Employing the Structural Diversity of Nature: Development of Modular Dipeptide-Analogue Ligands for Ruthenium-Catalyzed Enantioselective Transfer Hydrogenation of Ketones

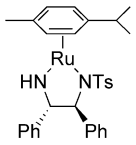
Isidro M. Pastor, Patrik Västilä, and Hans Adolfsson*[a]

Abstract: A library of novel dipeptide-analogue ligands based on the combination of *tert*-butoxycarbonyl(*N*-Boc)-protected α-amino acids and chiral vicinal amino alcohols were prepared. These highly modular ligands were combined with $[\{RuCl_2(p\text{-cymene})\}_2]$ and the resulting metal complexes were screened as catalysts for the enantioselective reduction of acetophenone under transfer hydrogenation conditions using 2-propanol as the hydrogen donor. Excellent enantioselectivity of 1-phenylethanol (up to 98% *ee*) was achieved with several of the novel catalysts. Although most of the ligands contained two stereocenters, it was demonstrated that the absolute configuration of the product alcohol was determined by the configuration of the amino acid part of the ligand. Employing ligands based on L-amino acids generated *S*-configured products, and catalysts based on D-amino acids favored the formation of the *R*-configured alcohol. The combination *N*-Boc-L-alanine and (*R*)-phenylglycinol (**Boc-L-Ab**) or its enantiomer (*N*-Boc-D-alanine and (*S*)-phenylglycinol, **Boc-D-Aa**) proved to be the best ligands for the reduction process. Transfer hydrogenation of a number of aryl alkyl ketones were evaluated and excellent enantioselectivity, up to 96% *ee*, was obtained.

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

Introduction

Transition-metal catalyzed transfer hydrogenation has emerged as an efficient and practical method for the enantioselective reduction of prochiral ketones to secondary alcohols. In recent years, a considerable number of chiral metal complexes have been prepared and examined as catalysts in the reduction reaction.[1] The most successful catalysts so far are based on $[\{RuCl_2(arene)\}_2]$ combined with chiral, enantiomerically pure 1,2-amino alcohols or mono-*N*-sulfonated 1,2-diamines (e.g. TsDPEN).[2] The most common hydrogen source for catalytic transfer hydrogenation of ketones is 2-propanol, although the use of formic acid, in particular a 5:2 formic acid/triethyl amine azeotropic mixture, is usually the preferred terminal reductant because of the favorable irreversible process. The latter reductant is, however, limited to only a few ruthenium catalysts. For example, the highly efficient and selective catalyst **1**, introduced by Noyori and co-workers, reduces ketones with high enantioface selectivity and in high conversions using the formic acid/triethylamine system,[3] whereas the corresponding catalyst formed from $[Ru^{II}(arene)]$ complexes and 1,2-amino alcohols only give the product in the presence of a secondary alcohol, typically 2-propanol.[4, 5] The catalytic activity (TOF), however, is generally higher when amino alcohols are employed as ligands.[2a, 6]



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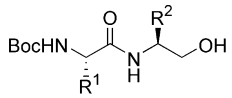

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We have recently introduced a novel class of ligands for asymmetric transfer hydrogenation.[7] The dipeptide analogues **2**, obtained from *tert*-butoxycarbonyl(*N*-Boc)-protected α-amino acids and 1,2-amino alcohols, were combined with $[Ru^{II}(arene)]$ complexes to generate highly active and selective catalysts for the reduction of aryl alkyl ketones. The use of amino acids,[8, 9] amino amides,[10, 11] and even dipeptides[8] as ligands for the reduction process has previously been reported but the resulting catalysts nearly all produced the secondary alcohols with low to moderate enantioselectivity. Furokawa and co-workers employed a number of α-amino acids as ligands together with $[\{RuCl_2(p\text{-cymene})\}_2]$ as catalysts for the reduction of acetophenone in 2-propanol and the secondary alcohols were formed with enantioselectivity ranging from 3–81%.[8a] The use of dipeptide ligands resulted in *ee* values

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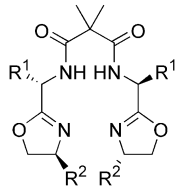
 DOI: 10.1002/chem.200304900

ranging from 0–43%.[8b] Carmona and co-workers reported on the preparation of self-assembled trimeric metal–arene complexes (Rh, Ir, and Ru) containing amino acids as bridging ligands. These complexes were employed as catalysts in the transfer hydrogenation of acetophenone using either 2-propanol or sodium formate as the hydrogen source. The catalysts were reasonably active at high temperature (83 °C) and the enantioselectivities ranged from 2–73%.[9] Simple amides derived from α-amino acids have been shown to be somewhat better ligands than the parent acids. Hence, L-prolineamide combined with $[\{RuCl_2(p\text{-cymene})\}_2]$ or $[\{Cp^*RhCl_2\}_2]$ catalyzed the reduction of aryl alkyl ketones using 2-propanol with selectivities ranging from 35–93% *ee*.[10] The *N*-aryl prolineamides introduced by Chung and co-workers turned out to be even more efficient ligands, thus when combined with $[Ru^{II}(arene)]$ complexes, high conversions and selectivities (up to 98% *ee*) were obtained in the transfer hydrogenation of a number of substituted aryl alkyl ketones.[11] The source of hydrogen used in the latter reductions was either the 5:2 formic acid/triethyl amine azeotropic mixture or simply sodium formate in aqueous solution.

The results obtained by the Chung group inspired us to investigate a class of carboxamido-oxazoline ligands (**3**) in the ruthenium-catalyzed transfer hydrogenation of ketones. We recently prepared these tetradentate bisamides and employed them in the titanium-catalyzed enantioselective addition of diethylzinc to aryl aldehydes.[12]



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When used in the reduction of acetophenone under transfer hydrogenation conditions with either $[Ru(PPh_3)_3Cl_2]$ or $[\{RuCl_2(p\text{-cymene})\}_2]$ as ruthenium sources, poor reactivity and selectivity were observed. Interestingly, we discovered that a precursor used in the preparation of ligand **3**, when combined with the $[\{RuCl_2(p\text{-cymene})\}_2]$ complex, catalyzed the formation of 1-phenylethanol (in 2-propanol) with significantly better selectivity. The actual ligand employed in this crucial experiment was the *N*-Boc-protected amide **2** ($R^1 = R^2 = i$Pr); when we analyzed the reaction mixture we found that the secondary alcohol was formed with modest conversion (13% after 2 h), but in good enantioselectivity (93% *ee*). This result encouraged us to further investigate the effect of employing differently substituted dipeptide-like ligands formed by the combination of amino acids and amino alcohols. Herein we report in detail on the formation of these modular ligands and on the results obtained employing this ligand library in the ruthenium-catalyzed transfer hydrogenation of prochiral ketones.

Results and Discussion

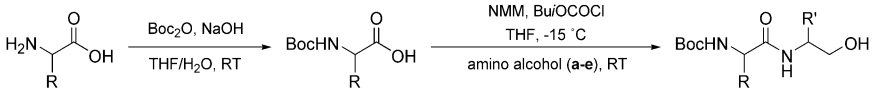
The structural diversity of Nature has provided us with a vast supply of material for the preparation of chiral, enantiomerically pure ligands for asymmetric catalysis. The ready availability of naturally occurring, inexpensive building blocks like amino acids makes these compounds excellent as starting materials. The great variety of functionality displayed by the amino acids further increases the power of employing them in the search for highly active and selective catalysts. The promising initial results obtained with the dipeptide analogue **2** as a ligand for ruthenium in the transfer hydrogenation of acetophenone invited an extended study in search of catalysts of higher activity and selectivity. Thus, from the initial combination of L-valine and L-valinol, we set out to prepare a library of analogous ligands and to study the influence of different ligand substituents in the reduction reaction.

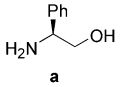
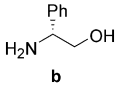
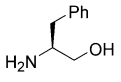
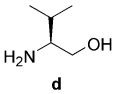
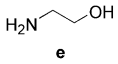
Preparation of the ligand library: The dipeptide-like structure of the ligand is particularly attractive since it is easily modified by the choice of starting materials. In addition, the short and simple route to these compounds allows them to be prepared on a multigram scale. A library of 45 dipeptide ligands, using a combination of nine amino acids (i.e. L-phenyl-Gly, D-phenyl-Gly, L-Phe, L-Leu, L-Ala, D-Ala, L-Val, D-Val, and L-*t*Leu) and five amino alcohols (i.e. L-phenylglycinol, D-phenylglycinol, L-phenylalaninol, L-valinol, and 2-aminoethanol) was readily obtained as outlined in Table 1. The ligands were prepared in a straightforward two-step synthesis: *N*-protection of the amino acid with Boc_2O, using a standard procedure,[13] was followed by coupling with the corresponding 1,2-amino alcohol. For the latter step we found that the use of isobutyl chloroformate as coupling reagent worked particularly well.[13] The ligands were isolated in good yields (Table 1) after recrystallization (the ligands containing 2-aminoethanol were, however, isolated as oils).

Moreover, to elucidate the importance and influence of the different possible coordinating atoms and stereocenters of the ligand in the activity and selectivity of the Ru^{II} catalyst during the hydrogen transfer reaction, other ligands of potential interest were prepared. Thus, the following carbamates (benzyl carbamate (Z), allyl carbamate (Alloc), and 9-fluorenylmethyl carbamate (Fmoc)) and amides (acetamide, trifluoroacetamide, and tosylamide) were used as protecting groups for the *N*-terminal in the amino acid part. For this study, the combination of L-valine (**L-V**) and (*R*)-phenylglycinol (**b**) was chosen. Cleavage of the Boc group in ligand **Boc-L-Vb** was also performed to obtain the compound with a free amine functionality (**L-Vb**). The synthesis of the ligands containing different carbamates was carried out in the same way as previously outlined, initial *N*-protection followed by formation of the peptide bond with *R*-phenylglycinol (**b**). The Alloc and Fmoc protection was performed by reacting L-valine (**L-V**) with allyloxy and 9-fluorenylmethyloxy chloroformate, respectively, under basic conditions. The Z-*N*-L-valine (**Z-L-V**) was prepared by using *N*-(benzyloxycarbonyloxy)succinimide (Scheme 1).

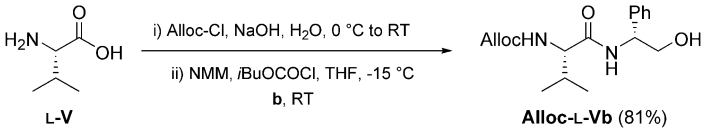
The reaction of L-valine with a mixture of acetic acid and acetic anhydride or with trifluoroacetic acid/trifluoroacetic anhydride gave the corresponding acetamide (**Ac-L-V**) and trifluoroacetamide (**TFA-L-V**) derivatives, which yielded the ligands **Ac-L-Vb** and **TFA-L-Vb** after the typical coupling with (*R*)-phenylglycinol (Scheme 2).

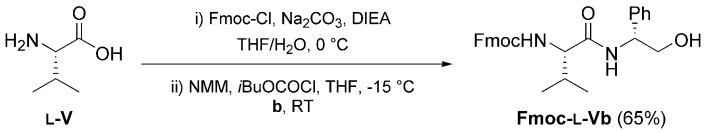
Table 1. Preparation of the library of *N*-Boc-protected ligands.[a]

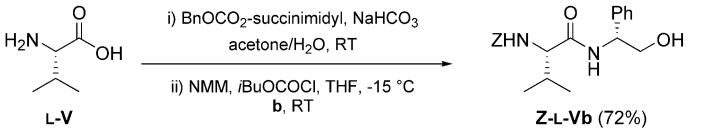


Amino acid	Amino alcohol				
	 **a**	 **b**	 **c**	 **d**	 **e**
L-PhG	**Boc-L-PhGa** (68)	**Boc-L-PhGb** (77)	**Boc-L-PhGc** (76)	**Boc-L-PhGd** (68)	**Boc-L-PhGe** (57)
D-PhG	**Boc-D-PhGa** (73)	**Boc-D-PhGb** (81)	**Boc-D-PhGc** (76)	**Boc-D-PhGd** (82)	**Boc-D-PhGe** (61)
L-F	**Boc-L-Fa** (82)	**Boc-L-Fb** (80)	**Boc-L-Fc**(90)	**Boc-L-Fd** (76)	**Boc-L-Fe** (59)
L-L	**Boc-L-La** (74)	**Boc-L-Lb** (84)	**Boc-L-Lc** (89)	**Boc-L-Ld** (92)	**Boc-L-Le** (80)
L-A	**Boc-L-Aa** (83)	**Boc-L-Ab** (85)	**Boc-L-Ac** (81)	**Boc-L-Ad** (74)	**Boc-L-Ae** (53)
D-A	**Boc-D-Aa** (95)	**Boc-D-Ab** (85)	**Boc-D-Ac** (89)	**Boc-D-Ad** (68)	**Boc-D-Ae** (52)
L-V	**Boc-L-Va** (82)	**Boc-L-Vb** (91)	**Boc-L-Vc** (73)	**Boc-L-Vd** (89)	**Boc-L-Ve** (63)
D-V	**Boc-D-Va** (79)	**Boc-D-Vb** (85)	**Boc-D-Vc** (79)	**Boc-D-Vd** (81)	**Boc-D-Ve** (58)
L-tL	**Boc-L-tLa** (65)	**Boc-L-tLb** (62)	**Boc-L-tLc** (63)	**Boc-L-tLd** (47)	**Boc-L-tLe** (41)

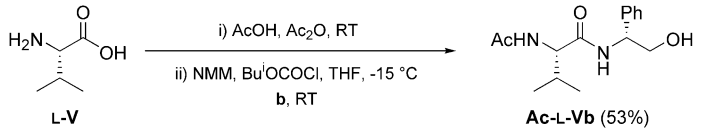
[a] The values given in parentheses refer to yields of the dipeptide analogues based on the amino acid after the two steps.

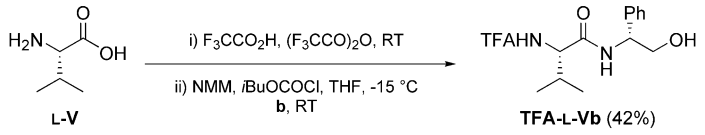






Scheme 1. Preparation of ligands **Alloc-L-Vb**, **Fmoc-L-Vb**, and **Z-L-Vb**.



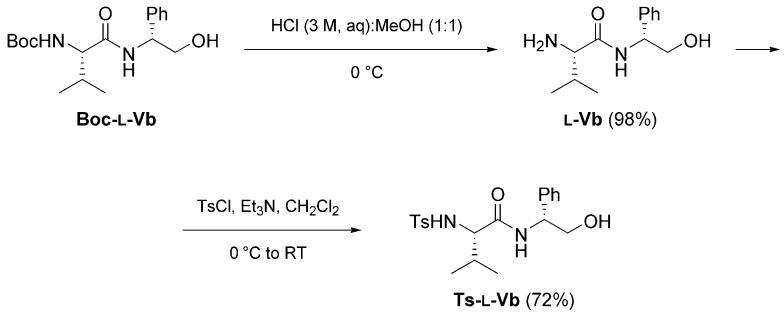


Scheme 2. Preparation of ligands **Ac-L-Vb** and **TFA-L-Vb**.

For the generation of the unprotected ligand (**L-Vb**), compound **Boc-L-Vb** was treated with a 1:1 mixture of methanol and HCl (3 M aq.) at low temperature, according to the synthetic route developed for the preparation of the C_2-symmetric oxazoline ligands.[12] This compound (**L-Vb**) was also used for the preparation of the tosylamide derivative (**Ts-L-Vb**) as outlined in Scheme 3. Although *N*-tosylation of amino acids using tosyl chloride usually results in high yields of the *N*-sulfonated amino acid, the use of this route for the preparation of **Ts-L-Vb** did not give good results in our hands.

Asymmetric transfer hydrogenation, screening of the ligand library: The library containing 45 ligands was evaluated in the reduction of acetophenone using 2-propanol as hydrogen source (0.2 M of the ketone in 2-propanol). The reactions were carried out with a substrate/ruthenium/ligand/base ratio of 100:1:3:5. The active catalyst was prepared in situ by mixing the ligand (3 mol%), [{$RuCl_2$(*p*-cymene)}$_2$] (0.5 mol%), and the base (NaOH, 5 mol%) in 2-propanol for 10–15 min at room temperature. The reaction mixture usually turned a purple or reddish color in the beginning, which sometimes changed after few minutes to light brown. The ketone was added to the reaction mixture and the transfer hydrogenation was performed at room temperature for 2 h. The reactions were quenched using ammonium chloride (aqueous solution) and the conversion and stereochemical outcome were then analyzed by GLC. The results are summarized in Figure 1, which shows conversions (a) and enantioselectivity/product configuration (b).

From the plots in Figure 1 it is evident that structural variations of the ligand play an important role for the activity and selectivity of the ruthenium catalyst formed in situ. Focusing on catalytic activity, the plot in Figure 1a shows that using ligands containing two stereocenters, one in the amino acid part and one in the amino alcohol, generally resulted in lower conversion to the secondary alcohol (series **a–d**) as compared with the ligand combination between all *N*-Boc-protected amino acids and 2-aminoethanol (series **e**). In the latter series (**e**), the ligands derived from L- or D-phenylglycine had the highest activity, resulting in almost quantitative formation of the product after 2 h. When amino acids containing other side chains were employed, lower conversions were obtained. The general trend indicates that an increased number of substituents at the β-carbon atom, which increase the steric hindrance, have a detrimental effect on the



Scheme 3. Preparation of the ligands **L-Vb** and **Ts-L-Vb**.

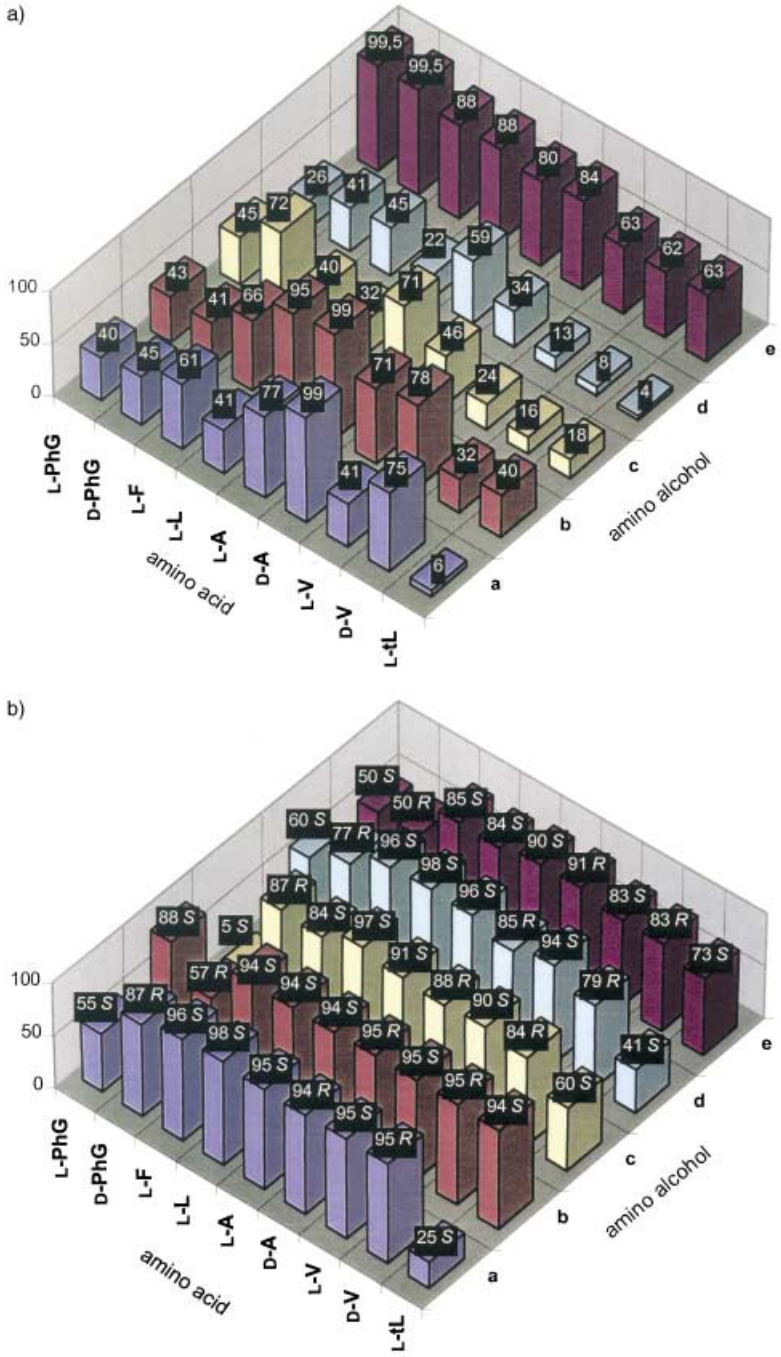


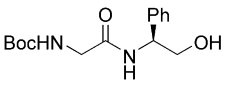
Figure 1. a) Conversion of acetophenone after 2 h using the ligand library presented in Table 1. b) Enantioselectivity and product configuration of 1-phenylethanol using the different ligands.

catalytic activity. This is particularly striking when comparing ligands derived from *t*-leucine or valine with those based on the less sterically demanding alanine or leucine; the catalytic transfer hydrogenation employing the latter ligands resulted in about 20% better conversion. Regarding the ligands in series **a**–**d**, there are only a few combinations for which comparable activity was obtained. Moderate to good conversion was achieved employing phenylglycinol combined with leucine, alanine, or valine. A remarkable difference in activity is observed comparing ligands **Boc-PhGa** or **Boc-PhGb** (phenylglycine and phenylglycinol) and the highly-productive **Boc-PhGe** (phenylglycine and 2-aminoethanol). Furthermore, comparing the results obtained based on the amino alcohols employed (series **a**–**d**), the general trend of activity goes from **L-A** and **L-L** (high) to **L-V** (moderate) and **L-tL** (poor). These results confirm the observation that steric hindrance is of high importance for catalytic activity (with 2-aminoethanol the tendency is not so obvious). Another interesting observation that can be made from Figure 1a is the distinct difference in activity between diastereomeric ligands. When ligand **Boc-L-Ab** and its mirror image, ligand **Boc-D-Aa**, were employed in the transfer hydrogenation reaction, excellent conversions were obtained, however the use of the diasteromeric ligands **Boc-D-Ab** and **Boc-L-Aa** only resulted in moderate formation of the product alcohol. The same trend can be seen when comparing ligands derived from valine and phenylglycinol. This matched/mismatched scenario is most often observed when comparing the stereoselective outcome of a catalytic reaction involving diastereomeric ligands. Here, however, this effect is most pronounced in the

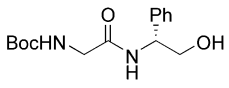
catalytic activity, as will be discussed below. To summarize the results concerning catalytic activity, the structure of the catalyst is highly sensitive towards steric hindrance imposed by the coordinating ligand. Furthermore, the proper combination of the two stereocenters present in most of the ligands is of high importance for the outcome of the reaction.

The stereoselectivity obtained by using the library of ligands is depicted in Figure 1b. With a few exceptions, high enantioface selectivity (>85% *ee*) was attained with most combinations of amino acids and amino alcohols. It is noteworthy that, regardless of the chiral information provided by the 1,2-amino alcohol, the absolute configuration of the product was, in all entries, determined by the stereocenter present in the amino acid part of the ligand. Hence, ligands based on natural amino acids generated products of *S* configuration and when an unnatural amino acid was present in the ligand, the *R*-configured product was obtained. The highly active (in terms of conversion) catalysts generated from the ligand combination of *N*-Boc-phenylglycine and 2-aminoethanol (**Boc-L-PhGe** and **Boc-D-PhGe**) and $[\{RuCl_2(p\text{-cymene})\}_2]$, produced the secondary alcohol with only moderate enantioelectivity (50%). Excellent product *ee* values were reached by using the leucine based ligands **Boc-L-La**, **Boc-L-Lc**, and **Boc-L-Ld** (97–98%). The low chemical yields obtained with these catalysts, however, make them less interesting. On the other hand, employing ligands based on alanine and phenylglycinol (**Boc-Aa** and **Boc-Ab**) resulted in catalysts that reduced acetophenone in high yield and with good enantioselectivity. The matched/mismatched relationship observed for the catalytic activity was only slightly visible in the stereodifferentiation. In fact, the least productive enantiomeric ligand pair turned out to be somewhat more selective, although the difference is certainly insignificant. With the above results in hand, we concluded that the best ligands in the above library for the ruthenium-catalyzed reduction of acetophenone under transfer hydrogenation conditions are the enantiomers **Boc-D-Aa** and **Boc-L-Ab**.

In addition to the above catalytic experiments, we thought it would be interesting to prepare and examine ligands lacking a chiral center in the amino acid moiety (i.e. starting from glycine, **G**). For these experiments we chose phenylglycinol as the amino alcohol, since the results in Figure 1 show that ligands containing this particular group were superior, especially with respect to the selectivity. Following the synthetic procedure described above for *N*-Boc protection and then coupling with the amino alcohol, ligands **Boc-Ga** and **Boc-Gb** were isolated in 65 and 63% yield, respectively.



Boc-Ga



Boc-Gb

Employing ligand **Boc-Gb** in the reduction of acetophenone (using the same conditions as above) resulted in conversion to the *R* alcohol with moderate yield (56%) and enantioselectivity (64% *ee*) (reaction monitored after 2 h). Interestingly, when the chiral information was uniquely located in the amino alcohol (*R*-phenylglycinol), the *R*-configured product was obtained. In contrast, when the same amino alcohol is combined with an L-amino acid, for example L-alanine, a dramatic switch in selectivity was observed. Performing the catalytic reaction with ligand **Boc-L-Ab** gave a 94% *ee* of the *S* isomer. At first sight, it appears that the stereocenter present in the amino alcohol part of the ligand is completely overruled by the chirality present in the amino acid. On closer examination, however, it becomes evident that the amino alcohol actually amplifies the selectivity obtained with this particular ligand (cf. in reactions using ligand **Boc-L-Ae**, 90% *ee* of the (*S*)-1-phenylethanol was obtained). Using **Boc-Ga** gave, as expected, complementary results to **Boc-Gb** (60% conversion and 63% *ee* of the *S* enantiomer after 2 h).

On the basis of these results, it is evident that the choice of amino acid is important for the activity and enantioselectivity of the active catalyst. Nevertheless, improvements both in activity and selectivity of the catalytic process can be accomplished by combining the amino acid with a proper amino alcohol.

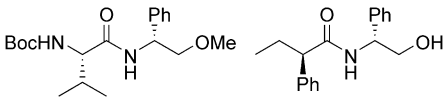
Asymmetric transfer hydrogenation, ligand structure versus catalytic activity: As observed above, when screening the ligand library, the side-chain structure of the pseudopeptides plays an important role in determining the activity and selectivity displayed by the ruthenium catalyst. In connection to the results obtained by using Boc-protected peptide analogues as ligands, we set out to investigate how changes in the functional groups would affect the catalytic activity (Table 2). Initially we focused on using ligands in which the Boc group had been replaced by other carbamates. Catalytic transfer hydrogenation of acetophenone using ligands protected either with allyl carbamate (Alloc) or with benzyl carbamate (Z) proceeded smoothly and generated the secondary alcohol in good conversion and enantioselectivity (Table 2, entries 2 and 4). Employing the Fmoc-protected ligand resulted in practically no product formation (Table 2, entry 3).

Table 2. Ruthenium-catalyzed transfer hydrogenation of acetophenone.[a] Effects of ligand functional group variation.

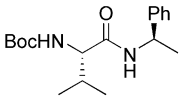
Entry	Ligand	Conversion [%][b]	Enantioselectivity [%][c]
1	**Boc-L-Vb**	78	95
2	**Alloc-L-Vb**	81	93
3	**Fmoc-L-Vb**	<1	–
4	**Z-L-Vb**	80	93
5	**Ac-L-Vb**	<2	–
6	**TFA-L-Vb**	6	66
7	**L-Vb**	<2	–
8	**Ts-L-Vb**	<2	–
9	**4**	4	7
10	**5**	<2	–
11	**6**	<2	–

[a] Reaction conditions: Acetophenone (1 equiv, 0.2 M in 2-propanol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (1 mol% in Ru), ligand (3 mol%), and NaOH (5 mol%). All reactions were performed at ambient temperature for 2 h. [b] Conversion was determined by GLC analysis. [c] Enantiomeric excess was determined by GLC (CP Chirasil DEX CB).

Changing the protecting group on the *N*-terminal to a carboxamide functionality resulted in ligands that performed poorly in the catalytic reaction (Table 2, entries 5 and 6). Furthermore, running the reduction with ligands containing an unprotected (Table 2, entry 7) or a sulfonate-protected (Table 2, entry 8) *N*-terminal gave virtually no product. A possible explanation for the poor reactivity observed using **Fmoc-L-Vb** could be found in the result obtained with the unprotected ligand **L-Vb**. Owing to the base-lability of the Fmoc-protecting group it is highly plausible that ligand **L-Vb** was rapidly formed during the reduction reaction. Thus, we can conclude that a stable carbamate, positioned at the N-terminal, is a necessary prerequisite for a productive ligand. For the C-terminal, the hydroxyl functionality turned out to be of equal importance. Low conversion and *ee* of the product alcohol was obtained when the *O*-methylated ligand **4** was employed in the catalytic reaction (Table 2, entry 9). Additionally, the use of ligands **5** and **6** did not yield the desired product (Table 2, entries 10 and 11). The latter results demonstrate the importance of employing ligands with proper functional groups at both termini.



4 **5**



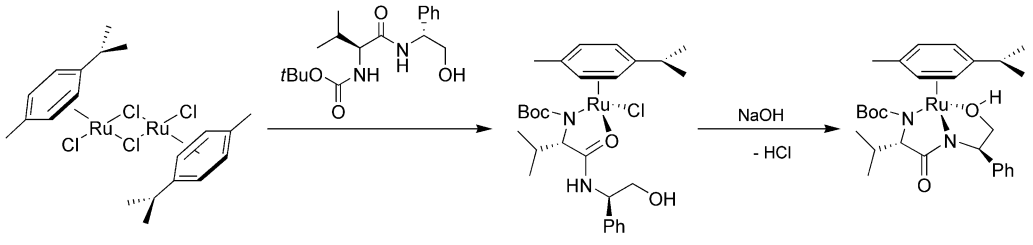
6

Asymmetric transfer hydrogenation, influence of the metal precursor: Variation of the arene moiety in the Ru^{II} precursor has been demonstrated to influence the outcome of the transfer hydrogenation reaction.[6] Performing the reduction of acetophenone with [{$RuCl_2$(benzene)}$_2$] and either of the ligands, **Boc-L-Vb** or **Boc-D-Va**, resulted in conversions comparable to those obtained using the *p*-cymene complex (ca. 75% conversion after 2 h). The enantioselectivity, however, dropped significantly to 81% *ee* of (*S*)-1-phenylethanol using **Boc-L-Vb** and 80% *ee* of the *R* enantiomer using **Boc-D-Va**.

It has previously been reported that the use of Rh^{III} complexes as catalysts in the transfer hydrogenation of ketones gave comparable results to those obtained using Ru^{II}-based catalysts.[14] The Rh^{III} catalysts were prepared from [{Cp*$RhCl_2$}$_2$] and monotosylated diamine ligands, and the reductions were, as in the case of the corresponding Ru^{II}-catalyzed reactions, performed by using either 2-propanol or formic acid as the hydrogen source. To examine whether this would also be applicable in our system, we prepared the analogous Rh^{III} catalyst by mixing **Boc-L-Vb** with [{Cp*$RhCl_2$}$_2$] and base (NaOH) in 2-propanol. Using this catalyst for the reduction of acetophenone (in 2-propanol) at room temperature resulted in 50% conversion and a moderate 80% *ee* of the (*S*)-1-phenylethanol after 2 h. The use of the diastereomeric ligand (**Boc-L-Va**), which was less active with the Ru^{II} precursor, resulted in only 8% conversion and 28% *ee* of the *S* product. Similar results were obtained when the pair of ligands derived from D-valine were employed in the catalytic reaction together with the rhodium precursor, although in these cases an excess of the *R* enantiomer of the alcohol was formed.

Nature of the catalyst: To further our understanding of the structure of the active catalyst, or rather the pre-catalyst, attempts were made to obtain a crystalline sample of the ruthenium complex. This process was, however, unsuccessful, and we decided to examine the catalytic mixture by means of spectroscopic methods. Thus, using ^{1}H NMR spectroscopy (in CD_3OD) we observed that simply mixing ligand **Boc-L-Vb** and [{$RuCl_2$(*p*-cymene)}$_2$] in a 2:1 ratio (L/Ru 1:1) resulted in a spectrum in which the signal from the proton on the carbamate nitrogen was absent. Upon addition of one equivalent of NaOH, the proton signal of the amide disappeared. These observations indicate that an initial complexation reaction occurs, forming a postulated ruthenium complex **7** (Scheme 4),[15] in which the deprotonated carbamate and the amide functionality coordinate to the metal. The removal of the amide proton upon addition of base then allows for the formation of complex **8a**.[16] In the latter complex we believe that the alcohol functionality plays an important role in generating an 18-electron complex, hence stabilizing the ruthenium catalyst. This is in direct contrast to the Noyori catalyst ([{Ru(*p*-cymene)Cl_2}$_2$] and (*S*,*S*)- or (*R*,*R*)-TsDPEN)), which generates a 16-electron complex upon addition of base.[3]

Regarding the mechanism of this transfer hydrogenation, it is likely that the reaction proceeds by the concerted route recently proposed by Noyori and co-workers.[17] According to this mechanism, there is a simultaneous transfer of a hydride



7 **8a**

Scheme 4. Proposed route for the formation of the pre-catalyst.

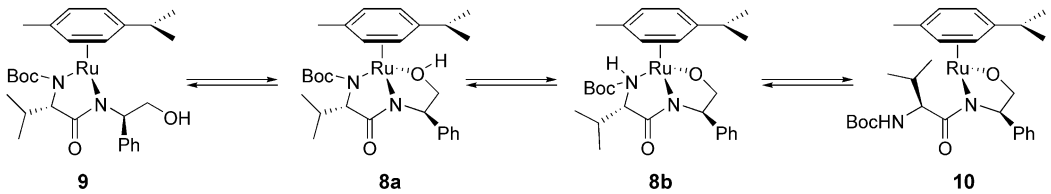
and a proton between the hydrogen donor/substrate and the ruthenium complex. The formation of a catalytically active ruthenium hydride from **8a** must be preceded by the release of one of the coordinating groups of the ligand. Hence, the existence of an equilibrium, as depicted in Scheme 5,[15] is a necessary prerequisite for the catalytic system.

Either of the two 16-electron complexes, **9** or **10**, can in principle react to form the active ruthenium hydride, but at this stage it is difficult to predict which one is operating in the system. An intricate balance in ligand acidity seems, however, to be operating. As described above, ligands containing protecting groups other than carbamates at the N-terminal, gave ruthenium complexes with little or no catalytic activity. Thus, an overly acidic proton at the N-terminal (e.g. using ligand **Ts-L-Vb**) would favor a complex with a structure similar to **9**. This 16-electron complex could generate a ruthenium hydride species upon reaction with 2-propanol, although the low activity observed with ligand **Ts-L-Vb** indicates this process to be unfavorable. Removal of the N-protecting group (i.e. using ligand **L-Vb**) would also favor a complex similar to **9** because of the enhanced coordinating ability of the primary amine. This ligand also turned out to generate a catalyst with low activity. Furthermore, removal of the hydroxyl functionality strongly affected the activity of the catalyst. Using ligand **4** would again favor the formation of a ruthenium complex with a structure closely related to **9**, but the low activity observed with this catalyst demonstrates the importance of the alcohol functionality. The above observations would indicate that the ruthenium hydride is formed from complex **10**, although this is not consistent with the absolute configuration of the product alcohol.

Regardless of the configuration of the stereocenter present in the amino alcohol part of the ligand, we achieved the *S*-configured secondary alcohol as the major isomer when the ligands were based on L-amino acids. Performing the reaction with ligands based on D-amino acids gave the corresponding *R*-configured alcohol. This strongly indicates coordination of the amide and the carbamate in the active catalyst. The additional stereocenters created upon the formation of complexes **9** and **10** (i.e. amide and carbamate nitrogens and the ruthenium center), could certainly influence the observed selectivity. However, the strong correlation between the absolute configuration of the amino acid and the product formed indicates that the configuration of these centers is strictly controlled by the ligand. Furthermore, if either of complexes **9** or **10** is the active 16-electron species in the catalytic reaction, it is clear that the hydride is transferred to ruthenium, but the site of protonation is less obvious. Until further studies concerning the structure of these ruthenium complexes have been conducted it would only be speculative to propose a more detailed mechanism.

Asymmetric transfer-hydrogenation, scope of the reaction: With the results from the ligand optimization study described above, we continued with an examination of the substrate scope. The enantiomeric pair of ligands **Boc-L-Ab** and **Boc-D-Aa** was chosen for this study, since using these compounds gave the best results in terms of activity and selectivity during the reduction of acetophenone. Even though the screening of the library was performed using a 3:1 ligand/Ru ratio, we established that a 1.1:1 ligand/metal ratio gave the same results in terms of catalytic activity and, most importantly, that the enantioselectivity was unaffected. Thus, unless otherwise stated, using a ratio of substrate/ligand/[Ru^{II}]/NaOH in 200:1.1:1:5 in 2-propanol (concentration of the ketone 0.2 M), a number of different aryl alkyl ketones were reduced at room temperature (Table 3).

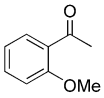
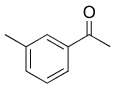
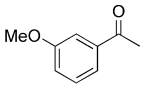
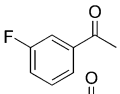
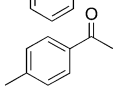
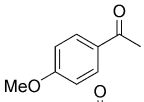
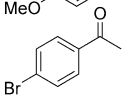
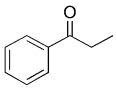
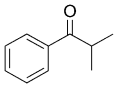
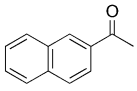
As seen in Table 3, enantiomeric excess and the reaction rate in the transfer hydrogenation of various alkyl aryl ketones were found to depend on both steric and electronic factors. The reduction of acetophenone gave the secondary alcohol in high yield and *ee* using only 0.5 mol% of the ruthenium catalyst. Introducing substituents in the *ortho* position of the substrate, (Table 3, entries 3–5) significantly slowed down the rate of the reaction, probably because of increased steric hindrance, and we had to double the amount of catalyst to reach acceptable yields. In the case of 2-methylacetophenone, excellent enantioselectivity was obtained (entries 3 and 4), whereas the more electron-rich 2-methoxy-acetophenone was reduced in moderate *ee* (Table 3, entry 5). A plausible explanation for the poor reactivity and selectivity obtained with the latter substrate can be found in deactivation of the catalyst by substrate coordination, in which the chiral ligand gets displaced by the substrate.[18] Performing the transfer hydrogenation reaction with aryl methyl ketones substituted in either the *meta*- or *para*-position resulted in considerably better yields and selectivity. Hence, 3-substituted acetophenones were readily reduced in high yield and enantioselectivity regardless of the nature of the substituent (Table 3, entries 6–9). The possibility for substrate chelation using 3-methoxyacetophenone is completely lost, and this particular ketone was reduced in good yield and in excellent enantioselectivity (Table 3, entry 7). The *para*-substituted substrates were smoothly reduced to their corresponding secondary alcohols (Table 3, entries 10–13). The lower reactivity observed for 4-methoxyacetophenone as compared with its 3-substituted analogue is most likely due to electronic effects (Table 3, entries 11 and 12). Interestingly, somewhat poorer selectivity was obtained using



9 **8a** **8b** **10**

Scheme 5. Postulated pre-catalyst equilibrium.

Table 3. Enantioselective transfer hydrogenation of aromatic ketones[a]

Entry	Ketone	Ligand	*t* [h]	Yield [%][b]	*ee* [%][c]
1		**Boc-L-Ab**	5	95	93 (*S*)
2		**Boc-D-Aa**	5	91	93 (*R*)
3[d]		**Boc-L-Ab**	10	74	96 (*S*)
4[d]		**Boc-D-Aa**	10	74	96 (*R*)
5[d]		**Boc-L-Ab**	10	57	84 (*S*)
6		**Boc-L-Ab**	5	89	92 (*S*)
7		**Boc-L-Ab**	5	85	91 (*S*)
8		**Boc-L-Ab**	5	93	89 (*S*)
9		**Boc-D-Aa**	5	93	88 (*R*)
10		**Boc-L-Ab**	5	85	91 (*S*)
11		**Boc-L-Ab**	10	63	95 (*S*)
12		**Boc-D-Aa**	10	65	96 (*R*)
13		**Boc-L-Ab**	2.5	90	88 (*S*)
14		**Boc-L-Ab**	5	91	95 (*S*)
15[e]		**Boc-L-Ab**	10	53	86 (*S*)
16		**Boc-L-Ab**	14	38	84 (*S*)
17		**Boc-L-Ab**	5	85	87 (*S*)
18		**Boc-L-Vb**	5	80	95 (*S*)

[a] Reaction conditions: Ketone (1 equiv, 0.2 M in 2-propanol), [{$RuCl_2$(*p*-cymene)}$_2$] (0.5 mol% in Ru), ligand (0.55 mol%), and NaOH (2.5 mol%). All reactions were performed at ambient temperature. [b] Yields of isolated product. [c] Enantiomeric excess and absolute configuration were determined by GLC (CP Chirasil DEX CB). [d] Reaction conditions: [{$RuCl_2$(*p*-cymene)}$_2$] (1.0 mol% in Ru), ligand (1.1 mol%), and NaOH (5 mol%). [e] Reaction conditions: [{$RuCl_2$(*p*-cymene)}$_2$] (2.0 mol% in Ru), ligand (2.2 mol%), and NaOH (10 mol%).

either 3-methyl or 4-methylacetophenone as compared with the 2-substituted compound. This can possibly be explained by additional positive steric interactions between the catalyst and the substrate. Ketones possessing electron-withdrawing groups in *meta*- and *para*-position (Table 3, entries 8 and 13) reacted readily although they produced the alcohol products in slightly lower enantiomeric excess. We have previously reported that higher enantioselectivity was obtained in the reduction of 4-bromoacetophenone using ligand **Boc-L-Vb** (95% *ee*, 97% conversion after 2 h using 1 mol% catalyst).[7] This shows that certain ligands are better suited for specific substrates, and the power of having easy access to a variety of ligand structures makes this approach especially attractive.

Propiophenone reacted readily under the optimized conditions, and the corresponding secondary alcohol was ob-

tained in good yield and in high enantioselectivity (Table 3, entry 14). The sterically more demanding isobutyrophenone, turned out to be a considerably more problematic substrate. Even though we used 2 mol% of the catalyst, the product alcohol was obtained in mediocre yield and in moderate enantioselectivity (Table 3, entry 15). The reduction of 1-tetralone resulted in poor yield and moderate *ee* of the corresponding secondary alcohol (Table 3, entry 16). Surprisingly, the reduction of 2-acetonaphthone resulted in the formation of the alcohol product in moderate enantioselectivity (Table 3, entry 17). Again, changing the ligand to **Boc-L-Vb** resulted in a catalyst that performed considerably better, and (*S*)-1-(2-naphthyl)ethanol could be obtained in high enantioselectivity (Table 3, entry 18). Comparing the outcome of the reactions using the two different catalysts, it is evident that the interaction between ligand and substrate has a noticeable effect on the enantioselectivity. This further implies that certain ligands may be a better match with specific ketones and thus result in better reactivity and selectivity.

To demonstrate that both isomers of the product can be obtained we performed a few reactions using ligand **Boc-D-Aa** (Table 3, entries 4, 9, and 12). As can be seen in Table 3, the same degree of enantioselectivity was obtained using this ligand.

Conclusions

We have demonstrated that novel *N*-Boc protected dipeptide analogues function as efficient ligands for the ruthenium-catalyzed asymmetric transfer hydrogenation of aryl alkyl ketones. The ligands were prepared in a straightforward manner from commercially available α-amino acids and 1,2-amino alcohols. When combined with $[\{RuCl_2(p\text{-cymene})\}_2]$, several of these ligands generated highly enantioselective catalysts, although the most successful ligand combination proved to be **Boc-L-Ab** or its enantiomer **Boc-D-Aa**. Interestingly, of the two stereogenic centers present in the ligand structure, it was the chirality originating from the amino acid that determined the absolute configuration of the product alcohol. Thus, by the proper choice of amino acid, either *S*- or *R*-configured product alcohols could be obtained in high enantiomeric excess. The presence of appropriate protecting groups at the N-terminal along with a free hydroxyl group at the C-terminal of the ligands turned out to be of utmost importance for a successful outcome of the catalytic process. High conversion to and enantioselectivity of the secondary alcohol were only achieved when ligands containing carbamates resistant to basic reaction conditions (e.g Boc, Z, and Alloc) were employed. We are currently investigating why these structural features are so important for this new class of ligands in the ruthenium-catalyzed asymmetric transfer hydrogenation of ketones.

As a final remark, we believe that the simplicity with which these novel and highly modular ligands can be prepared, in combination with their efficiency in generating the desired product isomer should make this reduction process attractive for the enantioselective formation of secondary alcohols.

Experimental Section

General procedure for the preparation of library ligands, exemplified by the preparation of *tert*-butyl *N*-[(1*S*)-1-({[(1*R*)-2-hydroxy-1-phenylethyl]-amino}carbonyl)-2-methylpropyl]carbamate (Boc-L-Vb): NaOH (66 mmol, 2.6 g), followed by Boc_2O (33 mmol, 7.3 g) was added to a stirred solution of L-valine (30 mmol, 3.56 g) in THF/H_2O (50 mL of each solvent) at room temperature and the resulting mixture was stirred for 18 h. THF was removed under vacuum and the aqueous layer was extracted with CH_2Cl_2 (40 mL). The aqueous layer was acidified with HCl (1N) to pH 4, and then extracted with CH_2Cl_2 (4×25 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under vacuum. The resulting crude *N*-Boc-L-valine was used without further purification in the next step.

N-methylmorpholine (NMM, 35 mmol, 3.93 mL) and isobutylchloroformate (35 mmol, 4.62 mL) were slowly added to a solution of the *N*-Boc-protected valine in THF (60 mL) at $-15\,^{\circ}C$ (a white solid was formed during the addition of the *i*BuOCOCl). The reaction mixture was stirred for 45 min at $-15\,^{\circ}C$, and then the (*R*)-phenylglycinol (30 mmol, 4.25 g) was added and the resulting mixture was stirred at room temperature for another 3 h. The mixture was filtered through silica gel ($5\,cm \times 5\,cm$) and eluted with ethyl acetate (400 mL). The solvent was concentrated under vacuum and the resulting solid was recrystallized from CH_2Cl_2/*n*-pentane, giving the pure product.

Boc-L-Vb: (9.2 g, 91% yield). m.p. 153–154 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (m, 6H), 1.43 (s, 9H), 2.08 (m, 1H), 3.43 (brs, 1H), 3.77 (dd, $J = 11.4$ and 6.9 Hz, 1H), 3.85 (dd, $J = 11.4$ and 4.4 Hz, 1H), 3.99 (deft, $J = 7.6$ Hz, 1H), 5.10 (dt, $J = 7.0$ and 4.2 Hz, 1H), 5.44 (brd, $J = 8.3$ Hz, 1H), 7.30 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.2$, 19.5, 28.5 (3C), 31.1, 55.9, 60.6, 66.1, 80.3, 127.0 (2C), 127.8, 128.8 (2C), 139.2, 156.6, 172.6 ppm; (MALDI-TOF): *m/z*: 374.161 $[M-K]^+$, 359.172 $[M-Na]^+$, 337.172 $[M-H]^+$; elemental analysis calcd (%) for $C_{18}H_{28}N_2O_4$: C 64.26, H 8.39, N 8.33; found: C 64.33, H 8.20, N 8.20.

***tert*-Butyl *N*-((1*S*)-2-{[(1*S*)-2-hydroxy-1-phenylethyl]amino}-2-oxo-1-phenylethyl)carbamate (Boc-L-PhGa)**: m.p. 125–126 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 9H), 2.53 (brs, 1H), 3.75 (d, $J = 5.7$ Hz, 2H), 5.01 (m, 1H), 5.21 (m, 1H), 5.72 (brd, $J = 6.6$ Hz, 1H), 6.75 (brd, $J = 7.5$ Hz, 1H), 7.18–7.43 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 56.2, 58.9, 66.1, 80.7, 126.9 (2C), 127.4 (2C), 128.1, 128.7, 129.1 (2C), 129.3 (2C), 138.1, 138.8, 155.6, 170.8 ppm; (MALDI-TOF): *m/z*: 409.026 $[M-K]^+$, 393.055 $[M-Na]^+$, 371.095 $[M-H]^+$; elemental analysis calcd (%) for $C_{21}H_{26}N_2O_4$: C 68.09, H 7.07, N 7.56; found: C 68.02, H 7.07, N 7.37.

***tert*-Butyl *N*-((1*S*)-2-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2-oxo-1-phenylethyl)carbamate (Boc-L-PhGb)**: m.p. 160–161 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (s, 9H), 2.83 (brs, 1H), 3.75 (dd, $J = 11.2$ and 5.8 Hz, 1H), 3.86 (dd, $J = 11.2$ and 4.1 Hz, 1H), 5.06 (m, 1H), 5.33 (brs, 1H), 5.84 (brd, $J = 6.2$ Hz, 1H), 6.91 (brs, 1H), 6.99 (m, 2H), 7.20 (m, 3H), 7.28–7.39 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 55.8, 59.0, 66.1, 80.6, 126.6 (2C), 127.6 (2C), 127.8, 128.6, 128.8 (2C), 129.1 (2C), 138.1, 138.8, 155.7, 170.8 ppm; (MALDI-TOF): *m/z*: 409.060 $[M-K]^+$, 393.088 $[M-Na]^+$, 371.128 $[M-H]^+$.

***tert*-Butyl *N*-((1*S*)-2-{[(1*S*)-1-benzyl-2-hydroxyethyl]amino}-2-oxo-1-phenylethyl)carbamate (Boc-L-PhGc)**: m.p. 117–118 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H), 2.69 (brs, 1H), 2.84 (m, 2H), 3.47–3.65 (m, 2H), 4.13 (m, 1H), 5.07 (m, 1H), 5.61 (brd, $J = 7.0$ Hz, 1H), 6.26 (brd, $J = 7.6$ Hz, 1H), 7.14 (m, 3H), 7.21–7.32 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 37.0, 53.5, 58.9, 63.7, 80.8, 126.9, 127.4 (2C), 128.7, 128.9 (2C), 129.3 (2C), 129.4 (2C), 137.7, 138.0, 155.6, 170.7 ppm; (MALDI-TOF): *m/z*: 423.072 $[M-K]^+$, 407.099 $[M-Na]^+$, 385.135 $[M-H]^+$.

***tert*-Butyl *N*-((1*S*)-2-{[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}-2-oxo-1-phenylethyl)-carbamate (Boc-L-PhGd)**: m.p. 127–128 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 1.42 (s, 9H), 1.85 (m, 1H), 2.69 (brt, $J = 5.8$ Hz, 1H), 3.56 (m, 2H), 3.65 (m, 1H), 5.15 (brd, $J = 5.2$ Hz, 1H), 5.76 (d, $J = 6.3$ Hz, 1H), 6.26 (brd, $J = 8.9$ Hz, 1H), 7.29–7.46 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.0$, 19.7, 28.5 (3C), 29.0, 57.8, 59.4, 63.3, 80.6, 127.4 (2C), 128.6, 129.2 (2C), 138.1, 155.7, 171.1 ppm; (MALDI-TOF): *m/z*: 375.086 $[M-K]^+$, 359.129 $[M-Na]^+$, 337.164 $[M-H]^+$.

***tert*-Butyl *N*-((1*S*)-2-[(2-hydroxyethyl)amino]-2-oxo-1-phenylethyl)carbamate (Boc-L-PhGe)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl

acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (s, 9H), 2.53 (brs, 1H), 3.24–3.50 (m, 2H), 3.60–3.90 (m, 2H), 5.20 (m, 1H), 5.80 (brs, 1H), 6.54 (brs, 1H), 7.25–7.40 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 28.5 (3C), 42.7, 58.8, 61.8, 80.5, 127.4 (2C), 128.6, 129.2 (2C), 138.3, 155.6, 171.4 ppm; (MALDI-TOF): *m*/*z*: 333.135 $[M-K]^+$, 317.165 $[M\text{Na}]^+$.

***tert*-Butyl *N*-((1*R*)-2-{[(1*S*)-2-hydroxy-1-phenylethyl]amino}-2-oxo-1-phenylethyl)carbamate (Boc-D-PhGa)**: m.p. 160–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (s, 9H), 2.85 (brs, 1H), 3.71–3.78 (m, 1H), 3.81–3.88 (m, 1H), 5.06 (m, 1H), 5.33 (brs, 1H), 5.85 (brd, $J = 6.1$ Hz, 1H), 6.98 (m, 2H), 7.20 (m, 3H), 7.27–7.39 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 55.8, 58.9, 66.1, 80.6, 126.6 (2C), 127.5 (2C), 127.8, 128.6, 128.8 (2C), 129.2 (2C), 138.1, 138.8, 155.7, 170.8 ppm; (MALDI-TOF): *m*/*z*: 409.093 $[M-K]^+$, 393.122 $[M-Na]^+$, 371.159 $[M-H]^+$.

***tert*-Butyl *N*-((1*R*)-2-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2-oxo-1-phenylethyl)carbamate (Boc-D-PhGb)**: m.p. 132–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 9H), 2.52 (brs, 1H), 3.76 (d, $J = 4.9$ Hz, 2H), 5.02 (dt, $J = 7.4$ and 4.9 Hz, 1H), 5.21 (brs, 1H), 5.71 (brd, $J = 6.3$ Hz, 1H), 6.72 (brd, $J = 7.4$ Hz, 1H), 7.22–7.41 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 56.2, 59.0, 66.1, 80.7, 126.9 (2C), 127.4 (2C), 128.1, 128.7, 129.0 (2C), 129.3 (2C), 138.1, 138.8, 155.6, 170.7 ppm; (MALDI-TOF: *m*/*z*: 409.146 $[M-K]^+$, 393.187 $[M-Na]^+$, 371.203 $[M-H]^+$; elemental analysis calcd (%) for $C_{21}H_{26}N_2O_4$: C 68.09, H 7.07, N 7.56; found: C 67.98, H 7.05, N 7.53.

***tert*-Butyl *N*-((1*R*)-2-{[(1*S*)-1-benzyl-2-hydroxyethyl]amino}-2-oxo-1-phenylethyl)carbamate (Boc-D-PhGc)**: m.p. 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (s, 9H), 2.66–2.80 (m, 3H), 3.54 (dd, $J = 11.2$ and 5.4 Hz, 1H), 3.66 (dd, $J = 11.2$ and 4.1 Hz, 1H), 4.20 (m, 1H), 5.13 (brs, 1H), 5.80 (d, $J = 6.7$ Hz, 1H), 6.21 (brs, 1H), 6.95 (m, 2H), 7.21 (m, 3H), 7.27–7.33 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 37.0, 53.0, 58.9, 63.9, 80.5, 126.7, 127.4 (2C), 128.5, 128.7 (2C), 129.2 (2C), 129.3 (2C), 137.3, 138.2, 155.6, 170.7 ppm; (MALDI-TOF: *m*/*z*: 423.162 $[M-K]^+$, 407.187 $[M-Na]^+$, 385.200 $[M-H]^+$.

***tert*-Butyl *N*-((1*R*)-2-{[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}-2-oxo-1-phenylethyl)-carbamate (Boc-D-PhGd)**: m.p. 138–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.65$ (d, $J = 6.6$ Hz, 3H), 0.81 (d, $J = 6.6$ Hz, 3H), 1.41 (s, 9H), 1.73 (m, 1H), 3.22 (brs, 1H), 3.59 (m, 1H), 3.64–3.78 (m, 2H), 5.23 (brs, 1H), 5.92 (d, $J = 6.6$ Hz, 1H), 6.39 (brs, 1H), 7.32 (m, 3H), 7.40 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.5$, 19.6, 28.5 (3C), 29.3, 57.3, 59.0, 63.4, 80.4, 127.4 (2C), 128.5, 129.1 (2C), 138.5, 155.6, 171,2 ppm; (MALDI-TOF): *m*/*z*: 375.163 $[M-K]^+$, 359.187 $[M-Na]^+$, 337.187 $[M-H]^+$.

***tert*-Butyl *N*-((1*R*)-2-[(2-hydroxyethyl)amino]-2-oxo-1-phenylethyl)carbamate (Boc-D-PhGe)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (s, 9H), 2.53 (brs, 1H), 3.23–3.53 (m, 2H), 3.59–3.90 (m, 2H), 5.26 (m, 1H), 5.78 (brs, 1H), 6.48 (brs, 1H), 7.27–7.46 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 28.5 (3C), 42.7, 58.8, 63.9, 80.6, 127.4 (2C), 128.6, 129.2 (2C), 138.3, 155.6, 171.4 ppm; (MALDI-TOF): *m*/*z*: 333.136 $[M-K]^+$, 317.170 $[M\text{Na}]^+$.

***tert*-Butyl *N*-((1*S*)-1-benzyl-2-{[(1*S*)-2-hydroxy-1-phenylethyl]amino}-2-oxoethyl)carbamate (Boc-L-Fa)**: m.p. 130–131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 9H), 2.58 (brs, 1H), 3.05 (m, 2H), 3.66 (m, 2H), 4.37 (m, 1H), 4.95 (m, 1H), 5.18 (d, $J = 7.5$ Hz, 1H), 6.59 (brd, $J = 6.9$ Hz, 1H), 7.13–7.35 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.4$ (3C), 38.7, 55.9, 56.4, 66.1, 80.6, 126.9 (2C), 127.2, 127.9, 128.9 (2C), 129.0 (2C), 129.5 (2C), 136.9, 138.8, 155.7, 171.6 ppm; (MALDI-TOF) (*m*/*z*) 423.168$[M-K]^+$, 407.184$[M-Na]^+$, 385.224$[M-H]^+$.

***tert*-Butyl *N*-((1*S*)-1-benzyl-2-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2-oxoethyl)carbamate (Boc-L-Fb)**: m.p. 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 9H), 2.68 (brs, 1H), 3.05 (d, $J = 7.1$ Hz, 2H), 3.76 (dd, $J = 11.5$ and 6.3 Hz, 1H), 3.83 (dd, $J = 11.5$ and 4.1 Hz, 1H), 4.37 (m, 1H), 5.03 (m, 1H), 5.23 (brs, 1H), 6.64 (brs, 1H), 7.05–7.32 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 38.6, 55.8, 56.6, 66.2, 80.7, 126.8 (2C), 127.1, 127.9, 128.9 (2C), 129.5 (4C), 136.6, 138.6, 156.0, 172.0 ppm; (MALDI-TOF): *m*/*z:* 423.133 $[M-K]^+$, 407.186 $[M-Na]^+$, 385.183 $[M-H]^+$; elemental analysis calcd (%) for $C_{22}H_{28}N_2O_4$: C 68.73, H 7.34, N 7.29; found: C 68.54, H 7.44, N 7.16.

***tert*-Butyl *N*-((1*S*)-1-benzyl-2-{[(1*S*)-1-benzyl-2-hydroxyethyl]amino}-2-oxoethyl)carbamate (Boc-L-Fc)**: m.p. 117–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (s, 9H), 2.33 (brs, 1H), 2.69–2.83 (m, 2H), 2.92–3.01 (m, 2H), 3.37–3.49 (m, 2H), 4.08 (m, 1H), 4.26 (m, 2H), 5.05 (brs, 1H), 5.97 (brd, $J = 7.6$ Hz, 1H), 7.10–7.34 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 37.0, 38.9, 53.0, 56.4, 63.5, 80.6, 126.8, 127.3, 128.8 (2C), 129.0 (2C), 129.4 (2C), 129.5 (2C), 136.9, 137.6, 155.7, 171.5 ppm; (MALDI-TOF): *m*/*z*: 437.180$[M-K]^+$, 421.219$[M-Na]^+$, 399.230$[M-H]^+$.

***tert*-Butyl *N*-((1*S*)-1-benzyl-2-{[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}-2-oxoethyl)-carbamate (Boc-L-Fd)**: m.p. 131–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$ (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H), 1.43 (s, 9H), 1.77 (m, 1H), 2.21 (brs, 1H), 3.02 (dd, $J = 13.6$ and 8.0 Hz, 1H), 3.12 (dd, $J = 13.6$ and 6.5 Hz, 1H), 3.48 (d, $J = 4.4$ Hz, 2H), 3.62 (m, 1H), 4.30 (m, 1H), 5.15 (brd, $J = 7.4$ Hz, 1H), 5.89 (brd, $J = 8.6$ Hz, 1H), 7.22–7.36 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.8$, 19.6, 28.5 (3C), 29.0, 38.6, 56.7, 57.5, 63.6, 80.6, 127.3, 129.0 (2C), 129.5 (2C), 137.1, 155.8, 171.9 ppm; (MALDI-TOF): *m*/*z*: 389.269 $[M-K]^+$, 373.261 $[M-Na]^+$, 351.270 $[M-H]^+$.

***tert*-Butyl *N*-((1*S*)-1-benzyl-2-[(2-hydroxyethyl)amino]-2-oxoethyl)carbamate (Boc-L-Fe)**: m.p. 103–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 9H, s), 2.79 (brs, 1H), 3.04 (d, $J = 7.3$ Hz, 2H), 3.31 (m, 2H), 3.49–3.65 (m, 2H), 4.33 (m, 1H), 5.27 (brd, $J = 7.6$ Hz, 1H), 6.51 (m, 1H), 7.18–7.34 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 39.0, 42.5, 56.4, 61.8, 80.6, 127.2, 128.9 (2C), 129.5 (2C), 136.9, 155.8, 172.5 ppm; (MALDI-TOF): *m*/*z*: 347.141 $[M-K]^+$, 331.157 $[M-Na]^+$, 309.183 $[M-H]^+$.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*S*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-3-methylbutyl]carbamate (Boc-L-La)**: m.p. 106–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (d, $J = 4.2$ Hz, 3H), 0.93 (d, $J = 4.2$ Hz, 3H), 1.41 (s, 9H), 1.47 (m, 1H), 1.67 (m, 2H), 3.15 (deft, $J = 6.1$ Hz, 1H), 3.74–3.90 (m, 2H), 4.17 (m, 1H), 5.01 (m, 1H), 5.07 (brs, 1H), 7.17–7.35 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.2$, 23.1, 24.9, 28.4 (3C), 40.8, 53.5, 55.9, 66.3, 80.5, 126.8 (2C), 127.8, 128.9 (2C), 139.1, 156.2, 173.0 ppm; (MALDI-TOF): *m*/*z*: 389.205 $[M-K]^+$, 373.246 $[M-Na]^+$, 351.230 $[M-H]^+$; elemental analysis calcd (%) for $C_{19}H_{30}N_2O_4$: C 65.12, H 8.63, N 7.99; found: C 65.12, H 8.75, N 7.99.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*R*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-3-methylbutyl]carbamate (Boc-L-Lb)**: m.p. 155–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (m, 6H), 1.43 (s, 9H), 1.49 (m, 1H), 1.63 (m, 2H), 3.37 (m, 1H), 3.76–3.89 (m, 2H), 4.18 (m, 1H), 5.07 (m, 1H), 5.29 (d, $J = 8.1$ Hz, 1H), 7.19–7.36 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.2$, 23.1, 24.9, 28.5 (3C), 41.3, 53.7, 55.9, 66.2, 80.5, 126.9 (2C), 127.9, 128.9 (2C), 139.2, 156.4, 173.4 ppm; (MALDI-TOF): *m*/*z*: 389.159 $[M-K]^+$, 373.176 $[M-Na]^+$, 351.203 $[M-H]^+$.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*S*)-1-benzyl-2-hydroxyethyl]amino}carbonyl)-3-methylbutyl]carbamate (Boc-L-Lc)**: m.p. 126–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (d, $J = 4.0$ Hz, 3H), 0.91 (d, $J = 4.0$ Hz, 3H), 1.39 (m, 1H), 1.43 (s, 9H), 1.51–1.69 (m, 2H), 2.88 (d, $J = 7.3$ Hz, 2H), 3.28 (m, 1H), 3.52–3.69 (m, 2H), 3.98–4.21 (m, 2H), 5.02 (brs, 1H), 6.65 (brd, $J = 8.4$ Hz, 1H), 7.17–7.31 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 22.1, 23.0, 24.9, 28.5 (3C), 37.1, 41.3, 53.1, 53.7, 63.6, 80.5, 126.7, 128.7 (2C), 129.4 (2C), 138.0, 156.1, 173.1 ppm; (MALDI-TOF): *m*/*z*: 403.170 $[M-K]^+$, 387.210 $[M-Na]^+$, 365.217 $[M-H]^+$.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}-carbonyl)-3-methylbutyl]carbamate (Boc-L-Ld)**: m.p. 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (m, 12H), 1.44 (s, 9H), 1.44–1.55 (m, 1H), 1.62–1.76 (m, 2H), 1.89 (m, 1H), 2.81 (t, $J = 5.6$ Hz, 1H), 3.58–3.76 (m, 3H), 4.06 (m, 1H), 4.96 (brd, $J = 7.5$ Hz, 1H), 6.44 ppm (brd, $J =$ 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.8$, 19.7, 22.2, 23.1, 25.0, 28.5 (3C), 29.2, 40.7, 53.8, 57.5, 64.1, 80.6, 156.2, 173.5 ppm; (MALDI-TOF): *m*/*z*: 355.134 $[M-K]^+$, 339.180 $[M-Na]^+$, 317.200 $[M-H]^+$.

***tert*-Butyl *N*-((1*S*)-1-{[(2-hydroxyethyl)amino]carbonyl}-3-methylbutyl)-carbamate (Boc-L-Le)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (m, 6H), 1.41 (s, 9H), 1.44–1.54 (m, 1H), 1.55–1.74 (m, 2H), 3.25–3.37 (m, 2H), 3.38–3.50 (m, 1H), 3.68 (m, 2H), 4.11 (m, 1H), 5.26 (brs, 1H), 7.02 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.1$, 23.1, 24.9, 28.5 (3C), 41.6, 42.5, 53.6, 61.9, 80.4, 156.3, 174.1 ppm; (MALDI-TOF): *m*/*z*: 313.160 $[M-K]^+$, 297.160 $[M-Na]^+$, 275.196 $[M-H]^+$.

***tert*-Butyl *N*-((1*S*)-2-{[(1*S*)-2-hydroxy-1-phenylethyl]amino}-1-methyl-2-oxoethyl)carbamate (Boc-L-Aa)**: m.p. 114–115 °C; ^{1}H NMR (300 MHz,

$CDCl_3$): $\delta = 1.34$ (d, $J = 7.1$ Hz, 3H), 1.42 (s, 9H), 3.14 (m, 1H), 3.74–3.90 (m, 2H), 4.20 (m, 1H), 5.02 (m, 1H), 5.18 (brs, 1H), 7.17 (brs, 1H), 7.21–7.41 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.0$, 28.5 (3C), 50.5, 55.9, 66.3, 80.6, 126.9 (2C), 127.9, 128.9 (2C), 139.1, 156.0, 173.2 ppm; (MALDI-TOF): m/z: 347.101 $[M-K]^+$, 331.158 $[M Na]^+$.

***tert*-Butyl *N*-((1*S*)-2-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-methyl-2-oxoethyl)carbamate (Boc-L-Ab)**: m.p. 111–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$ (3H, d, $J = 7.1$ Hz), 1.43 (s, 9H), 3.44 (m, 1H), 3.72–3.90 (m, 2H), 4.24 (m, 1H), 5.07 (m, 1H), 5.43 (brd, $J = 7.4$ Hz, 1H), 7.21–7.37 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.5$, 28.5 (3C), 50.6, 55.8, 66.2, 80.5, 126.9 (2C), 127.9, 128.9 (2C), 139.1, 156.2, 173.5 ppm; (MALDI-TOF): m/z: 347.119 $[M-K]^+$, 331.157 $[M-Na]^+$, 309.181 $[M-H]^+$; elemental analysis calcd (%) for $C_{16}H_{24}N_2O_4$: C 62.32, H 7.84, N 9.08; found: C 62.42, H 7.93, N 9.10.

***tert*-Butyl *N*-((1*S*)-2-{[(1*S*)-1-benzyl-2-hydroxyethyl]amino}-1-methyl-2-oxoethyl)carbamate (Boc-L-Ac)**: m.p. 113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (d, $J = 7.1$ Hz, 3H), 1.44 (s, 9H), 2.87 (d, $J = 7.3$ Hz, 2H), 3.16 (t, $J = 5.8$ Hz, 1H), 3.51–3.60 (m, 1H), 3.62–3.71 (m, 1H), 4.01–4.21 (m, 2H), 5.10 (d, $J = 6.9$ Hz, 1H), 6.58 (d, $J = 8.0$ Hz, 1H), 7.17–7.32 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.4$, 28.5 (3C), 37.1, 50.7, 53.0, 63.6, 80.6, 126.8, 128.7 (2C), 129.4 (2C), 138.0, 155.8, 173.2 ppm; (MALDI-TOF): m/z: 361.139 $[M-K]^+$, 345.158 $[M Na]^+$.

***tert*-Butyl *N*-((1*S*)-2-{[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}-1-methyl-2-oxoethyl)-carbamate (Boc-L-Ad)**: m.p. 83–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (d, $J = 6.8$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 1.37 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 1.90 (m, 1H), 3.13 (t, $J = 5.7$ Hz, 1H), 3.58–3.76 (m, 3H), 4.14 (m, 1H), 5.20 (brd, $J = 6.5$ Hz, 1H), 6.59 ppm (1H, brd, $J = 8.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.0$, 18.8, 19.7, 28.5 (3C), 29.1, 50.7, 57.3, 63.8, 80.6, 156.1, 173.7 ppm; (MALDI-TOF): m/z: 313.114 $[M-K]^+$, 297.163 $[M-Na]^+$, 275.163 $[M-H]^+$; elemental analysis calcd (%) for $C_{13}H_{26}N_2O_4$: C 56.91, H 9.55, N 10.21; found: C 57.02, H 9.73, N 10.21.

***tert*-Butyl *N*-{(1*S*)-2-[(2-hydroxyethyl)amino]-1-methyl-2-oxoethyl}carbamate (Boc-L-Ae)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (d, $J = 7.2$ Hz, 3H), 1.44 (s, 9H), 3.17 (brs, 1H), 3.31–3.52 (m, 2H), 3.70 (m, 2H), 4.17 (m, 1H), 5.35 (brs, 1H), 6.96 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.7$, 28.5 (3C), 42.5, 50.6, 61.8, 80.5, 156.0, 174.1 ppm; (MALDI-TOF): m/z: 271.098 $[M-K]^+$, 255.126 $[M-Na]^+$, 233.149 $[M-H]^+$.

***tert*-Butyl *N*-((1*R*)-2-{[(1*S*)-2-hydroxy-1-phenylethyl]amino}-1-methyl-2-oxoethyl)carbamate (Boc-D-Aa)**: m.p. 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (d, $J = 6.9$ Hz, 3H), 1.43 (s, 9H), 3.04 (brs, 1H), 3.81 (dd, $J = 11.5$ and 6.3 Hz, 1H), 3.88 (dd, $J = 11.5$ and 4.1 Hz, 1H), 4.21 (m, 1H), 5.07 (m, 1H), 5.25 (brs, 1H), 7.07 (brs, 1H), 7.24–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.3$, 28.5 (3C), 50.6, 55.9, 66.4, 80.6, 126.9 (2C), 128.0, 129.0 (2C), 139.0, 156.1, 173.4 ppm; (MALDI-TOF): m/z: 347.136 $[M-K]^+$, 331.171 $[M-Na]^+$, 309.175 $[M-H]^+$; elemental analysis calcd (%) for $C_{16}H_{24}N_2O_4$: C 62.32, H 7.84, N 9.08; found: C 62.20, H 7.93, N 9.00.

***tert*-Butyl *N*-((1*R*)-2-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-methyl-2-oxoethyl)carbamate (Boc-D-Ab)**: m.p. 119–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (3H, d, $J = 7.1$ Hz), 1.43 (9H, s), 2.76 (brs, 1H), 3.79–3.91 (m, 2H), 4.20 (m, 1H), 5.04 (m, 2H), 7.06 (brs, 1H), 7.23–7.37 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.9$, 28.5 (3C), 50.6, 56.0, 66.5, 80.8, 126.9 (2C), 128.0, 129.0 (2C), 139.0, 156.0, 173.1 ppm; (MALDI-TOF): m/z: 347.117 $[M-K]^+$, 331.116 $[M-Na]^+$, 309.170 $[M-H]^+$.

***tert*-Butyl *N*-((1*R*)-2-{[(1*S*)-1-benzyl-2-hydroxyethyl]amino}-1-methyl-2-oxoethyl)carbamate (Boc-D-Ac)**: m.p. 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.23$ (d, $J = 6.8$ Hz, 3H), 1.41 (s, 9H), 2.78–2.93 (2H, m), 3.08 (brs, 1H), 3.53 (dd, $J = 11.3$ and 5.2 Hz, 1H), 3.67 (dd, $J = 11.3$ and 3.6 Hz, 1H), 4.07 (m, 1H), 4.18 (m, 1H), 5.19 (brd, $J = 7.4$ Hz, 1H), 6.50 (brd, $J = 8.2$ Hz, 1H), 7.17–7.31 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.5$, 28.5 (3C), 37.2, 50.6, 52.9, 63.9, 80.5, 126.8, 128.8 (2C), 129.4 (2C), 137.8, 156.0, 173.4 ppm; (MALDI-TOF): m/z: 361.129 $[M-K]^+$, 345.179 $[M-Na]^+$, 323.196 $[M-H]^+$.

***tert*-Butyl *N*-((1*R*)-2-{[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}-1-methyl-2-oxoethyl)-carbamate (Boc-D-Ad)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (d, $J = 6.8$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 1.37 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 1.87 (m, 1H), 3.54–3.78 (m, 4H), 4.19 (m, 1H), 5.51 (brs, 1H), 6.71 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.7$, 18.8, 19.7, 28.5 (3C), 29.2, 50.6, 57.2, 63,5, 80.4, 156.0, 173.9 ppm; (MALDI-TOF): m/z: 313.094 $[M-K]^+$, 297.107 $[M-Na]^+$, 275.162 $[M-H]^+$.

***tert*-Butyl *N*-{(1*R*)-2-[(2-hydroxyethyl)amino]-1-methyl-2-oxoethyl}carbamate (Boc-D-Ae)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (d, $J = 7.2$ Hz, 3H), 1.44 (s, 9H), 3.24 (brs, 1H), 3.31–3.52 (m, 2H), 3.70 (m, 2H), 4.17 (m, 1H), 5.36 (brs, 1H), 6.97 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.7$, 28.5 (3C), 42.5, 50.6, 61.9, 80.5, 156.0, 174.1 ppm; (MALDI-TOF): m/z: 271.098 $[M-K]^+$, 255.126 $[M-Na]^+$, 233.136 $[M-H]^+$.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*S*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-2-methylpropyl]carbamate (Boc-L-Va)**: m.p. 126–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.93$ (d, $J = 6.6$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 1.42 (s, 9H), 2.10 (m, 1H), 2.96 (brs, 1H), 3.75–3.88 (m, 3H), 3.92 (m, 1H), 5.04 (m, 1H), 5.23 (brd, $J = 8.1$ Hz, 1H), 7.06 (brs, 1H), 7.23–7.37 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.3$, 19.6, 28.5 (3C), 30.7, 56.0, 60.8, 66.3, 80.4, 126.9 (2C), 127.9, 128.9 (2C), 139.1, 156.4, 172.4 ppm; (MALDI-TOF): m/z: 375.113 $[M-K]^+$, 359.141 $[M-Na]^+$, 337.169 $[M-H]^+$.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*S*)-1-benzyl-2-hydroxyethyl]amino}carbonyl)-2-methylpropyl]-carbamate (Boc-L-Vc)**: m.p. 144–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$ (brd, $J = 6.7$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 1.43 (s, 9H), 2.07 (m, 1H), 2.87 (m, 2H), 3.16 (brs, 1H), 3.56 (dd, $J = 11.2$ and 5.0 Hz, 1H), 3.64 (dd, $J = 11.2$ and 3.8 Hz, 1H), 3.83 (m, 1H), 4.17 (m, 1H), 5.09 (d, $J = 8.2$ Hz, 1H), 6.53 (brs, 1H), 7.16–7.30 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.9$, 19.4, 28.5 (3C), 30.7, 37.1, 53.0, 60.7, 63.7, 80.4, 126.8, 128.8 (2C), 129.4 (2C), 137.9, 156.2, 172.1 ppm; (MALDI-TOF): m/z: 389.117 $[M-K]^+$, 373.158 $[M-Na]^+$, 351.181 $[M-H]^+$.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}-carbonyl)-2-methylpropyl]carbamate (Boc-L-Vd)**: m.p. 149–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91–1.01$ (m, 12H), 1.45 (s, 9H), 1.89 (m, 1H), 2.17 (m, 1H), 2.71 (def t, $J = 5.7$ Hz, 1H), 3.60–3.77 (m, 3H), 3.84 (dd, $J = 8.1$ and 6.6 Hz, 1H), 5.04 (brs, 1H), 6.22 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.2$, 19.0, 19.6, 19.7, 28.5 (3C), 29.0, 30.4, 57.4, 61.0, 63.7, 80.3, 156.3, 172.6 ppm; (MALDI-TOF): m/z: 341.141 $[M-K]^+$, 325.176 $[M-Na]^+$, 303.194 $[M-H]^+$.

***tert*-Butyl *N*-((1*S*)-1-{[(2-hydroxyethyl)amino]carbonyl}-2-methylpropyl)-carbamate (Boc-L-Ve)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.95$ (6H, m), 1.44 (s, 9H), 2.10 (1H, m), 3.15 (brs, 1H), 3.31–3.53 (2H, m), 3.65–3.76 (2H, m), 3.88 (1H, m), 5.34 (brd, $J = 8.7$ Hz, 1H), 6.96 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.2$, 19.5, 28.5 (3C), 31.0, 42.5, 60.6, 62.0, 80.4, 156.4, 173.0 ppm; (MALDI-TOF): m/z: 299.099 $[M^+-K]$, 283.129 $[M^+-Na]$, 261.141 $[M^+-H]$.

***tert*-Butyl *N*-[(1*R*)-1-({[(1*S*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-2-methylpropyl]-carbamate (Boc-D-Va)**: m.p. 156–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88–0.94$ (m, 6H), 1.43 (9H, s), 2.08 (m, 1H), 3.36 (1H, brs), 3.85 (m, 2H), 3.99 (1H, def t, $J = 7.4$ Hz), 5.10 (m, 1H), 5.40 (brd, $J = 7.8$ Hz, 1H), 7.19 (1H, brs), 7.23–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.2$, 19.6, 28.5 (3C), 31.1, 55.9, 60.7, 66.2, 80.4, 127.0 (2C), 127.9, 128.9 (2C), 139.2, 156.7, 172.6 ppm; (MALDI-TOF): m/z: 375.153 $[M-K]^+$, 359.172 $[M-Na]^+$, 337.200 $[M-H]^+$; elemental analysis calcd (%) for $C_{18}H_{28}N_2O_4$: C 64.26, H 8.39, N 8.33; found: C 64.43, H 8.50, N 8.38.

***tert*-Butyl *N*-[(1*R*)-1-({[(1*R*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-2-methylpropyl]-carbamate (Boc-D-Vb)**: m.p. 69–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.9$ Hz, 3H), 1.00 (d, $J = 6.9$ Hz, 3H), 1.44 (s, 9H), 2.17 (m, 2H), 3.82–3.97 (m, 3H), 4.96–5.11 (m, 2H), 6.73 (m, 1H), 7.24–7.41 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.2$, 19.6, 18.5 (3C), 30.7, 56.0, 60.8, 66.4, 80.4, 126.9 (2C), 128.0, 129.0 (2C), 139.0, 156.3, 172.3 ppm; (MALDI-TOF): m/z: 375.165 $[M-K]^+$, 359.191 $[M-Na]^+$, 337.202 $[M-H]^+$.

***tert*-Butyl *N*-[(1*R*)-1-({[(1*S*)-1-benzyl-2-hydroxyethyl]amino}carbonyl)-2-methylpropyl]-carbamate (Boc-D-Vc)**: m.p. 131–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.77–0.92$ (m, 6H), 1.43 (s, 9H), 1.93 (m, 1H), 2.81 (dd, $J = 13.8$ and 7.9 Hz, 1H), 2.91 (dd, $J = 13.8$ and 7.1 Hz, 1H), 3.14 (brs, 1H), 3.54 (dd, $J = 11.2$ and 5.1 Hz, 1H), 3.69 (dd, $J = 11.2$ and 3.6, 1H),

3.73–3.84 (m, 1H), 4.25 (m, 1H), 5.24 (br d, J = 8.1 Hz, 1H), 6.41 (br d, J = 8.1 Hz, 1H), 7.17–7.31 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 19.3, 28.5 (3C), 30.9, 37.2, 53.0, 60.9, 64.1, 80.4, 126.8, 128.8 (2C), 129.4 (2C), 137.8, 156.5, 172.4 ppm; (MALDI-TOF): m/z: 389.200 [M^+ − K], 373.202 [M^+ − Na], 351.219 [M^+ − H].

***t*-Butyl *N*-[(1*R*)-1-({[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}carbonyl)-2-methylpropyl]-carbamate (Boc-D-Vd)**: m.p. 146–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91–1.01 (12H, m), 1.44 (9H, s), 1.86 (1H, m), 2.10 (1H, m), 3.22 (br s, 1H), 3.60 (1H, m), 3.65–3.79 (2H, m), 3.83 (1H, m), 5.25 (1H, br d, J = 7,8 Hz), 6.38 ppm (1H, br d, J = 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 19.1, 19.6, 19.8, 28.5 (3C), 29.1, 30.6, 57.5, 61.2, 63.7, 80.4, 156.6, 172.8 ppm; (MALDI-TOF): m/z: 341.169 [M − K]$^+$, 325.203 [M − Na]$^+$, 303.197 [M − H]$^+$.

***tert*-Butyl *N*-((1*R*)-1-{[(2-hydroxyethyl)amino]carbonyl}-2-methylpropyl)-carbamate (Boc-D-Ve)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (m, 6H), 1.43 (s, 9H), 2.11 (m, 1H), 2.78 (br s, 1H), 3.30–3.52 (m, 2H), 3.71 (m, 2H), 3.83–3.94 (m, 1H), 5.18 (m, 1H), 6.71 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 19.5, 28.5 (3C), 30.9, 42.5, 60.7, 62.1, 80.4, 156.4, 173.0 ppm; (MALDI-TOF): m/z: 299.149 [M − K]$^+$, 283.161 [M − Na]$^+$, 261.194 [M − H]$^+$.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*S*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-2,2-dimethylpropyl]-carbamate (Boc-L-tLa)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 9H), 1.43 (s, 9H), 3.84–3.90 (m, 3H), 5.07 (dt, J = 7.2 and 4.8 Hz, 1H), 5.18 (m, 1H), 6.44 (br d, J = 7.2 Hz, 1H), 7.26–7.39 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9, 28.5 (3C), 34.5, 56.2, 63.0, 66.7, 80.2, 126.9 (2C), 128.1, 129. 1 (2C), 138.8, 156.2, 171.5 ppm; (MALDI-TOF): m/z: 389.130 [M − K]$^+$, 373.159 [M − Na]$^+$, 351.195 [M − H]$^+$.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*R*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-2,2-dimethylpropyl]-carbamate (Boc-L-tLb)**: m.p. 177–178 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (s, 9H), 1.43 (s, 9H), 2.94 (br s, 1H), 3.78–3.93 (m, 3H), 5.10 (m, 1H), 5.31 (br d, J = 8.4 Hz, 1H), 6.64 (br d, J = 7.8 Hz, 1H), 7.24–7.39 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9 (3C), 28.5 (3C), 34.5, 56.0, 63.2, 66.2, 80.4, 127.1 (2C), 128.0, 129.0 (2C), 139.2, 156.5, 171.8 ppm; (MALDI-TOF): m/z: 389.181 [M − K]$^+$, 373.206 [M − Na]$^+$, 351.236 [M − H]$^+$; elemental analysis calcd (%) for $C_{19}H_{30}N_2O_4$: C 65.12, H 8.63, N 7.99; found: C 65.35, H 8.75, N 7.80.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*S*)-1-benzyl-2-hydroxyethyl]amino}carbonyl)-2,2-dimethylpropyl]-carbamate (Boc-L-tLc)**: m.p. 199–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 9H), 1.44 (s, 9H), 1.95 (br s, 1H), 2.88 (d, J = 7.2 Hz, 1H), 3.57 (dd, J = 11.1 and 5.1 Hz, 1H), 3.66–3.77 (m, 2H), 4.19 (m, 1H), 5.15 (br s, 1H), 5.97 (br s, 1H), 7.16–7.33 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8 (3C), 28.6 (3C), 34.3, 37.2, 53.1, 63.3, 63.9, 80.2, 126.9, 128.9 (2C), 129.4 (2C), 137.7, 156.1, 171.3 ppm; (MALDI-TOF): m/z: 403.211 [M − K]$^+$, 387.289 [M − Na]$^+$, 365.256 [M − H]$^+$.

***t*-Butyl *N*-[(1*S*)-1-({[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino}carbonyl)-2,2-dimethyl-propyl]carbamate (Boc-L-tLd)**: m.p. 139–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (m, 6H), 1.03 (s, 9H), 1.44 (s, 9H), 1.90 (m, 1H), 2.70 (br s, 1H), 3.62–3.78 (m, 3H), 3.80 (d, J = 8.7 Hz, 1H), 5.22 (br d, J = 8.7 Hz, 1H), 6.05 ppm (br d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.7, 26.9 (3C), 28.5 (3C), 29.1, 34.2, 57.5, 63.3, 63.9, 80.2, 156.3, 171.9 ppm; (MALDI-TOF): m/z: 355.179 [M − K]$^+$, 339.197 [M − Na]$^+$, 317.225 [M − H]$^+$.

***tert*-Butyl *N*-((1*S*)-1-{[(2-hydroxyethyl)amino]carbonyl}-2,2-dimethylpropyl)carbamate (Boc-L-tLe)**: After filtration an oil was obtained and further purification was done by column chromatography (silica gel, pentane/ethyl acetate mixtures): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 9H), 1.43 (s, 9H), 3.30–3.53 (m, 3H), 3.71 (m, 2H), 3.87 (m, 1H), 5.46 (br d, J = 9.3 Hz, 1H), 6.86 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8 (3C), 28.5 (3C), 34.5, 42.4, 62.0, 62.8, 80.2, 156.5, 172.3 ppm; (MALDI-TOF): m/z: 313.149 [M − K]$^+$, 297.194 [MNa]$^+$.

Allyl *N*-[(1*S*)-1-({[(1*R*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-2-methylpropyl]carbamate (Alloc-L-Vb): Allyl chloroformate (5 mmol, 547 μL) and NaOH (5 mL, 1M, aq.) were slowly added to a stirred solution of L-valine (5 mmol, 593 mg) in basic water (5 mL, aq. NaOH 1M) at 0 °C. The resulting mixture was stirred for an additional 30 min at room temperature. The reaction mixture was extracted with Et_2O (10 mL) and the aqueous layer was acidified with HCl (3M) and then extracted with CH_2Cl_2 (4 × 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under vacuum. The resulting crude **Alloc-L-V** (860 mg) was used without further purification in the next step.

N-methylmorpholine (NMM, 4.7 mmol, 541 μL) and isobutylchloroformate (4.7 mmol, 635 μL) were slowly added to a solution of **Alloc-L-V** in THF (15 mL) at −15 °C (a white solid was forming during the addition of the *i*BuOCOCl). The reaction mixture was stirred for 45 min at −15 °C, and then (*R*)-phenylglycinol (4.3 mmol, 609 mg) was added and the resulting mixture was stirred at room temperature for an additional 3 h. The mixture was filtered through silica gel (5 cm, 5 cm ∅) and eluted with ethyl acetate (100 mL). The solvent was concentrated under vacuum and the resulting solid was recrystallized from CH_2Cl_2/*n*-pentane, giving the pure product (1.3 g, 81% yield). m.p. 186–187 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (m, 6H), 2.06 (m, 1H), 3.37 (br s, 1H), 3.71–3.91 (m, 2H), 4.09 (m, 1H), 4.42–4.60 (m, 2H), 5.08 (m, 1H), 5.16–5.32 (m, 2H), 5.72 (br d, J = 8.7 Hz, 1H), 5.80–5.94 (m, 1H), 7.20–7.39 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 19.5, 31.5, 55.7, 60.9, 66.0, 66.2, 118.1, 127.0 (2C), 127.9, 128.9 (2C), 132.7, 139.2, 157.1, 172.2 ppm; (MALDI-TOF): m/z: 359.112 [M − K]$^+$, 343.140 [M − Na]$^+$, 321.156 [M − H]$^+$.

9*H*-9-fluorenylmethyl *N*-[(1*S*)-1-({[(1*R*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-2-methylpropyl]carbamate (Fmoc-L-Vb): Over a period of 30 min, 9-fluorenylmethyl chloroformate (5.5 mmol, 1.47 mg) in THF (5 mL), and diisopropylethylamine (5.5 mmol, 961 μL) were simultaneously added to a stirred solution of L-valine (5 mmol, 593 mg) and Na_2CO_3 (5 mmol, 530 mg) in THF/H_2O (5 mL/10 mL) at 0 °C. The resulting mixture was stirred for an additional 2 h at room temperature. The reaction mixture was extracted with Et_2O (10 mL) and the aqueous layer was acidified with HCl (3M) and extracted with CH_2Cl_2 (4 × 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under vacuum. The resulting white solid of **Fmoc-L-V** (1.3 g) was used without further purification in the next step.

N-methylmorpholine (NMM, 4.2 mmol, 483 μL) and isobutylchloroformate (4.2 mmol, 567 μL) were slowly added to a solution of the **Fmoc-L-V** in THF (15 mL) at −15 °C (a white solid was formed during the addition of the *i*-BuOCOCl). The reaction mixture was stirred for 45 min at −15 °C, and then (*R*)-phenylglycinol (3.8 mmol, 537 mg) was added and the resulting mixture was stirred at room temperature for a further 3 h. The mixture was filtered through silica gel (5 cm, 5 cm ∅) and eluted with ethyl acetate (100 mL). The solvent was evaporated and the resulting solid was recrystallized from CH_2Cl_2/*n*-pentane, giving the pure product **Fmoc-L-Vb** (1.4 g, 65% yield). m.p. 204–205 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.9 Hz, 6H), 2.10 (m, 1H), 2.88 (br s, 1H), 3.35–3.90 (m, 2H), 4.05 (m, 1H), 4.18 (deft, J = 6.9 Hz, 1H), 4.27–4.43 (m, 2H), 5.08 (m, 1H), 5.58 (m, 1H), 6.92 (br s, 1H), 7.23–7.31 (m, 7H), 7.38 (m, 2H), 7.55 (d, J = 7.5 Hz, 2H), 7.75 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 19.2, 31.2, 47.1, 55.7, 60.7, 65.2, 67.0, 119.9 (2C), 125.0 (2C), 126.7 (2C), 127.1 (2C), 127.6, 127.7 (2C), 128.5 (2C), 139.1, 141.3 (2C), 143.7 (2C), 157.1, 172.3 ppm; (MALDI-TOF): m/z: 496.986 [M − K]$^+$, 481.080 [M − Na]$^+$, 458.967 [M − H]$^+$.

Benzyl *N*-[(1*S*)-1-({[(1*R*)-2-hydroxy-1-phenylethyl]amino}carbonyl)-2-methylpropyl]carbamate (Z-L-Vb): *N*-(Benzyloxycarbonyloxy)succinimide (2 mmol, 508 mg) was added to a solution of L-valine (2 mmol, 237 mg) and $NaHCO_3$ (2 mmol, 169 mg) in H_2O/acetone (3 mL of each solvent) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL) and the aqueous layer was acidified with HCl (3M) and then extracted with EtOAc (3 × 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under vacuum. The resulting crude product of **Z-L-V** (377 mg) was used without further purification in the next step.

N-Methylmorpholine (NMM, 1.8 mmol, 203 μL) and isobutylchloroformate (1.8 mmol, 236 μL) were slowly added to a solution of the **Z-L-V** in THF (7 mL) at −15 °C (a white solid was formed during the addition of the *i*BuOCOCl). The reaction mixture was stirred for 45 min at −15 °C, and then (*R*)-phenylglycinol (1.5 mmol, 212 mg) was added and the resulting mixture was stirred at room temperature for another 3 h. The mixture was filtered through silica gel (5 cm, 5 cm ∅) and eluted with ethyl acetate (80 mL). The solvent was concentrated under vacuum and the resulting solid was recrystallized from CH_2Cl_2/*n*-pentane, giving the pure product **Z-L-Vb** (530 mg, 72% yield). m.p. 198–199 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (m, 6H), 2.04 (m, 1H)), 3.74 (dd, J = 11.5 and 6.7 Hz, 1H), 3.82

(dd, $J = 11.5$ and 4.4 Hz, 1H), 3.98 (m, 1H), 4.99–5.15 (m, 3H), 7.22–7.36 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.1$, 19.4, 31.3, 55.7, 60.7, 65.7, 67.3, 126.9 (2C), 127.8, 128.1 (2C), 128.3 (2C), 128.7, 128.8 (2C), 136.3, 139.2, 157.1, 172.1 ppm; (MALDI-TOF): m/z: 409.111 $[M-K]^+$, 393.121 $[M-Na]^+$, 371.110 $[M-H]^+$.

***N*-1-[(1*R*)-2-hydroxy-1-phenylethyl]-(2*S*)-2-(acetylamino)-3-methylbutanamide (Ac-L-Vb)**: Acetic anhydride (6 mmol, 566 μL) was added to a solution of L-valine (5 mmol, 593 mg) in acetic acid (3 mL) and the resulting mixture was stirred for 1.5 h. Toluene (10 mL) was added, resulting in the formation of a precipitate. The solid was filtered, washed with toluene (20 mL), and dried under vacuum. The solid product of **Ac-L-V** (635 mg) was used in the next step without further purification.

N-Methylmorpholine (NMM, 4.4 mmol, 506 μL) and isobutylchloroformate (4.4 mmol, 594 μL) were slowly added to a solution of the **Ac-L-V** in THF (15 mL) at −15 °C (a white solid was formed during the addition of the *i*BuOCOCl). The reaction mixture was stirred for 45 min at −15 °C, then (*R*)-phenylglycinol (4 mmol, 565 mg) was added and the resulting mixture was stirred at room temperature for an additional 3 h. The mixture was filtered through silica gel (5 cm, 5 cm ∅) and eluted with ethyl acetate (400 mL). The solvent was concentrated under vacuum and the resulting solid was recrystallized from CH_2Cl_2/*n*-pentane, giving the pure product **Ac-L-Vb** (735 mg, 53% yield). m.p. 229–230 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (d, $J = 6.6$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 2.00 (m, 1H), 2.03 (s, 3H), 3.72–3.82 (m, 3H), 4.17 (m, 1H), 5.01 (m, 1H), 7.24–7.41 (m, 6H), 7.94 ppm (br d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.3$, 19.2, 22.7, 31.0, 55.8, 59.2, 65.3, 126.8 (2C), 127.6, 128.6 (2C), 139.2, 171.8, 172.1 ppm; (MALDI-TOF): m/z: 317.085 $[M-K]^+$, 301.181 $[M-Na]^+$, 279.179 $[M-H]^+$.

***N*-1-[(1*R*)-2-hydroxy-1-phenylethyl]-(2*S*)-3-methyl-2-[(2,2,2-trifluoroacetyl)amino]butanamide (TFA-L-Vb)**: Trifluoroacetic anhydride (6 mmol, 880 μL) was added to a solution of L-valine (5 mmol, 593 mg) in trifluoroacetic acid (3 mL) and the resulting mixture was stirred for 1.5 h. Toluene (10 mL) was added and a precipitate was formed. The solid was filtered, washed with toluene (20 mL) and dried under vacuum. The solid product **TFA-L-V** (690 mg) was used in the next step without further purification.

N-Methylmorpholine (NMM, 3.6 mmol, 414 μL) and isobutylchloroformate (3.6 mmol, 486 μL) were slowly added to a solution of the **TFA-L-V** in THF (15 mL) at −15 °C (a white solid was formed during the addition of the *i*BuOCOCl). The reaction mixture was stirred for 45 min at −15 °C, then (*R*)-phenylglycinol (3.3 mmol, 466 mg) was added and the resulting mixture was stirred at room temperature for another 3 h. The mixture was filtered through silica gel (5 cm, 5 cm ∅) and eluted with ethyl acetate (400 mL). The solvent was concentrated under vacuum and the resulting solid was recrystallized from CH_2Cl_2/*n*-pentane, giving the pure product **TFA-L-Vb** (700 mg, 42% yield). m.p. 206–207 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (d, $J = 6.8$ Hz, 3H), 2.10 (m, 1H), 3.73 (dd, $J = 11.8$ and 6.9 Hz, 1H), 3.82 (dd, $J = 11.8$ and 4.5 Hz, 1H), 4.31 (m, 1H), 5.00 (m, 1H), 7.24–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.8$, 19.6, 32.0, 57.3, 60.9, 65.9, 117.4 (q, $J = 286.2$ Hz), 128.2 (2C), 128.5, 129.4 (2C), 141.0, 158.8 (q, $J = 37.7$), 172.1 ppm; (MALDI-TOF): m/z: 371.020 $[M-K]^+$, 355.124 $[M-Na]^+$, 333.090 $[M-H]^+$.

***N*-1-[(1*R*)-2-hydroxy-1-phenylethyl]-(2*S*)-2-amino-3-methylbutanamide (L-Vb)**: The *N*-Boc-protected amide **Boc-L-Vb** (10 mmol, 3.36 g) was dissolved in a 1:1 mixture of MeOH and HCl (3M, aq., 40 mL of each solvent) and the mixture was stirred for 3 h at 0 °C. MeOH was removed under vacuum keeping the bath at 30 °C and the resulting aqueous phase was basified using NaOH (50% solution) (note: the addition was done slowly to avoid an increase of the temperature. We strongly recommend the use of an ice bath). The basic phase (pH 14) was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic phases were dried over K_2CO_3 and the solvent was removed under vacuum to yield the deprotected amide **L-Vb** as a white solid (2.3 g, 98% yield). m.p. 134–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H), 2.31 (m, 1H), 2.48 (br s, 3H), 3.31 (d, $J = 4.2$ Hz, 1H), 3.86 (m, 2H), 5.06 (m, 1H), 7.26–7.40 (m, 5H), 8.04 ppm (br d, $J = 6.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.5$, 19.8, 31.2, 56.6, 60.3, 67.5, 127.0 (2C), 128.1, 129.1 (2C), 139.1, 175.2 ppm; (MALDI-TOF): m/z: 275.174 $[M-K]^+$, 259,102 $[M-Na]^+$, 237.193 $[M-H]^+$.

***N*-1-[(1*R*)-2-hydroxy-1-phenylethyl]-(2*S*)-3-methyl-2-{[(4-methylphenyl)-sulfonyl]amino}butanamide (Ts-L-Vb)**: TsCl (1 mmol, 194 mg) and Et_3N (1.2 mmol, 170 μL) were added to a solution of **L-Vb** (1 mmol, 236 mg) in CH_2Cl_2 (8 mL) at 0 °C. The reaction mixture was stirred for 5 h at room temperature. The crude product was washed with HCl (1M, 2 × 5 mL) and the acidic phase was washed with CH_2Cl_2 (10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under vacuum. The solid was recrystallized from Et_2O, giving the product **Ts-L-Vb** (280 mg, 72% yield). m.p. 193–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$ (m, 6H), 1.93 (br s, 1H), 2.09 (m, 1H), 2.43 (s, 3H), 3.53 (dd, $J = 8.1$ and 5.1 Hz, 1H), 3.71 (m, 2H), 4.90 (m, 1H), 5.29 (d, $J = 7.5$ Hz, 1H), 6.60 (br d, $J = 7.5$ Hz, 1H), 7.20–7.25 (m, 2H), 7.27–7.38 (m, 5H), 7.75 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.4$, 19.4, 21.8, 31.5, 56.0, 62.4, 66.3, 126.8 (2C), 127.7 (2C), 128.2, 129.1 (2C), 129.9 (2C), 136.6, 138.6, 144.2, 171.0 ppm; (MALDI-TOF): m/z: 429.077 $[M-K]^+$, 413.113 $[M-Na]^+$, 391.125 $[M-H]^+$.

***tert*-Butyl *N*-(2-{[(1*S*)-2-hydroxy-1-phenylethyl]amino}-2-oxoethyl)carbamate (Boc-Ga)**: This compound was prepared according to the general procedure for the preparation of the library ligands. Purification of the crude was done by column chromatography (silica gel, pentane/ethyl acetate mixtures) (570 mg, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H), 2.41 (s, 1H), 3.68–3.88 (m, 4H), 5.07 (m, 1H), 5.58 (br s, 1H), 7.21–7.35 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.5$ (3C), 44.6, 55.8, 66.0, 80.6, 126.9 (2C), 127.9, 128.9 (2C), 139.9, 156.7, 170.4 ppm; (MALDI-TOF): m/z: 333.064 $[M-K]^+$, 317.106 $[M-Na]^+$, 295.130 $[M-H]^+$.

***tert*-Butyl *N*-(2-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2-oxoethyl)carbamate (Boc-Gb)**: This compound was prepared according to the general procedure for the preparation of the library ligands. Purification of the crude was done by column chromatography (silica gel, pentane/ethyl acetate mixtures) (554 mg, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H), 2.76 (br s, 1H), 3.69–3.95 (m, 4H), 5.05 (m, 1H), 5.69 (br s, 1H), 7.21–7.34 (m, 5H), 7.41 ppm (br d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.4$ (3C), 44.4, 55.7, 65.8, 80.5, 126.8 (2C), 127.8, 128.8 (2C), 139.0, 156.6, 170.5 ppm; (MALDI-TOF): m/z: 333.156 $[M-K]^+$, 317.191 $[M-Na]^+$, 295.204 $[M-H]^+$.

***tert*-Butyl *N*-[(1*S*)-1-({[(1*R*)-2-methoxy-1-phenylethyl]amino}carbonyl)-2-methylpropyl]carbamate (4)**: A solution of **Boc-L-Vb** (0.6 mmol, 200 mg) in DMSO (2 mL) was slowly added to a 0 °C solution of NaH (0.72 mmol, 48 mg 60% oil dispersion) in DMSO (5 mL). After 10 min, MeI (0.66 mmol, 42 μL) was added and the reaction mixture was stirred for an additional 30 min. Water (10 mL) and CH_2Cl_2 (15 mL) were added and the organic phase was washed with water (2 × 5 mL). The combined aqueous phases were washed with CH_2Cl_2 (10 mL) and dried over Na_2SO_4. The solvent was then evaporated and the crude product was purified by column chromatography (silica gel, $CHCl_3$) (130 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 1.44 (s, 9H), 2.12 (m, 1H), 3.34 (s, 3H), 3.65 (m, 2H), 3.95 (m, 1H), 5.02–5.22 (m, 2H), 6.65 (br d, $J = 7.5$ Hz, 1H), 7.21–7.34 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.8$, 19.5, 28.5 (3C), 52.7, 59.2, 60.1, 75.0, 80.0, 127.0 (2C), 127.7, 128.7 (2C), 139.9, 156.1, 171.3 ppm; (MALDI-TOF): m/z: 389.184 $[M-K]^+$, 373.208 $[M-Na]^+$, 351.228 $[M-H]^+$.

***N*1-[(1*R*)-2-hydroxy-1-phenylethyl](2*R*)-2-phenylbutanamide (5)**: *N*-Methylmorpholine (NMM, 1.2 mmol, 135 μL) and isobutylchloroformate (1.2 mmol, 158 μL) were slowly added to a solution of the (*R*)-2-phenylbutyric acid (1 mmol, 166 mg) in THF (5 mL) at −15 °C (a white solid was formed during the addition of the *i*BuOCOCl). The reaction mixture was stirred for 45 min at −15 °C, then (*R*)-phenylglycinol (1 mmol, 141 mg) was added and the resulting mixture was stirred at room temperature for another 3 h. The mixture was filtered through silica gel (5 cm, 5 cm ∅) and eluted with ethyl acetate (70 mL). The solvent was concentrated under vacuum and the resulting solid was recrystallized from CH_2Cl_2/*n*-pentane, giving the pure product **5** (215 mg, 76% yield). m.p. 119–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.5$ Hz, 3H), 1.73–1.89 (m, 1H), 2.12–2.28 (m, 2H), 3.32 (t, $J = 7.6$ Hz, 1H), 3.84 (d, $J = 4.5$ Hz, 2H), 5.03 (dt, $J = 7.2$ and 4.5 Hz, 1H), 6.08 (br d, $J = 7.2$ Hz, 1H), 7.05 (m, 2H), 7.22–7.36 ppm (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.5$, 26.5, 55.4, 56.1, 67.0, 126.6 (2C), 127.5, 128.0, 128.2 (2C), 129.0 (2C), 129.1 (2C), 139.0, 139.9, 174.2 ppm; (MALDI-TOF): m/z: 322.184 $[M-K]^+$, 306.269 $[M-Na]^+$, 284.246 $[M-H]^+$.

***tert*-Butyl *N*-[(1*S*)-2-methyl-1-({(1*R*)-1-phenylethyl]amino}carbonyl)propyl]carbamate (6)**: *N*-Methylmorpholine (NMM, 3.5 mmol, 393 μL) and

isobutylchloroformate (3.5 mmol, 462 μL) were slowly added to a solution of **Boc-L-V** (3 mmol, 652 mg) in THF (10 mL) at −15 °C (a white solid was formed during the addition of the *i*-BuOCOCl). The reaction mixture was stirred for 45 min at −15 °C, then (*R*)-1-phenylethylamine (2.8 mmol, 386 μL) was added and the resulting mixture was stirred at room temperature for an additional 3 h. The mixture was filtered through silica gel (5 cm, 5 cm ∅) and eluted with ethyl acetate (100 mL). The solvent was removed under vacuum and the resulting solid was recrystallized from CH_2Cl_2/*n*-pentane, giving the pure product **6** (419 mg, 47 % yield). m.p. 125–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (d, $J = 6.9$ Hz, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 1.42 (s, 9H), 1.49 (d, $J = 7.2$ Hz, 3H), 2.15 (m, 1H), 3.84 (m, 1H), 4.94–5.18 (m, 2H), 6.27 (br d, $J = 7.8$ Hz, 1H), 7.22–7.38 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.2$, 19.6, 22.1, 28.5 (3C), 30.7, 49.0, 60.5, 80.1, 126.3 (2C), 127.6, 128.9 (2C), 143.1, 156.1, 170.8 ppm; (MALDI-TOF): *m*/*z*: 359.181 $[M-K]^+$, 343.217 $[M-Na]^+$, 321.223 $[M-H]^+$.

General procedure for the transfer hydrogenation of acetophenone using the ligand library: Ligand (0.03 mmol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.005 mmol),[19] and NaOH (5 mol %) were dissolved in 2-propanol (5 mL) in a dry Schlenck tube under inert atmosphere (N_2). The solution was stirred for 15 min and acetophenone (1 mmol) was added. The reaction mixture was stirred at ambient temperature. Aliquots were taken at different time intervals and quenched with NH_4Cl (1 mL, aq. sat.), extracted with EtOAc (1 mL), passed through a pad of silica and washed with EtOAc. The resulting solution was analyzed by GLC (CP Chirasil DEX CB conditions: hold 110 °C for 10 min, rate 80 °C min^{-1} to 200 °C and hold for 5 min): t_R(*R* isomer) = 6.21 min, t_R(*S* isomer) = 6.77 min.

General procedure for the transfer hydrogenation of aromatic ketones using Boc-L-Ab and Boc-D-Aa as ligands: Ligand (0.0275 mmol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.0125 mmol), and NaOH (2.5 mol %) were dissolved in 2-propanol (25 mL) in a dry Schlenck tube under inert atmosphere (N_2). The solution was stirred for 15 min and ketone (5 mmol) was added. The reaction mixture was stirred at ambient temperature. The reaction was quenched with NH_4Cl (15 mL, aq. sat.) and water (10 mL) and extracted with EtOAc (4 × 15 mL). The organic phase was dried with Na_2SO_4 and evaporated. Purification was done with Silica column using pentane/EtOAc (8:1) as eluent. The product alcohol was analyzed by GLC (CP Chirasil DEX CB, Hold 110 °C for 10 min, rate 80 °C min^{-1} to 200 °C and hold for 5 min).

(*S*)-1-phenylethanol: $R_f = 0.24$; Isolated yield: 0.590 g (95 % yield, 93 % *ee*); t_R(*R* isomer) = 6.21 min, t_R(*S* isomer) = 6.77 min.

(*R*)-1-phenylethanol: $R_f = 0.24$; yield: 0.565 g (91 % yield, 93 % *ee*); t_R(*R* isomer) = 6.21 min, t_R(*S* isomer) = 6.77 min.

(*S*)-1-(2-methylphenyl)ethanol: Ligand (0.055 mmol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.025 mmol), and NaOH (5.0 mol %). Eluent: pentane/EtOAc 20:1; $R_f = 0.16$; yield: 0.503 g (74 % yield, 96 % *ee*); t_R(*R* isomer) = 10.47 min, t_R(*S* isomer) = 10.76 min; $[\alpha]_D = -63.0$ ($c = 1.01$ in EtOH) (lit. $[\alpha]_D = -58.9$ ($c = 1.01$ in EtOH)).[20]

(*R*)-1-(2-methylphenyl)ethanol: Ligand (0.055 mmol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.025 mmol), and NaOH (5.0 mol %). Eluent: pentane/EtOAc 20:1; $R_f = 0.16$; yield: 0.501 g (74 % yield, 96 % *ee*); t_R(*R* isomer) = 10.47 min, t_R(*S* isomer) = 10.76 min; $[\alpha]_D = +61.9$ ($c = 1.01$ in EtOH) (lit. $[\alpha]_D = -58.9$ ($c = 1.01$ in EtOH)).[18]

(*S*)-1-(2-methoxyphenyl)ethanol: Ligand (0.055 mmol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.025 mmol), and NaOH (5.0 mol %). Eluent: pentane/EtOAc 30:1; $R_f = 0.09$; yield: 0.430 g (57 % yield, 84 % *ee*); (CP Chirasil DEX CB, Hold 110 °C for 2 mins, rate 1 °C min^{-1} to 125 °C, rate 20 °C min^{-1} to 200 °C and hold for 3 min): t_R(*S* isomer) = 13.23 min, t_R(*R* isomer) = 14.87 min; $[\alpha]_D = -23.9$ ($c = 2.00$ in $CHCl_3$) (lit. $[\alpha]_D = 32.3$ ($c = 2.00$ in $CHCl_3$, *R* isomer)).[21]

(*S*)-1-(3-methylphenyl)ethanol: Eluent: pentane/EtOAc 20:1; $R_f = 0.11$; yield: 0.606 g (89 % yield, 92 % *ee*); t_R(*R* isomer) = 10.07 min, t_R(*S* isomer) = 10.23 min.

(*S*)-1-(3-methoxyphenyl)ethanol: $R_f = 0.13$; yield: 0.645 g (85 % yield, 91 % *ee*); (CP Chirasil DEX CB, Hold 110 °C for 2 mins, rate 1 °C min^{-1} to 125 °C, rate 20 °C min^{-1} to 200 °C and hold for 3 min): t_R(*R* isomer) = 16.30 min, t_R(*S*-isomer) = 16.99 min. $[\alpha]_D = -30.9$ ($c = 1.00$ in MeOH) (lit. $[\alpha]_D = -34.9$ ($c = 0.849$ in MeOH)).[22]

(*S*)-1-(3-fluorophenyl)ethanol: $R_f = 0.20$; yield: 0.650 g (93 % yield, 89 % *ee*); t_R(*R* isomer) = 7.22 min, t_R(*S* isomer) = 8.12 min. $[\alpha]_D = -29.6$ ($c = 0.998$ in MeOH) (lit. $[\alpha]_D = +38.5$ ($c = 0.998$ in MeOH)).[23]

(*R*)-1-(3-fluorophenyl)ethanol: $R_f = 0.20$; yield: 0.653 g (93 % yield, 88 % *ee*); t_R(*R* isomer) = 7.22 min, t_R(*S* isomer) = 8.12 min; $[\alpha]_D = +32.4$ ($c = 0.998$ in MeOH) (lit. $[\alpha]_D = +38.5$ ($c = 0.998$ in MeOH)).[21]

(*S*)-1-(4-methylphenyl)ethanol: $R_f = 0.20$; yield: 0.580 g (85 % yield, 91 % *ee*); t_R(*R* isomer) = 8.33 min, t_R(*S* isomer) = 9.50 min; $[\alpha]_D = -40.2$ ($c = 0.994$ in MeOH) (lit. $[\alpha]_D = -43.5$ ($c = 0.994$ in MeOH)).[20]

(*S*)-1-(4-methoxyphenyl)ethanol: $R_f = 0.11$; yield: 0.479 g (63 % yield, 95 % *ee*); t_R(*R* isomer) = 11.17 min, t_R(*S* isomer) = 11.21 min.

(*R*)-1-(4-methoxyphenyl)ethanol: $R_f = 0.11$; yield: 0.494 g (65 % yield, 96 % *ee*); t_R(*R* isomer) = 11.17 min, t_R(*S* isomer) = 11.21 min.

(*S*)-1-(4-bromophenyl)ethanol: $R_f = 0.15$; yield: 0.904 g (90 % yield, 88 % *ee*); (CP Chirasil DEX CB, Hold 110 °C for 2 mins, rate 1 °C min^{-1} to 125 °C, rate 20 °C min^{-1} to 200 °C and hold for 3 min): t_R(*R* isomer) = 18.73 min, t_R(*S* isomer) = 19.01 min; $[\alpha]_D = -28.7$ ($c = 0.436$ in MeOH) (lit. $[\alpha]_D = +31.3$ ($c = 0.436$ in MeOH, *R* isomer)).[24]

(*S*)-1-phenylpropan-1-ol: Eluent: pentane/EtOAc 20:1; $R_f = 0.17$; yield: 0.620 g (91 % yield, 95 % *ee*); GLC (CP Chirasil DEX CB, Hold 110 °C for 8 mins, rate 80 °C min^{-1} to 200 °C and hold for 5 min): t_R(*R* isomer) = 8.53 min, t_R(*S* isomer) = 8.59 min; $[\alpha]_D = -32.9$ ($c = 1.00$ in MeOH) (lit. $[\alpha]_D = -28$ ($c = 1$ in MeOH)).[25]

(*S*)-2-methyl-1-phenylpropan-1-ol: Ligand (0.11 mmol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.050 mmol), and NaOH (10.0 mol %). Eluent: pentane/EtOAc 30:1; $R_f = 0.20$; yield: 0.396 g (53 % yield, 86 % *ee*); (CP Chirasil DEX CB, Hold 110 °C for 20 mins, rate 80 °C min^{-1} to 200 °C and hold for 5 min): t_R(*R* isomer) = 14.59 min, t_R(*S* isomer) = 14.98 min; $[\alpha]_D = -46.1$ ($c = 1.00$ in diethyl ether)(lit. $[\alpha]_D = -49.1$ ($c = 0.828$ in diethyl ether)).[20]

(*S*)-1,2,3,4-tetrahydronaphthalen-1-ol: Eluent: pentane:EtOAc 20:1; $R_f = 0.36$; yield: 0.280 g (38 % yield, 84 % *ee*); GLC (CP Chirasil DEX CB, Hold 80 °C for 10 min, rate 5 °C min^{-1} to 110 °C and hold for 10 min, rate 20 °C min^{-1} to 200 °C and hold for 5 min): t_R(*R* isomer) = 28.89 min, t_R(*S* isomer) = 29.00 min.

(*S*)-1-(2-naphthyl)ethanol: $R_f = 0.16$; yield: 0.620 g (85 % yield, 87 % *ee*); GLC (CP Chirasil DEX CB, Hold 110 °C for 20 mins, rate 10 °C min^{-1} to 200 °C and hold for 5 min): t_R(*R* isomer) = 27.42 min, t_R(*S* isomer) = 27.52 min; $[\alpha]_D = -32.6$ ($c = 2.00$ in MeOH) (lit. $[\alpha]_D = -25$ ($c = 2.2$ in MeOH)).[23]

Acknowledgements

We are grateful to the Swedish Research Council and the Carl Trygger Foundation for financial support. I. M. Pastor is grateful to the Wenner–Gren Foundation for a post-doctoral fellowship. We thank Dr. A. Bøgevig for valuable comments and suggestions.

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Received: February 28, 2003 [F4900]

