DOI: 10.1002/adsc.201600903

Advanced Synthesis & Catalysis

Third-Generation Amino Acid Furanoside-Based Ligands from D-Mannose for the Asymmetric Transfer Hydrogenation of Ketones: Catalysts with an Exceptionally Wide Substrate Scope

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Received: August 13, 2016; Revised: September 15, 2016; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600903.

Abstract: A modular ligand library of α-amino acid hydroxyamides and thioamides was prepared from 10 different N-*tert*-butyloxycarbonyl-protected α-amino acids and three different amino alcohols derived from 2,3-*O*-isopropylidene-α-D-mannofuranoside. The ligand library was evaluated in the half-sandwich ruthenium- and rhodium-catalyzed asymmetric transfer hydrogenation of a wide array of ketone substrates, including simple as well as sterically demanding aryl alkyl ketones, aryl fluoroalkyl ketones, heteroaromatic alkyl ketones, aliphatic, conjugated and propargylic ketones. Under the optimized reaction conditions, secondary alcohols were obtained in high yields and in enantioselectivities up to >99%. The choice of ligand/catalyst allowed for the generation of both enantiomers of the secondary alcohols, where the ruthenium-hydroxyamide and the rhodium-thioamide catalysts act complementarily towards each other. The catalytic systems were also evaluated in the tandem isomerization/asymmetric transfer hydrogenation of racemic allylic alcohols to yield enantiomerically enriched saturated secondary alcohols in up to 98% *ee*. Furthermore, the catalytic tandem α-alkylation/asymmetric transfer hydrogenation of acetophenones and 3-acetylpyridine with primary alcohols as alkylating and reducing agents was studied. Secondary alcohols containing an elongated alkyl chain were obtained in up to 92% *ee*.

Keywords: asymmetric transfer hydrogenation; hydroxyamide ligands; rhodium; ruthenium; sugar-based ligands; tandem reactions; thioamide ligands

Introduction

Optically pure secondary alcohols are useful intermediates in the synthesis of biologically active compounds and therapeutic drugs.[1] From an industrial and academic point of view, the preparation of optically pure secondary alcohols by asymmetric transfer hydrogenation (ATH) of ketones is an important alternative to other methodologies that use hazardous molecular hydrogen, or moisture-sensitive pyrophoric hydride reagents.[2] Among all the catalysts developed, those using transition metals, such as Ru,[3] Rh,[4] and Ir[4a–c,5] have dominated the scene. More recently Os[6] and Fe[7] based catalysts have also given promising results, but their scope is still limited compared to that of Ru and Rh catalysts. The first important breakthrough in ATH was reported in the mid 1990s when Noyori and co-workers introduced a new class of bifunctional ATH catalysts, Ru-arene complexes modified with chiral monosulfonated diamines or β-amino alcohols, which were able to efficiently reduce ketones and ketimines.[2f,i,3a,b] This discovery paved the way for the development of a large plethora of Noyori-type ligands that not only considerably expanded the substrate scope but also increased the stability of the catalysts and hence the turnover numbers (TON).[8] All those catalytic systems relied on a basic N–H ligand moiety to control an efficient proton and hydride transfer from the catalyst to the prochiral substrate. Later, several alternative ligands were developed that did not possess such an N–H moiety, for example, the Ru diphosphonite and Ru

pyrazolyl-pyridyl-oxazolinyl catalysts developed by the research groups of Reetz[9] and Yu,[10] respectively. These catalysts were successfully applied in the ATH of a limited range of aryl alkyl and alkyl alkyl ketones. Adolfsson's group also reported on another relevant type of ligands without the basic NH group. These ligands were based on the simple combination of readily available N-Boc-protected α-amino acids and β-amino alcohols (for hydroxyamide ligands **1**) or on thioamides (for thioamide ligands **2**). These highly modular amino acid-derived hydroxyamides and thioamides ligands (Figure 1) in combination with Ru or

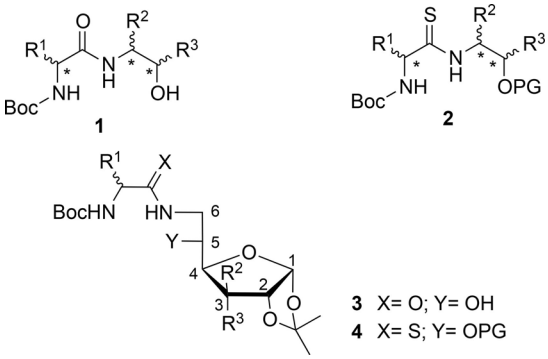


Figure 1. General structure of hydroxyamide ligands **1**, thioamide ligands **2** and sugar-based hydroxyamide **3** and thioamide ligands **4**.

Rh half-sandwich complexes displayed high enantioselectivity in the ATH of a broad range of aryl alkyl ketones.[11] Despite all these important contributions, most successful catalysts developed afforded the desired products in a range 95–99% *ee* but have not provided secondary alcohols in enantiopure form (>99% *ee*) for a wide range of substrates as compared to protocols based on enzymes. To overcome this limitation, in 2011 we developed a new series of hydroxyamide ligands **3** (Figure 1) in which the β-amino alcohol in **1** was replaced by a readily available sugar β-amino alcohol moiety.[12] The introduction of a furanoside amino sugar moiety represented an important breakthrough. Ru catalysts modified with carbohydrate hydroxyamide ligands **3** (Figure 1) efficiently catalyzed the reduction of a wide range of aryl alkyl ketones (typically 99% *ee*), surpassing the enantioselectivities obtained with previous successful hydroxyamide ligands **1**. However the modified catalytic systems were not able to reduce industrially relevant heteroaromatic ketones and, additionally, only one of the product enantiomers was accessible. 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]

Despite all the important advances made by the development of the first and second generation catalytic systems based on furanoside ligands, further improvements in terms of increased substrate scope, better selectivity, and higher turnover frequency are still required to make the process competitive towards conventional hydrogenations. For instance, the ATH of substrates such as trifluoromethyl-containing ketones, aryl alkyl ketones containing bulky substituents, propargylic ketones and alkyl alkyl ketones, still needs to be further optimized. With this aim, we set out to design new hydroxyamide (**L1**–**L3a**–**j**) and thioamide (**L4**–**L6a**–**j**) ligand libraries, derived from readily available D-(+)-mannose. This was accomplished by introducing several systematic variations in the furanoside-based ligands **3** and **4**, namely by varying the configuration of C-2 of the furanoside backbone and by varying the position of the acetal protecting group (Figure 2). These novel ligand libraries also allowed us to study the effect of coupling the amide/thioamide either at C-6 (ligands **L1** and **L4**) or at C-5 (ligands **L2** and **L5**), the effect of the configuration of C-5 (ligands **L2** and **L5** *vs.* **L3** and **L6**, respectively) and the effect of the substituent/configuration of the amide/thioamide moiety (**a**–**j**). The simple modifications of the ligand structure expand the substrate versatility in the ATH and the catalytic system was shown to be highly efficient. In addition, we have applied these new Ru/Rh catalysts in the simple tandem isomerization/ATH of readily available allylic alcohols and the tandem α-alkylation/ATH to produce chiral alcohols with an elongation of the alkyl chain.

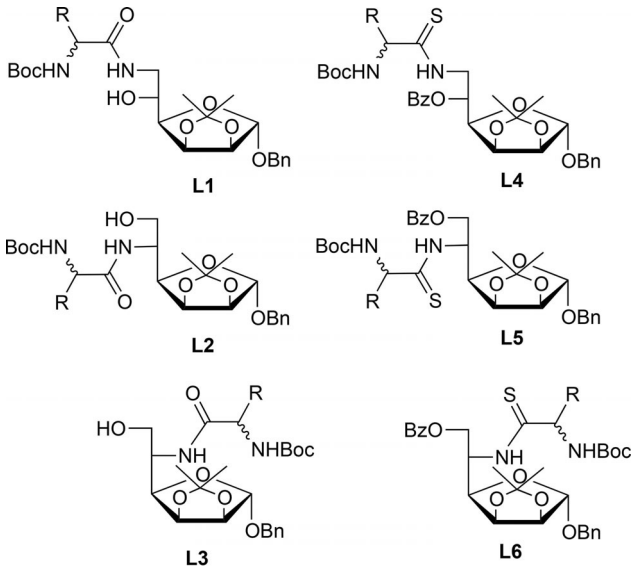


Figure 2. Hydroxyamide and thioamide ligands **L1**–**L6a**–**j**.

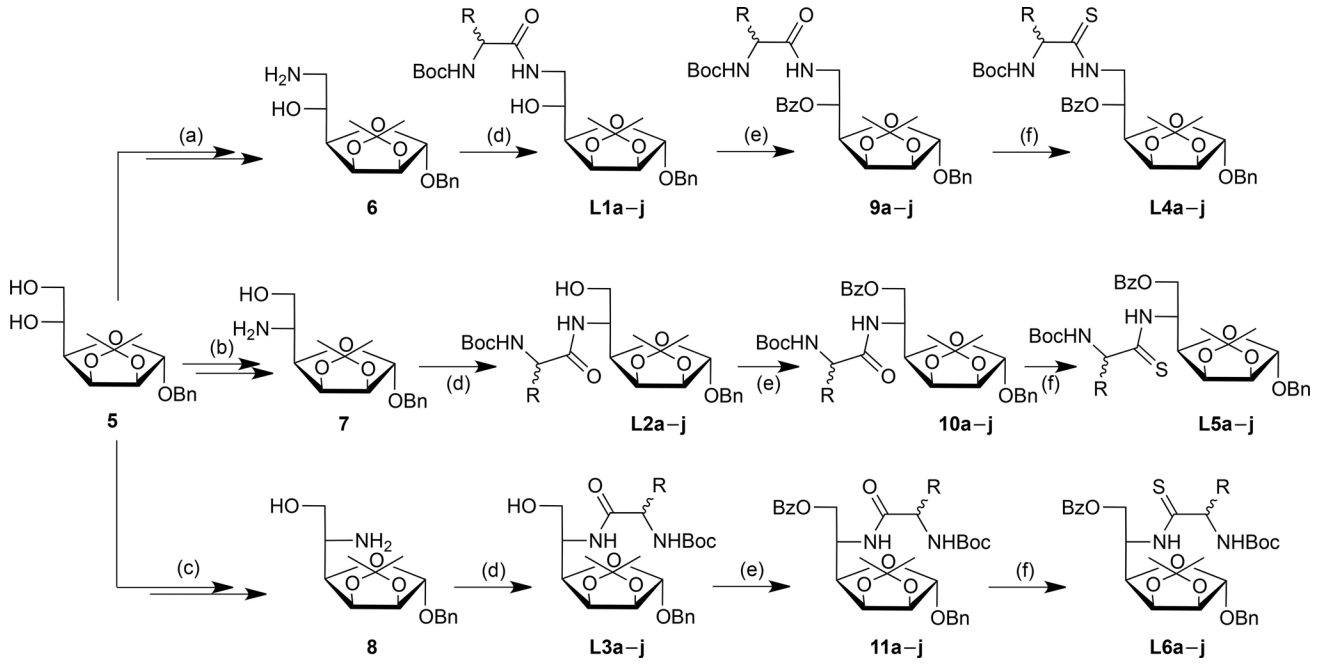
Results and Discussion

Synthesis of Ligands

A library of potential 30 hydroxyamide **L1–L3a–j** and 30 thioamide **L4–L6a–j** ligands was prepared as outlined in Scheme 1 using a combination of ten amino acids (i.e., L-Val, L-*t*-Leu, L-Leu, L-Phe, L-phenyl-Gly, L-Ala, Gly, D-Val, D-phenyl-Gly and D-Ala) and 3 amino alcohols (**6–8**). The diversity in the sugar backbone was achieved from benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside **5**, which was easily prepared on a multigram scale from readily available D-mannose.[14] Taking advantage of the different reactivity of the hydroxy groups attached to C-5 and C-6 in **5**, we prepared key amino-alcohol intermediates **6–8** that made it possible to study the catalytic efficiency depending on the substitution pattern of the amide/thioamide functionality (either C-6 in compound **6** or C-5 in compound **7**), as well as the effect of the configuration at C-5 (compound **7** *vs.* **8**).

Hydroxyamide ligands **L1–L3a–j** were prepared in a straightforward one-step procedure by coupling the corresponding commercially available *N*-Boc-protected amino acid derivatives with the desired amino alcohol **6–8**, using isobutyl chloroformate as coupling reagent. These ligands were obtained in good yields (see Experimental Section) after purification on neutral silica gel as white solids. In this step the desired diversity in the substituents and configuration of the amino acid part (**a–j**) was also achieved. Thioamide ligands **L4–L6a–j** were prepared from hydoxyamides **L1–L3** following a two-step procedure, benzoylation of the free hydroxy group in compounds **L1–L3** [step (e)], and subsequent treatment of intermediates **9–11** with Lawesson's reagent gave access to thioamide ligands [step (f)]. It should be pointed out that, in agreement with earlier observations,[11m] we could not obtain the desired thioamides when *tert*-butyl groups were present in the α-amino acid moiety. The thioamide ligands **L4–L6a–j** were isolated as white solids.

All ligands were characterized by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, mass spectrometry and elemental analysis. All data were in agreement with the assigned structures. The spectral assignments were supported by the information obtained from ^{1}H-^{1}H, and ^{1}H-^{13}C correlation measurements. The expected ^{1}H and ^{13}C patterns for the furanoside backbone (positions 1–6) and for the protecting groups were observed (see the Experimental Section). The vicinal ^{1}H-^{1}H couplings in the sugar ring were in the normal range (0–7 Hz). As expected, the anomeric proton appears as one singlet in all cases. For ligands **L1** and **L4**, with the amide/thioamide groups at C-6, the diastereotopic protons (H-6) appeared as a multiplet due to extra coupling with NH, whereas for ligands **L2** and **L3** and **L5** and **L6**, with the amide/thioamide at C-5, the H-6 diastereotopic protons appeared as a doublet of doublets. The expected signals for the different amide/thioamide groups were also observed.



Scheme 1. Synthesis of hydroxyamide and thioamide ligands **L1–L6a–j**. (a–c) See Supporting Information for details. (d) *N*-Boc-protected α-amino acid/*i*-BuOCOCl/NMM/THF/−15 °C. (e) BzCl/NEt_3/DMAP/CH_2Cl_2/0 °C to room temperature. (f) Lawesson's reagent/THF/60 °C.

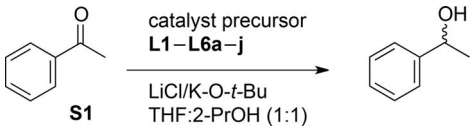
Asymmetric Transfer Hydrogenation of Acetophenone

In a first set of experiments, acetophenone **S1** was used as the benchmark substrate to study the effectiveness of catalysts containing the new ligands. For comparison purposes, we evaluated them using the optimal reaction conditions found in previous studies with hydroxyamide/thioamide ligands.[11] In these previous studies it has been found that the optimal combination of catalysts has been achieved using Ru hydroxyamide and Rh thioamide catalysts precursors. Reactions were therefore performed at room temperature, using 0.5 mol% of *in-situ* generated catalyst $[RuCl_2(p\text{-cymene})]_2$ for ligands **L1–L3** and $[RhCl_2Cp^*]_2$ for ligands **L4–L6**] in the presence of KO-*t*-Bu as base. The results are collected in Table 1. The catalytic performance was found to be highly dependent on the position of the α-amino acid/thioamide moieties at either C-5 or C-6 of the sugar backbone and also dependent on the configuration at C-5. This dependence was different for the hydroxyamide ligands compared to the thioamide ligands. Changing the amino acid substituents in the hydroxyamide ligands did not affect the enantioselectivity of the formed product, however, these substituents did have an important effect using the corresponding thioamide ligands. By the appropriate choice of ligands (hydroxyamide **L1a** and thioamides **L5a** and **L6h**) we obtained both enantiomers of the secondary alcohol in excellent enantioselectivities (*ee* up to >99%) and yields, comparable to the best results reported.

Hydroxyamide ligands **L1a-f** provided excellent enantioselectivities, ranging from 95% to >99% *ee*, regardless of the electronic and steric properties of the *S*-amino acid moieties (Table 1, entries 1–6). The best trade-off between activity and enantioselectivity was achieved with ligand **L1a** (entry 1). Note also that the use of ligand **L1g**, with an achiral Gly α-amino acid moiety, also provided high enantioselectivities (up to 95% *ee*; Table 1, entry 7). This indicates that, contrary to other Ru hydroxyamide catalysts described in the literature, enantioselectivity is mainly controlled by the sugar backbone rather than by the α-amino acid moiety. Hence, inexpensive achiral α-amino acid derivatives can be used as long as the sugar backbone is selected properly. Finally, hydroxyamide ligands **L1h–j** with *R*-amino acid moieties were found to be a mismatched combination providing low catalytic activities and enantioselectivities (Table 1, entries 8–10).

The use of hydroxyamide ligands **L2**, with the α-amino acid moiety in C-5 instead of in C-6 (ligands **L1**) also provided high enantiomeric excesses, albeit with very low conversions (Table 1, entries 11 and 12 *vs.* 1 and 6). Previous mechanistic studies with successful Ru hydroxyamide catalysts showed that hydroxyamide ligands coordinate to the metal in a tridentate manner, through both nitrogens and the oxygen atom.[11h] The lower activity with ligands **L2** can be attributed to the higher rigidity of these ligands, which hinders the coordination to the metal center in contrast to the less steric environment generated by ligand **L1**. Note that for ligands **L1**, the amido group is attached to the flexible primary C-6.

Table 1. Asymmetric transfer hydrogenation reaction of **S1** using ligands **L1–L6a–j**.[a]



Entry	Ligand	Conv.[%] (Time [h])[b]	*ee* [%][b]
1	**L1a**	100 (3)	>99 (*S*)
2	**L1b**	56 (3)	95 (*S*)
3	**L1c**	86 (3)	99 (*S*)
4	**L1d**	54 (3)	98 (*S*)
5	**L1e**	84 (3)	98 (*S*)
6	**L1f**	87 (3)	99 (*S*)
7	**L1g**	95 (3)	95 (*S*)
8	**L1h**	10 (3)	4 (*S*)
9	**L1i**	11 (3)	8 (S)
10	**L1j**	9 (3)	4 (*S*)
11	**L2a**	4 (3)	99 (*S*)
12	**L2f**	6 (3)	99 (*S*)
13	**L3a**	27 (3)	80 (*S*)
14	**L3f**	68 (3)	85 (*S*)
15	**L3h**	29 (3)	72 (*R*)
16	**L3j**	26 (3)	40 (*R*)
17	**L4a**	87 (3)	87 (*R*)
18	**L4c**	68 (3)	82 (*R*)
19	**L4d**	90 (3)	80 (*R*)
20	**L4e**	83 (3)	62 (*R*)
21	**L4f**	91 (3)	62 (*R*)
22	**L4g**	74 (3)	2 (*R*)
23	**L4h**	79 (3)	79 (*S*)
24	**L4i**	62 (3)	52 (*S*)
25	**L4j**	65 (3)	77 (*S*)
26	**L5a**	93 (3)	98 (*R*)
27	**L5f**	96 (3)	50 (*R*)
28	**L6a**	80 (3)	88 (*R*)
29	**L6h**	90 (3)	98 (*S*)
30[c]	**L1a**	35 (3)	99 (*S*)
31[d]	**L1a**	30 (3)	>99 (*S*)
32[e]	**L1a**	99 (3)	>99 (*S*)

[a] *Reaction conditions:* **S1** (1 equiv., 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (for ligands **L1–L3**, 0.25 mol%) or $[RhCl_2Cp^*]_2$ (for ligands **L4–L6**, 0.25 mol%), ligand (0.55 mol%), KO-*t*-Bu (5 mol%), LiCl (10 mol%) and at room temperature.
[b] Conversion and enantiomeric excess were determined by GC (CP Chirasil DEX CB).
[c] Reaction carried out in EtOH/THF (1/1).
[d] Reaction carried out in EtOH/MeTHF (1/1).
[e] Reaction carried out in 2-PrOH/MeTHF (1/1).

The use of ligands **L3**, with an opposite configuration at C-5 than in **L2**, provided somewhat higher activities than **L2**, but lower enantioselectivities (entries 13–16).

As mentioned above, the Rh thioamide catalytic systems followed a different trend than the Ru hydroxyamide catalysts. With ligands **L4a–j**, enantioselectivity was affected by the type of thioamide (Table 1, entries 17–25). Enantioselectivities increased with more sterically hindered substituents (i.e., *i*-Pr > *i*-Bu > Bn > Ph ≈ Me). Moreover, in contrast to hydroxyamide ligands, the configuration of the thioamide controlled the sense of enantioselectivity, with a cooperative effect between the configuration of the thioamide and the sugar backbone that resulted in a matched combination for the Rh-**L4a** catalytic system (entry 17). Advantageously, we also found that moving the thioamide group from C-6 to C-5 (ligands **L5**) increased enantioselectivities from 87% to 98% (Table 1, entry 26 *vs.* 17). Comparing the results using ligands **L5** and **L6**, a cooperative effect can be observed between the configuration of C-5 of the furanoside backbone and the configuration of the thioamide substituent, which results in a matched combination with ligands **L5a** and **L6h**, containing *S*- and *R*-thioamide isopropyl groups, respectively (entries 26 and 29). This behavior is highly advantageous because it allows both enantiomers to be obtained in high enantioselectivities, which were not possible using Ru-**L1** catalysts.

Finally, we studied the use of environmentally friendly solvents, such as ethanol and MeTHF. We were pleased to see that the process can also be carried out in these solvent mixtures with no loss of enantioselectivity (Table 1, entries 30–32).

Substrate Scope

To establish the versatility of the reaction with the new ligand families, we evaluated a series of substrates with the optimized catalytic systems. We initially considered the ATH of a broad range of aryl ketones. Table 2 shows the results using catalysts Ru-**L1a** and Rh-**L5a** that, together with Rh-**L6h**, provided the best results in the asymmetric transfer hydrogenation of **S1** (full set of results in Table SI.1 in the Supporting Information). Again, both enantiomers of the resulting products were accessible in high enantiomeric excess.

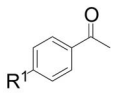
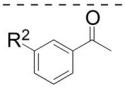
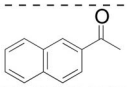
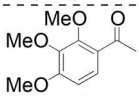
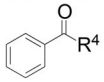
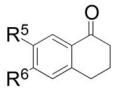
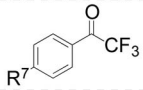
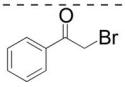
We noted that Ru-**L1a** and Rh-**L5a** catalytic systems easily tolerate variations of the electronic properties of the substituents in the aryl moiety of the substrate. A broad range of aryl ketones (17 of them, Table 2, entries 1–17) with electron-withdrawing or electron-donating substituents were reduced in high yields and with excellent enantioselectivities, comparable to those achieved with substrate **S1**. Among the excellent results it should be noted that the electron-rich ketones (**S7** and **S18**), and the *ortho*-substituted aryl ketones (**S12–S16**) in general proceeded with significantly lower activities and yields.

We next considered the asymmetric transfer hydrogenation of aryl ketones bearing increasingly sterically demanding alkyl substituents (Table 2, entries 18–23). Despite its relevance, few successful examples can be found in the literature and they are limited in substrate scope. One of these examples reported by Feringa and co-workers, showed that **S22** and **S23** could be efficiently reduced using mild reaction conditions.[15] They needed, however, to synthesize and isolate the precatalyst prior to use. More recently Slagbrand et al. have disclosed that the combination of earlier *in-situ* formed Ru/amino acid hydroxyamide catalysts together with the appropriate choice of reaction conditions could efficiently reduce a small selection of these challenging substrates.[16] The results with Ru-**L1a** and Rh-**L5a** indicate that enantioselectivities are again quite unaffected by the nature of the alkyl substituent, with *ee*s typically above 97%. We could therefore reach high yields and *ee*s up to > 99% in the reduction of a broad range of these challenging substrates. Even more remarkable is the high catalytic performance of the reduction of substrates **S19–S21** and **S24** using standard (milder) reaction conditions. Moreover, this represents the first successful application of readily available Rh/thioamide catalysts in the reduction of such substrates, which allows for the formation of both enantiomers of the secondary alcohols in high enantioselectivities by simply changing the catalyst precursor.

Ru-**L1a** and Rh-**L5a** catalytic systems also proved to be highly efficient in the reduction of benzo-fused cyclic ketones such as α-tetralones (**S25–S27**), indanone **S28** and chromanone **S29** (Table 2, entries 24–28). In all cases excellent enantiocontrol was achieved. The effective reduction of these substrates is important because the resulting products are often intermediates in the synthesis of biologically active products.

Furthermore, we investigated the asymmetric transfer hydrogenation of aryl/fluoroalkyl ketones **S30** and **S31** (Table 2, entries 29 and 30).[17] The formation of optically active α-trifluoromethyl alcohols has attracted the attention of many researchers because they are intermediates in the improvement of medicines, agrochemicals and other materials owing to the unique properties of the fluorine atom.[18] The preparation of chiral α-trifluoromethyl alcohols relies mainly on the use of asymmetric hydrogenation and hydroboration, or using biocatalysts.[19] The asymmetric transfer hydrogenation of these challenging substrates will open up a new straightforward and sustainable route for preparing α-trifluoromethyl alcohols. So far, only

Table 2. Asymmetric transfer hydrogenation of aryl ketones **S2**–**S32**.[a]

Entry	Substrate		Ru-**L1a**		Rh-**L5a**	
			Conv. [%] (Yield [%])[b]	*ee* [%][c]	Conv. [%] (Yield [%])[b]	ee [%][c]
1		**S2** $R^1 = NO_2$	100 (94)	99 (*S*)	100 (92)	98 (*R*)
2		**S3** $R^1 = CF_3$	99 (92)	98 (*S*)	100 (93)	98 (*R*)
3		**S4** R^1 = Br	97 (90)	99 (*S*)	100 (90)	97 (*R*)
4		**S5** R^1 = F	100 (93)	98 (*S*)	100 (93)	97 (*R*)
5		**S6** R^1 = Me	100 (95)	96 (*S*)	100 (93)	98 (*R*)
6		**S7** R^1 = OMe	62 (55)	98 (*S*)	57 (49)	97 (*R*)
7		**S8** $R^2 = CF_3$	82 (76)	98 (*S*)	92 (84)	99 (*R*)
8		**S9** R^2 = Br	98 (91)	>99 (*S*)	100 (94)	99 (*R*)
9		**S10** R^2 = Me	80 (75)	99 (*S*)	100 (89)	98 (*R*)
10		**S11** R^2 = OMe	90 (82)	99 (*S*)	95 (84)	99 (*R*)
11		**S12** $R^3 = CF_3$	50 (46)	98 (*S*)	62 (55)	99 (*R*)
12		**S13** R^3 = Br	84 (80)	98 (*S*)	100 (92)	98 (*R*)
13		**S14** R^3 = F	99 (87)	97 (*S*)	100 (91)	98 (*R*)
14		**S15** R^3 = Me	71 (64)	98 (*S*)	84 (79)	98 (*R*)
15		**S16** R^3 = OMe	75 (69)	98 (*S*)	83 (71)	98 (*R*)
16		**S17**	75 (70)	98 (*S*)	94 (91)	98 (*R*)
17		**S18**	51(49)	>99 (*S*)	47 (43)	97 (*R*)
18		**S19** R^4 = Et	90 (84)	>99 (*S*)	98 (91)	98 (*R*)
19		**S20** $R^4 = CH_2CH_2Ph$	100 (86)	99 (*S*)	100 (83)	99 (*R*)
20		**S21** R^4 = *i*-Bu	44 (39)	97 (*S*)	76 (72)	97 (*R*)
21		**S22** R^4 = *i*-Pr	100 (92)[d]	90 (*S*)	51 (43)	93 (*R*)
22		**S23** R^4 = Cy	52 (47)[d]	99 (*S*)	40 (32)	>99 (*R*)
23		**S24** $R^4 = C_4H_7$	100 (93)	99 (*S*)	97 (92)	97 (*R*)
24		**S25** $R^5 = R^6$ = H	84 (78)	>99 (*S*)	52 (48)	>99 (*R*)
25		**S26** R^5 = H; R^6 = OMe	100 (84)	99 (*S*)	69 (53)	>99 (*R*)
26		**S27** R^5 = OMe; R^6 = H	92 (86)	>99 (*S*)	53 (45)	>99 (*R*)
27		**S28**	94 (81)	95 (*S*)	59 (50)	96 (*R*)
28		**S29**	79 (70)	>99 (*S*)	61 (58)	>99 (*R*)
29		**S30** R^7 = OMe	100 (91)	76 (*R*)	100 (90)	82 (*S*)
30		**S31** R^7 = H	100 (87)	74 (*R*)	100 (92)	81 (*S*)
31[e]		**S32**	100 (-)	>99 (*S*)	81 (-)	97 (*R*)

[a] *Reaction conditions:* ketone (1 equiv., 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) for ligand **L1a** or $[RhCl_2Cp^*]_2$ (0.25 mol%) for ligand **L5a**, ligand (0.55 mol%), KO-*t*-Bu (5 mol%), LiCl (10 mol%) and at room temperature for 3 h.

[b] Conversion measured by ^{1}H NMR. Isolated yield in parenthesis.

[c] Enantiomeric excess were determined by GC (CP Chirasil DEX CB) or HPLC.

[d] Reaction carried out at 40 °C for 18 h using THF/EtOH (1/3).

[e] The ATH of **S32** led to the corresponding epoxide.

a few reports have been published and with limited success.[20] We were pleased to see that Ru-**L1a** and Rh-**L5a** could also reduce these demanding fluoroalkyl ketones in high yields and high enantioselectivities, to produce both enantiomers of the resulting chiral products (Table 2, entries 29 and 30). These results represent a significant improvement in comparison to those obtained using the Ru/TSDPEN catalyst (38% *ee*), which is considered to be the state of the art in ATH reactions.[17]

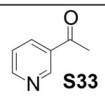
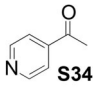
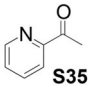
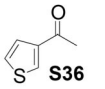
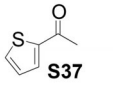
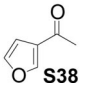
We finally turned our attention to the asymmetric transfer hydrogenation of α-halo ketone **S32**, which upon reduction results in the formation of styrene oxide (Table 2, entry 31). Among the existing methods for the preparation of chiral epoxides, the reduction of α-halo ketones is one of the most sustainable and most straightforward. The synthesis of chiral epoxides has received considerable attention, as they are valuable intermediates which can be stereoselectively opened by azides,[21] cyanide derivatives,[22] and amines,[23] to provide an easy access to aziridines and β- and γ-amino alcohols. Gratifyingly, Ru-**L1a** and Rh-**L5a** were successfully applied in the reduction of the α-halo ketone **S32** to form the corresponding epoxide in excellent enantioselectivities (Table 2, entry 31).

Heteroaromatic ketones are another relevant set of substrates that are receiving much consideration. The reduction of these substrates is an elegant route for producing chiral heteroaromatic alcohols that are found in biologically active compounds. The reduction of heteroaromatic ketones has been less investigated, since the coordination of the heteroaromatic group of the substrate to the metal often drastically reduces the activity of the catalyst. Hence, very few catalytic systems have provided high enantioselectivities in the reduction of heteroaromatic ketones under transfer hydrogenation conditions.[24] Table 3 shows that several types of heteroaromatic ketone (3- and 4-acetylpyridines, acetylfurans and acetylthiophenes) can be efficiently reduced with Ru-**L1a** and Rh-**L4a** to provide both enantiomers of the corresponding alcohols in high yields, and enantioselectivities up to >99% *ee* (Table 3, entries 1, 2 and 4–6). The reduction of 2-acetylpyridine **S35** proceeded also smoothly, albeit with lower levels of enantioselectivity (entry 3).

Ru/hydroxyamide **L1a** provided the best catalytic performance, which is in line with the previous substrate evaluation, however, in the case of the thioamide ligands in combination with rhodium, ligand **L4a** outperformed ligand **L5a** which was most efficient in the substrate screenings presented above (full set of results in Table SI.2 in the Supporting Information).

The excellent results achieved up to this point encouraged us to evaluate the reduction of alkyl alkyl, α,β-unsaturated and propargylic ketones (Table 4).

Table 3. Asymmetric transfer hydrogenation of heteroaromatic ketones **S33**–**S38**.[a]

		Ru-**L1a**		Rh-**L4a**	
Entry	Substrate	Yield [%][b]	*ee* [%][c]	Yield [%][b]	ee [%][c]
1	 **S33**	91	99 (*R*)	89	>99 (*S*)
2	 **S34**	89	98 (*S*)	90	99 (*R*)
3	 **S35**	87	51 (*R*)	84	46 (*S*)
4	 **S36**	92	>99 (*R*)	91	97 (*S*)
5	 **S37**	88	99 (*S*)	90	95 (*R*)
6	 **S38**	90	95 (*S*)	87	88 (*R*)

[a] *Reaction conditions:* ketone (1 equiv., 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) for ligand **L1a** or $[RhCl_2Cp^*]_2$ (0.25 mol%) for ligand **L4a**, ligand (0.55 mol%), KO-*t*-Bu (5 mol%), LiCl (10 mol%) and at room temperature for 3 h.

[b] Isolated yield. Full conversions were achieved in all cases.

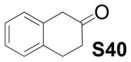
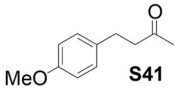
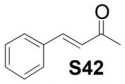
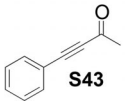
[c] Enantiomeric excess were determined by HPLC.

For these substrates only a limited number of catalytic systems have provided high yields and enantioselectivities.[2] The results for alkyl alkyl ketones **S39**–**S41** indicated that to achieve high enantioselectivities the steric demands between the two alkyl substituents must be very different (Table 4, entries 1–3). For instance, while enantioselectivities were only moderate for β-tetralone **S40**, the reduction of cyclohexyl methyl ketone **S39** proceeded with excellent *ee*s (up to 98%).

Ru-**L1a** and Rh-**L5a** were able to reduce the α,β-unsaturated ketone **S42** in high *ee*s (up to 95%; Table 4, entry 4). However, large amounts of 4-phenylbutan-2-one and 4-phenylbutan-2-ol were also isolated, which indicates that isomerization of the ATH product (4-phenylbut-3-en-2-ol) takes place under the reaction conditions.

Finally, the scope of this novel set of catalysts was expanded to the ATH of propargylic ketones. The stereoselective construction of propargylic alcohols is important because these alcohols are versatile building blocks widely used to synthesize biologically active compounds and structurally interesting molecules. As such, the enantioselective transfer hydrogenation is currently being studied as a more direct and atom-efficient method than the existing methods.

Table 4. Asymmetric transfer hydrogenation of alkyl/alkyl, α,β-unsaturated and propargylic ketones **S39**–**S43**.[a]

		Ru-**L1a**		Rh-**L5a**	
Entry	Substrate	Yield [%][b]	*ee* [%][c]	Yield [%][b]	*ee* [%][c]
1	 **S39**	85	98 (*S*)	85	96 (*R*)
2	 **S40**	91	59 (*S*)	88	61 (*R*)
3	 **S41**	93	50 (*S*)	90	48 (*R*)
4[d]	 **S42**	34	95 (*S*)	32	82 (*R*)
5[d]	 **S43**	89	96 (*S*)	90	87 (*R*)

[a] *Reaction conditions:* ketone (1 equiv., 0.2 M in 2-propanol/THF: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (0.25 mol%) for ligand **L1a** or $[RhCl_2Cp^*]_2$ (0.25 mol%) for ligand **L5a**, ligand (0.55 mol%), KO-*t*-Bu (5 mol%), LiCl (10 mol%) and at room temperature for 3 h.

[b] Isolated yield. Full conversions were achieved in all cases.

[c] Enantiomeric excess were determined by HPLC.

[d] Ketone (1 equiv., 0.2 M in 2-propanol/toluene: 1/1), $[RuCl_2(p\text{-cymene})]_2$ (1 mol%), ligand (2.2 mol%), KO-*t*-Bu (10 mol%), LiCl (10 mol%) and at room temperature for 10 min.

However, few successful examples have been reported so far.[25] Shatskiy et al. have recently reported the successful use of Ru/hydroxyamide type catalysts in this transformation under milder reactions conditions than the existing ATH protocols reported.[25d] Using the optimized reaction conditions presented by Shatskiy et al., we found that Ru-**L1a** and Rh-**L5a** provided high yields and enantioselectivities comparable to the best one reported in the literature (Table 4, entry 5). For the first time Rh/thioamide catalysts were employed in the reduction of this class of substrates, allowing for both enantiomers of this propargylic alcohol to be formed in high enantioselectivity.

Tandem Isomerization/ATH and α-Alkylation/ATH Reactions

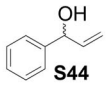
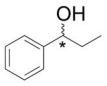
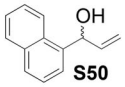
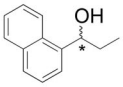
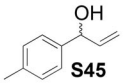
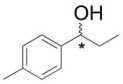
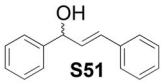
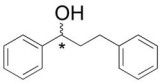
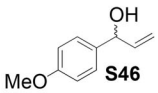
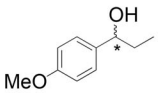
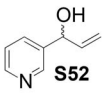
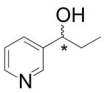
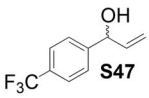
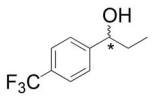
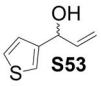
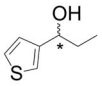
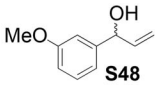
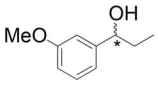
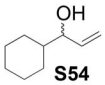
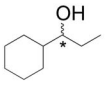
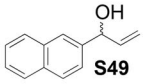
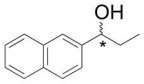
Tandem reactions offer cost-effective synthetic pathways with a reduced overall reaction time, reduced chemical waste and little energy consumption. Therefore, the search for a single catalyst able to promote two or more successive transformations in the same reaction medium has attracted the interest of many researchers. In this section we show that the Ru/Rh catalysts can be successfully used in two types of tandem reactions that involve ATH reactions.

The first reaction is the simple tandem isomerization/asymmetric transfer hydrogenation of allylic alcohols. Allylic alcohols are readily available natural feedstocks. This justifies their use as starting materials for the transformation into more valuable compounds.[26] The isomerization of allylic alcohols followed by enantioselective ketone reduction allows for the formation of chiral saturated alcohols in a straightforward manner. An alternative sustainable path to obtain these compounds is *via* direct hydrogenation, although this method often results in poor selectivity due to the allylic and benzylic nature of this type of substrate. To date only a very limited number of reports have been published on the asymmetric isomerization/transfer hydrogenation of allylic alcohols, and in these studies enantioselectivities between 11–98% *ee* were obtained.[27] Moreover, the results largely depend on the substrate and important differences in enantioselectivity were obtained by simple modifications in the electronic properties of α-vinylbenzyl alcohols. To be of practical interest, isomerization/ATH still requires substantial improvements in terms of enantioselectivity, chemical yield and substrate versatility. Table 5 shows the results of using Ru/**L1a** in the tandem isomerization/ATH of eleven allylic alcohols (**S44**–**S54**) under standard reaction conditions. In all cases only the desired alcohol was obtained. Neither the intermediate aryl alkyl ketone, nor the undesired alkylated ketones were detected. Improving previous published results, we found that Ru-**L1a** is quite tolerant to varying electronic and steric properties of the substrate phenyl ring (Table 5, entries 1–8). A broad range of allylic alcohols were therefore converted into the saturated products with excellent yields and high enantioselectivities (*ee*s ranging from 94% to 98%). Interestingly, we could also reach *ee*s (up to 97%) and high yields in the isomerization/reduction of secondary allylic alcohols containing heteroaromatic groups (Table 5, entries 9 and 10). In addition, in contrast to previously studied Ru hydroxyamide catalytic systems,[28] the Ru-**L1a** catalyst is also able to efficiently perform the isomerization/reduction of alkyl allylic alcohols, such as **S54** (Table 5, entry 11).

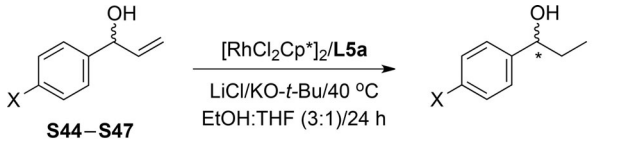
We also evaluated the efficiency of the Rh-thioamide catalytic systems in this transformation, and gratifyingly found that Rh-**L5a** can be used in the tandem isomerization/ATH of allylic alcohols, affording the desired chiral saturated alcohols in good yields and enantioselectivities (Scheme 2).

Using this catalyst we are able to easily obtain the other enantiomer of the alcohol product. These results open up the potential application of a large plethora of Rh-thioamide catalysts for this important tandem transformation.

Table 5. Tandem isomerization/ATH reactions of allylic alcohols using Ru-**L1a**.[a]

Entry	Substrate	Product	Conv. [%] (Yield [%])[b]	*ee* [%][c]	Entry	Substrate	Product	Conv. [%] (Yield [%])[b]	*ee* [%][c]
1	 **S44**		100 (91)	96 (*S*)	7	 **S50**		100 (90)	96 (*S*)
2	 **S45**		100 (92)	95 (*S*)	8	 **S51**		100 (87)	98 (*S*)
3	 **S46**		100 (89)	94 (*S*)	9	 **S52**		100 (88)	97 (*S*)
4	 **S47**		98 (90)	95 (*S*)	10	 **S53**		96 (87)	86 (*S*)
5	 **S48**		100 (93)	95 (*S*)	11	 **S54**		100 (91)	92 (*S*)
6	 **S49**		100 (88)	95 (*S*)					

[a] *Reaction conditions:* ketone (1 equiv., 0.5 M in ethanol/THF: 3/1), $[RuCl_2(p\text{-cymene})]_2$ (1 mol%), **L1a** (1.1 mol%), KO-*t*-Bu (30 mol%), LiCl (10 mol%) and at 40 °C for 24 h.
[b] Conversion measured by ^{1}H NMR. Isolated yield in parenthesis.
[c] Enantiomeric excess were determined by GC or HPLC.

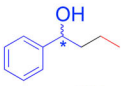
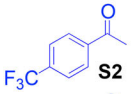
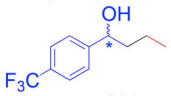
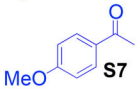
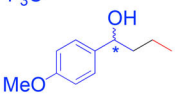
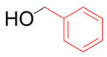
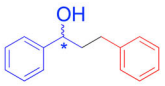
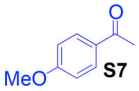
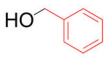
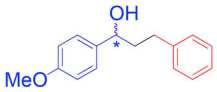
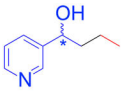
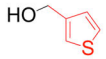
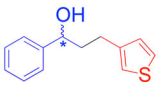


Substrate	X	% Conv. (% yield)	%ee
S44	H	100 (80)	93 (*R*)
S45	Me	100 (83)	94 (*R*)
S46	OMe	100 (84)	93 (*R*)
S47	CF_3	100 (88)	92 (*R*)

Scheme 2. Tandem isomerization/ATH reactions of allylic alcohols using Rh-**L5a**.

The second tandem reaction studied is the α-alkylation/asymmetric transfer hydrogenation of acetophenones with primary alcohols to produce chiral alcohols with an elongation of the alkyl chain. This is an environmentally friendly catalytic reaction that forms water as the only by-product. Despite its importance, only two reports exist with limited substrate scope.[29] The one reported by Uemura et al. showed the α-alkylation/asymmetric transfer hydrogenation of substituted acetophenones with good-to-excellent enantioselectivities (88–98%) and moderate-to-high yields (50–80%).[29a] However, drastic reaction conditions and two different catalysts were required. The other recently report by Kovalenko et al. showed that one single catalyst can mediate the α-alkylation/ATH process with moderate-to-good enantioselectivities (57–89%) under milder reaction conditions than the Uemura systems. Unfortunately, the yields were low-to-moderate (15–40%) due to the fact that high amounts of the acetophenones were reduced under reaction conditions and also because intermediate alkylated ketones were present.[29b] Although fewer substrates were alkylated/reduced than with the Uemura's systems, the transformation took place with a single catalyst, which is advantageous for a sustainable industrial process. Table 6 shows the results using Ru/**L1a** in the tandem α-alkylation/ATH of acetophenones. In all cases conversion was complete, but as previously observed,[29b] the yields of the desired products were moderate, which are in line with what is expected for enolate condensation reactions. The enantioselectivities were highly affected by the electronic nature of the acetophenone and substrates with electron-rich aryl substituents gave the best *ee* (Table 6, entries 3 *vs.* 1 and 2). We were pleased to see that we could also use benzyl alcohol as alkylating reagent, with enantioselectivity up to 86% *ee* in the desired product (Table 6, entries 4 and 5). In addition, we accomplished for the first time the tandem α-alkylation/ATH of heteroaromatic ketones (Table 6, entry 6) and also using functionalized heteroaromatic primary alcohols as coupling partners (Table 6, entry 7). The latter results greatly increase the synthetic value of this methodology because it allows for the introduction of heteroaromatic moieties in two different posi-

Table 6. Tandem α-alkylation/asymmetric reactions of arylketones using Ru-**L1a**.[a]

Entry	Substrate	Alcohol	Product	Conv. [%] (Yield [%])[b]	*ee* [%][c]
1				100 (41)	84 (*S*)
2				100 28)	70 (*S*)
3				100 (38)	90 (*S*)
4				98 (31)	77 (*S*)
5				100 (35)	86 (*S*)
6				100 (10)	92 (*S*)
7				100 (13)	84 (*S*)

[a] *Reaction conditions:* ketone (5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), ligand (0.055 mmol), KO-*t*-Bu (2.5 mmol), LiCl (0.5 mmol), DMSO (1.6 mL), alcohol (15 mmol) and at 65 °C for 0.5 h then 40 °C for 4.5 h.
[b] Conversion measured by ^{1}H NMR. Isolated yield in parenthesis.
[c] Enantiomeric excess were determined by GC or HPLC.

tions of the alcohol product, which not only form part of many biologically active compounds but also easily allow further functionalization.

Conclusions

A library of modular furanoside-based hydroxyamide and thioamide ligands **L1**–**L6a**–**j** was synthesized and evaluated in the ATH of a broad range of ketones, including more challenging ones such as trifluoromethyl-containing ketones, propargylic and alkyl alkyl ketones. These ligands were readily prepared from commercial D-mannose and α-amino acids, inexpensive natural chiral feedstocks. Moreover, the modular nature of the ligand library allows several ligand parameters 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 excellent enantioselectivities (*ee*s typically ranging between 95% and >99%) in a broad range of ketones. Both enantiomers of the secondary alcohols can be obtained with excellent enantioselectivities by simply changing either the Ru hydroxyamide catalyst precursor for the Rh thioamide (i.e., Ru-**L1a** *vs.* Rh-**L5a**) or using the ligand with the opposite absolute configuration of the thioamide substituent. The results of the mannose-based catalyst library compare well with the best ones reported in the literature. Moreover, the process can be carried out in environmentally friendly solvents, such as ethanol and 2-methyltetrahydrofuran, with no loss of enantioselectivity. In addition, we have shown the potential application of the new catalysts in the simple tandem isomerization/ATH of readily available allylic alcohols and in tandem α-alkylation/ATH to produce chiral alcohols with an elongation of the alkyl chain. These findings represent an improvement on the previously reported furanoside-derived hydroxyamide and thioamide ligands used in ATH of ketones, and the novel ligands provide an additional class of catalysts for the highly enantioselective reduction of industrially relevant substrates as well as their use in reductive tandem reactions.

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. 1-*O*-Benzyl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **5** was prepared as previously described.[14] All other reagents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded using

a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard. ^1H and ^{13}C assignments were made on the basis of ^1H-^1H gCOSY and ^1H-^{13}C gHSQC experiments.

General Procedure for the Preparation Hydroxyamide Ligands L1–L3a–j

To a cooled solution (−15 °C) of the desired *N*-Boc-protected amino acid (2 mmol) in THF (4 mL), *N*-methylmorpholine (2.3 mmol, 252 μL) and isobutyl chloroformate (2.3 mmol, 300 μL) were slowly added. After 45 min, a solution of the desired amino alcohol (2 mmol), in THF (4 mL) was added and the resulting mixture was stirred at room temperature for 2 h. The crude mixture was purified by SiO_2-flash chromatography (ethyl acetate/petroleum ether: 2/3 for ligands **L1a–e** and **L1h** and **L1i** or ethyl acetate/petroleum ether: 3/2 for ligands **L1f**, **g**, **j**, **L2a**, **f** and **L3a–j**) to produce the corresponding ligands as white solids. See the Supporting Information for characterization details.

General Procedure for the Benzoylation of L1–L3a–j

Benzoyl chloride (1.1 mmol, 128 μL) was slowly added to a cooled solution (0 °C) in dichloromethane (2 mL) of the desired hydroxyamide (1 mmol) in triethylamine (7.2 mmol, 1 mL) and DMAP (0.11 mmol, 13.4 mg). The reaction mixture was stirred overnight. Then water was added and the mixture was extracted with dichloromethane (3 × 20 mL), the extract was dried over $MgSO_4$, evaporated to dryness and the residue was purified by SiO_2-flash chromatography (petroleum ether/ethyl acetate: 3/1 for compounds **9a–e** and **9h**, **9i** or petroleum ether/ethyl acetate: 1/1 for ligands **9f**, **g**, **j**, **10a–h** and **11a–j**) to produce the corresponding benzoylated product as white solids. See the Supporting Information for characterization details.

General Procedure for the Preparation of Thioamide Ligands L4–L6a–j

To a cooled solution of the desired benzoylated product (1 mmol) in THF (4 mL), Lawesson's reagent (0.8 mmol, 317 mg) was added at 0 °C. The reaction mixture was stirred for two days at 60 °C. Then, the reaction mixture was evaporated to dryness and the residue was purified by SiO_2-flash chromatography (petroleum ether/ethyl acetate: 1/4 for ligands **L4a–e** and **L4h**, **i** or petroleum ether/ethyl acetate: 1/2 for ligands **L4f**, **g**, **j**, **L5a**, **f** and **L6a–j**) to afford the corresponding thioamide ligands as white solids. See the Supporting Information for characterization details.

Typical Procedure for the ATH of Ketones

The desired ligand (0.0055 mmol), catalyst precursor ($[RuCl_2(p\text{-cymene})_2]_2$ or $[RhCl_2Cp^*_2]_2$) (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 mixture was stirred for 15 min. The reaction was initiated by adding KO-*t*-Bu (0.1 M, 0.5 mL, 0.05 mmol) to the solution. After completion of the reaction the solution was filtered through a plug of silica and eluted with Et_2O, and the solvents were evaporated. The resulting solutions were analyzed by ^1H NMR spectroscopy. The resulting oily residue was purified by column chromatography and enantiomeric excesses were measured by chiral GC or chiral HPLC. For characterization and *ee* determination details see the Supporting Information.

Typical Procedure for the Tandem Isomerization/ATH of Ketones

The catalyst precursor $[RuCl_2(p\text{-cymene})_2]_2$ or $[RhCl_2Cp^*_2]_2$ (6.2 mg, 0.01 mmol) and LiCl (4.4 mg, 0.10 mmol, 10 mol%) were treated under vacuum for 10 min. Dry THF (0.50 mL) and dry ethanol (0.9 mL) were added, followed by the corresponding ligand (0.011 mmol) and the allylic alcohol (1 mmol). The resulting mixture was stirred for 15 min at 40 °C. The reaction was initiated by addition of a 1.0 M stock solution of KO-*t*-Bu in dry ethanol (0.30 mL, 0.30 mmol, 30 mol%). After 24 h at 40 °C, the solution was passed through a pad of silica with ethyl acetate as the eluent. The resulting solutions were analyzed by ^1H NMR spectroscopy. The resulting oily residue was purified by column chromatography. Enantiomeric excesses were measured by chiral GC or chiral HPLC. For characterization and *ee* determination details see the Supporting Information.

General Procedure for the Tandem α-Alkylation/ATH of Ketones

The catalyst precursor $[RuCl_2(p\text{-cymene})_2]_2$ (15.3 mg, 0.025 mmol), the corresponding ligand (0.055 mmol) and LiCl (21.2 mg, 0.50 mmol) were treated under vacuum for 10 min. Dry DMSO (1.6 mL), the corresponding alcohol (15.0 mmol), and substrate (5.0 mmol) were added. The mixture was allowed to stir for 10 min, thereafter KO-*t*-Bu (280 mg, 2.5 mmol) was added. The reaction mixture was allowed to stir at 65 °C for 30 min. Thereafter, the temperature in the bath was decreased to 40 °C, and the stirring was continued for additional 4.5 h. Brine (20 mL) was added, and the mixture was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting oily residue was purified by column chromatography. Enantiomeric excesses were measured by chiral HPLC.

Acknowledgements

Financial support from the K & A Wallenberg Foundations, the Swedish Research Council, the Spanish Government (CTQ2013-40568P), the Catalan Government (2014SGR670), and the ICREA Foundation (ICREA Academia awards to M. Diéguez and O. Pàmies) is gratefully acknowledged.

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14 Third-Generation Amino Acid Furanoside-Based Ligands from D-Mannose for the Asymmetric Transfer Hydrogenation of Ketones: Catalysts with an Exceptionally Wide Substrate Scope

Adv. Synth. Catal. **2016**, *358*, 1 – 14

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