Graphical Abstract

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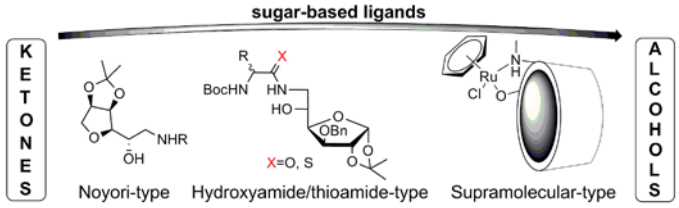

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Designing new readily available sugar-based ligands for asymmetric transfer hydrogenation of ketones. In the guest to expand the substrate scope

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ABSTRACT

Asymmetric transfer hydrogenation (ATH) has emerged as one of the most effective and sustainable synthetic tool for synthesizing enantiopure alcohols. Since Noyori's group successfully applied Ru-catalysts modified with chiral β-amino alcohols or diamines as ligands, a large number of catalytic systems has been successfully developed. However, further improvement in terms of substrate scope, selectivity and turnover frequency are required to make the process competitive with conventional hydrogenations. Overcoming these limitations requires research toward the design of new ligands. Such a task becomes easier if readily modulable chiral ligands are at hand. Sugar-based ligands are particularly useful for addressing this need. They are readily available, highly functionalized and their modular constructions are easy. Series of chiral ligands can be screened in the search for high activities and selectivities for each type of substrate. This digest paper will discuss the progress on the use of sugar-based ligands in ATH reactions.

Contents

Introduction

Enantiopure alcohols are valuable and versatile synthetic building blocks for the synthesis of many natural, pharmaceutical and agricultural products.[1] The enantioselective reduction of prochiral ketones has emerged as an efficient and direct synthetic tool for preparing these compounds. Transition metal-catalyzed asymmetric transfer hydrogenation (ATH) provides a powerful alternative to asymmetric hydrogenation due to its operational simplicity, the easy availability of hydrogen sources, low cost and safety.[2] Most transfer hydrogenations are performed using Ru[3], Rh[4] or Ir-catalysts[4a-c,5]. Recently, the use of iron[6] and osmium[7]-based catalysts has also provided interesting results, but their scope is still low compared to that of the Ru, Rh and Ir-catalysts. Since Noyori and coworkers successfully applied Ru-arene catalysts modified with chiral β-amino alchohol or diamines as ligands in 1990,[2f,i,3a-b] (Figure 1) the scope of this ligand class has been expanded with the development of a large number of new ligands.[8]

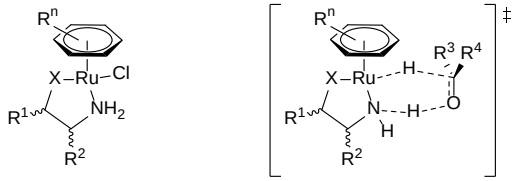

Figure 1. General structure of Noyori-type catalyst precursors and structure of the proposed key reaction intermediate for ATH reactions.

Adolfsson's group reported a new type of ligands -amino acid-derived hydroxy amides and thioamides- that in combination with Ru and Rh half-sandwich complexes are also excellent catalysts for the ATH of aryl-alkyl ketones (Figure 2).[8f-g,9] These ligands are based on the combination of several N-Boc-protected α-amino acids and β-amino alcohols[8f,9a-f,h] (for type **1**) or on thioamides[8g,9g] (for type **2**), respectively. The main difference between previously successful catalysts is the lack of a basic NH group in the latter's ligand structures. The authors also found that the presence of a chiral α-amino acid is crucial to obtain high enantioselectivity and that enantioselectivity is affected by the configuration of the stereogenic center of amino acid part. In addition, changing the amide group in hydroxy amides **1** to the

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thioamide as in **2**, results in most cases in a switch of the product's absolute configuration. Highly enantiomerically enriched secondary alcohols of either configuration can be therefore achieved using catalysts ligated with **1** or **2**, where the ligands are constructed from the same amino acid with the same sense of chirality.

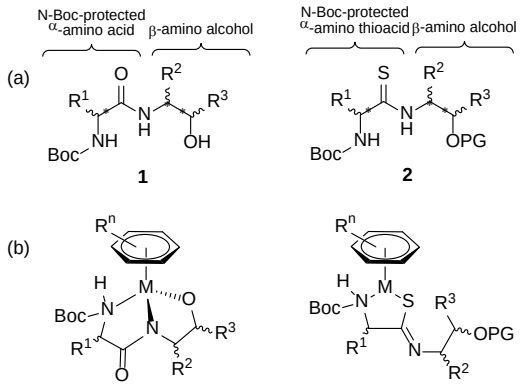


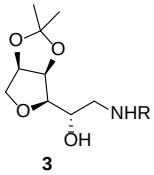
Figure 2. (a) General structure of hydroxy amide and thioamide ligands and (b) structure of the proposed key reaction intermediate for ATH reactions.

Despite all these important contributions, further improvement in terms of substrate scope, selectivity and turnover frequency are required to make the process competitive with conventional hydrogenations. Overcoming these limitations requires research toward the development of new ligands. Such a task becomes significantly more facile if readily modulable chiral ligands are at hand. Carbohydrate-based ligands are particularly useful for addressing this need.[10,11] They are readily available, highly functionalised with several stereogenic centres and they have a highly modular construction. Series of chiral ligands can be synthesised and screened in the search for high activities and selectivities for each type of substrate.

Taking advantage of these features, we and others have designed carbohydrate-based ligands for asymmetric transfer hydrogenation reactions. This digest paper will therefore discuss the progress on the use of sugar-based ligands in asymmetric metal-catalyzed transfer hydrogenation reactions.

ATH using sugar-based Noyori-type catalysts

Since Noyori and coworkers successfully applied Ru-arene catalysts modified with chiral β-amino alcohols and diamines, many research groups further developed β-amino alcohol or diamine-based catalysts. However, the first carbohydrate-derived β-amino alcohols were not reported until 2008 (Figure 3).[12] These ligands were synthesized in only 3 steps from isosorbide, a byproduct from starch industry (Scheme 1). They were applied in the reduction of the standard substrate acetophenone using $[Ru(benzene)Cl_2]_2$ as source of metal. The conversion into the 1-phenylethanol was low to high (10-95%), while enantioselectivity (0-78%) was highly dependent on the β-amino alcohol ligand structure (Table 1). The chiral amino alcohol **3g** proved to be the most efficient, albeit the enantioselectivity achieved is low compared to the state of art.

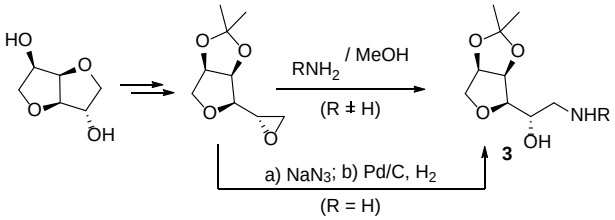


3

	R
a	H
b	Me
c	^{i}Pr
d	Cy
e	^{t}Bu
f	Ph

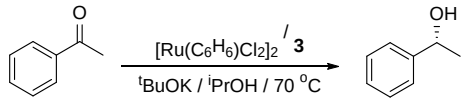
	R
g	Bn
h	(*R*)-CH(Me)Ph
i	(*S*)-CH(Me)Ph
j	(*R*)-CH(Et)CH$_2$OH
k	(*S*)-CH(Et)CH$_2$OH

Figure 3. General structure of β-amino alcohol **3** derived from isosorbide.



Scheme 1. Synthesis of chiral β-aminoalcohols **3**.

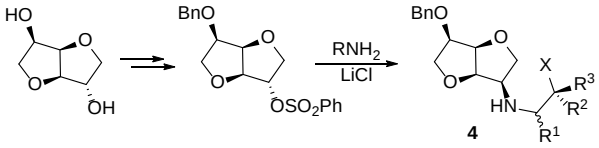
Table 1. Asymmetric transfer hydrogenation of acetophenone using β-amino alcohols **3**.[a]



Entry	L	% Conv (h)	% ee	Entry	L	% Conv (h)	% ee
1	**3a**	72 (21)	64 (*R*)	7	**3g**	96 (21)	60 (*R*)
2	**3b**	48 (21)	< 5	8	**3h**	83 (21)	21 (*R*)
3	**3c**	83 (21)	30 (*R*)	9	**3i**	90 (21)	18 (*R*)
4	**3d**	86 (21)	6	10	**3j**	28 (21)	24 (*R*)
5	**3e**	67 (21)	<5	11	**3k**	10 (21)	<5
6	**3f**	66 (21)	20 (*R*)	12[b]	**3g**	58 (3)	78 (*R*)

[a] Reaction carried out in a 0.2M solution in 2-propanol with substrate/^{t}BuOK/**3**/Ru = 100/1.5/1.5/1. [b] Substrate/^{t}BuOK/**3**/Ru = 100/4/4/1.

Then a new contribution on the use of isosorbide as chiral renewable resource was developed, however no significant improvements on enantioselectivities were obtained.[13] The authors developed new β-amino alcohol or diamine-based catalysts where the skeleton of the bicycle of the isosorbide was retained (Scheme 2).



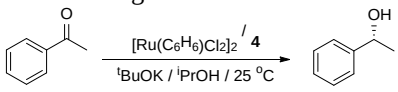
	X	R^1	R^2	R^3
a	OH	H	H	H
b	OH	(*S*)-^{i}Pr	H	H
c	OH	(*R*)-^{i}Pr	H	H
d	OH	(*S*)-Ph	H	H
e	OH	(*R*)-Ph	H	H

	X	R^1	R^2	R^3
f	OH	H	Ph	H
g	OH	H	H	Ph
h	OH	H	Ph	Ph
i	NH_2	H	H	H
j	NHTs	H	H	H

Scheme 2. Synthesis of chiral β-aminoalcohols **4a-h** and diamines **4i-j**.

Another difference with previous isosorbide derived ligands **3** is that the sugar unit acts as a chiral substituent of the amine moiety. Although the highest enantioselectivities in the reduction of acetophenone was achieved using ligand **4f** containing an *R*-phenyl group adjacent to the hydroxyl group (Table 2; ee's up to 91%, entry 6), ligand **4a** showed the highest ability for transfer hydrogenation of various ketones with good conversion (Figure 4). They found that steric and electronic properties of the substrates also affected the chemical yields and enantioselectivities. Thus, the presence of electron-withdrawing or electron-donating groups on the phenyl group and the increase of the steric demands of the substrate has a negative effect on both yields and enantioselectivities.

Table 2. Asymmetric transfer hydrogenation of acetophenone using isosorbide-based ligands **4**.[a]



Entry	L	% Conv (h)	% ee	Entry	L	% Conv (h)	% ee
1	**4a**	99 (2)	70 (*R*)	6	**4f**	94 (24)	91 (*R*)
2	**4b**	63 (24)	3 (*R*)	7	**4g**	95 (24)	60 (*R*)
3	**4c**	32 (24)	36 (*R*)	8	**4h**	10 (2)	65 (*R*)
4	**4d**	28 (24)	47 (*R*)	9[b,c]	**4i**	97 (21)	5[d]
5	**4e**	55 (24)	35 (*R*)	10[b]	**4j**	65 (24)	73[d]

[a] Reaction carried out in a 0.2M solution in 2-propanol with substrate/^{t}BuOK/L/Ru = 40/2/2/1. [b] Substrate/^{t}BuOK/L/Ru = 40/1/1/2. [c] T= 50 °C. [d] Absolute configuration not reported.

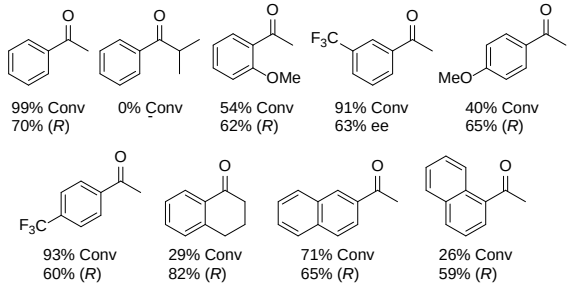


Figure 4. Selected results for the ATH of aromatic ketones using ligand **4a**.

ATH using sugar-based hydroxy amide and thioamide ligands

A breakthrough in the development sugar based ligand for this process appeared in 2011 when our group in collaboration with the Adolfsson's group developed a new sugar based ligand library (Figure 5).[14] These ligands are based on previous hydroxy amide ligands **1** in which the β-amino alcohol part was replaced by a readily available sugar β-amino alcohol moiety. The new ligands **5-7a-g** were efficiently prepared by coupling a series of *N*-Boc protected amino acids with the corresponding sugar amino alcohols by using isobutyl chloroformate in the presence of *N*-methylmorpholine (Scheme 3). The corresponding sugar amino alcohols were readily prepared on a large scale from inexpensive D-glucose.

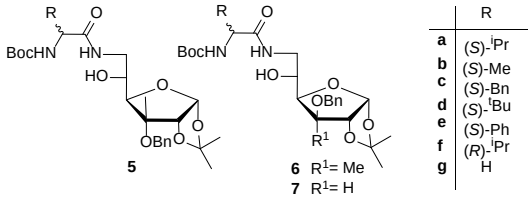
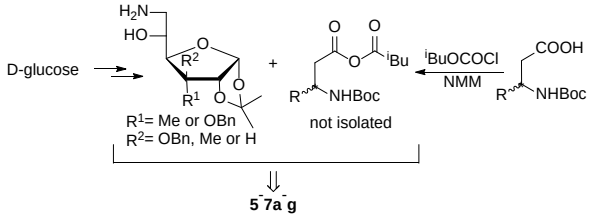


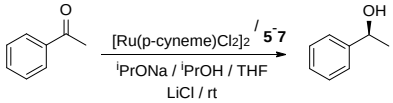
Figure 5. Furanoside hydroxy amide ligands **5-7a-g**.



Scheme 3. Synthesis of furanoside hydroxy amide ligands **5-7a-g**.

With these ligands it was studied the catalytic performance by systematically varying the substituents/configuration of the α-amino acid moiety and the substituent/configuration of C-3 of the sugar backbone (Table 3). The results indicated that varying the substituents of the α-amino acid has not effect on enantioselectivity (>99% ee in all cases) although the highest activities were obtained with catalysts based on ligands **5a-c** (Table 3, entries 1-3). The use of ligand **5g**, with an achiral or racemic α-amino acid moiety into the ligand design also provided excellent enantioselectivity (entry 7). In contrast to previous successful hydroxy amides **1**, the enantioselectivity is therefore exclusively controlled by the sugar moiety which enables the use of inexpensive achiral or racemic α-amino acid derivatives. The use of ligand **6a**, with opposite configuration at C-3 of the furanoside backbone in comparison to **5a**, has no effect on activity and enantioselectivity (Table 3, entry 1 vs 8). Interestingly, the use of ligands **7**, which are synthesized in fewer steps than corresponding ligands **5** and **6**, also provided excellent enatioselectivities (Table 3, entries 9 and 10). Finally, these ligands were also successfully applied in a broad range of other ketones (Figure 6). $[RuCl_2(\pi\text{-cymene})]_2$/**5a** and **7a**, efficiently catalyze the ATH of several other aryl-alkyl ketones. The results show that the catalytic performance is not affected by the steric and electronic properties of the aryl group. This behavior contrasts with the electronic and steric effect on enantioselectivity observed for previous hydroxy amide ligands **1**. As previously observed, the use of LiCl as additive had a positive effect on both activity and selectivity. This has been explained by an intimate involvement of the lithium ion in the process.[9f] Thus, Adolfsson and coworkers have demonstrated that a bifuntional catalyst is formed. In the key transition state the lithium coordinates to both the alkali metal alcoxide and the oxygen of ketone which forms a tighter transition state than without the presence of the smaller cation.

Table 3. Asymmetric transfer hydrogenation of acetophenone using hydroxy amide ligands **5-7a-g**.[a]



Entry	L	% Conv (h)	% ee	Entry	L	% Conv (h)	% ee
1	**5a**	80 (3)	>99 (*S*)	6	**5f**	1 (3)	n.d.
2	**5b**	80 (3)	>99 (*S*)	7	**5g**	56 (3)	99 (*S*)
3	**5c**	81 (3)	>99 (*S*)	8	**6a**	78 (3)	>99 (*S*)
4	**5d**	49 (3)	>99 (*S*)	9	**7a**	79 (3)	>99 (*S*)
5	**5e**	42 (3)	>99 (*S*)	10	**7g**	51 (3)	99 (*S*)

[a] Reaction conditions: substrate (1 equiv, 0.2M in 2-propanol/THF (1:1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol% in Ru), ligand (0.55 mol%), NaO^{i}Pr (5 mol%), LiCl (10 mol%)

In summary, it was found that the introduction of a furanoside aminosugar moiety into the ligand design was advantageous; surpassing the enantioselectivities obtained with previous successful hydroxy amide ligands **1**. Ru-catalysts modified with carbohydrate hydroxy amide ligands **5-7a-g** (Figure 5) therefore proved to efficiently catalyze the reduction of a wide range of aryl alkyl ketones (ee's ranging from 99% to >99%).

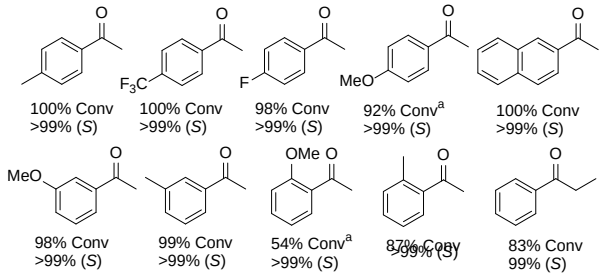


Figure 6. Selected results for the ATH of aromatic ketones using **5a**. Reaction conditions: 0.25 mol% $[RuCl_2(p\text{-cymene})]_2$, 0.55 mol% **5a**, 1 mmol substrate, 3 h at room temperature. [a] 1 mol% of $[RuCl_2(p\text{-cymene})]_2$, 2.2 mol% **5a** 24 h.

Following this contribution came the developments of new hydroxy amide and also the synthesis of thioamides ligand libraries based on carbohydrates.

The first of these described the application of a new carbohydrate-based library of 36 potential hydroxyl amide ligands (**8-11a-i**; Figure 7).[15] These ligands are based on the previous sugar-based hydroxyl amide ligands **5-7**, in which a 1,3-aminoalcohol sugar core was used instead of a classical 1,2-amino alcohol motif. These ligands were prepared from the corresponding easily accessible 1,3 amino alcohol sugar derivatives, which were prepared from the D-xylose (ligands **8-9**) or D-glucose (ligands **10-11**). Ligands **8-11a-i** were synthesized following the general methodology depicted in Scheme 3.

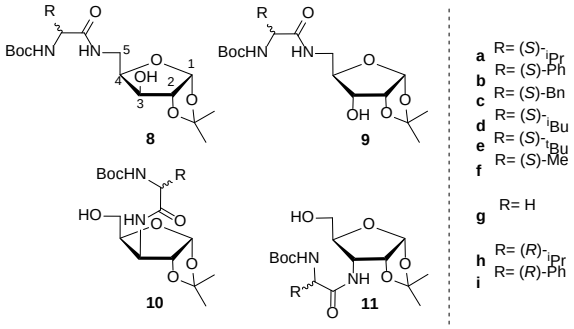


Figure 7. Furanoside hydroxyl amide ligands **8-11a-i**.

The use of either Ru/**8-11a-i** or Rh/**8-11a-i** catalytic systems provided low activities and enantioselectivities (typically conversions were below 10%, even at 50 °C, and ee's were up to 18%). This behavior can be explained by the previous mechanistic studies using hydroxy amides **1** (Figure 2).[9d,f] The species responsible for the catalytic activity is an intermediate where the ligand coordinates to the metal through both nitrogens and the oxygen atom forming two five-membered chelate rings (Figure 2). Our hydroxyl amide ligand library **8-11a-i** differs from previous successful hydroxyl amide ligands **1** in the fact that 1,3-aminoalcohols are used instead of previously described 1,2-aminoalcohols. This change should result in the formation of a reaction intermediate in which the coordination of the alcohol as an alkoxide forms a six-membered chelate, which is less favored than when 1,2-amino alcohols are used, thus favoring catalyst decomposition after only a few turnovers.

With the aim to improve catalytic performance the same authors developed the corresponding thioamide ligand library **12-15a-i**, where the peptide bond in the previous ligands **8-11a-i** was converted to a thioamide group (Figure 8).[15] Its design was based in previous mechanistic studies with successful thioamide ligands **2** that showed that this type of ligand coordinates to the metal in a bidentate fashion, through the carbamate nitrogen and the thioamide sulfur atoms, to form a five-membered ring (Figure 2).[9g] In order to obtain the same coordination pattern the thioamide ligands **12-15a-i** in which the hydroxyl group is protected to prevent its coordination to the metal in the form of alkoxide was developed.

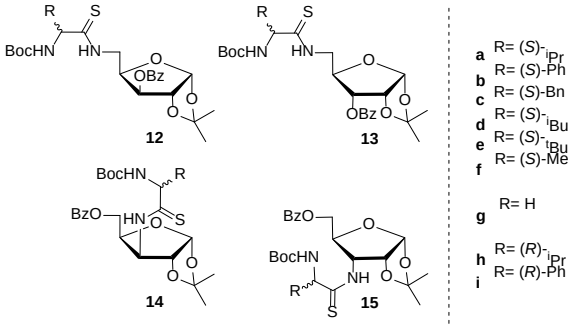
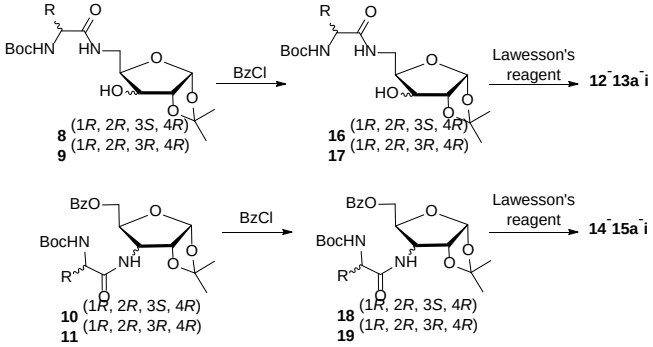


Figure 8. Furanoside thioamide ligands **12-15a-i**.

These ligands were synthesized, from the previously obtained hydroxyl amide ligands **8-11a-i** in a two step procedure (Scheme 4). The first step was the benzoylation of the hydroxyl group attached at either C-3 (**16** and **17**) or C-5 (**18** and **19**) of the furanoside backbone. The second step is the formation of the desired thioamide ligands **12-15a-i** by treating the corresponding benzoyl protected hydrozyamide compounds with Lawesson's reagent.

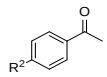
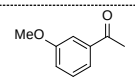
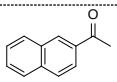
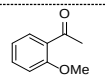


Scheme 4. Synthesis of furanoside thioamide ligands **12-15a-i**.

The authors found that both activity and enantioselectivity are better using $[RhCl_2Cp^*]_2$ as the catalyst precursor than $[RuCl_2(\pi\text{-cymene})]_2$. These results are line with those previously observed using related thioamide-based ligands **2**.[8g,9g] Both enantiomers of the reduction products were obtained for a range of substrates in high enantioselectivity simply by changing the absolute configuration of the thioamide substituent (Table 4). This represents an advantage compared with the hydroxyl amide analogues **5-7** which only give access to the (*S*)-alcohols. The results indicate that enantioselectivity is highly affected by the position of the thioamide group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3 and the substituents/configurations in the thioamide moiety. The best results were obtained with ligands **14a** and **14h**, containing bulky thioamide substituents at C-3 of the xylofuranoside backbone (ee's up to 99%). Interestingly, they provided higher enantioselectivities than those obtained using previously described Rh-**2** catalysts (ee's up to 96%).

Table 4. Selected results for the Rh-catalyzed asymmetric transfer hydrogenation of aryl ketones using thioamide ligands **12-15-i**.[a]

			14a		**14h**	
Entry	Substrate	R	% Conv	% ee	% Conv	% ee
1		R^1=Me	85	98 (*R*)	64	93 (*S*).
2[b]		R^1=Et	76	96 (*R*)	57	92 (*S*).
3[b]		R^1=^{i}Pr	68	98 (*R*)	51	93 (*S*).

4		R^2=Me	68	98 (*R*)	56	94 (*S*)
5		R^2=Br	94	97 (*R*)	84	94 (*S*)
6		R^2=F	95	97 (*R*)	81	94 (*S*)
7		R^2=CF_3	90	96 (*R*)	88	95 (*S*)
8		-	87	95 (*R*)	54	93 (*S*)
9		-	87	99 (*R*)	59	97 (*S*)
10		-	18	37 (*S*)	-	-

[a] Reaction conditions: Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature for 3 h. [b] Reaction carried out for 24 h.

Despite the good results obtained with this family of furanoside-based ligands further improvements in terms of substrate scope are required. Then, the decision was made to replace in the previous privileged ligand **5-7a-g** the carbonyl oxygen by a thioamide group (Figure 9, ligands **20-23a-f**).[16] Ligands **20-23a-f** were efficiently prepared from the corresponding hydroxyl amide compounds in a two step process following the methodology described for previous ligands **12-15a-i** (Scheme 4).[16] Interesting, these new furanoside-based ligand library containing the thioamide functionality (Figure 9) gave access to both enantiomers of the desired alcohols, while maintaining the excellent enantiocontrol exhibited by hydroxyl amide **5-7a-g**, and allowed to expand the scope of the substrates to include more challenging heteroaromatic ketones.

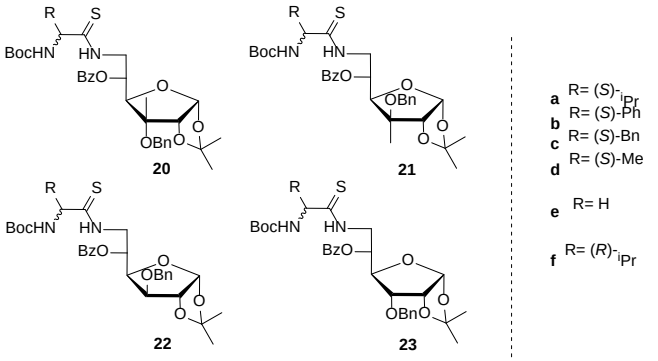
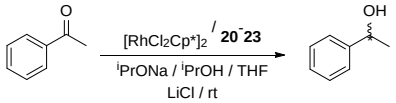


Figure 9. Furanoside-based thioamide ligands **20-23a-f**.

The authors found that enantioselectivities were mainly controlled by the steric properties of thioamide substituents and were higher when more sterically demanding substituents were present (i.e. ^{i}Pr>Bn>Ph>Me; Table 5, entries 1, 3-6). In addition, the presence of a chiral thioamide substituent is crucial if levels of enantioselectivity are to be high (entry 6 vs 1, 3-5). This behavior contrasts with the results achieved using related hydroxy amide analogues **5-7** (Figure 5). Rh-**20e** also led to the lowest activity of the series, which suggest that the presence of an alkyl or aryl thioamide substituent stabilizes the catalytic intermediates.

Table 5. Asymmetric transfer hydrogenation of acetophenone using thioamide ligands **20-23a-f**.[a]



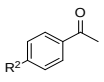
Entry	L	%Conv (h)	% ee	Entry	L	%Conv (h)	% ee
1	**20a**	25 (3)	91 (*R*)	7	**21a**	30 (3)	82 (*R*)
2	**20f**	32 (3)	89 (*S*)	8	**22a**	75 (3)	94 (*R*)
3	**20b**	29 (3)	88 (*R*)	9	**22f**	70 (3)	93 (*S*)
4	**20c**	32 (3)	84 (*R*)	10	**23a**	41 (3)	93 (*R*)
5	**20d**	31 (3)	78 (*R*)	11	**23f**	39 (3)	92 (*S*)
6	**20e**	12 (3)	23 (*R*)	12[b]	**22a**	100 (3)	92 (*R*)

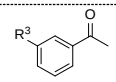
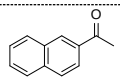
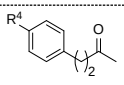
[a] Reaction conditions: substrate (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%) and LiCl (10 mol%). [b] Reaction carried out at 40 °C.

It was also found that the sense of enantioselectivity is governed by the absolute configuration of the substituent in the thioamide moiety (Table 5, entries 1 vs 2). Both enantiomers of the reduction products can therefore be accessed in high enantioselectivity. Concerning the effect of the substituents/configuration at C-3 of the furanoside backbone, the presence of a methyl substituent at C-3 has a negative effect on enantioselectivity. Ligands **20-21** afforded therefore lower enantioselectivities than ligands **22-23**. Interestingly, glucofuranoside ligands **22** afforded higher activities than the rest of ligands. In summary the highest activities and enantioselectivities in both enantiomers of the reduction product were achieved using glucofuranoside ligands **22a** and **22f** containing bulky isopropyl groups at the thioamide ligands. Note that from an application point of view this is advantageous because glucofuranoside ligands **22** are prepared in fewer steps than ligands **20**, **21** and **23**.

Finally, this family of ligands (**20-23a-f**) we evaluated in the asymmetric Rh-catalyzed transfer hydrogenation of other aryl/alkyl, alkyl/alkyl and heteroaryl/alkyl ketones (Table 6). Both enantiomers of the secondary alcohol products were obtained in high enantioselectivities (ee's up to 99%). The results show that the electronic properties of the substrate have little effect at activity and enantioselectivity although the highest enantioselectivity of the series was achieved in the reduction of *p*-tolyl methyl ketone (Table 6, entry 3). In contrast to previous **5-7**, the catalytic performance, however, was influenced by steric factors on the aryl substituent. Activity and enantioselectivity decreased considerably when *ortho*-substituted aryl ketones were used (i.e. entry 10). Nevertheless, the use of several meta-substituted ketones led to activities and enantioselectivities as high as those achieved using *para*-substituted ones (ee's up to 98%; entries 7-9). On the other hand, enantioselectivities are not affected by the steric bulk of the alkyl substituent (entries 1 and 2). Unfortunately, the reduction of alkyl-alkyl ketones proceeded with low enantiocontrol (entry 11)

Table 6. Selected results for the Rh-catalyzed asymmetric transfer hydrogenation of aryl ketones using thioamide ligands **20-23a-f**.[a]

			22a		**22f**	
Entry	Substrate	R	%Conv	% ee	%Conv	% ee
1		R^1=Me	75	94 (*R*)	70	93 (*S*).
2		R^1=Et	79	93 (*R*)	78	92 (*S*).
3		R^2=Me	100	99 (*R*)	100	99 (*S*)
4		R^2=Br	81	94 (*R*)	79	93 (*S*)
5		R^2=F	83	94 (*R*)	84	92 (*S*)
6		R^2=CF_3	81	93 (*R*)	80	92 (*S*)

7		R^3=OMe	96	97 (*R*)	87	96 (*S*)
8		R^3=CF_3	86	97 (*R*)	87	98 (*R*)
9		-	88	94 (*R*)	91	93 (*S*)
10		-	49	38 (*R*)	45	34 (*S*)
11		R^4=OMe	18	34 (*R*)	17	31 (*S*)

[a] Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature for 3 h.

Enantiopure alcohols with heteroaromatic substituents are crucial intermediates in the synthesis of biologically active compounds, and developing new methods for their synthesis is therefore of high relevance for the pharma- and agrochemical industries. For this substrate class, coordination of the heteroaromatic moiety to the metal-catalysts has to be avoided to achieve high enantioselectivities. There are therefore very few catalytic systems able to reduce heteroaromatic ketones under transfer hydrogenation conditions in high enantioselectivities.[17] Figure 10 shows the most notable results uisng ligands **20**-**23a**-**f**. Advantageously, by suitable tuning the ligand parameters, both enantiomers of the resulting heteroaromatic alcohols were obtained in high enantioselectivities (ee's up to 99%). Although as expected the activities were lower than in the reduction of acetophenone, they were similar to those obtained using other successful ligands under similar reaction conditions.[17]

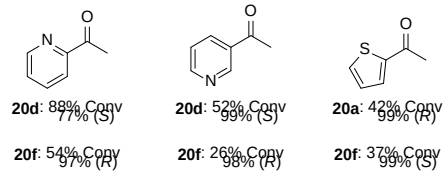


Figure 10. Selected results for the ATH of heteroaromatic ketones using thioamide ligands **20**-**23a**-**f**. Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (1 mol%), ligand (2.2 mol%), NaO^iPr (10 mol%), LiCl (10 mol%) and at room temperature for 3h.

With the aim to increase even further the number and type of substrates that can be successfully reduced our group developed a new carbohydrate-based library of 24 potential hydroxy amide **24**-**26a**-**h** and 24 potential thioamide **27**-**29a**-**h** ligands, with a pyranoside backbone (Figure 11).[18] Pyranoside ligands **24**-**26a**-**h** were synthesized from the corresponding sugar amino alcohols, easily made from D-glucose (ligands **24** and **26**) and D-glucosamine (ligands **25**), by coupling them with a series of N-Boc-protected amino acids as depicted in Scheme 3. The thioamide ligands **27**-**29a**-**h** were prepared from hydroxy amide compounds **24**-**26a**-**h** by benzoylation of the alcohol followed by the thiation of the amide as depicted in Scheme 4.

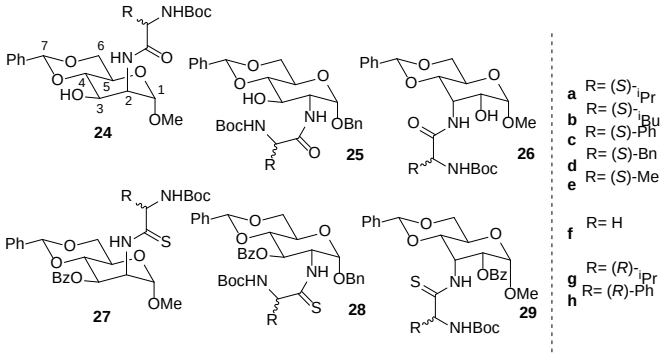


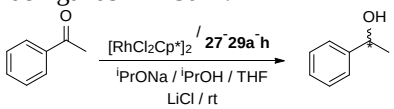
Figure 11. Pyranoside-based α-amino acid hydroxy amide/thioamide ligands **24**-**29a**-**h**.

In this study it was investigated the effect of systematically varying the substituents/configurations at the amide/thioamide moiety (**a**-**h**), the replacement of the hydroxy amide group (ligands **24**-**26**) with thioamide (ligands **27**-**29**), the position of the amide/thioamide moiety at either C-2 (ligands **24**-**25** and **27**-**28**) or C-3 (ligands **26** and **29**) of the pyranoside backbone and the configuration at C-2 (**24**-**25** and **27**-**28**). By thoroughly selecting the ligand components we obtained both enantiomers of the desired alcohols in high-to-excellent enantioselectivities and yields for a wide range of substrates, including the more challenging aryl/fluoroalkyl and heteroaromatic ketones.

In contrast to previously reported furanoside-based hydroxy amide ligands **5**-**7** (Figure 5),[14] the use of hydroxy amide ligands **24**-**26** led to poor catalytic activity (typically conversion below 5%). This can be attributed to the higher rigidity of the pyranoside backbone which hinders its coordination to the metal center in contrast to the less steric environment generated by the furanoside backbone. Note that for furanoside ligands **5**-**7**, the amido group was attached to the flexible primary carbon (C-6), which facilitates the coordination in a tridentate fashion. In contrast, thioamide ligands **27**-**29** provided high conversion and activities. Even more interesting, is that these pyranoside thioamide ligands displayed higher activities and enantioselectivities than previously reported furanoside-based thioamide ligands **20**-**23**.

Concerning the effect of the ligand parameters it was found that enantioselectivities were higher when more sterically demanding amide substituents were present (i.e. ^{i}Pr>^{i}Bu>Bn>Ph>Me>>H; Table 7, entries 1-6). As observed for other thioamide ligands, the sense of the enantioselectivity is governed by the absolute configuration of the substituent in the thioamide moiety (entries 1 vs 7). Varying the configuration of the pyranoside carbon in which the thioamide is coupled has little impact on the activity and stereochemical outcome of the reaction. Finally, ligands **27** and **28**, which contain the thioamide group at the C-2 position, produced better activities and enantioselectivities than ligands **29**, with the thioamide group at C-3 (i.e. entries 1 and 9 vs 14). The lower catalytic activity can be due to the higher steric congestion around the metal center exerted using this latter pyranoside backbone.

Table 7. Asymmetric transfer hydrogenation of acetophenone using thioamide ligands **27**-**29a**-**h**.[a]



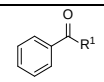
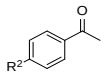
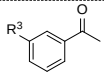
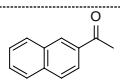
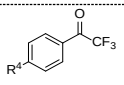
Entry	L	%Conv (h)	% ee	Entry	L	%Conv (h)	% ee
1	**27a**	88 (3)	99 (*R*)	9	**28a**	82 (3)	98 (*R*)
2	**27b**	91 (3)	97 (*R*)	10	**28e**	84 (3)	86 (*R*)

3	**27c**	76 (3)	90 (*R*)	11	**28f**	79 (3)	8 (*R*)
4	**27d**	92 (3)	96 (*R*)	12	**28g**	72 (3)	95 (*S*)
5	**27e**	88 (3)	86 (*R*)	13	**28h**	69 (3)	89 (*S*)
6	**27f**	86 (3)	33 (*S*)	14	**29a**	19 (3)	84 (*R*)
7	**27g**	76 (3)	98 (*S*)	15	**29e**	38 (3)	93 (*R*)
8	**27h**	72 (3)	89 (*S*)	16	**29g**	18 (3)	83 (*S*)

[a] Reaction conditions: substrate (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%) and LiCl (10 mol%).

Thioamide ligands **27-29a-h** were also evaluated in the asymmetric Rh-catalyzed transfer hydrogenation of other aryl alkyl/trifluoroalkyl ketones (Table 8). Both enantiomers of the secondary alcohol products were obtained in high-to-excellent enantioselectivities (ee's up to 99%), regardless the *para* and *meta*-substituents on the aryl ketone group (entries 5-12). Excellent enantioselectivities were obtained in the ATH of several aryl/alkyl ketones bearing increasingly sterically demanding alkyl substituents (entries 1 and 4). For the reduction of the more hindered cyclohexyl-containing ketone the enantioselectivity was highest with ligand **27e**, which contained the smallest methyl thioamide substituent (footnote b in Table 8). Finally, it should be noted the high enantioselectivity obtained with catalyst precursors Rh/**27a** and Rh/**27g** in ATH of aryl trifluoroalkyl ketones (ee's up to 89%, entries 14 and 15). These results compete favourably with the results obtained using the Ru/TSDPEN catalyst (38% ee), which is considered the state of art in ATH reactions.[19]

Table 8. Selected results for the Rh-catalyzed asymmetric transfer hydrogenation of aryl ketones using thioamide ligands **27-29a-h**.[a]

			27a		**27g**	
Entry	Substrate	R	%Conv	% ee	%Conv	% ee
1		R^1=Me	88	99 (*R*)	76	97 (*S*)
2		R^1=Et	82	97 (*R*)	77	96 (*S*)
3		R^1=^{i}Bu	64	91 (*R*)	68	90 (*S*)
4[b]		R^1=Cy	16	72 (*R*)	15	70 (*S*).
5		R^2=Me	64	98 (*R*)	61	97 (*S*)
6		R^2=Br	87	98 (*R*)	72	98 (*S*)
7		R^2=F	92	99 (*R*)	84	99 (*S*)
8		R^2=CF_3	99	96 (*R*)	92	98 (*S*)
9		R^2=OMe	74	99 (*R*)	68	98 (*S*)
10		R^3=OMe	98	99 (*R*)	92	98 (*S*)
11		R^3=CF_3	99	99 (*R*)	96	99 (*S*)
12		-	92	98 (*R*)	87	98 (*S*)
13		-	40	56 (*S*)	34	55 (*R*)
14		R^4=H	92	87 (*S*)	93	87 (*R*)
15		R^4=OMe	81	89 (*S*)	79	88 (*R*)

[a] Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^iPr (5 mol%), LiCl (10 mol%) and at room temperature for 3 h. [b] The use of ligand **27e** affords 18% conversion and 79% (*R*) ee.

Finally, these ligands were also successfully applied to a range ketones containing pyridine, furan and thiophene groups (Figure 12).

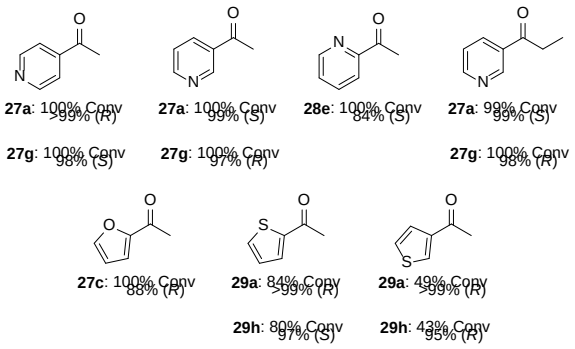
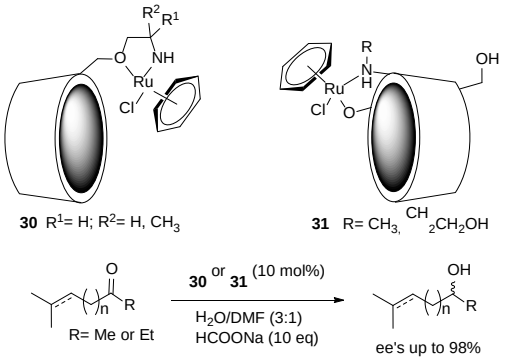


Figure 12. Selected results for the ATH of heteroaromatic ketones using thioamide ligands **27-29a-h**. Reaction conditions: ketone (1 equiv, 0.2M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (1 mol%), ligand (2.2 mol%), NaO^iPr (10 mol%), LiCl (10 mol%) and at room temperature for 3h.

ATH using β-cyclodextrin-based catalysts

In the last decade, Woggon et al. have made use of a supramolecular approach where the β-cyclodextrin provides the ligand sphere for Ru-catalysts for ATH reactions (Scheme 5).[20] The hydrophobic cavity of the water soluble cyclodextrins facilitates the binding orientation and activation of lipophilic substrates. Therefore, ruthenium-η-arene complexes attached to the primary (**30**) or to the secondary (**31**) face of β-cyclodextrin catalyzed the enantioselective reduction of aliphatic and aromatic ketones (ee's up to 98%) in aqueous medium in the presence of sodium formate, albeit with low activity (typically reactions were carried out using 10 mol% catalyst during 12-24 h; Scheme 5).



Scheme 5. ATH of ketones using β-cyclodextrin Ru-catalysts **30** and **31**.

Conclusions and outlook

Carbohydrate-based ligands provide a promising approach in the search for effective catalysts in asymmetric transfer hydrogenation reactions. As we have seen during this digest paper, the structural diversity of carbohydrates offer a wide variety of opportunities for derivatization and tailoring of synthetic tools in the search of the right ligand for each substrate type. Another important feature of carbohydrate-based cores compared with other sources of chiral ligands is they are readily available from cheap feedstocks. In this respect, the sugar ligands collected in this digest are synthesized from isosorbide, D-xylose, D-glucose, D-glucosamine and β-cyclodextrin all cheap natural sources. In addition, thanks to their high modularity both enantiomers of the reaction product can be obtained without the use of expensive unnatural, prohibitively expensive L-carbohydrate. Although important progress has been made, especially in the successful ATH of a variety of substrates

including the more demanding heteroaromatic ketones and the aliphatic ketones using cyclodextrin-based catalysts in water there still remain challenges such as to further increase the substrate scope and to develop a system that provides high activities in water media.

Acknowledgments

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