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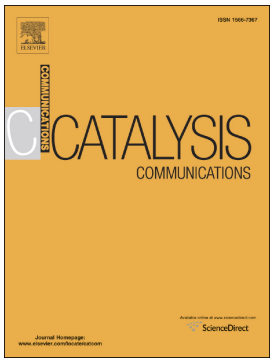


# Highly enantioselective reduction of ketones in air catalyzed by Rh-based macrocycles

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# Highly Enantioselective Reduction of Ketones in Air Catalyzed by Rh-Based Macrocycles

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## Abstract

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The asymmetric transfer hydrogenation (ATH) of ketones catalyzed by Rh-based macrocycles proceeded smoothly in the presence of air with high catalytic activity and enantioselectivity. Even though the S/C ratio (substrate to catalyst molar ratio) was increased up to 2000:1, the ATH of ketone still afforded 92% isolated yield with 92% ee. Notably, the Rh-based macrocycles could be successfully used to catalyze the ATH of ketones without any need of inert atmosphere, which further highlighted its advantage over those generally air-sensitive transition catalysts. The addition of $NH_4I$ greatly improved both the catalytic activity and enantioselectivity. On the basis of NMR evidence, we postulate that the $NH_4I$ significantly enhanced the coordination between chiral macrocyclic ligands and rhodium center.

## Keywords

Asymmetric transfer hydrogenation; Ketones; Rhodium complex; Chiral macrocyclic ligands; Air-stable chiral catalyst

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## 1. Introduction

Enantioselective reduction of prochiral ketones is a powerful method to obtain chiral alcohols, which are important intermediate in pharmaceuticals, agricultural chemicals, and other fine chemical industries [1-19]. Among the enantioselective reduction of ketones, asymmetric hydrogenation (AH) catalyzed by transition metal is an atom economic process. However, it was generally conducted under high-pressure hydrogen gas, which would cause safety problems. Compared with AH, asymmetric transfer hydrogenation (ATH) uses reducing agents, such as *i*PrOH, and HCOONa instead of hydrogen gas as a source of hydrogen [20-22]. In the past few decades, ATH has been developed as an alternative to AH processes because of its simple and safe operation as well as easy availability of hydrogen sources.

Most ATH reactions require an inert atmosphere because those transition metal catalysts are sensitive to the air and/or the moisture. Therefore, the ATH conducting in air will deliver a convenient and green procedure [23,24]. Herein, we demonstrated the ATH of ketones catalyzed by Rh-based macrocycles catalysts, which could be conveniently employed in air with high catalytic activity and enantioselectivity.

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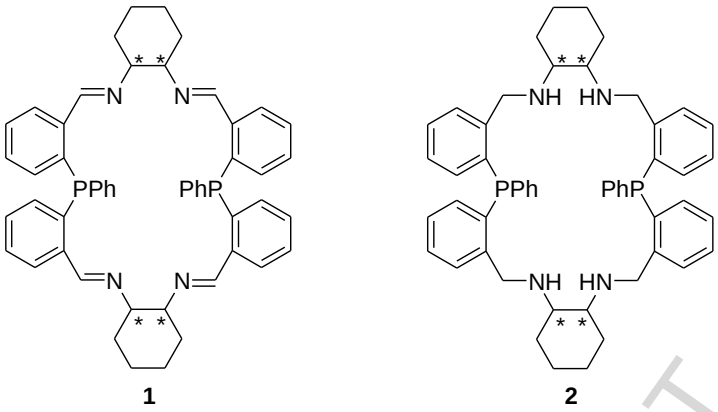


**1** **2**

**Figure 1.** Chiral macrocyclic ligands **1** and **2**.

## 2. Experimental

**Typical procedure for ATH of ketones.** Chiral macrocycles **1** and **2** were synthesized using the same procedure we previously reported [25]. Under air atmosphere, the complex $RhH(CO)(PPh_3)_3$ (9.2 mg, 0.01 mmol), (*R, R, R', R'*)-**2** (8.0 mg, 0.01 mmol), and $NH_4I$ (22.0 mg, 0.15 mmol) were placed in a tube equipped with a Teflon-coated magnetic stirring bar. Then, *i*PrOH was added and the mixture was stirred at 65 $^{o}$C for 30 min. Next, an appropriate amount of KOH/*i*PrOH solution was added, and the mixture was continually stirred for another 10 min. Later, ketone was introduced, and the mixture was stirred at the desired temperature for the required reaction time. At the end of experiment, the reaction products were determined by GC using a chiral CP-Chiralsil-Dex CB column.

**Synthesis of Rh-based macrocycle 3**. The reaction was conducted in air.

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A solution of $RhH(CO)(PPh_3)_3$ (92.0 mg, 0.1 mmol), (*S,S,S',S'*)-**2** (80.0 mg, 0.1 mmol), and $NH_4I$ (218.0 mg, 1.5 mmol) in *i*PrOH (35 mL) was stirred at 65 $^oC$ for 30 min. The resulting brown solution was cooled to room temperature. Removal of the solvent under reduced pressure afforded a brown solid. The brown solid was dissolved in $CH_2Cl_2$ and washed thrice with $H_2O$. The organic layers were dried over anhydrous $Na_2SO_4$. After filtration and removing the solvent in vacuum, the crude product was recrystallized from $CH_2Cl_2$/*n*-hexane solution to give brown solid, Rh-based macrocycle **3**.

## 3. Results and Discussion

Using *i*PrOH as hydrogen source and solvent, we chose propiophenone as the model substrate for ATH. With the catalyst formed *in situ* from rhodium complexes and chiral macrocycles **1** or **2**, the enantioselective reduction of propiophenone was conducted in the presence of air (Table 1). Among the tested catalyst systems, the catalyst generated *in situ* from $RhH(CO)(PPh_3)_3$ and chiral macrocycle **2** afforded good enantioselectivity (70% ee, Table 1, entry 6). The activity difference between macrocycle **1** and **2** was attributed to the promoting effect of NH functions in the ligand **2**, which was similar to our previous results [25]. Notably, the reaction proceeded in open air without any need of inert

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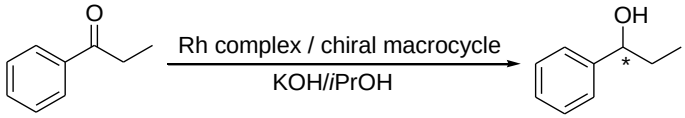
atmosphere, leading to more convenient operations.

**Table 1** ATH of propiophenone catalyzed by Rh-based macrocycles in air [a]




| Entry | Catalyst | Conv. (%)[b] | Ee (%)[b] | Config. [b] |
|---|---|---|---|---|
| 1 | $RhCl_3 \cdot 3H_2O$/(*R, R, R', R'*)-**1** | 15 | 35 | *S* |
| 2 | $RhCl_3 \cdot 3H_2O$/(*R, R, R', R'*)-**2** | 17 | 33 | *S* |
| 3 | $RhCl(PPh_3)_3$/(*R, R, R', R'*)-**1** | 26 | 11 | *S* |
| 4 | $RhCl(PPh_3)_3$/(*R, R, R', R'*)-**2** | 22 | 51 | *S* |
| 5 | $RhH(CO)(PPh_3)_3$/(*R, R, R', R'*)-**1** | 7 | 6 | *S* |
| 6 | $RhH(CO)(PPh_3)_3$/(*R, R, R', R'*)-**2** | 24 | 70 | *S* |
| 7 | $[Rh(COD)Cl]_2$/(*R, R, R', R'*)-**1** | 13 | 19 | *S* |
| 8 | $[Rh(COD)Cl]_2$/(*R, R, R', R'*)-**2** | 18 | 27 | *S* |
| 9 | $[Cp^*RhCl_2]_2$/(*R, R, R', R'*)-**1** | 21 | 57 | *S* |
| 10 | $[RhCl_2Cp^*]_2$/(*R, R, R', R'*)-**2** | 16 | 37 | *S* |
| 11 | $(C_2H_4)_4Rh_2Cl_2$/(*R, R, R', R'*)-**1** | 15 | 5 | *S* |
| 12 | $(C_2H_4)_4Rh_2Cl_2$/(*R, R, R', R'*)-**2** | 20 | 23 | *S* |

[a] Propiophenone (1 mmol) with ketone/Rh/macrocycles/KOH = 100:1:1:8 (molar ratio), *i*PrOH (10 mL), 65 °C, 4 h. [b] Conversion and enantiomeric excesses (ee) were determined by GC analysis using a chiral CP-Chiralsil-Dex CB column. The

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absolute configuration was determined by comparison of the retention times with the literature data.

It has been demonstrated that the addition of salt could improve the catalytic activity and enantioselectivity in some degree for some ATH reaction [26]. Therefore, we investigated the effect of additives on ATH of propiophenone with the catalyst formed *in situ* from $RhH(CO)(PPh_3)_3$ and chiral macrocycle **2** (Table 2). It was observed that both the catalytic activity and enantioselectivity increased by the addition of salts. It was very interesting to note that ammonium salts are more favorable to high activity and enantioselectivity. For example, for the potassium salts and ammonium salts with the same anions, higher activity and enantioselectivity were obtained when ammonium salts were used as additives (Table 2, entry 2 versus 6 and entry 3 versus 8). More interestingly, for the ammonium salts with different anions as additives, both yields and ees increased gradually from $F^-$, $Cl^-$, and $Br^-$ to $I^-$ (Table 2, entries 5-8). When 10 eq. (related to catalyst) of $NH_4I$ were added, the ATH of propiophenone catalyzed by Rh-based macrocycles proceeded smoothly with excellent yield and enantioselectivity in 4 h (99% yield and 95% ee, Table 2, entry 8).

**Table 2** Effect of additive on ATH of propiophenone catalyzed by $RhH(CO)(PPh_3)_3$/(*R, R, R', R'*)-**2** [a]

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| Entry | Additive | S/M/L/A/$OH^-$ | Conv. (%)[b] | Ee (%)[b] |
|---|---|---|---|---|
| 1 | None | 100:1:1:0:8 | 24 | 70 |
| 2 | KCl | 100:1:1:10:8 | 37 | 72 |
| 3 | KI | 100:1:1:10:8 | 39 | 72 |
| 4 | $NH_4Ac$ | 100:1:1:10:18 | 46 | 79 |
| 5 | $NH_4F$ | 100:1:1:10:18 | 71 | 86 |
| 6 | $NH_4Cl$ | 100:1:1:10:18 | 82 | 91 |
| 7 | $NH_4Br$ | 100:1:1:10:18 | 99 | 93 |
| 8 | $NH_4I$ | 100:1:1:10:18 | 99 | 95 |
| 9 | $(CH_3)_4NBr$ | 100:1:1:10:18 | 67 | 79 |

[a] Propiophenone (1 mmol), S/M/L/A/$OH^-$ = ketone/$RhH(CO)(PPh_3)_3$/(*R*,*R*,*R'*, *R'*)-**2**/additive/KOH (molar ratio), *i*PrOH (10 mL), 65 °C, 4 h. [b] Conversion and ee were determined by GC analysis using a chiral CP-Chiralsil-Dex CB column.

Encouraged by the results, we expanded the ATH catalyzed by Rh-based macrocycles under air atmosphere to a wide range of ketones. The catalyst systems prepared *in situ* from $RhH(CO)(PPh_3)_3$, chiral macrocycle **2,** and $NH_4I$ in *i*PrOH can efficiently catalyze enantioselective reduction of ketones in the presence of base, giving the corresponding secondary alcohols with high yields and excellent ees (Table 3). It is worth noting that the reaction rates and enantioselectivities

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were mildly affected by the steric property of the substrates in alkyl moiety. Acetophenone was reduced smoothly with 77% ee (Table 3, entry 1). While the methyl group was replaced with ethyl, propyl, *n*-butyl, and isopropyl, high yield and up to 99% ee were obtained (Table 3, entries 2-5). Even the reduction of the more hindered cyclohexyl phenyl ketone proceeded with 94% isolated yield and 99% ee (Table 3, entry 6). The rate and enantioselectivity of the reduction were also influenced by electronic properties of the substituents on the ketones. For example, ketone with an electron-donating substituent such as the methyl group to meta position was reduced smoothly with a moderate enantioselectivity (73% ee, Table 3, entry 7). The introduction of an electron-withdrawing substituent, as 3'-chloroacetophenone, tends to lower enantioselectivity but higher yield (91% yield and 73% ee, Table 3, entry 8). Furthermore, the heteroaromatic ketones, such as 1-(thiophen-2-yl)propan-1-one and 1-(thiophen-2-yl)butan-1-one, were also reduced with high enantioselectivity under mild conditions, furnishing 96-97% ee at 45 °C in 24 h (Table 3, entries 9 and 10). With higher S/C ratios (substrate to catalyst molar ratio), the present Rh-based macrocycle catalyst still exhibited high enantioselectivity. For instance, the reduction of cyclohexyl phenyl ketone with an S/C of 2000 afforded 92% isolated yield with 92% ee (Table 3, entry 12). Compared with the rhodium catalyst containing open-chain chiral diaminodiphosphine ligands [27],

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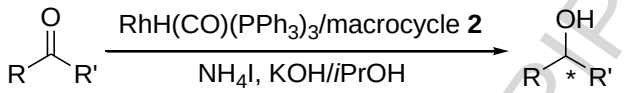
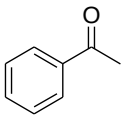
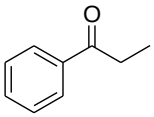
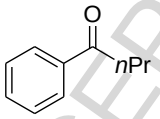
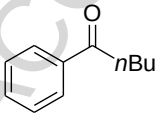
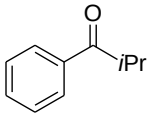
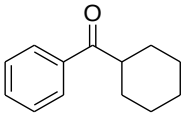
the Rh-based macrocycles exhibited high catalytic activity and enantioselectivity. Notably, the reaction can be conducted without the need for inert atmosphere, which further highlighted its advantage over those air-sensitive transition catalysts.

**Table 3** ATH of ketones catalyzed by $RhH(CO)(PPh_3)_3$/macrocycle **2**[a]




| Entry | Substrate | Temp. (°C) | Time (h) | Isolated Yield (%) | Ee (%)[b] | Config. [b] |
|---|---|---|---|---|---|---|
| 1 |  | 65 | 4 | 91 | 77 | *S* |
| 2 |  | 65 | 3 | 92 | 96 | *S* |
| 3[c] |  | 65 | 4 | 94 | 93 | *R* |
| 4[c] |  | 65 | 4 | 94 | 96 | *R* |
| 5 |  | 65 | 6 | 90 | 99 | *S* |
| 6[c] |  | 65 | 4 | 94 | 99 | *R* |

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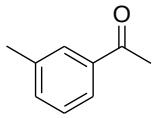
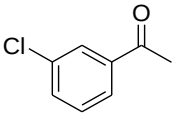
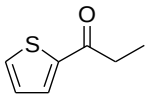
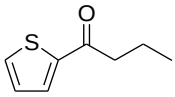
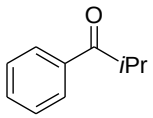
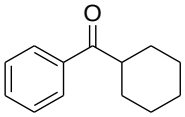
| | | | | | | |
|---|---|---|---|---|---|---|
| 7 |  | 65 | 8 | 92 | 73 | *S* |
| 8 |  | 65 | 3 | 91 | 73 | *S* |
| 9 |  | 45 | 42 | 76 | 97 | *S* |
| 10[d] |  | 45 | 22 | 76 | 96 | *S* |
| 11[e] |  | 80 | 46 | 87 | 91 | *S* |
| 12[f] |  | 80 | 24 | 92 | 92 | *S* |

[a] Substrate (1 mmol), S/M/L/A/B = substrate: $RhH(CO)(PPh_3)_3$: (*R, R, R', R'*)-**2**: $NH_4I$: KOH = 200:1:1:15:23 (molar ratio), *i*PrOH (10 mL). [b] Determined by GC analysis using a chiral CP-Chiralsil-Dex CB column. The absolute configuration was determined by comparison of the retention times with the literature data. [c] (*S, S, S', S'*)-**2** was used. [d] S/M/L/A/B = 100:1:1:15:23. [e] S/M/L/A/B = 1000:1:1:15:40. [f] S/M/L/A/B = 2000:1:1:15:40.

Given the promoting effect of the additives, the mechanism experiments were conducted to understand the active effect role of $NH_4I$ on the above-described ATH. The NMR experiments provided evidence for the effect of $NH_4I$ during the generation of precatalyst in the catalytic

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reaction. As shown in Figure 2, the $^{31}P$ NMR spectrum of $RhH(CO)(PPh_3)_3$ exhibited signal at δ 29.94 ppm while the $^{31}P$ NMR spectrum of macrocycle **2** exhibited signal at δ -27.51 ppm in *i*PrOH. When they were mixed together and stirred for 30 min at 65 °C, a new signal at δ -5.95 ppm appeared. This signal was regarded as free triphenylphosphine ($PPh_3$), indicating that the dissociation process of $PPh_3$ from $RhH(CO)(PPh_3)_3$ happened. However, the interaction between metal precursor and macrocycle **2** was sluggish at this time. With the addition of $NH_4I$, the mixture of $RhH(CO)(PPh_3)_3$, macrocycle **2,** and $NH_4I$ was stirred for 30 min at 65 °C. The $^{31}P$ NMR spectrum showed another new signal at δ 35.45 ppm, accompanying the disappearance of signal at δ -27.51 ppm and the increase of signal at δ -5.94 ppm. It demonstrated that the phosphino groups of macrocycle **2** were coordinated to the rhodium atom. The NMR results showed that the addition of $NH_4I$ enhanced the generation of coordinated Rh-macrocycle species, which is the key active catalytic intermediate for the catalytic cycle.

**Figure 2.** $^{31}P$ NMR spectrum of Rh-based macrocycle catalyst system in *i*PrOH.

Generally, a well-defined complex would be convincing evidence to

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understand the catalytic mechanism. Therefore, we synthesized the precatalyst Rh-based macrocycle **3**. As outlined in Scheme 1, the air-stable compound **3** could be conveniently obtained by simple one-pot method. The $^{31}P$ NMR spectrum of Rh-based macrocycle **3** in $CDCl_3$ exhibited single signal at δ 36.54 ppm (Figure 3), which means that all the phosphino groups of compound **3** coordinating to the rhodium center are in the same chemical environment. Infrared transmittance spectra could give valuable information for the functional groups of catalyst, particularly for the carbonyl groups (CO). The IR spectra of $RhH(CO)(PPh_3)_3$ and Rh-based macrocycle **3** (please see SI) showed that $RhH(CO)(PPh_3)_3$ exhibits characteristic bands at 1920 $cm^{-1}$ $\nu_{(CO)}$, which is consistent with the literature [9]. In the IR spectra of Rh-based macrocycle **3**, the characteristic bands of carbonyl group disappeared, suggesting that in this compound, the CO group was replaced by the macrocycle ligand. The HRMS spectrum of Rh-based macrocycle **3** is presented in SI. Combined with the above results of the $^{31}P$ NMR spectrum and IR spectrum, it can be confirmed that the signal at 1045.21746 corresponds to [Rh-**2**]·$NH_4I$, whereas the signal at 945.29787 corresponds to **2**·$NH_4I$. Therefore, the interaction between $NH_4I$ and macrocycle **2** most likely occurred through hydrogen bond.

**Scheme 1.** Synthesis of precatalyst Rh-based macrocycle **3**.

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Using Rh-based macrocycle complex **3** as catalyst, we investigated the ATH of propiophenone in air. Without additional $NH_4I$, the reaction occurred smoothly with high catalytic activity and enantioselectivity (ketone/**3**/KOH=100:1:18 (molar ratio), 99% yield, 96% ee, 65 °C, and 3 h). This result is as good as that obtained by in-situ catalyst (Table 2, entry 8). On the basis of the spectroscopic evidence and catalytic performance, the proposed promotion role of $NH_4I$ is favorable as, on the one hand, ammonium ions ($NH_4^+$) interacted with chiral macrocycle through hydrogen bonds. This was confirmed from the previous catalytic experiments (Table 2). For KI and $NH_4I$, higher catalytic activity and enantioselectivity were achieved when $NH_4I$ was used as the additives (Table 2, entry 3 versus 8). This indicated that the interaction between $NH_4^+$ and chiral macrocyclic ligands could effectively promote the catalytic activity and ees. On the other hand, $I^-$ was coordinated to the rhodium center. This can also be further confirmed from the previous catalytic experiments (Table 2, entries 5-8). With the increase in negative ion coordination ability, the catalytic activity and enantioselectivity increased correspondingly. Therefore, $NH_4I$ can significantly improve the coordination between chiral macrocyclic ligands and rhodium center. These results proved that the final Rh-based macrocyclic complex **3** is a high catalytic active and enantioselective catalyst.

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**Figure 3.** $^{31}P$ NMR spectrum of Rh-based macrocycle complex **3** in $CDCl_3$.

## 4. Conclusions

In summary, the ATH of ketones catalyzed by Rh-based macrocycles proceeded smoothly with highly catalytic activity and enantioselectivity. The enantioselective reduction could be successfully conducted without any need of inert atmosphere, which offers an easy, convenient, and efficient method to achieve chiral alcohols with high enantioselectivity. Addition of ammonium halide greatly improved the catalytic activity and enantioselectivity. These findings may offer useful insight in the development of novel chiral catalysts. Further investigations on the reaction mechanism are currently ongoing in our laboratory.

## Acknowledgments

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## Supplementary data

## Appendix A. Supplementary material

Supplementary data to this article can be found online.

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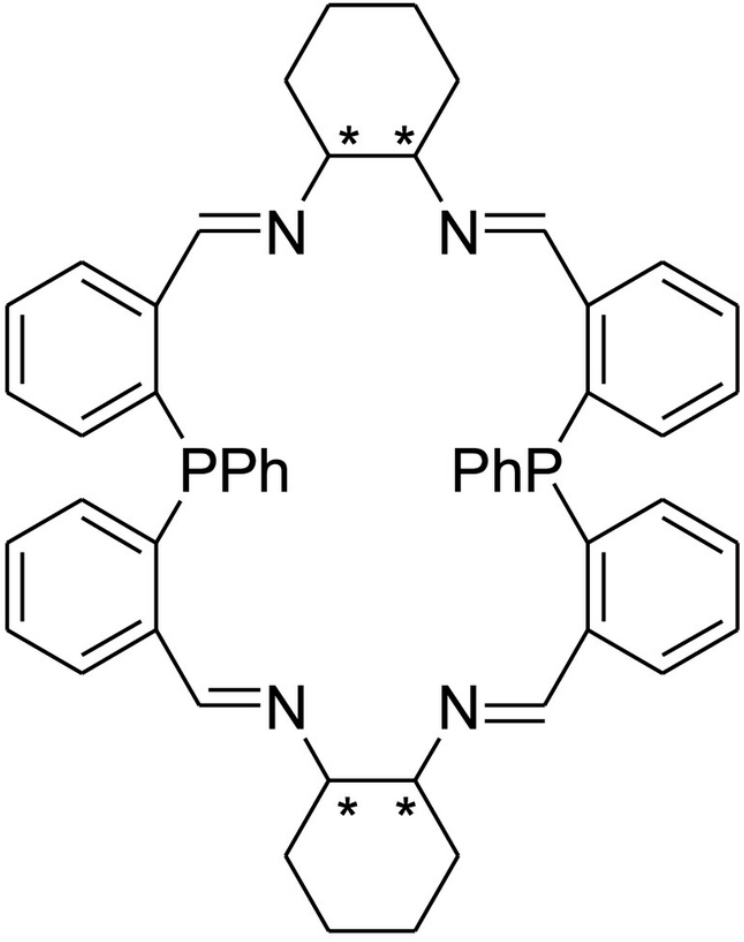
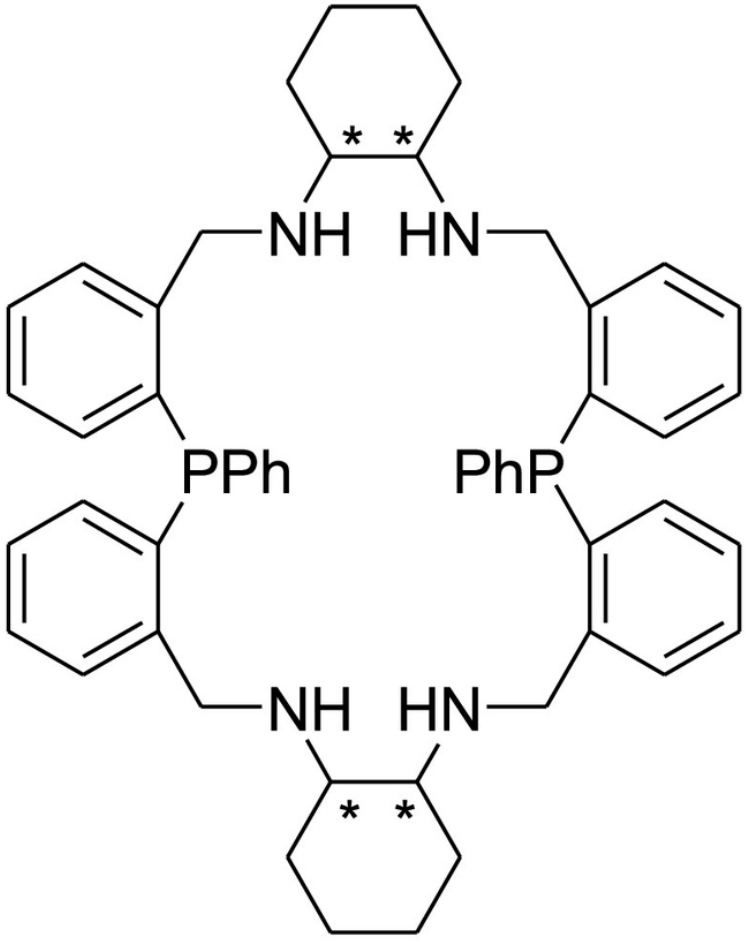
## Highlights

- Highly enantioselective asymmetric transfer hydrogenation of ketones (up to 99% ee).
- The enantioselective reductions proceed smoothly without any need of inert atmosphere.
- Addition of $NH_4I$ greatly improved the catalytic activity and enantioselectivity.




**1**




**2**

Figure 1

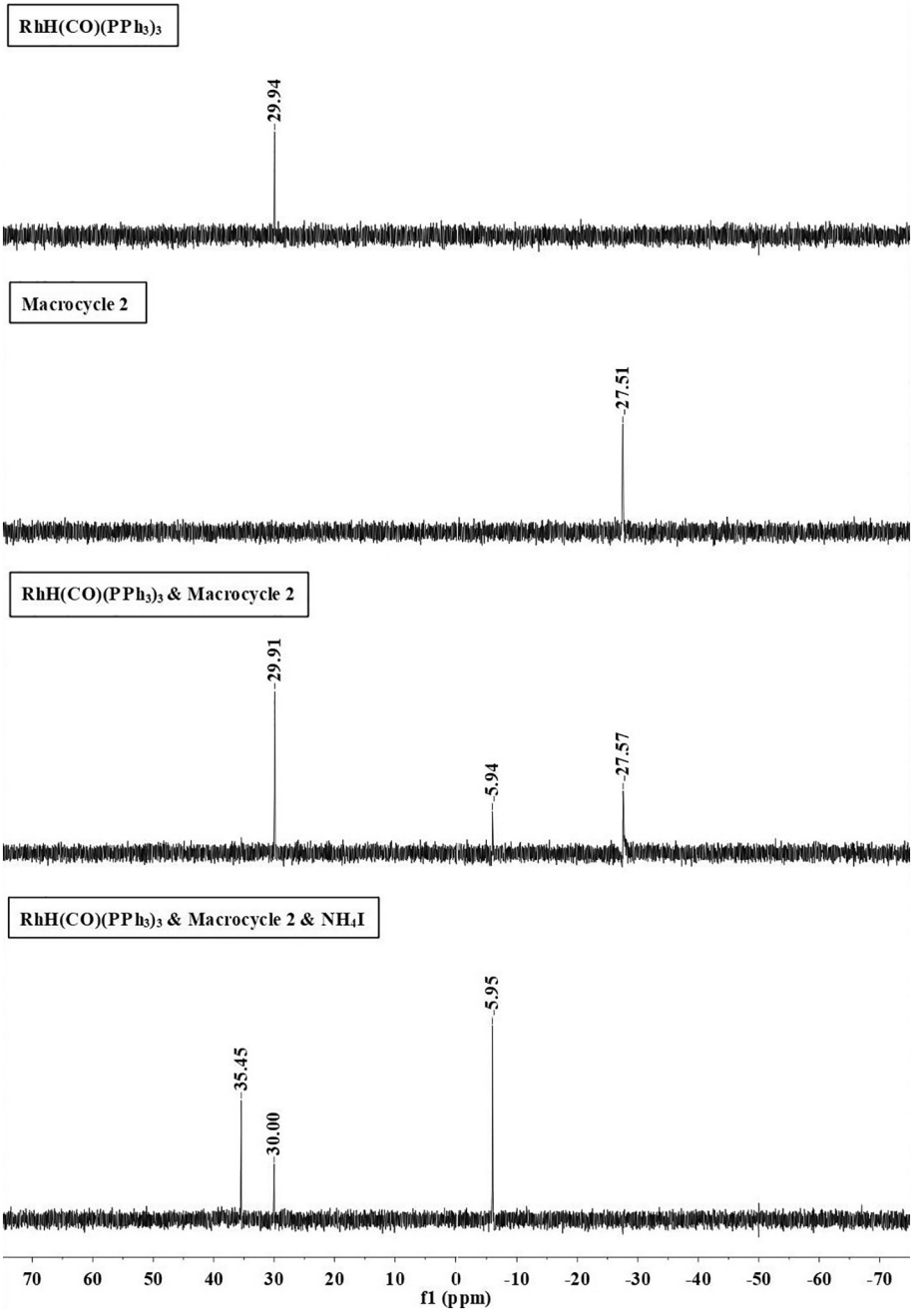

RhH(CO)(PPh3)3
29.94
Macrocycle 2
27.51
RhH(CO)(PPh3)3 & Macrocycle 2
29.91
5.94
27.57
RhH(CO)(PPh3)3 & Macrocycle 2 & NH4I
5.95
35.45
30.00
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70
f1 (ppm)

Figure 2

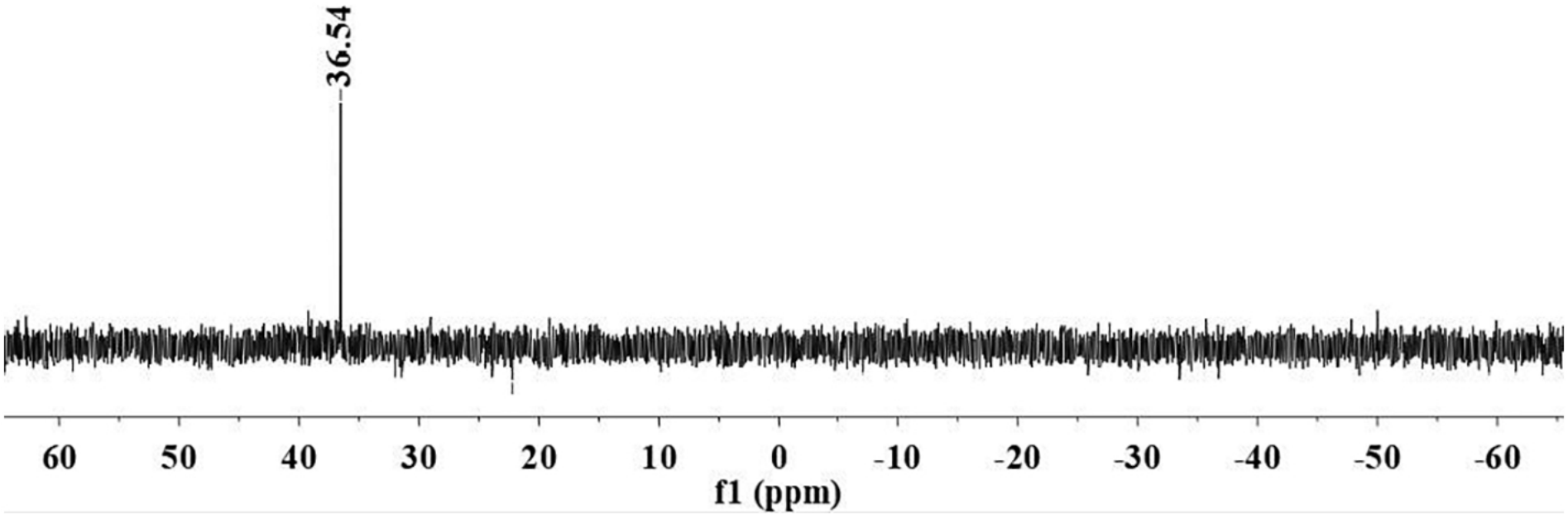



Figure 3