Vietnam Journal of Chemistry, International Edition, **54**(4): 471-476, 2016
DOI: 10.15625/0866-7144.2016-00349

Spectrometric elucidation of intermediates in asymmetric transfer hydrogenation of ketones catalyzed by complex of ruthenium (II) and isosorbide-based ligand

Huynh Khanh Duy

Faculty of Chemical Engineering, Ho Chi Minh City University of Technology

Received 7 June 2016; Accepted for publication 12 August 2016

Abstract

The use of electrospray ionization mass spectrometry for the detection of the intermediate species involved in the ruthenium(II)/β-amino-alcohol derived from isosorbide reduction of ketones to alcohols is described. The formation of active complex of ruthenium (II) for catalyzing the asymmetric transfer hydrogenation of ketones was observed from ^{1}H-NMR spectra. From high resolution mass spectra, peaks of group of isotopes allow to conform the existence of active species of ruthenium (II) in the presence of isosorbide-based ligand. The recorded high resolution mass spectra when following the typical protocol for the asymmetric transfer hydrogenation of acetophenone confirmed an involvement of the active complex mono-hydride ruthenium in the catalytic circle. As a result, high resolution mass spectra in research on catalytic mechanism can be therefore employed as an alternative tool for studying catalytic mechanism.

Keywords. Asymmetric catalysis, isosorbide, asymmetric transfer hydrogenation.

1. INTRODUCTION

Isosorbide **1**, also known as (3*R*,3a*R*,6*S*,6a*R*)-hexahydrofuro[3,2-b]furan-3,6-diol, is a renewable, and commercially available chiral carbohydrate. Isosorbide is basically two fused tetrahydrofuran rings having the cis-arrangement at the ring junction, giving a wedge-shaped molecule [1]. The compound bears two hydroxyl groups, one at C_6 having the *exo*-orientation with respect to the wedge-shaped molecule, and the other at C_3 having the endo-orientation, which makes possible the intramolecular hydrogen bonding with the oxygen atom of the neighbouring tetrahydrofuran ring (Fig. 1).

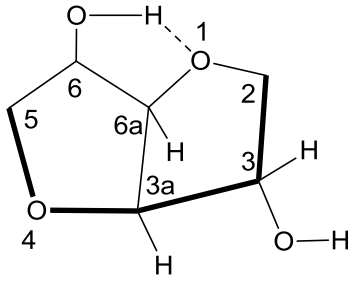
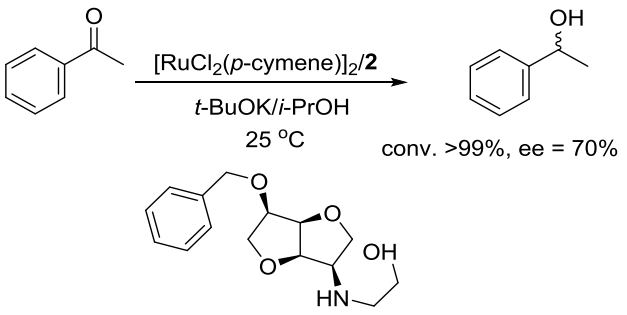


Fig. 1: Structure of isosorbide **1**

Isosorbide is industrially obtained by dehydration of D-sorbitol, and can therefore be considered as a biomass product. It was widely used for the synthesis of sophisticated molecules including chiral ionic liquids [2], phase-transfer catalysts [3], and ligands (amino alcohols, amines, mono- and diphosphines, diphosphites, bis-diaminophosphites, etc) [4, 5].

As a part of our studies, we have recently described the rhodium-catalyzed asymmetric transfer hydrogenation (ATH) of acetophenone using new chiral β-amino-alcohol **2** derived from isosorbide (Fig. 2) [6]. A quantitative conversion and an enantioselectivity (ee) of 70 % were observed when carrying out the ATH in the presence of chiral β-amino-alcohol **2** as chiral ligand. Interestingly, the 1-phenylethanol product could be obtained with an



2

Fig. 2: ATH reaction in the presence of **2**

ee of 80 % in the ATH reaction carried out at -10 ^{o}C. In order to gain an insight into the mechanism of the asymmetric reduction using ruthenium (II) complexes of β-amino-alcohol **2**, an identification of the key intermediates likely to be involved in the process is aimed to be pointed out. We report here the studying on the formation of intermediates in asymmetric transfer hydrogenation of ketones catalyzed by complex of ruthenium (II) and isosorbide-based ligand.

2. EXPERIMENTAL

2.1. General information

The NMR spectra were recorded in $CDCl_3$. ^{1}H NMR spectra were recorded at 300 MHz or 360 MHz. The chemical shifts (δ) are reported in parts per million relative to TMS as internal standard. *J* values are given in hertz. Mass spectra were recorded on a MAT 95S Finnigan-Thermo mass spectrometer using flow injection technique. All reagents and solvents were purchased from commercial sources (Acros, Aldrich) and were used without further purification.

2.2. Characterization of ligand 2 derived from isosorbide 2-((3*R*,3a*R*,6*R*,6a*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-ylamino)ethanol

$[\alpha]_D^{25}$= +123.1 (c 1.1, $CHCl_3$); IR (neat) υ = 3376, 2941, 2872, 1667, 1455, 1369, 1312, 1260, 1208, 1137, 1069, 1026, 924, 823, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, NH), 2.71-2.79 (m, 1H), 2.83-2.91 (m, 1H), 3.31-3.49 (m, 2H), 3.61-3.69 (m, 2H), 3.89 (dd, *J* = 6.6 and 9.0 Hz, 1H), 4.06 (dd, *J* = 4.8 and 6.0 Hz, 1H), 4.11-4.17 (m, 1H), 4.40 (dd, *J* = 4.5 and 4.5 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.62 (dd, *J* = 4.5 and 4.5 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 731-7.34 (m, 5H, benzyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 49.9 (CH_2), 61.3 (CH_2), 62.6 (CH), 71.4 (CH_2), 72.6 (CH_2), 72.6 (CH_2), 79.7 (CH), 80.8 (CH), 81.4 (CH), 127.97, 128.5 (5CH_{Ar}), 137.7 (C); HRMS (EI) m/z 280.1541 (calculated for $C_{15}H_{22}NO_4$ ([M+H]$^+$), 280.1549).

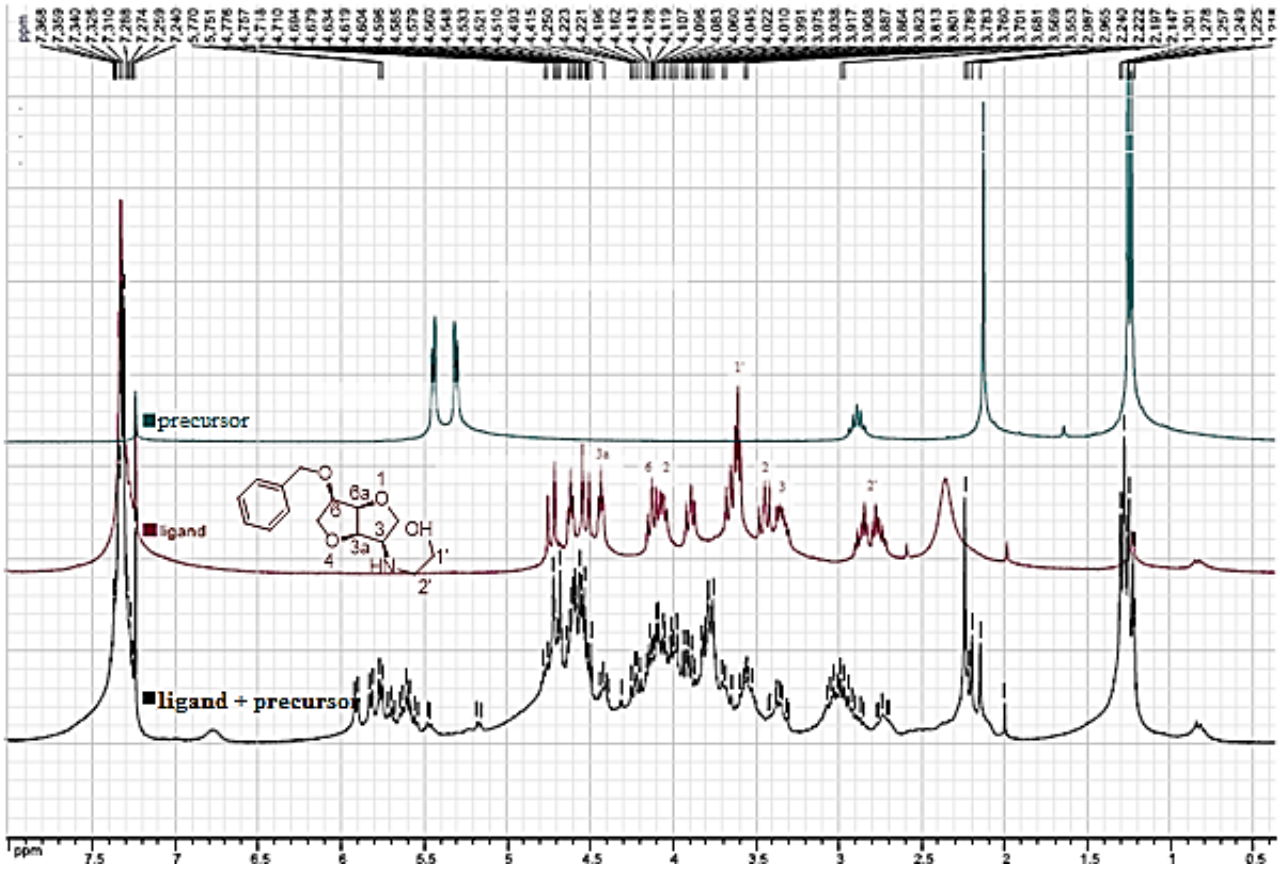


Fig. 3: ^{1}H NMR spectrum of solution of chiral ligand **2** and the precursor $[RuCl_2(p\text{-cymene})]_2$

2.3. ^{1}H NMR spectrum of solution containing ligand 2 and the precursor [$RuCl_2$ (*p*-cymene)]$_2$ with ([Ru]/ligand = 1/2) in $CDCl_3$

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22-1.30 (m, 3H), 2.15-2.24 (m, 1.5H), 2.70-2.77 (m, 0.5H), 2.85-3.07 (m, 2H), 3.30-3.43 (m, 1H), 3.52-3.60 (m, 1H), 3.76-3.82 (m, 2H), 3.86-4.20 (m, 5H), 4.51-4.63 (m, 3H), 4.68-4.78 (m, 2H), 5.54-5.92 (m, 2H_{Ar}), 7.26-7.37 (m, 5H_{Ar}).

2.4. General procedure for the asymmetric transfer hydrogenation of ketones in isopropanol

At first, 0.125 mol% of [$RuCl_2$(*p*-cymene)]$_2$ and 2.5 mol% of the amino alcohol ligand in isopropanol were stirred at 25 ^{o}C for 30 min; 2.5 mol% of potassium *tert*-butoxide, 0.1 M in isopropanol (0.5 mL), and ketone (1 mmol) were added, respectively. The reaction was followed by ^{1}H NMR spectroscopy analysis for calculating the conversion. Enantiomeric excess was monitored with chiral HPLC analysis at 2 h and 24 h reaction times. The reaction was stopped when no evolution of enantiomeric excesses was observed.

Enantiomeric excess was determined by chiral HPLC (column Chiralcel-ODH, hexane : *i*-PrOH = 90 :10, 0.5 mL/min, 254 nm, t_R (*R* isomer) = 10.8 min, t_S (*S* isomer) = 12.2 min). ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.47 (d, *J* = 6.5 Hz, 3H), 1.97 (s broad, OH), 4.86 (q, *J* = 6.5 Hz, 1H), 7.24-7.27 (m, 1H_{Ar}), 7.32-7.36 (m, 4H_{Ar}). ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 25.4 (CH_3), 70.6 (CH), 125.7, 127.7, 128.8 (5CH_{Ar}), 146.1 (C). The analytical data of this compound were in agreement with those previously reported in the literature.

3. RESUTLS AND DISCUSSION

In order to understand the mechanism of the reaction, including the step of asymmetric induction, we were interested in determining structure of the metal complex formed during the reduction of acetophenone in the presence of the chiral ligand **2**. Unfortunately, the various attempts to isolate the desired complex were not successful. No crystal structure by X-ray diffraction was obtained. NMR spectroscopic study was therefore considered. By comparison of the ^{1}H NMR spectrum of the solution containing ligand **2** and the metal precursor [$RuCl_2$ (*p*-cymene)]$_2$ ([Ru]/ligand = 1/2) in $CDCl_3$, with respect to that of ligand **2** only and that of metal precursor only, we observed a significant displacement of chemical shift of the protons of the aromatic ring of *p*-cymene toward 5.5-6 ppm. The displacement of chemical shifts of the protons at position α respect to the nitrogen atom (protons H-2') and those respect to the oxygen atom (protons H-1') of the ethanolamine moiety was clearly observed. The displacement of chemical shifts of the protons H-3, H-3a, H-6 on the isosorbide skeleton was also noted (Fig. 3).

This observation confirms a coordination between the chiral ligand **2** and the metal precursor [$RuCl_2$(*p*-cymene)]$_2$ in solution. We therefore proposed structures **3** to **5** based on the work described by Noyori (structures **6** to **8**) as the possible structures of complexes derived from the precursor [$RuCl_2$(*p*-cymene)]$_2$ and the chiral ligand **2** (Fig. 4) [7].

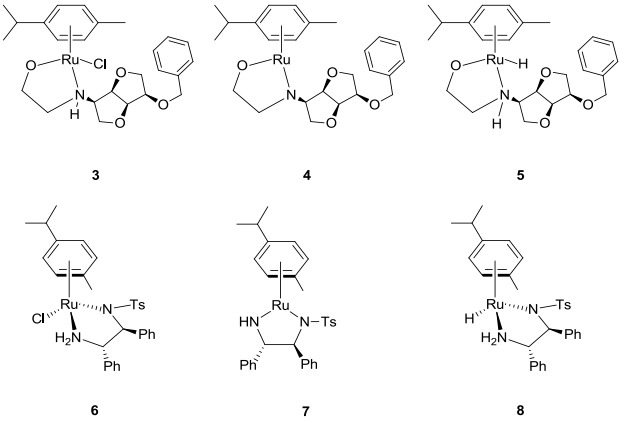


Fig. 4: Proposed structures of intermediates

To confirm this proposal, a series of high resolution mass spectrometric analysis with electrospray ionization (ESI) of solution containing ligand **2** and the metal precursor [$RuCl_2$ (*p*-cymene)]$_2$ in isopropanol (Ru/ligand = 1/2) was performed. An aliquot of the solution was directly introduced into the mass spectrometer by the help of a micro-syringe pump. The high resolution mass spectrum shown in Fig. 5 shows mainly a group of isotopes centralized around the principal mass with the mass/charge ratio (m/z) = 514.1470. Mass of the peaks observed for this group of isotopes conforms perfectly to the data calculated for the expected protonated molecule $C_{25}H_{34}NO_4Ru$ **4**. Interestingly, another group of isotopes for the expected molecule $C_{25}H_{35}ClNO_4Ru$ **3** whose mass/charge ratio = 550.1289 was found. This observation is contrary to studies of Noyori [7], Carpentier [8] in which the complex **7** (similar to the structure **4**) is found only after the addition of an excess of a strong base, for example potassium hydroxide, and can easily turn back to the complex similar to complex **6** (similar to the structure **3**). It is therefore allowed to state in our

case that that the structure **4** is easy to form, stable and predominantly present in the solution in the absence of the base, confirming the need for its preparation at room temperature and the failure of obtaining crystal structure by X-ray diffraction, including the structure **3**.

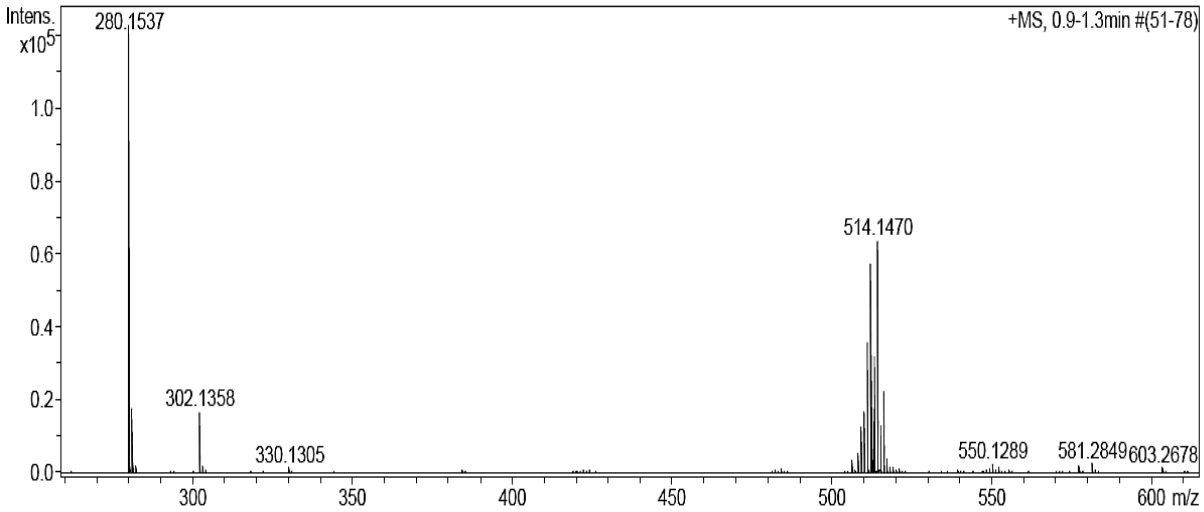


Fig. 5: High-resolution mass spectrum of solution of chiral ligand **2** and the precursor $[RuCl_2(p\text{-cymene})]_2$

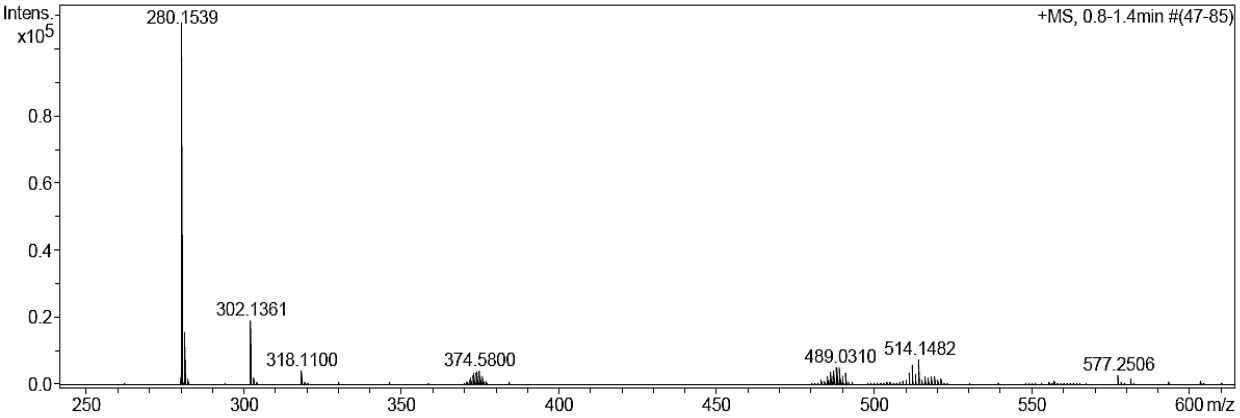


Fig. 6: Decrease in the intensity of the group of isotopes of the structure **4** after the addition of potassium hydroxide

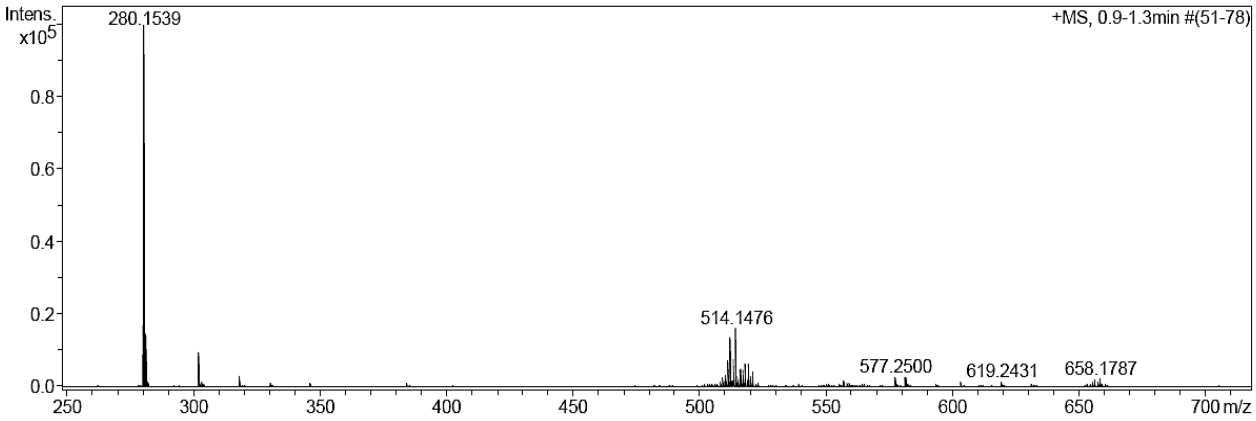
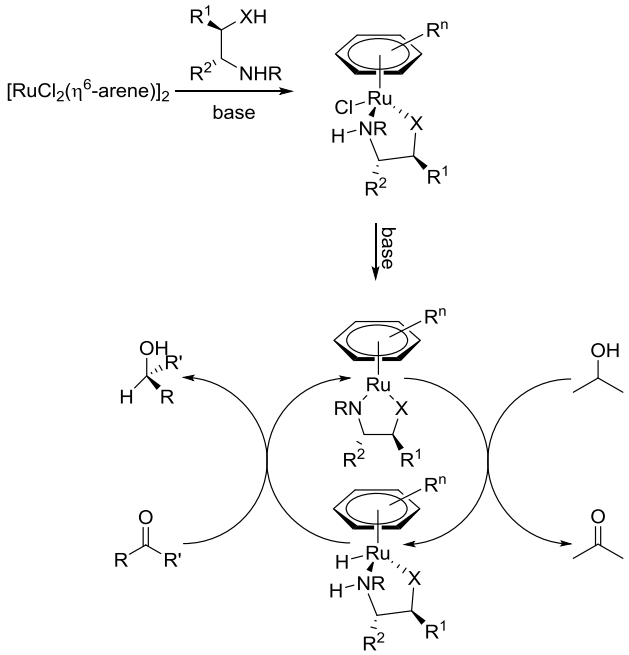


Fig. 7: Increase in the intensity of the group of isotopes of the structure **4** after the addition of acetophenone

For the next step, 2 eq. of potassium hydroxide (based on ruthenium) in isopropanol solution of 0.1 M were added to the solution, with stirring for a period of 5-10 minutes before the mass spectrometric measurement. An aliquot of the resulting solution was withdrawn and then directly introduced into the mass spectrometer by the help of a micro-syringe pump. The obtained mass spectrum shows a significant decrease in the intensity of the group of isotopes of the structure **4**, centralized around the mass/charge ratio 514.1482, and a disappearance of the isotope group of the structure **3** (Fig. 6). The presence of the structure **5** in this solution which involves in the catalytic cycle could not be confirmed due to either the superposition of the spectra, the spectrum of the structure **4** and **5**, or the instability of the latter in its solution or in the analytical conditions.

Interestingly, an increase in the intensity of the group of isotopes of the structure **4** was observed after the addition of the reagent acetophenone (Fig. 7). During the reduction of acetophenone, no further change in this intensity was observed. The presence of ketone probably allows a stability of the intermediates involving in the catalytic cycle of the reaction. These observations confirm that the asymmetric reduction by hydrogen transfer in this case is catalyzed by the active complex mono-hydride ruthenium as described in the literature for amino alcohols and diamines (scheme 1).



Scheme 1: Catalytic cycle of the reduction catalyzed by mono-hydride ruthenium complex

4. CONCLUSION

In conclusion, the formation of intermediates in asymmetric transfer hydrogenation of ketones catalyzed by complex of ruthenium (II) and isosorbide-based ligand was elucidated by using spectrometric techniques. The displacement of chemical shift of specific protons in the structure of isosorbide-based ligand allows a confirmation on the formation of active complex of ruthenium (II) for catalyzing the asymmetric transfer hydrogenation of ketones. The formation of these structures was clarified through observations from high resolution mass spectra, confirming the asymmetric transfer hydrogenation catalyzed by the active complex mono-hydride ruthenium. High resolution mass spectra in research on catalytic mechanism can be therefore employed as an alternative tool for studying on catalytic mechanism.

Acknowledgement. *This research is funded by the Ho Chi Minh City University of Technology, VNU-HCM under grant number T-KTHH-2015-74. We are grateful to the Ho Chi Minh City University of Technology for financial supports.*

REFERENCES

1. H. B. Kagan and O. Riant. *Catalytic asymmetric Diels Alder reactions,* Chem. Rev., **92(5)**, 1007-1019 (1992).
2. (a) O. Nguyen Van Buu, A. Aupoix, T. H. N. Doan and G. Vo-Thanh. *Chiral ionic liquids derived from isosorbide: synthesis, properties and applications in asymmetric synthesis*, New J. Chem., **33**, 2060-2072 (2009); (b) O. Nguyen Van Buu, A. Aupoix and G. Vo-Thanh,. *Synthesis of novel chiral imidazolium-based ionic liquids derived from isosorbide and their applications in asymmetric aza Diels-Alder reaction*, Tetrahedron, **65**, 2260-2265 (2009); (c) O. Nguyen Van Buu and G. Vo-Thanh, *Synthesis of novel chiral ammonium-based ionic liquids derived from isosorbide and their applications in an asymmetric aza Diels-Alder reaction*, Lett. Org. Chem., **4**, 158-167 (2007); (d) V. Kumar, C. E. Olsen, S. J. C. Schaffer, V. S. Parmar and S. V. Malhotra. *Synthesis and applications of novel bis(ammonium) chiral ionic liquids derived from isomannide*, Org. Lett., **9(5)**, 3905-3908 (2007).
3. S. Kumar and U. Ramachandran. *The synthesis and applications of asymmetric phase-transfer catalysts derived from isomannide and isosorbide*, Tetrahedron, **61**, 4141-4148 (2005).
4. Amino-alcohols, diamines: (a) S. Guillarme and T. X. M. Nguyen. *New chiral ligands from isosorbide: application in asymmetric transfer hydrogenation*, Tetrahedron: Asymmetry, **19**, 1450-1454 (2008); (b)

C. Paolucci and G. Rosini. *Approach to a better understanding and modeling of (S)-dihydrofuran-2-yl, (S)-tetrahydrofuran-2-yl-, and furan-2-yl-β-dialkylaminoethanol ligands for enantioselective alkylation*, Tetrahedron: Asymmetry, **18**, 2923-2946 (2007); (c) F. W. Lui, L. Yan, J. Y. Zhang and H. M. Liu. *Highly stereoselective synthesis and structural characterization of new amino sugar derivatives*, Carbohydr. Res., **341**, 332-338 (2006); (d) G. De Coster, K. Vandyck, E. Van der Eycken, J. Van der Eycken, M. Elseviers and H. Röper. *d-Isomannide in synthesis: asymmetric Diels–Alder reactions with novel homochiral bis-imine Cu^{2+}-catalysts*, Tetrahedron: Asymmetry, **13**, 1673-1679 (2002).

5. Phosphorus ligands: (a) M. Diéguez, O. Pàmies and C. Claver, *Palladium-diphosphite catalysts for the asymmetric allylic substitution reactions*, J. Org. Chem., **70(9)**, 3363-3368 (2005); (b) K. N. Gavrilov, S. V. Zheglov, P. A. Vologzhanin, M. G. Maksimova, A. S. Safronov, S. E. Lyubimov, V. A. Davankov, B. Schäffner and A. Börner, *A P⁎-chiral bisdiamidophosphite ligand with a 1,4:3,6-dianhydro-d-mannite backbone and its application in asymmetric catalysis*, Tetrahedron Lett., **49**, 3120-3123 (2008); (c) M. T. Reetz and T. Neugebauer. *New diphosphite ligands for catalytic asymmetric hydrogenation: the crucial role of conformationally enantiomeric diols*, Angew. Chem. Int. Ed., **38**, 179-181 (1999); (d) C. Carcedo, A. Dervicsi, I. A. Fallis, L. Ooi and K. M. A. Malik. *A concise synthesis of a rigid isomannide-based diphosphine ligand and structural characterisation of an alkoxyphosphonium intermediate*, Chem. Commun., 1236-1237 (2004); (e) J. Bakos, B. Heil and L. Marko. *1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-l-iditol. A new chiral ligand for asymmetric hydrogenation with rhodium complexes as catalysts* , J. Organomet. Chem., **253**, 249-252 (1983); (f) H. Zhou, J. Hou, J. Cheng, S. Lu, H. Fu and H. Wang. *Asymmetric hydroesterification of styrene by $PdCl_2$-$CuCl_2$-chiral phosphine catalyst systems*, J. Organomet. Chem., **543**, 227-228 (1997).

6. Khanh-Duy Huynh, Houssein Ibrahim, Martial Toffano, Giang Vo-Thanh. *New class of chiral ligands derived from isosorbide: first application in asymmetric transfer hydrogenation*, Tetrahedron: Asymmetry **21**, 1542–1548 (2010).

7. K.-J Haack., S Hashiguchi, A. Fujii, T. Ikariya, R. Noyori. *The catalyst precursor, catalyst, and intermediate in the Ru^{II}-promoted asymmetric hydrogen transfer between alcohols and ketones*, Angew. Chem. Int. Ed. Engl., **36**, 285-287 (1997).

8. (a) K. Everaere, A. Mortreux, M. Bulliard, J. Brussee, A. van de Gen, G. Nowogrocki, J.-F Carpentier. *(β-amino alcohol)(arene)ruthenium(II)-catalyzed asymmetric transfer hydrogenation of functionalized ketones-scope, isolation of the catalytic intermediates, and deactivation processes*, Eur. J. Org. Chem., 275-291 (2001); (b) K. Everaere, A. Mortreux, J. -F Carpentier. *Ruthenium(ii)-catalyzed asymmetric transfer hydrogenation of carbonyl compounds with 2-propanol and ephedrine-type ligands*, Adv. Synth. Catal., **345**, 67-77 (2003).

Corresponding author: **Huynh Khanh Duy**
Ho Chi Minh CityUniversity of Technology
268 Ly Thuong Kiet, 10 District, Ho Chi Minh City 740128,
E-mail: hkduy@hcmut.edu.vn.