Molecular Catalysis 469 (2019) 10–17

Contents lists available at ScienceDirect

Molecular Catalysis

journal homepage: www.elsevier.com/locate/mcat

Lewis acid promoted double bond migration in *O*-allyl to Z-products by Ru-H complexes

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ARTICLE INFO

Keywords:
Isomerization
Ruthenium complexes
Stereoselectivity
Lewis acid
Z-product

ABSTRACT

In catalytic double bond migration reaction, *E*-configuration olefins were normally generated as the dominant product because *E*-configuration was thermodynamically favored. However, Z-configuration products are sometimes desired in pharmaceutical chemistry owing to the structure-activity relationship. In this paper, we have demonstrated a new strategy that Lewis acid promoted an widely employed and convenient ruthenium(II) complex for the catalytic isomerization of O-allylethers, leading to thermodynamic-unfavored Z-product under mild conditions. The model substrate of allyl phenyl ether can be simply scaled up to 20 mmol to produce Z-product with TON of 2453 and TOF of 13,430 h^{-1} at 40–60 °C. The system of Ru(II)/Lewis Acid catalysts was suitable for various substituted *O*-allylethers and other types of substrates. Through mechanism study including kinetic study, ligand inhibition effect and molecular spectroscopy, the dissociation of PPh_3 ligand by the addition of Lewis acid, and the formation a five-membered Ru complex from anchimeric assistance were both recognized as essential steps to improve the reactivity and to control the stereoselectivity of catalytic double bond migration reaction through metal hydride addition-elimination mechanism. This new strategy may provide a new opportunity to produce thermodynamic-unfavored product in heterocyclic compounds for pharmaceutical chemistry.

1. Introduction

Double bond migration has attracted great interests due to its extensive applications [1–3]. For instance, isomerization is an initial step for the synthesis of vinyl ethers, which are important intermediates of heterocyclic compounds [4], and also a vital procedure of the protection and deprotection of free OH groups [5]. Comparing with acid-base catalysts that maybe caused the break of double bond or led to the polymerization or olefin or isomerization [6–9], transition metals including Pt [10], Cr [11], Fe [12], Co [13,14], Ni [15], Ru [16], Rh [17], Pd [18,19] and Ir [20,21] complexes were widely studied as catalysts to achieve the desired reactivity in the olefin isomerization. In most cases, *E*-configuration olefins were normally generated as the dominant product because *E*-configuration was thermodynamically favored [22].

In relation to this, Z-configuration products are sometimes desired in pharmaceutical chemistry owing to the structure-activity relationship. For instance, 3,5-dihydroxystilbene have the inhibitory effects on the activity of mushroom tyrosinase, whereas the inhibitory effects of *Z*-isomer was much stronger than that of corresponding *E*-isomer [23]. Another example is THSG (2,3,5,4′-tetrahydroxystilbene-2-*O*-β-D-glycoside), the main component of polygonum multiflorum plant, which has the effects of anti-oxidation, hypolipidemic action, inhibition of osteoporosis and excessive proliferation of vascular endothelial cells. Recent studies suggested that *Z*-THSG was much more effective than *E*-THSG [24–26]. Therefore, in the catalytic isomerization reactions, manipulating the selectivity of *Z* and *E* products in a desired way is of great importance. As far as we know, to gain kinetically controlled Z-alkenes is still a challenge. Only limited cases were reported including neutral Rh(I) complex catalyzing isomerization of *β,γ*-unsaturated ketones to *α,β*-unsaturated Z-ketones [27], rhodium-catalyzed pathway from allylaziridines to stable Z-enamines [28], and in-situ formed Ru complex for *Z*-selective isomerization of allylamides [29]. However, effective catalysts with satisfying efficiency, selectivity, stability and wide range of substrates were still in great demand, and the mechanism based on which transition metal catalysts favored *Z*-product in isomerization needs to be disclosed.

Recently, the promotional effect to the catalytic property of transition metal complex through the addition of non-redox metal ions as Lewis acid (L.A.) has attracted considerable attentions in diverse types of reactions. In particular, we found the acceleration effect from Al(III)

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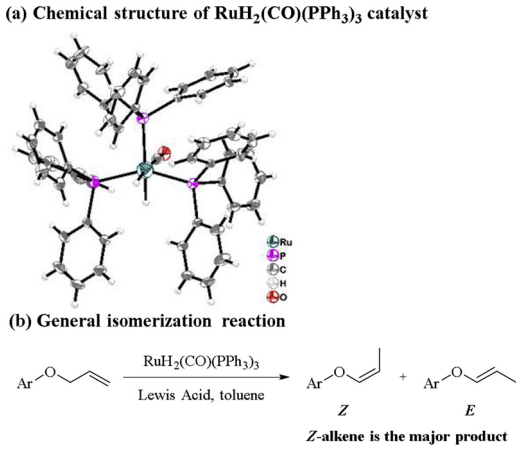
https://doi.org/10.1016/j.mcat.2019.02.007
Received 28 November 2018; Received in revised form 31 January 2019; Accepted 12 February 2019



Scheme 1. (a) Chemical structure of $RuH_2(CO)(PPh_3)_3$ catalyst and (b) general isomerization reaction investigated in this work.

in oxidovanadium(IV) complexes catalyzed hydrogen atom abstraction [30]. We also observed that Sc(III) can promote Pd(II)-catalyzed Wacker-type oxidations even better than Cu(II) [31], enhance oxidative coupling of indoles with olefins by the palladium(II) acetate catalyst [32], and accelerate the dehydrogenation of saturated C—C bond by a ruthenium catalyst [33]. Further mechanism studies revealed that the Lewis acid can change the coordination of metal complex to form new active intermediates or transient states, then enhance the activity of the catalyst or even change the reaction pathway. Inspired by these studies, transition metals/L.A. may be considered as an alternative approach to modulate the desired product selectivity in isomerization reactions.

In this paper, Ru(II)/LA catalyst was reported for the isomerization of *O*-allyl compounds (Scheme 1). We surprisingly found that kinetically controlled Z-configuration was the main product for certain substrates. as far as we know, this is the first report on Lewis acid promoted isomerization that lead to the kinetically controlled product by Ru-H catalyst. The toleration for extensive unsaturated compounds was explored, and remarkable performances could be found under mild conditions. The influence of different redox-inactive metals and the ratio of Ru(II)/L.A. was investigated, and gram scale experiments were tested. Moreover, isomerization mechanism was disclosed through kinetic study, HMR and spectroscopic characterization.

2. Experimental section

2.1. Chemicals

Allyl phenyl ethers with substitutes were synthesized according to literatures [34–36]. ((2-methylallyl)oxy)benzene, *N*,*N*-diallyl-2,2-dichloroacetamide and allyl glycidyl ether were purchased from adamas. Allyl(phenyl)sulfane, *N*-allylaniline and pent-4-enoic acid were purchased from Energy Chemistry. Allylbenzene was purchased from Meryer. Methyl undec-10-enoate was purchased from Heowns. Ruthenium(III) chloride hydrate, $Yb(OTf)_3$ and $Y(OTf)_3$ were purchased from Accela ChemBio Co., Ltd. Sodium NaOTf, $Mg(OTf)_2$, $In(OTf)_3$, $Sc(OTf)_3$ came from Aladdin. Other trifluoromethanesulfonates including $Ca(OTf)_2$, $Zn(OTf)_2$, $Ba(OTf)_2$ and $Al(OTf)_3$ were purchased from Shanghai DiBai Chemical Co. Triphenylphosphine came from Alfa Aesar. Common solvents and inorganic magnesium salts were purchased from Sinopharm Chemical Reagent Co., Ltd. Other chemical reagents were commercially available and used without further purify unless otherwise stated.

The ruthenium catalyst $RuH_2(CO)(PPh_3)_3$ was synthesized according to the literatures [20,37–41]. The detailed procedures for catalyst synthesis was exhibited in the supporting information.

2.2. reaction procedure

2.2.1. General procedure for isomerization by $RuH_2(CO)(PPh_3)_3$ / Lewis acid

In a typical experiment, 0.002 mmol $RuH_2(CO)(PPh_3)_3$ complex, 0.004 mmol non-redox metal salts and 0.4 mmol allyl phenyl ethers (or more concentration for different ethers) in 2 mL solvent was mixed in a glass tube. Then the reaction mixture was magnetically stirred at 60 ℃ in an oil bath for 30 min. After the reaction, the analysis was conducted by GC using the internal standard method. GC data were colledted on FL-5090 with XE-60. The colum temperature was programmed from 100 ℃ held for 5 min to 130 ℃ held for 3 min at a rate of 30 ℃/min. The injector temperature was 250 ℃. Naphthalene was chosen as the internal standard. Chloroform-d or toluene-d_8 was selected as the reaction solvent for qualitative analysis in ^{1}H NMR. Control experiments using $RuH_2(CO)(PPh_3)_3$ or non-redox metal salts individually as the catalyst were carried out in parallel. Reactions were performed at least in triplicate, and average data were used in the results and discussion section.

2.2.2. General procedure for kinetics study

In a typical experiment, 0.002 mmol $RuH_2(CO)(PPh_3)_3$, 0.004 mmol non-redox metal salts and 3 mmol ethers were added in 2 mL of solvent in a glass tube. Then the reaction solution was magnetically stirred at 60 ℃ in an oil bath. The quantitative product analysis was conducted by GC using the internal standard method at set intervals. Control experiments using $RuH_2(CO)(PPh_3)_3$ or non-redox metal salt alone as catalyst were also carried out in parallel. Reactions were performed at least in triplicate, and average data were used in the catalytic kinetics results.

2.2.3. General procedure for FT-IR study

In a typical experiment, 0.002 mmol $RuH_2(CO)(PPh_3)_3$, 0.004 mmol non-redox metal salt were added in 5 mL of chloroform in a glass tube. Then the mixture solution was magnetically stirred at 60 ℃ in the oil bath for 10 min. After the reaction, the solvent was removed and the product was dried for several minutes. Then the solid sample was detected by FT-IR spectrum. Control experiments using $RuH_2(CO)(PPh_3)_3$ or non-redox metal salts individually were also carried out in parallel.

2.2.4. General procedure for UV–vis study

In a typical experiment, in 10 mL of chloroform containing 0.1 mM $RuH_2(CO)(PPh_3)_3$, a certain amount of Lewis Acid were added. Then the mixture were monitored by Agilent UV 8454 at 30 ℃ after mixed in ten minutes.

2.3. Characterization equipment

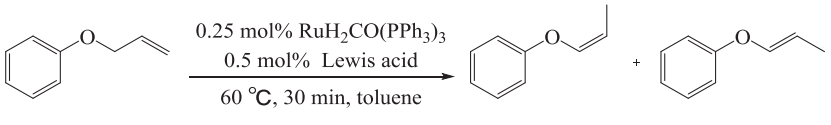
Gas chromatography-mass spectrometry (GC–MS) analysis was performed on an Agilent 7890 A/5975C spectrometer. FT-IR spectra were obtained on Bruker VERTEX70. ^{1}H NMR spectra were collected on a Bruker AV-400 using TMS as an internal reference. UV–vis analysis was proceed on Agilent UV 8454.

3. Results and discussion

3.1. Lewis acid promoted isomerization by the Ru(II) catalyst

At the outset, allyl phenyl ether was employed as the model compound for $RuH_2(CO)(PPh_3)_3$-catalyzed isomerization. As shown in Table 1, with the presence of 0.25% of $RuH_2(CO)(PPh_3)_3$ alone as the catalyst, the isomerization of allyl phenyl ether in toluene provided only 36.7% conversion with 27.4% *Z*-products and 8.3% *E*-products within 0.5 h (Table 1, entry 1). Introducing 0.5 mol% NaOTf showed no influence on the conversion (Table 1, entry 2), and a further increase to 1.5 mol% NaOTf (Table 1, entry 3) was still sluggish, providing only

Table 1
Screening of Lewis acids for the isomerization of allyl phenyl ether [a].



1a **2a-*Z*** **2a-*E***

Entry	Lewis acid	Conv. (%)	Yield (%)	
			2a-*Z*	2a-*E*
1	–	36.7	27.4	8.3
2	NaOTf	27.4	20.1	6.4
3[b]	NaOTf	33.8	24.7	8.0
4	$Ca(OTf)_2$	24.9	17.8	5.8
5	$Ba(OTf)_2$	27.6	18.6	6.0
6	$Mg(OTf)_2$	34.5	25.8	7.7
7	$Zn(OTf)_2$	52.9	41.9	10.1
8	$Yb(OTf)_3$	47.8	37.6	9.3
9	$Y(OTf)_3$	49.6	40.0	8.6
10	$Sc(OTf)_3$	90.9	76.4	12.1
11	$Al(OTf)_3$	92.6	77.4	12.5
12	$In(OTf)_3$	99.8	84.5	13.2
13[c]	$In(OTf)_3$	trace	trace	trace

33.8% conversion. This phenomenon clearly supported that the addition of OTf^- anion had no influence on the catalytic efficiency of the isomerization of allyl phenyl ether by $RuH_2(CO)(PPh_3)_3$. On the other hand, the addition of 2 equiv. of Zn^{2+} obviously accelerates the isomerization, with 52.9% conversion, 41.0% *Z*-products and 10.1% *E*-products (Table 1, entry 7). In this case Z/E ratio was increased to 4.1. However, the promotional effect from other bivalents metal ions like Ca^{2+}, Ba^{2+} and Mg^{2+} was not that obvious (Table 1, entry 4–6), which was attributed to their very limited solubility in toluene. Meanwhile, adding trivalent metal ions like Y^{3+}, Yb^{3+}, Al^{3+} and Sc^{3+} can greatly promote the catalytic efficiency of $RuH_2(CO)(PPh_3)_3$, achieving 47.8%, 49.6%, 90.9% and 92.6% conversion, respectively (Table 1, entry 8–11). Particularly, in the case of $In(OTf)_3$, the conversion of allyl phenyl ether can be improved up to 99.8%. It was worthy to mention that, 84.5% yield of *Z*-configuration product was collected in the Ru(II)/In^{3+} system. Meanwhile, the yield of *E*-configuration, which was the thermodynamically controlled product, was only 13.2%. Accordingly the ratio of *Z/E* was found to be 6.4. In control experiments, $In(OTf)_3$ alone as the catalyst demonstrated no activity for isomerization under identical conditions (Table 1, entry 13). Taking together, all these experiments illustrated that Ru(II) or In^{3+} alone was sluggish for the catalytic isomerization of ally phenyl ethers, but the grateful efficiency and selectivity on Z-product can be obtained in $In(OTf)_3$/$RuH_2(CO)(PPh_3)_3$ system. Additionally, the screening of solvent, temperature and more control experiments under Ar were listed in Table S1-S3 in supporting information.

Reaction conditions: [a] allyl phenyl ether (0.8 mmol), $RuH_2(CO)(PPh_3)_3$ (0.25 mol%), Lewis acid (0.5 mol%), toluene (2 mL) at 60 ℃ for 0.5 h. [b] NaOTf (1.5 mmol%). [c] $In(OTf)_3$ alone as the catalyst.

The effect of $In(OTf)_3$/$RuH_2(CO)(PPh_3)_3$ ratio on the isomerization of allyl phenyl ether was further investigated, and results were showed in Figure S1. One can see that increasing the ratio from 0 to 1 sharply accelerate the reaction, evidenced by the increase of conversion from 36.7% to 89.8%. A maximum conversion of 99.8% were achieved when 2 equiv. of $In(OTf)_3$ was introduced, while a further increase the ratio expressed a negative effect, and this phenomenon was similar to our previous reports of L.A. accelerated oxidation processes [31,42,43]. It was worthy to mention that, the effect of $In(OTf)_3$/$RuH_2(CO)(PPh_3)_3$ ratio on the reactivity of catalytic isomerization was highly consistent with the effect of this ratio on UV–vis spectra, which would be discussed in mechanism section (vide infra).

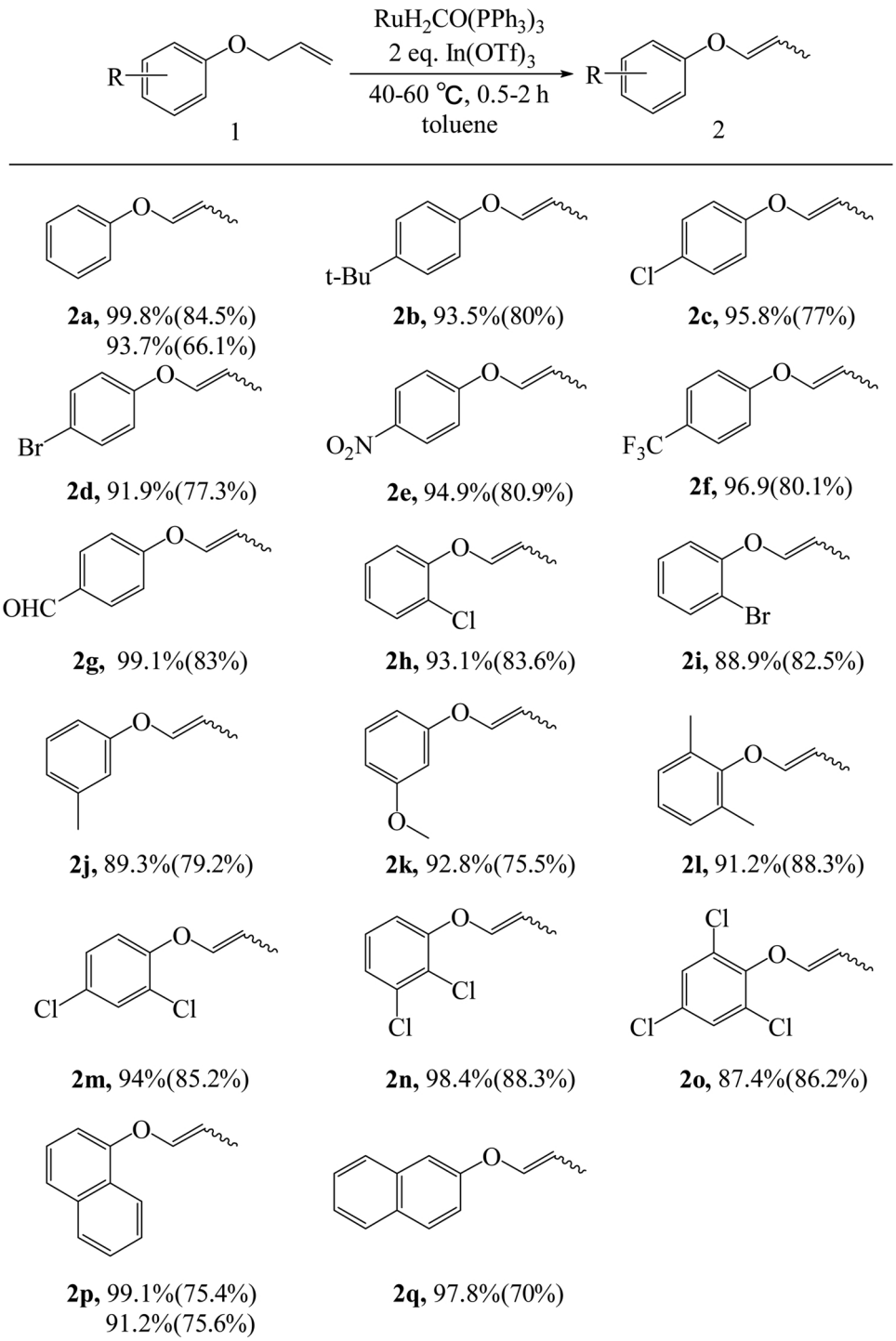
With the optimized conditions in hand, the substrate scope and the functional group tolerance for the present bimetallic Ru(II)/In^{3+} catalyst were next examined for isomerization, and the results were summarized in Scheme 2. Different substituents such as methyl, methoxyl, halogens, nitryl, trifluoromethyl, aldehyde were tested. For the model substrate allyl phenyl ether, the catalyst loading can be reduced to 0.04 mol% while 93.7% conversion could be achieved at 60 ℃ within 1 h, with the major product in *Z*-configuration (**2a**). It is worth emphasizing that allyl phenyl ether with both electron-donating (**2b**) and withdrawing (**2c**, **2d**, **2e, 2f**) substituents in the *para* position could proceed smoothly to provide the corresponding *O*-(1-propenyl) products at 50 ℃ within 0.5 or 1 h. For example, isomerization of allyl 4-(*tert*-butyl)phenyl ether offered 93.5% conversion with 80.0% *Z*-products and 14.9% *E*-products at 50 ℃ for 0.5 h (**2b**), allyl 4-nitrylphenyl ether offered 94.9% conversion with 80.9% *Z*-products and 10.5% *E*-products at 50 ℃ for 1 h (**2e**). The similar phenomenon were found in the *ortho* and *meta* position. For instance, isomerization of allyl 2-chlorophenyl ether and allyl 2-bromophenyl ether gave 93.1% and 88.9% conversion at 50 ℃ for 1 h (**2 h**, **2i**). Allyl 3-methylphenyl ether and allyl 3-methoxyphenyl ether also proceed smoothly at 40 or 50 ℃ for 1 h (**2 j**, **2k**). While for allyl 4-formylphenyl ether as substrates, higher catalyst loading of 1% was needed to provide 99.1% conversion (**2 g**). It was noteworthy that when multiple substituents were present on the phenyl ring, the reaction was also effective, while a high selectivity of Z-product was still observed (**2l-2q**). It was interesting to find that when 1-(allyloxy)naphthalene was chosen for isomerization, the catalyst loading can be reduced to even 0.1 mol%, and 91.2% conversion with a *Z/E* ratio of 5.3was still achieved.

Reaction conditions: $RuH_2(CO)(PPh_3)_3$ (0.002 mmol), $In(OTf)_3$ (0.004 mmol), toluene (2 mL). The value under the substrates were GC yield and the value in parentheses were the yield of *Z*-product. The detail condition were on Table S4 in supporting information.

In particular, the isomerization of **2a** was further performed in a scale of substrate/catalyst = 2500:1, in which a yield of 98.1% with 70.6% yield of Z-product would be found. The maximum TON reached 2453 with TOF at 13,431 h^{-1} (Table S5), which additionally demonstrate the efficiency and selectivity of Ru(II)-H/LA in isomerization reaction.

3.2. Reaction mechanism of isomerization by the Ru(II)-Lewis acid

In our previous study [30–33,42–44], it was observed that non-redox metal ions as Lewis acid can modulate the reactivity of transition



Scheme 2. Substrate scope for the Ru(II)/In^{3+}-catalyzed isomerization.

metal catalysis in versatile homogeneous reactions because the presence of non-redox metal ions can substantially manipulate the coordination structure of reactive species, thus further regulate the catalytic activities, or even alter the reaction pathway. However, as far as we know, this is the first report on Lewis acid promoted isomerization that lead to the kinetically controlled product by Ru-H catalyst. Herein, the mechanism study was conducted to disclose the reaction pathway.

Firstly, the interaction between $RuH_2(CO)(PPh_3)_3$ and olefin substrate was investigated. We previously found that the dissociation of PPh_3 ligand played the essential role due to the fact that this dissociation in turn offered some certain coordination sites that free alkene could interact with the ruthenium hydride species [45]. In this case, the existence of extra PPh_3 could inhibit the reaction. Herein, the kinetic of allyl phenyl ether isomerization by $RuH_2(CO)(PPh_3)_3/In^{3+}$ system were recorded through the externally addition of free PPh_3, and clearly a negative influence on the reaction rate was observed. More importantly, the reciprocal of the rate constant and the concentration was found as a linear relationship to the concentration of extra PPh_3 (Fig. 1), which was in good agreement with our previous result and other reports [44,46].

The Ru(II)-catalyzed isomerization of allyl phenyl ether were detected by ^1H NMR. In Fig. 2A, $RuH_2(CO)(PPh_3)_3$ or $In(OTf)_3$ alone

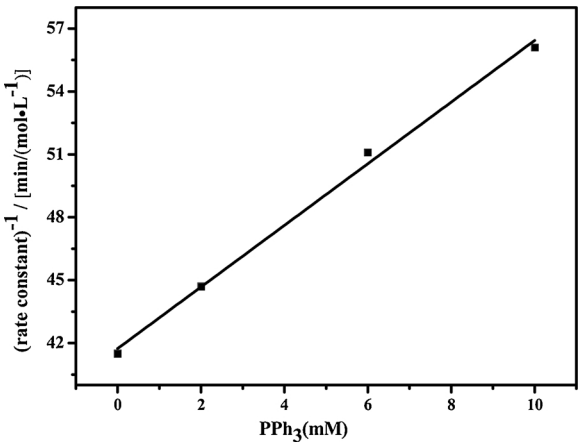
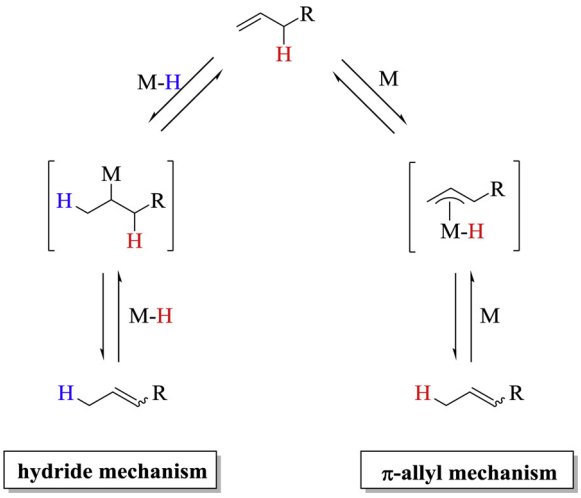


Fig. 1. The influence of extra PPh_3 on isomerization. Reaction conditions: allyl phenyl ether (0.6 mmol), $RuH_2(CO)(PPh_3)_3$ (0.002 mmol), $In(OTf)_3$ (0.004 mmol), PPh_3 (0-0.02 mmol) in 2 mL toluene at 60 ℃ for 10 min.



Scheme 3. Generally accepted mechanisms for isomerization of olefins.

showed no signals in the region from 6.5 ppm to 4.2 ppm, while allyl phenyl ether alone gave four clear signals, that is, 6.05 ppm for methine, 5.42 and 5.27 ppm for terminal alkene, and 4.53 ppm for methylene (Fig. 2A (c)). Meanwhile, with the addition of 1 equiv. of $RuH_2(CO)(PPh_3)_3$, these four typical signals remained without any change, indicating the isomerization could not be initiated with $RuH_2(CO)(PPh_3)_3$ alone. On the other hand, the presence of 2 equiv. $In(OTf)_3$ led to several new signals, which once again demonstrated the promotional effect from Lewis acid, and was highly consistent with results in Table 1.

As shown in Fig. 2B, $RuH_2(CO)(PPh_3)_3$ also gave two characterized resonances with the same integral area in the region from -4.0 to -10.0 ppm. These two resonances were attributed to the fact that two hydride coordinated to the Ru center were not equal in chemical environment. One hydride was in the contraposition of CO (chemical shift at -6.9 ppm) while the other one (chemical shift at -8.8 ppm) was against PPh_3. With the addition of $In(OTf)_3$, a new Ru-H signal located at -4.46 ppm was found, indicating the formation of a new species as the adduct of Ru(II)-H/In(III). Meanwhile, signals at -8.8 ppm and -6.9 ppm could still be found, suggesting that part of $RuH_2(CO)(PPh_3)_3$ complex remained in the reaction system. Additionally, when allyl phenyl ether (**1a**) was added, all resonances from Ru-hydride species quickly vanished, which clearly indicated that the Ru(II)-H/In(III) species was responsible for the accelerated isomerization reaction. This process was supposed to be through the classic metal hydride addition-elimination mechanism, during which free alkene firstly coordinated to ruthenium hydride species, then insertion into the metal-hydride bond yielded a secondary metal-alkyl, subsequent β-hydride elimination yielded the isomerized product and regenerated the initial ruthenium hydride catalyst (scheme 3). Therefore, the addition of allyl phenyl ether would be responsible for the disappearance of the resonances from ruthenium hydride complex.

To explore the interaction of Lewis acid and $RuH_2(CO)(PPh_3)_3$, UV–vis spectra were carried out and shown in Fig. 3A. $RuH_2(CO)(PPh_3)_3$ alone showed a characteristic shoulder band centered at around 335 nm in $CHCl_3$. Noticeably, when different Lewis acid was added, the shifting of this characteristic band from $RuH_2(CO)(PPh_3)_3$ was different in each case. 2 equiv. of NaOTf or $Mg(OTf)_2$ as the additive slightly lower the intensity of this peak (Fig. 3(B)), while the location of shoulder band did not shift. On the contrast, the addition of 2 equiv. $In(OTf)_3$ significantly changed the adsorption spectra of $RuH_2(CO)(PPh_3)_3$, in which the intensity of 335 nm band decreased dramatically while an obvious larger adsorption band raised in the region lower than 330 nm. This trend was highly consistent with previous results that the enhancement on isomerization from Na^+ or Mg^{2+} was neglect, while the promotional effect from In(III) was remarkable (Table 1). Once again, the distinctions in UV–vis spectra demonstrated the interaction between In^{3+} and Ru-H complex.

Furthermore, the interaction between In(III) and Ru-H complex was further disclosed by adding different amount of In(III) from 0.2 to 4 equiv. to $RuH_2(CO)(PPh_3)_3$ (Fig. 3(C)). Obviously an isobestic point at 305 nm could be found, which further suggested that the addition of In (III) led to the change of coordination sphere of Ru center, and a transformation from $RuH_2(CO)(PPh_3)_3$ to another reactive species of Ru (III)/In(III) adduct was revealed. This observation was highly consistent with previous ^{1}H-NMR tests, in which a new Ru-hydride signal at -4.46 ppm could be found with the addition of In(III). Additionally, this change in UV–vis spectra became stable after the concentration of In

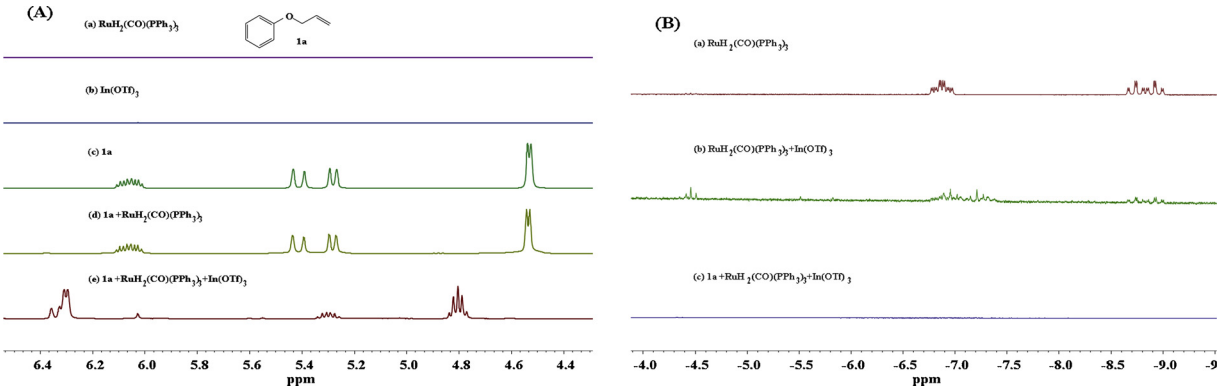


Fig. 2. ^{1}H NMR studies on the reaction of allyl phenyl ether (**1a**) with $RuH_2(CO)(PPh_3)_3$ and $In(OTf)_3$.

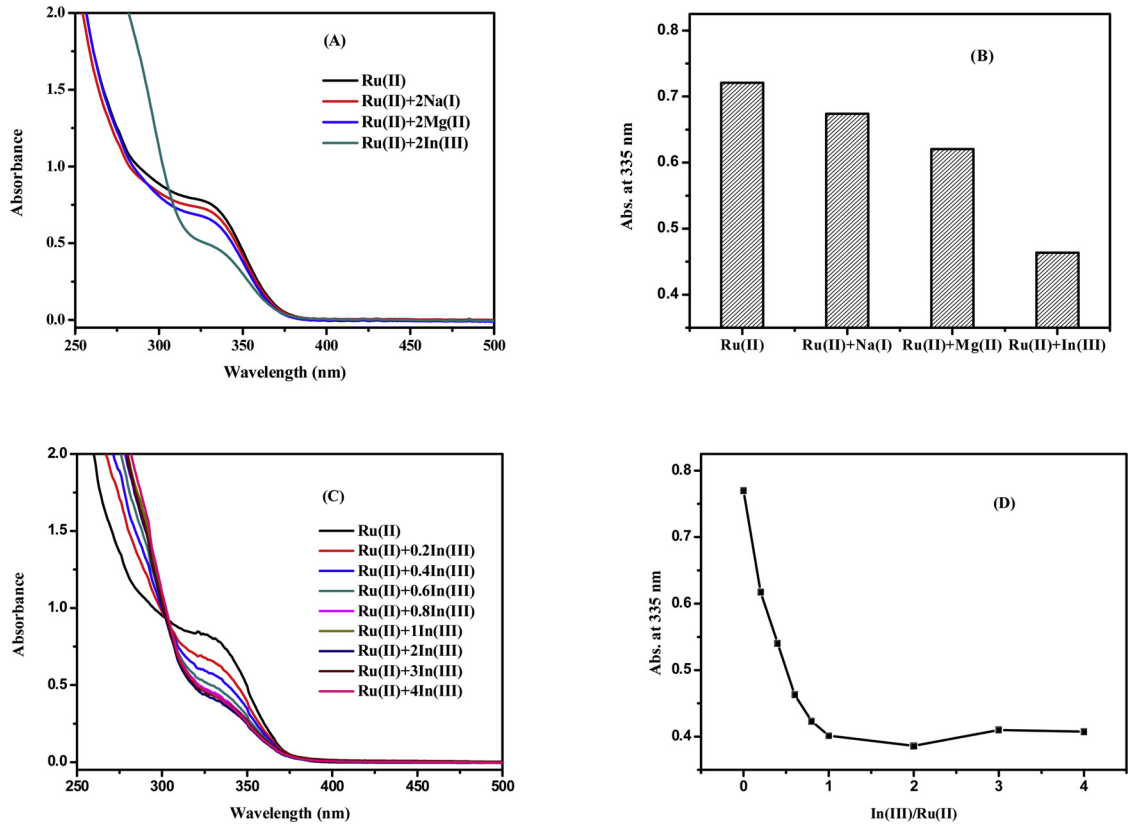


Fig. 3. UV–vis spectra of $RuH_2(CO)(PPh_3)_3$ and $In(OTf)_3$ mixture in $CHCl_3$ (Ru(II) 0.1 mM).

(III) reached 2 equiv., and the spectra of Ru(II) plus 2, 3 and 4 equiv. In (III) overlapped with each other. To further testify this pattern, the adsorption intensity at 335 nm was recorded along with the increasing amount of In(III) (Fig. 3(D)), and a minimum adsorption intensity could be reached with the addition of 2 equiv. In(III), and remained after the further increase of In^{3+} dosage. From these data it was suggested that a ratio of In(III):Ru(II) at 2:1 already achieved the equilibrium in the transformation from $RuH_2(CO)(PPh_3)_3$ to Ru(III)/In(III) adduct. Once again, this observation was in good agreement with the fact that the ratio of In(III):Ru(II) at 2:1 was determined as the optimized ratio in catalytic isomerization reaction (Table 1 and Figure S1).

Aforementioned results indicated that the presence of Lewis acid such as In(III) could induce the dissociation of PPh_3 ligand and the formation of Ru(III)/In(III) adduct as the reactive species, and then catalyze the double bond migration through the classic metal hydride addition-elimination mechanism. However, the binding site between Ru-H center and Lewis acid was not clear yet. In FT-IR spectra, the vibration carbonyl group in $RuH_2(CO)(PPh_3)_3$ gave a characteristic adsorption band around 1940 cm^{-1}, and two week absorption from Ru-H, which theoretically located at 1960 and 1900 cm^{-1} but was normally obscured by the strong signal from the carbonyl group. As shown in Figure S2, along with the addition of increasing amount of $In(OTf)_3$, the original absorption of carbonyl at 1943 cm^{-1} was found shifting to a new location at 1973 cm^{-1}. This shifting suggested that Lewis acid may bind and influence the carbonyl group in Ru-H complex through the linkage of OC-Ru-H_2—In(III) or H_2-Ru − CO—In(III). If the addition of the electron acceptor (In^{3+}) was through the coordination with oxygen in carbonyl group, it would imply an increase in electron density on the bridging carbonyl ligand, and then cause the decrease in frequency. Alternatively, if this binding of electron acceptor was through Ru-H, it would decrease the electron density on the terminal carbonyl ligand and then cause the increase in frequency [44,47–49]. Thus, it was speculated that the Lewis acid interacted with ruthenium species through the linkage of OC-Ru-H_2—In(III), which led to the increased wavenumbers of carbonyl group, rather than H_2-Ru − CO— In (III). This speculation of OC-Ru-H_2—In(III) as the Ru(II)/In(III) adduct was also in accordance with the ^{1}H-NMR discussed before.

The catalytic kinetics of allyl phenyl ether isomerization gave further information for the isomerization process. As revealed in Fig. 4B, with $RuH_2(CO)(PPh_3)_3$ and 2 equiv. $In(OTf)_3$ as the catalyst, 96.7% conversion with 74.6% *Z*-products and 20.8% *E*-products was observed using allyl phenyl ether **2a** as the substrate, and longer reaction time did not change *Z-E* stereoselectivity, during which *Z/E* ratio remained at 4.0 after 1 h. This phenomena revealed that the generation of *Z* and *E* products were simultaneous, and no transformation between two products was observed in the isomerization of allyl phenyl ether. However, under similar conditions, when $RuH_2(CO)(PPh_3)_3$ plus Lewis acid were conducted as the catalyst, the isomerization of eugenol (Fig. 4A) was found with *E* products as the major one, while the transformation from *Z* to *E* product was clearly observed from the kinetic observation: the yield of Z products increased initially, but decreased slowly after 15 min [44]. Therefore, distinguished stereoselectivity was found between allyl phenyl ether and eugenol, which accordingly suggested that the difference in the structure of the substrate may be essential to this stereoselectivity.

To further explore the mechanism of the reaction, other substrates were also tested and the results were summarized in Scheme 4. In the case of methyl substituted substrate **3**, the isomerization was much slower comparing with the case of model compound **2a**, which was probably attributed to the steric disturbing of the coordinative sphere to Ru center. Therefore, longer reaction time and higher reaction temperature were required to obtain 94.1 conversion and 93% yield. On the other hand, when terminally di-substituted substrate **11** was tested under the same conditions, isomerization product could not be found due to the much stronger steric hindrance. To further testify the role of oxygen in **2a**, *N*-allyl phthalimide (**5**) was used as the substrate, and the

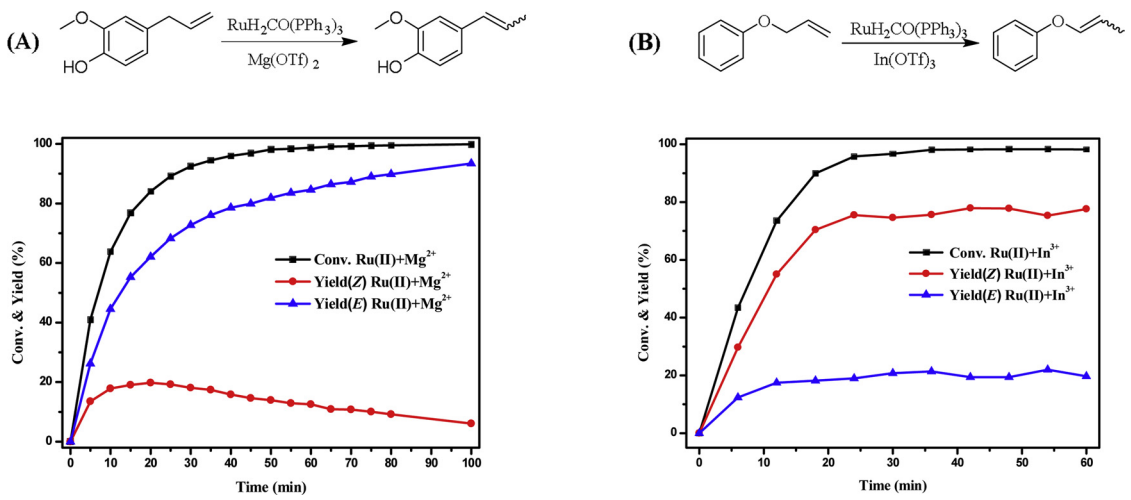
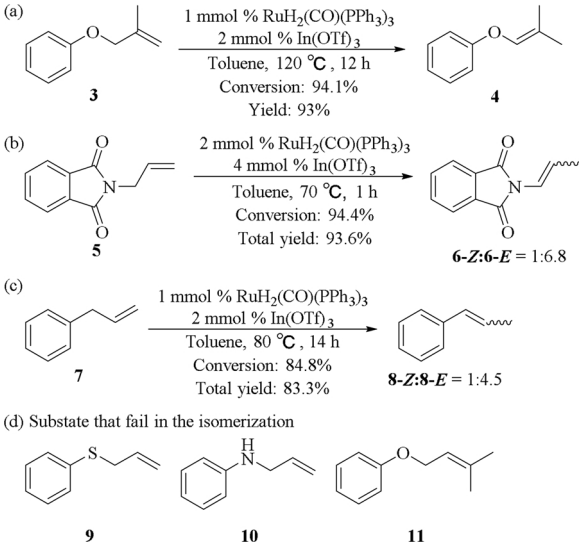


Fig. 4. Lewis acid accelerated isomerization kinetics by the ruthenium complex. Reaction condition: (A) eugenol (2 mmol), $RuH_2(CO)(PPh_3)_3$ (0.002 mmol), $Mg(OTf)_2$ (0.004 mmol), EtOH (2 mL) at 80 °C. (B) allyl phenyl ether (3 mmol), $RuH_2(CO)(PPh_3)_3$ (0.002 mmol), $In(OTf)_3$ (0.004 mmol), toluene (2 mL) at 60 °C.



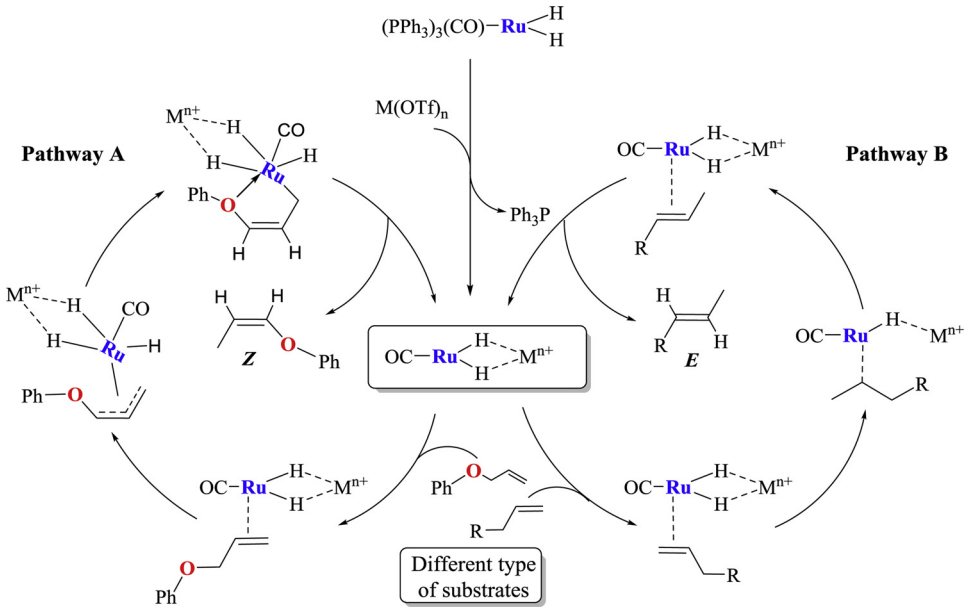
Scheme 4. Substrates scope of $RuH_2(CO)(PPh_3)_3/In(OTf)_3$ catalyzed isomerization.

isomerization reaction generated **6-*E*** as main product. When allylbenzene (**7**) was employed as substrate, the selectivity still followed the trend that thermodynamically favored E-configuration as the main product. Additionally, substrate **9** and **10** with S and N instead of a oxygen atom also failed in the isomerization reaction. These experiments thus demonstrated the essential role of the oxygen atom for the selectivity. During the reaction, the oxygen atom may coordinate to the central Ru to form five- or six-membered ring, and this anchimeric assistance can not only accelerate reaction, but also stable the intermediate configuration to form thermodynamic-unfavored product. Further more we added little EtOH in Ru(II)-In^{3+} system, we found EtOH delayed the reaction and reduced the *Z-E* ratio. When the amount of EtOH and toluene almost the same, the Z-product and E-product are very close, also the conversation is reduced (Table S6). These results were proportional to the O-Ru coordination in this system.

Taken together all the data from catalytic reactions and characterizations, a possible reaction pathway was proposed in Scheme 5. $RuH_2(CO)(PPh_3)_3$ possessed a saturated coordination sphere in its first coordination sphere, which caused the steric hindrance for free alkene to coordinate, and was accordingly demonstrated with limited catalytic reactivity in double bond migration by itself. The addition of non-redox metal ions such as In(III) influenced the coordination sphere of Ru and formed an adduct as OC-Ru-H_2—In(III). The interaction between Ru(II) and In(III) twisted of the first coordination sphere of ruthenium center, and induced the dissociation of PPh_3 ligand that favored the formation of unoccupied coordination site for alkene; On the other hand, the strain associated with Ru-H bond could be relieved by invoking a In(III) Ru(II)-bridged species that benefitted the isomerization of alkene., Therefore, significantly higher activity of OC-Ru-H_2—In^{3+} species could be found comparing with $RuH_2(CO)(PPh_3)_3$. Complete isomerization reaction was through metal hydride addition-elimination mechanism, including the free alkene coordinates to ruthenium hydride species, then insertion into the metal-hydride bond yields a secondary metal-alkyl, subsequent *β*-hydride elimination yields the isomerized product and regenerates the initial ruthenium hydride catalyst. During this process, allyl phenyl ether could offer one extra oxygen atom, which was also involved into the first coordination sphere of central Ru (pathway A). In this case, because the oxygen atom would turn to *O*-(1-propenyl) phenyl ether in the secondary metal-alkyl. Therefore, *Z*-configuration olefin would be the main product afterβ-hydride elimination. However, in the case of other olefins such as allylbenzene, *E*-configuration olefin as the thermodynamic favored one would become the dominant product (pathway B).

4. Conclusions

In summary, we have demonstrated a new strategy that Lewis acid promoted the efficiency and the stereoselectivity of widely employed and convenient ruthenium(II) catalysts for the isomerization of *O*-allyl ethers. More importantly, thermodynamic-unfavored Z-products were generated dominantly. The model substrate of allyl phenyl ether can be simply scaled up to 20 mmol to achieve TON of 2453 and TOF of 13430 h^{-1} under mild conditions. This Ru(II)/L.A. catalyst system was suitable for various substituted *O*-allyl ethers and different types of substrates. Due to the addition of L.A., the dissociation of PPh_3 ligand was recognized as the initial step, followed by which the formation a five-membered Ru complex was suggested as the key intermediate in the isomerization process. The anchimeric assistance in this five-membered intermediate was essential in controlling the configuration of the product. Through metal hydride addition-elimination mechanism, thermodynamic-unfavored *Z*-configuration product was observed as the dominant product.



Scheme 5. Proposed mechanism for Ru(II)/M^{n+}-catalyzed isomerization.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 21671072 and 21573082). NMR and GC–MS tests were performed in the Analytical and Testing Center of Huazhong University of Science and Technology.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mcat.2019.02.007.

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