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Platinum-catalyzed reductive coupling of activated alkenes under hydrogenation conditions

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ABSTRACT

The Pt complex generated from $PtCl_2$, PR_3, and $SnCl_2$ catalyzes the reductive coupling of activated alkenes under environmentally benign hydrogenation conditions. Various bis-enones participated in the intramolecular cyclization, forming the desired cyclization products in moderate to good yield. Intermolecular reductive coupling of the enone and the aldehyde provided the coupling product in good yield. This methodology illustrates the first use of platinum complexes in hydrogen-mediated couplings of activated alkenes.

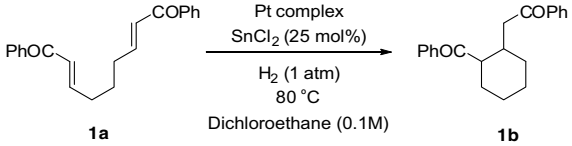
Transition metal-catalyzed reductive couplings have been widely investigated due to their versatile applications in the synthesis of biologically active compounds.[1] Among reductive coupling protocols, Krische and co-workers have reported Rh- and Ir-catalyzed reductive coupling involving hydrogen as a terminal reductant.[2,3] In contrast to commonly used reductants such as silane, borane, and alane, hydrogen is a mild hydride source providing high selectivity of coupling products and functional group tolerance. Moreover, due to the environmentally benign nature of hydrogenation, the hydrogen-mediated reductive coupling has received much interest.

Despite the extensive studies regarding the hydrogen-mediated reductive coupling of unsaturated systems containing alkenes, alkynes, and carbonyls, the reductive cyclization of bis-enones under hydrogenation conditions (Michael addition) remains challenging.[1g,4,5] Considering the benefits of such cyclizations in the synthesis of natural products and pharmaceutically useful building blocks, investigations into new catalytic systems for the reductive cyclization of bis-enones under mild and ecologically benign hydrogenation conditions are vital.

Among transition metal complexes, $PtCl_2$ with $SnCl_2$ has exhibited excellent activity in hydrogen-mediated processes such as hydroformylation.[6] Recently, Pt-catalyzed hydrogen-mediated reductive cyclizations of diynes and enynes have been reported.[7] To conduct these cyclizations, platinum complexes possessing the N-heterocyclic carbene (NHC) ligand, a well-known σ-donor with $SnCl_2$, are required. Despite the remarkable activity of Pt–NHC complexes in these reductive cyclizations, Pt–NHC has shown no activity toward bis-enones under the same hydrogenation conditions. While we were screening Pt complexes with various phosphine ligands for the reaction of activated alkenes, the novel reactivity of $PtCl_2$ with phosphine ligands toward the reductive cyclization of bis-enones was observed. In this account, we are pleased to report the platinum complex-catalyzed reductive cyclization of bis-enones, and the intermolecular reductive coupling of the enone and the aldehyde under hydrogenation conditions. Noticeably, this is the first account to present the hydrogen-mediated cyclization of bis-enones.

Initially (2*E*,7*E*)-1,9-diphenylnona-2,7-diene-1,9-dione **1a** was subjected to reductive cyclization conditions using a platinum complex generated in situ by mixing $PtCl_2$ (5 mol %), PPh_3 (5 mol%), and $SnCl_2$ (25 mol %) in dichloroethane under 1 atm of H_2 (Table 1, entry 1). The desired α,β-coupling product **1b** was observed in 76% yield as a mixture of cis and trans isomers (cis:trans = 1:2.8). While most reductive cyclizations of bis-enones have provided the β,β-coupling product in the presence of reductants such as SmI_2, Bu_3SnH, Mg, and R_2Zn, the hydrogen-mediated cyclization affords the α,β-coupling product similar to Co- and In-catalyzed reductive cyclizations of bis-enones using silane and

Table 1
Optimization of hydrogen-mediated reductive cyclizations of **1a**



1a **1b**

Entry	Pt complex	Ligand	Yield (%) (cis:trans)
1	$PtCl_2$ (5 mol %)	PPh_3 (5 mol %)	76 (1:2.8)
2	$PtCl_2$ (5 mol %)	P(Ph-*p*OMe)$_3$ (5 mol%)	66 (1:2.6)
3	$PtCl_2$ (5 mol %)	P(Ph-*p*CF_3)$_3$ (5 mol %)	98 (1:2.0)
4	$PtCl_2$ (5 mol %)	P(Ph-F_5)$_3$ (5 mol %)	69 (1:3.5)
5	$PtCl_2$ (5 mol %)	P(Ph-*p*CF_3)$_3$ (10 mol%)	42 (1:4)

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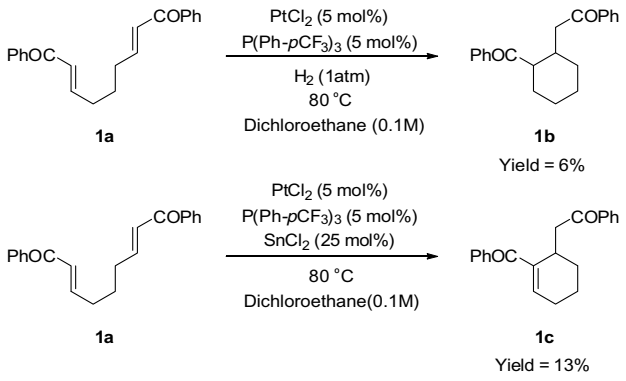
organocatalyzed reductive cyclizations of enone–enal using the Hantzsch ester.[1g,4,5,8]

Generally, electronic properties of ligands are known to affect the reaction yield as well as selectivity. Thus, electron rich phosphines such as P(Ph-*p*OMe)$_3$, and electron deficient phosphines such as P(Ph-*p*CF$_3$)$_3$ and P(Ph-F$_5$)$_3$ were utilized for the reductive cyclization of **1a**. Different electronic properties of the phosphine ligands did affect the yield. The platinum catalyst involving P(Ph-*p*OMe)$_3$ afforded the reductive cyclized product **1b** in 66% (Table 1, entry 2), a somewhat lower yield than that of the Pt complex with PPh$_3$. Employing P(Ph-*p*CF$_3$)$_3$ improved the catalytic activity of the Pt complex to provide **1b** in 98% (Table 1, entry 3). In the presence of P(Ph–F$_5$)$_3$, which has more fluorides than P(Ph–*p*CF$_3$)$_3$ and is expected to be more electron deficient, the product yield is diminished to 69%. In terms of the diastereoselectivity, the cis:trans ratio was observed from 1:2.0 to 1:3.5, depending on the phosphine ligand. The strong σ-donor N-heterocyclic carbene (NHC) was examined for the reductive cyclization of **1a** using Pt(NHC)(allyl)Cl with SnCl$_2$, which previously demonstrated an excellent reactivity in the hydrogenative cyclization of diynes and enynes.[7] However, Pt(NHC)(allyl)Cl with SnCl$_2$ did not afford the reductive cyclization product under hydrogen, confirming that the platinum complex, along with the electron deficient phosphine, promoted the formation of **1a**.

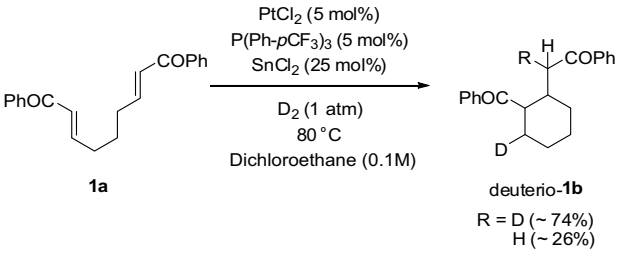
In addition to the electronic effects, the stoichiometry of the phosphine ligands affects the catalytic activity of the Pt complex in this transformation. As shown in entry 5 of Table 1, the Pt complex with 10 mol % of P(Ph–*p*CF$_3$)$_3$ affords product **1b** in 42% yield with the 1:4 cis:trans ratio. Adding 10 mol % of phosphine to 5 mol % of PtCl$_2$ might retard reactivity of the catalyst while favoring trans product formation. As an optimal catalyst, the combination of 5 mol % of PtCl$_2$, 5 mol % of P(Ph–*p*CF$_3$)$_3$, and 25 mol % of SnCl$_2$ was chosen for the hydrogen-mediated intra- and intermolecular coupling of activated alkenes.

SnCl$_2$ has been utilized not only as a co-catalyst in hydroformylation but also as a reductant.[6,9] To identify the role of SnCl$_2$, the following control experiments were performed. In the absence of SnCl$_2$, a mixture of PtCl$_2$ and P(Ph–*p*CF$_3$)$_3$ was used for the hydrogen-mediated cyclization of bis-enone **1a** to form product **1b** in 6% yield (Scheme 1). Under the optimized cyclization conditions omitting hydrogen, compound **1a** was not converted to product **1b**, yet cycloisomerization product **1c** was formed in 13% yield (Scheme 1).[10] Based on these results, SnCl$_2$ acts not as a reductant but as a co-catalyst to activate the Pt complex.

Subsequent to the control experiments, a deuterium labeling experiment using **1a** was performed to provide deuterio-**1b** in quantitative yield (Scheme 2). The structure and deuterium contents of deuterio-**1b** were assigned by NMR. As indicated in Scheme 2, deuteriums were incorporated at the α-position of the



Scheme 1. Control experiments.



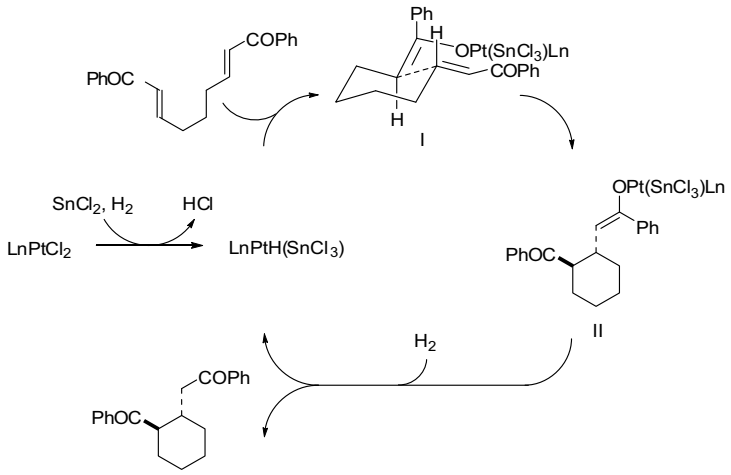
Scheme 2. Deuterium labeling experiment.

ketone out of the ring (74%). The extent of deuterium incorporation at the β-position of the ketone in the ring was not determined by NMR or Mass spectrometry.[11] Based on the deuterium labeling result, the following proposed mechanism which involves hydrometalation of the platinum-deuteride to the alkene can be supported.

A plausible mechanism for the reductive cyclization is the following proposed catalytic cycle (Scheme 3). Based on a previously reported mechanism of platinum catalyzed hydrogen-mediated reductive cyclizations, the catalytic cycle begins with the formation of LnPtH(SnCl$_3$) from PtCl$_2$, phosphine, and SnCl$_2$ in the presence of hydrogen.[7,12] The Pt complex reacts with hydrogen to form the dihydrido-platinum (IV) complex which undergoes facile reductive elimination to afford LnPtH(SnCl$_3$).[13] The hydrido platinum complex possessing SnCl$_3^-$ is catalytically competent in hydrogenative processes such as hydroformylation.[4b,12,14] Subsequent hydrometalation of the alkene by LnPtH(SnCl$_3$) affords intermediate **I** where the coordination of the platinum metal ion is not strong enough toward the pendant alkene, resulting in cis and trans mixture of cyclized intermediate **II**. Intermediate **II** undergoes oxidative addition with the incoming hydrogen, followed by reductive elimination, forming the cyclized product with the concomitant generation of LnPtH(SnCl$_3$).

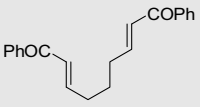
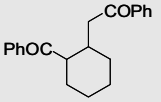
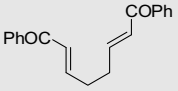
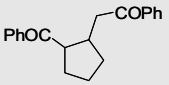
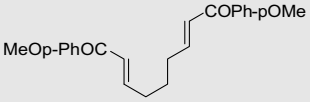
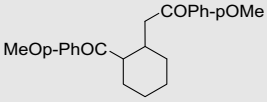
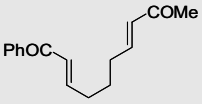
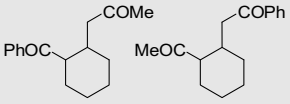
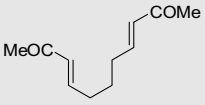
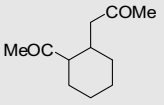
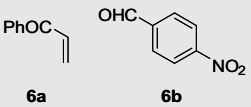
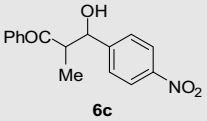
To explore the scope of the substrates, a variety of bis-enones (**1a**–**5a**) and enone **6a** were evaluated under hydrogen-mediated reductive coupling conditions (Table 2). Using the optimized conditions from Table 1, aromatic bis-enone **2a** derived from succinaldehyde underwent reductive cyclization, affording the 5-membered ring **2b** as a mixture of cis and trans isomers (1:1) in 71% yield (entry 2). Aromatic bis-enones **3a** possessing electron-donating groups participated effectively to provide cyclized product **3b** in 91% yield (entry 2). In the case of bis-enone **4a**, hydride addition occurs at the β-position with respect to the phenyl ketone as well as the β-position with respect to the methyl ketone (4:1 ratio). The combined yields of **4b** and **4c** were 72% with a 1:1 cis:trans ratio, while the methyl-substituted bis-enone **5a** gave a 59% yield with the 1:1 cis:trans ratio as well. In the case of the bis-enoate containing the ethyl ester and oxygen tethered aromatic bis-enone, the alkene reduction occurred without cyclization under the hydrogenation conditions. As an intermolecular coupling example, enone **6a** was tested. The Pt catalysts with various phosphine ligands did not promote reductive dimerization of **6a**, providing instead simple reduction products. However, in the presence of aldehyde **6b**, the optimized catalyst for the reductive cyclization involving P(Ph-*p*CF$_3$)$_3$ afforded **6c** in 50% yield. Under these conditions, employing electron rich phosphine P(Ph–*p*OMe)$_3$ can increase the yield of intermolecular coupling up to 83%.

In summation, the first hydrogen-mediated reductive cyclization of aromatic and aliphatic bis-enones has been presented. The desired cyclized products were formed in good yield with modest diastereoselectivity. In the case of the methyl substituted bis-enone, a good conversion was observed. In particular, α,β-coupling of aliphatic enones has not been reported under other transi-



Scheme 3. A plausible mechanism for the reductive cyclization of **1a**.

Table 2
Reductive coupling of various activated alkenes

Entry	Substrate	Product	Yield (%) (cis:trans)
1	 **1a**	 **1b**	98 (1:2.0)
2	 **2a**	 **2b**	71 (1:1)
3	 **3a**	 **3b**	91 (1:3.5)
4	 **4a**	 **4b** **4c**	72 (1:1) **4b**:**4c**=4:1
5	 **5a**	 **5b**	59 (1:1)
6	 **6a** **6b**	 **6c**	83[a] (1.3:1)

Hydrogen-mediated reductive cyclization conditions: To a premixed solution of $PtCl_2$ (5 mol %), P(Ph-*p*CF_3)$_3$ (5 mol %), and $SnCl_2$ (25 mol %), in dichloroethane (0.1 M) was added each substrate under H_2 (1 atm) at room temperature. The resulting mixture was allowed to run at 80 °C for 2 h or until the starting material was completely consumed.

[a] To the premixed solution of $PtCl_2$ (5 mol %), P(Ph-*p*OMe)$_3$ (5 mol %), and $SnCl_2$ (25 mol %) in dichloroethane (0.1 M) were added 200 mol % of **6a** and 100 mol % of **6b** under H_2 (1 atm) at room temperature. The resulting mixture was allowed to run at 80 °C for 2 h.

tion metal-catalyzed reductive cyclization conditions.[5,8] Intermolecular reaction of the enone proceeded in the presence of aldehydes in good yield without dimerization of the enone. With regard to the mechanism, the hydrometalation of the activated alkenes with LnPtH($SnCl_3$) followed by cyclization was proposed in the hydrogen-mediated cyclization, which was supported by a

deuterium labeling experiment result. Using the powerful catalytic system involving $PtCl_2$, phosphine, and $SnCl_2$, this methodology would resolve limitations previously reported with hydrogenative couplings. Further mechanistic studies to support the currently proposed mechanism and modification of catalysts to improve the activity are ongoing.

Acknowledgments

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