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Asymmetric addition of *n*-butyllithium to aldehydes: new insights into the reactivity and enantioselectivity of the chiral amino ether accelerated reaction

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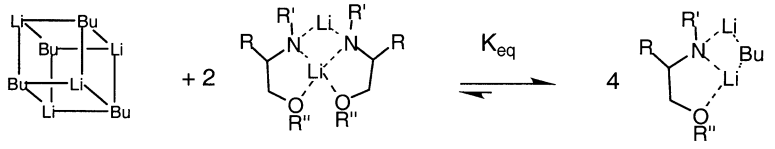
Abstract—Enantioselective butylation of benzaldehyde with *n*-butyllithium was mediated by a series of chiral lithium amide analogues to give 1-phenylpentanol in good to moderate enantioselectivities. In order to achieve high enantiomeric excess in the reaction, the lithium amide must have a substituent larger than methyl on both the carbon at the stereogenic center and the nitrogen. Computational studies, using semi-empirical (PM3) and density functional (B3LYP) methods, show that the stabilities of the transition states for the chiral lithium amide accelerated butylation of isobutyraldehyde are in agreement with experiments.

1. Introduction

Asymmetric carbon–carbon bond forming reactions between *n*-butyllithium (*n*-BuLi) and aldehydes can be a particularly versatile reaction in the construction of enantiopure alcohols.[1] The enantioselectivity is obtained using chiral lithium amides as chiral auxiliaries and catalysts, non-covalently bonded to the reagent *n*-BuLi. Our interest in this field began in 1993 when we initiated NMR spectroscopic studies of a chiral lithium amide reported by Hogeveen and Eleveld to induce asymmetry in the addition of *n*-BuLi to benzaldehyde.[2,3] So far, the enantioselectivities obtained with organolithium compounds in the alkylation reaction of aldehydes have not been as high as those with dialkyl zinc reagents.[4] However, the readily available alkyllithium reagents and their high reactivity are properties that motivate more effort to find conditions in which organolithium compounds also can become useful nucleophilic reagents in asymmetric synthesis.

By low temperature NMR spectroscopic studies we have observed an equilibrium between homo complexed chiral lithium amide dimers, tetrameric *n*-BuLi and a mixed dimer consisting of one lithium amide and one *n*-BuLi (Scheme 1).[5]

Most of the NMR spectroscopic studies were carried out in diethyl ether (DEE) solution. Later, the effect of different solvents and substituents on the equilibrium and enantioselectivity of addition to an aldehyde were investigated.[6] At that time, our results indicated the importance of a high complexation constant in order to observe high enantioselectivity. Since then, we have remained in this field with the aim of better understanding the factors governing the enantioselectivity. This work includes the search for new mixed complexes between *n*-BuLi and chiral inducers. We hope that details regarding this issue could be helpful in the design of new and more efficient chiral inducers for this important class of reaction. Herein, we report our continued studies of chiral lithium amides and their use in the asymmetric addition reaction to prochiral aldehydes. Based on quantum chemical calculations we also



(n-BuLi)$_4$ (Li-Amide)$_2$ Li-Amide/*n*-BuLi

Scheme 1.

Keywords: lithium; amides; alkylation; asymmetric.
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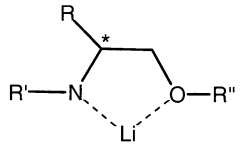


Scheme 2.

propose transition state structures that explain the observed enantioselectivity.

2. Results and discussion

2.1. Enantioselectivity and steric requirements

Often in organolithium chemistry small changes in ligand structure or reaction conditions result in large effects on organolithium structure and/or enantioselectivity. However, the amino ether catalyzed system for addition of *n*-BuLi to aldehydes is a particularly robust and reliable system allowing a large number of modifications to be studied.

The amino ethers were prepared in high yield from readily available amino acids. The amino acids were first reduced using lithium aluminum hydride. Alkylation of the amine in two steps via the imine yielded the secondary amino alcohols, which were then converted into the respective amino ethers.

We have focused our modifications to three positions of the amino ether: the alkyl group (R′) on the nitrogen, the alkyl group on the oxygen (R″) and the bulky group attached to the stereogenic center (R) (Scheme 2). The results of the stereoselective alkylation of benzaldehyde employing lithium amides **1**–**4** are given in Table 1. The reactions have mainly been performed in three different ethereal or coordinating solvents, e.g. DEE, a 50:50 mixture of dimethoxy methane (DMM) and DEE and a 50:50 mixture of DEE and tetrahydrofuran (THF). In addition, a few of the reactions were also performed in a 50:50 mixture of pentane and toluene (pent/tol), a non-coordinating solvent mixture.

All chiral lithium amides catalyzed the formation of the alcohol with the opposite configuration compared to that of the amide. This indicates that the reaction is robust in nature even though it requires the formation of a hetero-complex.

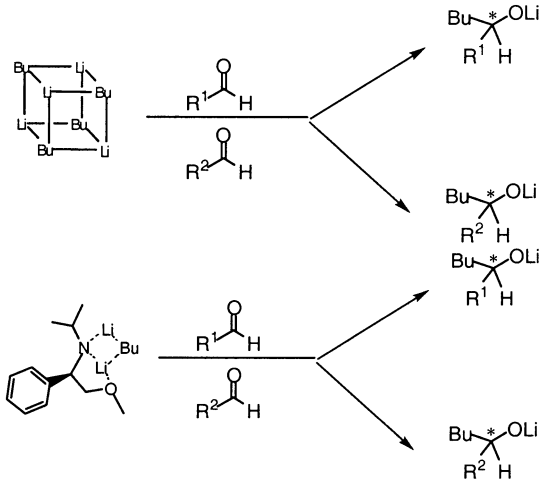
Previous studies only involved phenylsubstituted lithium amides while this work also includes aliphatic R groups. The enantioselectivity obtained with the various lithium amides indicates that the phenyl group is not crucial to obtain high enantioselectivity. Replacing the phenyl ring with an isopropyl group results in similar enantioselectivity in the asymmetric alkylation reaction. This shows that it is the steric requirements of the R group and not the stereo-electronic effects of having the phenyl substituent that are crucial for high enantioselectivity.

From the results of Table 1 it is clear that a methyl group, as in the alanine derivative **1a**, is not large enough to induce asymmetry in the alkylation reaction. We believe that the asymmetry in the reaction comes from the steric requirements of the alkyl group on the nitrogen. The chirality of the nitrogen is transferred from the carbon to the lithium amide nitrogen. Based on this, it is evident that a methyl group on the lithium amide nitrogen yields very low enantioselectivity. However, with a secondary carbon on the amide nitrogen, a much higher enantioselectivity was achieved. Among these larger substituents there are small differences, i.e. isopropyl, 3-pentyl or cyclohexyl on the nitrogen result in approximately the same enantioselectivity. In DEE, the highest enantioselectivity was found with the isopropyl

Table 1. Asymmetric alkylation of benzaldehyde (0.10 equiv.) with *n*-BuLi (0.45 equiv.) in the presence of chiral lithium amides **1a**, **2a**–**j**, **3a**–**c** and **4a**–**e** (1.0 equiv.), resulting in alcohols with configuration opposite to that of the lithium amide. The reactions were performed in four different solvents or solvent mixtures at −116°C. All reactions proceeded in quantitative yield according to the chiral stationary phase GC analysis

Li-amide	R	R′	R″	ee (%)			
				DEE	DEE/DMM	DEE/THF	Pentane/toluene
(*S*)-**1a**	Me	*i*-Pr	Me	36	–	–	–
(*R*)-**2a**	Ph	Me	Me	2[a]	–	–	–
(*S*)-**2b**	Ph	*i*-Pr	Me	82[a]	91[a]	85	–
(*S*)-**2c**	Ph	*i*-Pr	Et	60	76	79	–
(*S*)-**2d**	Ph	*i*-Pr	*i*-Pr	50	73	77	–
(*S*)-**2e**	Ph	3-Pentyl	Me	48	63	72	–
(*S*)-**2f**	Ph	3-Pentyl	Et	29	63	70	–
(*S*)-**2g**	Ph	Cyclohexyl	Me	75	87	86	17
(*S*)-**2h**	Ph	Cyclohexyl	Et	66	86	89	–
(*R*)-**2i**	Ph	2-Methoxybenzyl	Me	6	27	47	–
(*R*)-**2j**	Ph	2-Methoxybenzyl	Et	2	32	45	8
(*S*)-**3a**	Benzyl	*i*-Pr	Me	60	68	67	38
(*S*)-**3b**	Benzyl	*i*-Pr	Et	41	74	69	–
(*S*)-**3c**	Benzyl	*i*-Pr	*i*-Pr	52	74	72	–
(*S*)-**4a**	*i*-Pr	*i*-Pr	Me	61	78	78	8
(*S*)-**4b**	*i*-Pr	*i*-Pr	Et	44	76	74	–
(*S*)-**4c**	*i*-Pr	*i*-Pr	*i*-Pr	48	77	71	–
(*S*)-**4d**	*i*-Pr	2-Methoxybenzyl	Me	15	29	42	–
(*S*)-**4e**	*i*-Pr	2-Methoxybenzyl	Et	17	32	48	20

[a] Ref. 6.



Scheme 3.

group. But in the DMM/DEE and THF/DEE mixtures we found that cyclohexyl gave similar values of enantioselectivity compared to isopropyl.

There is a very small dependence on the enantioselectivity versus the size of the alkyl group of the ether. Methyl-, ethyl-, and isopropyl ethers yield about the same chiral induction. Although, generally the methyl is the better followed by ethyl and isopropyl.

We also investigated some tridentate lithium amides as chiral inducers. Similar chiral tridentate amines have been reported to achieve high enantioselectivity in the asymmetric addition of methyllithium to imines.[7] Our tridentate amines were formed by condensing 2-methoxybenzaldehyde with chiral amino alcohols followed by reduction and alkylation of the alcohol. However, the enantioselectivities of the butylation of benzaldehyde were disappointing with ees up to 48% at most. Only low enantioselectivities were observed for all lithium amides employed in the non-coordinating solvents. The solvent dependence of the enantioselectivity was larger for the tridentate lithium amides than for the bidentate, despite their additional coordinating group. Interestingly, the enantioselectivities are similar for these amides in DEE and in the non-coordinating solvent mixture. This indicates that the transition state structures could be similar. Possibly there are mixed dimers in both DEE and the non-coordinating solvent mixture and DEE is not capable of solvating the mixed dimer while THF is. Altogether, the enantioselectivity appears to be significantly influenced by the solvent, indicating that coordinating solvent molecule(s) are involved in the rate determining activated complex.

To test the versatility of the asymmetric alkylation reactions we also added methyllithium to benzaldehyde with the bidentate chiral lithium amide **4a** as chiral inducer. However, the results were not promising, an enantioselectivity of 45% was observed in THF/DEE. Surprisingly, the tridentate amide **4e** that we believed would be more successful generated only racemic mixtures of the methyl adduct. The butylation of trifluoroacetophenone mediated by **4e** was found to proceed with 58% ee in THF/DEE. This promising result shows that the lithium amides may also be used for asymmetric alkylation of prochiral ketones.

2.2. Enantioselectivity versus mixed complex formation

Our preliminary results indicated that the high degree of complexation between the chiral lithium amide and the nucleophile *n*-BuLi is prerequisite for success in the asymmetric reaction. This was supported by the low enantioselectivities obtained with diamines, which generally gave lower amounts of mixed complexes. However, it is important to take into account the concentrations used in these asymmetric reactions. Even if the apparent equilibrium constants differ by five orders of magnitude, the actual concentration of reactive *n*-BuLi/Li-amide differ by less than a factor of 2 ([*n*-BuLi/Li-amide]≈0.03–0.05 M). Although the concentration of free tetrameric *n*-BuLi varies at the same time from 0.005 M to an infinitely small number ($<10^{-5}$ M).

Thus there is only a weak correlation between the equilibrium constant and the observed enantioselectivity, due to the fact that the amount of uncomplexed *n*-BuLi at the studied concentrations is low compared to the amount complexed. Below, we have based the calculations on the actual equilibrium constants and the total concentrations calculated from the theoretical concentrations of free tetrameric *n*-BuLi and lithium amide/*n*-BuLi complexes.

$[\text{Li-amide}]_{tot} = 0.116$ M; $[n\text{-BuLi}]_{tot} = 0.052$ M(0.45 equiv.)

K=0.1 M⇒
[Li-amide/*n*-BuLi]=0.032 M; $[(n\text{-BuLi})_4]$= 0.0051 M
K=4 M⇒
[Li-amide/*n*-BuLi]=0.048 M; $[n\text{-BuLi})_4]$= 0.0011 M
K=10,000 M⇒
[Li-amide/*n*-BuLi]=0.052 M; $[(n\text{-BuLi})_4]$= $<10^{-5}$ M

It is also found that most of the *n*-BuLi is present in the mixed complex even when the equilibrium constant is as small as 4. The $[(n\text{-BuLi})_4]$ concentration is less than 25% of the concentration [Li-amide/*n*-BuLi]. Since the asymmetric alkylation reactions are performed with only 0.25 equiv. or less of the aldehyde and the mixed complex is much more reactive than tetrameric *n*-BuLi,[9] we conclude that the amount of aldehyde that reacts via tetrameric *n*-BuLi is consequently only a fraction even when the equilibrium constant is unfavorable.

2.3. NMR spectroscopy

We have previously reported on the solution structures of the lithium amides **2b** and **4a** and have now studied **3a** and the tridentate **1j** by NMR spectroscopy.[6] There is only a small solvent dependence between different coordinating solvents. However, there is a pronounced change upon going from an ether solvent to a non-coordinating solvent. All investigated lithium amides in this series form mixed dimers with *n*-BuLi in coordinating solvents. The equilibrium constants vary significantly, but the fundamental equilibrium is the same. However, in non-coordinating

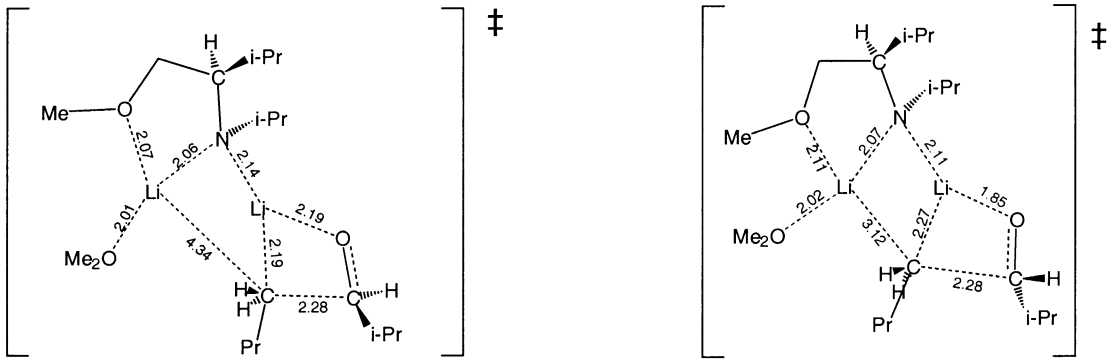


Figure 1. Schematic drawings of the calculated transition state structures (*R*)-**TS** and (*S*)-**TS** for the alkylation with the mixed dimer lithium amide **4a**/*n*-BuLi yielding (*R*)-alcohol and (*S*)-alcohol. The DFT calculations were performed at the B3LYP/6-31G+(d)//PM3 level of theory. Distances are given in Angstrom (Å) and the relative energies are given in kcal mol^{-1}.

solvents mixed trimers, containing two lithium amides and one *n*-BuLi, of the type found by Williard dominate.[8] Two lithium amides, **3a** and **4a** form this sort of complex as found by NMR spectroscopy. These trimers are C_2-symmetric and should have potential as chiral nucleophiles.

2.4. Reactivity studies

How important are the steric requirements of the R-group of the aldehyde for the reaction rate? The alkylation reactions are irreversible and if several aldehydes are added simultaneously there are as many concurrent independent modes of reaction (Scheme 3). However, the product compositions in such parallel reactions are directly related to their individual rate constants. In separate experiments, a mixture of two different aldehydes, both in excess (each in 5 equiv.), were added to *n*-BuLi (1 equiv.) and to the mixture of *n*-BuLi/lithium amide (1 equiv.), respectively. With no lithium amide present, benzaldehyde was found to react 13 times faster than cyclohexanecarboxaldehyde with *n*-BuLi in DEE at -116°C. However, in the presence of the lithium amide **2b**, the reaction rate was only 1.4 times higher. The reaction of isobutyraldehyde was 3.2 times faster than cyclohexanecarboxaldehyde without catalyst present but 1.6 times slower in the presence of **2b**. Apparently, **2b** catalyzes the alkylation of cyclohexanecarboxaldehyde more efficiently than benzaldehyde and isobutyraldehyde. The alkylation reactions of isobutyraldehyde and cyclohexanecarboxaldehyde mediated by **2b** resulted in ees of $>8.5\%$ higher than that of benzaldehyde.[9] Therefore, it is surprising to find a large difference in accelerating not only between benzaldehyde and cyclohexancarboxaldehyde but also between isobutyraldehyde and cyclohexanecarboxaldehyde.

What is the reactivity of *n*-BuLi vs aldehyde and methanol, respectively? Methanol is usually used to quench these types of reactions and has previously been used in an attempt to measure the reaction rate of the alkylation of aldehydes.[9] Alkylation experiments in the presence of 1, 10 and 50 equiv. of methanol show that the rate of the alkylation reaction of benzaldehyde and the quenching reaction with methanol are about the same. The presence of the lithium amides **2b** and **3a** did not make any considerable difference. Thus addition of 1 mL methanol to quench the reaction is sufficient to remove all available *n*-BuLi instantaneously.

2.5. Computational studies

The asymmetric alkylation reaction must proceed through a transition state consisting of a complex between a chiral lithium amide, *n*-BuLi and the aldehyde in order to observe enantioselectivity. We have studied this reaction using the semi-empirical PM3 method with Anders parameters for lithium to obtain geometries of high quality and then single point DFT calculations of the energies were performed.[10] This method has previously been employed with good results by several groups in the field.[11]

The lithium amide **4a** was chosen as chiral lithium amide in the calculations since this lithium amide is the smallest amongst the investigated amides that still results in good selectivity. We used dimethyl ether as the solvent. There are several possible conformers of the ground state structure according to the PM3 calculations, considering the coordination of the prochiral aldehyde. The interconversion among the different conformers is assumed to follow the Curtin–Hammett principle. Thus, the $\delta\Delta G$ between the favored transition states leading to the (*R*)- and the (*S*)-alcohols should be responsible for the enantioselectivity observed experimentally.

The favored transition states for the transfer of the butyl group to the carbonyl are shown in Fig. 1. We observed a large gain in enthalpy of solvation by adding one ether to the lithium coordinated by isobutyraldehyde. However, there was no gain of solvation upon adding a second ether to the tri-coordinated lithiums. Apparently, the steric hindrance at the tri-coordinated lithiums is too large to accommodate a coordinating ether.

At the B3LYP(6-31+G(d))//PM3 level of theory it appears that transition state (*R*)-**TS** is 3.4 kcal mol^{-1} less stable than

Table 2. Enantiomeric excesses obtained from the addition of *n*-BuLi to benzaldehyde with **3a** as chiral auxiliary at various temperatures

T (°C)	ee (%)	
	DEE/THF	Pentane/toluene
−116	67.3	38.2
−78	47.6	25.9
−46	31.6	18.1
−21	23.9	17.9
0	18.9	17.9
20	10.3	13.4

(*S*)-**TS**, qualitatively in agreement with the experimental results which give the (*S*)-alcohol. Interestingly, the methoxy coordinated lithium is located 4 Å away from the α-carbon of *n*-BuLi in (*R*)-**TS**. This transition state is an open dimer transition state. Such structures have been suggested previously to be important in the reaction between an aldehyde and methyllithium.[12] This appears to be due to a larger steric hindrance in (*R*)-**TS** than in (*S*)-**TS**. The structure of transition state (*S*)-**TS** resembles a ladder structure of a lithium amide (i.e. a trimer). At the B3LYP-(6-31+G(d))//PM3, a second transition state with a shorter methoxy-lithium distance leading to the (*R*)-alcohol was also found, but at slightly higher energy (+4.0 kcal mol^{-1}). The central core of the respective transition states are planar or nearly planar, i.e. the two lithiums, the amide nitrogen, the α-carbon of *n*-BuLi and the carbonyl group form a plane.

It is difficult to rationalize how the enantioselectivity could be induced in these transition states. There is only one stereogenic center in the chiral lithium amide, but in the complex, the nitrogen and the tetracoordinated lithium also become additional stereogenic centers. The chirality of the carbon is thus being transferred from carbon to both the nitrogen and the tetracoordinated lithium. If either the alkyl group on the carbon or the nitrogen is too small, this transfer of chirality will not be as effective resulting in a lowering in enantioselectivity. Furthermore, the solvent ether is also important for the enantioselectivity as can be expected for the transition states shown in Fig. 1.

It must however be added that the error in PM3 calculations might exceed the energy difference observed experimentally corresponding to a selectivity of 98%. Since the calculations are performed in vacuum, the addition of solvent continuum could lead the calculations closer to the experimentally observed values.

2.6. Temperature dependence of the asymmetric alkylation reaction

The asymmetric alkylation reaction was also studied as a function of temperature to obtain the absolute difference in free energies, $\delta\Delta G^{\ddagger}$, of the two diastereomeric transition states leading to the enantiomers of the product and its temperature dependence. Is the selectivity between the *R* and *S* transition states due to entropy or enthalpy of activation? The $\delta\Delta S^{\ddagger}$ and $\delta\Delta H^{\ddagger}$ terms for the asymmetric alkylation, employing **3a** as chiral auxiliary, were determined from the temperature dependence of $\delta\Delta G^{\ddagger}$ in both DEE/THF and pentane/toluene mixtures (Table 2).

The alkylation reactions are irreversible, hence the rates of formation of *R* and *S* alcohols are described by k_R and k_S, with the ratio k_R/k_S corresponding to the molar free energy difference, $\delta\Delta G^{\ddagger}$, of the two reactions (Fig. 2).

The enthalpic terms were determined to be −3.9 and −1.4 kJ mol^{-1} in DEE/THF and pentane/toluene, respectively. The entropy terms were 11.6 and 2.7 J K^{-1} mol^{-1}. As expected, the selectivity is largely governed by entropy in the DEE/THF mixture, since the transition states are most likely solvated by THF. However, in a pentane/toluene mixture the transition states are most likely unsolvated and there is consequently less entropic differences between the two diastereomeric transition states.

3. Conclusion

No major electronic effects are operating since phenyl groups on either the aldehyde or lithium amide have no effect on the enantioselectivity compared to bulky aliphatic substituents. Isopropyl groups on the lithium amide appear to yield the highest enantioselectivity. Chiral lithium amides can be useful reagents for asymmetric synthesis but we still know too little about this class of compounds for truly rational design of new and better chiral lithium amides. The surprisingly large effect that a seemingly small change on the lithium amide or solvent does not have to be a disadvantage, it can possibly also turn out to be a great

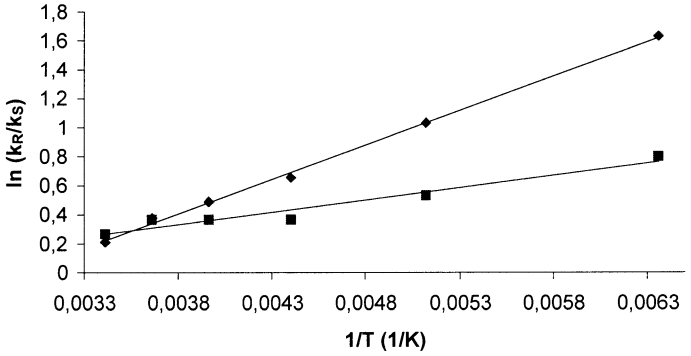


Figure 2. Eyring plot of the temperature dependence of the free energy difference between the two diastereomeric transition states, in DEE/THF (◆) and pentane/toluene (■) mixtures, respectively, for the addition of *n*-BuLi to benzaldehyde mediated by **3a**.

advantage. Among several reaction pathways of similar free energy, there is a possibility to fine tune reactions to proceed in a certain wanted direction. The solvent molecules have a large effect on the enantioselectivity of the alkylation reactions. The bidentate lithium amides only show a small difference in selectivity using different ethers, however in the case of the tridentate lithium amides we see a much stronger variation among DEE and THF, which indicates that the transition states are specifically solvated by THF but not with DEE.

4. Experimental

4.1. General

NMR spectra were recorded on a Varian 400 MHz spectrometer using $CDCl_3$ as solvent. Optical rotations were measured using a Perkin–Elmer 341 LC polarimeter. IR spectra were recorded on a Perkin–Elmer 1600 Series FTIR spectrometer. HRMS (FAB) spectra were recorded on a VG ZabSpec using a beam of Cs atoms as ionization source and glycerol to dissolve the sample. GC analysis were carried out using a Varian Star 3400 CX gas chromatograph equipped with a chiral stationary phase column (CP-Chirasil-DEX CB, 25 m, 0.32 mm) from Chrompack.[9] Analyses were done using He (1.5 mL min^{-1}) as carrier gas (injector 225°C, detector 250°C). Dried solvents were distilled from sodium/benzophenone.

4.2. Alkylation reactions

Inside a glove box containing a nitrogen atmosphere, the chiral amine (0.22 mmol, 1.00 equiv.) was dissolved in the dry solvent/solvent mixture (2.0 mL) in a dry reaction vessel, equipped with a septum and a magnetic stirrer bar. The vessel was sealed and taken out of the glove box and put under an inert atmosphere (argon or nitrogen). *n*-BuLi (129 μL, 2.5 M in hexanes, 0.32 mmol, 1.45 equiv.) was added and the mixture kept at room temperature for 15 min. The reaction mixture was cooled to −116°C in a liquid nitrogen/DEE cooling bath and its temperature allowed to equilibrate for 15 min before a solution of benzaldehyde (18.5 μL, 1.23 M in DEE, 0.022 mmol, 0.10 equiv.) was added dropwise. After 15 min, the reaction was quenched with methanol (1.00 mL) and allowed to reach room temperature before it was acidified using aqueous hydrochloric acid (0.60 mL, 5%) and diluted with DEE (3.00 mL). The crude mixture containing the 1-phenyl pentanol was analyzed on the chiral stationary phase GC. All reactions proceeded in quantitative yields according to the GC analysis.

4.3. Computational methods

Geometries were optimized at PM3 level of theory. In Spartan, the option HHon,[13] was used to eliminate the too positive HH attraction of the PM3 method. All structures were characterized as either minimum or transition states by frequency calculations. All energies were calculated at the B3LYP/6-31+G(d)//PM3. The calculations were performed either using the Spartan program package[14] or the Gaussian98W.[15]

4.4. Reduction of amino acids, general procedure

The amino acid (1.0 equiv.) was added slowly, in small portions, to an ice cooled solution of lithium aluminum hydride (2.0 equiv.) in dry THF (40 mL g^{-1} $LiAlH_4$). The mixture was allowed to react at 0°C for 1 h followed by reflux overnight. The solution was cooled to 0°C and the excess of $LiAlH_4$ quenched with aqueous sodium hydroxide (2.0 M). The precipitate was filtered off and extracted with boiling THF for an hour. The combined ethereal extract was concentrated under reduced pressure and the remaining mixture extracted with dichloromethane. The combined organic extract was washed with brine, dried over sodium sulfate and the solvent evaporated under reduced pressure to give the known amino alcohols.

4.4.1. (*S*)-Phenylalaninol. White solid (100%); spectral data consistent with literature.[16]

4.4.2. (*S*)-Phenylglycinol. White solid (95%); spectral data consistent with literature.[17–19]

4.4.3. (*S*)-Valinol. Colorless oil (85%); spectral data consistent with literature.[16,18]

4.5. *N*-Alkylation of the amino alcohol, general procedure

The amino alcohol (1.0 equiv.) and the carbonyl compound (acetone; 2.0 equiv., 3-pentanone and cyclohexanone; 1.5 equiv. or 2-methoxybenzaldehyde 1.1 equiv.) were dissolved in dry benzene (30 mL g^{-1} amino alcohol) and refluxed overnight with a Dean–Stark trap to collect water. The mixture was allowed to cool and the solvent evaporated under reduced pressure. The residue was dissolved in dry ethanol (30 mL g^{-1} of amino alcohol) and sodium borohydride (1.5 equiv.) added in small portions. The mixture was allowed to react at room temperature until no more gas evolved, usually after only a few hours. Water was added and most of the ethanol evaporated. The residue was extracted with DEE and the combined organic extract washed with brine, dried over sodium sulfate and the solvent evaporated under reduced pressure.

4.5.1. (*S*)-*N*-Isopropylalaninol. Pale yellow oil (60%); spectral data consistent with literature.[20]

4.5.2. (*S*)-*N*-Isopropylphenylglycinol. White crystals (90%); spectral data consistent with literature.[20]

4.5.3. (*S*)-*N*-(3-Pentyl)phenylglycinol. Slightly yellow crystals (84%); ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, J=7.4 Hz, 3H, $(CH_3CH_2)_2CHN$), 0.87 (t, J=7.6 Hz, 3H, $(CH_3CH_2)_2CHN$), 1.28–1.39 (m, 1H, $(CH_3CH_2)_2CHN$), 1.39–1.49 (m, 3H, $(CH_3CH_2)_2CHN$), 2.38 (quint., J=5.8 Hz, 1H, $(Et)_2CHN$), 3.48 (dd, J=8.8, 10.4 Hz, 1H, CH_2OH), 3.68 (dd, J=4.6, 10.4 Hz, 1H, CH_2OH), 3.86 (dd, J=4.6, 8.8 Hz, 1H, $PhCHCH_2$), 7.27–7.31 (m, 3H, Ph), 7.33–7.38 (m, 2H, Ph); $[\alpha]_D^{20}$=+81.8 (c 2.9, ethanol); ν_{max} (KBr) 3155 (br), 1146, 1066, 1041, 1029 cm^{-1}; HRMS (FAB): MH^+, found 208.1663. $C_{13}H_{22}NO$ requires 208.1701.

4.5.4. (*S*)-*N*-Cyclohexylphenylglycinol. Colorless needle-shaped crystals, recrystallized from ethyl acetate/hexane 25:75 (70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04–1.22 (m, 5H, $(CH_2)_5CHN$), 1.57 (m, 1H, $(CH_2)_5CHN$), 1.66–1.72 (m, 3H, $(CH_2)_5CHN$), 1.97 (m, 1H, $(CH_2)_5CHN$), 2.42 (m, 1H, $(CH_2)_5CHN$), 3.47 (dd, J=9.4, 10.4 Hz, 1H, CH_2OH), 3.67 (dd, J=4.4, 10.4 Hz, 1H, CH_2OH), 3.94 (dd, J=4.4, 9.4 Hz, 1H, $PhCHCH_2$), 7.27–7.32 (m, 3H, Ph), 7.34–7.39 (m, 2H, Ph); $[\alpha]_D^{20}$=+75.2 (c 2.5, ethanol); ν_{max} (KBr) 3270, 3132 (br), 1500, 1451, 1040 cm^{-1}; HRMS (FAB): MH^+, found 220.1659. $C_{14}H_{22}NO$ requires 220.1701.

4.5.5. (*R*)-*N*-(2-Methoxybenzyl)phenylglycinol. Colorless rhombic crystals, recrystallized from ethyl acetate/hexane 20:80 (70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (m, 2H, $ArCH_2N$), 3.73 (m, 1H, $PhCHCH_2$), 3.81 (m, 2H, $PhCHCH_2$), 3.82 (s, 3H, CH_3O), 6.84–6.94 (m, 2H, Ar), 7.19 (m, 1H, Ar), 7.24 (m, 1H, Ar), 7.27–7.39 (m, 5H, Ph); $[\alpha]_D^{20}$=−91.6 (c 4.4, ethanol); ν_{max} (KBr) 3315, 3164 (br) 1239, 1124, 1045 cm^{-1}; HRMS (FAB): MH^+, found 258.1456. $C_{16}H_{20}NO_2$ requires 258.1494.

4.5.6. (*S*)-*N*-Isopropylphenylalaninol. White solid (95%); spectral data consistent with literature.[20]

4.5.7. (*S*)-*N*-Isopropylvalinol. Colorless oil (80%); spectral data consistent with literature.[20]

4.5.8. (*S*)-*N*-(2-Methoxybenzyl)valinol. White crystals (50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.0 (d, J=6.8 Hz, 3H, $(CH_3)_2CHC$), 1.02 (d, J=6.8 Hz, 3H, $(CH_3)_2CHC$), 2.14 (m, 1H, $(CH_3)_2CHC$), 2.70 (s (broad), 1H, i-$PrCHCH_2$), 3.82 (s (broad), 2H, $CHCH_2OH$), 3.94 (s, 3H, CH_3O), 4.22 (d, J=13.2 Hz, 1H, $ArCH_2N$), 4.30 (d, J=13.2 Hz, 1H, $ArCH_2N$), 6.91–7.00 (m, 2H, Ar), 7.35–7.40 (m, 1H, Ar), 7.43–7.47 (m, 1H, Ar); $[\alpha]_D^{20}$=+7.0 (c 1.7, ethanol); ν_{max} (KBr) 3348 (br) 1245, 1026 cm^{-1}; HRMS (FAB): MH^+, found 224.1617. $C_{13}H_{22}NO_2$ requires 224.1651.

4.6. *p*-Toluenesulfonic acid isopropyl ester

A solution of 2-propanol (6.00 g, 7.64 mL, 100 mmol, 1.0 equiv.) in dry pyridine (200 mL) was cooled to 0°C and *p*-toluenesulfonic acid chloride (28.60 g, 150 mmol, 1.5 equiv.) was added in small portions over 15 min. The mixture was allowed to react overnight while warming to room temperature. The mixture was then poured onto crushed ice (200 g). The resulting mixture was extracted with 7×50 mL DEE. The combined organic extract was washed with 4×50 mL aqueous hydrochloric acid (6.0 M), 4×50 mL aqueous sodium bicarbonate (saturated), 4×50 mL brine, dried over sodium sulfate and the solvent removed under reduced pressure yielding the product as a clear, slightly yellowish oil (17.94 g, 85%). Spectral data consistent with literature.[21]

4.7. *O*-Alkylation, general procedure

The amino alcohol (1.0 equiv.), dissolved in dry THF (15 mL g^{-1} of amino alcohol), was added to a suspension of sodium hydride (1.5 equiv., 60% dispersion in mineral oil) in dry THF (100 mL g^{-1} of sodium hydride). The mixture was allowed to react at room temperature for 2 h before the alkylating reagent (methyl iodide 1.0 equiv., ethyl iodide 1.5 equiv., *p*-toluenesulfonic acid isopropyl ester 2.0 equiv.) was added. The mixture was then left to react at room temperature overnight (when *p*-toluenesulfonic acid isopropyl ester was used the mixture was refluxed overnight). Distilled water was added and the ethereal solvent removed under reduced pressure. The residue was extracted with dichloromethane and the combined extract washed with brine, dried over sodium sulfate and the solvent removed under reduced pressure. Kügelrohr distillation under reduced pressure afforded the respective amines as colorless oils.

4.7.1. (*S*)-*N*-Isopropyl-*O*-methylalaninol (1a). Colorless oil (40%); spectral data consistent with literature.[20]

4.7.2. (*R*)-*N*-Methyl-*O*-methylphenylglycinol (2a). This compound was prepared according to literature methods.[5]

4.7.3. (*S*)-*N*-Isopropyl-*O*-methylphenylglycinol (2b). Colorless oil (90%); spectral data consistent with literature.[20,22,23]

4.7.4. (*S*)-*N*-Isopropyl-*O*-ethylphenylglycinol (2c). Colorless oil (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J=6.4 Hz, 3H, $(CH_3)_2CHN$), 1.05 (d, J=6.4 Hz, 3H, $(CH_3)_2CHN$), 1.20 (t, J=7.0 Hz, 3H, CH_3CH_2O), 2.65 (sept., J=6.3 Hz, 1H, $(Me)_2CHN$), 3.40 (t, J=9.2 Hz, 1H, $PhCHCH_2$), 3.46–3.55 (m, 3H, $PhCHCH_2$ and CH_3CH_2O), 4.02 (dd, J=4.0, 8.8 Hz, 1H, $PhCHCH_2$), 7.25–7.28 (m, 1H, Ph), 7.31–7.35 (m, 2H, Ph), 7.36–7.39 (m, 2H, Ph); $[\alpha]_D^{20}$=+68.4 (c 3.6, ethanol); ν_{max} (liquid film) 3327, 1107 cm^{-1}; HRMS (FAB): MH^+, found 208.1708. $C_{13}H_{22}NO$ requires 208.1701.

4.7.5. (*S*)-*N*-Isopropyl-*O*-isopropylphenylglycinol (2d). Colorless oil (40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J=6.4 Hz, 3H, $(CH_3)_2CHN$), 1.05 (d, J=6.4 Hz, 3H, $(CH_3)_2CHN$), 1.15 (t, J=6.0 Hz, 6H, $(CH_3)_2CHO$), 2.65 (sept., J=6.4 Hz, 1H, $(CH_3)_2CHN$), 3.35 (t, J=9.2 Hz, 1H, $PhCHCH_2$), 3.52 (dd, J=4.0, 9.2 Hz, 1H, $PhCHCH_2$), 3.58 (sept., J=6.0 Hz, 1H, $(CH_3)_2CHO$), 3.97 (dd, J=4.0, 9.2 Hz, 1H, $PhCHCH_2$), 7.25–7.28 (m, 1H, Ph), 7.30–7.35 (m, 2H, Ph), 7.37–7.40 (m, 2H, Ph); $[\alpha]_D^{20}$=+63.7 (c 3.0, ethanol); ν_{max} (liquid film) 3327, 1127, 1074 cm^{-1}; HRMS (FAB): MH^+, found 222.1851. $C_{14}H_{24}NO$ requires 222.1858.

4.7.6. (*S*)-*N*-(3-Pentyl)-*O*-methylphenylglycinol (2e). Colorless oil (40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J=7.4 Hz, 6H, $(CH_3CH_2)_2CHN$), 1.24–1.39 (m, 2H, $(CH_3CH_2)_2CHN$), 1.41–1.48 (m, 2H, $(CH_3CH_2)_2CHN$), 2.25 (m, 1H, $(Et)_2CHN$), 3.36 (s, 3H, OCH_3), 3.41 (m, 2H, $PhCHCH_2$), 4.01 (dd, J=4.8, 8.0 Hz, 1H, $PhCHCH_2$), 7.23–7.28 (m, 2H, Ph), 7.30–7.35 (m, 2H, Ph), 7.37–7.41 (m, 1H, Ph); $[\alpha]_D^{20}$=+71.1 (c 2.8, ethanol); ν_{max} (liquid film) 3338, 1120 cm^{-1}; HRMS (FAB): MH^+, found 222.1829. $C_{14}H_{24}NO$ requires 222.1858.

4.7.7. (*S*)-*N*-(3-Pentyl)-*O*-ethylphenylglycinol (2f). Colorless oil (60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (m, 6H, $(CH_3CH_2)_2CHN$), 1.20 (t, J=7.2 Hz, 3H, CH_3CH_2O), 1.22–1.36 (m, 2H, $(CH_3CH_2)_2CHN$), 1.45 (m, 2H, $(CH_3CH_2)_2CHN$), 2.26 (m, 1H, $(Et)_2CHN$), 3.40 (t, J=

9.0 Hz, 1H, PhCHCH_2), 3.45–3.58 (m, 3H, PhCHCH_2 and CH_3CH_2O), 3.99 (dd, J=3.8, 9.0 Hz, 1H, PhCHCH$_2$), 7.23–7.27 (m, 1H, Ph), 7.30–7.34 (m, 2H, Ph), 7.38–7.41 (m, 2H, Ph); $[\alpha]_D^{20}$=+73.5 (c 3.0, ethanol); ν_{max} (liquid film) 3340, 1109 cm^{-1}; HRMS (FAB): MH$^+$, found 236.2052. $C_{15}H_{26}NO$ requires 236.2014.

4.7.8. (*S*)-*N*-Cyclohexyl-*O*-methylphenylglycinol (2g). Colorless oil (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98–1.18 (m, 5H, (CH_2)$_5$CHN), 1.54 (m, 1H, (CH_2)$_5$CHN), 1.62–1.73 (m, 3H, (CH_2)$_5$CHN), 2.02 (m, 1H, (CH_2)$_5$CHN), 2.28 (m, 1H, (CH$_2$)$_5$CHN), 3.36 (s, 3H, OCH_3), 3.37 (dd, J=8.8, 9.2 Hz, 1H, CH_2OMe), 3.43 (dd, J=4.0, 9.2 Hz, 1H, CH_2OMe), 4.09 (dd, J=4.0, 8.8 Hz, 1H, PhCHCH$_2$), 7.24–7.29 (m, 1H, Ph), 7.31–7.39 (m, 4H, Ph); $[\alpha]_D^{20}$=+75.4 (c 2.3, ethanol); ν_{max} (liquid film) 3328, 1110 cm^{-1}; HRMS (FAB): MH$^+$, found 234.1886. $C_{15}H_{24}NO$ requires 234.1858.

4.7.9. (*S*)-*N*-Cyclohexyl-*O*-ethylphenylglycinol (2h). Colorless oil (90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00–1.18 (m, 5H, (CH_2)$_5$CHN), 1.20 (t, J=7.0 Hz, 3H, CH_3CH$_2$O), 1.54 (m, 1H, (CH_2)$_5$CHN), 1.63–1.74 (m, 3H, (CH_2)$_5$CHN), 2.02 (m, 1H, (CH_2)$_5$CHN), 2.29 (m, 1H, (CH$_2$)$_5$CHN), 3.77 (t, J=9.2 Hz, 1H, PhCHCH_2), 3.46–3.56 (m, 3H, PhCHCH_2 and CH_3CH_2O), 4.09 (dd, J=4.0, 9.2 Hz, 1H, PhCHCH$_2$), 7.25–7.28 (m, 1H, Ph), 7.30–7.35 (m, 2H, Ph), 7.36–7.40 (m, 2H, Ph); $[\alpha]_D^{20}$=+70.1 (c 2.3, ethanol); ν_{max} (liquid film) 3326, 1110 cm^{-1}; HRMS (FAB): MH$^+$, found 248.2016. $C_{16}H_{26}NO$ requires 248.2014.

4.7.10. (*R*)-*N*-(2-Methoxybenzyl)-*O*-methylphenylglycinol (2i). Colorless oil (40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 3H, CH_3OCH$_2$), 3.41–3.45 (m, 2H, PhCHCH_2), 3.55 (d, J=13.4 Hz, 1H, ArCH_2N), 3.74 (d, J=13.4 Hz, 1H, ArCH_2N), 3.83 (s, 3H, CH_3OAr), 3.92 (dd, J=5.4, 7.8 Hz, 1H, PhCHCH$_2$), 6.83–6.94 (m, 2H, Ar), 7.13–7.16 (m, 1H, Ar), 7.20–7.25 (m, 1H, Ar), 7.25–7.31 (m, 1H, Ph), 7.33–7.39 (m, 2H, Ph), 7.40–7.44 (m, 2H, Ph); $[\alpha]_D^{20}$=+71.6 (c 2.7, ethanol); ν_{max} (liquid film) 3336, 1240, 1128, 1100, 1026 cm^{-1}; HRMS (FAB): MH$^+$, found 272.1660. $C_{17}H_{22}NO_2$ requires 272.1651.

4.7.11. (*R*)-*N*-(2-Methoxybenzyl)-ethylphenylglycinol (2j). Colorless oil (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, J=7.0 Hz, 3H, CH_3CH$_2$O), 3.40–3.50 (m, 4H, CH_3CH_2O and PhCHCH_2), 3.56 (d, J=13.6 Hz, 1H, ArCH_2N), 3.74 (d, J=13.6 Hz, 1H, ArCH_2N), 3.84 (s, 3H, CH_3O), 3.91 (dd, J=4.0, 9.6 Hz, 1H, PhCHCH$_2$), 6.85–6.92 (m, 2H, Ar), 7.13–7.16 (m, 1H, Ar), 7.21–7.26 (m, 1H, Ar), 7.28–7.31 (m, 1H, Ph), 7.33–7.38 (m, 2H, Ph), 7.41–7.45 (m, 2H, Ph); $[\alpha_D^{20}$=+76.4 (c 3.2, ethanol); ν_{max} (liquid film) 3345, 1241, 1108 cm^{-1}; HRMS (FAB): MH$^+$, found 286.1794. $C_{18}H_{24}NO_2$ requires 286.1807.

4.7.12. (*S*)-*N*-Isopropyl-*O*-methylphenylalaninol (3a). Colorless oil (80%); spectral data consistent with literature.[20,22,23]

4.7.13. (*S*)-*N*-Isopropyl-*O*-ethylphenylalaninol (3b). Colorless oil (50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, J=6.4 Hz, 3H, (CH_3)$_2$CHN), 1.12 (d, J=6.4 Hz, 3H, (CH_3)$_2$CHN), 1.26 (t, J=6.8 Hz, 3H, CH_3CH$_2$O), 2.82 (m, 2H, (PhCH_2), 2.99 (sept., J=6.4 Hz, 1H, (CH$_3$)$_2$CHN), 3.08 (m, 1H, PhCH$_2$CHCH$_2$), 3.34 (m, 2H, PhCH$_2$CHCH_2), 3.52 (m, 2H, CH$_3$CH_2O), 7.22–7.32 (m, 3H, Ph), 7.33–7.39 (m, 2H, Ph); $[\alpha]_D^{20}$=+13.8 (c 3.1, ethanol); ν_{max} (liquid film) 3322, 1113 cm^{-1}; HRMS (FAB): MH$^+$, found 222.1873. $C_{14}H_{24}NO$ requires 222.1858.

4.7.14. (*S*)-*N*-Isopropyl-*O*-isopropylphenylalaninol (3c). Colorless oil (10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J=6.4 Hz, 3H, (CH_3)$_2$CHN), 1.05 (d, J=6.4 Hz, 3H, (CH_3)$_2$CHN), 1.14 (d, J=6.0 Hz, 3H, (CH_3)$_2$CHO), 1.15 (d, J=6.0 Hz, 3H, (CH_3)$_2$CHO), 2.76 (m, 2H, PhCH_2CHCH), 2.93 (sept., J=6.4 Hz, 1H, (CH$_3$)$_2$CHN), 2.99 (m, 1H, PhCH$_2$CHCH$_2$), 3.27 (m, 2H, PhCH$_2$CHCH_2), 3.52 (sept., J=6.0 Hz, 1H, (CH$_3$)$_2$CHO), 7.17–7.23 (m, 3H, Ph), 7.27–7.32 (m, 2H, Ph); $[\alpha]_D^{20}$=+14.2 (c 2.6, ethanol); ν_{max} (liquid film) 3323, 1173, 1128, 1080 cm^{-1}; HRMS (FAB): MH$^+$, found 236.2011. $C_{15}H_{26}NO$ requires 236.2014.

4.7.15. (*S*)-*N*-Isopropyl-*O*-methylvalinol (4a). Colorless oil (60%); spectral data consistent with literature.[20,22,23]

4.7.16. (*S*)-*N*-Isopropyl-*O*-ethylvalinol (4b). Colorless oil (60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J=7.2 Hz, 6H, (CH_3)$_2$CHC), 1.05 (d, J=6.2 Hz, 3H, (CH_3)$_2$CHN), 1.05 (d, J=6.2 Hz, 3H, (CH_3)$_2$CHN), 1.19 (t, J=6.8 Hz, 3H, CH_3CH$_2$O), 1.85 (m, 1H, (CH$_3$)$_2$CHC), 2.55 (q, J=5.6 Hz, 1H, i-PrCHCH$_2$), 2.86 (sept., J=6.2 Hz, 1H, (CH$_3$)$_2$CHN), 3.22 (dd, J=5.6, 9.4 Hz, 1H, i-PrCHCH_2), 3.41 (dd, J=5.6, 9.4 Hz, 1H, i-PrCHCH_2), 3.48 (q, J=6.8 Hz, 2H, CH$_3$CH_2O); $[\alpha]_D^{20}$=−3.6 (c 2.9, ethanol); ν_{max} (liquid film) 3327, 1173, 1119 cm^{-1}; HRMS (FAB): MH$^+$, found 174.1889. $C_{10}H_{24}NO$ requires 174.1858.

4.7.17. (*S*)-*N*-Isopropyl-*O*-isopropylvalinol (4c). Colorless oil (25%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J=6.4 Hz, 6H, (CH_3)$_2$CHCH), 1.04 (m, 6H, (CH_3)$_2$CHN), 1.14 (d, J=6.0 Hz, 6H, (CH_3)$_2$CHO), 1.83 (m, 1H, (CH$_3$)$_2$CHCH), 2.50 (m, 1H, i-PrCHCH$_2$), 2.84 (sept., J=6.4 Hz, 1H, (CH$_3$)$_2$CHN), 3.29 (m, 1H, i-PrCHCH_2), 3.39 (m, 1H, i-PrCHCH_2), 3.52 (sept., J=6.0 Hz, 1H, (CH$_3$)$_2$CHO); $[\alpha]_D^{20}$=−5.0 (c 1.9, ethanol); ν_{max} (liquid film) 3330, 1174, 1127, 1085 cm^{-1}; HRMS (FAB): MH$^+$, found 188.1999. $C_{11}H_{26}NO$ requires 188.2014.

4.7.18. (*S*)-*N*-(2-Methoxybenzyl)-*O*-methylvalinol (4d). Colorless oil (30%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J=6.8 Hz, 6H, (CH_3)$_2$CHC), 1.92 (m, 1H, (CH$_3$)$_2$CHC), 2.55 (m, 1H, i-PrCHCH$_2$), 3.85 (s, 3H, CH_3O), 3.41–3.44 (m, 2H, i-PrCHCH_2), 3.82 (m, 2H, ArCH_2N), 3.32 (s, 3H, CH_3OAr), 6.85–6.95 (m, 2H, Ar), 7.22–7.30 (m, 2H, Ar); $[\alpha]_D^{20}$=−10.2 (c 2.2, ethanol); ν_{max} (liquid film) 3337, 1240, 1113, 1049, 1030 cm^{-1}; HRMS (FAB): MH$^+$, found 238.1854. $C_{14}H_{24}NO_2$ requires 238.1807.

4.7.19. (*S*)-*N*-(2-Methoxybenzyl)-*O*-ethylvalinol (4e). Colorless oil (60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J=7.6 Hz, 6H, (CH_3)$_2$CHCH), 1.19 (t, J=7.0 Hz, 3H, CH_3CH$_2$O), 1.93 (m, 1H, (CH$_3$)$_2$CHCH), 2.56 (m, 1H, i-PrCHCH$_2$), 3.38 (m, 1H, i-PrCHCH_2), 3.42–3.50 (m, 3H, i-PrCHCH_2 and CH$_3$CH_2O), 3.83 (s. 2H, ArCH_2N),

3.85 (s, 3H, CH_3O), 6.85–6.94 (m, 2H, Ar), 7.21–7.30 (m, 2H, Ar); $[\alpha]_D^{20}=-8.0$ (*c* 2.7, ethanol); ν_{max} (liquid film) 3321, 1241, 1120 cm^{-1}; HRMS (FAB): MH^+, found 252.1998. $C_{15}H_{26}NO_2$ requires 252.1964.

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References

1. (a) Kozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, *9*, 4097–4098. (b) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455–1460. (c) Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585–4586.
2. Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187–5190.
3. (a) Hilmersson, G.; Davidsson, Ö. *J. Org. Chem.* **1995**, *60*, 7660–7669. (b) Hilmersson, G.; Davidsson, Ö. *J. Organomet. Chem.* **1995**, *489*, 175–179. (c) Hilmersson, G.; Arvidsson, P. I.; Davidsson, Ö.; Håkansson, M. *J. Am. Chem. Soc.* **1998**, *120*, 8143–8149.
4. (a) Itsuno, S.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4140–4142. (b) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111–7115. (c) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657–1660. (d) Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem.* **1991**, *56*, 2218–2224. (e) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4254–4268.
5. Arvidsson, P. I.; Hilmersson, G.; Davidsson, Ö. *Chem. Eur. J.* **1999**, *5*, 2348–2355.
6. Hilmersson, G. *Chem. Eur. J.* **2000**, *6*, 3069–3075.
7. (a) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527–2533. (b) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron Lett.* **2000**, *41*, 5533–5536.
8. (a) Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119*, 11693–11694. (b) Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7829–7830. (c) Hilmersson, G.; Malmros, B. *Chem. Eur. J.* **2001**, *7*, 337–341.
9. Arvidsson, P. I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527–534.
10. (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. (b) Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301–1312.
11. (a) Weiss, H.; Yakimansky, A. V.; Müller, A. H. E. *J. Am. Chem. Soc.* **1996**, *118*, 8897–8903. (b) Arvidsson, P. I.; Hilmersson, G.; Ahlberg, P. *J. Am. Chem. Soc.* **1999**, *121*, 1883–1887. (c) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255–11268.
12. Nakamura, E.; Nakamura, M.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016–11017.
13. (a) Csonka, G. I. *J. Comput. Chem.* **1993**, *14*, 895–898. (b) Nilsson Lill, S. O.; Arvidsson, P. I.; Ahlberg, P. *Tetrahedron: Asymmetry* **1999**, *10*, 265–279.
14. *PC SPARTAN pro*, Version 1.0.5; Wavefunction, Inc.: 18401 Von Karman Ave., #370 Irvine, CA 92715 USA, 1995.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian98*; Gaussian Inc.: Pittsburg, PA, 1998.
16. Welch, J. T.; Seper, K. W. *J. Org. Chem.* **1988**, *53*, 2991–2999.
17. Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586–3591.
18. Ando, A.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1987**, 656–658.
19. García Ruano, J. L.; Alcudia, A.; del Prado, M.; Barros, D.; Maestro, M. C.; Fernández, I. *J. Org. Chem.* **2000**, *65*, 2856–2862.
20. Ando, A.; Shioiri, T. *Tetrahedron* **1989**, *45*, 4969–4988.
21. Yang, D.; Han, O.; Liu, H. *J. Org. Chem.* **1989**, *54*, 5402–5406.
22. Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543–545.
23. Shirai, R.; Sato, D.; Aoki, K.; Tanaka, M.; Kawasaki, H.; Koga, K. *Tetrahedron* **1997**, *53*, 5963–5972.