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Platinum–triethylamine-catalyzed hydrogenation of aldehydes and cyclohexanones

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ABSTRACT

The first hydrogenation of aldehydes and chemoselective hydrogenation of cyclohexanones catalyzed by PtO_2–Et_3N are presented. An additionally attractive feature of this hydrogenation is being applicable to the complicated molecules. Three equivalent of triethylamine and 0.05 equiv of PtO_2 in 95% ethanol are found to be the optimal condition.

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As part of our ongoing program on the modification of paclitaxel analogs, $\Delta^{6,7}$ olefinic double bond in compound **1** was envisioned to be reduced by PtO_2-catalyzed hydrogenation, by analogy with our successful reduction of the conjugated olefinic double bond in diterpenoid alkaloid **2**.[1] Initially, we misjudged that the olefinic double bond in compound **1** did not undergo the hydrogenation catalyzed by platinum dioxide over 24 h barely based on the TLC behavior (silica gel GF254; cyclohexane/acetone 2:1, and chloroform/methanol 98:2). At this point, we compared the structural difference between **1** and **2**, which indicated that the diterpenoid alkaloid **2** possessed an additional tertiary amine substructure relative to compound **1**. With the notion that the extra tertiary amine substructure in **2** might promote the hydrogenation of olefinic double bond, we next investigated on the hydrogenation of compound **1** in the presence of platinum dioxide and triethylamine. Very interestingly, not only $\Delta^{6,7}$ olefinic double bond but also C-5 ketone group in compound **1** was hydrogenated in the presence of platinum dioxide and triethylamine (Scheme 1). This interesting experimental result spurred us to investigate the generality and the best reaction conditions of this catalytic hydrogenation of aldehydes and ketones.

It is well known that reduction of C=O double bonds using molecular hydrogen is a very important process in industrial organic synthesis due to its low cost and complete atom efficiency.[2] Homogeneous Rh, Ru, and to a lesser degree Ir complexes are used for the enantioselective hydrogenation with both hydrogen and organic donors as reducing agent. Elegant work by Noyori and co-workers has demonstrated the efficient synthesis of a variety of chiral secondary alcohols via the Ru-binap-catalyzed hydrogenation of simple ketones.[3] For the heterogeneous hydrogenation of carbonyl groups, the preferred catalysts are Pd, Pt, and Ni. The most interesting point was Orito's catalytic system, platinum catalysts modified with cinchona alkaloids, for the hydrogenation of activated ketones.[4] As summarized in a recent review,[5] several groups tried to improve catalyst performance by using different supports or catalyst pre-treatments. For example, metal-supported Pt,[6] polysulfosiloxane–Pt complex,[7] and platinum nanocatalyst[8] have been applied to the hydrogenation of ketones. However, the scope of this technology is still restricted to the hydrogenation of ketones activated in α or β position. It was reported in the literature[9] that the substituted cyclohexanones could be hydrogenated in the presence of PtO_2. However, neither the PtO_2/Et_3N system nor the hydrogenation of aldehydes and other ketones was mentioned. The PtO_2/Et_3N system has already been applied to the hydrogenation of other functionalities, such as pyridinium salt,[10a] nitryl group,[10b,c] and alkyne,[10d] but there was no detail explanation on it. To the best of our knowledge, PtO_2–Et_3N-catalyzed hydrogenation of aldehydes and ketones has not been reported yet. It is therefore significant to present herein the first example of catalytic and chemoselective hydrogenation of aldehydes and cyclohexanones catalyzed by platinum dioxide and triethylamine, proceeding under room temperature and atmospheric pressure.

Our initial experiments demonstrated that treatment of compound **1** with H_2 in the presence of Pd/C at room temperature afforded only $\Delta^{6,7}$ double bond reduced product **1a** in 95% yield. Further hydrogenation of **1a** in the presence of platinum dioxide and triethylamine provided the C-5 ketone-reduced product **1b** with high yield (95%), which suggested that both saturated and unsaturated cyclohexanones could be reduced to the corresponding cyclohexanols by the PtO_2–Et_3N-catalyzed hydrogenation (Scheme 1).

The scope of this novel transformation was examined on a series of aldehydes at room temperature and atmospheric pressure of hydrogen in the presence of platinum dioxide and triethylamine (Table 1). Aldehydes in either simple aliphatic compounds (entries 1–2), simple aromatic compounds (entries 3–4), or complicated natural analogs (entries 5–6) were reduced uneventfully in

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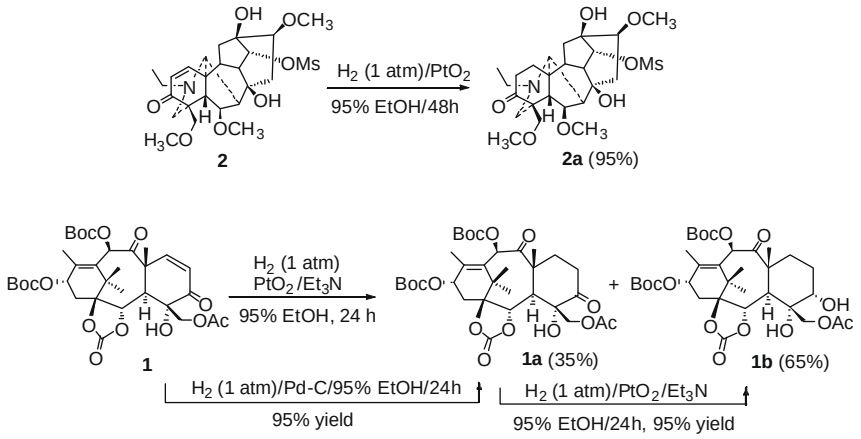
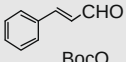
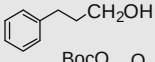
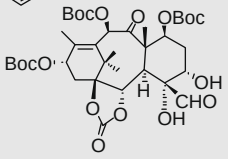
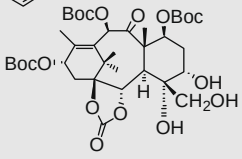
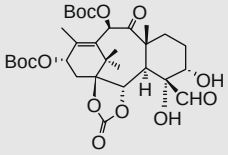
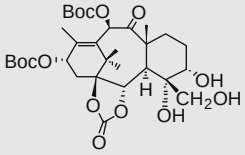


Scheme 1. Hydrogenation of compounds **1** and **2**.

Table 1
PtO_2–Et_3N-catalyzed hydrogenation of aldehydes[a]

Entry[a]	Aldehydes	Alcohols[b]	*T* (h)	Yield (%)
1	Propylaldehyde	Propyl alcohol	12	>99
2	Pivalaldehyde	2,2-Dimethylpropanol	12	>99
3	Benzaldehyde	Phenylmethanol	12	>99
4			16	>99
5			24	>99
6			24	98

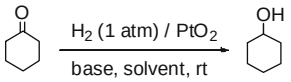
[a] Reaction conditions: PtO_2 (5 mol %), Et_3N (1 equiv), 95% EtOH (solvent) at 25 °C under an atmospheric pressure of H_2.
[b] Yields reported were calculated based on the ^1H NMR data.

12–24 h reaction time. Both carbonate and Boc protecting groups (entries 5–6) were perfectly compatible with the reaction conditions. All the corresponding alcohols were obtained in almost quantitative yields after simple filtration and evaporation.

Next, we began our optimization by testing the effect of several different bases on the hydrogenation with cyclohexanone as model substrate (Table 2). It was found that employment of other commonly used inorganic and organic bases (such as Et_2NH, DBU, DIPEA, Pyridine, NaOH, and EtONa) in combination with platinum dioxide also allowed hydrogenation of cyclohexanone, but the conversion did not proceed to completion and thereby gave relatively low yields. Moreover, the reaction was found to proceed smoothly in excellent yield with not less than 3 equivalent of triethylamine. Further optimization with platinum dioxide-triethylamine showed that 95% ethanol, instead of methanol and THF, was the most suitable solvent for this hydrogenation. To this end, 3 equiv of triethylamine and 0.05 equiv of PtO_2 in 95% ethanol were found to be the optimal condition.

The high activity of this catalytic hydrogenation of aldehydes and cyclohexanones naturally led us to evaluate the possibility of hydrogenation of other cyclic ketones and acyclic ketones. Many cyclic ketones were prepared and treated with hydrogen in the presence of PtO_2–Et_3N (Table 3). Notably, no (or with low yield) reduction product was observed from the hydrogenation of five-, seven-, eight-, or ten-membered cyclic ketones. The only exception is cyclohexanones, which could be hydrogenated in high yields

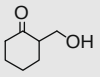
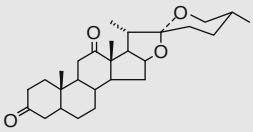
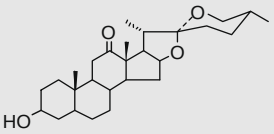
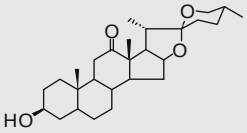
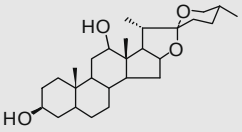
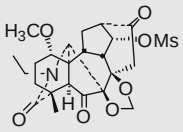
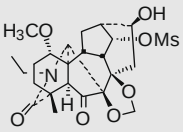
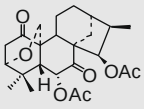
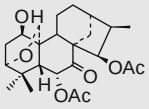
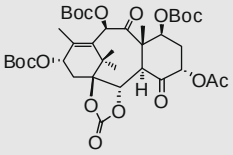
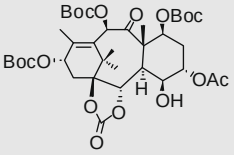
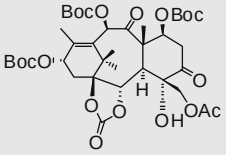
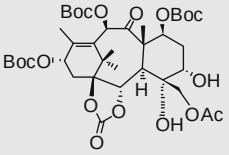
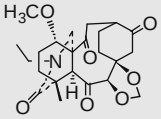
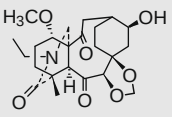
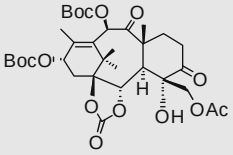
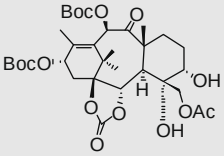
Table 2
Base and solvent optimization for PtO_2-catalyzed hydrogenation of cyclohexanone[a]



Entry[a]	Base (equiv)	Solvent	Yield[b] (%)
1	Et_3N (3.0)	95% EtOH	97.5
2	Et_3N (6.0)	95% EtOH	97.5
3	Et_3N (1.5)	95% EtOH	75.0
4	Et_3N (0.5)	95% EtOH	65.0
5	Et_3N (3.0)	MeOH	85.0
6	Et_3N (3.0)	THF	70.0
7	Et_3N (3.0)	CH_2Cl_2	25.0
8	Et_3N (3.0)	Toluene	20.0
9	Et_3N (3.0)	DMF	65.0
10	Et_2NH (3.0)	95% EtOH	90.0
11	DBU (3.0)	95% EtOH	45.0
12	DIPEA (3.0)	95% EtOH	25.0
13	Pyridine (3.0)	95% EtOH	45.0
14	NaOH (3.0)	95% EtOH	40.0
15	EtONa (3.0)	EtOH	50.0

[a] Reaction conditions: cyclohexanone (10.0 mmol), PtO_2 (5 mol %), base (5.0–30.0 mmol), and solvent (5.0 ml) under H_2 (1 atm) for 24 h.
[b] Yields reported were calculated based on the ^1H NMR data.

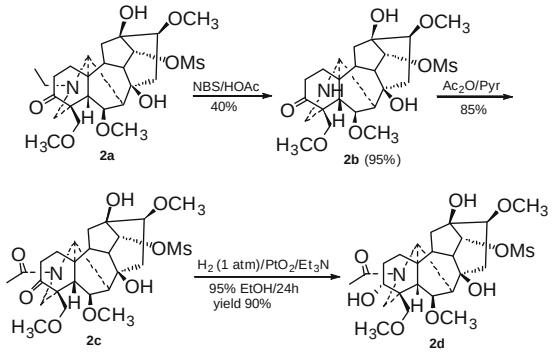
Table 3
PtO_2–Et_3N-catalyzed hydrogenation of cyclohexanones

Entry	Cyclohexanones	Alcohols	Yield (%)
1		 cis:trans = 3:1	95
2		 α:β = 1:3	95
3		 α:β = 1:3	90
4			85
5			90
6			80
7			90
8		 α:β = 4:6	90
9			90

(Table 3). At this point, we paid our attention to the evaluation of the chemoselective hydrogenation of simple cyclic ketones to exclude the possibility of steric effect on the reaction. Accordingly, cyclopentanone, cyclohexanone, and cycloheptanone were hydrogenated under 1 atm H_2 for 24 h, respectively. It was found that only cyclohexanone was quantitatively converted to cyclohexanol, and that almost all of cyclopentanone (85%) and cycloheptanone (90%) were recovered from the hydrogenation (Supplementary data). Several acyclic ketones (such as butan-2-one, 3-methylbutan-2-one, 3,3-dimethylbutan-2-one, acetophenone, and benzophenone) were treated with hydrogen in the presence of PtO_2–Et_3N as well, which only furnished the corresponding alcohols in less than 30% yield. This chemoselective hydrogenation of cyclohexanones would be particularly useful in the synthesis and structural modifications of complicated natural products.

Interestingly, the cyclohexanone in alkaloid **2a** did not undergo the hydrogenation under this condition. Consideration of the possible influence of alkalinity, the nitrogen atom in alkaloid **2a** was deactivated by N-deethylation[11] followed by acetylation to give **2c** (Scheme 2). Very happily, the N-deactivated compound **2c** was readily hydrogenated to alcohol under our aforementioned reaction condition (Scheme 2), which indicated that the alkalinity of the nitrogen atom is detrimental to the hydrogenation reaction catalyzed by PtO_2–Et_3N.

The mechanistic understanding of heterogeneous catalytic hydrogenation of ketones is still relatively poor as compared with that of



Scheme 2. Preparation and hydrogenation of compound **2c**.

homogeneous catalysts.[4] Despite the impressive development in the field of the hydrogenation of activated ketones by supported platinum catalyst (usually Pt/Al_2O_3) modified with cinchona alkaloids, the mechanistic details at the base of the reaction are still under debate.[12] Several models have been developed, and the conflicting opinions reflect the great scientific interest of this topic.

It was demonstrated that the bifunctional M–H/N–H motif, a hydride and amine cis-coordinated on the metal center, plays an important role for the hydrogenation of ketones.[3e,12–17] Similarly, we presumed that PtO_2/Et_3N has the bifunctional Pt–H/N–H motif, which could enhance the catalytic ability of Platinum based on the following observations: (i) when triethylamine was replaced by other bases, such as NaOH, diisopropylethylamine, pyridine, and isobutylamine, the conversion rate of the hydrogenation was significantly decreased; (ii) Benzophenone (a ketone that cannot be enolized) can be hydrogenated in about 25% yield under the aforementioned condition; and (iii) Benzaldehyde (an aldehyde that cannot be enolized) was hydrogenated in the presence of PtO_2/Et_3N in quantitative yield. In addition, it was reported that the enol form can also be the reactive species in the hydrogenation of the activated ketone on modified platinum.[12] The triethylamine might lead to the formation of a protonated amine-enolate salt of ketones and aldehydes. Accordingly, we surmised that the hydrogenation of ketones and aldehydes catalyzed by PtO_2/Et_3N might experience the enol form intermediate alternatively. In this case, the different stability of the enol might elucidate the ring size-selectivity hydrogenation observed in our experiments because the cyclic six-membered enols are most stable among the cyclic enols.

In summary, the first hydrogenation of aldehydes and chemoselective hydrogenation of cyclohexanones catalyzed by PtO_2–Et_3N was presented. This novel method is quite general, and proceeds efficiently at ambient temperature and under atmospheric H_2 pressure. The aldehydes can be hydrogenated in high yields; and cyclohexanones can be selectively reduced to the corresponding alcohols in the presence of other cyclic ketones, which would be greatly beneficial to the complicated natural product chemistry. In addition, PtO_2 and Et_3N are commercially available, easy to handle, and the products can be easily separated by filtration and evaporation. An additionally attractive feature of this hydrogenation is being applicable to the complicated molecules. Extension of this work and investigation of its reaction mechanism are currently in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.006.

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