Selective Construction of Aliphatic Polycycles Utilizing Platinum-Catalyzed Cyclization of 2-(Enynyl)cycloalkenals

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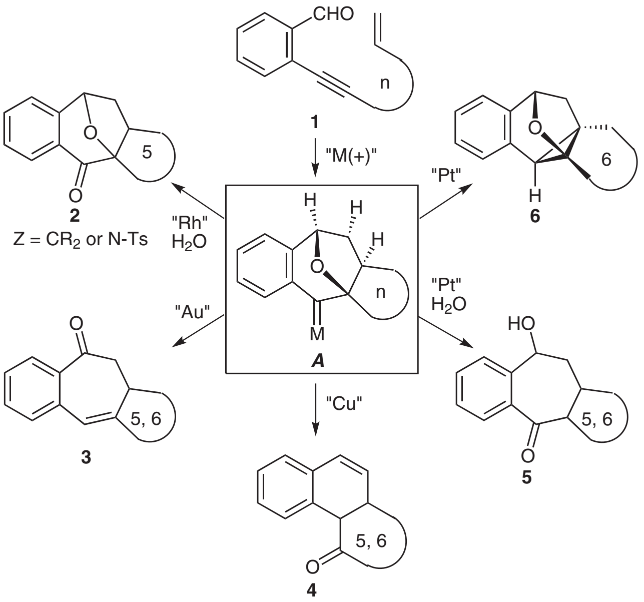
Abstract: An efficient method for the selective construction of aliphatic polycycles through platinum-catalyzed cyclization of 2-(enynyl)cycloalkenals has been developed by considering electronic (ligand) and structural (olefinic tether) effect. The presence or absence of ligand and the length of olefinic tether determine the course of the reaction after the formation of platinum–carbene complex, so that four types of aliphatic polycycles can be formed selectively.

Key words: cyclization, homogeneous catalysis, platinum, carbenes, carbocycles

Conjugated enynals serve versatile substrates for the synthesis of [m,7,n]-tricyclic skeletons via metal-catalyzed reactions[1] since those readily form metal–pyrylium intermediates which undergo cycloaddition with an alkene inter- and/or intramolecularly.[2] Such [m,7,n]-tricyclic structural motifs are found in a variety of natural products, many of which have very challenging structures and a broad spectrum of biological activities.[3] We have been interested in constructing [m,7,n]-tricyclic skeletons bearing a central seven-membered ring. Among various strategies for the construction of seven-membered carbocycles,[4] transition metals are utilized as catalysts because of their inherent potential for causing a rapid increase in skeletal complexity.[5] During the course of our scientific endeavors leading to a general and modular entry to polycycles, we have reported a highly unique behavior of metal–carbene complexes **A**, formed via a Huisgen-type [3+2] cycloaddition between metal–pyrylium species and a double bond (Scheme 1).[6] In the substrates involving an aromatic ring such as 2-enynylbenzaldehydes, we observed a variety of polycycles depending on the type of substrates, catalysts, and reaction conditions. First, 2-(6-en-1-ynyl)benzaldehydes (**1**, n = 5) would form the metal–carbene intermediates **A** in the presence of transition-metal cations: 1) $[Rh(COD)Cl]_2$ (5 mol%) and dppp (10 mol%) in refluxing wet xylene yielded the type **2** products;[7] 2) $AuBr_3$ in 1,2-dichloroethane (DCE) yielded the type **3** products;[8] 3) $Cu(OTf)_2$ yielded the type **4** products;[9] 4) $PtCl_2$ in wet toluene yielded the type **5** products.[10] Second, 2-(7-en-1-ynyl)benzaldehydes (**1**, n = 6) would form the metal–carbene intermediates **A** in the presence of transition-metal cations: 1) $AuBr_3$ in DCE yielded the type **3** products; 2) $Cu(OTf)_2$ yielded the type **4** products; 3) $PtCl_2$ in wet toluene yielded the type **5** products; 4) $PtCl_2$ in toluene yielded the type **6** products.[11]



Scheme 1 Metal-catalyzed cyclization of 2-enynylbenzaldehydes **1**

These results could provide an interesting approach, not only for simple fused polycycles but also for the synthesis of complex natural products, which have a core skeleton of seven-membered carbocycles.[12] However, in the majority of cases, it has been necessary to use aromatic substrates for the efficient formation of the pyrylium species.[13]

In the line of our extension of this protocol, we turned our attention to the aliphatic version using 2-(enynyl)cycloalkenals **7** (Scheme 2). Previously, we have reported a preliminary result that both 2-(6-en-1-ynyl)cycloalkenals and 2-(7-en-1-ynyl)cycloalkenals underwent cyclization into the corresponding tricycles **8** having a diene group when $PtCl_2(PPh_3)_2$ was used as a catalyst.[14] Note that the intermediate **A** could be rearranged into the [m,6,6]-tricycle **9**. In continuing study, we found that 2-(7-en-1-ynyl)-cycloalkenals catalyzed into the corresponding **10** when $PtCl_2$ was used as a catalyst.[15] Here we wish to report the $PtCl_2$-catalyzed cyclization of 2-(6-en-1-ynyl)cycloalkenals into the corresponding [m,7,5]-tricycles **11** in a highly efficient manner. First of all, modes of cyclization are very sensitive to the catalytic conditions: $PtCl_2(PPh_3)_2$ in dioxane and $PtCl_2$ in toluene resulted in the formation of

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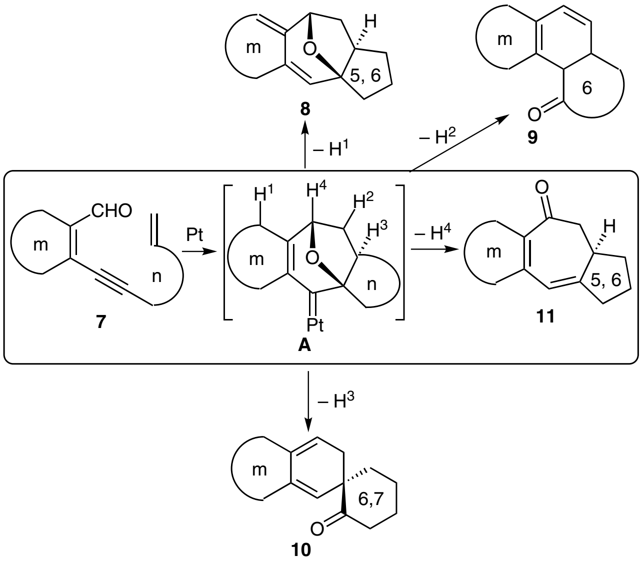
different products. The platinum cation is alkynophilic and is prone to form platinum-bound pyrylium complexes via the 6-*endo*-dig mode which would react with the pendant double bond to form the intermediate **A**.[16]

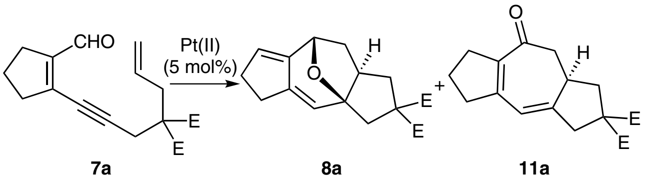


Scheme 2 Four possible reaction pathways for the platinum–carbene complex **A**

Depending on the natures of C–H bonds, intermediate **A** might undergo subsequent reactions: deprotonation (of H^1, H^2, and H^3) and subsequent fragmentations leading to **8**, **9**, and **10**, respectively. Our investigation scrutinizing a path to deprotonation of H^4 was rather achieved simply by using $PtCl_2$ as a catalyst.

Although not known deeply, platinum–carbene complexes **A**, generated by $PtCl_2$ with 2-(6-en-1-ynyl)cycloalkenals, could undergo deprotonation of H^4 to furnish the [m,7,5]-tricyclic enones **11** in excellent yields under mild conditions. We initiated our studies by focusing on the selective reactivity depending on structural aspects derived from core skeletons. In order to make a systematic construction of a core substructure such as **11**, we first designed the substrate **7a** as a simplified model compound and reexamined its cyclization reaction under a variety of platinum-catalysis conditions (Table 1). First of all, the reaction of **7a** with $PtCl_2$ as the catalyst proceeded well at 80 °C in toluene to furnish products **8a** and **11a** in 15% and 68% yields, respectively (Table 1, entry 1). However, increased temperature to 120 °C under the same conditions resulted in product **11a** in 98% yield without forming product **8a** (Table 1, entry 2). It is noted that more elevated temperature facilitates elimination of H^4 from intermediate **A** to form the carbocyclic products **11**. This reaction was also working in other solvents such as DCE and *p*-dioxane to afford product **11a** in 48% and 42% yields, respectively (Table 1, entries 3 and 4).Whereas the use of tetrahydrofuran (THF) gave product **8a** as a sole product (Table 1, entry 5). In the cases of *n*-hexane and diethyl ether, selectivity of the reaction has diminished under similar reaction conditions (Table 1, entries 6 and 7). $PtCl_4$ exhibited similar catalytic activity toward **7a** to **11a** (Table 1, entry 8). Interestingly, when $PtCl_2(PPh_3)_2$ was used as the catalyst in *p*-dioxane, diene product **8a** was

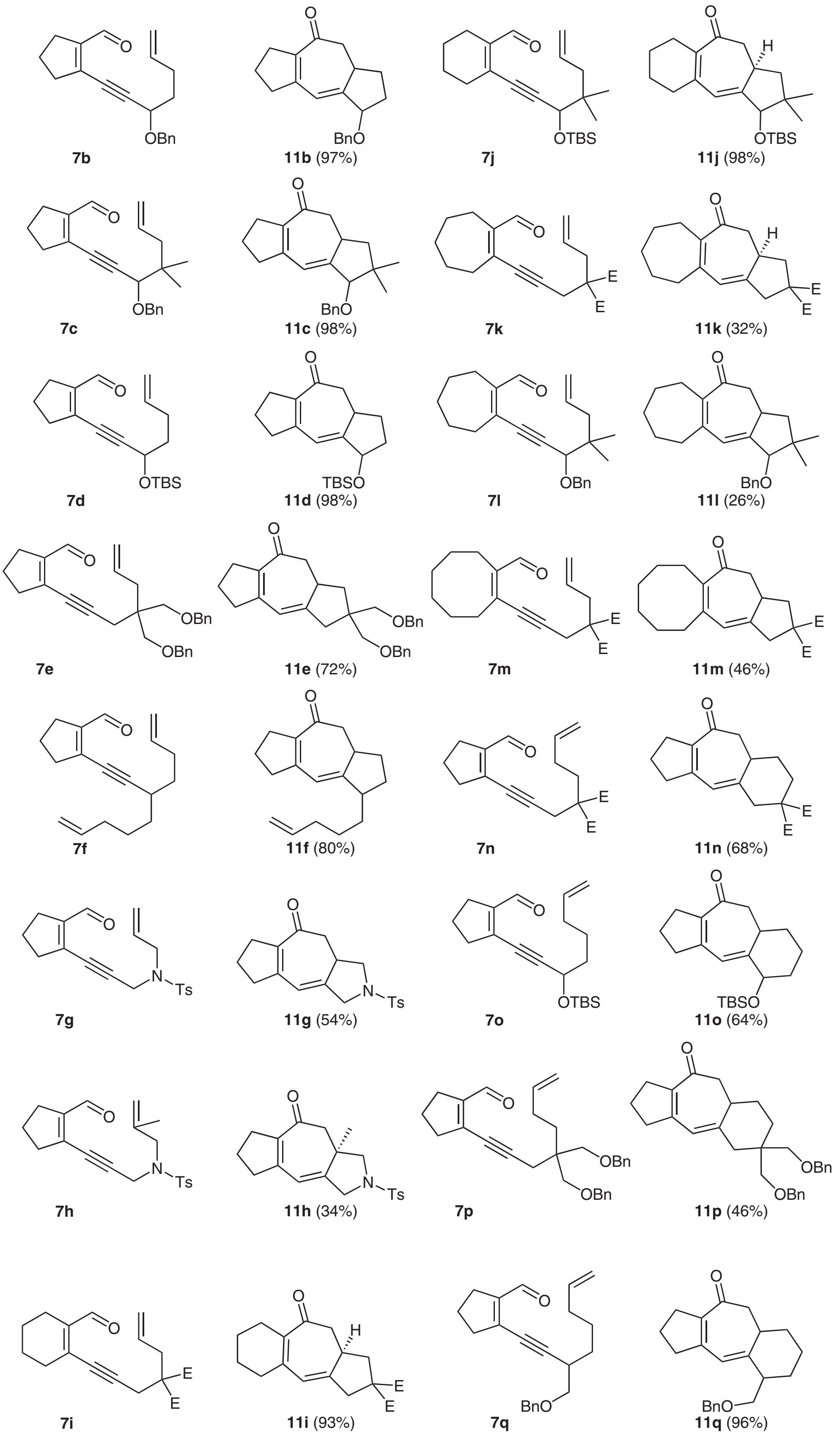
Table 1 Platinum-Catalyzed Cyclization of Enynal **7a**[a]



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield of products (%)[b]
1	$PtCl_2$	toluene	80	6	**8a** 15, **11a** 68
2	$PtCl_2$	toluene	120	1	**11a** 98
3	$PtCl_2$	DCE	100	3	**11a** 48
4	$PtCl_2$	1,4-dioxane	100	3	**11a** 42
5	$PtCl_2$	THF	100	12	**8a** 54
6	$PtCl_2$	*n*-hexane	100	12	**8a** 16, **11a** 32
7	$PtCl_2$	Et_2O	100	8	**8a** 15, **11a** 28
8	$PtCl_4$	toluene	120	1	**11a** 74
9	$PtCl_2(PPh_3)_2$	1,4-dioxane	100	2	**8a** 78
10	$PtCl_2(PPh_3)_2$	toluene	120	18	**8a** 62, **11a** 28

[a] Catalyst loading: 5 mol%, E = CO_2Et.
[b] Isolated yield.

formed as the major product (78%; Table 1, entry 9). In the treatment with $PtCl_2(PPh_3)_2$ in toluene, **8a** and **11a** were isolated in 62% and 28% yields, respectively (Table 1, entry 10).



7b **11b** (97%) **7j** **11j** (98%)

7c **11c** (98%) **7k** **11k** (32%)

7d **11d** (98%) **7l** **11l** (26%)

7e **11e** (72%) **7m** **11m** (46%)

7f **11f** (80%) **7n** **11n** (68%)

7g **11g** (54%) **7o** **11o** (64%)

7h **11h** (34%) **7p** **11p** (46%)

7i **11i** (93%) **7q** **11q** (96%)

Figure 1 Products **11** of Pt-catalyzed cyclization of substrates **7**

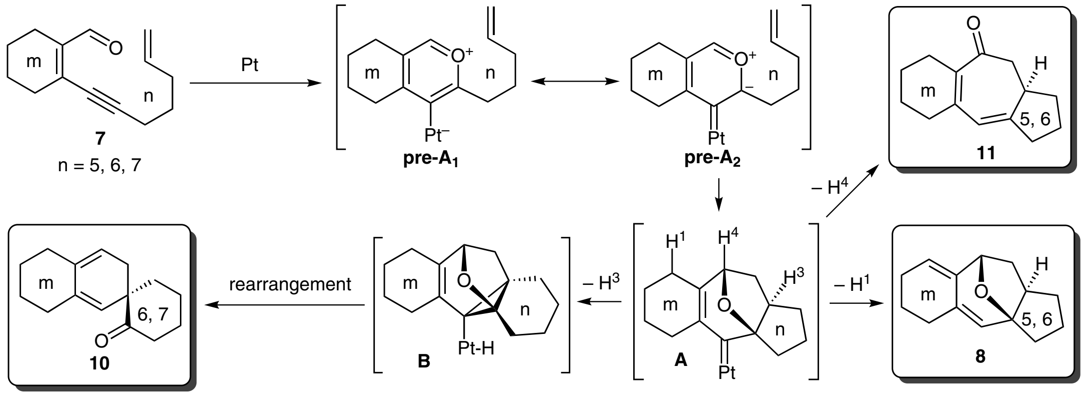
Various substrates were subjected to optimized reactions for the formation of **11a** to explore the scope and limitation of this process (Figure 1). The substrates **7b** and **7c**, with a benzyloxy group (OCH_2Ph) attached to the propargylic carbon atom, were designed and prepared to consider the insertion of the highly electron-deficient carbene in complex **A** into a benzylic bond. In the case of these compounds, elimination of H^4 occurred easier than benzylic C–H insertion and afforded **11b** and **11c** in 97% and 98% yield, respectively. It is noteworthy that rigid ring sizes in these polycyclic skeletons had a great impact an access to a core reaction site such as platinum–carbene. The treatment of **7d** and **7e**, which contains two bulky benzyl ether (CH_2OCH_2Ph) and *tert*-butyldimethylsilyl ether (OTBS) groups, under our optimized conditions provided also the corresponding carbocycles **11d** and **11e** in high yield. Substrate **7f**, having three- and four-atom tethers, was also converted into the five-membered ring (3th cycle) product **11f** without forming the six-membered cycle. Note that the formation of 5-membered cycle was more easily than six-membered cycle in cycloaddition process. Additionally, nitrogen-containing substrates **7g** and **7h** were investigated for this transformation and smoothly underwent the present reaction to afford the corresponding products **11g** and **11h**, respectively. In order to survey impact on reactivity according to ring size (1st cycle) increased from five to eight, substrates **7i**–**m** were treated with the platinum-catalyst system. The cyclization of these substrates proceeded well under suitable conditions to furnish products **11i**–**m** in good yields, respectively. Although these reactions involve several reaction pathways, all products **11** were formed with high selectivity and high efficiency. We next examined substrates **7n**–**q** with remote olefinic tethers (n = 6). At high temperatures, all substrates were converted into the products **11n**–**q** in high yields. However, reduced temperature to about 80 °C under the same conditions resulted in products **11n**–**q** with forming **10n**–**q** as minor products.

Based on the above experimental results, a possible mechanism was proposed as shown in Scheme 3. The electrophilic activation of the alkyne moiety in enynals **7** by platinum catalyst produces the platinum-bound pyrylium species pre-**A** through the attack of the carbonyl oxygen atom onto the alkyne in a 6-*endo* mode. Platinum-bound pyrylium species pre-**A** were successfully cyclized via Huisgen-type [3+2] cycloaddition to the tetracyclic platinum–carbene complexes **A**. These complexes subsequently undergo selective proton abstraction followed by elimination of H^4 to produce aliphatic carbocycles **11**. Here, the platinum catalyst in the presence of a ligand such as $PtCl_2(PPh_3)_2$ may possibly serve as an elimination of H^1 from platinum–carbene intermediate **A**. That is, electronic (ligand) effect[17] could result in selective H^1 abstraction eventually to form the oxygen-bridged dienes **8**. Increasing olefinic tether (n = 6 or larger) in enynals **7** affect the potential flexibility of platinum–carbene complexes **A** which undergo insertion into a C–H bond of the β-position to afford the fused cyclopropane intermediates **B**. Their tandem rearrangement afforded diverse types of spiranes **10** depending on the tethered alkenes of the enynals.

In conclusion, we have developed an efficient method for the selective construction of aliphatic polycycles through platinum-catalyzed cyclization of the 2-(enynyl)cycloalkenals **7** by considering electronic (ligand) and structural (olefinic tether) effect. The presence or absence of ligand and the length of olefinic tether determine the course of the reaction after the formation of platinum–carbene complex **A**, so that four types of aliphatic polycycles can be formed selectively.

To a 5 mL test tube were placed $PtCl_2$ (2.2 mg, 0.0084 mmol, 5.0 mol%) and dried toluene (1.0 mL) under argon atmosphere. To this solution was cannulated a substrate **7a** (56.1 mg, 0.168 mmol) solution in toluene (1.0 mL) over 1 min at 0 °C. The reaction mixture was sealed and stirred at 120 °C for 1 h. After the reaction was completed, the reaction mixture was cooled down to r.t., quenched with a drop of Et_3N, and concentrated under reduced pressure. The concentrated residue was then rapidly purified by flash silica gel chromatography by using a 1:10 mixture of EtOAc and hexane to give the product **11a** (54.7 mg, 98% yield) as a colorless oil. All other substrates **11b**–**q** were subjected to similar conditions with different reaction temperatures and times and specified in the Supporting Information.

Compound **11a**: IR (NaCl): 2978, 1731, 1672, 1647, 1566, 1242 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.95$ (d, $J = 2.4$ Hz, 1 H), 4.25–4.13 (m, 4 H), 3.13 (dd, $J = 2.4$, 17.2 Hz, 1 H), 3.02–2.81 (m, 2 H), 2.65–2.57 (m, 1 H), 2.54–2.39 (m, 2 H), 2.36–2.25 (m, 3 H),



Scheme 3 A possible mechanism for the formation of **8**, **10**, and **11**

2.08–1.86 (m, 3 H), 1.69–1.64 (m, 1 H), 1.27–1.21 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.21, 170.75, 170.71, 155.17, 143.68, 124.60, 122.70, 61.86, 61.82, 53.96, 44.76, 34.98, 33.50, 32.07, 31.87, 30.78, 24.97, 14.07. HRMS: *m/z* calcd for $C_{19}H_{25}O_5$ [M + H]: 333.1702; found: 333.1708.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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