Synthetic Methods

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Intramolecular Huisgen-Type Cyclization of Platinum-Bound Pyrylium Ions with Alkenes and Subsequent Insertion into a Benzylic C–H Bond**

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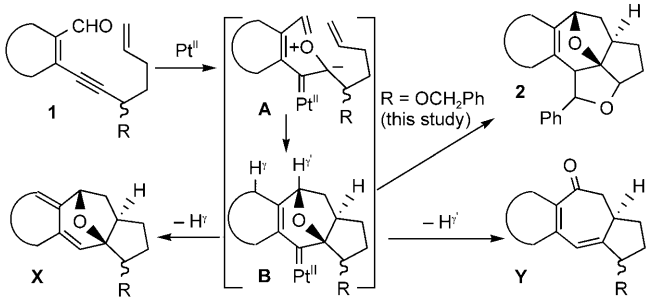
The discovery of new and efficient synthetic routes to polycycles containing a central seven-membered carbocycle is still an important challenge for organic and medicinal chemists, as numerous natural products, including taxol and its analogues, have a core skeleton of this type.[1] Among the various strategies for the construction of seven-membered carbocycles, cycloaddition routes ([4+3] or [5+2]) are particularly attractive because of their inherent potential for causing a rapid increase in skeletal complexity.[2] During the course of our scientific endeavors to develop a general and modular route to seven-membered-ring-containing natural products, we observed a unique reactivity of platinum–carbene complexes **B** (Scheme 1) formed through a Huisgen-type [3+2] cycloaddition between a metal-bound pyrylium ion and an alkene side chain.[3]

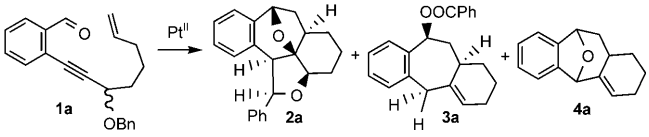
Platinum–pyrylium intermediates **A** with a double bond in their side chain underwent [3+2] cycloaddition to form platinum–carbene complexes **B**, the deprotonation of which at the γ position in the presence of a basic solvent, followed by protodemetalation, provided dienes **X**. Alternatively, deprotonation at the γ′ position (removal of a proton from the CH center bonded to the oxygen atom) led to oxidative fragmentation of the pyrylium ring, and subsequent protodemetalation afforded ketones **Y** (Scheme 1).[4] In the light of these previous investigations, we were prompted to consider the insertion of the highly electron deficient carbene in complex **B** into a specific C–H bond. Herein we report a Pt-catalyzed domino process involving a Huisgen-type [3+2] cyclization and subsequent insertion of the proposed platinum–carbene intermediate into a benzylic bond to form furans of type **2**.

We designed the substrate **1a** as a model compound to study the trapping of the Pt–carbene complex by C–H insertion.[5] Substrate **1a** with a benzyloxy substituent at the propargylic position was prepared by the Sonogashira coupling of 2-bromobenzaldehyde with 3-benzyloxy-7-octen-1-yne.[6] The versatility of catalytic reactions with substrate **1a** was explored under various conditions (Table 1).



Scheme 1. Three possible reaction pathways for the platinum–carbene complex **B**.

Table 1: Metal-catalyzed reactions of enynal **1a**.[a]



Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	Products (yield [%])
1	$PtCl_2$	toluene	120	1	**2a** (25), **4a** (35)
2	$PtCl_4$	toluene	120	1	**2a** (20), **3a** (40)
3	$PtCl_2$	*p*-dioxane	60	3	**2a** (35), **4a** (10)
4	$PtCl_2$	DCE	80	5	**2a** (20), **4a** (40)
5	$[Pt(PPh_3)_4]$	toluene	120	12	**2a** (20)
6	$[PtCl_2(PPh_3)_2]$	toluene	120	4	**2a** (77)
7	$[PtCl_2(PPh_3)_2]$	*p*-dioxane	60	3	**2a** (30), **4a** (25)
8	$[PtCl_2(PPh_3)_2]$	DCE	80	12	**2a** (20), **3a** (50)
9	$[PtCl_2(dppe)]$	toluene	120	1	**2a** (61), **3a** (10)

[a] Catalyst loading: 5 mol%. Bn = benzyl, dppe = 1,2-bis(diphenylphosphanyl)ethane.

When **1a** was treated with $PtCl_2$ at 120°C in toluene for 1 h, the reaction afforded two products, **2a** and **4a**, in 25 and 35% yield, respectively (Table 1, entry 1). In the presence of $PtCl_4$ under similar reaction conditions, **3a** was isolated instead of **4a** in 40% yield, along with **2a** (20%; Table 1, entry 2). Interestingly, when $PtCl_2$ was used as the catalyst in *p*-dioxane, the insertion product **2a** was formed as the major product (35%; Table 1, entry 3), whereas **4a** was obtained as the major product (40%) when the reaction was carried out with the same catalyst in 1,2-dichloroethane (DCE) at 80°C (Table 1, entry 4). The Pt^0 complex $[Pt(PPh_3)_4]$ showed very weak catalytic activity, with product **2a** formed in only 20%

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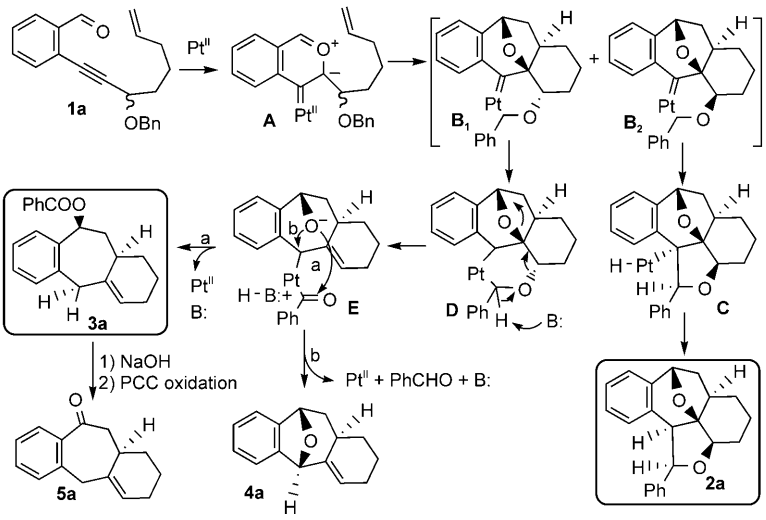
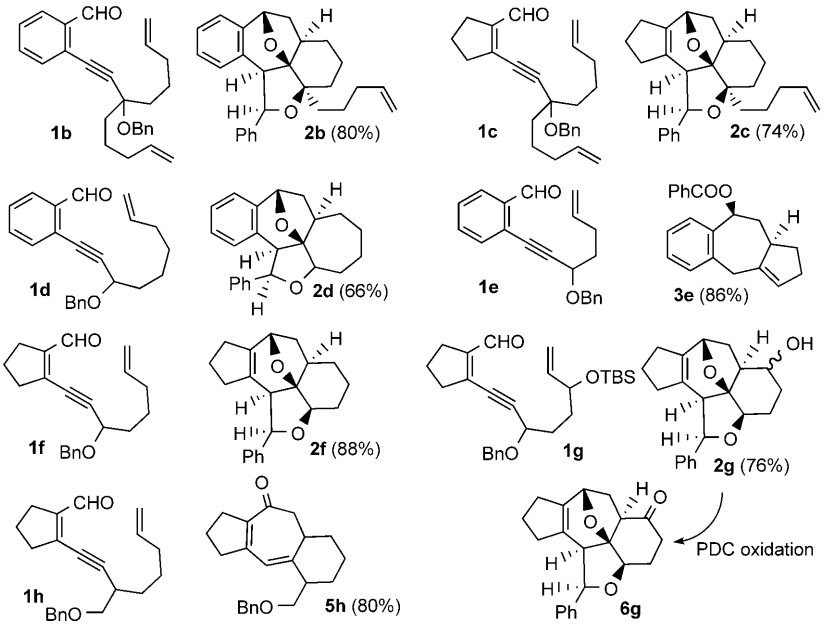
yield (Table 1, entry 5). $[PtCl_2(PPh_3)_2]$ proved to be the catalyst of choice: When **1a** was treated with this catalyst in toluene at 120 °C, **2a** was formed in excellent yield (77 %; Table 1, entry 6). In the solvents *p*-dioxane and DCE, treatment with $[PtCl_2(PPh_3)_2]$ furnished **2a** along with **4a** and **3a**, respectively (Table 1, entries 7 and 8). These results are similar to those observed under the same conditions with PtC_2 (Table 1, entries 3 and 4). Finally, $[PtCl_2(dppe)]$ also catalyzed this reaction to afford **2a** and **3a** in 61 and 10 % yield, respectively.

The formation of **2a**, **3a**, and **4a** can be understood by considering two different modes of C–H insertion of the platinum–carbene intermediates $\mathbf{B_1}$ and $\mathbf{B_2}$, which are presumably formed by a Huisgen-type [3+2] cyclization of a platinum-bound pyrylium ion with an alkene side chain (Scheme 2). The platinum–carbene moiety in the intermediate $\mathbf{B_2}$ can undergo insertion into the benzylic C–H bond to construct the intermediate **C**, which would be converted into the product **2a** upon the regeneration of the platinum catalyst. Alternatively, if the platinum complex **D** derived from $\mathbf{B_1}$ is taken into consideration as an intermediate, the formation of the two products **3a** and **4a** can be explained simultaneously. Complex **D** might be formed through the opposite mode of insertion of the Pt–carbene into the benzylic C–H bond. A base, expected to form from the solvent at high temperature, might abstract a proton from the benzylic position of **D**. Fragmentation would follow to provide the benzoyl platinum complex **E**, which could undergo transformation by two possible pathways, depending on the orientation of the PhCOPt group and the activation energy available under the specific reaction conditions. The proximity between the alkoxy oxygen atom (or its protonated hydroxy group) and the benzoyl group in a *cis* relationship would result in transfer of the benzoyl group by path a and subsequent protolysis to provide **3a**.[7] The other isomer of **E** with a *trans* relationship between these two groups, however, could undergo internal S_N2-type attack by the oxygen nucleophile to furnish the product **4a** and benzaldehyde as a fragmentation product. The structure of the unusual product **3a** was confirmed by chemical modification: The hydrolysis of **3a** by aqueous NaOH, followed by oxidation with PCC, gave the corresponding ketone **5a**.



Scheme 2. A possible mechanism for the formation of **2a** and **3a**. PCC = pyridinium chlorochromate.



Scheme 3. Products **2** of platinum-catalyzed cyclization, and the corresponding substrates **1**. PDC = pyridinium dichromate, TBS = *tert*-butyldimethylsilyl.

Various substrates were subjected to the optimized reaction conditions for the formation of **2a** to explore the scope and limitations of this process (Scheme 3). The substrates **1b** and **1c**, with two 4-pentenyl groups attached to the propargylic carbon atom, were designed and prepared to investigate competition between cyclopropanation and insertion of the carbene.[8] These compounds were shown to have a higher propensity to undergo insertion over cyclopropanation to afford **2b** and **2c** in 80 and 74 % yield, respectively. It is significant that non-aromatic cyclopentene-linked substrate **1c** was also transformed successfully. Substrate **1d**, with a 5-hexenyl group on the propargylic carbon atom, also underwent a cyclization–insertion process to produce **2d**. However, the treatment of **1e**, which contains a 3-butenyl group, under our optimized conditions provided only the tricyclic benzoate ester **3e** in 86 % yield, rather than

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the product of carbene insertion. The present procedure can be extended to similar systems. Thus, **1f** and **1g** were prepared according to known procedures[9] and converted into the corresponding products **2f** and **2g** (after desilylation with tetrabutylammonium fluoride (TBAF) in THF) in 88 and 76% yield, respectively. Finally, **1h**, a homologue of **1f**, underwent γ′ elimination rather than C–H insertion under various conditions to give the ketone **5h** in 80% yield; no product of C–H insertion at the ε position was observed.

Although these reactions involve a multistep process, all products **2** were formed with high stereoselectivities and high efficiency. To confirm the relative configuration of the products, we oxidized **2g** to the corresponding ketone **6g** with PDC. The X-ray crystal structure of **6g** is shown in Figure 1.[10]

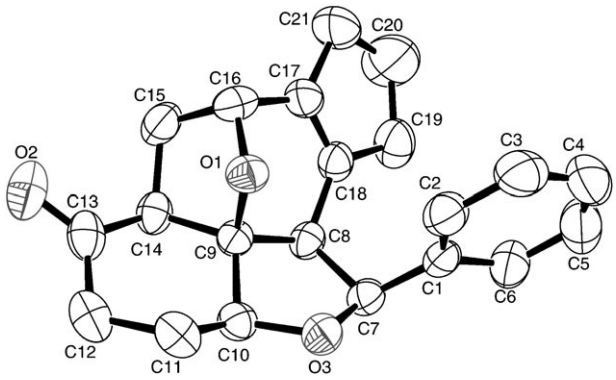

Figure 1. X-ray crystal structure of **6g**.

In conclusion, enynals **1** with a terminal alkene double bond in side chain underwent cyclization through a Huisgen-type [3+2] cycloaddition in the presence of a platinum catalyst to give a tetracyclic platinum–carbene complex of type **B** (Scheme 2). This intermediate undergoes C–H insertion at the δ position to afford highly complex products of type **2** that are difficult to access by other means.

Experimental Section

The enynal (**1a**–**h**; 0.10 mmol), $[PtCl_2(PPh_3)_2]$ (5 mol%), and the dry solvent (0.5 mL) were placed in a new 5 mL test tube at 0°C. The reaction mixture was stirred under an argon atmosphere in a preheated oil bath (60–120°C) for 1–12 h. Upon completion of the reaction (as indicated by TLC), the solvent was removed under vacuum. Flash column chromatography of the residue afforded the pure product(s). In the case of product **2g**, the reaction mixture was cooled to 0°C after completion of the reaction and treated with a solution of TBAF (1.0 M, 1.0 mmol) in THF. Extractive workup and flash chromatography gave the desilylated compound **2g** as a diastereomeric mixture in 76% combined yield. To obtain a crystal for X-ray crystallographic analysis, the alcohol **2g** was oxidized with PDC (2 equiv) in dichloromethane. Filtration over celite and flash chromatography gave the ketone **6g** (72%).

2a: IR (NaCl): $\tilde{\nu}$ = 3024, 2932, 2853, 1488, 1453, 1075, 996 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.21 (m, 2H), 7.05–6.99 (m, 3H), 6.88–6.82 (m, 2H), 6.72 (td, J = 7.2, 2.0 Hz, 1H), 6.47 (d, J = 8.0 Hz, 1H), 5.35 (d, J = 10.0 Hz, 1H), 5.10 (dd, J = 6.0, 3.0 Hz, 1H), 3.88 (t, J = 8.4 Hz, 1H), 3.39 (d, J = 10.0 Hz, 1H), 2.29–2.24 (m, 1H), 2.03–1.89 (m, 5H), 1.82–1.76 (m, 1H), 1.48–1.36 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 139.0, 132.2, 130.8, 129.3, 127.3, 127.2, 125.8, 125.3, 122.2, 86.5, 84.0, 80.4, 75.7, 50.4, 42.3, 40.2, 31.8, 23.6, 23.3 ppm; HRMS: m/z calcd for $C_{22}H_{22}NaO_2$: 341.1517 $[M+Na]^+$; found: 341.1515.

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[7] The identity of all products was confirmed by FTIR, ^1H NMR, and ^{13}C NMR spectroscopy and HRMS, and further supported by the X-ray crystal structure of **6g**. The structure of **3a** was confirmed further by chemical transformations.

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[10] CCDC 697658 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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