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Pt(II)-Catalyzed Cyclization of Alkyne-aldehydes

Jong-Tai Hong, Min-Jung Kang, and Hye-Young Jang*

*Division of Energy Systems Research, Ajou University, Suwon 443-749, Korea. *E-mail: hyjang2@ajou.ac.kr*
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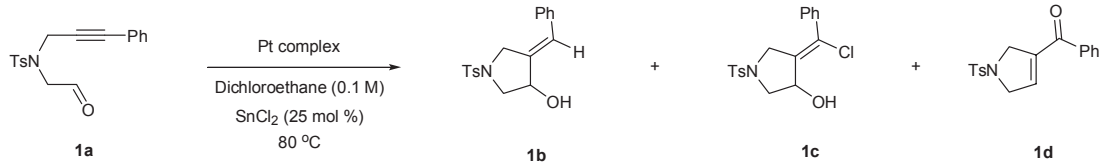
The reductive cyclization of alkyne-aldehydes has received considerable attention because the corresponding cyclized products involving the allylic alcohol unit can be used as useful building blocks in natural products and pharmaceuticals.[1] Therefore, transition metal-catalyzed alkyne-aldehyde cyclization has been investigated in the presence of a range of reductants. Among the reductive cyclization conditions, hydrogen-mediated reductive cyclizations are considered environmentally benign methods, providing a wide range of cyclized products in good yield with excellent selectivity.[1f,1g,2,3]

As an ongoing effort to develop green chemical processes utilizing hydrogen, we previously reported the Pt-catalyzed hydrogenative cyclization of a variety of unsaturated π-systems including limited examples of alkyne-aldehydes.[3] This study examined a wide range of substrate scopes of alkyne-aldehydes under the Pt-catalyzed hydrogenative cyclization conditions, providing the mechanistic details and full understanding of this reaction mode.

To optimize the reaction conditions, 4-methyl-*N*-(2-oxoethyl)-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide **1a** was added to a solution containing $PtCl_2$ (5 mol %), P(Ph-2,4,6-OMe_3)$_3$ (5 mol %), and $SnCl_2$ (25 mol %) under 1 atm of H_2 to afford the reductive cyclization product **1b**, chlorine added cyclization product **1c**, and rearrangement product **1d** in 32%, 23%, and 14% yield, respectively (entry 1, Table 1). Compound **1c** was presumed to have formed by $SnCl_2$ since a number of Lewis acids, such as $TiBr_4$, BCl_3, and $SnCl_4$ can promote the cyclization/halogenation of alkyne-acetals.[4-7] Indeed, only $SnCl_2$ (25 mol %) could mediate the cyclization/halogenation of **1a** in the absence of a platinum complex, yielding compound **1c** (30%). Compound **1d** was formed through a heteroenyne methathesis type reaction, which is catalyzed by various Lewis acids.[8] With the addition of the P(Ph-*p*OMe)$_3$ ligand, a similar product distribution was observed (entry 2, Table 1). However, no reductive cyclization product **1b** was obtained in the presence of PPh_3, P(Ph-*p*CF_3)$_3$, and P(Ph-F_5)$_3$, and the amount of heteroenyne metathesis product **1d** increased (entries 3, 4, and 5, Table 1). In accordance with these results, the Pt complex with electron rich phosphines may promote hydrometalation to the alkyne, leading to the desired reductive cyclization. With electron deficient phosphines, the Pt complex functions as a Lewis acid, which accelerates the heteroenyne methathesis process. As an alternative reducing agent, Et_3SiH were utilized for the cyclization of compound **1a**, affording a mixture of compounds **1b**, **1c** and **1d** in reduced yield (entry 6). According to the optimization result of this reaction, the catalyst of entry 1 or 2 was chosen and hydrogen was selected as the reductant to obtain the reductive coupling product as a major product in the following reaction.

A wide range of substrates were evaluated employing $PtCl_2$ (5 mol %), P(Ph-*p*OMe)$_3$ (5 mol %), and $SnCl_2$ (25 mol %) under 1 atmosphere of H_2. Table 2 lists the cyclization results of each example.[9] The effect of the substituent at the alkyne terminal position was evaluated (entries 1, 2 and 3 of Table 2). Compared to the product mixtures derived from compound **1a**, compound **2a** was cyclized to afford only the reductive cyclization product **2b**. Compound **2e** was formed through dehydration and the olefin migration of the *exo*-methylene group of compound **2b**.[3b] Only chlorination/cyclization product **3c** was obtained when an aliphatic group (*n*-butyl) was attached

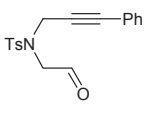
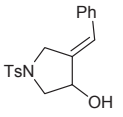
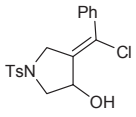
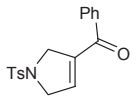
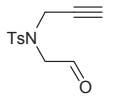
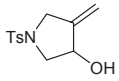
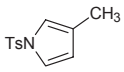
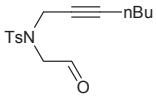
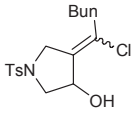
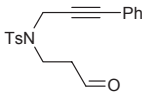
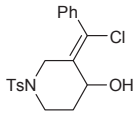
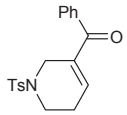
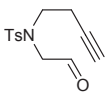
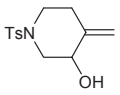
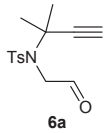
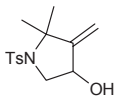
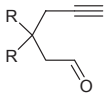
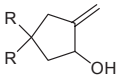
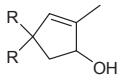
Table 1. Optimization of reductive cyclization of compound **1a**



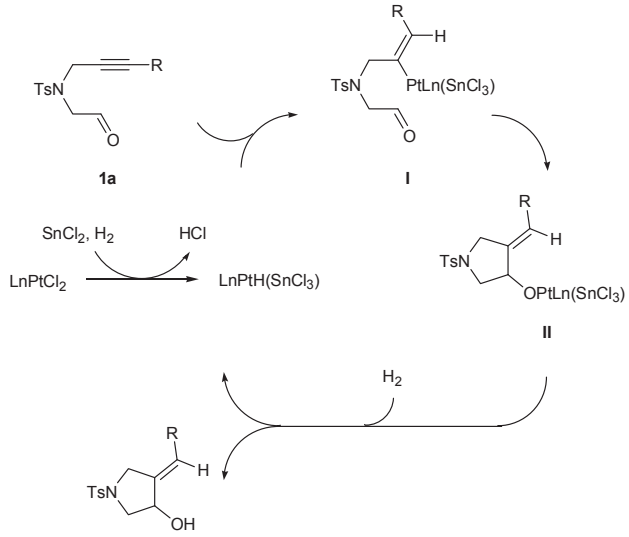
1a **1b** **1c** **1d**

Entry	Pt complex	Ligand	[H]	Yield (**1b**:**1c**:**1d**)
1	$PtCl_2$ (5 mol %)	P(Ph-2,4,6-OMe_3)$_3$ (5 mol %)	H_2 (1 atm)	32%:23%:14%
2	$PtCl_2$ (5 mol %)	P(Ph-*p*OMe)$_3$ (5 mol %)	H_2 (1 atm)	28%:21%:16%
3	$PtCl_2$ (5 mol %)	PPh_3 (5 mol %)	H_2 (1 atm)	0%:19%:14%
4	$PtCl_2$ (5 mol %)	P(Ph-*p*CF_3)$_3$ (5 mol %)	H_2 (1 atm)	0%:31%:38%
5	$PtCl_2$ (5 mol %)	P(Ph-F_5)$_3$ (5 mol %)	H_2 (1 atm)	0%:28%:59%
6	$PtCl_2$ (5 mol %)	P(Ph-*p*OMe)$_3$ (5 mol %)	Et_3SiH (120 mol %)	6%:23%:9%

Table 2. Examples of cycloreduction

Entry	Substrate	Products		
1	 **1a**	 **1b** (28%)	 **1c** (21%)	 **1d** (16%)
2	 **2a**	 **2b** (17%)	 **2e** (46%)	
3	 **3a**	 **3c** (35%)		
4	 **4a**	 **4c** (18%)	 **4d** (32%)	
5	 **5a**	 **5c** (37%)		
6	 **6a**	 **6b** (54%)		
7	 **7a** R = CO_2Me	 **7b** (68%)	 **7e** (16%)	

to the acetylene unit (compound **3a**). In the case of compounds forming a six-membered ring (entry 4 of Table 2), the formation of chlorination/cyclization products and heteroenyne metathesis products was favored over reductive cyclization. Interestingly, a slightly different reactivity was observed in the reaction of compound **5a**, even though compound **5a** has a same tether length to form a six membered-ring like **4a**. While compound **4a** was transformed to compound **4c** and **4d**, compound **5a** was converted to the reductive cyclization compound **5b** under the same reaction conditions. The *gem*-dimethyl group substituted compound **6a** was cyclized, affording the reductive cyclization product **6b**. By installing the dimethyl group on the propargyl position, the migration of the exo-methylene double bond was blocked unlike compound **2b**. Carbon tethered compound **7a** was next tested. The results showed that hydrogen substituted alkyne **7a** forms only reductive cyclization product **7b** and **7e**. The oxygen tethered substrates were examined under standard hydrogenative cyclization conditions and the decomposition of the starting materials was observed. According to the results shown in Table 2, the substituent at the alkyne plays an important role to direct the reaction pathway. The presence of phenyl or *n*-butyl group retards hydrometalation by the Pt catalyst due to the steric hindrance.



Scheme 1. Proposed catalytic cycle

A catalytic cycle is proposed to account for the reductive cyclization under Pt-catalyzed hydrogenative conditions (Scheme 1). $LnPtH(SnCl_3)$ was assumed to be derived from $PtCl_2$, phosphine, $SnCl_2$ under 1 atm of H_2. The Pt-hydride complex has been proposed to hydrometalate alkynes or alkenes during the hydrogenation and hydrogenative coupling reaction involving these π-unsaturated systems.[3] The hydrometalation of compound **1a** with $LnPtH(SnCl_3)$ produced intermediate **I**. Depending on the R group, hydrometalation can be accelerated or retarded, providing a different product distribution. The addition of H_2 to intermediate **II** produced the reductive cyclization product and regenerated the catalyst.

In summary, the cyclization of a range of alkyne-aldehydes under Pt-catalyzed hydrogenative conditions was examined as an environmental-friendly process. While the reductive cyclization product was formed under these standard conditions, other side products such as chlorination/cyclization products and heteroenyne metathesis products were detected. Based on the reaction optimization and screening of the substrate scope, some requirements of the catalyst and substrate for the reductive cyclization were found. A Pt catalyst possessing electron-rich ligands is favored for reductive cyclization. An electron-deficient Pt complex prefers the heteroenyne metathesis route. In addition, as important factors for reductive cyclization, the substituent and length of the tether of the substrates were included.

Experimental Section

Representative experimental procedure for cyclization of alkyne-aldehydes. Each substrate under H_2 (1 atm) at room temperature was added to a premixed solution of $PtCl_2$ (5 mol %),

phosphine (5 mol %), and $SnCl_2$ (25 mol %) under H_2 (1 atm) in dichloroethane (0.1 M). The resulting mixture was allowed to react at 80 ^oC until the starting material had been consumed completely.

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9. The characterization data of new compounds and references for known compounds (supporting information) are available on request from the correspondence author (email address: hyjang2@ajou.ac.kr, Fax: +82-31-219-1615).