Synthesis of new class of ligands derived from isosorbide and their application to asymmetric reduction of aromatic ketones by transfer hydrogenation

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Abstract: A new class of β-amino alcohol and diamine ligands has been prepared from isosorbide as a chiral renewable source. The efficiency of these ligands has been evaluated for the metal-catalyzed enantioselective reduction of aromatic ketones by transfer hydrogenation, giving excellent conversion and good enantioselectivity.
Keywords: Asymmetric transfer hydrogenation, chiral ligand, isosorbide, aromatic ketones.

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 (Figure 1).

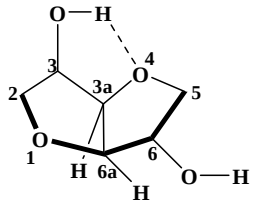

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Figure 1: Structure of isosorbide **1**

Isosorbide is industrially obtained by dehydration of *D*-sorbitol, and can therefore be

considered as 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]

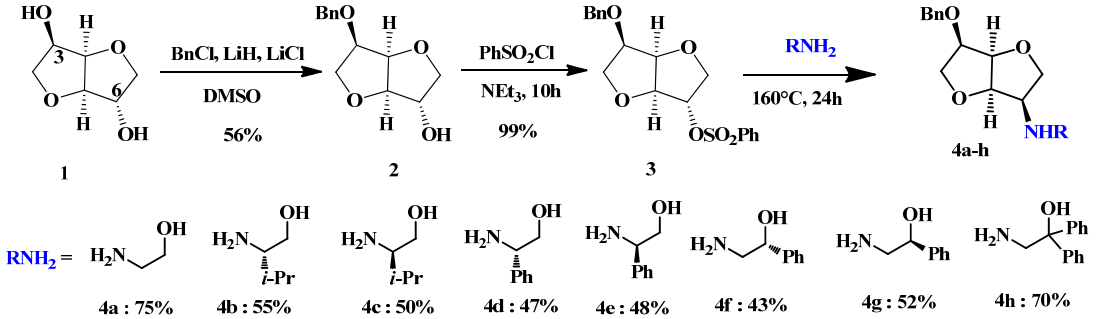
The reduction of carbonyl compounds to the corresponding alcohols is one of the most fundamental and useful reactions that are important in the pharmaceutical and chemical industry. The asymmetric transfer hydrogenation (ATH) of ketones has recently emerged as a highly efficient method for the synthesis of enantiomerically enriched secondary alcohols that are key intermediates for the manufacture of a variety of molecules and molecular scaffolds of biological and therapeutic interest.[6] Transition metal-catalyzed asymmetric transfer hydrogenation of prochiral ketones provides a powerful alternative to asymmetric hydrogenation owing to its ease of handling, the easy availability of hydrogen sources, lower cost and safety.[7] Many chiral ligands and transition metals have been developed and applied to this reaction. The common catalysts are rhodium, ruthenium and iridium complexes with chiral phosphine and chiral diamine ligands.[8]

As a part of our own program of studies, we have recently described the rhodium-catalyzed ATH of acetophenone using chiral *N*-Heterocyclic Carbene ligands, derived from (*S*)-pyroglutamic.[9] We report here the synthesis of new chiral β-amino-alcohols and diamines derived from isosorbide **1**, and investigate their catalytic application to ATH of aromatic ketones.

Results and discussion.

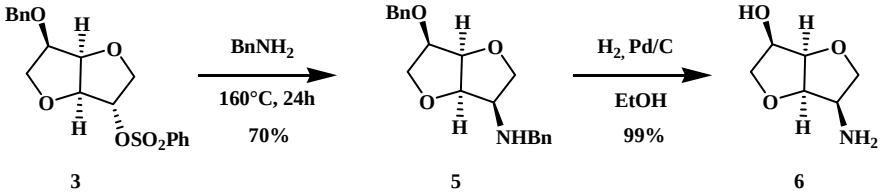
Synthesis of chiral ligands.

The synthesis of ligands **4a-h** derived from isosorbide **1** is summarized in Scheme 1. Our synthesis was initiated by the selective monobenzylation of the hydroxyl group at the *endo* position C_3 of isosorbide. The best yield (56%) of compound **2** was obtained when performing the reaction using one equivalent of benzyl chloride along with lithium hydride and lithium chloride in stoichiometric quantities. The free hydroxyl group at the *exo* position C_6 was then activated as its sulfonate by treatment with benzenesulfonyl chloride using an excess of triethylamine, affording the sulfonate **3** in 99% yield. Subsequently, the sulfonate **3** was treated with an excess of amino alcohol in a sealed tube at 160 °C in the presence of lithium chloride, giving the corresponding compounds **4a-h** *via* a S_N2 substitution reaction with complete inversion of configuration.



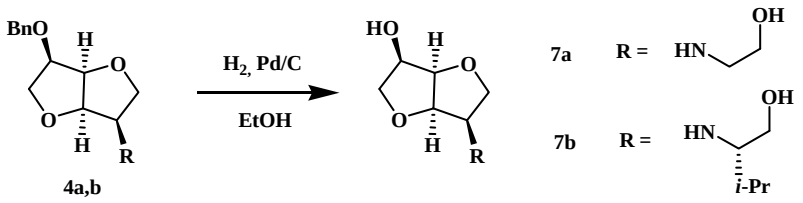
Scheme 1: Synthesis of amino alcohols **4a-h**.

On the other hand, amino alcohol **6** was obtained by two-step procedure, including a substitution of sulfonate **3** with benzylamine, following by a removing the benzyl protecting groups of **5** by hydrogenolysis in the presence of Pd/C (Scheme 2).



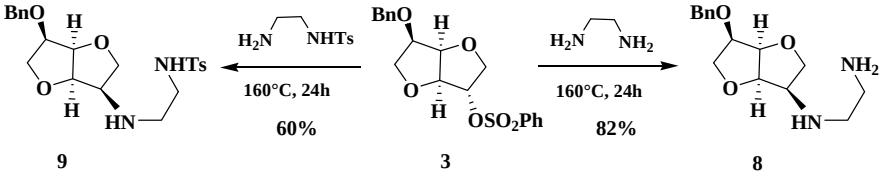
Scheme 2: Synthesis of amino alcohol **6**.

Debenzylation of ligands **4a** and **4b** gave dihydroxy compounds **7a** and **7b** respectively in quantitative yields (Scheme 3).



Scheme 3: Synthesis of amino alcohols **7a-b**.

Using the similar reaction conditions previously described for the synthesis of amino alcohol ligands **4**, diamine **8** and *N*-tosylated amine **9** were synthesized from sulfonate **3** with 82% and 60% yields respectively (Scheme 4).



9 3 8

Scheme 4: Synthesis of diamine **8** and *N*-tosylated amine **9**.

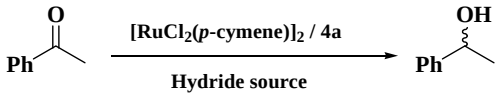
Asymmetric transfer hydrogenation reaction

After achieving the synthesis of these amino alcohols and diamines, we were interested in testing their potential as ligands for asymmetric catalysis.

The reduction of acetophenone to 1-phenylethanol by asymmetric transfer hydrogenation was chosen as a model reaction to explore the catalytic behaviours of complexes. From a practical point of view, the application of *in situ* prepared catalysts has significant advantages. The complex formation conditions are described in details in the experimental section.

We have initiated by screening the hydride sources effect on catalytic activity and asymmetric induction of the reduction of acetophenone using the ligand **4a**. The catalytic trials were carried out using ligand **4a** (5 mmol), acetophenone (1.0 mmol), $[RhCl_2(p\text{-cymene})]_2$ catalyst precursor (1 mol%). The reaction conversion was monitored by ^1H NMR and the enantiomeric excess was determined by chiral HPLC analysis. Some significant results are presented in Table 1.

Table 1: ATH of acetophenone with various hydride sources.



Entry	Hydride source	Time (h)	Temp.(°C)	Solvent	Conv. (%)[a]	Ee (%)[b]
1[c]	HCO_2H-NEt_3	24	40	CH_2Cl_2	10	7
2[d]	HCO_2Na	96	25	H_2O	85	46
3[e]	***i*-PrOH**	**2**	**25**	***i*-PrOH**	**99**	**70**

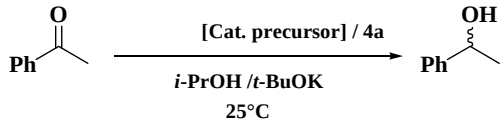
[a] Determined by ^1H NMR. [b] Determined by chiral HPLC analysis using Chiralcel OD-H column. [c] HCO_2H-NEt_3 (0.5mL). [d] HCO_2Na (5 mmol). [e] *t*-BuOK (5mol%) is used as base. Ratio *t*-BuOK/**4a**/Ru = 2/2/1. [acetophenone]= 0.2M in *i*-PrOH.

Using *i*-PrOH as hydride source afforded the desired product with 99% conversion and

70% ee after 2h. This conventional hydrogen source offers interesting properties such as its stability, its ease of handling, non toxic, environmentally friendly, inexpensive and a good solvent for many organic compounds.

Next, we decided to screen catalyst precursors using *i*-PrOH as hydrogen source and *t*-BuOK as promoter for the asymmetric reduction of acetophenone. The reactions were performed at room temperature using ligand **4a** (Table 2).

Table 2: ATH of acetophenone with various catalyst precursors.[a]



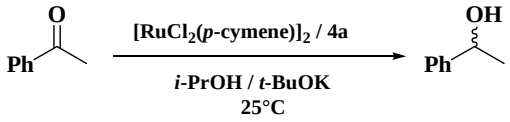
Entry	Time (h)	Catalyst precursor	Conv. (%)[b]	Ee (%)[c]
1	2	$[RuCl_2(benzene)]_2$	34	40
2	**2**	**$[RuCl_2(p\text{-cymene})]_2$**	**99**	**70**
3	24	$[RuCl_2(mesitylene)]_2$	14	0
4	2	$[CpRhCl_2]_2$	64	63
5	2	$[CpIrCl_2]_2$	25	24

[a] Conditions : catalyst precursor (1.25 mol%), ligand **4a** (5 mol%), molar ratio of acetophenone/*t*-BuOK/ligand **4a**/Ru = 40/2/2/1. [acetophenone]=0.2M in *i*-PrOH. [b] Determined by ^{1}H-NMR. [c] Determined by chiral HPLC analysis.

Changing the arene ligand from *p*-cymene to benzene or mesitylene gave negative effect on both conversion and enantioselectivity (Entries 1 and 3). $[CpRhCl_2]_2$ catalyst precursor conducted to almost equivalent enantiomeric excess, but lower yield compared to $[RuCl_2(p\text{-cymene})]_2$ one (Entries 4 and 2). On the other hand, $[CpIrCl_2]_2$ catalyst precursor gave both lower yield and enantioselectivity (Entry 5).

We decided thus to pursue our studies by varying base/ligand/metal (B/L/M) ratio using $[RuCl_2(p\text{-cymene})]_2$ as catalyst precursor and *t*-BuOK as promoter in the presence of ligand **4a**. (Table 3).

Table 3: ATH reduction of acetophenone using *i*-PrOH as hydride source and $[RuCl_2(p\text{-cymene})]_2$ as catalyst precursor[a].

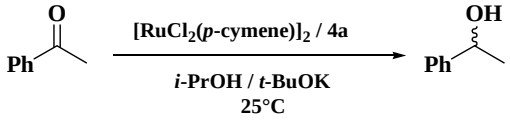


Entry	Time (h)	Molar ratio[b]	Conv.(%)[c]	ee (%)[d]
1	48	1/ 1/ 1	17	0
2	48	1/ 2/ 1	8	0
3	2	2/ 1/ 1	22	70
4	2	2/ 4/ 1	97	70
5	**2**	**2/ 2/ 1**	**99**	**70**
6	24	2/ 2/ 1	99	70
7	2	4/ 4/ 1	88	70
8	24	4/ 4/ 1	98	70
9	2	6/ 4/ 1	22	67
10	24	6/ 4/ 1	23	60

[a] Conditions : molar ratio acetophenone/Ru = 40/1. [acetophenone] = 0.2 M in *i*-PrOH. [b] *t*-BuOK/ ligand/ Ru ratio [c] Determined by ^{1}H-NMR, no by products were observed. [d] Determined by chiral HPLC analysis.

Table 3 showed a crucial effect on reactivity and especially on asymmetric induction by varying base/ligand/metal (B/L/M) ratio. The best conversion and enantioselectivity were obtained at B/L/M 2/2/1. In these conditions, the product was obtained with 99% conversion and 70% ee after 2h (Entry 5). Furthermore, the enantiomeric excess did not decrease after 24h of reaction time (Entries 5 and 6). The similar results were observed at B/L/M 4/4/1 (Entries 6 and 8). Decreasing of concentration of base, racemic products were observed with a deteriorated conversion (Entries 1 and 2). When using an excess of base with regard to the ligand, the enantiomeric excess and especially the conversions dropped (Entries 9 and 10). These optimal conditions 2/2/1 ratio for *t*-BuOK/ligand/Ru were then selected for evaluating the influence of substrate concentration (Table 4).

Table 4: Effect of substrate concentration on the ATH of acetophenone.[a]

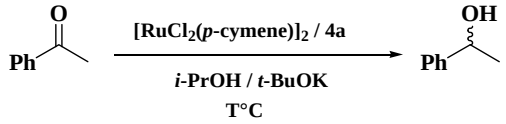


Entry	Time (h)	[C] (mol)[b]	Conv. (%)[c]	ee (%)[d]
1	2	0.1	60	56
2	24	0.1	67	70
3	2	0.2	99	70
4	24	0.2	99	70
5	2	0.4	90	70
6	24	0.4	93	65

[a] Conditions : $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol%), ligand **4a** (5 mol%), molar ratio of acetophenone/*t*-BuOK/ligand **4a**/Ru = 40/2/2/1.[b] Concentration of acetophenone. [c] Determined by ^{1}H-NMR. [d] Determined by chiral HPLC analysis.

The concentration of acetophenone was changed by modifying the volume of *i*-PrOH. As we can observe, only 60% conversion were obtained after 2h of reaction time when using 0.1M concentration of substrate (Entry 1). The reaction time was extended to 24h in order to obtain better conversion, but unsuccessful. With higher concentration, 0.4M for example, the enantiomeric excesses slightly decreased after 24h, probably owing to the reaction reversibility (Entries 5 and 6). The best results were obtained when performing the reaction at [substrate] = 0.2M without any racemisation of product (Entries 3 and 4). These conditions were applied to examine the reaction temperature effect (Table 5).

Table 5: Effect of temperature on ATH of acetophenone.[a]



Entry	Time (h)	Temp.(°C)	Conv. (%)[b]	Ee (%)[c]
1	2	25	99	70
2	2	0	39	75
3	40	0	99	77
4	**96**	**-10**	**83**	**80**

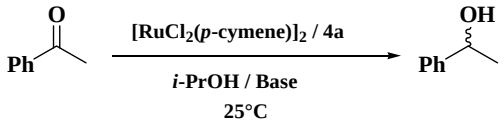
[a] Conditions : $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol%), ligand **4a** (5 mol%), molar ratio of acetophenone/*t*-BuOK/ligand **4a**/Ru = 40/2/2/1. [acetophenone] = 0.2M in *i*-PrOH. [b] Determined by ^{1}H-NMR. [c] Determined by chiral HPLC analysis.

The best enantioselectivity (80% ee) was obtained when performing the reaction at -10°C. However, the reaction time dramatically increased from 2h up to 96h (Entries 3 and 4).

It is well-known that transfer hydrogenations are sensitive to the nature of the base. Thus, the

influence of *t*-BuOK, *i*-PrONa and KOH, used as promoter, on selectivity and conversion was investigated. In all cases, good to excellent conversions were observed (Table 6). Despite that the nature of the base has limited effect on the selectivity, we observed that longer reaction time was needed in the case of KOH. The best conversion and enantioselectivity were obtained in the presence of 5 mol% *t*-BuOK, one of the most common bases for transfer hydrogenation (Table 6, entry 1).

Table 6**:** ATH of acetophenone with various bases.[a]

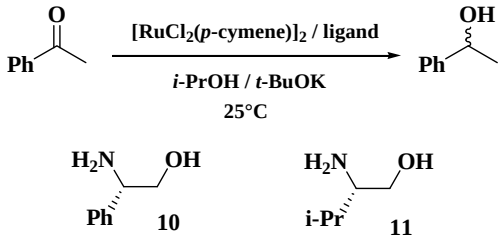


Entry	Time (h)	Base	Conv. (%)[b]	Ee (%)[c]
1	2	*t*-BuOK	99	70
2	2	*i*-PrONa	93	67
3	3	*i*-PrONa	96	67
4	20	*i*-PrONa	96	62
5	2	KOH	28	70
6	24	KOH	70	70

[a] Conditions : $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol%), ligand **4a** (5 mol%), molar ratio of acetophenone/*t*-BuOK/ligand **4a**/Ru = 40/2/2/1. [acetophenone] = 0.2M in *i*-PrOH. [b] Determined by ^{1}H-NMR. [c] Determined by chiral HPLC analysis.

Next, the influence of the ligand nature was investigated. As shown in Table 7, we examined 14 aminoalcohol ligands **4a-h**, **5**, **6**, **7a-b**, **10**, **11** under the previously optimized conditions for the transfer hydrogenation of acetophenone.

Table 7: Variation of ligands in the ATH of acetophenone.[a]



Entry	Time (h)	Ligand	Conv. (%)[b]	Ee (%)[c]
1	2	**4a**	99	(*R*)-70
2	2	**4b**	30	(*R*)-27
3	24	**4b**	63	(*R*)-3
4	2	**4c**	10	(*R*)-40
5	24	**4c**	32	(*R*)-36
6	2	**4d**	25	(*S*)-60
7	24	**4d**	28	(*S*)-47
8	2	**4e**	18	(*R*)-44
9	24	**4e**	55	(*R*)-35
10	2	**4f**	94	(*R*)-87
11[d]	**24**	**4f**	**94**	**(*R*)-91**
12	2	**4g**	74	(*S*)-60
13	24	**4g**	95	(*S*)-60
14	2	**4h**	10	(*R*)-65
15	48	**5**	nd[e]	-
16	48	**6**	nd[e]	-
17	2	**7a**	89	(*R*)-66
18[f]	2	**7a**	77	(*R*)-65
19	2	**7b**	12	(*S*)-26
20	24	**7b**	40	(*S*)-26
21	1	**10**[g]	100	(*S*)-24
22	1	**11**[h]	100	(*S*)-29

[a] Conditions : $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol%), ligand (5 mol%), molar ratio of acetophenone/*t*-BuOK/ligand/Ru = 40/2/2/1, [acetophenone] = 0.2M in *i*-PrOH. [b] Determined by ^{1}H-NMR. [c] Determined by chiral HPLC analysis. Absolute configuration assigned by comparison of the specific rotation with literature values. [d] Reaction was carried out at 0°C. [e] Not determined. [f] 2 eq. LiCl was added. [g] (*S*)-2-amino-2-phenylethanol **10** as ligand. [h] (*S*)-2-amino-3-methylbutan-1-ol **11** as ligand.

Both ligands **5** and **6** showed no activity in term of conversion and enantioselectivity. The distance between hydroxyl group and amine function is probably important to assure the formation of the Ru-complex. With the *O*-benzylated amino alcohol ligands **4b** to **4e**, enantiomeric excesses and conversions of the reduction did not exceed to 60% and 63% respectively, compared to ligand **4a** (70% ee with 99% conversion). Substitutents at the α-position of the nitrogen atom of amino alcohol have a negative influence both on the

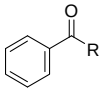
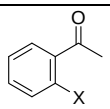
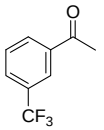
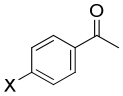
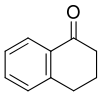
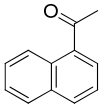
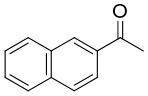
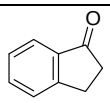
enantioselectivity and reaction rate (compare entries 2-9 to entry 1). On the other hand, the introduction of a phenyl group at the α-position of the oxygen atom, ligand **4f**, has a positive effect on the enantioselectivity. The asymmetric induction increased up to 91% ee without lost of catalytic activity (94% conversion) (Entries 10 and 11). However, its diastereoisomer **4g** conducted lower enantioselectivities and conversions. Moreover, supplementary substitution with two phenyl groups for ligand **4h**, resulted in very low conversion (10%) with a slight decrease of ee value (Entry 14). Debenzylated aminoalcohol ligand **7a** gave similar results than *O*-benzylated one **4a** in terms of conversion and enantioselectivity (Entries 1 and 17). This showed a very weak effect of free hydroxyl group at C_3 position of isosorbide skeleton. Surprisingly, in the case of **7b** (Entries 19 and 20), we observed an inversion of absolute configuration of product ((*S*)-26% ee) compared to (*R*)-27% ee for **4b** (Entries 2 and 3). More interestingly, the enantiomeric excess value did not decrease in time when comparing to ligand **4b** (26% ee for **7b** and 3% ee for **4b** after 24h). Finally, when (*S*)-2-amino-2-phenylethanol **10** and (*S*)-2-amino-3-methylbutan-1-ol **11** were used as chiral ligands for ATH of acetophenone, excellent catalytic activities with total conversion after only 1h of reaction time, but moderate asymmetric induction, only 24% and 29% ee respectively were observed (Entries 21 and 22).

As we can observe, when using ligands **4b** and **4d** possessing an isosorbide skeleton, compared to their analogues **11** and **10,** similar or better enantioselectivities were observed (Entries 6 and 21, 2 and 22). Moreover, a good asymmetric induction was obtained with the ligand **4a** bearing an ethanolamine chain**.** These results confirmed that the presence of isosorbide moiety is fundamental for asymmetric induction.

To extend the scope of the amino-alcohol **4a** and **7a** ligand-Rh (I) complexes as chiral catalysts in this reaction, some functionalized acetophenone derivatives which are more difficult to hydrogenate were tested. The substrates were selected so as to have either electron-donating or electron-withdrawing moieties on the phenyl ring. According to the literature, no decomposition or side reactions of these substituted ketones in transfer hydrogenation has been detected.[10]

The indicated reaction times were optimized. No improvement of conversion or lost of enantiomeric excesses of products were observed in extending reaction time.

Table 8: Asymmetric transfer hydrogenation of aromatic ketones with ligand **4a**.[a]

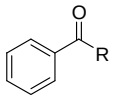
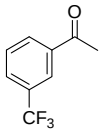
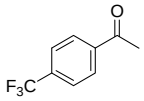
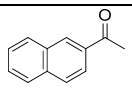
Entry	Ketone		Time [h]	Conv. (%)[b]	ee (%)[c]
1		R= CH_3	2	99 (96) [d]	(*R*)-70
2		R= *i*-Pr	48	0	-
3		R= CH_2Cl	48	0	-
4		X= MeO	2	54	(*R*)-62
5		X= Cl	2	74	(*R*)-54
6			24	91	63
7		X= OMe	24	40	(*R*)-65
8		X= Cl	2	75	(*R*)-61
9		X= Br	24	79	(*R*)-60
10		X= CF_3	3	93 (93) [d]	(*R*)-60
11			2	29	(*R*)-82
12			24	26	(*R*)-59
13			24	71	(*R*)-65
14			3	40	(*R*)-66

[a] Conditions : $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol%), ligand **4a** (5 mol%), molar ratio of acetophenone/*t*- BuOK/ligand **4a**/Ru = 40/2/2/1. [acetophenone] = 0.2M in *i*-PrOH. T = 25°C . [b]Determined by ^{1}H-NMR.[c] Determined by chiral HPLC analysis. Optical rotation assigned by comparison of the specific rotation with literature values. [d] Isolated yield.

Ligand **4a** showed high capacity for transfer hydrogenation of various ketones with good conversion and moderate to good enantioselectivity (up to 82% ee). The steric and electronic properties of substrates affected considerably on the chemical yield and enantioselectivity. Introduction of an electron-withdrawing group or an electron-donating group on the phenyl led to

much lower yields and enantioselectivities (Entries 4 - 10). On the other hand, negative effects on conversion and asymmetric induction were observed when performing the ATH with 1- or 2-acetonaphthone in lieu of acetophenone, presumably due to increased substrate bulk (Entries 1 and 12, 13). This was confirmed when increasing the bulkiness of the R group, next to the active center, very low or no activity and enantioselectivity were recorded (Entries 14, or 2 and 3). The best enantiomeric excess of 82% was obtained using 3,4-dihydronaphtalen-1(*2H*)-one as substrate. However, low conversion was observed (Entry 11).

Table 9: Asymmetric transfer hydrogenation of aromatic ketones with ligand **7a**.[a]

Entry	Ketone		Time [h]	Conv. [%][b]	ee [%][c]
1		R= CH_3	2	89	(*R*)-66
2		R= CH_2Cl	48	0	-
3		R= CF_3	3	32	(*S*)-33
4			3	99	(*R*)-56
5			2	88	(*R*)-55
6			2	35	(*R*)-80
7			2	100	(*R*)-55

[a] Conditions : $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol%), ligand **7a** (5 mol%), molar ratio of acetophenone/*t*-BuOK/ligand **7a**/Ru = 40/2/2/1. [acetophenone] = 0.2M in *i*-PrOH. T = 25°C. [b] Determined by ^{1}H-NMR. [c] Determined by chiral HPLC analysis. Optical rotation assigned by comparison of the specific rotation with literature values.

As showed in Table 9, in general, the complex formed with ligand **7a** offers better catalytic activity, but with a little lower in enantioselectivity when comparing to ligand **4a** (Table 8 and Table 9 **)**. For example, 2-acetonaphthone was completely reduced in 2 hours leading to 55% ee (Table 9, entry 7). On the other hand, only 71% conversion and 65% ee was obtained with ligand **4a** in 24 hours with the same substrate (Table 8, entry 13).

In other respect, diamine and *N*-tosyldiamine are well-known as efficient ligands for ruthenium[11] or iridium-catalyzed[12] ATH reaction. For first investigation, diamine **8** was tested for the reduction of acetophenone in the presence of $[RuCl_2(p\text{-cymene})]_2$ or $Ir[(COD)Cl]_2$ as pre-catalyst. The preparation of catalysts needs to heat the system at 80°C to give good conversion of substrate. However, low enantioselectivity was observed (ee < 23%) (Table 10).

Table 10: ATH of acetophenone with ligand **8**.[a]

Entry	Pre-catalyst	ratio[b]	Temp.[°C]	Time [h]	Conv. [%][c]	ee [%][d]
1	$[RuCl_2(p\text{-cymene})]_2$	40/1/1/2	50	21h	97	5
2	$Ir[(COD)Cl]_2$	40/1/1/2	25	1h	100	16
3	$Ir[(COD)Cl]_2$	40/1/2/2	25	1h	74	23

[a] Conditions : pre-catalyst (1.25 mol%), ligand **8** (2.5 mol%), complex is prepared by heating at 80°C for 30 mn., [acetophenone] = 0.2M in *i*-PrOH. T = 25°C. [b]ratio : substrate/metal/ligand/*t*-BuOK. [c] Determined by ^{1}H-NMR. [d] Determined by chiral HPLC analysis.

Next, *N*-monotosylated diamine **9** was evaluated as ligands for the ATH of ketones. The complexes ligand **9**-[M] give generally better results in term of enantioselectivity (Table 11).

Table 11: ATH of acetophenone with ligands **9**.[a]

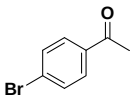
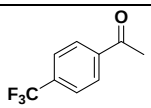
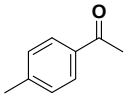
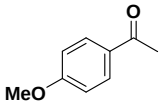
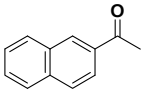
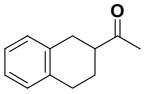
Entry	Pre-catalyst[b]	ratio [c]	Temp.Cat. (°C) [d]	Time [h]	Conv. [%][e]	ee [%][f]
1[g]	Ru	40/ 1/ 1/ 2	80	20	36	75
2	Ru	40/ 1/ 1/ 2	80	48	10	60
3	Ru	40/ 1/ 1/ 2	25.	24	65	73
4	Ru	40/ 1/ 1/ 1	25	48	16	72
5	Ru	40/ 1/ 1/ 4	25	20	8	72
6	Ru	40/ 1/ 1/ 6	25	20	8	72
7	Ru	40/ 1/ 1/ 10	25	18	0	-
8	Ir	40/ 1/ 1/ 2	80	24	91	51
9	Ir	40/ 1/ 1/ 2	25	20	77	30

[a] Conditions: pre-catalyst (1.25 mol%), ligand **9** (2.5 mol%), [acetophenone] = 0.2M in *i*-PrOH. T = 25°C. [b] Ru = $[Ru(p\text{-cymene})Cl_2]_2$, Ir = $[Ir(COD)Cl]_2$. [c] ratio : substrat/metal/ligand/ *t*-BuOK. [d] Temperature for preparation of complex during 30mn. [e] Determined by ^{1}H-NMR. [f]Determined by chiral HPLC analysis. [g] Reaction at 50°C.

Despite acceptable enantioselectivity (up to 75% ee, entry 1), long reaction time was needed with ligand **9** in all cases. For the best result, the product was obtained with 65% conversion and 73% ee after 24h (Entry 3). In the case of iridium-catalyzed ATH reaction, the conversion is clearly better, but enantiomeric excesses is lower when comparing to ruthenium-catalyzed reaction (Entries 8 and 9).

The next step was to evaluate the efficiency of ligand **9** in ruthenium-catalyzed transfer hydrogenation. Some aromatic ketones were tested. The results are summarized in Table 12.

Table 12: Asymmetric transfer hydrogenation of aromatic ketones with ligand **9**.[a]

Entry	Ketone	Conv. [%][b]	ee [%][c]
1		61	54
2		97	65
3		25	70
4		11	59
5		58	58
6		0	-

[a] Conditions : $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol%), ligand **9** (2.5 mol%), [acetophenone] = 0.2M in *i*-PrOH. T = 25°C, Time : 24h. [b] Determined by ^{1}H-NMR. [c] Determined by chiral HPLC analysis.

The reduction works no complicated leading to the products with moderate enantiomeric excesses (up to 70% ee, entry 3). The conversion clearly increases in the presence of electron-

withdrawing groups such as bromide (61%, entry 1) or trifluoromethyl (97%, entry 2). As the opposite, the presence of electron-donating groups or hindered substrates decreases the reaction rate (Entries 3, 4, 6).

Conclusion

In summary, we have described the flexible procedure for the synthesis of new chiral amino alcohols and diamines derived from isosorbide, a naturally renewable resource. These ligands were obtained in moderate to excellent yields. We have also shown that isosorbide-based amino alcohols and diamines could be used as ligands for Ru-catalyzed asymmetric transfer hydrogenation reaction of aromatic ketones. The reduction of acetophenone by ATH reaction with ligand **4f** gave excellent conversion and good enantioselectivity up to 91% ee. These results indicated clearly the efficiency of the isosorbide structure for the synthesis of new chiral ligands for asymmetric catalysis applications. Development of new chiral compounds derived from isosorbide as ligands or organocatalysts in asymmetric catalysis is currently underway in our Laboratory.

Experimental

General Information

Melting points were measured on a Kofler bank. The NMR spectra were recorded in $CDCl_3$, DMSO-d_6, MeOD-d_4 or in acetone-d_6. ^1H NMR spectra were recorded at 360 or 300, or 250 MHz. The chemical shifts (δ) are reported in parts per million relative to TMS as internal standard. *J* values are given in hertz. ^{13}C NMR spectra were recorded at 360, 300, 250 or 62.5 MHz. IR spectra were recorded on a FT-IR Perkin–Elmer instrument. Mass spectra were recorded on a MAT 95S Finnigan-Thermo mass spectrometer. TLC experiments were carried out in 0.25 mm thick silica gel plates Merck Kiesegel F_{254} and visualization was accomplished by UV light or phosphomolybdic acid solution. The columns were hand-packed with silica gel 60 (200–300). Isopropanol was redistilled over calcium hydride under argon atmosphere. All reagents and solvents were purchased from commercial sources (Acros, Aldrich) and were used without further purification. Ruthenium and iridium complexes have been generously provided

by Johnson Matthey Technology Centre, Reading.

Characterization of ligands.

(3*S*, 3a*R*, 6*R*, 6a*R*)-6-(benzyloxy)hexahydrofuro[3,2-b]furan-3-ol 2:

A mixture of isosorbide **1** (140 mmol, 20g), lithium hydride (140 mmol, 1.11g), lithium chloride (140 mmol, 5.91g) in DMSO (65 mL) was stirred at 90 ^{o}C for 20 min. Benzyl chloride (140 mmol, 16 mL) was added and the resulting mixture was then stirred for 18 h. The reaction mixture was acidified with 2N HCl (65 mL) and extracted with ethyl acetate (3 x 150 mL). The organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo and the residual oil was purified by flash column chromatography on silica gel (cyclohexane : ethyl acetate = 1 : 1; 5 : 5; 1.5 : 8.5) to afford a product as white crystals in 56% yield.

Mp: 60 ^{o}C; $[\alpha]_D^{25}$ +109.4 (c 0.83, $CHCl_3$); IR (neat) ν = 3429, 2945, 2877, 1497, 1455, 1132, 1069, 1018, 979 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.75 (d, *J* = 4.7 Hz, OH), 3.59 (dd, *J* = 8.6 and 7.9 Hz, 1H), 3.83 (dd, *J* = 8.6 and 6.8 Hz, 1H), 3.90-4.07 (m, 3H), 4.25 (s, 1H), 4.38 (d, *J* = 4.7 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.68 (dd, *J* = 4.3 and 4.7 Hz, 1H), 4.75 (d, *J* = 11.9 Hz, 1H), 7.25-7.38 (m, 5H, benzyl); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 69.8 (CH_2), 72.2 (CH_2), 75.6 (CH_2), 76.2 (CH), 79.0 (CH), 79.8 (CH), 88.1 (CH), 127.7, 128.2 ($5CH_{Ar}$), 137.4 (C). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; O, 27.09. Found: C, 65.98; H, 6.81; O, 27.11.

(3*R*, 3a*R*, 6*S*, 6a*S*)-3-(Benzyloxy)hexahydrofuro[3,2-b]furan-6-yl benzenesulfonate 3:

A mixture of the alcohol **2** (65 mmol, 15.4 g), triethylamine (390 mmol, 55 mL) and benzenesulfonyl chloride (78 mmol, 10 mL) was stirred under an argon atmosphere for 10 h. The reaction mixture was diluted with water (200 mL), acidified with 5N HCl (60 mL) and the hydrolysis was continued for further 2 h. The resulting mixture was extracted with dichloromethane (3 x 120 mL). The organic phases were washed with brine, dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane/ethyl acetate = 1 : 1) to afford a product as white crystals in 99% yield.

Mp: 93 ^{o}C; $[\alpha]_D^{25}$ +92.7 (c 0.25, $CHCl_3$); IR (neat) ν = 3065, 3032, 2877, 1449, 1367, 1189, 1100, 1043, 971, 947, 902, 820, 750 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.57 (dd, *J* = 7.6 and 9.0 Hz, 1H), 3.82 (dd, *J* = 6.6 and 9.0 Hz, 1H), 3.95–4.08 (m, 3H), 4.52 (d, *J* = 4.3 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.68 (dd, *J* = 4.3 and 5.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.91 (m, 1H), 7.26–7.40 (m, 5H, benzyl), 7.54–7.71 (m, 3H, phenyl), 7.91–7.97 (m, 2H, phenyl); ^{13}C NMR

(62.5 MHz, $CDCl_3$) δ 70.5 (CH_2), 72.5 (CH_2), 73.2 (CH_2), 78.9 (CH), 80.6 (CH), 84.2 (CH), 85.8 (CH),127.8,127.9,128.0,128.5,129.5,134.1 (10 CH_{Ar}), 136.3 (C), 137.5 (C). Anal. Calcd for $C_{19}H_{20}O_6S$: C, 60.62; H, 5.36; O, 25.50; S, 8.52. Found: C, 60.44; H, 5.25; O, 25.41; S, 8.49

2-((3*R*, 3a*S*, 6*R*, 6a*R*)-3-(benzyloxy)hexahydrofuro[3,2-b]furan-6-ylamino)ethanol 4a:

A mixture of the sulfonate **3** (8 mmol), distilled ethanolamine (32 mmol), lithium chloride (4 mmol) was heated in a sealed tube at 160 ^oC for 4h. The reaction mixture was brought to room temperature and the excess of ethanolamine was then removed under vacuum. The residual oil was purified by flash column chromatography on silica gel (dichloromethane : methanol = 98 : 2 and 95 : 5, consecutively) to give the product as a dark yellow oil in 75% yield.

$[\alpha]_D^{25}$ +123.1 (c 1.1, $CHCl_3$); IR (neat) ν = 3376, 2941, 2872, 1667, 1455, 1369, 1312, 1260, 1208, 1137, 1069, 1026, 924, 823, 743 cm^{-1}; ^1H 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, 1H), 4.62 (dd, *J* = 4.5 and 4.5 Hz, 1H), 4.74 (d, *J* = 12.0, 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 (5 CH_{Ar}), 137.7 (C). HRMS (ESI) calcd for $C_{15}H_{22}NO_4$ ($[M+H]^+$): 280.1549, found: 280.1541.

(*S*)-2-((3*R* ,3a*S* ,6*R* ,6a*R*)-3-(benzyloxy) hexahydrofuro [3,2-b]furan-6-ylamino)-3-methylbutan-1-ol 4b: Compound **4b** was prepared following the same procedure previously described for the synthesis of compound **4a**. The reaction time was 24 h. The purification was carried out by flash column chromatography on silica gel (cyclohexane : ethyl acetate = 1 : 1) to give a dark yellow liquid in 50% yield from **3** and (*S*)-2-amino-3-methylbutan-1-ol.

$[\alpha]_D^{25}$ +115.57 (c 1.05, $CHCl_3$); IR (neat) ν = 3456, 2956, 2873, 1650, 1455, 1366, 1195, 1135, 1069, 1027, 928, 826, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 1.63-1.74 (m, 1H), 2.35-2.41 (m, 1H), 3.37-3.47 (m, 3H), 3.60 (dd, *J* = 3.6 and 11.4 Hz, 1H), 3.66 (dd, *J* = 7.2 and 8.7 Hz, 1H), 3.90 (dd, *J* = 6.6 and 8.7 Hz, 1H), 4.06-4.16 (m, 2H), 4.39 (dd, *J* = 4.2 and 4.2 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.62 (dd, *J* = 4.5 and 4.8 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 7.30-7.36 (m; 5H, benzyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.8, 19.4 (2 CH_3), 61.5 (CH), 62.3 (CH_2), 64.1 (CH), 71.6 (CH_2), 72.7 (CH_2), 72.8 (CH_2), 79.7 (CH), 81.4 (CH), 81.5 (CH), 127.9, 128.1, 128.5 (5 CH_{Ar}), 137.7 (C). HRMS (ESI) calcd for $C_{18}H_{28}NO_4$ ($[M+H]^+$): 322.2018, found: 322.2010.

(*R*)-2-((3*R* ,3a*S* ,6*R* ,6a*R*)-3-(benzyloxy) hexahydrofuro [3,2-b]furan-6-ylamino)-3-methylbutan-1-ol 4c: Compound **4c** was prepared following the same procedure previously described for the synthesis of compound **4a**. The reaction time was 24 h. The purification was carried out by flash column chromatography on silica gel (cyclohexane : ethyl acetate = 1 : 1) to give a dark yellow liquid in 50% yield from **3** and (*R*)-2-amino-3-methylbutan-1-ol.

$[\alpha]_D^{25}$ +136.16 (c 1.0, $CHCl_3$); IR (neat) ν = 3414, 2957, 2873, 1641, 1455, 1368, 1310, 1207, 1136, 1071, 1027, 930, 825, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 1.20-1.25 (m, 1H), 2.38-2.43 (m, 1H), 3.30-3.44 (m, 3H), 3.52 (dd, *J* = 4.2 and 10.8 Hz, 1H), 3.59 (dd, *J* = 7.8 and 8.7 Hz, 1H), 3.86 (dd, *J* = 6.6 and 8.7 Hz, 1H), 4.01-4.10 (m, 2H), 4.34 (dd, *J* = 4.2 and 4.2 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.56 (dd, *J* = 4.5 and 4.5 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 7.30-7.36 (m; 5H, benzyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.5, 19.7 (2 CH_3), 29.5 (CH), 60.9 (CH), 60.9 (CH_2), 63.9 (CH), 71.3 (CH_2), 72.6 (CH_2), 73.1 (CH_2), 79.9 (CH), 80.6 (CH), 81.4 (CH), 127.9, 128.0, 128.5 (5 CH_{Ar}), 137.7 (C). HRMS (ESI) calcd for $C_6H_{12}NO_3$ ($[M+H]^+$): 146.0817, found: 146.0811.

(*R*)-2-((3*R* ,3a*S* ,6*R* ,6a*R*)-3-(benzyloxy) hexahydrofuro [3,2-b]furan-6-ylamino)-2-phenylethanol 4d:

Compound **4d** was prepared following the same procedure previously described for the synthesis of compound **4a**. The reaction time was 24 h. The purification was carried out by flash column chromatography on silica gel (cyclohexane : ethyl acetate = 1 : 1) to give a bright yellow paste in 47% yield from **3** and (*S*)-2-amino-2-phenylethanol.

$[\alpha]_D^{25}$ +178.15 (c 0.5, $CHCl_3$); IR (neat) ν = 3420, 2943, 2871, 1648, 1494, 1454, 1366, 1202, 1135, 1068, 1025, 845, 756 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.34 (s, NH), 3.20-3.26 (m, 1H), 3.34 (dd, *J* = 8.6 and 10.4 Hz, 1H), 3.52 (dd, *J* = 8.6 and 10.8 Hz, 1H), 3.64-3.70 (m, 2H), 3.86-3.94 (m, 3H), 4.02-4.07 (m, 1H), 4.39 (dd, *J* = 4.7 and 3.9 Hz, 1H), 4.49-4.52 (m, 2H), 4.69 (d, *J* = 11.5 Hz, 1H), 7.31-7.33 (m, 10H, phenyl); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 60.7 (CH), 63.6 (CH), 67.7 (CH_2), 71.7 (CH_2), 72.7 (CH_2), 72.8 (CH_2), 80.0 (CH), 80.6 (CH), 81.4 (CH), 127.6, 128.0, 128.2, 128.7, 128.9 (10 CH_{Ar}), 138.0 (C), 140.8 (C). HRMS (ESI) calcd for $C_{21}H_{26}NO_4$ ($[M+H]^+$): 356.1856, found: 356.1865.

(*S*)-2-((3*R* ,3a*S* ,6*R* ,6a*R*)-3- (benzyloxy) hexahydrofuro [3,2-b]furan-6-ylamino)-2-phenylethanol 4e:

Compound **4e** was prepared following the same procedure previously described for the synthesis

of compound **4a**. The reaction time was 24 h. The purification was carried out by flash column chromatography on silica gel (cyclohexane : ethyl acetate = 1 : 1) to give a brown solid in 48% yield from **3** and (*R*)-2-amino-2-phenylethanol.

Mp: 82 °C; $[\alpha]_D^{25}$ +61.70 (c 1.0, $CHCl_3$); IR (neat) ν = 3377, 3029, 2887, 1658, 1495, 1453, 1366, 1219, 1137, 1081, 1038, 1017, 916, 845, 752 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.06 (s, NH), 3.17-3.23 (m, 1H), 3.48 (dd, *J* = 8.6 and 9.7 Hz, 1H), 3.56-3.67 (m, 3H), 3.74-3.77 (m, 1H), 3.83 (dd, *J* = 6.8 and 8.6 Hz, 1H), 3.96-4.02 (m, 1H), 4.06 (dd, *J* = 7.6 and 7.9 Hz, 1H), 4.12 (dd, *J* = 4.7 and 4.0 Hz, 1H), 4.40 (dd, *J* = 4.7 and 4.7 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 7.31-7.33 (m, 10H, phenyl); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 60.2 (CH), 64.0 (CH), 67.0 (CH_2), 71.3 (CH_2), 72.6 (CH_2), 72.9 (CH_2), 79.9 (CH), 80.8 (CH), 81.9 (CH), 127.5, 127.9, 128.0, 128.1, 128.5, 128.7 (10 CH_{Ar}), 137.8 (C), 140.4 (C). HRMS (ESI) calcd for $C_{21}H_{26}NO_4$ ($[M+H]^+$): 356.1862, found: 356.1854.

(*R*)-2-((3*R* ,3a*S* ,6*R* ,6a*R*)-3-(benzyloxy) hexahydrofuro [3,2-b]furan-6-ylamino)-1-phenylethanol 4f:

Compound **4f** was prepared following the same procedure previously described for the synthesis of compound **4a**. The reaction time was 24 h. The purification was carried out by flash column chromatography on silica gel (cyclohexane : ethyl acetate = 3 : 7) to give a bright yellow solid in 43% yield from **3** and (*R*)-2-amino-1-phenylethanol.

Mp: 56 °C; $[\alpha]_D^{25}$ +99.43 (c 0.5, $CHCl_3$); IR (KBr) ν = 3311, 3028, 2869, 1668, 1492, 1452, 1346, 1258, 1207, 1115, 1084, 1025, 983, 911, 844, 748, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, NH), 2.53, (dd, *J* = 9.6 and 12.3 Hz, 1H), 2.96 (dd, *J* = 3.3 and 12.3 Hz, 1H), 3.26-3.33 (m, 1H), 3.37 (dd, *J* = 8.1 and 10.1 Hz, 1H), 3.58 (dd, *J* = 7.5 and 9.0 Hz, 1H), 3.82 (dd, *J* = 6.6 and 9.0 Hz, 1H), 3.99-4.11 (m, 2H), 4.33 (dd, *J* = 4.5 and 4.5 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.55-4.63 (m, 2H), 4.67 (d, *J* = 12.0 Hz, 1H); 7.24-7.31 (10 H, phenyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 56.4 (CH_2), 63.0 (CH), 71.5 (CH_2), 72.3 (CH), 72.6 (2 CH_2), 79.7 (CH), 81.1 (CH), 81.5 (CH), 125.8, 127.6, 127.9, 128.4, 128.5 (10 CH_{Ar}), 137.7 (C),142.0 (C). HRMS (ESI) calcd for $C_{21}H_{26}NO_4$ ($[M+H]^+$): 356.1856, found: 356.1841.

(*S*)-2-((3*R* ,3a*S* ,6*R* ,6a*R*)-3-(benzyloxy) hexahydrofuro [3,2-b]furan-6-ylamino)-1-phenylethanol 4g:

Compound **4g** was prepared following the same procedure previously described for the synthesis of compound **4a**. The reaction time was 24 h. The purification was carried out by flash column

chromatography on silica gel (cyclohexane : ethyl acetate = 3 : 7) to give a bright yellow solid in 52% yield from **3** and (*S*)-2-amino-1-phenylethanol ; mp: 90 ^{o}C; $[\alpha]_D^{25}$ +180.98 (c 0.5, $CHCl_3$); IR (KBr) ν = 3286, 3087, 2875, 1663, 1491, 1452, 1344, 1303, 1211, 1156, 1103, 1060, 934, 880, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (dd, *J* = 8.7 and 12.0 Hz, 1H), 2.85 (dd, *J* = 3.6 and 12.0 Hz, 1H), 3.33-3.40 (m, 1H), 3.42 (dd, *J* = 8.1 and 10.2 Hz, 1H), 3.60 (dd, *J* = 7.8 and 9.0 Hz, 1H), 3.86 (dd, *J* = 6.6 and 9.0 Hz, 1H), 4.03-4.13 (m, 2H), 4.43 (dd, *J* = 4.2 and 4.5 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.59 (dd, *J* = 4.8 and 4.5 Hz, 1H), 4.67-4.70 (m, 1H), 4.71 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.9 (CH_2), 62.7 (CH), 71.7 (CH_2), 72.3 (CH), 72.8 (CH_2), 72.9 (CH_2), 79.9 (CH), 80.7 (CH), 81.5 (CH), 126.0, 127.8, 128.2, 128.6, 128.7 (10 CH_{Ar}), 138.0 (C), 142.1 (C). HRMS (ESI) calcd for $C_{21}H_{26}NO_4$ ($[M+H]^+$): 356.1856, found: 356.1845.

2-((3*R* ,3a*S* ,6 *R*,6a*R*)-3-(benzyloxy)hexahydrofuro[3,2-b]furan-6-ylamino)-1,1-diphenylethanol 4h:

Compound **4h** was prepared following the same procedure previously described for the synthesis of compound **4a**. The reaction time was 24 h. The purification was carried out by flash column chromatography on silica gel (cyclohexane : ethyl acetate = 3 : 7) to give a bright yellow viscous liquid in 70% yield from **3** and 2-amino-1,1-diphenylethanol.

$[\alpha]_D^{25}$ +67.52 (c 0.5, $CHCl_3$); IR (NaCl) ν = 3419, 3060, 3028, 2943, 2969, 1598, 1492, 1449, 1367, 1312, 1261, 1135, 1083, 1070, 1026, 942, 910, 826, 752, 670 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.11 (d, *J* = 12.0 Hz, 1H), 3.33-3.39 (m, 1H), 3.44 (t, *J* = 8.76 Hz, 1H), 3.65 (dd, *J* = 7.3 and 8.9 Hz, 1H), 3.74 (d, *J* = 12.0 Hz, 1H), 3.94 (dd, *J* = 6.6 and 8.9 Hz, 1H), 4.10-4.15 (m, 2H), 4.46 (q, *J* = 4.12 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.65 (dd, *J* = 4.4 and 4.9 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 7.25-7.59 (m, 15H, 3 phenyl); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 57.9 (CH_2), 63.7 (CH), 71.7 (CH_2), 72.7, 72.8 (2 CH_2), 76.5 (C), 79.9 (CH), 80.9 (CH), 81.7 (CH), 126.0, 126.5, 127.1, 127.2, 128.1, 128.4, 128.5, 128.7 (15 CH_{Ar}), 138.0 (C), 145.5, 145.9 (2 C). HRMS (ESI) calcd for $C_{27}H_{30}NO_4$ ($[M+H]^+$): 432.2169, found: 432.2173.

(3*R* ,3a*R* ,6*R* ,6a*S*)-*N*-benzyl-6-(benzyloxy) hexahydrofuro [3,2-b]furan-3-amine 5:

A mixture of the sulfonate **3** (20 mmol), distilled benzyl amine (120 mmol), lithium chloride (10 mmol) was heated in a sealed tube at 160 ^{o}C for 24h. The reaction mixture was brought to room temperature and the excess of amine was then removed under vacuum. The residual oil was purified by flash column chromatography on silica gel (cyclohexane : ethyl acetate = 1 : 1) to give the product as a yellow oil in 70% yield. $[\alpha]_D^{25}$ +145.3 (c 1.47, $CHCl_3$); IR (neat) ν = 3321,

3087, 3062, 3029, 2942, 2871, 1496, 1463, 1455, 1367, 1136, 1084, 1045, 1027, 738 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.27 (s, NH), 3.27-3.46 (m, 2H) 3.62 (dd, *J* = 7.8 and 8.5 Hz, 1H), 3.72 (d, *J* = 12.3 Hz, 1H), 3.85 (d, *J* = 12.3 Hz, 1H), 3.87 (dd, *J* = 8.5 and 6.75 Hz, 1H), 3.98-4.11 (m, 2H), 4.40 (dd, *J* = 4.0 and 4.3 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.51-4.54 (m, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 7.14-7.40 (m, $10H_{Ar}$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 52.3 (CH_2), 62.1 (CH), 71.1 (CH_2), 72.4 (CH_2), 72.6 (CH_2), 79.8 (CH), 80.2 (CH), 81.1 (CH), 127.0, 127.8, 128.0, 128.3 (10 CH_{Ar}), 137.7 (C), 140 (C). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12, O, 14.75; N, 4.30. Found: C, 73.52; H, 7.11; O, 14.77; N, 4.46.

(**3*R*, 3a*R* ,6*R* ,6a*R*)-6-aminohexahydrofuro[3,2-b]furan-3-ol 6**:

Amino ether **5** (5 mmol) and the same weight of palladium 10% on charcoal in 10 mL of ethanol were stirred under a 1 bar hydrogen pressure for 24 h. Filtration of the catalyst, evaporation of the solvent and then purification of the residue by flash chromatography on silica gel with dichloromethane/methanol (98/2) in the presence of 1% NH_3 afforded white crystals in 96 % yield. Mp: 115 ^oC; $[\alpha]_D^{25}$ +110.9 (c 0.5, CH_3OH); IR (KBr) ν = 3329, 2942, 2859, 1612, 1491, 1475, 1408, 1372, 1302, 1156, 1128, 1085, 1022, 926, 815, 777 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 3.32 (dd, *J* = 8.4 and 10.2 Hz, 1H), 3.48-3.54 (m,2H), 3.97-4.08 (m, 2H), 4.35-4.42 (m, 1H), 4.43 (dd, *J* = 4.5 and 4.5 Hz, 1H) , 4.55 (dd, *J* = 4.5 and 4.8 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 54.54 (CH), 71.81 (CH_2), 72.17 (CH), 72.70 (CH_2), 82.21 (CH), 82.65 (CH). HRMS (EI) calcd for $C_6H_{12}NO_3$ ($[M+H]^+$): 146.0817, found: 146.0811.

(3*R* ,3a*R* ,6*R* ,6a*R*)-6-(2-hydroxyethylamino) hexahydrofuro [3,2-b]furan-3-ol 7a:

Compound **7a** was prepared following the same procedure previously described for the synthesis of compound **6**. The reaction time was 4 days. The purification was carried out by flash column chromatography on silica gel (dichloromethane : methanol = 98 : 2) to give a bright yellow solid in 96 % yield from **4a**; mp: 62 ^oC; $[\alpha]_D^{25}$ +106.95 (c 0.5 CH_3OH); IR (KBr) ν = 3315, 2925, 2890, 1656, 1460, 1376, 1123, 1057, 1015, 927, 825 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 2.63-2.73 (m, 1H), 2.76-2.86 (m, 1H), 3.35-3.57 (m, 4H), 3.59-3.66 (m, 1H), 3.96 (dd, *J* = 6.5 and 8.8 Hz, 1H), 4.10 (dd, *J* = 4.8 and 5.8 Hz, 1H), 4.35-4.42 (m, 1H), 4.56 (dd, *J* = 4.3 and 4.8 Hz, 1H), 4.62 (dd, *J* = 4.0 and 4.4 Hz, 1H); ^{13}C NMR (250 MHz, D_2O) δ 49.4 (CH_2), 61.2 (CH_2), 62.0, (CH), 72.0 (CH_2), 72.5 (CH_2), 72.9 (CH), 81.1 (CH), 83.0 (CH). HRMS (ESI) calcd for $C_8H_{16}NO_4$ ($[M+H]^+$): 190.1079, found: 190.1076.

(3*R* ,3a*R* ,6*R* ,6a*R*)-6-((*R*)-1-hydroxy-3-methylbutan-2 ylamino)hexahydrofuro[3,2-b]furan-

3-ol 7b:

Compound **7b** was prepared following the same procedure previously described for synthesis of compound **6**. The reaction time was 4 days. The purification was carried out by flash column chromatography on silica gel (dichloromethane : methanol = 98 : 2) to give a bright yellow liquid in 96 % yield from **4b**; $[\alpha]_D^{25}$ +81.84 (c 0.75, CH_3OH); IR (neat) ν = 3369, 2958, 2873, 1644, 1467, 1389, 1354, 1228, 1193, 1127, 1085, 1058, 927, 826, 741 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 0.85 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); 1.83-1.96 (m, 1H), 2.58-2.63 (m, 1H), 3.44-3.60 (m, 3H), 3.62-3.72 (m, 2H), 3.96 (dd, *J* = 6.3 and 8.8 Hz, 1H), 4.14 (dd, *J* = 7.5 and 8.0 Hz, 1H), 4.34-4.42 (m, 1H), 4.57-4.64 (m, 2H); ^{13}C NMR (90.5 MHz, CD_3OD) δ 18.9, 19.4 (2 CH_3), 30.2 (CH), 61.4 (CH), 62.6 (CH_2), 64.5 (CH), 73.5 (CH_2), 74.0 (CH), 74.9 (CH_2), 82.4 (CH), 84.1 (CH). HRMS (ESI) calcd for $C_{11}H_{22}NO_4$ ($[M+H]^+$): 232.1543, found: 232.1542.

(3*R*, 3a*R*, 6*R*, 6a*S*)-*N*-(2-aminoethyl)-6-(benzyloxy)-hexahydrofuro[3,2-b]furan-3-amine 8.

To a solution of sulfonate **3** (700mg, 1.8 mmol) were added 1,2-diamino ethane (0.72 mL, 10.8 mmol) and LiCl (38 mg, 0.9 mmol). The solution was heated in a sealed tube at 160 ^oC for 24h. The reaction mixture was brought to room temperature and the excess of amine was then removed under vacuum. The residual oil was purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH = 95 : 5 with 3 % NEt_3) to give the product as a yellow oil in 82% yield. $[\alpha]_D^{25}$ +135.4 (c = 1.02 ; $CHCl_3$) ; IR (NaCl) ν = 3305, 3029, 2939, 2869, 1660, 1495, 1454, 1367, 1308, 1208, 1135, 1083, 1027, 825, 742, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.42 (s broad, $NH+NH_2$), 2.52-2.60 (m, 1H), 2.66-2.78 (m, 3H), 3.24-3.30 (m, 1H), 3.37 (dd, *J* = 10.4 and 8.2 Hz, 1H), 3.58 (dd, *J* = 8.6 and 8.2 Hz, 1H), 3.85 (dd, *J* = 8.6 and 6.8 Hz, 1H), 3.99-4.09 (m, 2H), 4.38 (dd, *J* = 4.1 and 4.5 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.54 (dd, *J* = 4.1 and 5.0 Hz, 1H), 4.69 (d, *J* = 11.8 Hz, 1H), 7.19-7.30 (m, $5H_{ar}$). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 42.4 (CH_2), 51.4 (CH_2), 63.2 (CH), 71.5 (CH_2), 72.7 (CH_2), 73.0 (CH_2), 80.1 (CH), 80.8 (CH), 81.4 (CH), 128.0, 128,1, 128,6 (5 CH_{ar}) ; 138;0 (C_q). HRMS (ESI) calcd for $C_{15}H_{22}N_2O_3$ ($[M+H]^+$): 279.1717, found: 279.1703.

(3*R*, 3a*R*, 6*R*, 6a*S*)-6-(benzyloxy)-hexahydrofuro-*N*-(2(tosylamino)ethyl)furo[3,2-b]furan-3-amine 9 : Compound **9** was prepared following the same procedure previously described for synthesis of compound **8**, from **3** (2,6 mmol), *N*-(-4-toluenesulfonyl)-1,2-ethylenediamine (16 mmol), and lithium chloride (1,3 mmol). The product was purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH = 99 : 1 and 92 : 2) to give a liquid in 60% yield.

$[\alpha]_D^{25}$+97,3 (c = 1, $CHCl_3$). IR (NaCl) ν = 3543, 3273, 3031, 2943, 2872, 1598, 1495, 1455, 1368, 1330, 1209, 1158, 1092, 1022, 817, 740, 665 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.48 (s broad, 1 NH), 2.34 (s, 3H), 2.56-2.76 (m, 2H), 2.82-2.98 (m, 2H), 3.06-3.12 (m, 1H), 3.26 (dd, *J* = 10.0 and 8.6 Hz, 1H), 3.55 (dd, *J* = 8.6 and 7.7 Hz, 1H), 3.80 (dd, *J* = 8.6 and 6.8 Hz, 1H), 3.93-4.01 (m, 2H), 4.24 (t, *J* = 4.5 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.51 (dd, *J* = 5.0 and 4.5 Hz, 1H), 4.67 (d, *J* = 11.8 Hz, 1H), 5.15 (s large, 1 NH), 7.13-7.34 (m, $7H_{ar}$), 7.66 (d, *J* = 8.2 Hz. $2H_{ar}$). ^{13}C NMR (90.5 MHz. $CDCl_3$) δ 21.5 (CH_3), 42.8 (CH_2),46.8 (CH_2) ; 62.3 (CH), 71.5 (CH_2), 72.5 ($2CH_2$), 79.7 (CH) ; 80.5 (CH), 81.4 (CH),127.1, 127.9, 128.4, 129.6 (9 CH_{ar}), 136.6 (C_q), 137.7 (C_q), 143.3 (C_q). HRMS (ESI) calcd for $C_{15}H_{22}N_2O_3$ ($[M+H]^+$): 433.1810. found: 433.1792.

General procedure for Ru-catalyzed asymmetric transfer hydrogenation of ketones in isopropanol.

In a 20 mL dry Schlenk tube under argon atmosphere, the *in situ* catalyst was prepared by stirring a solution of amino alcohol (5 mol%) and $[RuCl_2(p\text{-cymene})]_2$ (1.25 mol%) in isopropanol at 25 ^oC for 30mn. Potassium tert-butoxide (5 mol%), and ketone (1 mmol) were added respectively. The reaction was followed by ^1H-NMR spectroscopy analysis for calculating the conversion. Enantiomeric excess were monitored by chiral HPLC analysis. The reaction was stopped when no evolution of enantiomeric excesses was observed.

The obtained alcohols are known compounds and their ^1H NMR and ^{13}C NMR were identical to authentic samples. [13, 14]

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