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Tetrahedron 61 (2005) 2105–2109
Tetrahedron

# The effects of added ammonium chloride in the reductive amination of some carbonyl compounds over Ru and Pd catalysts

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Received 8 October 2004; accepted 20 December 2004

Available online 21 January 2005

**Abstracts**—The reductive amination of acetophenone, (+)-camphor, and 5α-cholestan-3-one over Ru and Pd metals as well as their carbon-supported catalysts gave corresponding amines together with alcohols as by-products. However, we found that the corresponding amines are selectively synthesized by the addition of ammonium chloride to the reaction system with depression of the formation of alcohol, as exemplified with acetophenone. Although alcohols are usually not formed over Pd with alicyclic ketones, the alcohols formation was effectively depressed over Ru in the presence of ammonium chloride. The effects of the additive on the stereoselectivity of the formation of amines are also discussed in the cases of (+)-camphor and 5α-cholestan-3-one.


## 1. Introduction

Reductive amination of carbonyl compounds with ammonia[1] is one of the most frequently used procedures in the preparation of amines. However, the reaction is complicated by the formation of primary, secondary or tertiary amines. Furthermore, the hydrogenation of carbonyl compounds to alcohols occurs as a significant side reaction. Therefore, the controlling of the reaction conditions is required for the selective synthesis of the desired amines. The product distribution may be influenced by the molar ratio of the carbonyl compound to ammonia, the molecular structure of the carbonyl compound, additives such as acids or bases, and the nature of catalysts.

In the preceding papers,[2–5] we reported that the reductive amination of carbonyl compounds over platinum metal catalysts exhibited different reactivity and selectivity according to the catalysts used and the compounds subjected to the reaction.

In the reductive amination, the carbonyl compound and ammonia first undergo an addition reaction to give a hemiaminal as an intermediate that may undergo hydrogenolysis directly to give a primary amine and/or be dehydrated to give an imine. The hydrogenation of the formed imine gives the primary amine (Scheme 1). In addition, the reaction between the primary amine formed and the imine or the carbonyl compounds may lead to formation of a secondary amine. Concurrently, simple hydrogenation of the carbonyl compound to give an alcohol may also occur.

In this paper the selective synthesis of the primary amine from the carbonyl compounds such as acetophenone (**I**), (+)-camphor (**II**) and 5α-cholestan-3-one (**III**) has been studied with unsupported and carbon-supported Ru and Pd as catalysts. The selective synthesis of the primary amine could be achieved with depression of the alcohol formation by the addition of ammonium chloride to the reaction system.

## 2. Results and discussion

The formation of primary amines in the reductive amination of carbonyl compounds proceeds via steps 1 and 2 or step 3 in Scheme 1. The reaction to give an imine (step 1) formation may be competitive with the formation of alcohols (step 7). Various additives have been used to promote the formation of the imine intermediate.[6] Previously, Alexander[7] reported the effect of additives in the reductive amination of acetophenone over an Adams Pt catalyst. The addition of ammonium chloride to the reaction system increased the yield of the primary amine with depression of formation of secondary amine. However, as reported previously, in the reductive amination of nonanal, the formation of secondary amine was not depressed and the yield of primary amine was not increased by addition of

*Keywords*: Reductive amination; Platinum metal catalysts; Acetophenone; (+)-Camphor; 5α-Cholestan-3-one.
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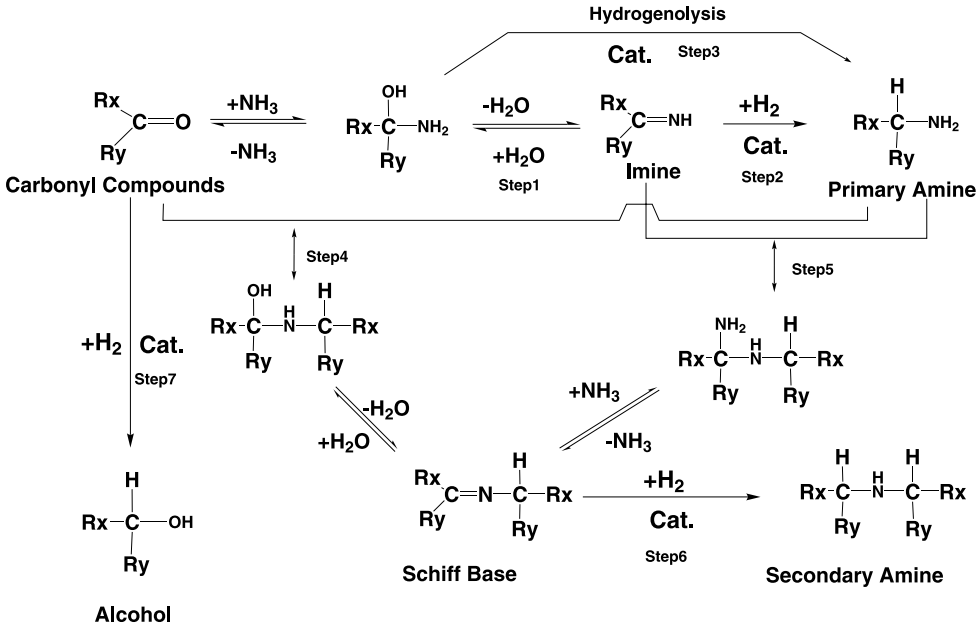
0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.12.062




**Scheme 1.** Reductive amination of carbonyl compounds.

ammonium chloride over platinum metals including platinum as catalysts.[4]

In this study, we examined in detail the effects of the addition of ammonium chloride in the reductive amination of acetophenone (**I**), (+)-camphor (**II**), and 5α-cholestan-3-one (**III**) over Ru and Pd blacks as well as 5%Ru and 5%Pd on carbon as catalysts. The results are shown in Tables 1 and 2.

Although the formation of the secondary amine is usually very slight with alicyclic ketone in both the presence and absence of ammonium chloride, the secondary amine was obtained in 36 and 16% yields, respectively, with **I** over Ru black and with **II** over Pd black in the presence of ammonium chloride. This result is not consistent with those reported by Alexander with Adams Pt catalyst. Probably, it is due to the different properties of the catalysts used. The corresponding alcohols were also obtained by simple hydrogenation of the carbonyl compounds, in particular in the absence of ammonium chloride, as seen from the results in Tables 1 and 2. Thus, the formation of alcohols is markedly depressed by the addition of ammonium chloride.

It is well known that the dehydrative condensation reaction between a carbonyl compound and an amine or ammonia is promoted in acidic media. Therefore, it is suggested that the formation of the imine intermediate is promoted by the acidic function of ammonium chloride. Thus the amines are produced in preference to the corresponding alcohols.

## 2.1. The reductive amination of acetophenone (I)

Usually, over Pd black or 5% Pd–C catalysts the hydrogenation of **I** tends to give ethylbenzene by cleavage

**Table 1**. Reductive amination of carbonyl compounds over platinum metals

| Substrate | Catalyst | Additive | Conversion (%) | Composition of reaction mixture/% | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Primary amine | | Alcohol | | *N*-Alkylamine | | Secondary amine | Schiff base |
| | | | | A | B | A | B | A | B | | |
| Acetophenone | Pd | None | 100 | 0 | | 100 | | 0 | | 0 | 0 |
| | | $NH_4Cl$ | 97 | 82 | | 15 | | 0 | | 0 | 0 |
| | Ru | None | 97 | 0 | | 97 | | 0 | | 0 | 0 |
| | | $NH_4Cl$ | 98[a] | 0 | | 55 | | 0 | | 36 | 0 |
| (+)-Camphor | Pd | None | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | $NH_4Cl$ | 86 | 55 | 10 | 1 | 0 | 3 | 0 | 16 | 1 |
| | Ru | None | 30 | 0 | 0 | 27 | 3 | 0 | 0 | 0 | 0 |
| | | $NH_4Cl$ | 79 | 23 | 34 | 4 | 1 | 3 | 1 | 7 | 4 |
| 5α-Cholestan-3-one | Pd | None | 100 | 81 | 19 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | $NH_4Cl$ | 100 | 79 | 21 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Ru | None | 100 | 54 | 26 | 12 | 8 | 0 | 0 | 0 | 0 |
| | | $NH_4Cl$ | 100 | 82 | 16 | 1 | 1 | 0 | 0 | 0 | 0 |

Reaction conditions: acetophenone, $2.5\times10^{-3}$ mol; $H_2$, 8 MPa; temp., 50 °C; time, 5 h. (+)-camphor, $5.0\times10^{-3}$ mol; $H_2$, 8 MPa; temp., 200 °C; time, 5 h. 5α-cholestan-3-one, $2.0\times10^{-4}$ mol; $H_2$, 6 MPa, temp., 50 °C, time, 4 h, additive. $NH_4Cl$, 0.2 g ($3.73\times10^{-3}$ mol) $NH_3$, 1.0 g ($6.0\times10^{-2}$ mol), catalyst, $1.0\times10^{-2}$ g. A; *exo*- or β-position, B; *endo*- or α-position.

[a] Yield of α-methylcyclohexylalcohol as by-product was 7%.

**Table 2**. Reductive amination of carbonyl compounds over 5% carborn supported platinum metals

| Substrate | Catalyst | Additive | Conversion (%) | Composition of reaction mixture/% | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Primary amine | | Alcohol | | *N*-Alkylamine | | Secondary amine | Schiff base |
| | | | | A | B | A | B | A | B | | |
| Acetophenone | Pd/C | None | 100 | 0 | | 100 | | 0 | | 0 | 0 |
| | | $NH_4Cl$ | 98 | 7 | | 91 | | 0 | | 0 | 0 |
| | Ru/C | None | 96 | 5 | | 91 | | 0 | | 0 | 0 |
| | | $NH_4Cl$ | 97 | 44 | | 53 | | 0 | | 0 | 0 |
| (+)-Camphor | Pd/C | None | 88 | 67 | 0 | 0 | 0 | 11 | 0 | 4 | 5 |
| | | $NH_4Cl$ | 99 | 69 | 10 | 2 | 0 | 15 | 1 | 1 | 2 |
| | Ru/C | None | 94 | 1 | 6 | 37 | 18 | 9 | 22 | 0 | 0 |
| | | $NH_4Cl$ | 99 | 32 | 29 | 15 | 3 | 13 | 7 | 0 | 0 |
| 5α-Cholestan-3-one | Pd/C | None | 100 | 78 | 22 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | $NH_4Cl$ | 100 | 87 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Ru/C | None | 100 | 73 | 18 | 4 | 5 | 0 | 0 | 0 | 0 |
| | | $NH_4Cl$ | 100 | 87 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |

Reaction conditions: acetophenone, $2.5\times10^{-3}$ mol; $H_2$, 8 MPa; temp., 50 °C; time, 5 h. (+)-Camphor, $5.0\times10^{-3}$ mol; $H_2$, 8 MPa; temp., 200 °C; time, 5 h. 5α-Cholestan-3-one, $2.0\times10^{-4}$ mol; $H_2$, 6 MPa, temp., 50 °C, time, 4 h. Additive; $NH_4Cl$. 0.2 g ($3.73\times10^{-3}$ mol). $NH_3$, 1.0 g ($6.0\times10^{-2}$ mol). Catalyst, 0.2 g. A; *exo*- or β-position, B; *endo*- or α-position.

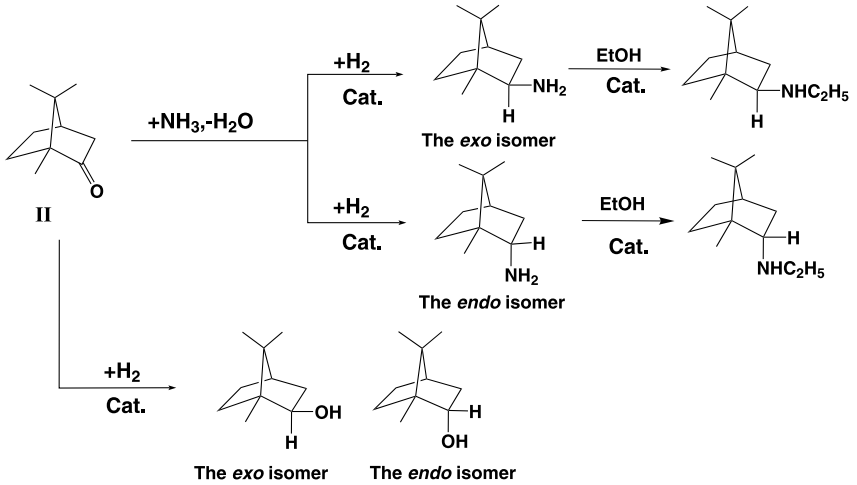
of the C–O bond together with 1-phenylethanol, but the addition of a small amount of organic bases such as morpholine or tetrahydroquinoline depresses the hydrogenolysis to give ethylbenzene.[8]

In the present reaction conditions of reductive amination, the hydrogenolysis did not occur and the yield of 1-phenylethanol was quantitative over both Pd black and 5% Pd–C. Over Pd black, however, the addition of ammonium chloride to the reaction system gave preferentially 1-phenyethylamine with depression of the formation of 1-phenylethanol, as can be seen in Table 1.

On the other hand, over 5% Pd–C the yield of 1-phenylethylamine was only 7.0% in the presence of ammonium chloride. Thus, a great difference was found between the results with Pd black and with 5% Pd–C. We suggest that the hydrogenation of the carbonyl compound may be much faster over highly dispersed palladium metal on carbon than over Pd black. Actually, the hydrogenation rate of **I** in the initial stage over 5% Pd–C was ten times as great as that with Pd black on the basis of unit weight of the metal. In contrast, the reaction of **I** with Pd black proceeded 7.5 times as rapidly in the presence of ammonium chloride as that without the additive. The reductive amination of **I** over Ru black or 5% Ru–C produced almost exclusively 1-phenylethanol. However, both the catalysts provided markedly different results in the formation of amines in the presence of ammonium chloride. On Ru black, bis(1-phenylethyl)-amine was obtained in a yield corresponding to a decrease in the yield of 1-phenylethanol, while on 5% Ru–C the yield of 1-phenylethylamine increased with the decrease in the yield of the benzyl alcohol. Thus, no primary amine was formed on Ru black and no secondary amine was produced on 5% Ru–C in the presence of ammonium chloride. In the reaction with Raney Ni, Robinson, Jr. and co-workers obtained 1-phenylethylamine in 44–52% yield,[9] whereas the yield of the amine was increased to 91% by the addition of small amounts of glacial acetic acid to the reaction mixture as described by another investigators.[10] On Pd black, the addition of ammonium acetate, instead of ammonium chloride, resulted in a decrease to 47% in the yield of 1-phenylethylamine.

## 2.2. The reductive amination of (+)-camphor (II)

In the reductive amination of **II** and cholestan-3-one(**III**) it is possible to observe not only the selectivity on the




**Scheme 2.**

formation of the amines and alcohols but also the stereoselectivity of the formation of stereoisomeric amines or alcohols. A higher reaction temperature of 200 °C was required to promote the reaction for the hindered ketone **II**.

The reaction with Pd black did not proceed at all in the absence of ammonium chloride while isobornylamine (the *exo* isomer) and bornyl amine (the *endo* isomer) (see Scheme 2) were obtained in 55% and 10% yields, respectively, in the presence of ammonium chloride (see Table 1). The yield of isobornyl alcohol was only 1%. Without ammonium chloride the appearance of Pd black has changed from a finely divided particle form (surface area: 33.4 $m^2$/g) before the reaction to a silvery white metallic form (surface area: 0.47 $m^2$/g) after the reaction. In the presence of ammonium chloride, the catalyst apparently did not change before and after the reaction, but the surface area of the Pd black was found to decrease to about 4–6 $m^2$/g. Evidently, the metallic Pd black suffered from an extreme sintering in the absence of the additive. It is of interest that the extreme sintering was prevented in the presence of ammonium chloride and the reductive amination of **II** proceeded smoothly. It is probable that the sintering was inhibited by a strong adsorption to the catalyst surface of the imine intermediate formed rapidly in the presence of ammonium chloride. It is known that the sintering of a platinum catalyst slowed down appreciably when the chloride ion content of the catalyst is maintained to about 1 wt%.[11] Therefore, it may be possible that the sintering of the Pd catalyst was also inhibited by the chloride ion from the ammonium chloride added.

On 5% Pd–C, the reductive amination proceeded readily both with or without ammonium chloride. However, the formation of the primary amine was further increased by the addition of ammonium chloride as can be seen from Table 2.

With respect to the stereoselectivity of the primary amine formed, isobornylamine (the *exo* isomer) was formed predominantly together with a small amount of bornylamine (the *endo* isomer) in the presence of ammonium chloride over both Pd black and 5% Pd–C. Unexpectedly, the *exo* isomer was exclusive over 5% Pd–C in the absence of ammonium chloride.

A high reaction temperature led to the formation of *N*-ethylbornylamines consisting of the *exo* and the *endo* isomers (see Scheme 2).

It is probable that the *N*-ethyl derivatives were formed by the reaction between the *exo* or the *endo* amine isomers and the acetaldehyde formed by the dehydrogenation of ethanol used as the solvent on the catalyst. It is noted that the stereoisomeric composition of the *N*-ethylamines is not much different from that of the amines.

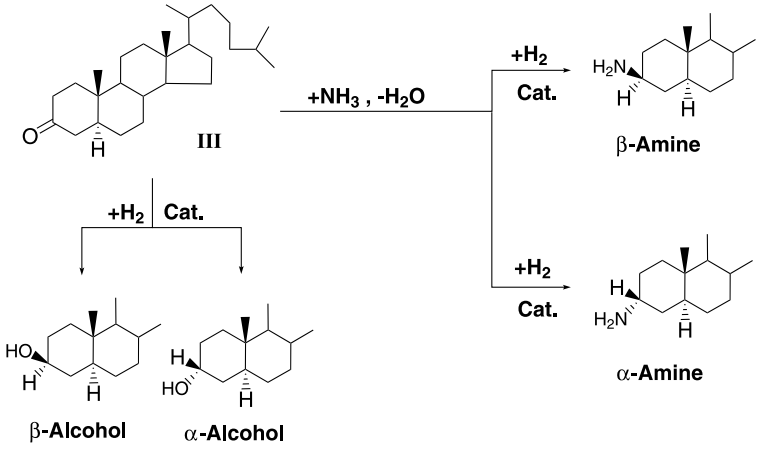
On Ru black and 5% Ru–C, the formation of the primary amine was also increased by the addition of ammonium chloride, while the alcohol was produced largely in the absence of ammonium chloride.

As described previously, the reductive amination of **II** with or without ammonium chloride over 5% Pd–C gave mainly the *exo* isomer. The thermodynamically more stable isomer of the primary amines is likely to be the *endo* isomer.[12] Thus over 5% Pd–C, the unstable *exo* isomer was formed predominantly with or without ammonium chloride. The formation of the *exo* isomer would probably result by the addition of hydrogen preferentially from a less hindered side (*endo* side) to the imine intermediate formed from **II**. On the other hand, the reductive amination of **II** in the presence of ammonium chloride over 5% Ru–C gave almost the same amounts of both the isomers. The formation of the *endo* isomer may be increased by increasing the addition of hydrogen to the more stable half-hydrogenated states of those formed from the imine intermediate.

### 2.3. The reductive amination of 5α-cholestan-3-one (III)

The reductive amination of **III** proceeded more smoothly under the addition of ammonium chloride than in the absence of the additive. Over Ru black and 5% Ru–C, the production of the alcohol was almost completely depressed by the addition of ammonium chloride.

With respect to the stereoselectivity of the steroid amine formed, the β-amino isomer (see Scheme 3) was obtained in larger amounts than the α-amino isomer (see Scheme 3) over both Pd black and 5% Pd–C.




**Scheme 3.** Reductive amination of 5α-cholestan-3-one.

Previously, Nishimura and co-workers reported[13] that the hydrogenation of **III** over Pd metal catalyst overwhelmingly gave the β-alcohol isomer. This result has been explained on the basis of an attractive interaction of the steroid α-face with the Pd catalyst. In the reductive amination, the structure of the steroid imine intermediate may be similar to that of **III**. Therefore it is presumed that the addition of hydrogen to the α-side of the steroid imine intermediate may occur predominantly, as in the hydrogenation of **III**.

The reductive amination of III over Ru and 5% Ru–C also gave the β-amino isomer in greater amounts than the α-amino isomer and the selectivity to the β-amino isomer further increased in the presence of ammonium chloride. It is probable that the stereochemistry is controlled more to give the β-amino isomer by the hydrogenation step of the steroid imine which would be produced more rapidly in the presence of ammonium chloride.

## 3. Experimental

*Catalyst*. The Pd or Ru metal catalysts were prepared by reducing the corresponding metal hydroxides (1.0 g) in distilled water (20 $cm^3$) for 30 min at room temperature and under 0.2–0.3 MPa of hydrogen pressure in a Parr hydrogenation apparatus. The metal black thus produced was washed with distilled water until the washing was neutral, and then dried in a desiccator under vacuum at room temperature.

Commercial 5% Pd or Ru on carbon catalysts were purchased from N.E.Chemcat Co., Ltd.

*Material*. Compound **I** (a purity of over 98%), compound **II** (a purity of over 98%) and compound **III** (a purity of over 97%) were purchased from Wako Pure Chemical Ind., Ltd, Tokyo, Tokyo Kasei Kogyo Co., Ltd Tokyo, and Aldrich Chemical Co., USA, respectively. These compounds in a purity of over 97–98% as judged by gas chromatography were used without further purification.

Reductive amination and analysis of reaction mixtures: A 30 $cm^3$ autoclave (for reaction of **I**) and a 100 $cm^3$ autoclave (for reaction of **II** and **III**) of an electromagnetically stirring type were charged with the catalyst (0.01 g of Pd or Ru metal, or 0.2 g of 5% Pd or Ru metal on carbon catalyst), the carbonyl compound [**I** (0.30 g, $2.5\times10^{-3}$ mol), **II** (0.77 g, $5.0\times10^{-3}$ mol), and **III** (0.077 g, $2.0\times10^{-4}$ mol)], and 10–20 $cm^3$ of the solvent EtOH at an initial hydrogen pressure of 6-8 MPa. The temperature was maintained constant at 50 °C for **I**, at 200 °C for **II** and at 50 °C for **III**, during the reductive amination. Ammonia gas was led into chilled ethanol solvent (10–20 $cm^3$) through a soda-lime tube from the ammonia bomb and then the amount of ammonia dissolved [about 1.0 g ($6.0\times10^{-2}$ mol)] was determined by balance. Ammonium chloride [0.2 g ($3.73\times10^{-3}$ mol)] was added to the solvent. After the completion of the reaction, all products were analyzed by gas chromatography (SHIMADZU GC-14A) using a capillary column (25 m for reaction mixture of **I** and **II** and 50 m for reaction mixture of **III**) containing CBP1 and also identified by direct comparison with authentic samples. The temperature was raised to 260 °C at 5 °C/min after holding 60 °C for 20 min for the reaction mixture of **I**. For the reaction mixture of **II**, it was raised to 200 °C at 5 °C/min after holding at 70 °C for 10 minutes. The temperature was maintained constant at 280 °C for the reaction mixture of **III**. The structure of bornylamine (the *endo* isomer), isobornylamine (the *exo* isomer), and α- and β-5α-cholestan-3-amines produced from **II** and **III** were confirmed by GC-MS (JMS-Automass 150, JEOL Ltd, Tokyo) and $^1$H NMR (Fourier Transform NMR Spectrometer Model R-90H, Hitachi, Ltd, Tokyo). The structure of *N*-ethylbornylamine and *N*-ethylisobornylamine were confirmed by measurements with GC-MS and $^1$H NMR, and a related study[14] for their analysis. The surface area of Pd metal blacks was measured by SHIMADZU FLOW SORB II 2300, Shimadzu Co., Ltd Tokyo.

## Acknowledgements

We are grateful to Professor emeritus Shigeo Nishimura of Tokyo Univ. of Agriculture and Technology for his helpful comments.

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