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COMMUNICATION

Carbohydrate-based pseudo-dipeptides: new ligands for the highly enantioselective Ru-catalyzed transfer hydrogenation reaction†

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Ruthenium-complexes of novel carbohydrate based pseudo-dipeptide ligands effectively and selectively catalyze the reduction of a broad range of aryl–alkyl ketones under ATH conditions. Excellent enantioselectivities (>99% ee) are obtained using aminosugars as the sole source of chirality.

The value of enantiopure secondary alcohols lies mainly in their use as important building blocks for the synthesis of natural, pharmaceutical and agricultural products.[1] The enantioselective reduction of prochiral ketones has emerged as an efficient and direct synthetic tool for preparing these compounds. In this context, asymmetric metal-catalyzed transfer hydrogenation (ATH) is an alternative method that is operationally simpler and significantly safer than direct hydrogenation with molecular hydrogen.[2] The most commonly used catalysts in transfer hydrogenations are based on transition metal catalysts (*i.e.* ruthenium, rhodium, or iridium complexes) modified with monosulfonated diamines,[3,4] β-amino alcohols,[5] or 2-(aminomethyl)pyridines[6] as chiral ligands.[7] Recently, iron-based catalysts have also shown useful activity and selectivity.[8]

Adolfsson *et al.* have reported the use of a new type of ligand **1**—pseudo-dipeptides—(Fig. 1) for the enantioselective transfer hydrogenation of a broad range of aryl–alkyl ketones.[9] These ligands are based on the combination of different *N*-Boc-protected α-amino acids and β-amino alcohols. The fundamental difference between previously described successful catalysts and these pseudo-dipeptide counterparts is the lack of a basic NH group in the latter's ligand structure. The main features of ligands **1** are that: (i) the presence of a chiral α-amino acid is crucial if significant levels of enantioselectivity are to be achieved. However, the enantioselectivity value is dictated by the combination of substituents/configurations in both the amino acid and the amino alcohol parts;[9] and (ii) the sense of enantioselectivity is controlled by the configuration in the amino acid part. Catalysts based on L-amino acids, then, predominantly gave *S* configuration products while the use of ligands based on D-amino acids resulted in the formation of the *R* alcohols as the major enantiomer.[9] Despite all these important contributions, there is still a lack of a catalyst able to provide the desired secondary alcohols in enantiopure form (>99% ee) for a broad range of substrates as the enzymes do. The most successful catalysts developed to date afford the desired alcohols in a range of 95–99% ee.[2] Therefore, the development of extremely enantioselective ATH catalysts containing ligands based on simple starting materials and that have high modularity still need to be further explored.

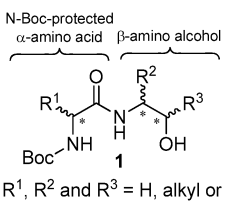

Fig. 1 General structure of pseudo-dipeptide ligands **1**.

One of the simplest ways to synthesize chiral ligands is to rely on nature to provide appropriate chiral synthons. For this purpose, carbohydrates are particularly useful because they are cheap, they have several stereogenic centers and their modular constructions are easy. In this respect, carbohydrates have become an important natural source for preparing chiral ligand libraries, which have been successfully applied in several metal-catalyzed asymmetric transformations.[10,11] Despite this success, carbohydrate-based ligands have hardly been used for this transformation and in all the examples low-to-moderate enantioselectivities (<78% ee) have been reported.[12]

In this communication, we describe a new class of pseudo-dipeptide ligands, derived from carbohydrates, for the highly enantioselective Ru-catalyzed transfer hydrogenation of a broad range of substrates (Fig. 2). The main benefit of incorporating the sugar core is that excellent enantioselectivities (typically >99% ee) can be obtained using the sugar amino alcohol part as a sole source of chirality. This feature allows for the use of non-enantiopure α-amino acid derivatives (even achiral or racemic ones).

The synthesis of the carbohydrate-based pseudo-dipeptide ligands **L1–L10** is straightforward (Scheme 1). They were efficiently prepared by coupling a series of *N*-Boc protected amino

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† Electronic supplementary information (ESI) available: (i) Experimental procedures and characterization of new ligands **L1–L10** and sugar intermediates **2–4**; and (ii) ATH results using ligands **L2** and **L7**. See DOI: 10.1039/c1cc15024c

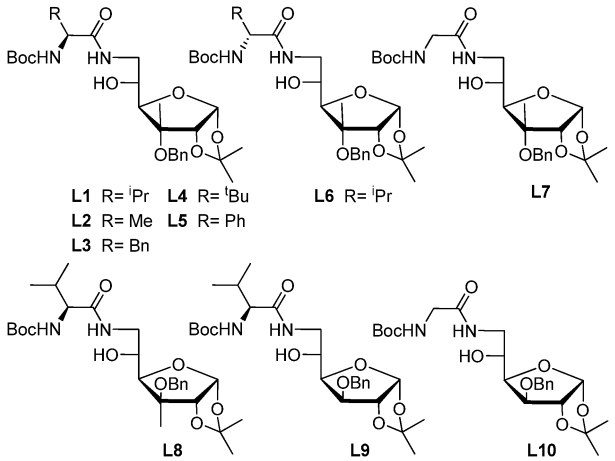
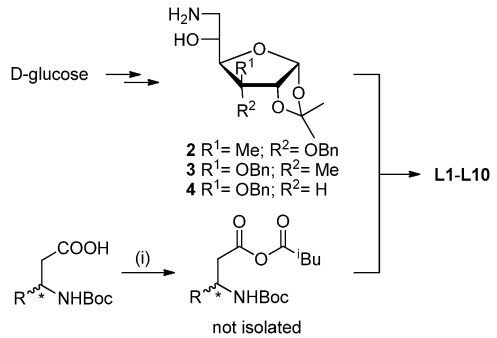


Fig. 2 Carbohydrate-based pseudo-dipeptide ligands **L1–L10**.



Scheme 1 Synthesis of ligands **L1–L10**. (i) ^{i}BuOCOCl/NMM/THF/-15 °C.

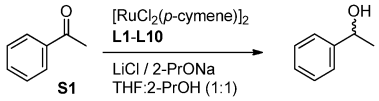
acids with the corresponding sugar amino-alcohols **2–4** by using isobutyl chloroformate in the presence of *N*-methylmorpholine (Scheme 1).[9b,c] Sugar amino-alcohols **2–4** are readily prepared on a large scale from inexpensive D-glucose (see ESI† for experimental details).

To initially evaluate these new ligands (**L1–L10**), we chose the Ru-catalyzed ATH of acetophenone **S1**. As this reaction was carried out with a wide variety of ligands bearing different donor groups, we were able to compare the efficacy of the various ligand systems. The results are summarized in Table 1.

We first investigated the effect of the α-amino acid substituents on the catalytic performance with ligands **L1–L5**. We found that enantioselectivities were excellent (>99% ee) in all cases (Table 1, entries 1–5). The results indicate that varying the α-amino acid substituent does not affect enantioselectivity. However, our results also indicate that activity is affected by these α-amino acid substituents. The highest activities were obtained with catalysts based on ligands **L1–L3**.

Interestingly, changing the configuration of the α-amino acid from *S* (ligand **L1**) to *R* (ligand **L6**) inhibits the catalytic activity almost completely (Table 1, entries 1 *vs.* 6 and 7). This result prompted us to study whether high levels of enantioselectivity can be maintained by introducing an achiral or racemic α-amino acid moiety into the ligand design. For this purpose we evaluated ligand **L7**, derived from glycine, and a 1 : 1 mixture of **L1** and **L6** ligands (Table 1, entries 8 and 9), respectively. In both cases enantioselectivities were excellent (99% ee). This is unprecedented behavior which confirms that

Table 1 Ru-catalyzed asymmetric transfer hydrogenation reaction of **S1** using ligands **L1–L10**[a]



Entry	Ligand	mol% Ru	T/°C	% Conv[b]/h	% ee[b]
1	**L1**	0.25	25	80 (3)	>99 (*S*)
2	**L2**	0.25	25	80 (3)	>99 (*S*)
3	**L3**	0.25	25	81 (3)	>99 (*S*)
4	**L4**	0.25	25	49 (3)	>99 (*S*)
5	**L5**	0.25	25	42 (3)	>99 (*S*)
6	**L6**	0.25	25	1 (3)	n.d.
7	**L6**	1	25	6 (3)	6 (*R*)
8	**L7**	0.25	25	56 (3)	99 (*S*)
9	**L1** + **L6**	0.25	25	48 (3)	99 (*S*)
10	**L8**	0.25	25	78 (3)	>99 (*S*)
11	**L9**	0.25	25	79 (3)	>99 (*S*)
12	**L10**	0.25	25	51 (3)	99 (*S*)
13	**L1**	0.25	50	98 (0.5)	>99 (*S*)
14[c]	**L1**	0.25	25	21 (3)	98.7 (*S*)
15[c]	**L6**	1	25	2 (3)	4 (*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% in Ru), ligand (0.55 mol%), NaO^{i}Pr (5 mol%), LiCl (10 mol%) and at room temperature. [b] Conversion and enantiomeric excess was determined by GC. [c] No LiCl added.

the enantioselectivity is dictated by the sugar amino alcohol part. The results contrast with the "cooperative" effect between the substituents/configurations at both the aminoalcohol and the α-amino acid moieties previously observed for other successful pseudo-dipeptide ligands.[9] On the other hand, the configuration of the amino acid has an impact on the conversion, therefore, it has to be matched to the configuration of the carbohydrate part for constructing efficient ligands.

The use of ligand **L8**, with opposite configuration at C-3 of the furanoside backbone in comparison to **L1**, has no effect on activity and enantioselectivity (Table 1, entry 1 *vs.* 10). This result encouraged us to study whether high ee's can also be achieved using 3-benzyl aminoalcohol **4** derived ligands (**L9** and **L10**), which are synthesized in fewer steps than corresponding ligands derived from aminoalcohols **2** and **3**. We were pleased to find out that again excellent enantioselectivities were obtained using ligands **L9** and **L10** (Table 1, entries 11 and 12).

We also performed the reaction at a higher temperature (50 °C) using ligand **L1** (entry 13). Activity increased considerably (up to 98% conversion in 30 minutes), and the excellent enantioselectivity was maintained (>99% ee (*S*)).

Finally, we evaluated the efficiency of these catalysts without the addition of LiCl (entries 14 and 15). The results are in line with the decrease in activity and enantioselectivity previously observed using pseudo-dipeptides **1**, which suggest a similar coordination mode, and mechanism for the ATH-reaction.[9f] The reason for the change in enantiocontrol is most likely due to interactions between the ligand and the *p*-cymene when the Ru-hydride complex is formed.

Encouraged by the excellent results obtained up to this point, and in order to study the potential of these readily available ligands further, we evaluated them in the ATH of other ketones (**S2–S11**). The results are summarized in Fig. 3. We found that the combination of $[RuCl_2(p\text{-cymene})]_2$ and **L1**

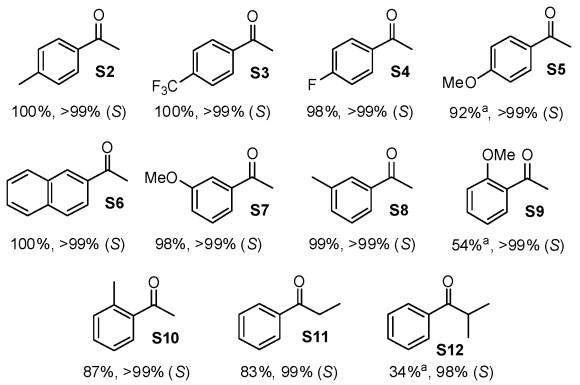


Fig. 3 Selected asymmetric transfer hydrogenation results. Reaction conditions: 0.25 mol% $[RuCl_2(p\text{-cymene})]_2$, 0.55 mol% **L1**, 1 mmol substrate, 3 h at room temperature. [a]1 mol% of $[RuCl_2(p\text{-cymene})]_2$, 24 h.

or **L9**, respectively, efficiently catalyze the ATH of several other aryl–alkyl ketones. The results show that the catalytic performance (activity and enantioselectivity) is not affected by the steric and electronic properties of the aryl group, except for substrates **S5**, **S9** and **S12**, which required higher catalyst loadings (1 mol% of $[RuCl_2(p\text{-cymene})]_2$) to achieve good conversions. This behavior contrasts with the electronic and steric effect on enantioselectivity observed for previous pseudo-dipeptide ligands.[9] Furthermore, enantioselectivities were excellent (>99%) in all cases, surpassing the enantioselectivities obtained with previous successful pseudo-dipeptide ligands.[9] The carbohydrate-functionalized pseudo-dipeptides represent a powerful ligand library that provides the highest levels of enantioselectivity (>99%) for a wide range of aryl–alkyl ketones.

In summary, we have successfully designed and evaluated a new pseudo-dipeptide ligand library in the Ru-catalyzed ATH of several ketones. The ligand library is based on the combination of various *N*-Boc-protected α-amino acids and a sugar amino alcohol unit. Interestingly, we have demonstrated that the introduction of a furanoside aminosugar moiety into the ligand design is highly advantageous and it efficiently transfers the chiral information to the products (ee's ranging from 98% to >99% in the reduction of a range of ketones). In contrast to previous successful pseudo-dipeptides, the enantioselectivity is exclusively controlled by the sugar moiety which enables the use of inexpensive achiral or racemic α-amino acid derivatives. Moreover, catalysts formed with the carbohydrate-based pseudo-dipeptides showed a higher degree of substrate versatility than the corresponding pseudo-dipeptide analogues **1**. These novel carbohydrate pseudo-dipeptide compounds constitute therefore an exceptional ligand system that favorably competes in terms of enantioselectivity with other successful catalytic systems including enzymatic kinetic resolution (KR) and dynamic kinetic resolution (DKR).[2,13] Because of the modular construction of these carbohydrate-based ligands, structural diversity is easy to achieve, so activities and enantioselectivities can be maximized for other substrates as required. Further studies of this kind, as well as mechanistic studies, are currently underway.

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