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1,3-Dipolar cycloaddition of 4-platinumisochromenyliums with an olefin and tandem insertion into benzylic C–H bonds†

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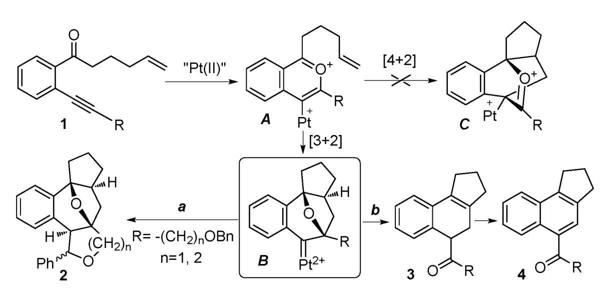
Isochromenylium-4-ylplatinum(II) species, generated from 1-(2-alkynylphenyl)hex-5-en-1-ones and Pt(II), reacted with a pendant olefin *via* [3+2] cycloaddition to form tetracyclic Pt–carbene complexes, which underwent C–H insertion with a benzyloxy group at δ or ε positions to give highly complex polycycles, which are otherwise hard to access.

The development of new and efficient methodologies for the formation of medium sized carbocycles is still challenging due to entropic and enthalpic factors.[1] Among them, the synthesis of 7-membered carbocycles has drawn attention due to their presence as core skeletons in natural products.[2] Various strategies for the construction of 7-membered carbocycles include cycloaddition routes (4+3 or 5+2),[3] as some of the popular methods, while we mainly deal with the [3+2] mode of cycloaddition.[4,5] During our efforts toward an efficient synthesis of 7-membered ring-containing polycyclic compounds, we have long studied chemistry of 2-(enynyl)benzaldehydes towards transition metal catalysts and reported a highly unique behaviour of metal–carbene complexes.[6]

Compared to 2-(enynyl)benzaldehydes, the corresponding enynones (like **1**) are electronically similar but sterically different when these are activated with alkynophilic metal cations.[7] Yamamoto and co-workers also investigated Cu-catalyzed reactions of enynones like **1** to isolate the benzannulation products like **3** exclusively.[8] Based on our study, a hypothesis was made that incorporation of a benzyloxy group into enynones could afford the insertion products **2** *via* their metal-catalyzed cyclizations. Thus, we have focussed on the Pt catalysis, mainly intercepting Pt–carbene species **B** as intermediates derived from **1** (Scheme 1). The competitive formation of three different products (**2–4**) *via* paths a and b could be possible by considering the involvement of intermediate **A**. It is reasonable to assume that the electrophilic activation of alkynes toward nucleophilic attacks by carbonyl oxygen might have occurred through coordination of Pt(II) to the triple bond, facilitating the formation of isochromenylium **A**. Although the intermediate **C** was proposed to explain the formation of **3**, mechanistically all the products could be rationalized from the intermediates **B**, implying that the intermediates **A** undergoes [3+2] cycloaddition to form **B**, rather than [4+2] cycloaddition.[9] Although a number of reactions terminating in C–H insertion of metal carbenes are known, the investigation of their application in the synthesis of polycycles containing 7-membered rings is still in demand.[10] Herein, we wish to report an efficient synthetic method involving Pt–carbene species leading to the complex polycyclic compounds.



Scheme 1 Plausible mechanism for the formation of products **2–4**.

The platinum-catalyzed cyclization of enynones **1a–d** was explored to optimize the reaction conditions for efficient C–H insertion of the intermediates **B**. Interesting trends were observed for **1a–c** with a benzyloxymethyl group (Table 1). While a mixture of **2a** and **4a** was obtained in 1,2-dichloroethane and methylene chloride for **1a** with a benzyloxy group at the propargylic position, only **2a** without formation of **4a** was obtained in THF and toluene in the presence of a $PtCl_2$ catalyst (entries 1–4). $PtCl_4$, which is cationic in nature, was also proved to give **2a** as the sole product. In all cases, **2a** was obtained as a 1 : 3 (α : β) diastereomeric mixture.[11] When $PtCl_2(PPh_3)_2$ was used as a catalyst, **3a** was obtained as the major product along with **2a** and **4a** in small amounts (entry 6). Substrate **1b**, a one carbon homolog of **1a**, was found to undergo C–H insertion even more readily, forming tetrahydropyran in the $PtCl_2$-catalyzed reaction to afford **2b** selectively (entry 7). Changing the catalyst to $PtCl_2(PPh_3)_2$ facilitated the formation of **3b** as the sole product, which is consistent with the

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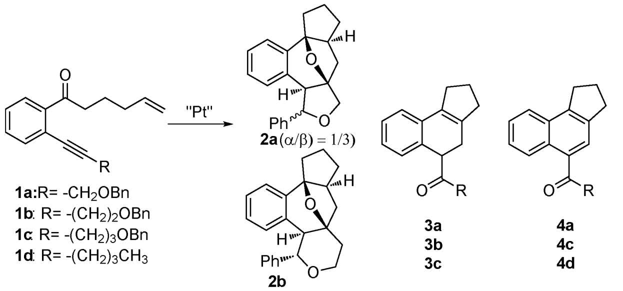
Table 1 Platinum-catalyzed cyclization of enynones **1a–d**



Entry	1	Catalyst[a]	Solvent/T (°C)/t (h)	Products (yield (%))
1	**1a**	$PtCl_2$	DCE/60/2	**2a**/**4a** (53/25)
2	**1a**	$PtCl_2$	MC/60/2	**2a**/**4a** (61/10)
3	**1a**	$PtCl_2$	THF/25/2	**2a** (65)
4	**1a**	$PtCl_2$	Toluene/25/2	**2a** (76)[b]
5	**1a**	$PtCl_4$	Toluene/25/2	**2a** (72)
6	**1a**	$PtCl_2(PPh_3)_2$	Toluene/100/2	**2a**/**3a**/**4a** (15/56/16)
7	**1b**	$PtCl_2$	Toluene/25/1	**2b** (80)
8	**1b**	$PtCl_2(PPh_3)_2$	Toluene/100/1	**3b** (76)
9	**1c**	$PtCl_2$	Toluene/60/2	**3c**/**4c** (40/42)
10	**1c**	$PtCl_2$	MC/25/24	**3c**/**4c** (35/49)
11	**1c**	$PtCl_2$	THF/25/24	**3c**/**4c** (32/52)
12	**1c**	$PtCl_4$	Toluene/25/24	**3c**/**4c** (44/29)
13	**1c**	$PtCl_2(PPh_3)_2$	Toluene/100/1	**3c**/**4c** (68/14)
14	**1d**	$PtCl_2$	Toluene/25/1	**4d** (78)

[a] Catalyst loading: 5 mol%. [b] **3a** was obtained as a 1 : 3 (α : β) mixture; DCE = 1,2-dichloroethane; MC = methylene chloride.

aforementioned observations (entry 8). The drastic variation with a change in catalytic conditions which distinguishes the formation of **2** and **3** was unsolved, presumably due to the low electrophilicity of $PtCl_2(PPh_3)_2$. The catalyst specifically promoted the abstraction of protons *anti* to the C–O bond from intermediate **B**, finally making the 1,2-alkyl migration feasible,[12] followed by protodemetallation to give dihydronaphthalenes (**3a** and **3b**). Otherwise, $PtCl_2$, which is far less basic, subsides the proton abstraction, resulting in intramolecular benzylic C–H insertion of the intermediate **B**. $PtCl_2$-catalyzed conditions for the two carbon homolog **1c** led to the formation of **3c** and **4c**, while $PtCl_2(PPh_3)_2$ in toluene afforded **3c** as a major product in 68% yield along with 14% of **4c** (entries 9–13). The application of $PtCl_4$ could also initiate C–H insertion, finally affording **4c** and **5c**. It is noteworthy that none of the reaction conditions for **1c** could afford the type-**2** product generated from C–H insertion of the Pt–carbene intermediate (**B**), instead a type-**3** product was formed and oxidized to **4** under reaction conditions, affording a mixture of products. Substrate **1d**, carrying a butyl group instead of a benzyloxy methyl group, had no chance to undergo C–H insertion and finally resulted in **4d** in 78% yield (entry 14). From these results it is clear that the Pt–carbene species **B** could not undergo C–H insertion in the substrates in which either the benzyloxy group was missing (**1d**) or located far away from the triple bond (**1c**).

Encouraged by this challenging outcome, we proceeded further with a set of similar substrates (**1e–n**), different from each other either electronically or sterically, and examined the mode of reaction toward Pt(II) catalysts (Fig. 1 and Table 2). Our standard condition, 5 mol% of $PtCl_2$, was employed for all the substrates. It should be noted that the formation of products from the intermediates **B** was affected by the nature of substituents. It was interesting to find the pronounced substituent effect in the *p*-methoxy derivative (**1e**), which dictated the formation of **2e** as a major product. Attempts to isolate **2e** using various Pt catalysts (for example, $Pt(acac)_2$, $PtCl_4$, and $Pt(PPh_3)_4$) resulted in failure, while $PtCl_2(PPh_3)_2$ still afforded **3e**. However, the *m*-methoxy derivative (**1f**) afforded the desired product **2f**. Both **1g** and **1h** provided **2g** and **2h**, respectively. With such dramatic selectivity changes, we further extended the study to **2i** and **2j** in which the anchoring benzene was replaced by naphthalene. Products **3i** and **3j** were isolated, respectively. Notably, the methoxy group did not interrupt the formation of **3j**, implying the feasibility of C–H insertion.

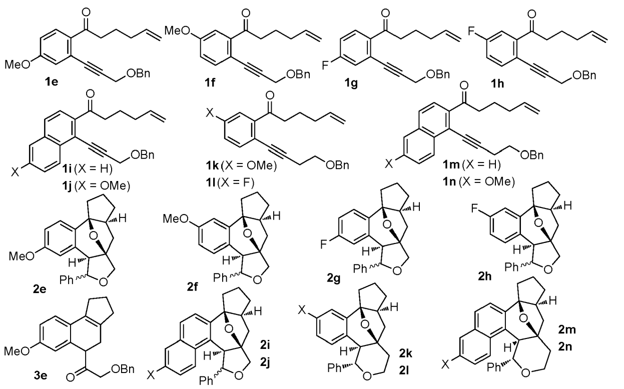


Fig. 1 $PtCl_2$-catalyzed cyclization of enynones (**1e–n**); **2f–j** were obtained as a 1 : 3 (α : β) mixture and separated by HPLC for characterization.

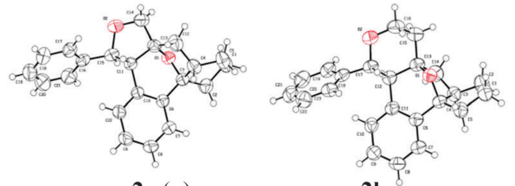
Next, we screened a series of 1-carbon homologs (**1k–n**) of **1a**. To our greatest surprise, all the enynones (**1k–n**) underwent C–H insertion at the ε position, resulting in the formation of the corresponding pyran type products in good yield as almost the indicated isomers (**2k–n**). The relative configuration of both the furan and pyran type products was confirmed by the X-ray crystal structure with the minor isomers **2a** (α) and **2b** (Fig. 2).[13]

During this study, it was hard to understand why **1e** exhibited discrimination in the mode of reaction toward Pt catalysts, when compared to **1a**. The intermediate **B** could undergo either C–H insertion at the benzylic position to give type-**2** products or abstraction of protons following an alkyl-shift to give type-**3** products (Scheme 2). Thus, the corresponding methyl substituted derivatives **1o** and **1p** of **1a** and **1e** were examined with a hope that the deprotonation in the first step could be blocked,

Table 2 $PtCl_2$-catalyzed cyclization of enynones **1e–n**

Substrates	T (°C)/t (h)	Products[a] (α/β ratio)	Yield (%)
1e	60/2	**2e**	46[b]
1f	25/6	**2f** (1 : 3)	75
1g	60/2	**2g** (β only)	71
1h	25/6	**2h** (1 : 3)	70
1i	25/12	**2i** (1 : 3)	48
1j	60/24	**2j** (1 : 3)	55
1k	25/1	**2k**	75
1l	25/1	**2l**	78
1m	25/24	**2m**	50
1n	25/24	**2n**	65

[a] The α : β ratios were determined by ^1H NMR analyses. [b] 76% of **3e** was isolated when using 5 mol% of $PtCl_2(PPh_3)_2$ in toluene.

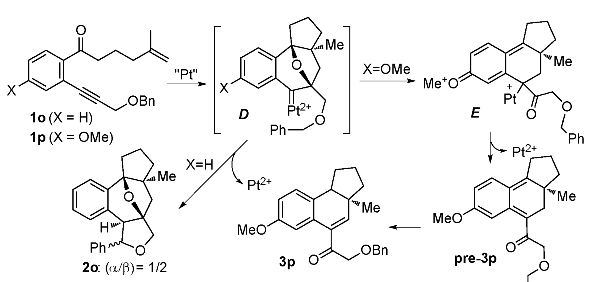


2a (α) 2b

Fig. 2 X-ray structures of **2a** and **2b**.

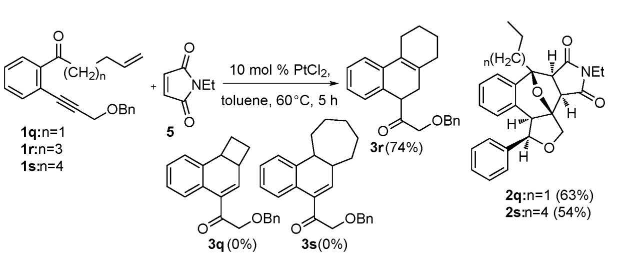
eventually preventing the formation of products as a result of alkyl migration. Although **1o** furnished the expected **2o** as a mixture of diastereomers ($\alpha:\beta = 1:2$) in 62% yield, **2p** still afforded a 1 : 1 mixture of **pre-3p** and **3p** in 79% yield. Due to the substituent effect in the *p*-methoxy derivative (**1p**) of **1o**, its reaction would proceed *via* an intermediate **E** to afford **pre-3p** selectively and then its rearranged product **3p**. The isolation of **pre-3p** in addition to **3p** approved the mechanistic interpretation.

Three more homologs **1q–s**, different from **1a** in the chain length, were examined for the competitive occurrence of intra- and inter-molecular cycloaddition. While **1r** underwent intramolecular cycloaddition, followed by alkyl shift to give **3r** exclusively, neither **1q** nor **1s** could afford either type-**2** or type-**3** product (Scheme 3). The reason for selectivity might be the fact that **1r** ($n = 3$) has to form a stable 6-membered intermediate to afford thermodynamically stable **3r** in 74% yield whereas **1q** and **1s** would require the formation of more strained 4- and 7-membered intermediates. However both **1q** and **1s** underwent intermolecular cycloaddition with *N*-ethylmaleic imide (**5**) following C–H insertion to afford **2q** and **2s**, respectively. **2q** and **2s** were each obtained as a single diastereomer. The finding that **1q** and **1s** formed the isochromenylium intermediates and further underwent intermolecular cycloadditions with an external dipolarophile **5** to give the corresponding **2q** and **2s**, while **1r** preferred intramolecular cycloaddition, is valuable.



Conditions **1o**, $PtCl_2$, toluene, 80 °C, 2 h; **1p**, $PtCl_2(PPh_3)_2$, 100 °C, 10 h

Scheme 2 Possible mechanism for the formation of **2o** and **3p**.



Scheme 3 Intramolecular *vs.* intermolecular cyclization of enynones.

In conclusion, the competitive occurrence of C–H insertion of platinum isochromenyliums over an alkyl shift has been highlighted. Enynones **1a–s** underwent Huisgen-type cycloaddition with an alkene to give the tetracyclic platinum–carbene complex **B**, which could form both tetrahydrofuran and tetrahydropyran *via* C–H insertion at δ or ε positions to give highly complex O-bridged polycycles, which are otherwise hard to access.

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