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Platinum-Catalyzed Hydrogenative Cyclization of Yne-Enones, Yne-Aldehydes, and Yne-Dienes

Mahadev P. Shinde,[a] Xi Wang,[a] Eun Joo Kang,[b] and Hye-Young Jang*[a]

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Pt complexes were used in the presence of phosphane ligands, $SnCl_2$, and H_2 for coupling reactions of alkynes with electrophiles under environmentally benign hydrogenation conditions, providing five- and six-membered cycloreduction products in moderate to good yield. Deuterium labeling studies suggested the occurrence of a catalytic cycle including the diploar intermediate derived from hydrometalation of a platinum–hydride complex to the alkyne.

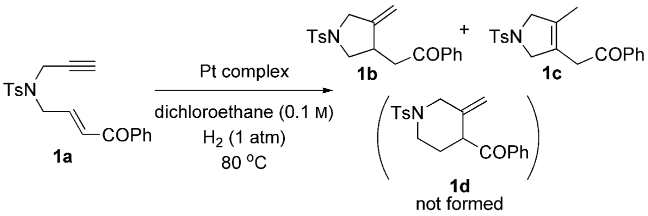
Introduction

Pt complexes are promising catalysts for the cyclizations of enynes,[1] dienes,[2] diynes,[3] hydroxy alkenes,[4] amino alkenes,[5] and arene–alkyne substrates,[6] where the Pt complex activates the alkynes (or the alkenes), facilitating the intramolecular addition of a nucleophile to the Pt–alkyne (alkene) complex. Although the Pt-catalyzed reaction of alkynes (and alkenes) with nucleophiles are a powerful strategy for the synthesis of synthetically and biologically important building blocks, there has been relatively less interest in the Pt-catalyzed reactions of alkynes (the alkenes) with electrophiles. In particular, there are few reports on the addition of a Pt–alkyne (alkene) complex to electrophiles under hydrogenation conditions.[7] In the context of the intramolecular addition of the Pt–alkene to the electrophiles, we previously reported the Pt-catalyzed Michael and aldol reaction under hydrogenation conditions.[8] As a possible mechanism, the LnPtH complex derived from $PtCl_2$, the ligands, and H_2 is expected to coordinate with the activated alkene to perform the subsequent cyclization with the α,β-unsaturated carbonyl compound (or the aldehyde).[9,10] As part of an ongoing study aimed at developing the reaction of a Pt–alkyne complex with electrophiles under hydrogen, this study examined the reaction mode of Pt catalysts exhibiting high catalytic activity with the yne-enones, yne-aldehydes, and yne-dienes. In addition to examples of the cyclizations of the alkyne with enones, aldehydes and, dienes, a plausible catalytic cycle is proposed to account for the deuterium labeling results.

Results and Discussion

To optimize the reaction conditions, *N*-(*E*)-4-methyl-*N*-(4-oxo-4-phenylbut-2-enyl)-*N*-(prop-2-ynyl)benzenesulfonamide (**1a**) was added to a solution containing $PtCl_2$ (5 mol-%), $P[2,4,6\text{-}(OMe)_3C_6H_2]_3$ (5 mol-%), and $SnCl_2$ (25 mol-%) under 1 atm of H_2 to afford product **1b** in 44% yield (Table 1, Entry 1). In the previous Michael and aldol cyclization, the Pt–enolate was generated from the hydrometalation of the enone treated with the aldehyde or enone. However, in the cyclization of yne-enones, the addition of the Pt–enolate to the alkyne, which was expected to afford six-membered ring product **1d**, was not observed. To im-

Table 1. Optimization of reductive cyclization of **1a**.



Entry	Pt complex (5 mol-%)	Ligand (5 mol-%)	Additive (25 mol-%)	Yield [%] (**1b/1c**)
1	$PtCl_2$	$P[2,4,6\text{-}(OMe)_3C_6H_2]_3$	$SnCl_2$	44 (**1b**)[a]
2	$PtCl_2$	$P[2,4,6\text{-}(OMe)_3C_6H_2]_3$	$SnCl_2$	30(**1b**)[b]
3	$PtCl_2$	$P[2,4,6\text{-}(OMe)_3C_6H_2]_3$	$SnCl_2$	35(**1b**)
4	$PtCl_2$	$P(p\text{-}OMeC_6H_4)_3$	$SnCl_2$	51 (2.7:1)
5	$PtCl_2$	PPh_3	$SnCl_2$	74 (1.2:1)
6	$PtCl_2$	$P(p\text{-}CF_3C_6H_4)_3$	$SnCl_2$	68 (1:1.6)
7	$PtCl_2$	$P(C_6F_5)_3$	$SnCl_2$	80 (5.2:1)
8	$PtCl_2$	–	$SnCl_2$	28 (**1b**)
9	$PtCl_2$	$P(C_6F_5)_3$	–	reduction
10	$PtCl_2$	$P(C_6F_5)_3$	$SnCl_2$	N.R.[c]
11	$PtBr_2$	$P(C_6F_5)_3$	$SnCl_2$	58 (**1b**)

[a] Dichloromethane, 40 °C, 18 h. [b] 60 °C, 8.5 h. [c] In the absence of H_2.

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[a] Division of Energy Systems Research, Ajou University,
Suwon 443-749, South Korea
Fax: +82-31-219-1615
E-mail: hyjang2@ajou.ac.kr
[b] Department of Applied Chemistry, Kyung Hee University,
Yongin 449-701, South Korea

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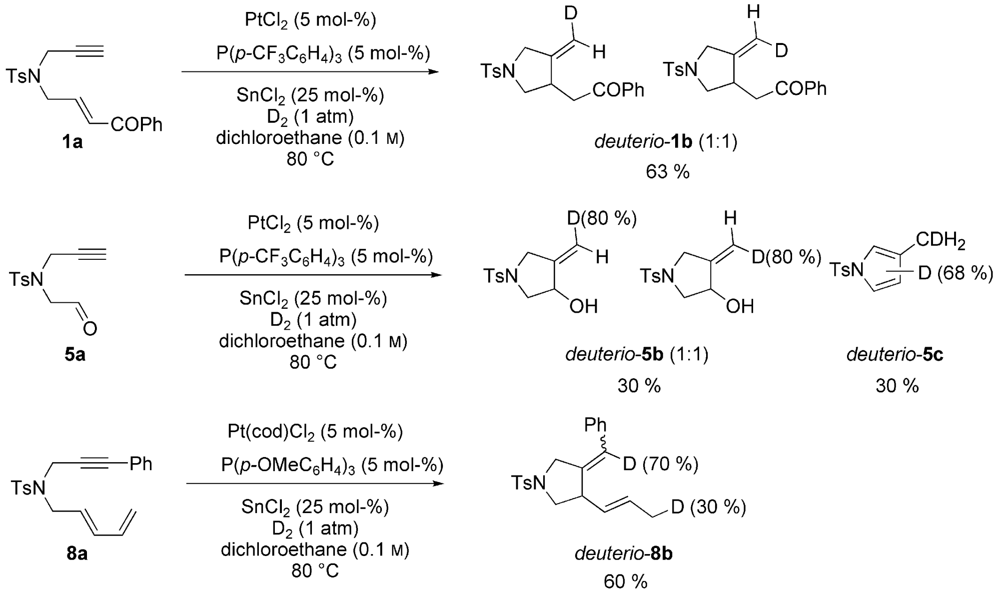
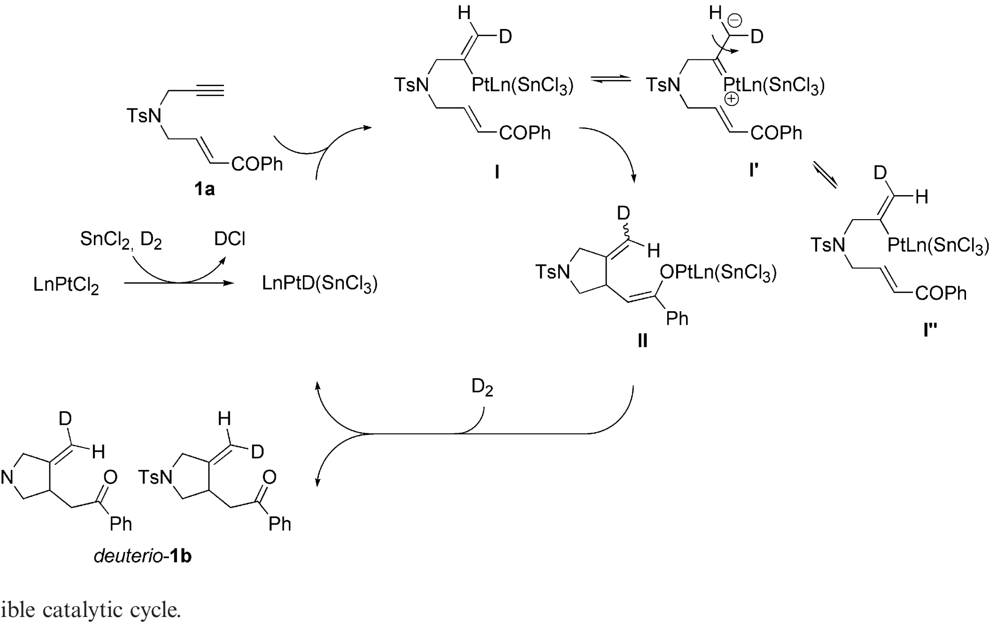
prove the yield, the temperature was increased, but the yield was still too low (Table 1, Entries 2 and 3). Next, a variety of phosphane ligands were evaluated. Upon the addition of relatively less electron-rich phosphanes, the yield increased with the concomitant formation of isomerized product **1c**, which was formed through isomerization of **1b** (Table 1, Entries 4–7).[11] In the absence of phosphane ligands, the reaction still proceeded to compound **1b** in 28 % yield (Table 1, Entry 8). The phosphane ligand is expected to modulate the reactivity of the catalyst. The critical role of $SnCl_2$ in Pt-catalyzed hydrogenations has been emphasized in previous reports.[12] It is likely that no cycloreduction proceeded in the absence of $SnCl_2$ (Table 1, Entry 9). Interestingly, when hydrogen was omitted, neither the desired reductive cyclization product nor the cycloisomerization product, which is often reported in the Pt-catalyzed cyclizations of enynes, was observed (Table 1, Entry 10).[1] An alternative Pt catalyst, $PtBr_2$, was used, affording compound **1b** in 58 % yield (Table 1, Entry 11).

A diverse range of substrates were evaluated employing a suitable set of reaction conditions using $PtCl_2$ (5 mol-%), phosphane ligands (5 mol-%), and $SnCl_2$ (25 mol-%) under 1 atm of H_2 (Table 2). Depending on the substituent on the substrate, either an electron-deficient or an electron-rich phosphane was needed to produce the cycloreduction product in good yield. In comparison to compound **1a**, oxygen-tethered substrate **2a**, which is known to be unstable under transition-metal catalysis conditions, showed a diminished yield (51 %). Compound **3a** possessing an acetyl-substituted enone participated in the reaction in the presence of P(*p*-



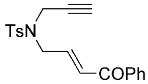
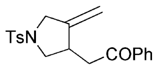
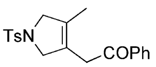
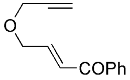
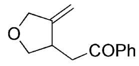
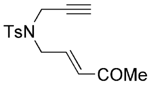
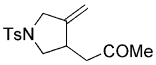
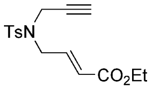
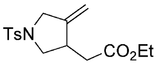
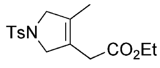
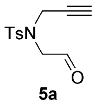
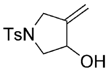
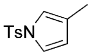
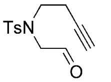
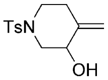
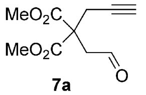
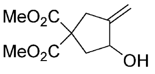
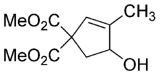
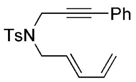
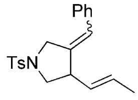
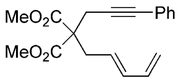
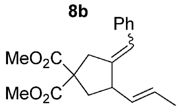
Scheme 1. Deuterium labeling studies.



Scheme 2. A plausible catalytic cycle.

$CF_3C_6H_4)_3$, affording compound **3b** in 78% yield. In the case of the ester substituted substrate, compound **4a** underwent cyclization to form the product in 39% yield due to the low reactivity of the ester-substituted alkene as an electrophile.

Table 2. Examples of cycloreduction.

Entry	Substrate	Product	Yield (**b**/**c**) [%]
1	 **1a**	 **1b**  **1c**	80 (5.3:1)[a]
2	 **2a**	 **2b**	51[b]
3	 **3a**	 **3b**	78[b]
4	 **4a**	 **4b**  **4c**	39 (1.4:1)[a]
5	 **5a**	 **5b**  **5c**	62 (1.6:1)[b]
6	 **6a**	 **6b**	52[b]
7	 **7a**	 **7b**  **7c**	82 (1:1)[b,d]
8	 **8a**	 **8b**	72[c]
9	 **9a**	 **9b**	98[c]

[a] $P(C_6F_5)_3$. [b] $P(p\text{-}CF_3C_6H_4)_3$. [c] $Pt(cod)Cl_2$ and $P(p\text{-}OMeC_6H_4)_3$ were used. Compounds **8b** and **9b** were obtained as isomeric mixtures of ratio 2.4:1 and 1.5:1, respectively. Indicated stereoisomers are major compounds.[15b] [d] The reaction was run at ambient temperature.

In addition to α,β-unsaturated carbonyl compounds, the aldehyde participated effectively in the reductive cyclization with the alkyne. Nitrogen-tethered 1,5-alkynal **5a** was subjected to these reaction conditions, affording cyclized product **5b** and pyrrole **5c** in 62% yield. Nitrogen-tethered 1,7-alkynal **6a** participated in the reductive cyclization, affording compound **6b** in 52% yield. Carbon-tethered substrate **7a** underwent the cyclization successfully but *exo*-methylene cyclopentenol **7b** isomerized to **7c** during the catalytic reaction. Both nitrogen-tethered yne-diene **8a** and carbon-tethered yne-diene **9a** underwent reductive cyclization effectively in the presence of $P(p\text{-}OMeC_6H_4)_3$, providing desired product **8b** and **9b** in 72 and 98% yield, respectively.

To probe the reaction mechanism, the cyclizations of compound **1a**, **5a**, and **8a** were carried out under D_2, providing *deuterio*-**1b**, *deuterio*-**5b**, and *deuterio*-**8b** as a mixture of two stereoisomers in 63, 30, and 60% yield, respectively (Scheme 1). In the case of compound **5a**, deuterated pyrrole derivative **5c** was observed in 30% yield, along with *deuterio*-**5b**. During the reaction in the presence of D_2, partially deuterated **5b**, **5c**, and **8b** were observed, which is attributed to the formation of Pt–H during the catalytic reaction. Although D_2 was employed for reductive cyclization, hydrometalation of Pt–D to the 1,3-diene functional group of **5c** and **8a** might occur and subsequent β-hydride elimination is assumed to provide the Pt–H complex to account for the incorporation of hydrogen in *deuterio*-**5b**, **5c**, and **8b**.[13]

To rationalize the present outcomes of deuterium labeling studies, a dipolar mechanism involving metastable **I**′ was considered[14] (Scheme 2). The catalytic cycle begins with the hydrometalation of LnPtD to the alkyne,[15] followed by *cis–trans* isomerization between intermediates **I** and **I**′′. Subsequently, each intermediate undergoes cyclization, forming intermediate **II**, which reacts with another molecule of deuterium to produce the cyclized products with the regeneration of the LnPtD catalysts. The generation of intermediate **I** and the equilibrium to intermediate **I**′′ can account for the formation of the two isomeric mixtures of *deuterio*-**1b**, **5b**, and **8b** (Scheme 1).

Conclusions

In summary, the cycloreductions of yne-enones, yne-aldehydes, and yne-dienes were explored by using a Pt catalyst generated from $PtCl_2$, $SnCl_2$, phosphane, and H_2. This catalytic system produced five-and six-membered cycloreduction products in moderate to good yields by using nitrogen- and carbon-tethered substrates. In the case of nitrogen-tethered yne-aldehyde substrate **5a**, pyrrole derivative **5c** was formed by dehydration and migration of the double bond of cycloreduction product **5b**. On the basis of the deuterium labeling study, it was speculated that the diploar intermediate was generated after hydrometalation of the alkyne, rendering a *cis–trans* isomerization. The knowledge gained from the Pt-catalyzed hydrogen-mediated cyclization of yne-enones, yne-aldehydes, and yne-dienes is expected to contribute to the design and development of efficient and versatile Pt catalysts for a wide variety of reductive couplings.

Experimental Section

Representative Experimental Procedure for Reductive Cyclization: To a premixed solution of Pt^{II} (5 mol-%), phosphane (5 mol-%), and $SnCl_2$ (25 mol-%) under an atmosphere of H_2 (1 atm) in dichloroethane (0.1 M) was added each substrate under an atmosphere of H_2 (1 atm) at room temperature. The resulting mixture was allowed to stir at 80 °C until the starting material was completely consumed.

Supporting Information (see footnote on the first page of this article): Spectral data for new compounds.

Acknowledgments

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