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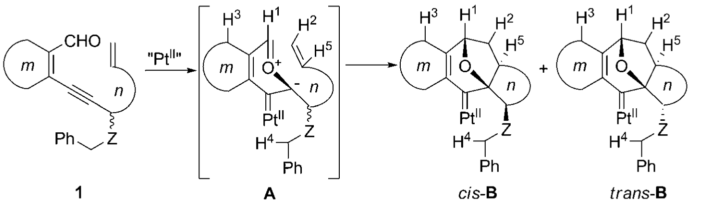
Divergent Insertion Reactions of Pt–Carbenes Generated from [3+2] Cyclization of Platinum-Bound Pyrylliums

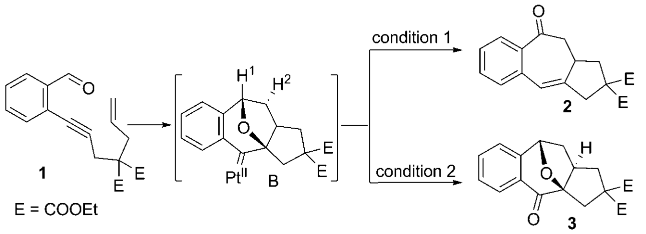
Chang Ho Oh,*[a] Ji Ho Lee,[a] Sung Min Lee,[a] Hyun Jik Yi,[a] and Chang Seop Hong[b]

Among the various synthetic strategies, which lead to polycycles containing a central seven-membered carbocycle, [4+3], or [5+2] cycloadditions are particularly attractive because of their inherent potential to achieve rapid increase in skeleton diversity.[1] During the course of our scientific endeavors to obtain a general and modular entry to seven-membered ring-containing natural products,[2] we recently reported a highly unique behavior of Pt–carbene complexes (such *cis*- and *trans*-**B**).[3] The *cis*-**B** and *trans*-**B** are two plausible intermediates formed via a Huisgen-type [3+2] cycloaddition of **A** [see Eq. (1)],[4] where the *cis*- and *trans*-relationship was assigned between the bridged oxygen and the group Z.



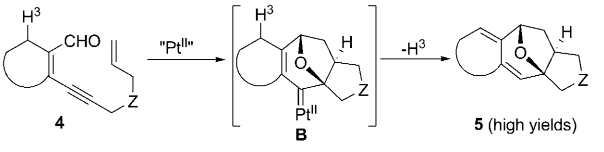
(1)

The preliminary results using molecular modeling show that *trans*-**B** is less likely to be formed due to the steric hindrance between the incoming double bond and the Z group; in addition *trans*-**B** has a anticoplanar relationship between the bridged oxygen and the group Z. In the cases involving a five-membered ring formation in the third cycle ($n = 5$), we have reported a Au-catalyzed reaction of enynals (such as **1**) to yield 2,3,10,10a-tetrahydrobenzo[*f*]azulen-9(1*H*)-one (like **2**) via [3+2] cycloaddition [Eq. (2)].[5] Pt-catalyzed cyclization of **1**, however, afforded **3** as the major product, presumably formed via oxygenation of intermediate **B**.[6] Note that elimination of H^1 from intermediate **B** would form **2**. Elimination of H^2 from **B** could result in sequential migration eventually to form the naphthalene derivative.[7] Contrarily, H^3, if attached to an sp^3 carbon as in **4**, would be eliminated to give diene product **5** [Eq. (3)].[8]



(2)

condition 1: AuBr$_3$ (3 mol%), EDC, RT, 8 h, **2** (84%)
condition 2: PtCl$_2$ (3 mol%), toluene, RT, 20 h, **3** (67%)



(3)

Z = NTs, C(COOEt)$_2$

During our extension of this methodology to the synthesis of the natural product dichotenone,[9] we needed a functionalized six-membered ring in the third cycle ($n = 6$). We previously reported the reaction of **6**, possessing a benzyloxy group at the propargylic position [Eq. (4)], where we found that the Pt–carbene intermediate (*cis*-**B**) could undergo CH insertion into C–H^4 of the δ-position to **6a**.[10]

Then, we focussed on substrates **7** which do not contain a benzyloxy group to elaborate other possible insertions

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[a] Prof. C. H. Oh, J. H. Lee, S. M. Lee, H. J. Yi
Department of Chemistry, Hanyang University
Sungdong-Gu, Seoul 133-791 (Korea)
Fax: (+82) 22299-0762
Homepage: http://hychemistry.hanyang.ac.kr/gos
E-mail: changho@hanyang.ac.kr

[b] Prof. C. S. Hong
Department of Chemistry, Korea University
Sungbook-Gu, Seoul 136-704 (Korea)

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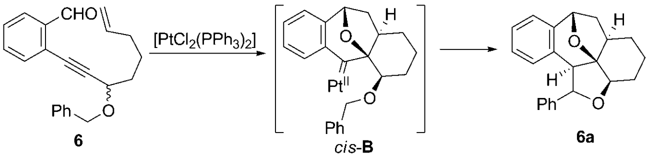
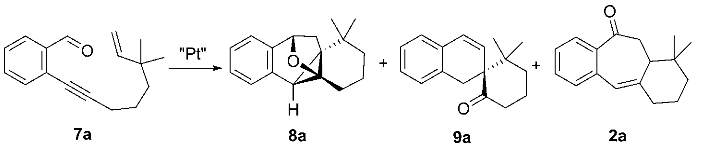


(4)

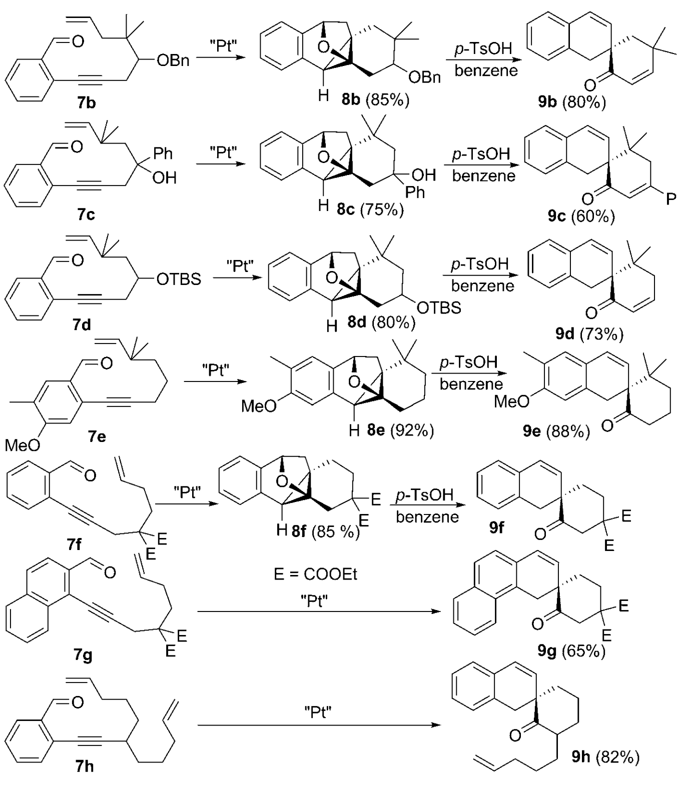
Table 1. Metal-catalyzed reactions of enynal **7a**.



	Catalysts (5 mol %)	Solvent	T [°C], t [h]	Products (Yield/%)
1	$PtCl_2$	toluene	120, 2	**8a** (54), **9a** (24)
2	$PtCl_2$	toluene	120, 4	**8a** (~0), **9a** (38)
3	[$PtCl_2$(dppe)]	toluene	120, 2	**8a** (83)
4	$PtCl_2$	toluene	80, 1	**8a** (95)
5	$PtCl_2$	CH_3CN, EDC	80, 12	**8a** (90), **9a** (5)
6	$PtCl_2$		80, 1	**8a** (95)
7	$PtCl_2$	*p*-dioxane	80, 12	**8a** (90), **9a** (5)
8	$PtCl_2$	toluene/air	80, 1	**8a** (95)
9	$PtCl_2$	toluene/water	80, 1	**8a** (5)

under Pt catalysis.[11] Here we wish to report the highly unique CH insertion into C–H^5 of the proposed intermediate **B** to form the corresponding fused cyclopropanes.[12] Thus, we examined the reaction of **7a** under various conditions in order to construct a core substructure such as **2a**, which is found in many natural products such as faveline,[13] barbatusol,[14] pisiferin,[15] rosmaridiphenol,[16] xochitlolone.[17] $PtCl_2$-catalyzed reaction of **7a** was summarized in Table 1. First of all, the reaction of **7a** with $PtCl_2$ as the catalyst proceeded well under reflux in toluene to furnish a mixture of unexpected products **8a** and **9a** in 54 and 24 % yields, respectively, without forming product **2a** (entry 1). This was a very unusual reaction in which the insertion of a Pt–carbene species into C–H$^\beta$ bond formed the corresponding cyclopropanes such as **8**.[18] Note that metal–carbenes generally undergo cyclopropanation in the reaction with alkenes. Several conditions were tested to optimize the reaction efficacy. The longer reaction time under the same conditions resulted in overreactions to yield **9a** as a major product (entry 2). Surprisingly, when **7a** was treated with [$PtCl_2$(dppe)] at 120 °C for 2 h in toluene, the reaction afforded **8a** exclusively in 83 % yield (entry 3). Simply lowering the reaction temperature (80 °C) and the reaction time (one hour) provided the best conditions leading to **8a** in 95 % yield (entry 4). This reaction was also successful in other solvents, such as CH_3CN, 1,2-dichloroethane (EDC), and *p*-dioxane (entries 5–7). This reaction was not affected by oxygen from air but severely affected by water (entries 8–9). On the basis of the reaction trends, we proposed that the spirocycle **9a** might be formed via the initial cyclopropane **8a**, since **9a** became a major after prolonged reaction times. To clarify this assumption, we examined the reaction of **8a** with 0.1 equivalent of *p*-toluenesulfonic acid in benzene under reflux, where **9a** was isolated in 91 % yield. TLC monitoring of the Pt-catalyzed reaction of **7a** also revealed that **8a** was initially formed as a sole product and then **9a** was formed upon prolonged heating.

Using the present conditions ($PtCl_2$ in toluene at 80 °C for 1–12 h), several substrates (**7b–h**) were examined to explore the scope and limitations of this reaction (Scheme 1). Overall all substrates seemed to afford the corresponding products **8** in good to excellent yields. The products **8a–f** were isolated in excellent yields. During the reaction **8g** and **8h** were spontaneously isomerized to spirocycles **9g** and **9h** in 65 and 82 % yields, respectively. Products **8a–f** also were smoothly isomerized to the corresponding spiro compounds **9a–f** with the retention of stereochemistry. It is worthwhile to note that all products **8** and **9** were isolated with high levels of stereoselectivity, although our reactions were expected to afford the complex reaction mixtures due to newly-forming multiple stereogenic centers.



Scheme 1. Pt-catalyzed cyclization under $PtCl_2$ in toluene at 80 °C for 1–4 h.

In order to confirm the structure of **8**, we needed at least one good single crystal of **8**. Fortunately, X-ray structure of **8b** could be obtained (see Figure 1, so that we were able to confirm the relative structures of our products **8** by comparison of the spectral data. Mechanistically, intermediates **A** would undergo [3+2] cycloaddition with a pendant double bond to form the Pt–carbene complex **B** (Scheme 2). Pt–carbene **B** would undergo insertion to form **3** if there is a benzylic–H of the δ position; if no such CH bond is present, the reaction would proceed with insertion into the tertiary CH bond to form the cyclopropane ring like **8**. Further heating of the reaction mixture or a TsOH-catalyzed reaction of isolated **8** cleanly resulted in an isomerization to form **9**.

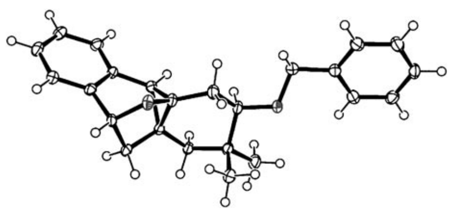
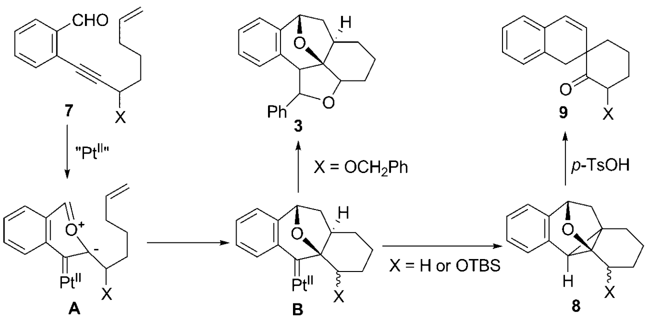


Figure 1. X-ray structure of **8b**.



Scheme 2. Proposed paths of Pt–carbene complex **B**.

In conclusion, enynals **7** bearing an olefinic pendant were successfully cyclized via Huisgen-type [3+2] cycloaddition to the tetracyclic Pt–carbene complex **B** which would undergo insertion into a C−H bond of the β-position to afford the fused cyclopropanes **8** which are otherwise not accesable. Acid-catalyzed rearrangement of cyclopropanes **8** smoothly occurred to form the corresponding spiranes **9** with excellent levels of stereoselectivity.

Experimental Section

In a 5 mL new test tube, *o*-alkynylbenzaldehyde **7a** (100 mg, 0.41 mmol), $PtCl_2$ (11 mg, 0.04 mmol) and dry toluene (1.5 mL) were allowed to react at 0 °C and the reaction mixture was kept under argon atmosphere. The resulting mixture was then stirred for 1 h in a preheated oil bath (80 °C) by monitoring the reaction by TLC periodically. Upon completion, the solvent was removed under vacuum and the crude product was subjected for flash column chromatography (silica gel, *n*-hexane/EtOAc 20:1) to afford the pure products **8a** (95.2 mg, 95 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.25$–7.23 (m, 2H), 7.14–7.08 (m, 2H), 4.97 (d, $^3J=6.0$ Hz, 1H), 2.28–2.22 (m, 1H), 2.07–2.01 (m, 2H), 1.98 (s, 1H), 1.65–1.56 (m, 1H), 1.50–1.43 (m, 1H), 1.32–1.22 (m, 3H), 1.13 (s, 3H), 0.99 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.24$, 133.41, 127.46, 126.30, 124.21, 121.81, 74.98, 63.64, 36.12, 31.24, 29.46, 29.15, 28.50, 27.14, 26.99, 24.20, 18.15 ppm; IR (NaCl): $\tilde{\nu}=3026$, 2950, 2865, 1608, 1487, 1462, 1024, 952 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{17}H_{20}NaO$: 263.1412; found: 263.1469. The spiro compounds **9a–h** were formed upon prolonged heating of the Pt reaction mixture or by TsOH-catalyzed isomerisation. Thus, a benzene solution (2.0 mL) of **8a** (24.0 mg, 0.10 mmol) in the presence of about 10 % TsOH was heated for 2 h. The reaction solution was cooled down to room temperature and partially concentrated under vacuum and the residue was subjected for flash column chromatography (silica gel, *n*-hexane/EtOAc 20:1) to afford the pure products **9a** (21.1 mg, 88 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.17$–7.07 (m, 3H), 6.97 (d, $^3J=7.2$ Hz, 1H), 6.53 (d, $^3J=10.0$ Hz, 1H), 6.07 (d, $^3J=9.6$ Hz, 1H), 3.07 (ABq, $\Delta\delta=76.0$ Hz, $^2J=16$ Hz, 2H), 2.70–2.63 (m, 1H), 2.20–2.14 (m, 1H), 2.06–1.99 (m, 1H), 1.94–1.82 (m, 2H), 1.51 (dt, $^3J=13.6$, 4.0 Hz, 1H), 0.98 (s, 3H), 0.90 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=211.02$, 135.42, 131.87, 129.97, 128.20, 127.97, 127.61, 126.41, 126.35, 57.51, 41.66, 37.40, 35.38, 30.31, 25.88, 23.64, 22.84 ppm; IR (NaCl): $\tilde{\nu}=3018$, 2961, 2870, 1701, 1488, 1450, 1387, 1310, 1175, 1072 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{17}H_{20}NaO$: 263.1412; found, 263.1440.

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