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Platinum(II)-Catalyzed Generation and [3+2] Cycloaddition Reaction of α,β-Unsaturated Carbene Complex Intermediates for the Preparation of Polycyclic Compounds

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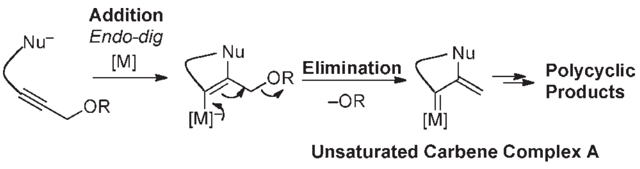
S *Supporting Information*

ABSTRACT: Pt(II)-catalyzed generation of unsaturated carbene complex intermediates from various propargyl ether derivatives based on electrophilic activation of alkynes was realized. These *in situ* generated unsaturated carbene complexes undergo [3+2] cycloaddition reaction with various vinyl ethers, leading to efficient formation of indoles, naphthols, and benzofuran fused with a five-membered ring in high yields.

Scheme 1. Catalytic Generation of α,β-Unsaturated Carbene Complex Intermediates



Transition metal-catalyzed generation of carbene complex and related species based on the electrophilic activation of alkynes has attracted much attention as a useful method for the construction of cyclic carbon skeletons.[1] In contrast, catalytic generation of α,β-unsaturated carbene complex species based on this strategy has been limited to the study utilizing 1,2-acyloxy migration of propargyl ester derivatives,[2] and only a few additional examples have been reported, such as the reactions of homopropargyl azide,[3a] propargyl ketals,[3b] propargyl thioketal,[3c] etc.[3d,3e] Furthermore, the reaction of generated α,β-unsaturated carbene complexes was mostly limited to cyclopropanation,[4] 1,2-hydrogen shift,[3a] ylide formation,[3b] etc.[5]

We have become interested in developing a general method for catalytic generation of α,β-unsaturated carbene complex intermediates and in utilizing the intermediates for further unique carbon−carbon bond formation to realize a facile method for the preparation of synthetically useful polycyclic compounds. Our basic strategy is as follows: By treatment of propargyl alcohol derivatives containing a nucleophilic part in an appropriate position with an electrophilic transition metal catalyst, cyclic α,β-unsaturated carbene complexes **A** would be generated by intramolecular addition of the nucleophilic moiety to the electrophilically activated alkyne in an *endo* manner, followed by elimination of the leaving group at the propargylic position. Furthermore, we expected that [3+2] cycloaddition reaction of the generated α,β-unsaturated carbene complexes **A** with electron-rich alkenes[6−9] would be a new type of transformation to realize efficient synthesis of various useful polycyclic compounds (Scheme 1). In this paper we describe successful realization of this type of reaction using Pt(II) catalysts.

We have chosen a propargyl ether **1a** connected with a Boc-protected amine as a nucleophile through the aromatic ring, with the expectation that the rigid planar structure would facilitate *endo*-cyclization to the electrophilically activated alkyne part and that the alkoxy group at the propargylic position would work not only as an appropriate leaving group to generate unsaturated carbene complex **C** but also as a base to deprotonate from the ammonium part in the cyclized zwitterionic intermediate **B**. We further expected that the generated unsaturated carbene complex **C** would react with an electron-rich olefin in a [3+2] cycloaddition manner to give a tricyclic indole derivative with regeneration of the catalyst (Scheme 2).

Based on these considerations, the reaction of 2-(3-methoxyprop-1-ynyl)aniline derivative **1a** with 10 equiv of *n*-butyl vinyl ether as a trapping reagent of the α,β-unsaturated carbene complex intermediate was examined, employing typical electrophilic transition metal catalysts. While most of the catalysts examined, such as gold(I), rhenium(I), and tungsten(0) complexes, afforded a complex mixture of products or recovery of the starting material, the desired [3+2] cycloadduct **2a** was obtained when **1a** was treated with platinum(II) catalysts.[1] Although $PtCl_2$ itself was not so efficient due to its lower solubility, $[PtCl_2(C_2H_4)]_2$ gave better results, and addition of an equimolar amount (based on Pt) of PPh_3 somewhat improved the yield, probably because the higher electron density on the platinum(II) would promote elimination of methoxide from the zwitterionic intermediate.[10]

Thus, by carrying out the reaction of **1a** and butyl vinyl ether with 2.5 mol % of the $[PtCl_2(C_2H_4)]_2$ (5 mol % based on Pt) and 5 mol % of PPh_3 at 100 °C in 1,4-dioxane in the presence of Na_2CO_3 as base,[11] tricyclic indole **2a** could be obtained in 83% yield.

The proposed mechanism for the formation of **2a** is shown in Scheme 2. 5-*Endo* nucleophilic attack of the amine nitrogen onto the alkyne, activated electrophilically by Pt(II), occurred to give a zwitterionic intermediate **B**. Elimination of the methoxy group by electron-donation from the alkenyl metallic part, along with

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Scheme 2. Reaction of Aniline Derivative 1a with *n*-Butyl Vinyl Ether

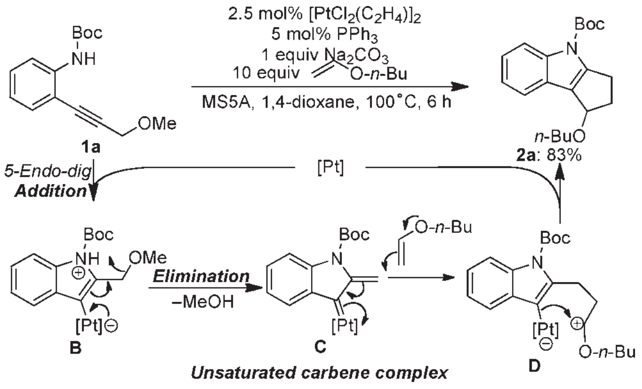
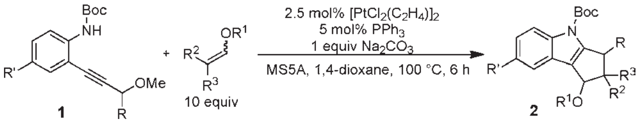


Table 1. Generality of the Reaction



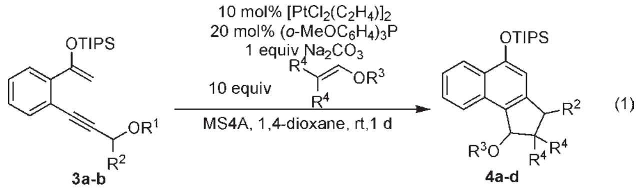
entry	R^1	R^2	R^3	R	R′	yield (%)[a]
1	*t*-Bu	H	H	H	H (**1a**)	79 (**2b**)
2	*c*-Hex	H	H	H	H (**1a**)	88 (**2c**)
3	$-(CH_2)_2Cl$	H	H	H	H (**1a**)	70 (**2d**)
4	PMB	H	H	H	H (**1a**)	82 (**2e**)
5	$-(CH_2)_2-$		H	H	H (**1a**)	63 (**2f**)
6[b]	Et	Me	H	H	H (**1a**)	70 (**2g**)[c]
7	Et	Me	Me	H	H (**1a**)	73 (**2h**)
8	*n*-Bu	H	H	Me	H (**1b**)	68 (**2i**)[d]
9	*n*-Bu	H	H	H	MeO (**1c**)	67 (**2j**)
10	*n*-Bu	H	H	H	F(**1d**)	80 (**2k**)

[a] Isolated yield. [b] $PtCl_2$ (5 mol %) was used as catalyst. [c] Diastereomer ratio 66:34 determined by ^1H NMR. [d] Diastereomer ratio 4:1 determined by ^1H NMR.

deprotonation from the ammonium nitrogen, then occurred to give unsaturated carbene complex **C**. Nucleophilic attack of *n*-butyl vinyl ether to the β-carbon of the α,β-unsaturated carbene moiety generated alkenyl metallic intermediate **D**, which underwent intramolecular nucleophilic attack onto the oxonium carbon to afford the final product **2a** with regeneration of the catalyst. It should be noted that there is no general method for the [3+2] cycloaddition reaction with electron-rich alkenes[6−8] of unsaturated carbene complexes generated catalytically, based on the electrophilic activation of alkynes.

The generality of this tricyclic indole synthesis[12] is quite high, and various alkyl vinyl ethers, such as *tert*-butyl and *p*-methoxybenzyl vinyl ethers (Table 1, entries 1−4) and di- and trisubstituted vinyl ethers (Table 1, entries 5−7), reacted smoothly to afford the corresponding substituted tricyclic indoles in good yield.[13] Furthermore, aniline derivatives having a methyl substituent at the propargylic position **1b** and an electron-donating or -withdrawing group on the aromatic ring **1c** or **1d** could also be employed as substrate to give the corresponding tricyclic indoles **2i**, **2j**, and **2k** in good yield (Table 1, entries 8−10).[13]

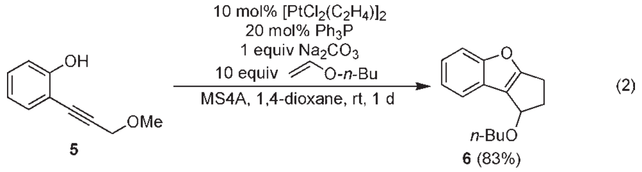
Furthermore, substrates containing other kinds of nucleophilic parts could also be employed in this reaction. When the substrates **3** having a silyl enol ether as carbon nucleophile were applied to this reaction, a variety of naphthol derivatives **4**, fused with a five-membered ring, were obtained in good yield (eq 1).[13,14] Even phenol derivative **5** gave the corresponding benzofuran derivative **6** in 83% yield (eq 2). Therefore, this reaction could be applied to propargyl ethers containing a nucleophilic moiety in general for the efficient synthesis of various polycyclic compounds.



3a (R^1 = Me, R^2 = H)
3b (R^1 = Et, R^2 = OEt)

4a (R^2 = H, R^3 = *n*-Bu, R^4 = H, Yield 82%) from **3a**
4b (R^2 = H, R^3 = PMB, R^4 = H, Yield 60%) from **3a**
4c (R^2 = H, R^3 = Et, R^4 = Me, Yield 79%)[a] from **3a**
4d (R^2 = OEt, R^3 = *n*-Bu, R^4 = H, Yield 62% (*one isomer*))[a] from **3b**

[a] 100 °C, 3 h.



In conclusion, we have developed a Pt(II)-catalyzed generation of unsaturated carbene complex intermediates from various propargyl ether derivatives based on electrophilic activation of alkynes. These *in situ* generated unsaturated carbene complexes undergo [3+2] cycloaddition reaction with various vinyl ethers as a two-carbon unit, leading to efficient formation of indoles, naphthols, and benzofuran fused with a five-membered ring in high yields.

■ ASSOCIATED CONTENT

Supporting Information. Preparative methods and spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Recently, [3+2] cycloaddition reaction with electron-deficient alkynes of α,β-unsaturated carbene complexes generated catalytically from propargyl esters using Rh(I) catalyst based on electrophilic activation of the alkyne moiety was reported: Shibata, Y.; Noguchi, K.; Tanaka, K. *J. Am. Chem. Soc.* **2010,** *132*, 7896–7898.

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(13) The relative configuration of **2g**, **2i**, and **4d** could not be determined by NOE measurement.

(14) When this reaction was performed by using PPh_3 instead of tris(*o*-$MeOC_6H_4$)$_3$P, **4a** was obtained in 73% yield.