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Pt-Catalyzed Hydrative Cyclization of 2-Enynylbenzaldehydes and Its Application to Faveline Synthesis

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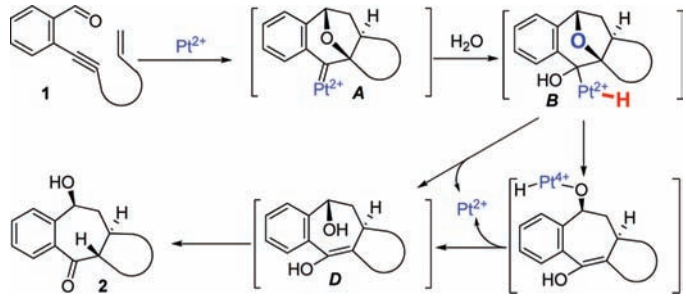
ABSTRACT



Various 2-[6-en-1-ynyl]benzaldehydes and their analogues were successfully cyclized via Huisgen-type [3+2] cycloaddition to the tetracyclic platinum−carbene complex, which would subsequently undergo hydration to afford the tricyclic products in good yields with excellent stereoselectivities. This hydrative cyclization was also applied to the faveline synthesis.

Discovery of efficient synthetic methods toward polycycles containing a central 7-membered carbocycle is a challenging task to organic and medicinal chemists because many 7-membered ring containing polycycles have been isolated in recent years and some of them turned out to be biologically active natural products.[1] For example, a number of cytocidal compounds have been isolated in 1991 from the bark of the Brazilian plant favela (*Cnidoscolus Phyllacanthus*); faveline, its methyl ether, and deoxyfaveline display significant activity against P-388 murine leukemia cells.[2] Therefore, several groups synthesized the faveline family successfully. Ghatak et al. reported the first total synthesis of faveline; Majetich et al. synthesized 6,7,6-fused tricyclic compounds using cycloalkylation of functionalized arenes with Lewis acid-activated dienones. In 2005, Banerjee et al. synthesized (±)-komaroviquinone and (±)-faveine methyl ester through an intramolecular Heck reaction.[3]

Among various strategies for constructing 7-membered carbocycles, cycloaddition routes (4+3 or 5+2) are particularly attractive because of their inherent potential for achieving a rapid increase in skeletal complexity.[4] During the course of our scientific endeavors leading to a general and modular entry to seven-membered-ring-containing natural products, we have reported divergent behaviors of metal−carbene complexes (**B**), formed via a Huisgen-type [3+2] cycloaddition between metal-bound pyryliums and a pendant alkene (Scheme 1).[5]

We first reported a gold-catalyzed reaction of the enynal **1** to yield 2,3,10,10a-tetrahydrobenzo[*f*]azulen-9(1*H*)-one (**2**) via [3+2] cycloaddition.[6] Rh-catalyzed cyclization of **1**

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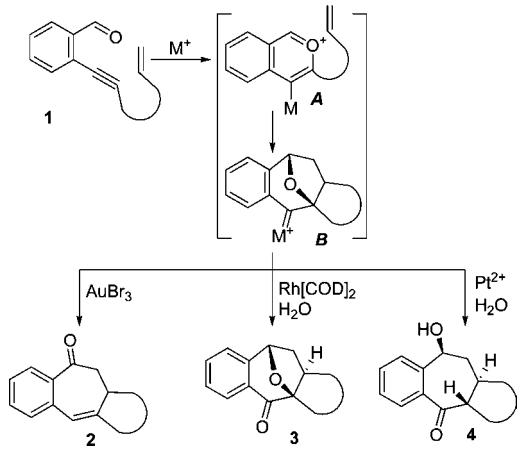
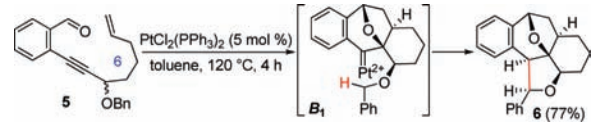
Scheme 1. Pathways of Metal−Carbene Intermediates (**B**)



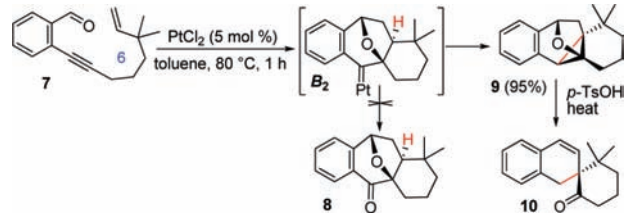
afforded **3** as a major product.[7] The same types of intermediates **A** and **B**, except the bounded metals, were proposed from both reactions. Pt-catalyzed reaction of **1**, however, afforded a mixture of **3** and **4** as major products. A source of an oxygen atom in **3** and **4** would be water. Since the discovery of Au-, Rh-, and Pt-catalyzed cyclizations of enynal **1** to the corresponding [6,7,5]-tricyclic compounds, we became interested in applying our protocol for the synthesis of faveline and its analogues. Synthesis of faveline, possessing a [6,7,6]-carbocycle, was thought to be straightforward. Thus, we prepared a simple model substrate **5** for testing feasibility to construct the [6,7,6]-tricycle. Unfortunately, neither Au- nor Rh-catalyzed cyclization occurred, but we observed unusual unique insertion of the Pt−carbene intermediate **B** into the benzylic C−H of the δ-position to afford **6** (Scheme 2).[8]

Scheme 2. Insertion of Pt−Carbene $\mathbf{B_1}$ into Benzylic CH



Next, we expected that another substrate **7** could provide access to the [6,7,6]-tricyclic compound, demethoxydemethylfaveline derivative **8**, under our conditions. Again, neither gold nor rhodium catalyst did catalyze **7** to **8** but $PtCl_2$ catalyzed **7** to the unexpected cyclopropane **9** along with a small amount of **10**. Heating the reaction solution of **7** or TsOH-catalyzed isomerization of the isolated **9** furnished **10** in high yield (Scheme 3).[9]

Scheme 3. Insertion of Pt−Carbene $\mathbf{B_2}$ into *t*-CH



Our results prompted us to pursue more insight into the origin of diverse chemoselectivity on Pt-catalyzed cyclizations of 2-(enynyl)benzaldehydes and here we wish to report our results. We have examined various Pt-catalysis conditions with 2-enynylbenzaldehyde **1a** and summarized in Table 1. When **1a** was treated with $PtCl_2$ at rt in toluene for 7 h, two products, **3a** and **4a**, were isolated in 28% and 49% yield, respectively, without forming a trace amount of **2a** (entry 1). Use of $PtCl_2(PPh_3)_2$ as a catalyst required higher temperature to complete this reaction to **3a** and **4a** in 40% and 40% yields (entry 2), respectively. This reaction was also working in other solvents such as 1,2-dichloroethane (EDC), CH_3CN, and *p*-dioxane (entries 3−5). We became interested in seeking the origin of an oxygen in the products **3a** and **4a**. Surprisingly, when **1a** was treated with $PtCl_2$ and

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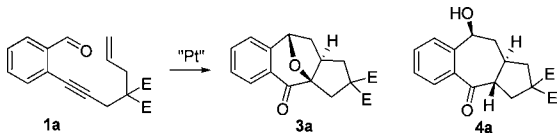
Table 1. Platinium-Catalyzed Reactions of Enynal **1a**[a]



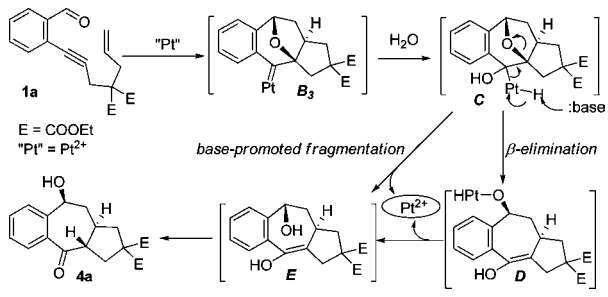
	catalysts (10 mol %)	solvent	additive (equiv)	temp (°C), time (h)	products[b] (% yield)[c]
1	$PtCl_2$	toluene		rt, 7 h	**3a** (28), **4a** (49)
2	$PtCl_2(PPh_3)_2$	toluene		110 °C, 20 h	**3a** (40), **4a** (40)
3	$PtCl_2$	EDC		rt, 3 h	**3a** (22), **4a** (42)
4	$PtCl_2$	CH_3CN		80 °C, 24 h	**3a**(15), **4a**(40)
5	$PtCl_2$	*p*-dioxane		80 °C, 1 h	**3a** (15), **4a** (45)
6	$PtCl_2$	toluene	H_2O (10)	rt, 3 h	**3a** (10), **4a** (80)
7	$PtCl_2$	toluene	H_2O (10)	60 °C, 0.5 h	**4a** (88)
8	$PtCl_2$	toluene	H_2O (1)	rt, 5 h	**4a** (92)
9	$PtCl_2$	toluene	H_2O (1)	60 °C, 0.5 h	**4a** (92)

[a] Reaction conditions: The reaction was carried out with **1a** in the presence of 10 mol % of the Pt catalyst under the given conditions. [b] E = COOEt. [c] Isolated yields.

H_2O (10 equiv) in toluene, **4a** was formed as a major product (entries 6 and 7). Finally, we could optimize this reaction by using an equivalent of H_2O at 60 °C or lower temperature, where **4a** was isolated in 92% yield in gram-scaled reaction (entries 8 and 9). blopck

Mechanistically, platinum−pyrylium intermediate, generated from **1a**, with a double bond would undergo cycloaddition to form the platinum−carbene complex $\mathbf{B_3}$, which underwent hydration to form **C** in the presence of a water molecule. We postulated two possible pathways. *β*-Oxyelimination of **C** to **D** involving C−O bond cleavage and the following reductive elimination could form **E** (Scheme 4).

Scheme 4. Proposed Mechanism



Base-promoted fragmentation of **C** might be induced by any nonbonding electron pair from either solvent or reagent to afford **E** directly.[10] The enol **E** would be tautomerized to the corresponding ketone **4a**.

To explore the scope and limitations of this method, we prepared various *o*-(enynyl)benzaldehyde and its equivalents **1b**−**k** by the known methods. Then we tested these substrates under our optimized conditions: $PtCl_2$ (10 mol %) and H_2O (1 equiv) in toluene (Figure 1). Several important features

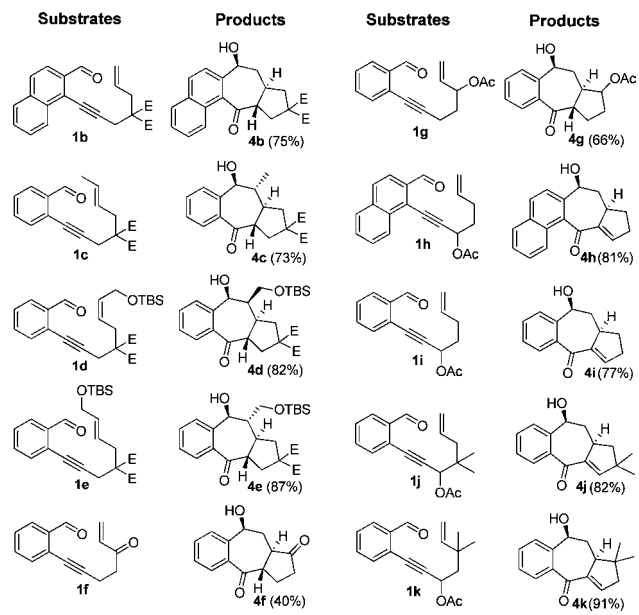


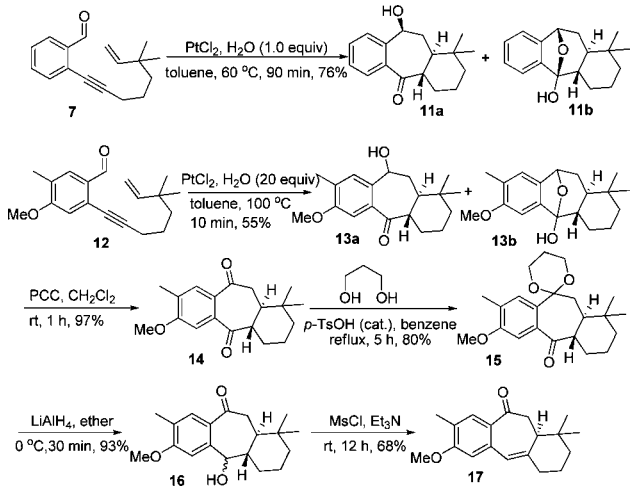
Figure 1. Structures of substrates **1b**−**k** and their cyclization products **4b**−**k**.

have to be noted. First of all, all substrates **1a**−**k** were successfully transformed into the corresponding tricycles **4a**−**k** under our conditions. Second, the present method would provide the tricyclic products **4** with excellent stereoselectivities and gram-scalable practicality. To demonstrate the excellent stereoselectivity, we carried out ^{1}H NMR studies of two isomeric substrates **1d** and **1e** and found the products from **1d** and **1e** to be **4d** and **4e**, respectively. Therefore, this reaction should be highly stereoselective or even stereospecific, implying that the first step, [3+2] cyclization, is stereospecific. To confirm the relative configuration of **4**, we could obtain one good single crystal of **2**. Fortunately, the X-ray structure of **4i** could be obtained.[11] We hoped to extend this protocol to access a general entry to [6,7,6]-tricycles and eventually to the faveline family (Scheme 5). Again, we applied our conditions to the substrate **7** having one-carbon longer tether between ene- and yne-group. The reaction worked very well but furnished a mixture of the product **11a** and its hemiketal **11b** in combined 76% yield. With this success, we prepared the faveline precursor **12** and cyclized it to the corresponding tricycle **13** in 55% yield as a mixture of **13a** and **13b**. The combined products **13a** and **13b** were oxidized with PCC in dichloromethane to furnish **14** almost quantitatively. Sterically less-hindered

(10) In the presence of methanol instead of water, acetal of **1a** was formed exclusively. Therefore the pyrylium formation might be blocked, so that the corresponding methyl ether of **E** would not be formed.

(11) Crystallographic data for compound **4i**: monoclinic, space group $P2_1/c$, $a = 7.9979(4)$ Å, $b = 7.4197(4)$ Å, $c = 19.349$ (9) Å, $\beta = 92.978(2)°$, $V = 1146.70(10)$ Å^3, $T = 293$ K, $Z = 4$, $R_1(I > 2\sigma(I)) = 0.0469$, $wR_2 = 0.1264$. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 760089. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or at www.ccdc.cam.ac.uk/data_request/cif.

Scheme 5. Synthesis of Faveline Methyl Ether **17**



ketone was selectively protected with 1,3-propanediol to afford **15** in refluxing benzene in the presence of a catalytic amount of *p*-TsOH. The **15** was reduced with $LiAlH_4$ and hydrolyzed with 1.0 M hydrochloric acid solution to afford **16**. Mesylation of the resulting hydroxyl group of **16** in triethylamine furnished the olefin **17**, faveline methyl ether. Although all steps in faveline synthesis are not fully optimized, this synthesis at least is showing that the present Pt-catalyzed hydrative cyclization could apply to the structurally similar natural products.

In conclusion, we discovered a new Pt-catalyzed hydrative cyclization of 2-(6-en-1-ynyl)benzaldehydes **1a**−**k** and 2-(7-en-1-ynyl)benzaldehydes **7** and **12** leading to synthetically valuable [6,7,5]-tricycles **4a**−**k** and [6,7,6]-tricycles **11** and **13** in good to excellent yields, respectively. Utilizing this protocol, we were able to accomplish the total synthesis of faveline methyl ether (**17**) in five steps with 14% overall yield based on the readily preparable enynal **12**. Using this method, we are actively working to synthesize various natural products having a central seven-membered ring and our results will be reported in the near future.

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Supporting Information Available: Full experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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