and aryl group on the nitrogen atom, to afford the corresponding nitrogen-containing tetracyclic compounds **2**, via N−O bond cleavage,[8] in good to excellent yields (eq 1).



Initially, the catalytic activities of various transition metal salts toward the reaction of *N*-methoxy-*N*′-methyl-*N*′-(2-(pent-1-ynyl)phenyl)-*N*-phenylurea **1a** were evaluated, as summarized in Table 1. Among the metal salts examined, only PtI_4 showed excellent catalytic activity; the reaction of **1a** in the presence of PtI_4 (10 mol%) in ethyl acetate at 100 °C for 24 h afforded **2a** in 88% isolated yield (entry 1). In contrast, the use of $PtBr_4$ (entry 2) and $PtBr_2$ (entry 5) resulted in lower yields of **2a**, whereas the use of PtI_2 (entry 4), $PtCl_2$ (entry 6), and $PtCl_4$ (entry 3) gave only trace amounts of **2a** along with recovery of **1a**. Copper salts, such as $CuCl_2$ (entry 7) and CuCl (entry 8), along with $AuBr_3$ (entry 9), AuCl (entry 10), and $InBr_3$ (entry 11) were ineffective. Furthermore, the use of Brønsted acids, such as TfOH and HCl, and radical initiators, such as AIBN and iodine, did not promote the reaction, indicating that the presence of PtI_4 is essential. Among the reaction solvents, 1,4-dioxane was significantly more effective than other solvents, such as ethyl acetate, toluene, acetonitrile, methanol, and CH_2Cl_2 (entries 12−16).

Next, the optimal conditions (Table 1, entry 12) were employed for the cyclization reaction using various substrates, as summarized in Table 2. The reaction of **1b** bearing a cyclohexyl group at the alkynyl terminus gave **2b** in good yield (entry 1), while that of **1c** having a bulky *tert*-butyl required the use of 20 mol% of PtI_4 and a slightly elevated temperature (110 °C) to obtain **2c** in 39% yield (entry 2). The reactions of **1d**, **1e**, and **1f** proceeded smoothly, irrespective of the electronic properties of the R^1 aromatic moiety (entries 3−5). Although the reaction was slow, substrate **1g** having an ester group at R^1 was effectively converted to **2g** (entry 6). The nature of the *para*-substituent R^3 on the aromatic ring bound onto the nitrogen did not affect the reaction (entries 7 and 8). The reaction of **1j** having a benzyloxy group afforded **2a** in 82% yield, along with roughly 80% of benzyl alcohol (entry 9). The structure of **2** was confirmed by spectroscopic methods; additionally, the structure of **2f** was unambiguously determined by X-ray crystallographic analyses (see Supporting Information).

Scheme 1

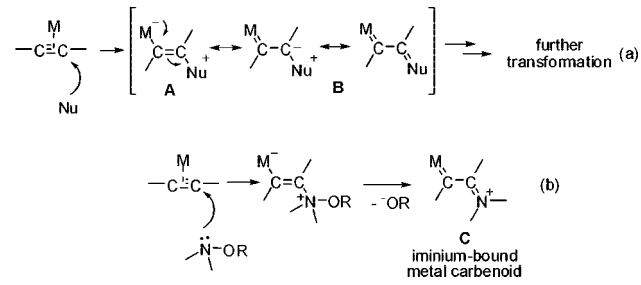
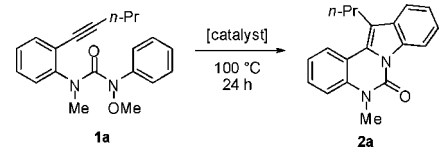


Table 1. Reaction Development[a]



entry	catalyst	solvent	yield/%[b]
1	PtI_4	EtOAc	(88)[c]
2	$PtBr_4$	EtOAc	32
3	$PtCl_4$	EtOAc	no reaction
4	PtI_2	EtOAc	7
5	$PtBr_2$	EtOAc	19
6	$PtCl_2$	EtOAc	12
7	$CuCl_2$	EtOAc	20
8	CuCl	EtOAc	17
9	$AuBr_3$	EtOAc	no reaction
10	AuCl	EtOAc	no reaction
11	$InBr_3$	EtOAc	no reaction
12[d]	PtI_4	1,4-dioxane	(93)[c]
13	PtI_4	toluene	52
14	PtI_4	MeCN	20
15	PtI_4	MeOH	20
16	PtI_4	CH_2Cl_2	no reaction

[a] The reaction of **1a** (0.25 mmol) was carried out in the presence of catalyst (10 mol%) in the indicated solvent (1 mL) at 100 °C for 24 h. [b] ^{1}H NMR yield using CH_2Br_2 as an internal standard. [c] Isolated yield in parentheses. [d] For 12 h.

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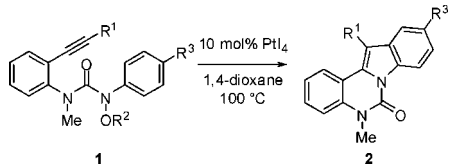
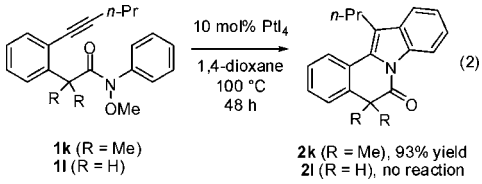
Table 2. PtI_4-Catalyzed Cyclization of **1**[a]



1 **2**

entry	**1**	R^1	R^2	R^3	**2**	time/h	yield/%[b]
1	**1b**	Cy	Me	H	**2b**	48	90
2[c]	**1c**	*t*-Bu	Me	H	**2c**	72	39
3	**1d**	*p*-$F_3CC_6H_4$	Me	H	**2d**	48	91
4	**1e**	Ph	Me	H	**2e**	48	92
5	**1f**	*p*-$MeOC_6H_4$	Me	H	**2f**	48	92
6	**1g**	CO_2Et	Me	H	**2g**	60	68
7	**1h**	*n*-Pr	Me	Me	**2h**	8	94
8	**1i**	*n*-Pr	Me	CO_2Et	**2i**	8	93
9	**1j**	*n*-Pr	Bn	H	**2a**	24	82

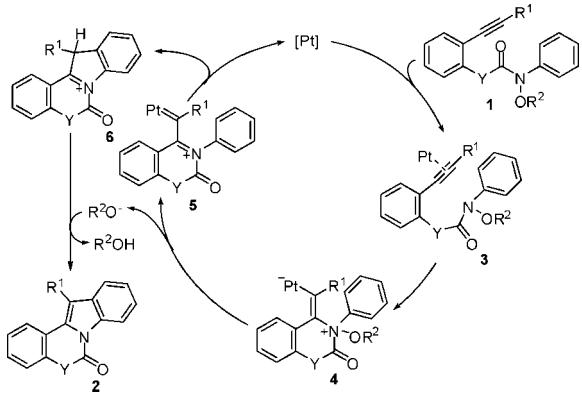
[a] The reaction of **1** (0.25 mmol) was carried out in the presence of PtI_4 (10 mol%) in dioxane (1 mL) at 100 °C. [b] Isolated yield. [c] The reaction was conducted in the presence of PtI_4 (20 mol%) at 110 °C.

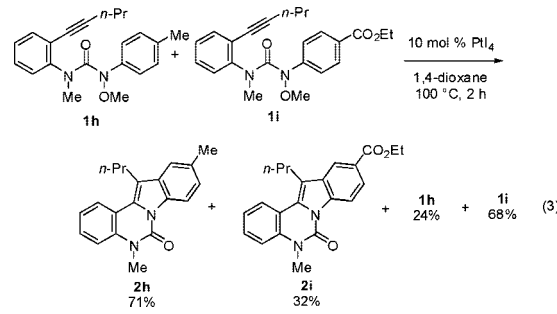


As shown in eq 2, the reaction of *N*-alkoxyamide **1k**, which possesses a *gem*-dimethyl group at the α-carbon of the carbonyl group, was effective in affording the corresponding indoloisoquinolinone **2k**. In contrast, the reaction of **1l**, which does not possess any substituents, did not proceed, indicating that the rigid structure in the tether moiety plays a crucial role in the present reaction.

As illustrated in Scheme 2, a plausible mechanism of the present reaction can be explained as follow: first, coordination between a Lewis acidic Pt catalyst and the alkynyl moiety of **1** would lead to π-complex **3**. Next, a nucleophilic attack by the N-atom onto the triple bond would give vinylplatinum species **4**, followed by elimination of the alkoxy group to afford iminium-bound Pt carbenoid **5**.[9] A C−H bond at the *ortho*-position of the phenyl group on the iminium N-atom would insert into the Pt carbenoid giving iminium species **6**,[10] followed by the elimination of a proton to afford product **2**.[11] Because the reaction involving a 1:1 mixture of **1h** and **1i**, under similar reaction conditions for 2 h, resulted in the preferential formation of **2h**, the activation of the C−H bond presumably proceeds via an electrophilic manner (eq 3). Further mechanistic investigations are currently underway in our laboratories.

Scheme 2. Plausible Mechanism





In conclusion, the dehydroalkoxylative cyclization of **1** via N−O bond cleavage followed by aromatic C−H insertion has been successfully achieved. Because of the importance of indoloquinazolinone and -isoquinolinone in the pharmaceutical field,[12] the present reaction can provide an efficient methodology in the syntheses of such molecules.

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Supporting Information Available: Experimental procedures and characterization of the products **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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