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# Epimerization of Isosorbide Catalyzed by Homogeneous Ruthenium-Phosphine Complexes: a New Step towards an Industrial Process

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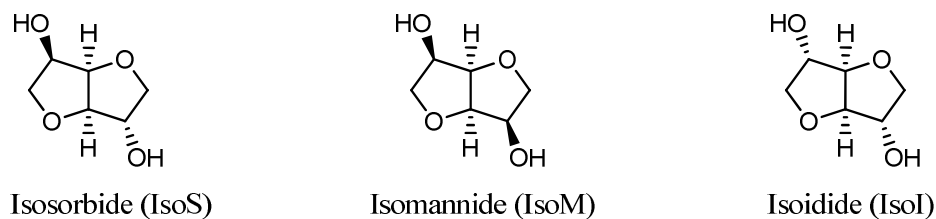
## Abstract:

An efficient process for obtaining isoidide by catalytic epimerization of isosorbide using HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos (1/1) as organometallic catalyst without hydrogen is reported. The epimerization of isosorbide led to a thermodynamic equilibrium mixture containing 37% isosorbide, 57% isoidide and 6% isomannide in 1 hour at 170°C in *tert*-amyl alcohol. The same proportions were reached by using the catalytic precursor HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> associated with sulfonated phosphines to isomerize isosorbide without solvent. Interestingly, the reaction can be also performed in a biphasic system (isosorbide/toluene) with the same catalytic activity. In this case, the mixture of isohexides was easily separated from toluene catalytic phase. Thus, by adding in each time a new isosorbide layer, nine successive cycles were performed without a loss of the catalytic activity. A scale-up leading to isomerize 1.3 Kg of

isosorbide using only 0.2 g of ruthenium was also performed showing the potentiality of this biphasic catalytic system for an industrial application.

## 1. Introduction

The use of bio-based molecules is becoming increasingly important in both academic research and industrial development. Indeed, the implication of renewable raw materials and the development of sustainable processes are key factors for future economic growth. In addition, declining reserves of fossil raw materials and the adverse effects of global warming are driving the development of such processes. In this context, sugar-derived isohexides are interesting biobased building blocks. More precisely, the most known are isosorbide (or 1,4:3,6-dianhydro-D-glucitol; IsoS) which has two hydroxyl groups on the C2 and C5 carbon atoms in an endo–exo configuration, isomannide (or 1,4:3,6-dianhydro-D-mannitol; IsoM) with an endo-endo configuration and isoidide (1,4:3,6-dianhydro-L-itol; IsoI) with an exo-exo configuration (Scheme 1). IsoS is produced from D-sorbitol, IsoM from D-mannitol and IsoI from L-itol [1]. These isohexides are mainly used as bio-monomers in the synthesis of polyester and polycarbonate [2-5]. Beside the greener approach of using such product, IsoS incorporation in polymeric material enhances the material properties such as better thermal properties, good transparency and chemical and UV resistance [6]. In addition, their diamine derivatives are used for polyamide synthesis [7]. Other potential industrial applications are also described such as the preparation of isosorbide nitrates used in cardiac or vascular disease, the preparation of alkyl derivatives used as solvents in pharmaceutical or cosmetic compositions. Among these three isohexides, isosorbide is the only industrially produced and commercially available in large amount. The Roquette company is one of the largest producers of IsoS [8].



Scheme 1. Structure of 1,4:3,6-dianhydrohexitols (isohexides)

IsoM is the less studied because of its lower reactivity whereas IsoI is the more reactive in polycondensation reaction [9]. IsoI has a great potential but its production is limited due to the low availability of L-iditol. In this context, the synthesis of IsoI from IsoS epimerization was a great challenge and was already explored. Wright and Brandner described the epimerization of isosorbide using a nickel-on-Kieselguhr catalyst at high-temperature (220-240°C) and under high hydrogen pressure (103 bar) [10]. By using these experimental conditions, the three isohexide isomers were obtained in a mixture of 35% IsoS, 59% IsoI, and 6% IsoM at the thermodynamic equilibrium. Raney nickel [11] ( $T = 200^{\circ}\text{C}$ ,  $P(\text{H}_2) = 250$  bar) and ruthenium on silica [12] ( $T = 260^{\circ}\text{C}$ ,  $P(\text{H}_2) = 40$  bar) were also reported to catalyze the epimerization of IsoS, giving approximately 40% IsoI. In 2013, Le Nôtre et al. described the epimerization of IsoS in water at 220°C, under hydrogen (40 bar) and using a Ru/C catalyst. After 2 h of reaction, a mixture containing a product ratio of 40/55/5 (IsoS/IsoI/IsoM) was obtained [13]. Apart heterogeneous catalytic systems, homogeneous catalysts were also efficient. In 2011, Mathias Beller and coll. have observed that unwanted isomerization of IsoS took place (IsoI and IsoM yields not given) during the amination reaction of IsoS by ammonia in the presence of Milstein's catalyst or  $\text{HRu}(\text{CO})\text{Cl}(\text{PPh}_3)_3/\text{Xantphos}$  (Scheme 2a) combination [14]. In 2013, Dieter Vogt and coll. described the epimerization of IsoM using  $\text{Ru}_3(\text{CO})_{12}$  and acridine-based diphosphine as catalytic system in *tert*-amyl alcohol without the use of hydrogen [15]. After 21 h of reaction at 170°C, the thermodynamic equilibrium was not reached since a product ratio of 44/33/23 (IsoS/IsoI/IsoM) was obtained. The

isomerization reaction is called “hydrogen shuttling” or “borrowing-hydrogen” methodology [15-19]. The mechanism involved a dehydrogenation-hydrogenation pathway, which included a ketone intermediate. Dieter Vogt and coll. extensively studied this mechanism in the case of Ru-catalyzed direct amination of alcohols with ammonia by the HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos system [20]. Herein, we first report the epimerization of IsoS into the mixture of the three isohexides at thermodynamic equilibrium (37% IsoS, 57% IsoI, 6% IsoM) by a catalytic system based on ruthenium and Xantphos [21]. The same proportions were reached by using the catalytic precursor HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> associated with sulfonated phosphines to isomerize IsoS without solvent [22]. Secondly, a biphasic catalytic system was employed to recover and recycle the catalytic layer by simple decantation.

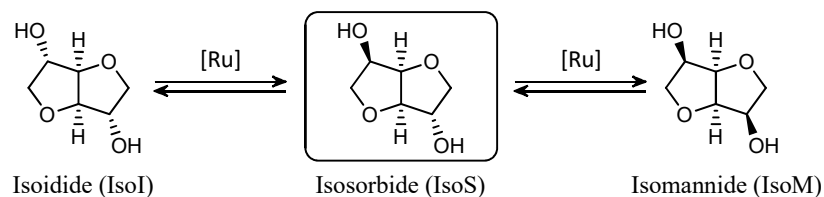
## **2. Results and Discussion**

### **2.1 Epimerization in a monophasic catalytic system**

#### **2.1.1 Epimerization of IsoS in *tert*-amyl alcohol: influence of the ruthenium precursor**

The influence of the ruthenium precursor on the epimerization of IsoS was studied. As the bidentate phosphine Xantphos was extendedly employed for dehydrogenation-hydrogenation reactions, a ruthenium hydride precursor was firstly employed in combination with Xantphos (Table 1, entry 1).

Table 1. Influence of the catalytic system on the epimerization of IsoS



Entry	Catalytic Precursor	<i>t</i> -BuOK	IsoS (%)	IsoI (%)	IsoM (%)
1	HRu(CO)Cl(PPh <sub>3</sub> ) <sub>3</sub>	No	37	57	6
2	Ru( <i>p</i> -cymene)Cl <sub>2</sub> (PPh <sub>3</sub> )	No	100	0	0
3	RuCp*Cl(PPh <sub>3</sub> ) <sub>2</sub>	No	100	0	0
4	RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub>	No	100	0	0
5	Ru( <i>p</i> -cymene)Cl <sub>2</sub> (PPh <sub>3</sub> )	Yes	38	58	6
6	RuCp*Cl(PPh <sub>3</sub> ) <sub>2</sub>	Yes	42	54	4
7	RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub>	Yes	40	56	4

Reaction conditions: Isosorbide (10 mmol), Catalytic precursor (0.2 mmol), Xantphos (0.2 mmol), *t*-BuOK (0 or 2 mmol), *tert*-amyl alcohol (40 mL), Temperature (170°C), Time (1 h).

So, Ru-catalyzed epimerization of IsoS was carried out under homogeneous conditions by using HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos (1/1) as catalytic system in *tert*-amyl alcohol. After 60 minutes at 170°C, ratios of 37/57/6 were reached for IsoS/IsoI/IsoM (Table 1, entry 1). Note that these same proportions were obtained at 200°C after the same reaction time. Contrariwise, a 44/51/5 mixture of IsoS/IsoI/IsoM was reached at 140°C, also after 60 minutes, showing that the thermodynamic equilibrium was not reached after 1 hour at this too low temperature. Therefore, three other catalytic precursors were evaluated with Xantphos at 170°C: Ru(*p*-cymene)Cl<sub>2</sub>(PPh<sub>3</sub>), RuCp\*Cl(PPh<sub>3</sub>)<sub>2</sub> and RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>. In the three cases, no catalytic activity was evidenced since IsoS was not epimerized (Table 1, entries 2-4). The addition of potassium *tert*-butylate (*t*-BuOK) in each case allowed to reach the same catalytic activity than observed with HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> catalytic precursor since the thermodynamic equilibrium was almost reached in each case (Table 1, entries 5-7). Based on these results and studies of Vogt team [20], catalytic cycles can be proposed (Figure 1). Whatever the catalytic precursor used, the ruthenium catalyzed epimerization of a secondary

alcohol function, *i.e.* the equilibrium between structures **(I)** and **(II)** (Figure 1), should be due to the interconversion between the corresponding ruthenium alkoxides **(I-Ru)** and **(II-Ru)** in the medium (Figure 1, a. and b.). Indeed, each ruthenium alkoxide can lead to the other one after a  $\beta$ -H elimination step (1), a dissociation-association of the formed ketone (steps (2) and (-2), respectively) and, finally, an insertion of this coordinated ketone in the Ru-H bond (step (-1)). On this basis, **(I)** can be converted into **(II)** by acido-basic reaction with **(II-Ru)**, leading to **(I-Ru)**, this transformation being equilibrated (steps (3) and (-3)). This mechanism can explain that HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> complex (symbolized by H-[Ru]-Cl, Figure 1, a.) is able to generate the epimerization reaction of isohexides without potassium *tert*-butylate added in the medium. Indeed, due to the basicity of this ruthenium hydride, ruthenium alkoxides essential to make possible the epimerization reaction would be formed in an initial step, with generation of dihydrogen (Figure 1, a.). On the other hand, with the non-hydride other Ru<sup>II</sup> complexes (symbolized by Cl-[Ru]-X, Figure 1, b.), potassium *tert*-butylate would be necessary because the formation of the potassium alkoxides corresponding to **(I)** and **(II)** would be essential to give further the **(I-Ru)** and **(II-Ru)** species, by a chloride atom substitution (Figure 1, b.).

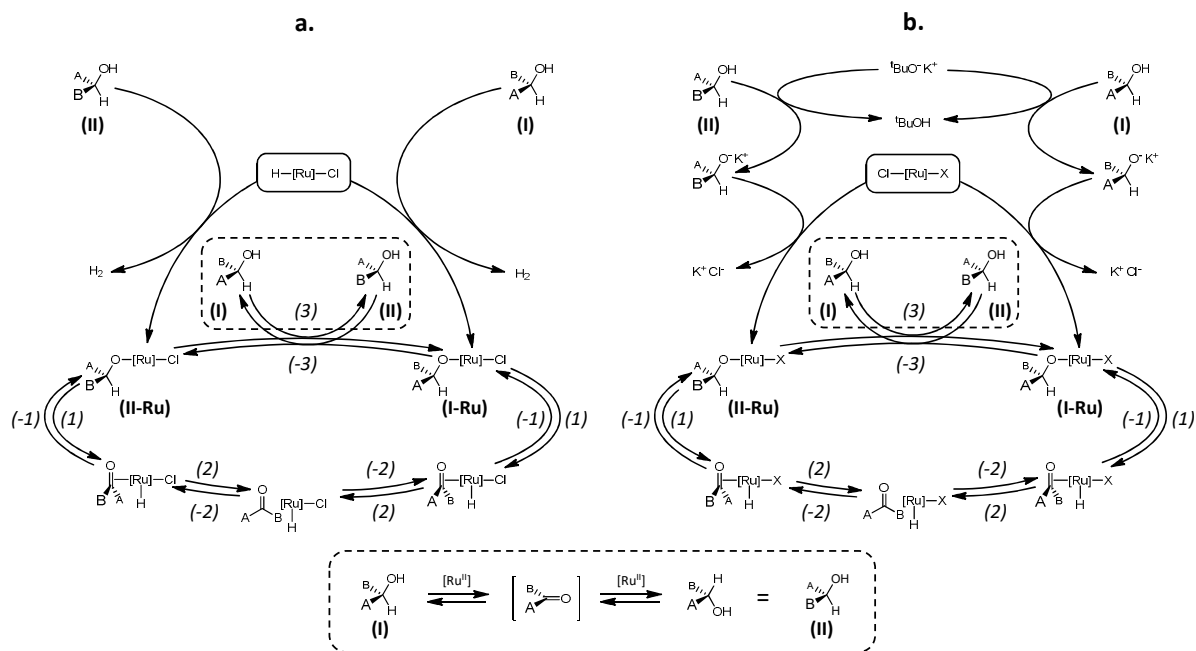


Figure 1. Proposed mechanisms for ruthenium<sup>(II)</sup> catalyzed alcohol epimerization using HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> (symbolized by H-[Ru]-Cl) without base (a.), and using Ru(*p*-cymene)Cl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>, RuCp\*Cl(PPh<sub>3</sub>)<sub>2</sub> or RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> (symbolized by Cl-[Ru]-X where X = Cl or Cp\*) in the presence of potassium *tert*-butylate (b.) (pure L ligands, *i.e.* CO, PPh<sub>3</sub> and *p*-cymene, are omitted for simplification).

In the following, HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos was used as catalytic system.

### 2.1.2 Epimerization of IsoS, IsoI and IsoM in *tert*-amyl alcohol



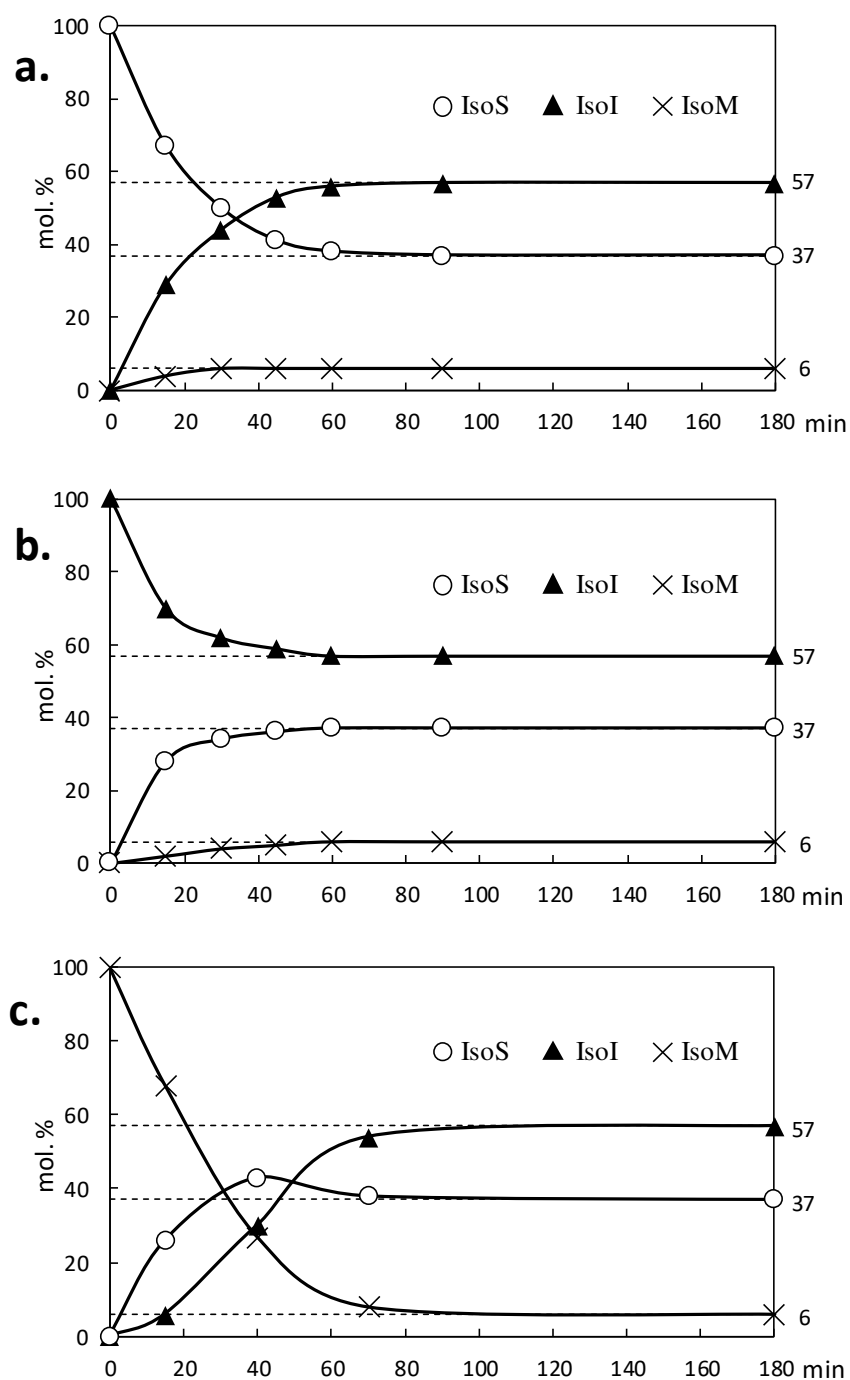


Figure 2: Ruthenium catalyzed epimerization of isosorbide (**a.**), isoidide (**b.**) and isomannide (**c.**) in *tert*-amyl alcohol; isohexide (10 mmol), HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> (0.2 mmol), Xantphos (0.2 mmol), *tert*-amyl alcohol (40 mL), Temperature (170°C).

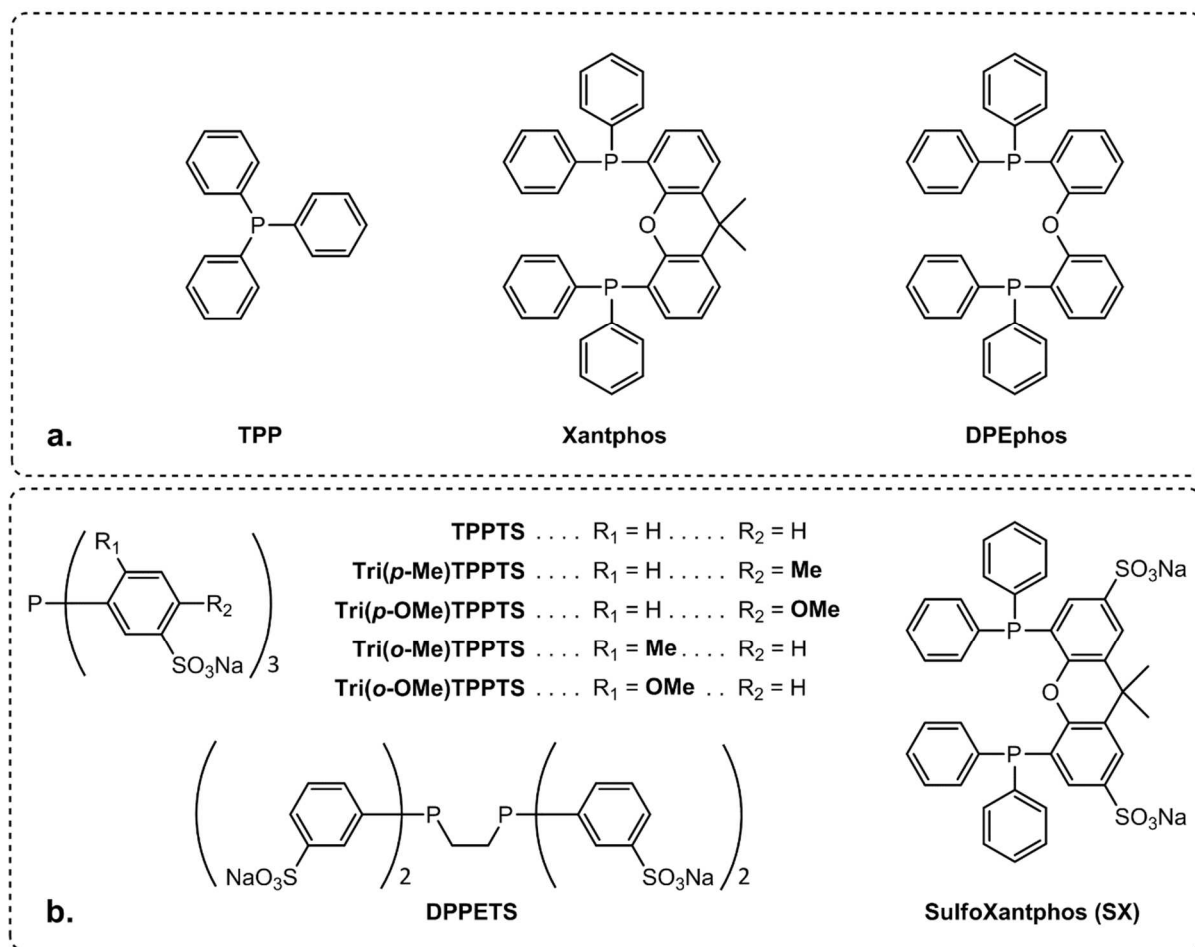
A kinetic monitoring of Ru-catalyzed epimerization of the three isohexides was performed by using the previous experimental conditions (HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos, *tert*-amyl alcohol, 170°C) (Figure 2). In the case of IsoS as substrate and in 60 minutes, proportions close to the

thermodynamic equilibrium were reached (IsoS/IsoI/IsoM: 37/57/6) (Figure 2a). For comparison, the same experiments were also performed with IsoI and IsoM as substrates (Figures 2b and 2c). With IsoI, the same proportions were also reached in 60 minutes. The reaction time was slightly longer for IsoM since 100 min was necessary. This behavior can be explained by considering the proportions of the different isomers at the equilibrium. Indeed, IsoM is the minor product (6%) followed by IsoS (37%) and the major product is IsoI (57%). Thus, 94% of IsoM has to be converted to reach equilibrium, whereas starting from IsoI only 43% must be converted to reach equilibrium. The shorter time observed with IsoS could be explained by the fact that only one of the hydroxyl positions has to be modified whereas for IsoM, both hydroxyl positions have to be converted to reach the proportion of 57% for IsoI. So, whatever the substrate, the same proportions of isohexides were reached.

These results demonstrated that the combination HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos was efficient to isomerize IsoS into the thermodynamic mixture at 170°C in *tert*-amyl alcohol without the use of hydrogen. In the following, the isomerization reaction was envisaged in pure IsoS.

### **2.1.3 Epimerization of IsoS without solvent**

As the isohexides are polar molecules (soluble in water, alcohols, ketones...) [1], it seemed interesting to employ, for IsoS epimerization, a polar catalytic system soluble in the isohexides mixture, liquid at the reaction temperature (reaction without solvent). So, the use of sulfonated monodentate and bidentate phosphines (Scheme 2b) was envisaged since these kind of phosphines are highly soluble in water and sometimes in polar solvents [23].

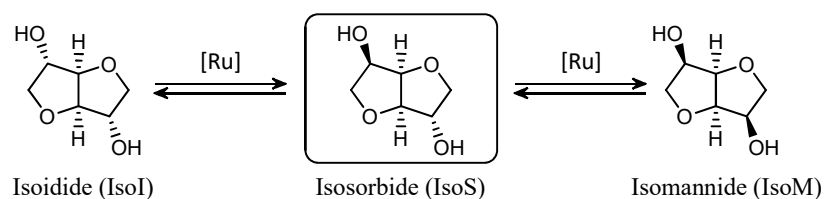


Scheme 2. Structures of the various apolar (**a.**) and polar (**b.**) phosphines used

Molar ratios equal to 500/1/3 for IsoS/Ru/Sulfonated Phosphine and a temperature of 150°C were chosen to obtain a complete solubilization of the catalytic system in molten IsoS. A control experiment using only HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> as catalyst was firstly performed. As this catalytic precursor was not soluble in IsoS, even at 150°C, no catalytic activity was observed after 18 h (Table 2, entry 1). The tris(3-sodium sulfonatophenyl)phosphine (TPPTS, P(*m*-C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>Na)<sub>3</sub>) was then used as polar ligand. Ru-catalyzed epimerization of IsoS was carried out in pure IsoS by using HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/TPPTS (1/3) as catalytic system at 150°C. After 6 h of reaction, a conversion of 31% was obtained (IsoS/IsoI/IsoM: 69/24/7) and it was necessary to wait 18 h of reaction to reach proportions close to the thermodynamic

equilibrium (IsoS/IsoI/IsoM: 37/54/9) (Table 2, entries 2 and 3). The influence of the nature of monodentate ligand was evaluated with two other monodentate phosphines: Tri(*p*-Me)TPPTS and Tri(*p*-OMe)TPPTS. The proportions of isohexides obtained after 18 h of reaction in the presence of these two phosphines were similar compared to TPPTS (Table 2, entries 3-5). In contrast, by using Tri(*o*-Me)TPPTS and Tri(*o*-OMe)TPPTS as ligand, the conversions of IsoS were lower (Table 2, entries 6-7). The steric hindrance of these ligands, which have a higher cone angle than their *para*-substituted counterparts, makes them less able to remove PPh<sub>3</sub> ligands from the HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> precursor [24]. So, the solubilisation of the ruthenium in IsoS was poorly achieved by these ligands explaining the low IsoS observed conversions.. For comparison with the system HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos, a mixture with a monodentate phosphine and a bidentate phosphine was then envisaged. Two sulfonated bidentate phosphines (SulfoXantphos (SX) and DPPETS) were used at 1 equivalent with respect to ruthenium, and in the presence of 1 equivalent of TPPTS (phosphorous atom/Ru total molar ratio of 3). In these two cases, the distribution of products was also similar and close to the thermodynamic proportions (Table 2, entries 8-9).

Table 2. Epimerization of IsoS without solvent



Entry	Ligand(s) (eq./Ru)	Time (h)	IsoS (%)	IsoI (%)	IsoM (%)
1	(-)	18	100	0	0
2	TPPTS (3)	6	69	24	7
3	TPPTS (3)	18	37	54	9
4	Tri( <i>p</i> -Me)TPPTS (3)	18	37	57	6
5	Tri( <i>p</i> -OMe)TPPTS (3)	18	41	47	12
6	Tri( <i>o</i> -Me)TPPTS (3)	18	76	11	3
7	Tri( <i>o</i> -OMe)TPPTS (3)	18	92	7	1
8	SX/TPPTS (1/1)	18	37	57	6
9	DPPETS/TPPTS (1/1)	18	40	55	5

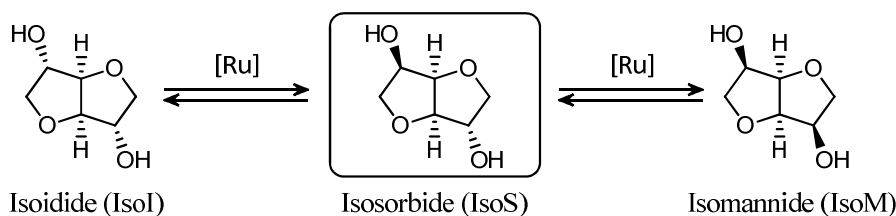
Reaction conditions: Isosorbide (100 mmol), HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> (0.2 mmol), Temperature (150°C).

So, as well as HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos system in *tert*-amyl alcohol, we have demonstrated that the combination HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Sulfonated Phosphine, without solvent, is able to isomerize IsoS. Nevertheless, for these two systems, the recycling of the catalyst would require a distillation at the end of the reaction in the aim to remove the solvent, in the first case, and then to separate the isohexides from the catalytic system, in both cases. Because of the high temperature needed for this distillation (boiling point of 160°C at 10 mmHg for isosorbide, for example), the heating of the crude product at high temperature during this extraction step would destabilized the catalytic system. Consequently, after addition of a new charge of isosorbide on the concentrated medium, this destabilization would decrease the catalytic activity for the next run. To circumvent this drawback, the use of a biphasic system seemed a good alternative.

## 2.2 Tuning of a work-up for a recyclable system

In order to develop an efficient workup for a recyclable catalytic system, a biphasic system was envisaged. Toluene was chosen as solvent for the catalytic system based on HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos. Indeed, HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> complex and Xantphos are fully soluble in toluene whereas IsoS is poorly soluble in this solvent. By this way, a biphasic liquid-liquid medium (catalytic system dissolved in toluene (light layer) and isohexides (heavy layer)) was obtained in reaction conditions. To facilitate the recycling step by decantation, the reaction was realized in a round-bottom flask, instead of an autoclave, at atmospheric pressure and at reflux temperature of toluene (110°C).

Table 3. Influence of the ligand on the epimerization of IsoS.



Entry	Ligand	Solvent	T (°C)	Time (h)	IsoS (%)	IsoI (%)	IsoM (%)
1	Xantphos	TAA	170	1	37	57	6
2	Xantphos	Toluene	170	1	36	57	7
3	Xantphos	Toluene	110	8	37	57	6
4	(-)	Toluene	110	2	37	57	6
5	TPP	Toluene	110	5	36	57	7
6	DPEphos	Toluene	110	12	37	57	6

Reaction conditions: Isosorbide (10 mmol), HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> (0.2 mmol), Ligand (0.2 mmol for Xantphos or 0.4 mmol for TPP), *tert*-amyl alcohol (TAA) or toluene (40 mL)

Nevertheless, for comparison, the experiments conducted in autoclave at 170°C by using *tert*-amyl alcohol (TAA) or toluene as solvent were firstly recalled or performed,

respectively (Table 3, entries 1 and 2). The experiment performed in biphasic medium (Toluene) led to the same time to reach the thermodynamic equilibrium than those performed in homogeneous medium (TAA). It should be noted that, at the end of the experiment, the system remained biphasic: a dense phase composed of the reaction products and a phase containing toluene solubilizing the catalyst. This experiment provided a qualitative validation of the proof of concept of this type of two-phase system. Surprisingly, the catalytic activities were equivalent for the homogeneous and biphasic systems. The solubility of isosorbide at 110°C in toluene was determined and equal to 6% weight. Note that, at room temperature, the solubility of IsoS in toluene was negligible. Based on these data, we can explain the similar reactivity obtained for the two systems. Indeed, for the biphasic system, the relatively high solubility of the substrate in the catalytic layer at reaction temperature can rationalize that mass transfer does not constitute the kinetic limiting step.

The time required to reach the thermodynamic equilibrium was higher for the experiments performed in the round-bottom flask compared to autoclave (compare entries 2 and 3 of Table 3). This behavior is coherent since the temperature was higher for the reaction performed in the autoclave (170°C), in comparison with the one performed at the reflux temperature of toluene (110°C). Nevertheless, it is possible to reach the thermodynamic equilibrium after 8 h of reaction in toluene at 110°C (Table 3, entry 3).

Other experiments were performed by using  $\text{HRu}(\text{CO})\text{Cl}(\text{PPh}_3)_3$  alone, with a monodentate phosphine (triphenylphosphine, TPP), or with another bidentate phosphine (bis[2-(diphenylphosphino)phenyl]ether, DPEphos) as added ligand instead of Xantphos (Table 3, entries 4, 5 and 6). As expected, the time to reach the thermodynamic equilibrium was shorter without added ligand. This behavior is classical for low coordinated catalytic species. Indeed, the addition of TPP in the medium gave ruthenium species more coordinated and so less active. DPEphos did not lead to better results than Xantphos. The recyclability of

the catalytic system was then investigated by reusing the toluene catalytic phase in three conditions: without added ligand, with added TPP, and with added Xantphos.

### **2.3 Recyclability of the catalytic system**

For these recyclability tests, the IsoS/ruthenium molar ratio was increased from 50 to 100 (concretely, 20 mmol of IsoS were used for each run, instead of the 10 mmol of Table 3) and the volume of toluene was divided by two (20 mL used instead of the 40 of Table 3). Three kinds of experiment were performed: without added phosphine, with added TPP and with added Xantphos (Figure 3). After the first run (2 h), the two phases were separated and the isohexides heavy layer analyzed. The initial turn over frequency ( $\text{TOF}^\circ$  ( $\text{h}^{-1}$ )) was determined for each experiment. The  $\text{TOF}^\circ$  provides a relevant information since a decrease along the recycling experiments is generally linked to a leaching of catalyst in the products layer.

The best  $\text{TOF}^\circ$  was obtained for experiments performed without ligand ( $47 \text{ h}^{-1}$ ), followed by those with TPP ( $22 \text{ h}^{-1}$ ) and then those with Xantphos ( $13 \text{ h}^{-1}$ ). As described previously, this behavior in terms of catalytic activity was expected. Nevertheless, for the second run, even if the ranking of  $\text{TOF}^\circ$  followed the same tendency, a decrease was highlighted for the experiments performed without ligand or with TPP whereas the  $\text{TOF}^\circ$  was in the same order of magnitude in the presence of Xantphos. This behavior was repeated for the following three recycling processes. In fact, the absence of additional ligand led to the formation of low coordinated phosphine species soluble in isohexides layer. In this case, the  $\text{TOF}^\circ$  was higher, but during the separation of the two layers, a part of catalyst was lost in isohexides layer. So, the amount of catalyst in toluene layer decreased progressively explaining the decrease of  $\text{TOF}^\circ$ . The same behavior was observed in the presence of TPP but to a lesser degree. On the



contrary, the organometallic species based on ruthenium coordinated by Xantphos stayed strongly immobilized in toluene layer. The  $\text{TOF}^\circ$  was lower but the catalytic activity stayed constant. In addition, for the two other catalytic systems (without added ligand or with added TPP), the isohexides layer is contaminated by the catalytic species since a leaching occurred. So, the system based on Ru/Xantphos offers the best compromise for an industrial application since a stable catalytic species is generated even if it is less active. This conclusion is consistent with the fact that Xantphos is well known to produce highly stabilized catalytic species due to the high ligand-to-metal bond strength leading to low catalytic activity but to a better catalyst stability [25].

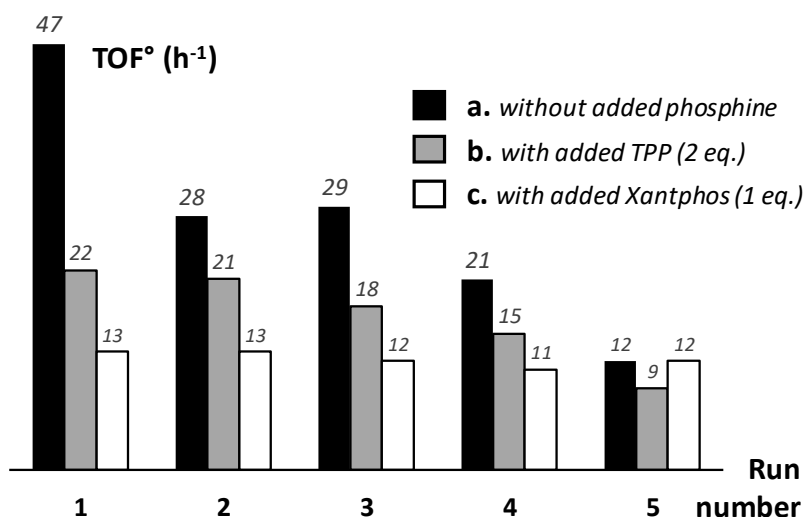


Figure 3: Reusability of the catalytic system in biphasic isosorbide epimerization;  $\text{TOF}^\circ$  ( $\text{h}^{-1}$ ) = initial turnover frequency = molar amount of isosorbide converted per mole of Ru, and per hour, in the early stage of the reaction; each run has been conducted for 2 h; isosorbide (20 mmol),  $\text{HRu}(\text{CO})\text{Cl}(\text{PPh}_3)_3$  (0.2 mmol) used without added phosphine (**a.**), with 2 molar eq. of added TPP per Ru (**b.**), and with 1 molar eq. of added Xantphos per Ru (**c.**), toluene (20 mL), Temperature ( $110^\circ\text{C}$ ).

## 2.4 Scale-up experiment

As the principle of recyclability on a laboratory scale was demonstrated, a larger scale recycling experiment was performed. The reaction was therefore carried out in a 1 L double-shell reactor equipped with a bottom outlet valve. The quantity of isosorbide introduced at the beginning and after the various recycling operations was set at 146 g (1 mol). The volume of toluene introduced was 500 mL with a catalyst charge of 0.2 % mol HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos (1:1) (IsoS/Ru molar ratio of 500). The reactor was heated to 110°C (toluene reflux) for a period of 24 hours. At the end of the reaction, the denser polar phase was removed through the bottom valve while leaving the toluene phase in the reactor. After this separation, a new quantity of 146 g of IsoS was added into the reactor to perform the recycling experiments.

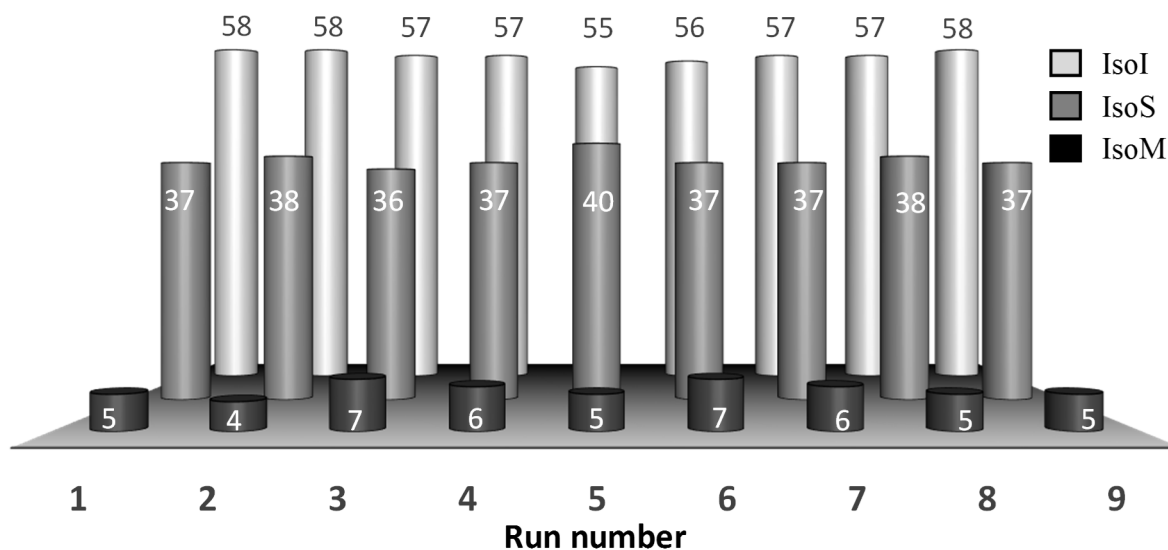


Figure 4: Isohexides amounts (%) obtained during a reusability test of the catalytic system in biphasic isosorbide epimerization; each run has been conducted for 24 h; isosorbide (1 mol, 146 g), HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> (2 mmol), Xantphos (2 mmol), toluene (500 mL), Temperature (110°C).

The catalytic system is fully recyclable over nine successive cycles (Figure 4). Thus, the quantity of the mixture of isomers produced with a 0.2 % mol catalytic charge was 1314 g (9 x 146 g; nine recycling experiments performed with 146 g of IsoS). This represents, in theory, after separation of the products, a quantity of more than 750 g of IsoI, the residual IsoS and IsoM being able to give IsoI again by a further isomerization reaction. A fraction of the first batch (70 g from the 146 g) was distilled in order to separate the different isohexides. The distillation was performed in 3 steps (3 h at 140°C, 2 h at 160°C and 3 h at 180°C under a reduce pressure of 2 mbar). After the three step, three fraction were obtained: (1<sup>st</sup>) 15.3 g containing IsoS/IsoI/IsoM (74/6/20), (2<sup>nd</sup>) 25.6 g containing IsoS/IsoI/IsoM (58/38/4) and (3<sup>th</sup>) 27.4 g containing IsoS/IsoI (5/95). Around 1.7 g of a brown viscous liquid remained in the vessel. A more efficient distillation apparatus such as plate column could be more efficient to fully separate the different isomers. So, an application at an industrial scale could be envisaged.

### 3. Conclusion

The catalytic combinations HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos, in *tert*-amyl alcohol, or HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Sulfonated Phosphine, without solvent, were efficient for the epimerization of industrially available IsoS to IsoI. These catalytic systems allowed reaching the thermodynamic equilibrium between the three isohexides at moderate temperature, without hydrogen. More interestingly, using HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub>/Xantphos in toluene, the reaction can be performed in a biphasic system allowing the recyclability of the catalytic layer up to nine times. A scale-up experiment was also performed with success showing the potentiality of this system for an industrial application.

## 4. Experimental part

### 4.1. General Remarks

Isosorbide, isoidide and isomannide were provided by Roquette compagny. Solvents, potassium *tert*-butylate, ruthenium complexes, Triphenylphosphine, Xantphos and DPEphos were purchased in their purest form from Fischer Scientific, Sigma-Aldrich and Strem Chemicals and were used without further purification. TPPTS [26], Tri(*p*-Me)TPPTS [27], Tri(*p*-OMe)TPPTS [27], Tri(*o*-Me)TPPTS [27] and Tri(*o*-OMe)TPPTS [27], SulfoXantphos [28] and DPPETS [29] were synthesized by procedures already described in the literature.

All experiments were done under nitrogen using Schlenk techniques.

Isomerization experiments conducted without solvent (at 150°C), or in *tert*-amyl alcohol (at 102°C), or in toluene (at 110°C) were carried out in a 100 mL round-bottom flask equipped with a hot plate stirrer, an oil bath and a condenser.

Isomerization experiments conducted in *tert*-amyl alcohol or in toluene at 170°C were carried out in a 110 mL stainless-steel autoclave equipped with a mechanical stirrer and supplied by Top Industrie society (model 2790 2000).

Scale-up experiments done in toluene at 110°C and involving 146 g of isosorbide (1 mol) for each run were done in a 1 L double-shell reactor equipped with a bottom outlet valve, a

mechanical stirrer and a condenser. The heating was provided by a RP240E cryostat from Lauda society.

Both NMR and gas chromatography were used to analyze the isohexides mixture obtained after reaction and gave always very similar results. NMR spectra were recorded in CD<sub>3</sub>OD with a Bruker spectrometer operating at 400 MHz for <sup>1</sup>H nuclei. Chromatograms were obtained on a 7890B gas chromatograph from Agilent technologies equipped with a J&W DB1 Agilent column (polydimethylsiloxane stationary phase; 30 m × 0.32 mm × 0.5 μm;) and using H<sub>2</sub> as carrier gas.

#### **4.1. Isohexides isomerization experiments conducted in *tert*-amyl alcohol or toluene at 170°C**

A ruthenium complex (0.2 mmol), Xantphos (115 mg, 0.2 mmol), an isohexide (1.46 g, 10 mmol; isohexide/Ru molar ratio of 50) and potassium *tert*-butylate (0 or 2 mmol), were introduced into the autoclave and then put under nitrogen. After that, 40 mL of a deoxygenated solvent (*tert*-amyl alcohol or toluene) were transferred into the reactor under nitrogen on the solids. The obtained medium was then stirred (1200 rpm) at 170°C during 1 h.

#### **4.2. Isosorbide isomerization experiments conducted without solvent at 150°C**

HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> (190 mg, 0.2 mmol), TPPTS, Tri(*p*-Me)TPPTS, Tri(*p*-OMe)TPPTS, Tri(*o*-Me)TPPTS, Tri(*o*-OMe)TPPTS (0.6 mmol; monophosphane/Ru molar ratio of 3) or a mixture of DPPETS or SulfoXantphos and TPPTS (0.2 mmol for the diphosphine ligand and 0.2 mmol for TPPTS) and isosorbide (14.6 g, 100 mmol; isosorbide/Ru molar ratio of 500),

were introduced under nitrogen into a 100 mL round-bottom flask equipped with an ovoid magnetic stirring bar, a hot plate stirrer, an oil bath, and a condenser. At 150°C, the mixture is liquid and homogeneous. The medium was then stirred (1500 rpm) at this temperature during 18 h.

#### **4.3. Isosorbide isomerization experiments conducted in *tert*-amyl alcohol or toluene at 102 and 110°C, respectively**

HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> (190 mg, 0.2 mmol), a potential added ligand (0.2 mmol of Xantphos, 0.2 mmol of DPEphos or 0.4 mmol of TPP), and isosorbide (1.46 g, 10 mmol; isosorbide/Ru molar ratio of 50) were introduced under nitrogen in a 100 mL round-bottom flask equipped with an ovoid magnetic stirring bar, a hot plate stirrer, an oil bath and a condenser. A deoxygenated solvent (40 mL of *tert*-amyl alcohol or toluene) was then transferred into the round-bottom flask. The medium was then stirred (1500 rpm) under solvent reflux (102 and 110°C for *tert*-amyl alcohol and toluene, respectively) during the desired reaction time.

For the catalytic system reusability experiments done at an isosorbide/Ru molar ratio of 100 (instead of 50), 2.92 g of isosorbide (20 mmol) were introduced at each run instead of 1.46 g and the solvent used was toluene (20 mL involved instead of 40 mL).

The Scale up experiments were conducted in the same way but in a 1 L double-shell reactor equipped with a mechanical stirrer used at 500 rpm and with these amounts: HRu(CO)Cl(PPh<sub>3</sub>)<sub>3</sub> (2 mmol), Xantphos (2 mmol), isosorbide (1 mol, 146 g; isosorbide/Ru molar ratio of 500 for each run), toluene (500 mL).

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## Graphical Abstract

