Highly Enantioselective Ruthenium-Catalyzed Reduction of Ketones Employing Readily Available Peptide Ligands

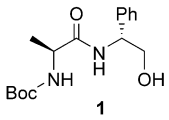
Anders Bøgevig, Isidro M. Pastor, and Hans Adolfsson*[a]

Abstract: Highly efficient and selective catalysts for the asymmetric reduction of aryl alkyl ketones under hydrogen-transfer conditions (2-propanol) were obtained by combining a novel class of pseudo-dipeptide ligands with $[\{RuCl_2(p\text{-cymene})\}_2]$. A library of 36 dipeptide-like ligands was prepared from *N*-Boc-protected α-amino acids and the enantiomers of 2-amino-1-phenylethanol and 1-amino-2-propanol. The catalyst library was evaluated with the reduction of acetophenone and excellent enantioselectivity of 1-phenylethanol was obtained with several of the novel catalysts. A ligand based on the combination of *N*-Boc-L-alanine and (*S*)-1-amino-2-propanol (ligand A-(*S*)-**4**) was found to be particular effective. When the situ formed ruthenium complex of this ligand was employed as the catalyst in the hydrogen-transfer reaction of various aryl alkyl ketones, the corresponding alcohol products were achieved in excellent enantioselectivity (up to 98% *ee*).

Keywords: amino acids · amino alcohols · asymmetric catalysis · hydrogen transfer · ruthenium

Introduction

The enantioselective reduction of ketones to secondary alcohols is an important functional group transformation. This rather simple transformation is extensively employed in small-scale laboratory experiments as well as in large-scale industrial applications. The transition-metal-catalyzed hydrogen-transfer protocol represents a proficient and particularly mild route towards the formation of chiral secondary alcohols.[1,2] The introduction of catalysts based on ruthenium complexes with chiral amino alcohol or diamine ligands, in combination with 2-propanol or formic acid as a hydride source, render this process highly selective and efficient.[3] We have recently introduced catalysts based on pseudo-dipeptide ligands for the enantioselective ruthenium-catalyzed transfer hydrogenation of aryl alkyl ketones in 2-propanol.[4,5] A library of novel "dipeptide" ligands was efficiently formed combining *N*-Boc-protected α-amino acids with a number of vicinal amino alcohols obtained from the corresponding natural and unnatural amino acids. These ligands were combined with a proper ruthenium(II) source (i.e. $[\{RuCl_2(arene)\}_2]$) and the complexes formed were screened as catalysts for the reduction of acetophenone. Although several of the ruthenium complexes were able to selectively catalyze the reduction reaction, we found that the catalyst based on ligand **1** was particularly effective, giving the product alcohol (1-phenylethanol) in high yield and enantioselectivity.



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This catalyst was successfully employed in the reduction of a number of aryl alkyl ketones, and enantioselectivity of up to 96% was obtained. Furthermore, we found that the product configuration was determined by the stereocenter present in the amino acid part of the "dipeptide" ligand. Using catalysts based on natural amino acids gave products of *S* configuration and the opposite enantiomer was obtained when D-amino acids were employed. The simplicity of the ligand structure in combination with the ready availability and low cost of α-amino acids render this system highly attractive. A disadvantage with this novel class of catalysts is that the ketone reduction only works using secondary alcohols as hydrogen donors. In efforts towards finding catalysts which would also tolerate formic acid as the hydrogen source, we examined various derivatives of the "dipeptide" ligands; but unfortunately no such catalyst could be developed. One of the compounds we examined, however, turned out to be more efficient and selective in comparison

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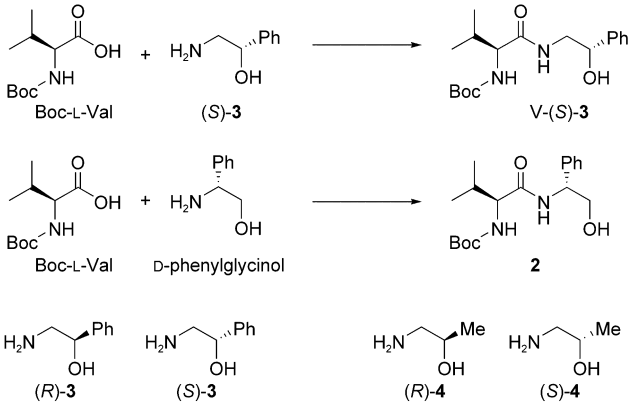
to the first-generation catalysts when the reaction was performed in 2-propanol. Here we present the preparation and evaluation of a novel class of pseudo-symmetric peptide-like ligands that, when combined with [{$RuCl_2$(*p*-cymene)}$_2$], result in catalysts exhibiting superior activity and selectivity in ketone reductions.

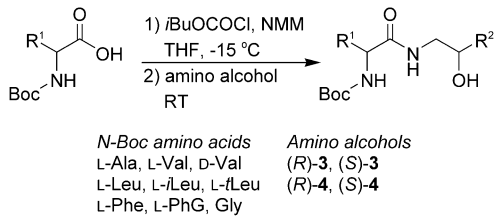
Results and Discussion

Preparation and evaluation of the catalyst library: Encouraged by the results we obtained using our first-generation ligands in the ruthenium-catalyzed transfer hydrogenation of ketones,[4] we decided to investigate how structural changes in the amino alcohol part of the ligand would affect the activity and selectivity of the catalyst. One obvious structural variation is of course to employ ligands that contain secondary alcohols instead of the primary hydroxyl functionality present in the initial ligand system. Hence, we prepared ligand V-(*S*)-**3** starting from *N*-Boc-protected L-valine and (*S*)-2-amino-1-phenylethanol ((*S*)-**3**) (Scheme 1). Employing



Scheme 1.

this ligand in the ruthenium-catalyzed reduction of acetophenone under hydrogen-transfer conditions resulted in the formation of 1-phenylethanol in 91% conversion and 93% *ee* after two hours. This should be compared to the result obtained with the analogous ligand **2**, which gave approximately the same enantioselectivity but significantly lower conversion when used in the same reaction. With this result in hand, we decided to prepare a library of ligands based on *N*-Boc-protected α-amino acids and the commercially available 2-amino-1-phenylethanols (*R*)-**3** and (*S*)-**3** and 1-amino-2-propanols (*R*)-**4** and (*S*)-**4** (Schemes 1 and 2).

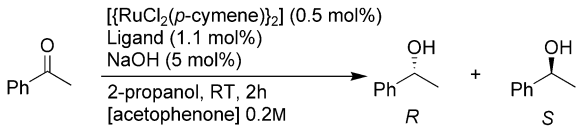


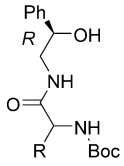
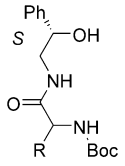
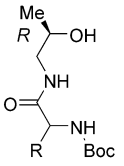
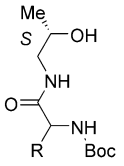
Scheme 2.

The successful construction of a library of compounds relies on efficient and selective synthetic procedures that allow the formation of the desired targets in high yield and purity.[6,7] Thus, to obtain a library of ligands with the fundamental structural features of V-(*S*)-**3**, a number of *N*-Boc-protected amino acids were coupled with the amino alcohols (**3** and **4**) by using isobutyl chloroformate in the presence of *N*-methylmorpholine (NMM).[8] This protocol was previously employed in the formation of our first-generation ligand library; however, when this reaction was reexamined we found that two factors turned out to be of crucial importance for obtaining the pseudo-dipeptides of high purity; 1) full conversion of the Boc-protected amino acid to the mixed anhydride, and 2) exact stoichiometry of the reactants. In the first case, it was found necessary to extend the time allowed for isobutyl chloroformate to react with the amino acid, forming the mixed anhydride intermediate. Secondly, excess of either the amino alcohol or the coupling reagent should be avoided. We found that any residual coupling reagent effectively reacted with the amino alcohol upon its addition. The separation of the obtained *N*-isobutylcarbamate-protected amino alcohol from the desired coupling product turned out to be less straightforward. On the other hand, the need for purification of the ligands is more cosmetic than absolutely necessary, since the byproducts act as very poor ligands relative to the pseudo-dipeptide (vide infra).

By employing the synthetic method described above, a library of 36 pseudo-dipeptides was prepared (Scheme 2 and Table 1), and these ligands were evaluated using the reduction of acetophenone as the model reaction. The reductions were carried out by using the following conditions: substrate/ruthenium/ligand/base in a 100:1:1.1:5 ratio, with 0.2 M concentration of acetophenone in 2-propanol. The catalyst was prepared by drying a mixture of [{$RuCl_2$(*p*-cymene)}$_2$] (0.5 mol%), the "dipeptide"-ligand (1.1 mol%), and NaOH (5 mol%) under vacuum for 15–30 minutes followed by addition of oxygen-free 2-propanol. The color of the obtained mixtures varied from yellow to purple, depending on the ligand employed. After 10 minutes, the substrate was added and the reaction progress was monitored by analyzing small samples using GLC methods. The results obtained after a two hour reaction time with the library of catalysts are presented in Table 1 and Figure 1. The catalytic activity varied significantly, with conversions ranging from 17 up to 93% depending on the structure of the ligand/catalyst. It is important to point out that under these reversible reaction conditions, the maximum theoretical conversion is limited to 96%.[9] One factor which seemed to govern the extent of conversion was the relative size of the side chains present in the ligand. Hence, ligands based on *t*Leu, containing the more sterically-demanding *tert*-butyl-group, were considerably less active relative to ligands that contained smaller side chains. An even more pronounced effect on the catalytic activity is clearly visible when comparing ligands of different stereochemistry. Out of the 36 ligands present in the library, all but four compounds contain two stereogenic centers; consequently two diastereomers were formed when each of the amino alcohols were employed. Taking the relative con-

Table 1. Ligand library screening. Ru-catalyzed hydrogen-transfer of acetophenone to 1-phenylethanol in 2-propanol.[a,b]



N-Boc amino acid (R=)				
L-Ala (Me)	A-(*R*)-**3** 25% conv. 60% *ee* (*S*)	A-(*S*)-**3** 91% conv. 92% *ee* (*S*)	A-(*R*)-**4** 23% conv. 59% *ee* (*S*)	A-(*S*)-**4** 90% conv. 96% *ee* (*S*)
L-Val (*i*Pr)	V-(*R*)-**3** 43% conv. 40% *ee* (*S*)	V-(*S*)-**3** 91% conv. 93% *ee* (*S*)	V-(*R*)-**4** 55% conv. 34% *ee* (*S*)	V-(*S*)-**4** 90% conv. 96% *ee* (*S*)
D-Val (*i*Pr)	D-V-(*R*)-**3** 92% conv. 93% *ee* (*R*)	D-V-(*S*)-**3** 43% conv. 38% *ee* (*R*)	D-V-(*R*)-**4** 90% conv. 96% *ee* (*R*)	D-V-(*S*)-**4** 48% conv. 36% *ee* (*R*)
L-Leu (*i*Bu)	L-(*R*)-**3** 30% conv. 20% *ee* (*S*)	L-(*S*)-**3** 87% conv. 84% *ee* (*S*)	L-(*R*)-**4** 17% conv. 36% *ee* (*S*)	L-(*S*)-**4** 81% conv. 95% *ee* (*S*)
L-Ile ((*S*)-*s*Bu)	I-(*R*)-**3** 43% conv. 37% *ee* (*S*)	I-(*S*)-**3** 93% conv. 94% *ee* (*S*)	I-(*R*)-**4** 30% conv. 31% *ee* (*S*)	I-(*S*)-**4** 85% conv. 97% *ee* (*S*)
L-*t*Leu (*t*Bu)	*t*L-(*R*)-**3** 30% conv. 35% *ee* (*S*)	*t*L-(*S*)-**3** 57% conv. 88% *ee* (*S*)	*t*L-(*R*)-**4** 25% conv. 31% *ee* (*S*)	*t*L-(*S*)-**4** 69% conv. 92% *ee* (*S*)
L-Phe (Bn)	F-(*R*)-**3** 24% conv. 28% *ee* (*S*)	F-(*S*)-**3** 86% conv. 95% *ee* (*S*)	F-(*R*)-**4** 41% conv. 29% *ee* (*S*)	F-(*S*)-**4** 36% conv. 97% *ee* (*S*)
L-PhGly (Ph)	PhG-(*R*)-**3** 55% conv. 24% *ee* (*R*)	PhG-(*S*)-**3** 92% conv. 92% *ee* (*S*)	PhG-(*R*)-**4** 3% conv. 46% *ee* (*R*)	PhG-(*S*)-**4** 89% conv. 94% *ee* (*S*)
Gly (H)	G-(*R*)-**3** 89% conv. 76% *ee* (*R*)	G-(*S*)-**3** 85% conv. 76% *ee* (*S*)	G-(*R*)-**4** 81% conv. 72% *ee* (*R*)	G-(*S*)-**4** 77% conv. 69% *ee* (*S*)

[a] For conditions, see scheme above table and the Experimental Section. [b] Conversion and enantioselectivity were determined by GLC methods (CP Chirasil DEX CB).

figuration into account, ligands prepared from L-amino acids (L-AA) and (*S*)-amino alcohols generated ruthenium complexes of high catalytic activity, whereas use of the corresponding diastereomeric ligands resulted in poor catalysts. This matched/mismatched behavior was further accentuated when the stereochemical outcome of the reaction was taken into account. As seen in Figure 1, catalysts generated from L-AA and (*S*)-amino alcohols generally gave the product alcohol in excellent enantioselectivity (>90%), whereas using the mismatched ligand combination resulted in a considerably lower *ee* of 1-phenylethanol. In line with our previous observations, the configuration of the product alcohol is determined by the absolute configuration of the amino acid part of the ligand. Thus, catalysts based on L-AA predominantly gave products of *S* configuration and the use of ligands based on D-AA resulted in the formation of the *R* alcohol as the major enantiomer. The only exceptions were observed with catalysts derived from L-PhG, whereby a small excess of the *R*-configured product was obtained when the mismatched ligands were used. The glycine-derived ligands possess only one stereogenic center and, therefore, the sole influence of this chiral center is displayed when catalysts based on these compounds are employed in the reduction reaction. In agreement with the observation that the L-configured amino acids predominantly give *S* alcohols, the combination of glycine and *S*-amino alcohols resulted in ligands that favored the same product stereoisomer. Catalysts based on the antipodes of these ligands naturally favored the formation of the product *R* alcohol.

Out of the 36 entries described in Table 1, ligands based on *N*-Boc-protected alanine, valine, or isoleucine and (*S*)-1-amino-2-propanol ((*S*)-**4**) gave superior catalysts with regard to conversion and selectivity.

Important factors influencing the catalytic system: Although several catalysts derived from the ligand library were able to reduce acetophenone to 1-phenylethanol with very high enantioselectivity, we chose to continue our studies with ligand A-(*S*)-**4**. The ruthenium complex of this particular ligand proved to be among the most active catalysts, in fact we observed 76% conversion (97% *ee*) after only 30 minutes reaction time.[10] In order to find the optimum reaction

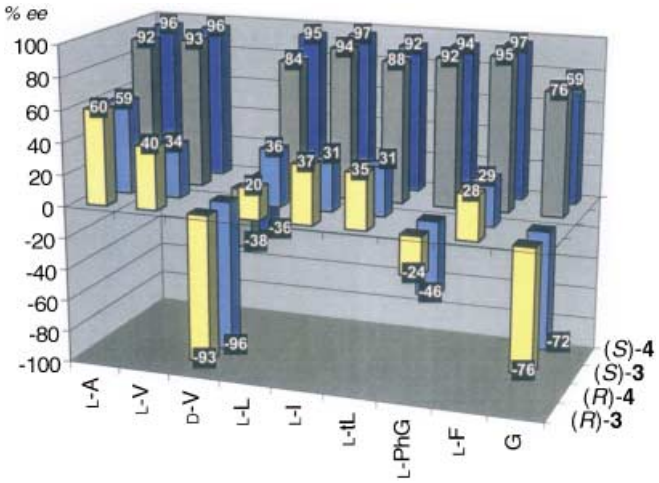


Figure 1. Enantiomeric excess of 1-phenylethanol obtained using catalysts derived from the ligands described in Table 1. The positive numbers refer to the formation of *S* isomer in excess, and the negative numbers to the *R* isomer.

conditions for ketone reductions with this catalyst, we conducted a series of experiments in which different parameters were varied. This resulted in a number of crucial observations. 1) The amount of base necessary for efficient catalyst formation was found to be three equivalents. Using less than three equivalents of NaOH resulted in low conversion, and below two equivalents of base, the catalytic activity was completely lost. 2) The ligand/ruthenium ratio was varied and we found an optimum value around 1, which indicates that a 1:1 complex is the active catalyst. Lower amounts of ligand gave significantly lower conversion and the use of more than one equivalent versus ruthenium resulted in a minor drop of the catalytic activity. 3) Most importantly, we discovered that the lifetime of the active catalyst was limited. The typical reaction setup involves mixing the ligand with the ruthenium precursor and NaOH in 2-propanol under oxygen-free conditions, followed by addition of the substrate. If the delay time between substrate addition and catalyst formation was too long, the activity of the system was severely reduced (Figure 2). We obtained the highest conversion when the substrate was added after 10 minutes. It should be noted that regardless of the catalytic activity, the enantioselectivity remained high in all cases (97 % *ee* after 30 min reaction time).

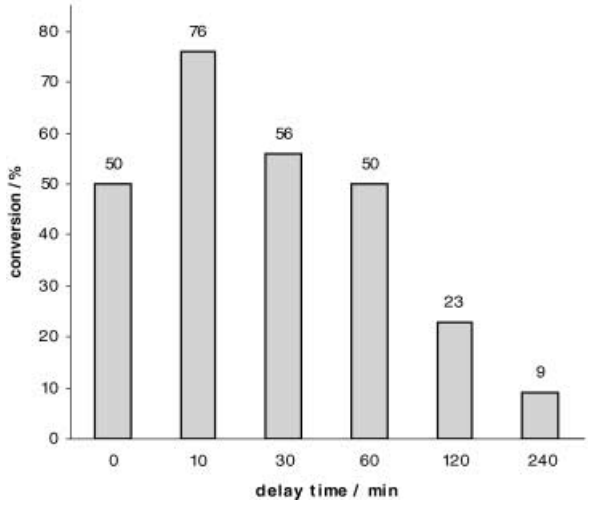


Figure 2. The effect of delaying the time of substrate addition. Conversion of acetophenone obtained after 30 minutes.

All of the above reactions were conducted at ambient temperature. In contrast to ruthenium-catalyzed transfer hydrogenations with phosphine-based metal precursors (e.g., $[RuCl_2(PPh_3)_3]$), the systems based on Ru^{II}(arene) complexes typically perform best at room temperature. However, in a recent study Lutsenko and Moberg reported on significant rate improvements for the transfer hydrogenation of acetophenone at elevated temperatures by using the Noyori catalyst (i.e., [Ru^{II}(*p*-cymene)(*R*,*R*)-TsDPEN]).[11] The reactions were performed by using microwave irradiation and resulted in high yields of the alcohol product in less than 10 minutes reaction time. The stereoselectivity was unfortunately rather poor with *ee* values ranging from 48 to 82 %. To investigate how the novel catalytic system employing "dipeptide" ligands behaved under different reaction temperatures, we performed a number of experiments using either conventional heating or microwave irradiation (Table 2).

Table 2. Catalytic hydrogen transfer of acetophenone in 2-propanol by [{$RuCl_2$(*p*-cymene)}$_2$] and A-(*S*)-**4** at elevated temperatures.[a]

	T [°C]	*t* [min]	Yield [%][b]	*ee* [%][c]
1[d]	60	9	92	95
2[d]	60	30	93	92
3[e]	60	4	63	95
4[e]	75	3	78	94
5[e]	90	2.5	88	93
6[e]	120	2.5	90	87
7[e]	150	2	87	78

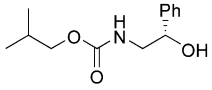
[a] Reaction conditions: acetophenone (1 eq, 0.2 M in 2-propanol), [{$RuCl_2$(*p*-cymene)}$_2$] (0.5 mol %), A-(*S*)-**4** (1.1 mol %) and NaOH (5 mol %). [b] Determined by GLC. [c] Enantiomeric excess (*ee*) was determined by GLC (CP Chirasil DEX CB). [d] Conventional heating using an oil bath. 7 minutes pre-stirring of catalyst mixture prior to substrate addition. [e] Microwave irradiation using an Emry's™ Creator, programmed at constant temperature. No pre-stirring of catalyst mixture.

Reactions performed at 60 °C using either an oil bath or microwave heating resulted in moderate to high yields and good enantioselectivity within a short period of time (Table 2, entries 1 and 3). Extending the reaction time under conventional heating did not improve the chemical yield and further resulted in a small drop of the *ee* (entry 2). Performing the reductions at higher temperatures resulted in shorter reaction times, but unfortunately with the cost of lower enantioselectivity (entries 4–7). Thus if time is crucial, the reactions can be performed at higher temperature (60 °C) without significant loss of stereoselectivity.

As stated above, some of the ligands presented in Table 1 contained up to 10 % of a byproduct that formed in the peptide coupling step, namely the *N*-isobutylcarbamate-protected amino alcohol. The presence of this byproduct did not severely hamper the performance of the catalytic system, but a small decrease in conversion and enantioselectivity was detected. Performing the reduction of acetophenone under hydrogen-transfer conditions with these byproducts (e.g., **5**

or **6**) as ligands resulted in low conversion (< 17% after 2 h) and poor enantioselectivity (up to 17% *ee* of the *R* isomer) of the secondary alcohol formed.

Scope of the system: The scope of the catalytic system was investigated using a number of ketone substrates with [{$RuCl_2$(*p*-cymene)}$_2$] and ligand A-(*S*)-**4** as the catalyst. The results are presented in Table 3.



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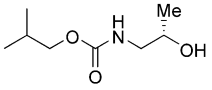

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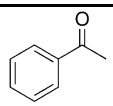
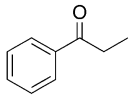
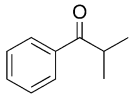
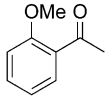
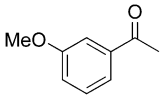
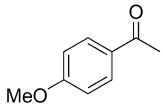
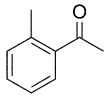
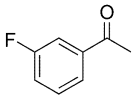
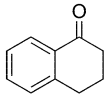
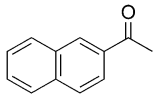
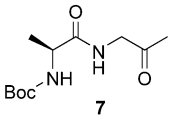
Table 3. Ru-catalyzed hydrogen transfer of aryl alkyl ketones in the presence of ligand A-(*S*)-**4**.[a]

	Substrate	*t* [min]	Yield [%][b]	*ee* [%][c]
1		90	75	96 (*S*)
2		150	67	98 (*S*)
3		180	14	96 (*S*)
4		210	49	94 (*S*)
5		90	85	97 (*S*)
6		210	59	94 (*S*)
7		210	37	97 (*S*)
8		90	87	96 (*S*)
9		180	47	96 (*S*)
10		90	96	97 (*S*)

[a] Reaction conditions: ketone (1 eq, 0.2 M in 2-propanol), [{$RuCl_2$(*p*-cymene)}$_2$] (0.5 mol%), A-(*S*)-**4** (1.1 mol%) and NaOH (5 mol%). All reactions were performed at ambient temperature. [b] Isolated yields. [c] Enantiomeric excess (*ee*) and absolute configuration was determined by GLC (CP Chirasil DEX CB).

Without exception, all substrates presented in Table 3 were reduced with excellent enantio-face selectivity (94% *ee* or better) by using this novel catalytic system. Regarding the catalytic activity, increased size of the alkyl group of the ketone effectively leads to lower isolated yields and the following trend was observed: 75% for acetophenone (entry 1), 67% for propiophenone (entry 2), 14% for isopropyl phenyl ketone (entry 3), and the sterically-hindered *tert*-butyl phenyl ketone completely failed to react. Theoretically, the yields should be similar for the four ketones, since their reduction potentials and, therefore, also the reaction equilibrium constants are similar. Hence, the observed decrease in reactivity is best explained by increased steric interactions between the substrate and the catalyst. The reduction of methoxy-substituted acetophenones followed the predicted pattern. The 2- and 4-methoxy substituted phenyl ethanols were isolated in moderate yields, whereas the reduction of the 3-substituted methoxyacetophenone gave a significantly better yield (entries 4–6). This can be attributed to electronic effects, although steric hindrance or possibly catalyst deactivation by substrate coordination could be responsible for the low activity observed for the 2-methoxy derivative. Steric hindrance was most probably the reason for the low yield obtained with 2-methylacetophenone (entry 7). 3-Fluoroacetophenone was converted to the corresponding secondary alcohol in good yield (entry 8). The reduction of 1-tetralone gave the secondary alcohol in 47% yield (entry 9), and 2-acetonaphthone was reduced in excellent yield (entry 10). In the ligand optimization study on the model compound acetophenone, several ligands, when combined with the ruthenium(II) precursor, resulted in catalysts with similar properties (Table 1). However, for other substrates more substantial differences were observed. This was evident when the ligand I-(*S*)-**4** was used in the reduction of 3-fluoroacetophenone; this resulted in considerably lower conversion to the secondary alcohol (68% after 30 min in comparison to 91% when ligand A-(*S*)-**4** is used). As expected when using a ligand derived from a natural amino acid, all products in Table 2 were obtained with the *S* isomer as the major enantiomer.

Nature of the catalyst: The gradual loss of catalytic activity observed using this system was initially believed to originate from slow catalyst decomposition due to ligand degradation. Since the ligands contain a secondary alcohol, which can undergo oxidation to the corresponding ketone, a less active complex could be the result of such a transformation. Therefore, ketone **7**, corresponding to the oxidized ligand A-(*S*)-**4**, was prepared separately by means of a Swern oxidation[12] of A-(*rac*)-**4**.[13]



7

When this compound was employed as the ligand in the reduction of acetophenone, the reaction reached 69% con-

version and 85 % *ee* after 2 h. This result clearly indicates that ligand oxidation is not the major deactivating path of the system. Another possibility for the observed decreased activity could be the formation of catalytically inert ruthenium complexes. The "dipeptides" are potential tridentate ligands, and, therefore, a number of structurally-different metal complexes can be formed.[14,15] Assuming that the hydrogen-transfer step occurs following the mechanism proposed by Noyori,[16,17] a 16-electron ruthenium complex needs to be present prior to the formation of the active ruthenium hydride. This 16-electron complex can be formed if only two out of the three available donors of the dipeptide ligand are coordinated to the metal center. Hence, if the initially formed, catalytically active ruthenium complex is rearranged into other complexes over time, these new species could have different catalytic properties. As seen above, the activity of the catalyst is rather sensitive towards the structure of the ligand (see Table 1 and Figure 1). In cases in which the "wrong" diastereomer of the ligand was employed, very low conversion and low enantioselectivity was obtained. A possible explanation could be that these mismatched ligands favor the formation of such inactive complexes. The matched ligands on the other hand, could, due to favorable steric interactions, significantly decrease the rate of such processes. The activity and selectivity obtained using either the matched or the mismatched ligand can also be explained by the inherent pseudo-symmetry of the ligands (Figure 3). In the matched cases, the combination of

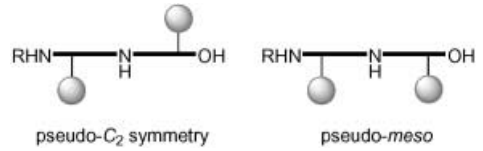


Figure 3. Schematic representation of the ligands in Table 1.

L-amino acids with (*S*)-amino alcohols, the ligands possess pseudo-C_2-symmetry, which could reduce the number of possible catalytically active complexes. In the mismatched cases, however, the pseudo-*meso* configuration of the ligands will open up for the formation of a significantly higher number of complexes.

We have not yet been able to isolate or spectroscopically identify any of the possible complexes, but additional investigations are currently being performed. Another piece of information regarding the nature of the catalyst was found when A-(*rac*)-**4** was employed as ligand(s) under standard conditions. In this experiment we obtained 1-phenylethanol in 80 % conversion and 92 % *ee* (*S*) after two hours. A closer inspection of the conversion and enantiomeric excess after 30 minutes showed that these numbers are the arithmetic mean values of reactions performed with the individual ligands (A-(*S*)-**4** and A-(*R*)-**4**). This result indicates that the catalysts formed in this system seem to operate totally independent of each other; this supports a model of the active catalyst being a 1:1 Ru–L complex.

Conclusion

In conclusion, we have designed a novel, highly efficient and structurally very simple catalytic system for the enantioselective reduction of aryl alkyl ketones under hydrogen-transfer conditions. The catalytic system is based on ruthenium complexes of modular pseudo-symmetric "dipeptide" ligands. The ligands were prepared in a straightforward reaction by coupling *N*-Boc-protected amino acids to commercially available 1-substituted aminoethanols. In accordance with our previously developed system, the amino acid part of the ligand dictates the stereochemical outcome of the reduction reaction. This efficiently allows for the formation of either of the product enantiomers, since both isomers of the ligands are readily available.

Experimental

General procedure for the ligand preparation: The Boc-protected amino acids were dissolved in dry THF at −15 °C and *N*-methylmorpholine (NMM; 1.1 equiv) and isobutyl chloroformate (1.0 equiv) were added to form the mixed anhydride. After 45 min to 3 h the amino alcohol (0.95 equiv) was added, and the reaction was allowed to reach room temperature. After >3 h the reaction mixture was filtered through a plug of silica, and the filtrate was evaporated to give the crude product. The crude ligand could either be used directly without any significant decrease in catalytic activity of the hydrogen-transfer reaction, or simply be purified by recrystallization. The ligands were isolated in yields varying from 30 to 95 %.

A-(*R*)-3 (Boc-L-Ala-(*R*)-Ph): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (d, ^3J = 7.2 Hz, 3H), 1.42 (s, 9H), 3.34 (m, 1H), 3.67 (m, 1H), 4.13 (brs, 1H), 4.82 (m, 1H), 5.13 (d, ^3J = 6.8 Hz, 1H), 6.75 (s, 1H), 7.25–7.35 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 28.5 (3C), 47.6, 50.6, 73.5, 80.6, 126.1, 128.1, 128.7, 141.8, 155.8, 174.2 ppm; MS: *m*/*z* $[M+K]^+$ calcd for $C_{16}H_{24}N_2KO_4$: 347.137; found: 347.132.

A(*S*)3 (Boc-L-Ala-(*S*)-Ph): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, ^3J = 7.2 Hz, 3H), 1.38 (s, 9H), 3.25 (ddd, ^3J = 5.4, 8.1 Hz, ^2J = 13.5 Hz, 1H), 3.60 (ddd, ^3J = 3.5, 6.7 Hz, ^2J = 13.8 Hz, 1H), 4.11 (m, 1H), 4.4 (brs, 1H), 4.77 (m, 1H), 5.54 (m, 1H), 7.08 (m, 1H), 7.19–7.37 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 28.4 (3C), 47.4, 50.4, 72.8, 80.2, 126.0 (2C), 127.8, 128.5 (2C), 141.8, 155.8, 174.2 ppm.

A-(*R*)-4 (Boc-L-Ala-(*R*)-Me): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, ^3J = 6.4 Hz, 3H), 1.33 (d, ^3J = 7.2 Hz, 3H), 1.40 (s, 9H), 3.11 (m, 1H), 3.35 (m, 1H), 3.54 (brs, 1H), 3.87 (m, 1H), 4.14 (m, 1H), 5.40 (m, 1H), 6.98 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 20.8, 28.5 (3C), 47.1, 50.6, 67.1, 80.5, 156.0, 174.0 ppm.

A-(*S*)-4 (Boc-L-Ala-(*S*)-Me): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, ^3J = 6.0 Hz, 3H), 1.36 (d, ^3J = 6.9 Hz, 3H), 1.44 (s, 9H), (OH missing), 3.13 (ddd, ^3J = 6.0, 7.5 Hz, ^2J = 13.5 Hz, 1H), 3.45 (ddd, ^3J = 3.3, 6.6 Hz, ^2J = 13.8 Hz, 1H), 3.86 (brs, 1H; *OH*), 3.92 (m, 1H), 4.15 (m, 1H), 5.09 (d, ^3J = 6.6 Hz, 1H), 6.65 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 20.7, 28.5 (3C), 47.2, 50.5, 67.0, 80.5, 156.0, 174.0 ppm; MS: *m*/*z* $[M+Na]^+$ calcd for $C_{11}H_{22}N_2NaO_4$: 269.148; found: 269.140.

V-(*R*)-3 (Boc-L-Val-(*R*)-Ph) and D-**V-(*S*)-3 (Boc-D-Val-(*S*)-Ph)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89–0.97 (m, 6H), 1.43 (s, 9H), 2.14 (m, 1H), 3.25 (d, ^3J = 3.0 Hz, 1H), 3.34 (m, 1H), 3.71 (m, 1H), 3.88 (m, 1H), 4.85 (m, 1H), 5.02 (brs, 1H), 6.43 (brs, 1H), 7.27–7.36 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 19.5, 28.5 (3C), 31.2, 47.6, 60.4, 73.4, 80.1, 126.1 (2C), 127.9, 128.6 (2C), 142.0, 156.3, 173.2 ppm.

V-(*S*)-3 (Boc-L-Val-(*S*)-Ph) and D-**V-(*R*)-3 (Boc-D-Val-(*R*)-Ph)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0,89 (d, ^3J = 6.3 Hz, 3H), 0.93 (d, ^3J = 6.3 Hz, 3H), 1.43 (s, 9H), 2.08 (m, 1H), 3.32 (ddd, ^3J = 5.1, 8.1 Hz, ^2J = 14.1 Hz, 1H), 3.46 (brs, 1H; *OH*), 3.72 (ddd, ^3J = 3.6, 7.2 Hz, ^2J = 14.1 Hz, 1H), 3.84 (m, 1H), 4.84 (dd, ^3J = 3.0, 7.8 Hz, 1H), 5.07 (m, 1H), 6.46 (brs, 1H), 7.27–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 19.5, 28.5 (3C),

31.0, 47.6, 60.6, 73.1, 80.3, 126.1 (2C), 128.0, 128.7 (2C), 141.8, 156.4, 173.1 ppm; MS: *m/z* $[M+Na]^+$ calcd for $C_{18}H_{28}N_2NaO_4$: 359.195; found: 359.189.

V-(*R*)-4 (Boc-L-Val-(*R*)-Me) and D-V-(*S*)-4 (Boc-D-Val-(*S*)-Me): ^{1}H NMR (400 MHz, $CDCl_3$): δ=0,93 (d, ^3J=6.8 Hz, 3H), 0.97 (d, ^3J=7.2 Hz, 3H), 1.18 (d, ^3J=6.0 Hz, 3H), 1.44 (s, 9H), 2.15 (m, 1H), 2.56 (d, ^3J=4.0 Hz, 1H; *OH*), 3.13 (ddd, ^3J=5.6, 8.0 Hz, ^2J=13.6 Hz, 1H), 3.45 (ddd, ^3J=3.2, 6.4 Hz, ^2J=13.6 Hz, 1H), 3.86 (dd, ^3J=6.4, 8.0 Hz, 1H), 3.92 (m, 1H) 5.00 (m, 1H), 6.38 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.2, 19.5, 20.9, 28.5 (3C), 30.9, 47.6, 60.6, 67.4, 80.3, 156.4, 172.9 ppm; MS: *m/z* $[M+Na]^+$ calcd for $C_{13}H_{26}N_2NaO_4$: 297.179; found: 297.181.

V-(*S*)-4 (Boc-L-Val-(*S*)-Me) and D-V-(*R*)-4 (Boc-D-Val-(*R*)-Me): ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (m, 6H) 1.10 (d, ^3J=5.9 Hz, 3H), 1.36 (s, 9H), 1.98 (m, 1H), 3.01 (m, 1H), 3.36 (m, 1H), 3.88 (m, 2H), 4.5 (brs, 1H; *OH*), 5.60 (d, ^3J=8.1 Hz, 1H), 7.26 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.4, 19.5, 20.7, 28.5 (3C), 31.1, 47.1, 60.5, 66.7, 80.0, 156.5, 173.2 ppm.

F-(*R*)-3 (Boc-L-Phe-(*R*)-Ph): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32 (s, 9H), 2.96 (m, 2H), 3.0 (brs, 1H; *OH*), 3.08 (m, 1H), 3.51 (m, 1H), 4.26 (m, 1H), 4.54 (m, 1H), 5.11 (br s, 1H), 6.31 (brs, 1H), 7.13–7.29 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=28.5 (3C), 39.1, 47.6, 56.4, 73.4, 80.6, 126.0 (2C), 127.2, 128.0, 128.7 (2C) 128.9 (2C), 129.6 (2C), 137.0, 141.6, 155.7, 172.4 ppm; MS: *m/z* $[M+K]^+$ calcd for $C_{22}H_{28}N_2KO_4$: 423.169; found: 423.164.

F-(*S*)-3 (Boc-L-Phe-(*S*)-Ph): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.37 (s, 9H), 3.00 (m, 2H), 3.20 (m, 1H), 3.58 (m, 2H), 4.32 (m, 1H), 4.73 (dd, ^3J=3.6, 8.1 Hz, 1H), 5.23 (d, ^3J=8.1 Hz, 1H), 6.52 (brs, 1H), 7.16–7.36 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=28.5 (3C), 38.8, 47.7, 56.4, 73.1, 80.6, 126.0 (2C), 127.2, 128.0, 128.7 (2C), 128.9 (2C), 129.5 (2C), 136.9, 141.7, 155.8, 172.7 ppm.

F-(*R*)-4 (Boc-L-Phe-(*R*)-Me): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.08 (d, ^3J=6.6 Hz, 3H), 1.39 (s, 9H), 2.64 (brs, 1H), 2.96 (m, 1H), 3.03 (d, ^3J=7.5 Hz, 1H), 3.31 (ddd, ^3J=3.0, 6.6 Hz, ^2J=13.5 Hz 1H), 3.71 (m, 1H), 4.31 (m, 1H) 5.25 (d, ^3J=7.8 Hz, 1H), 6.41 (m, 1H), 7.19–7.32 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.7, 28.5 (3C), 39.0, 47.2, 56.4, 67.1, 80.5, 127.2, 128.9 (2C), 129.5 (2C), 137.0, 155.8, 172.5 ppm; MS: *m/z* $[M+Na]^+$ calcd for $C_{17}H_{26}N_2NaO_4$: 345.179; found: 345.191.

F-(*S*)-4 (Boc-L-Phe-(*S*)-Me): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.06 (d, ^3J=6.3 Hz, 3H), 1.37 (s, 9H), 3.00 (m, 3H), 3.22 (brs, 1H), 3.34 (m, 1H), 3.80 (m, 1H), 4.33 (m, 1H) 5.37 (d, ^3J=8.4 Hz, 1H), 6.68 (m, 1H), 7.17–7.30 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.7, 28.5 (3C), 38.9, 47.2, 56.3, 66.8, 80.5, 127.1, 128.8 (2C), 129.5 (2C), 137.0, 155.9, 172.5 ppm.

L-(*R*)-3 (Boc-L-Leu-(*R*)-Ph): ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (m, 6H), 1.42 (s, 9H), 1.45 (m, 1H), 1.60 (m, 2H), 3.33 (ddd, ^3J=5.2, 8.0 Hz, ^2J=13.6 Hz, 1H), 3.59 (brs, 1H), 3.67 (ddd, ^3J=3.3, 7.0 Hz, ^2J=13.6 Hz, 1H), 4.08 (brs, 1H), 4.82 (m, 1H), 4.98 (d, ^3J=8.0 Hz, 1H), 6.71 (s, 1H), 7.24–7.36 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.2, 23.1, 24.9, 28.5 (3C), 41.7, 47.6, 53.5, 73.4, 80.3, 126.1 (2C), 127.9, 128.6 (2C), 142.0, 156.2, 174.3 ppm; MS: *m/z* $[M+K]^+$ calcd for $C_{19}H_{30}N_2KO_4$: 389.184; found: 389.233.

L-(*S*)-3 (Boc-L-Leu-(*S*)-Ph): ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.90 (m, 6H), 1.41 (s, 9H), 1.45 (m, 1H), 1.58 (m, 2H), 3.26 (ddd, ^3J=5.2, 8.0 Hz, ^2J=13.6 Hz, 1H), 3.50 (brs, 1H), 3.66 (ddd, ^3J=3.6, 8.0 Hz, ^2J=13.6 Hz, 1H), 4.07 (brs, 1H), 4.81 (m, 1H), 5.17 (d, ^3J=8.0 Hz, 1H), 6.88 (s, 1H), 7.24–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.2, 23.1, 24.9, 28.5 (3C), 41.5, 47.7, 53.5, 73.0, 80.5, 126.1 (2C), 127.9, 128.7 (2C), 141.9, 156.2, 174.1 ppm.

L-(*R*)-4 (Boc-L-Leu-(*R*)-Me): ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.90 (m, 6H), 1.13 (d, ^3J=5.6 Hz, 3H), 1.40 (s, 9H), 1.45 (m, 1H), 1.60 (m, 2H), 3.13 (m, 1H), 3.33 (m, 1H), 3.59 (brs, 1H), 3.87 (m, 1H), 4.09 (brs, 1H), 5.32 (d, ^3J=6.4 Hz, 1H), 7.07 (s, 1H), 7.24–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.8, 22.2, 23.1, 24.9, 28.5 (3C), 41.6, 47.1, 53.6, 67.2, 80.3, 156.2, 173.9 ppm; MS: *m/z* $[M+K]^+$ calcd for $C_{14}H_{28}N_2KO_4$: 327.169; found 327.165.

L-(*S*)-4 (Boc-L-Leu-(*S*)-Me): ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.90 (m, 6H), 1.15 (d, ^3J=5.6 Hz, 3H), 1.42 (s, 9H), 1.47 (m, 1H), 1.64 (m, 2H), 3.02 (m, 1H), 3.03 (m, 1H), 3.45 (ddd, ^3J=3.0, 6.8 Hz, ^2J=14.0 Hz, 1H), 3.89 (m, 1H), 4.08 (m, 1H), 5.32 (m, 1H), 6.88 (m, 1H), 7.24–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.8, 22.3, 23.1, 24.9, 28.5 (3C), 41.4, 47.3, 53.6, 67.0, 80.5, 156.2, 173.9 ppm.

I-(*R*)-3 (Boc-L-Ile-(*R*)-Ph): ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (m, 6H), 1.08 (m, 1H), 1.41 (s, 9H), 1.47 (m, 1H), 1.84 (m, 1H), 3.32 (m, 1H), 3.69 (ddd, ^3J=3.5, 7.0 Hz, ^2J=14.1 Hz, 1H), 3.92 (dd, ^3J=6.6, 8.6 Hz, 1H), 4.82 (dd, ^3J=3.4, 8.2 Hz, 1H), 5.15 (d, ^3J=8.8 Hz, 1H), 6.68 (m, 1H), 7.27–7.36 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.6, 15.8, 24.9, 28.5 (3C), 37.3, 47.6, 59.7, 73.6, 80.3, 126.1 (2C), 128.0, 128.7 (2C), 141.8, 156.2, 173.1 ppm.

I-(*S*)-3 (Boc-L-Ile-(*S*)-Ph): ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (m, 6H), 1.08 (m, 1H), 1.41 (s, 9H), 1.50 (m, 1H), 1.78 (m, 1H), 3.31 (m, 1H), 3.65 (ddd, ^3J=3.5, 7.0 Hz, ^2J=14.1 Hz, 1H), 3.91 (m, 1H), 4.12 (brs, 1H; *OH*), 4.81 (m, 1H), 5.35 (m, 1H), 6.90 (m, 1H), 7.22–7.36 ppm (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.5, 15.7, 24.9, 28.5 (3C), 37.2, 47.6, 59.8, 73.0, 80.3, 126.0 (2C), 127.9, 128.7 (2C), 141.8, 156.3, 174.2 ppm; MS: *m/z* $[M+K]^+$ calcd for $C_{19}H_{30}KN_2O_4$: 389.184; found: 389.192.

I-(*R*)-4 (Boc-L-Ile-(*R*)-Me): ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (m, 6H), 1.18 (d, ^3J=8.0 Hz, 3H), 1.22 (m, 2H), 1.44 (s, 9H), 1.89 (m, 1H), 2.66 (d, 4.0 Hz, 1H), 3.13 (ddd, ^3J=5.7, 8.1 Hz, ^2J=13.5 Hz, 1H), 3.44 (ddd, ^3J=3.3, 6.6 Hz, ^2J=13.5 Hz, 1H), 3.88 (dd, ^3J=6.6, 8.1 Hz, 1H), 3.93 (m, 1H), 5.01 (m, 1H), 6.43 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.5, 15.8, 20.9, 25.0, 28.5 (3C), 37.2, 47.1, 59.9, 67.4, 80.3, 156.3, 172.9 ppm.

I-(*S*)-4 (Boc-L-Ile-(*S*)-Me): ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.92 (m, 6H), 1.11 (m, 1H), 1.17 (d, ^3J=8.0 Hz, 3H), 1.43 (s, 9H), 1.51 (m, 1H), 1.85 (m, 1H), 3.06 (brs, 1H; *OH*), 3.06 (ddd, ^3J=5.4, 8.1 Hz, ^2J=13.5 Hz, 1H), 3.47 (ddd, ^3J=3.3, 6.6 Hz, ^2J=13.8 Hz, 1H), 3.88 (m, 1H), 3.93 (m, 1H), 5.14 (d, ^3J=7.8 Hz, 1H), 6.59 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.5, 15.8, 20.9, 25.0, 28.5 (3C), 37.1, 47.3, 59.9, 67.1, 80.4, 156.3, 172.9 ppm; MS: *m/z* $[M+Na]^+$ calcd for $C_{14}H_{28}N_2NaO_4$: 311.195; found: 311.200.

G-(*R*)-3 (Boc-Gly-(*R*)-Ph) and G-(*S*)-3 (Boc-Gly-(*S*)-Ph): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.38 (s, 9H), 3.21–3.28 (m, 1H), 3.55–3.64 (m, 1H), 3.71 (s, 2H), 4.46 (brs, 1H), 4.74 (dd, ^3J=3.0 Hz, 8.4 Hz, 1H), 5.69 (brs, 1H), 7.07 (brs, 1H), 7.20–7.36 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=28.5 (3C), 44.3, 47.4, 73.0, 80.5, 126.1 (2C), 127.9, 128.7 (2C), 141.9, 156.5, 171.0 ppm; MS: *m/z* $[M+Na]^+$ calcd for $C_{15}H_{22}N_2NaO_4$: 317.148; found: 317.148.

G-(*R*)-4 (Boc-Gly-(*R*)-Me) and G-(*S*)-4 (Boc-Gly-(*S*)-Me): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.13 (d, ^3J=6.0 Hz, 1H), 1.40 (s, 9H), 3.02–3.11 (m, 1H), 3.35–3.42 (m, 1H), 3.71 (d, ^3J=5.7 Hz, 2H), 3.85 (m, 1H), 5.72 (brs, 1H), 7.06 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.8, 28.5 (3C), 44.4, 47.0, 67.0, 80.5, 156.6, 171.0 ppm.

PhG-(*R*)-3 (Boc-L-PhGly-(*R*)-Ph): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.41 (s, 9H), 2.96 (brs, 1H), 3.31 (ddd, ^3J=5.7, 7.5 Hz, ^2J=14.1 Hz, 1H), 3.72 (ddd, ^3J=3.6, 6.9 Hz, ^2J=14.1 Hz, 1H), 4.77 (dd, ^3J=3.6, 7.5 Hz, 1H), 5.10 (brs, 1H), 5.72 (d, ^3J=7.2 Hz, 1H), 6.23 (brs, 1H), 7.21–7.38 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=28.5 (3C), 47.5, 58.7, 72.8, 80.5, 126.1 (2C), 127.4 (2C), 127.9, 128.5 128.6 (2C), 129.2 (2C), 138.3, 141.8, 155.6, 171.4 ppm.

PhG-(*S*)-3 (Boc-L-PhGly-(*S*)-Ph): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.37 (s, 9H), 3.27 (ddd, ^3J=5.7, 7.5 Hz, ^2J=13.5 Hz, 1H), 3.55 (ddd, ^3J=4.0, 6.6 Hz, ^2J=13.5 Hz, 1H), 3.99 (brs, 1H), 4.73 (dd, ^3J=3.6, 7.5 Hz, 1H), 5.22 (brs, 1H), 6.00 (d, ^3J=7.2 Hz, 1H), 6.83 (brs, 1H), 7.17–7.30 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=28.5 (3C), 47.5, 58.7, 72.8, 80.5, 126.1 (2C), 127.4 (2C), 127.9, 128.5, 128.6 (2C), 129.2 (2C), 138.3, 141.8, 155.6, 171.4 ppm; MS: *m/z* $[M+Na]^+$ calcd for $C_{21}H_{26}N_2NaO_4$: 393.179; found: 393.169.

PhG-(*R*)-4 (Boc-L-PhGly-(*R*)-Me): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.37 (s, 9H), 2.99 (brs, 1H), 3.10 (ddd, ^3J=5.7, 7.5 Hz, ^2J=13.5 Hz, 1H), 3.32 (ddd, ^3J=3.6, 6.6 Hz, ^2J=13.5 Hz, 1H), 3.82 (m, 1H), 5.17 (brs, 1H), 5.86 (d, ^3J=6.3 Hz, 1H), 6.73 (brs, 1H), 7.25–7.37 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.8, 28.5 (3C), 47.3, 59.0, 67.1, 80.5, 127.4 (2C), 128.5, 129.2 (2C), 138.3, 155.6, 171.4 ppm.

PhG-(*S*)-4 (Boc-L-PhGly-(*S*)-Me): ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.37 (s, 9H), 2.99 (brs, 1H), 3.10 (ddd, ^3J=5.7, 7.5 Hz, ^2J=13.5 Hz, 1H), 3.32 (ddd, ^3J=3.6, 6.6 Hz, ^2J=13.5 Hz, 1H), 3.82 (m, 1H), 5.17 (brs, 1H),

5.86 (d, ^3J=6.3 Hz, 1H), 6.73 (brs, 1H), 7.25–7.37 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.7, 28.5 (3C), 47.2, 58.7, 66.8, 80.4, 127.4 (2C), 128.4, 129.0 (2C), 138.3, 155.7, 171.5 ppm; MS: *m*/*z* $[M+K]^+$ calcd for $C_{16}H_{24}N_2NKO_4$: 347.137; found: 347.146.

***t*L-(*R*)-3 (Boc-L-*t*Leu-(*R*)-Ph)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.97 (s, 9H), 1.38 (s, 9H), 3.28 (m, 1H), 3.62 (ddd, ^3J=3.2, 6.4 Hz, ^2J=14.0 Hz, 1H), 3.89 (m, 1H), 4.77, (dd, ^3J=3.2, 8.0 Hz, 1H), 5.54 (d, ^3J=9.2 Hz, 1H), 6.99 (m, 1H), 7.20–7.33 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.8 (3C), 28.5 (3C), 34.7, 47.5, 62.6, 73.4, 80.1, 126.1 (2C), 127.9, 128.6 (2C), 142.0, 156.3, 172.3 ppm.

***t*L-(*S*)-3 (Boc-L-*t*Leu-(*S*)-Ph)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.93 (s, 9H), 1.40 (s, 9H), 3.27 (ddd, ^3J=4.8, 8.8 Hz, ^2J=13.6 Hz, 1H), 3.62 (ddd, ^3J=3.2, 6.8 Hz, ^2J=14.0 Hz, 1H), 3.89 (d, ^3J=8.8 Hz, 1H), 4.80, (dd, ^3J=3.2, 8.4 Hz, 1H), 5.55 (d, ^3J=9.2 Hz, 1H), 6.98 (m, 1H), 7.20–7.33 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.7 (3C), 28.5 (3C), 34.5, 47.6, 62.7, 73.0, 80.2, 126.1 (2C), 127.9, 128.6 (2C), 141.9, 156.5, 172.5 ppm; MS: *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{30}N_2NaO_4$: 373.210; found: 373.218.

***t*L-(*R*)-4 (Boc-L-*t*Leu-(*R*)-Me)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.96 (s, 9H), 1.13 (d, 3J=6.0 Hz, 3H), 1.38 (s, 9H), 3.11 (ddd, ^3J=6.0, 7.6 Hz, ^2J=13.6 Hz, 1H), 3.35 (ddd, ^3J=3.2, 6.4 Hz, ^2J=13.6 Hz, 1H), 3.78–3.93 (m, 2H), 5.47 (m, 1H), 7.05 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.9, 26.8 (3C), 28.5 (3C), 34.5, 47.0, 62.7, 67.3, 80.0, 156.4, 172.2 ppm.

***t*L-(*S*)-4 (Boc-L-*t*Leu-(*S*)-Me)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.96 (s, 9H), 1.12 (d, ^{3}J=6.4 Hz, 3H), 1.38 (s, 9H), 3.02 (m, 1H), 3.35 (ddd, ^3J=3.2, 6.4 Hz, ^2J=14.0 Hz, 1H), 3.84–3.90 (m, 2H), 5.49 (d, ^3J=9.2 Hz, 1H), 7.03 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.8, 26.8 (3C), 28.5 (3C), 34.4, 47.2, 62.9, 66.8, 80.1, 156.5, 172.3 ppm; MS: *m*/*z* $[M+K]^+$ calcd for $C_{14}H_{28}N_2KO_4$: 327.169; found: 327.175.

***(R)-N-iso*butoxycarbonyl-2-amino-1-phenylethanol (5)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (d, ^3J=6.9 Hz, 6H), 1.90 (m, 1H), 3.03 (brs, 1H), 3.29 (ddd, ^3J=5.4, 8.4 Hz, ^2J=13.8 Hz, 1H), 3.53 (ddd, ^3J=3.3, 6.9 Hz, ^2J=14.1 Hz, 1H), 3.84 (d, ^3J=6.6 Hz, 2H), 4.82 (m, 1H), 5.13 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.2 (2C), 28.2, 48.7, 71.5, 73.8, 126.1 (2C), 127.7, 128.1 (2C), 141.9, 157.9 ppm.

***(R)-N-iso*butoxycarbonyl-1-amino-2-propanol (6)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (d, ^3J=6.9 Hz, 6H), 1.18 (d, ^3J=6.6 Hz, 3H), 1.89 (m, 1H), 2.43 (brs, 1H), 3.04 (ddd, ^3J=6.0, 7.5 Hz, ^2J=13.5 Hz, 1H), 3.31 (ddd, ^3J=3.0, 6.6 Hz, ^2J=14.1 Hz, 1H), 3.83 (d, ^3J=7.2 Hz, 2H), 3.90 (m, 1H), 5.13 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.2 (2C), 20.8, 28.2, 48.5, 67.5, 71.4, 157.8 ppm.

***N*-(*N*′-Boc-L-alaninyl)-1-amino-2-propanone (7)**: Oxalyl chloride (1.1 mmol, 96 μL) dissolved in CH_2Cl_2 (2.5 mL) was placed in a flask equipped with a stirrer and a septum under N_2 (using a needle connected to a dry nitrogen supply). The flask was cooled to −78 °C, and a solution of DMSO (2.4 mmol, 176 μL) in CH_2Cl_2 (0.5 mL) was added with syringe and needle over 5 min followed by 10 min of stirring. A solution of the amido alcohol (1 mmol, 0.246 g) in CH_2Cl_2 (1.0 mL) was then added over 5 min. The resulting mixture was stirred for 15 min and triethylamine (5 mmol, 0.464 mL) was added at −78 °C over 5 min. The cooling bath was removed and when the mixture reached room temperature, water (3 mL) was added. After 10 min of stirring the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2×10 mL), and the combined organic phases evaporated to dryness. Yield: 199 mg, 80%;[12] ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.34 (d, ^3J=7.2 Hz, 1H), 1.41 (s, 9H), 2.16 (s, 3H), 4.10 (d, ^3J=4.8 Hz, 2H), 4.20 (m, 1H), 5.17 (brs, 1H), 6.97 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.7, 27.5, 28.5 (3C), 59.9, 50.3, 80.3, 155.6, 173.1, 203.1 ppm.

General procedure for the hydrogen-transfer reaction: Ligand (0.011 mmol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.005 mmol) and NaOH (0.05 mmol) were dried under vacuum for 30 min and dissolved in 2-propanol (5 mL) in a dry Schlenck tube under an inert atmosphere (N_2). The solution was stirred for 15 min and the ketone (1 mmol) added. The reaction mixture was stirred at ambient temperature. Samples were taken at different time intervals and either quenched with NH_4Cl (1 mL, aq. sat.), extracted with EtOAc (1 mL), passed through a pad of silica, and washed with EtOAc; or directly passed through a pad of silica. The resulting solution was analyzed by GLC (CP Chirasil DEX CB).[18]

General procedure for the hydrogen-transfer reaction under microwave irradiation: $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.005 mmol), and acetophenone (1 mmol) were added to a solution of ligand A-(*S*)-**4** (0.011 mmol) and NaOH (0.05 mmol) in 2-propanol (5 mL). The reaction mixture was heated in the microwave cavity according to times and temperatures reported in Table 2. After cooling, the reaction mixture was quenched with NH_4Cl (1 mL, aq. sat.), extracted with EtOAc (1 mL) and passed through a pad of silica. The resulting solution was analyzed by GLC (CP Chirasil DEX CB).[18]

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