Modular hydroxyamide and thioamide pyranoside-based ligand library from the sugar pool: new class of ligands for asymmetric transfer hydrogenation of ketones

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Abstract. A large library of pyranoside-based hydroxyamide and thioamide ligands has been synthesized for asymmetric transfer hydrogenation in an attempt to expand the scope of the substrates to cover a broader range of challenging heteroaromatic and aryl/fluoroalkyl ketones. These ligands have the advantage that they are prepared from commercial D-glucose, D-glucosamine and α-amino acids, inexpensive natural chiral feedstocks. By carefully selecting the ligand components (substituents/configurations at the amide/thioamide moiety, the position of amide/thioamide group and the configuration at C-2), we found that pyranoside-based thioamide ligands provided excellent enantioselectivities (in the best cases, ees of >99% were achieved) in a broad range of ketones, including the less studied heteroaromatics and challenging aryl/fluoroalkyls. Note that both enantiomers of the reduction products can be obtained with excellent enantioselectivities by simply changing the absolute configuration of the thioamide substituent.

Keywords: Asymmetric catalysis; Ruthenium; Rhodium; Carbohydrates; Transfer hydrogenation; Ketones

Introduction

Over the last four decades, transition-metal-based asymmetric catalysis has been a powerful strategy for accessing a wide range of optically pure compounds.[1] In particular, considerable effort has been made in the enantioselective reduction of prochiral ketones because the alcohols formed have important uses in the pharmaceutical, agrochemical, fragrance and flavor industries.[1] Asymmetric transfer hydrogenation (ATH) is an alternative, sustainable, efficient and mild method that is operationally simpler and significantly safer than direct hydrogenation with molecular hydrogen.[2] The most commonly used asymmetric transfer hydrogenation catalysts are based on transition metals (i.e. ruthenium,[3] rhodium,[4] iridium[4a-c,5] and more recently iron[6] and osmium[7]). In the mid 1990s, Noyori and coworkers disclosed that Ru-arene complexes modified with chiral β-aminoalcohols or monosulfonated diamines (i.e. TSDPEN, which constitutes one of the widely used ligands in this transformation) are efficient catalysts for reducing ketones and ketimines.[2f,i,3a-b] Since then the range of ligand classes has been expanded.[8] In this respect, Adolfsson's group reported that amino acid-derived hydroxyamides **1** and thioamides **2** (Figure 1) in combination with Ru or Rh half-sandwich complexes are excellent catalysts for the ATH of aryl alkyl ketones.[8h,i,9] These ligands are based on the combination of different N-Boc-protected α-amino acids and β-amino alcohols (for type **1**)[8h,9a-g] or on thioamides (for type **2**)[8i,9h-j], respectively. Both showed the advantage of possessing a modular ligand building block: the amino acid part. Despite all these important contributions, further improvement in terms of substrate scope, selectivity and turnover frequency was required to make the process competitive with conventional hydrogenations. Therefore, enantioselective ATH catalysts containing modular ligands based on simple starting materials needed to be developed.[10,11] In this context, in 2011 we developed new hydroxyamide ligands **3** (Figure 1) in which the β-amino alcohol part was replaced by a readily available sugar β-amino alcohol moiety.[12] The introduction of a furanoside aminosugar moiety into the ligand design represented an important breakthrough. Ru-catalysts modified with carbohydrate hydroxyamide ligands **3** (Figure 1) therefore proved to efficiently catalyze the reduction of a wide range of aryl alkyl ketones. The secondary alcohols formed were obtained in excellent enantioselectivities (typically 99% ee) surpassing the enantioselectivities obtained with previous successful hydroxyamide ligands **1**. However the latter catalytic systems cannot reduce industrially relevant heteroaromatic ketones and only one of the enantiomers of the product can be accessed. To overcome these limitations, we recently prepared a

second generation of the furanoside-based ligand library containing the thioamide functionality (**4**, Figure 1), based on previous sugar hydroxyamide ligands **3**.[13] Although the number and type of substrates that can be successfully reduced with these systems has increased, greater effort is still needed in the design of ligands to discover a catalytic system that can efficiently reduce a broader range of heteroaromatic ketones and other more challenging substrates such as aryl/fluoroalkyl ketones.[14]

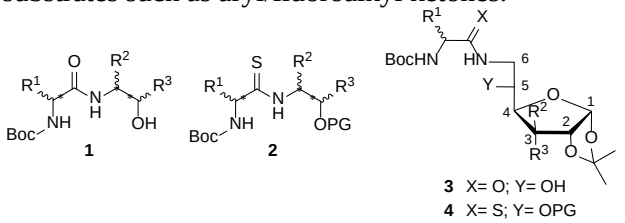


Figure 1. General structure of hydroxyamide ligands **1**, thioamide ligands **2** and sugar-based hydroxyamide **3** and thioamide ligands **4**

To address all these points, in this study, we prepared and evaluated a new carbohydrate-based library of 24 potential hydroxyamide **L1**-**L3a**-**h** and 24 potential thioamide **L4**-**L6a**-**h** ligands (Figure 2). The combination of commercially available ligand building blocks (D-glucose or D-glucosamine and α-amino acids) creates a highly modular ligand library, in which several ligand parameters can easily be tuned so that catalyst performance can be maximized for each substrate type. With this ligand library, we investigated the effect of systematically varying the substituents/configurations at the amide/thioamide moiety (**a**-**h**), the replacement of the hydroxyamide functionality (ligands **L1**-**L3**) with thioamide (ligands **L4**-**L6**), the position of the amide/thioamide group at either C-2 (ligands **L1**-**L2** and **L4**-**L5**) or C-3 (ligands **L3** and **L6**) of the pyranoside backbone and the configuration at C-2 (**L1**-**L2** and **L4**-**L5**). By carefully selecting the ligand components we achieved 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.

Results and Discussion

Ligand synthesis

Pyranoside ligands **L1**-**L6** were synthesized from the corresponding sugar amino alcohols **1**-**3**, easily made in few steps from D-glucose (compounds **1** and **3**)[15] and D-glucosamine (compound **2**)[16], following a straightforward methodology in a parallel way (Scheme 1). Compounds **1**-**3** were chosen as intermediates for preparing ligands because the various elements that make it possible to study the position at which the amide/thioamide is coupled (at either C2 or C-3) and the configuration of C-2 of the sugar amino alcohol can be easily incorporated. We first synthesized the α-amino acid hydroxyamide ligands **L1**-**L3** from intermediates **1**-**3** in a single step by coupling a series of *N*-Boc-protected amino acids using isobutyl chloroformate in the presence of *N*-methylmorpholine (Scheme 1, step a). In this step the desired diversity in the substituents and configuration of the amino acid part was also attained (**a**-**h**). We next synthesized thioamide ligands **L4**-**L6**, in a two step procedure, from hydroxyamide compounds **L1**-**L3** by first protecting the free hydroxyl group with benzoyl chloride (Scheme 1, step b). The subsequent reaction with Lawesson's reagent (Scheme 1, step c) provided direct access to pyranoside-based thioamide ligands **L4**-**L6**.

The ligands were characterized by elemental analyses and ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra (see Supporting Information). The elemental analyses were in agreement with the assigned structures. The spectral assignments were based on information from ^{1}H-^{1}H, and ^{1}H-^{13}C correlation measurements. The expected ^{1}H and ^{13}C NMR patterns for the pyranoside nucleus (positions 1-7) were observed (see experimental section). The vicinal ^{1}H-^{1}H couplings in the sugar ring were in the normal range (0-7 Hz). As expected, ligands **L1** and **L4**, with an *S* configuration at C-2, displayed the anomeric proton (H-1) as a singlet, while for compounds **L2**-**L3** and **L5**-**L6**, with an opposite configuration at C-2, the anomeric proton appears as a doublet due to the coupling with H-2. The expected signals for the different amide/thioamide groups were also observed.

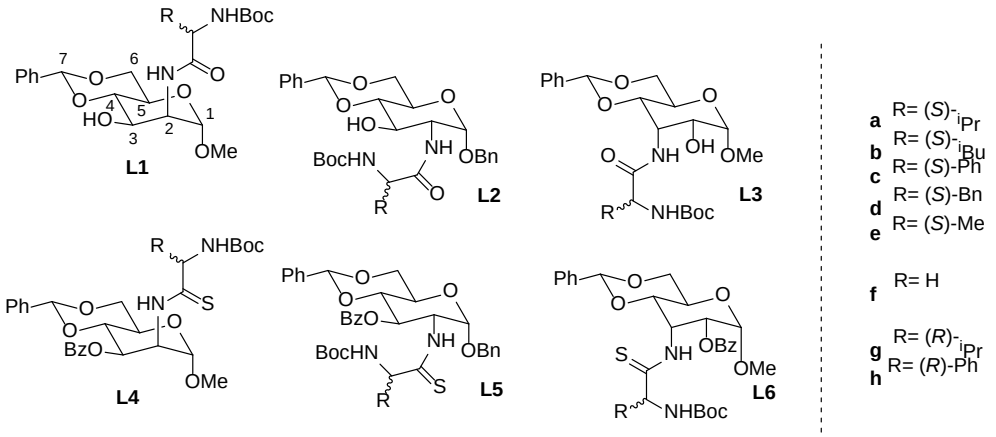
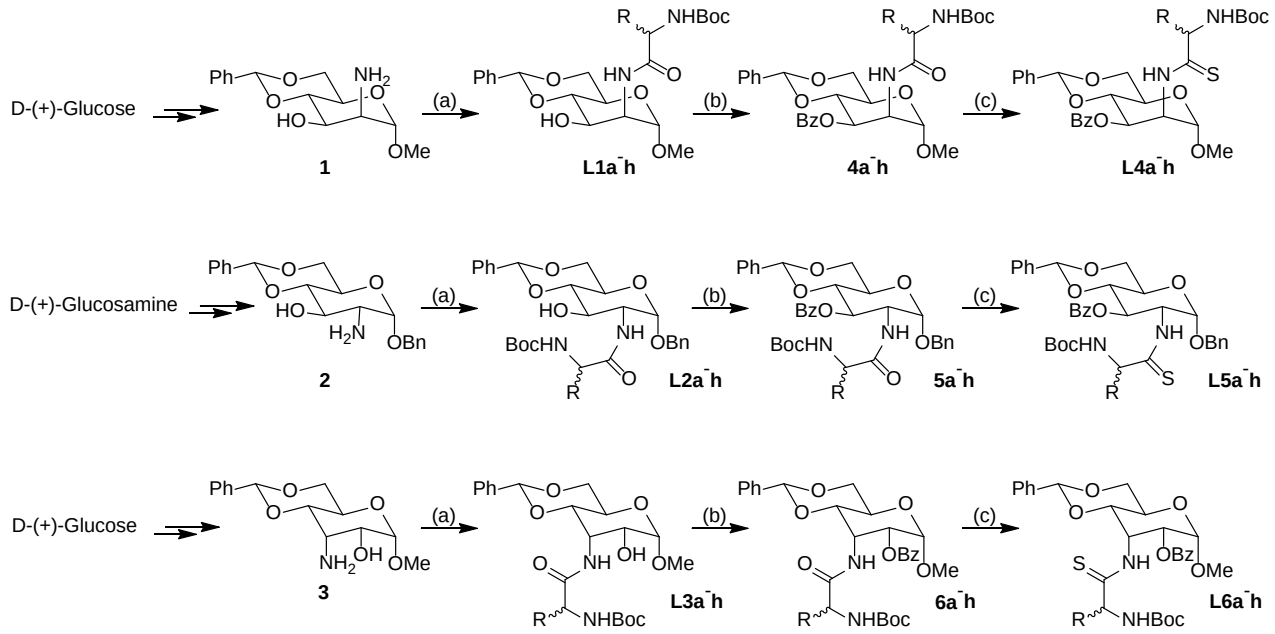


Figure 2. Pyranoside-based α-amino acid hydroxyamide/thioamide ligands **L1**-**L6a**-**h**



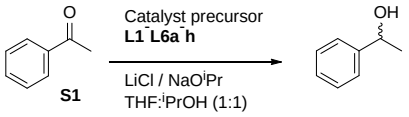
Scheme 1. Synthesis of pyranoside-based α-amino acid hydroxyamide/thioamide ligands **L1-L6a-h**. (a) *N*-Boc-protected α-amino acid / ^{i}BuOCOCl / NMM / THF / -15 °C; (b) BzCl / Py / CH_2Cl_2 / 0 °C to rt; (c) Lawesson's reagent / THF /60 °C

Asymmetric transfer hydrogenation of acetophenone

In the initial set of experiments we evaluated pyranoside-based hydroxyamide/thioamide ligands **L1-L6a-h** in the asymmetric Ru- and Rh-catalyzed transfer hydrogenation of acetophenone **S1**. Acetophenone was chosen as a model substrate because the reaction was performed with a wide range of ligands, which enabled the efficiency of the various ligand systems to be compared directly.[2-9] In all cases, the catalysts were generated *in situ* from the corresponding ligand and either $[RuCl_2(p\text{-cymene})]_2$ or $[RhCl_2Cp^*]_2$ in the presence of base.

We first investigated the effect of the catalyst precursor using ligands **L1-L6a** (Table 1). In contrast to previously reported furanoside-based hydroxyamide ligands **3** (Figure 1),[12] the use of ligands **L1-L3** led to poor catalytic activity when both types of catalyst precursors were used (Table 1, entries 1-6). Previous mechanistic studies with successful hydroxyamide ligands **1** showed that this type of ligand coordinates to the metal in a tridentate fashion, through both nitrogen atoms and the oxygen atom.[9h] The lower activity found with hydroxyamide ligands **L1-L3** can therefore 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 **3**, the amido group was attached to the flexible primary carbon (C-6), which allows the perfect coordination of the three groups. The results in Table 1 also showed that both activity and enantioselectivity were best when the thioamide ligands and $[RhCl_2Cp^*]_2$ were used as the catalyst precursor (entries 10-12).[17] These results are in line with those previously observed when related thioamide-based ligands **4** were used.[13] Interestingly, these pyranoside thioamide ligands displayed higher activities and enantioselectivities than previously reported furanoside-based thioamide ligands **4**.

Table 1. Ru- and Rh-catalyzed asymmetric transfer hydrogenation reaction of **S1** using ligands **L1-L6a-h**[a]



Entry	Ligand	Catalyst precursor	% Conv[b]	% ee[b]
1	**L1a**	$[RuCl_2(p\text{-cymene})]_2$	0	nd
2	**L2a**	$[RuCl_2(p\text{-cymene})]_2$	0	nd
3	**L3a**	$[RuCl_2(p\text{-cymene})]_2$	1	nd
4	**L1a**	$[RhCl_2Cp^*]_2$	6	19 (*S*)
5	**L2a**	$[RhCl_2Cp^*]_2$	5	16 (*S*)
6	**L3a**	$[RhCl_2Cp^*]_2$	4	11 (*S*)
7	**L4a**	$[RuCl_2(p\text{-cymene})]_2$	39	90 (*R*)
8	**L5a**	$[RuCl_2(p\text{-cymene})]_2$	42	87 (*R*)
9	**L6a**	$[RuCl_2(p\text{-cymene})]_2$	7	70 (*R*)
10	**L4a**	$[RhCl_2Cp^*]_2$	88	99 (*R*)
11	**L5a**	$[RhCl_2Cp^*]_2$	82	98 (*R*)
12	**L6a**	$[RhCl_2Cp^*]_2$	19	84 (*R*)

[a] Reaction conditions: **S1** (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) or $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^{i}Pr (5 mol%), LiCl (10 mol%) and at room temperature, 3 h. [b] Conversion and enantiomeric excess were determined by GC (CP Chirasil DEX CB).

We then moved on to investigate the effect of the ligand parameters on the catalytic performance. For purposes of comparison, we evaluated the remaining thioamide ligands using $[RhCl_2Cp^*]_2$ as the catalyst precursor. The results, which are summarized in Table 2, indicated that catalytic performance (activity and enantioselectivity) is mainly affected by the substituents/configurations at the thioamide moiety (**a**-**h**) and the position of the thioamide group at either C-2 or C-3 of the pyranoside backbone while the effect of the configuration of C-2 is less pronounced.

We first investigated the effect on catalytic performance of the substituents/configuration of the thioamide moiety with ligands **L4a**-**h** (Table 2, entries 1-6). Systematic variation of the electronic and steric properties of the thioamide substituents indicated that enantioselectivities were mainly controlled by the steric properties of these substituents and were higher when more sterically demanding substituents were present (i.e. ^{i}Pr>^{i}Bu>Bn>Ph>Me>>H; Table 2, entries 1-6). In addition, as observed for other thioamide ligands, the sense of the enantioselectivity is governed by the absolute configuration of the substituent in the thioamide moiety (Table 2, entries 1 vs 7). Both enantiomers of the reduction products can therefore be accessed in high enantioselectivity simply by changing the absolute configuration of the thioamide substituent.

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. Thus, the use of ligands **L4** and **L5**, with opposite configuration at C-2 of the pyranoside backbone, led to similar catalytic results (i.e. Table 2, entry 1 vs 9).

Finally we studied the effect of the position of the thioamide group at either C-2 (ligands **L4**-**L5**) or C-3 (ligands **L6**) of the pyranoside backbone. Ligands **L4** and **L5**, which contain the thioamide group at the C-2 position, produced better activities and enantioselectivities than ligands **L6**, with the thioamide group at C-3. The lower catalytic activity can be attributed to the higher steric congestion around the metal center exerted using this **L6** pyranoside backbone. This is further supported by the fact that the highest activity when ligands **L6** are used is achieved with the less sterically demanding methyl thioamide substituent (ligand **L6e**; entry 15 vs 16). Note that in contrast to **L4**-**L5**, ligand **L6e** also afforded the highest enantioselectivity of the **L6** series.

To sum up, the enantioselectivities (ee's up to 99%) were highest when thioamide ligands with bulky isopropyl groups were used (ligands **L4**-**L5a**,**g**). Both enantiomers of the alcohol product were achieved in excellent enantioselectivity by simply changing the configuration of the thioamide substituent. These results clearly show the efficiency of using highly modular scaffolds in the ligand design. Activity can be improved by controlling not only the structural but also the reaction parameters. In this case, activity was further improved (up to 100% conversion in 2 hours) by performing the reaction at a higher temperature (40 °C) and, interestingly, the high enantioselectivities were maintained (ee's up to 98%, entries 17 and 18). We also performed the reaction at low catalyst loading using ligands **L4a**,**g**. The excellent enantioselectivity (98% ee) and activity (up to 100% conversion after 4 h) were maintained. Interestingly, when these results are compared with the catalytic performance obtained with their corresponding furanoside-based thioamide **4** and hydroxyamide **1** systems, we can conclude that introducing a pyranoside moiety into ligands **L4**-**L5a**,**g** is advantageous. We therefore obtain enantioselectivities as high as those reported with the best catalytic systems reported for this process but our new thioamides **L4**-**L5a**,**g** provided higher activities than previous furanoside-based analogues **4**.

Table 2. Rh-catalyzed asymmetric transfer hydrogenation reaction of **S1** using thioamide ligands **L4**-**L6a**-**h**[a]

Entry	Ligand	% Conv(% Yield) [b]	% ee[b]
1	**L4a**	88 (81)[c]	99 (*R*)
2	**L4b**	91 (87)	97 (*R*)
3	**L4c**	76 (72)	90 (*R*)
4	**L4d**	92 (85)	96 (*R*)
5	**L4e**	88 (81)	86 (*R*)
6	**L4f**	86 (82)	33 (*S*)
7	**L4g**	76 (69)	98 (*S*)
8	**L4h**	72 (67)	89 (*S*)
9	**L5a**	82 (77)	98 (*R*)
10	**L5e**	84 (76)	86 (*R*)
11	**L5f**	79 (74)	8 (*R*)
12	**L5g**	72 (68)	95 (*S*)
13	**L5h**	69 (61)	89 (*S*)
14	**L6a**	19 (15)	84 (*R*)
15	**L6e**	38 (34)	93 (*R*)
16	**L6g**	18 (13)	83 (*S*)
17[d]	**L4a**	100 (91)	98 (*R*)
18[d]	**L4g**	100 (95)	98 (*S*)
19[d,e]	**L4a**	99 (94)	98 (*R*)
20[d,e]	**L4g**	100 (93)	98 (*S*)

[a] Reaction conditions: **S1** (1 equiv, 0.2 M in 2-propanol/THF: 1/1), $[RhCl_2Cp^*]_2$ (0.25 mol%), ligand (0.55 mol%), NaO^{i}Pr (5 mol%), LiCl (10 mol%), at room temperature, 3 h. [b] Conversion and enantiomeric excess were determined by GC (CP Chirasil DEX CB). Isolated yields are shown in parenthesis. [c] This reaction was also carried out at 0.1 mol scale, affording the reduced product in 85% yield and 98% ee. [d] Reaction carried out at 40 °C. [e] Reaction carried out using 0.1mol% of $[RhCl_2Cp^*]_2$.

Asymmetric transfer hydrogenation of other ketones. Scope and limitations

Asymmetric transfer hydrogenation of aryl alkyl and aryl fluoroalkyl ketones

To further study the potential of the readily available thioamide ligands, we evaluated them in the

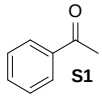
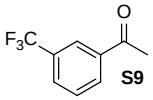
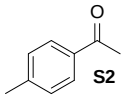
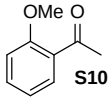
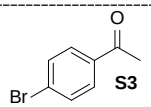
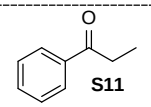
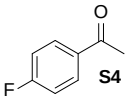
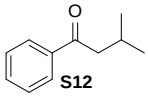
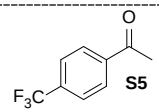
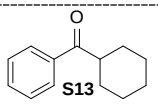
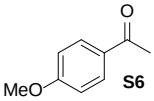
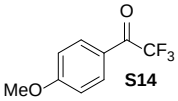
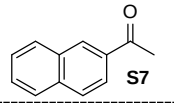
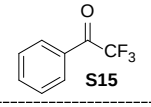
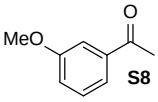
asymmetric Rh-catalyzed transfer hydrogenation of other aryl alkyl/trifluoroalkyl ketones **S2**-**S15** (Table 3). The ATH results indicated that the general trends were the same as for the ATH of **S1** (see Supporting Information for a full set of results). Results were therefore best with ligands **L4**-**L5a**,**g**, giving access to both enantiomers of the secondary alcohol products in high-to-excellent enantioselectivities (ee's up to 99%). Again, pyranoside-based thioamide ligands displayed higher activities and enantioselectivities than previously reported successful furanoside-based thioamide ligands **4**.

Our results using several *para*-substituted aryl ketones (**S1**-**S6**) indicated that enantioselectivity is relatively insensitive to the electronic effects in the aryl ring (Table 3, entries 1-12). However, enantioselectivities (up to 99%) were highest with electron-rich ketones **S4** and **S6** (Table 3, entries 7, 8, 11 and 12), and lowest (up to 96%) with the electron-deficient ketone **S5** (Table 3, entries 9 and 10). The catalytic performance of the reaction, however, was influenced by steric factors on the aryl substituent. Both activity and enantioselectivity decreased considerably when *ortho*-substituted aryl ketones were used (i.e. substrate **S10**; Table 3, entries 19 and 20). Nevertheless, the use of several *meta*-substituted ketones (**S7**-**S9**) led to activities and enantioselectivities as high as those achieved using *para*-substituted substrates. Therefore, several *para*- and *meta*-substituted aryl ketones, including those containing 2-naphthyl groups, can be efficiently reduced using Rh-**L4**-**L5a**,**g**.

We next studied several aryl/alkyl ketones bearing increasingly sterically demanding alkyl substituents (**S11**-**S13**). The results indicated that increasing the steric bulk has a negative effect on catalytic performance (i.e. Me≈Et>^{i}Bu>>Cy; entries 1-2 and 21-26). It should be pointed out that the reduction of the more hindered cyclohexyl-containing ketone **S13** followed a different trend than previous substrates. The enantioselectivity was therefore highest with ligand **L4e**, which contained the smallest methyl thioamide substituent (Table 3, entry 25 vs 26).

Finally, we investigated the asymmetric transfer hydrogenation of aryl/fluoroalkyl ketones **S14** and **S15**. Enantioenriched α-trifluoromethyl alcohols are important intermediates in the development of

Table 3. Selected results for the Rh-catalyzed asymmetric transfer hydrogenation reaction of ketones **S1**-**S15** using thioamide ligands **L4**-**L6a**-**h**[a]

Entry	Substrate	Ligand	% Conv (% Yield)[b]	% ee[b]	Entry	Substrate	Ligand	% Conv (% Yield)[b]	% ee[b]
1	 **S1**	**L4a**	88 (81)	99 (*R*)	17	 **S9**	**L4a**	99 (94)	99 (*R*)
2		**L4g**	76 (70)	97 (*S*)	18		**L4g**	96 (92)	99 (*S*)
3	 **S2**	**L4a**	64 (59)	98 (*R*)	19	 **S10**	**L4a**	40 (35)	56 (*S*)
4		**L4g**	61 (54)	97 (*S*)	20		**L4g**	34 (31)	55 (*R*)
5	 **S3**	**L4a**	87 (82)	98 (*R*)	21	 **S11**	**L4a**	82 (78)	97 (*R*)
6		**L4g**	72 (67)	98 (*S*)	22		**L4g**	77 (71)	96 (*S*)
7	 **S4**	**L4a**	92 (87)	99 (*R*)	23	 **S12**	**L4a**	64 (57)	91 (*R*)
8		**L4g**	84 (78)	99 (*S*)	24		**L4g**	68 (59)	90 (*S*)
9	 **S5**	**L4a**	99 (93)	96 (*R*)	25[c]	 **S13**	**L4e**	18 (14)	79 (*R*)
10		**L4g**	97 (92)	95 (*S*)	26[c]		**L4g**	15 (12)	70 (*S*)
11	 **S6**	**L4a**	74 (67)	99 (*R*)	27	 **S14**	**L4a**	81 (74)	89 (*S*)
12		**L4g**	68 (63)	98 (*S*)	28		**L4g**	79 (71)	88 (*R*)
13	 **S7**	**L4a**	92 (84)	98 (*R*)	29	 **S15**	**L4a**	92 (81)	87 (*S*)
14		**L4g**	87 (81)	98 (*S*)	30		**L4g**	93 (82)	87 (*R*)
15	 **S8**	**L4a**	98 (94)	99 (*R*)					
16		**L4g**	92 (87)	98 (*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^{i}Pr (5 mol%), LiCl (10 mol%), at room temperature, 3 h. [b] Conversion and enantiomeric excess were determined by GC (CP Chirasil DEX CB). Isolated yields are shown in parenthesis. [c] Conversion determined by ^{1}H NMR and enantiomeric excess determined by HPLC (Chiralcel OD-H).

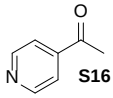
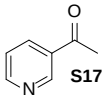
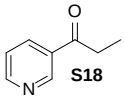
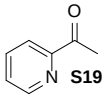
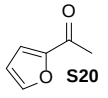
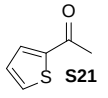
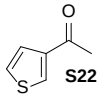
medicines, agrochemicals, and materials owing to the unique properties of the fluorine atom.[18] The formation of optically active α-trifluoromethyl alcohols relies mainly on the use of biocatalysts, metal-catalyzed asymmetric hydrogenation and hydroboration.[19] Few reports have been published on the use of asymmetric transfer hydrogenation of fluoroalkyl ketones.[20] Catalyst precursors Rh/**L4a** and Rh/**L4g** proved to be the most selective, giving the corresponding α-trifluoromethyl alcohols in high enantioselectivities (ee's up to 89%). It should be noted that these results compete favourably with the results obtained using the Ru/R_2NSO_2DPEN catalyst (38% ee), which is considered the state of art in ATH reactions.[14]

In summary, the modular ligand design (substituents/configurations at the thioamide moiety, position of thioamide group at either C-3 or C-2 of the pyranoside backbone and the configuration at C-2 of the pyranoside backbone) has been shown to be extremely successful at finding highly selective ligands for almost every substrate and identifying four general ligands **L4**-**L5a**,**g** with good performance over the entire range of substrates (ee's up to 99%). The results obtained so far are among the best reported and, more importantly, they overcome one of the limitations encountered with the use of previously successful furanoside-based thioamide and hydroxyamide ligand libraries, which were unable to reduce aryl/fluoroalkyl ketones in high enantiomeric excesses.[21]

Asymmetric transfer hydrogenation of heteroaryl alkyl ketones

Encouraged by the excellent results obtained up to this point, we decided to go one step further and evaluate the new ligand library in the asymmetric transfer hydrogenation of a more challenging class of substrates: the heteroaromatic ketones. The preparation of chiral heteroaromatic alcohols is of great importance for the pharmaceutical and agrochemical industries because they are found in many biologically active compounds. The ATH can be a more efficient approach for preparing these compounds. Unfortunately, due to the coordination ability of the heteroaromatic moiety, the ATH of heteroaryl alkyl ketones is extremely difficult. Coordination to the metal-catalysts has to be avoided if activities and enantioselectivities are to be high. There are therefore very few catalytic systems that can reduce heteroaromatic ketones under transfer hydrogenation conditions in high enantioselectivities.[22] Table 4 shows the most notable results in the reduction of a wide range of heteroaromatic substrates **S16**-**S22** using thioamide ligands **L4**-**L6a**-**h** (for a full set of results see Supporting Information). The results indicated again that the sense of enantioselectivity is dictated by the configuration at the thioamide moiety. Both enantiomers of the heteroaromatic alcohol products can therefore be obtained by simply changing the configuration at the thioamide group (i.e. Table 4, entry 1 vs 3). However, the effect of the ligand parameters on the catalytic performance depends on the substrate type. Nevertheless, we were again able to fine tune the ligand parameters to obtain high-to-excellent enantioselectivities for each heteroaromatic substrate.

Table 4. Selected results for the Rh-catalyzed asymmetric transfer hydrogenation reaction of several heteroaromatic ketones using thioamide ligands **L4**-**L6a**-**h**[a]

Entry	Substrate	Ligand	% Conv (% Yield)[b]	% ee[c]
1	 **S16**	**L4a**	100 (92)[e]	>99 (*R*)[d]
2		**L4e**	100 (94)	93 (*R*)[d]
3		**L4g**	100 (93)	98 (*S*)[d]
4		**L5a**	79 (71)	98 (*R*)[d]
5		**L6a**	21 (15)	51 (*R*)[d]
6	 **S17**	**L4a**	100 (91)	99 (*S*)
7		**L4e**	100 (91)	94 (*S*)
8		**L4g**	100 (90)	97 (*R*)
9		**L5a**	86 (74)	98 (*S*)
10		**L6a**	41 (36)	99 (*S*)
11	 **S18**	**L4a**	99 (90)	99 (*S*)
12		**L4g**	100 (93)	98 (*R*)
13		**L5a**	96 (89)	97 (*S*)
14		**L6a**	73 (62)	98 (*S*)
15	 **S19**	**L4a**	100 (90)	28 (*S*)
16		**L4d**	97 (91)	46 (*S*)
17		**L4e**	86 (80)	86 (*S*)
18		**L4g**	100 (92)	29 (*R*)
19		**L5e**	100 (93)	84 (*S*)
20		**L6e**	92 (84)	34 (*S*)
21	 **S20**	**L4a**	90 (81)	42 (*R*)
22		**L4c**	100 (93)	88 (*R*)
23		**L5a**	93 (85)	21 (*R*)
24		**L6a**	36 (21)	54 (*R*)
25	 **S21**	**L4a**	89 (81)	94 (*R*)
26		**L5a**	74 (64)	86 (*R*)
27		**L6a**	84 (76)	>99 (*R*)
28		**L6e**	64 (59)	>99 (*R*)
29		**L6h**	80 (72)	97 (*S*)
30	 **S22**	**L4a**	98 (93)	93 (*S*)
31		**L5a**	86 (81)	84 (*S*)
32		**L6a**	49 (42)	>99 (*S*)
33		**L6e**	30 (17)	>99 (*S*)
34		**L6h**	43 (39)	95 (*R*)

[a] 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%), at room temperature, 3 h. [b] Conversion measured by ^{1}H-NMR. Isolated yields are shown in parenthesis. [c] Enantiomeric excess was determined by chiral HPLC. [d] Enantiomeric excess was determined by chiral GC. [e] This reaction was also carried out at 0.1 mol scale, affording the reduced product in almost enantiopure form (99% ee) in 98% yield.

For pyridine-based substrates, we found that the reduction of 4-acetylpyridine **S16** (Table 4, entries 1-5) follows the same trend as for aryl/alkyl ketones **S1**-**S12**. Thus, full conversions and excellent enantioselectivities (in the best cases, ees of >99%

were achieved) were obtained with ligand **L4a**,**g** (Table 4, entries 1 and 3). On the other hand, the ATH of 3-acetylpyridine **S17** and 3-propionylpyridine **S18** behaves slightly differently regarding the ligand backbone (Table 4, entries 6-14). Excellent enantioselectivities are therefore achieved using ligands **L4**-**L6a**,**g** regardless of the ligand backbone (ee's up to 99%; Table 4, entries 6, 9, 10, 11, 13 and 14). As observed for acetophenone, the use of the more sterically demanding pyranoside ligand backbone **L6** led to low activity. The results achieved in the reduction of 2-acetylpyridine **S19** indicated that the thioamide substituent had a different effect on enantioselectivity than **S16**-**S18**. Enantioselectivity was therefore best with ligand **L4e**, with a methyl thioamide substituent (ee's up to 86%; Table 4, entry 17). Similarly, the effect on enantioselectivity of the thioamide substituent is also different in the reduction of 2-acetylfuran **S20**. Enantioselectivity was therefore best using ligand **L4c**, containing a phenyl thioamide substituent (entry 22). Finally, for acetylthiophenes **S21**-**S22**, enantioselectivities were excellent with ligands **L6** regardless of the nature of the thioamide substituent (Table 4, entries 27-29 and 32-34). These excellent results again showed that the presence of a pyranoside backbone in the ligand design of these thioamide ligands is highly advantageous. Our new Rh/pyranoside-based thioamide systems can therefore expand the scope to a broad range of heteroaromatic ketones. Again, the modular ligand design has been shown to be crucial in finding highly selective catalytic systems for each substrate.

Conclusions

A large library of pyranoside-based hydroxyamide and thioamide ligands **L1**-**L6a**-**h** has been synthesized for ATH in an attempt to expand the scope of the substrates to cover a broader range of challenging heteroaromatic and aryl/fluoroalkyl ketones. These ligands have the advantage that they are prepared from commercial D-glucose, D-glucosamine and α-amino acids, inexpensive natural chiral feedstocks. Moreover, the modular nature of the ligand library enables the substituents/configurations at the amide/thioamide moiety, the position of amide/thioamide group and the configuration at C-2 of the pyranoside backbone to be easily and systematically varied, so activities and enantioselectivities can be maximized for each substrate as required. By carefully selecting the ligand components, we found that pyranoside-based thioamide ligands provided excellent enantioselectivities (in the best cases, ees of >99% were achieved) in a broad range of ketones, including the less studied heteroaromatics and challenging aryl/fluoroalkyls. Note that both enantiomers of the reduction products can be obtained with excellent enantioselectivities by simply changing the absolute configuration of the thioamide substituent. In addition, the efficiency of this ligand design is also corroborated by the fact that these Rh-pyranoside-based thioamide catalysts provided higher activity and enantioselectivity and a broader substrate scope than their furanoside-based thioamide analogues. The results of our pyranoside-based thioamide catalyst library compare very well with the ones achieved using the furanoside-based thioamide and hydroxyamide ligands which have recently emerged as some of the most successful catalysts developed for this process, with the added advantage that our Rh/pyranoside-thioamide systems are able to expand the scope to a broad range of heteroaromatic substrates and to the successful reduction of aryl/fluoroalkyl ketones. These findings represent an improvement on the previously reported furanoside-derived hydroxyamide and thioamide ligands and open up a new type of ligand for the highly enantioselective reduction of industrially relevant heteroaromatic and aryl/fluoroalkyl ketones.

Experimental Section

General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Compound **2** was prepared as previously described.[15] ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts were relative to $SiMe_4$ as internal standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments.

Typical procedure for the preparation of hydroxyamide ligands L1-L3a-h

To a cooled solution (-15 °C) of the desired N-Boc-protected amino acid (2 mmol) in THF (4 mL), *N*-methylmorpholine (NMM, 2.3 mmol, 252 μL) and isobutylchloroformate (2.3 mmol, 300 μL) were slowly added. After 45 minutes, a solution of the desired aminoalcohol (2 mmol, 379.4 mg), previously azeotropically dried with toluene, in THF (4 mL) was added and the resulting mixture was stirred at room temperature for 2 h. The crude mixture was purified by flash chromatography to produce the corresponding ligands as white solids.

Typical procedure for the benzoylation of L1-L3a-h

A solution of benzoyl chloride (1.1 mmol, 130 μL) in dichloromethane (0.4 mL) was slowly added to a cooled solution (0 °C) of the desired pseudo-dipeptide (1 mmol) in pyridine (1 mL). The reaction was stirred overnight. Then ice was added and the product was extracted with dichloromethane (3 x 20 mL), dried over $MgSO_4$, evaporated to dryness and purified by flash chromatography (pentane/ethyl acetate: 2/1) to produce the corresponding benzoylated product as white solids.

Typical procedure for the preparation of thioamide ligands L4-L6a-h

To a cooled solution of the desired benzoylated product (0.5 mmol) in THF (2 mL) Lawesson's reagent (0.4 mmol, 158 mg) was added. The reaction was stirred overnight at 60 °C. Then, the reaction mixture was evaporated and chromatographed (pentane/ethyl acetate: 3/1) to produce the corresponding thioamides as white solids.

Typical procedure for the ATH of ketones

The desired ligand (0.0055 mmol), catalyst precursor ($[RuCl_2(p\text{-cymene})]_2$ or $[RhCl_2Cp^*]_2$) (0.0025 mmol), and LiCl (4.2 mg, 0.1 mmol) were treated under vacuum for 10 min. Under argon, substrate (1 mmol), propan-2-ol (2 mL) and THF (2.5 mmol) were sequentially added. The reaction was initiated by adding ^{i}PrONa (0.1M, 0.5 mL, 0.05 mmol) to the solution. After completion of the reaction the reaction mixture was evaporated and the product was purified by column chromatography (SiO_2). For substrates **S1**-**S12**,[9b,9d,9k] **S14** and **S15**,[14] the alcohol products were analyzed by GC (CP Chirasil DEX CB). For substrate **S16,** the alcohol products were analyzed by GC (Chiraldex β-DM).[6d] For substrates **S13**[23] and **S19**[6d], conversions were measured by ^{1}H-NMR and enantioselectivity by HPLC (Chiralcel OD-H). For substrates **S17**-**S18** and **S20**-**S22**, conversions were measured by ^{1}H-NMR and enantioselectivity by HPLC (Chiralcel OJ-H).[6d]

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