New Chiral Ligands Derived from Mandelic Acid: Synthesis and Application in the Asymmetric Phenyl Transfer Reaction to an Aromatic Aldehyde

Carsten Bolm,* Lorenzo Zani, Jens Rudolph, Ingo Schiffers

Institut für Organische Chemie der RWTH Aachen, Professor-Pirlet-Str. 1, 52056 Aachen, Germany
Fax +49(241)8092391; E-mail: carsten.bolm@oc.rwth-aachen.de

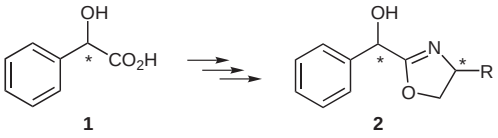
Received 17 May 2004

Abstract: Starting from inexpensive enantiopure (*R*)- and (*S*)-mandelic acid, a range of α-hydroxy-2-oxazolines has been prepared. The synthesis involves the condensation of the acid chloride with a vicinal amino alcohol, followed by intramolecular cyclization to form the oxazoline ring. The resulting compounds have been used as ligands in the asymmetric phenyl transfer reaction to 4-chlorobenzaldehyde, employing a mixture of triphenylborane and diethylzinc as the phenyl source. Good yields (up to 76%) and moderate enantioselectivities (up to 35%) have been achieved.

Key words: asymmetric catalysis, mandelic acid, organometallics, oxazolines, phenyl transfer, zinc

Asymmetric metal catalysis is one of the most important and rapidly growing research fields in organic chemistry.[1] In the search for more efficient ligands for enantioselective transformations, the structural diversity of nature has often been inspiring. Indeed, many natural molecules, constituting the so-called chiral pool,[2] represent an easily accessible and cheap source of chiral starting materials, which can be used in the preparation of ligands for asymmetric metal-catalyzed reactions.[3] Among those compounds, hydroxy and amino acids are of enormous synthetic value, and mandelic acid (**1**) appears particularly attractive. It is inexpensive and available in both enantiomeric forms. Moreover, its carboxyl group can easily be converted into many different structural motifs. Now we wondered about the transformation of mandelic acid into α-hydroxy-2-oxazolines **2** (Scheme 1). Oxazolines have originally been used as base-stable protecting groups for carboxylic acids[4] and more recently, they have found extensive applications as chiral auxiliaries[4a] and ligands in asymmetric catalysis.[5] In compounds of type **2**, two natural products from the chiral pool (mandelic acid and β-amino alcohols stemming from α-amino acids) are combined to give a set of potential ligands with most interesting properties: the stereogenic centers are adjustable (to give matched and mismatched combinations) and the sterics are tunable (by R-group modifications).

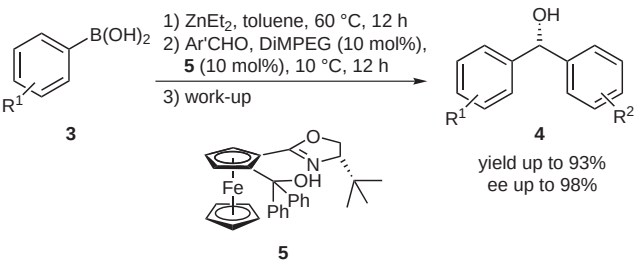
In the field of metal-mediated transformations, the catalyzed enantioselective addition of organozinc reagents to carbonyl compounds, and in particular aldehydes, is one of the most extensively investigated areas.[6] When aromatic aldehydes are used as substrates and an aryl group is



1 2

Scheme 1 Conversion of mandelic acid into α-hydroxy-2-oxazolines

transferred, this reaction gives rise to chiral diarylmethanols **4**, which are important intermediates in the synthesis of biologically active substances.[7] Over the past years several investigations have focussed on the synthesis of diarylmethanols by addition of phenylzinc reagents to aldehydes.[8–12] Alternative methods employing arylboronic acids,[13] arylstannanes[14] and arylsilanes[15] have also been reported. However, most of these protocols lack generality, and until recently, the asymmetric versions led to products with only moderate to good enantiomeric excesses. A more general approach for the enantioselective catalytic synthesis of diarylmethanols from aldehydes was introduced by us, utilizing planar chiral ferrocene-derived hydroxyoxazoline **5** and a zinc species, generated in situ from $ZnEt_2$ and $ZnPh_2$.[11] The substrate scope has later been increased by using arylboronic acids as aryl source (Scheme 2).[12]



3 4 5

yield up to 93%
ee up to 98%

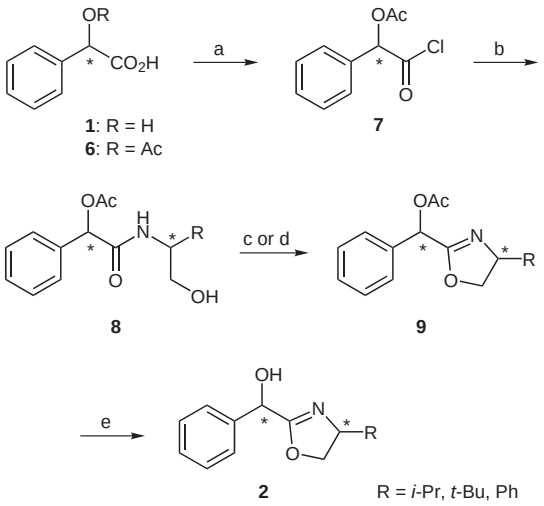
Scheme 2 Asymmetric aryl transfer reaction with arylboronic acids as aryl source

The results of these studies, together with the recently reported evidence that chiral hydroxyoxazolines can act as effective ligands for the enantioselective addition of diethylzinc towards aldehydes[16] and activated imines,[17] prompted us to investigate the potential of simple mandelic acid-derived α-hydroxy-2-oxazolines **2** as ligands in aryl transfer reactions towards aromatic aldehydes. Herein, we report the synthesis and the catalytic application of such compounds.

SYNTHESIS 2004, No. 13, pp 2173–2180
Advanced online publication: 27.07.2004
DOI: 10.1055/s-2004-829184; Art ID: Z09404SS

Ligand Synthesis

Formally, α-hydroxy-2-oxazolines **2** are condensation products of mandelic acid and β-amino alcohols. The availability of both enantiomeric forms of the acid as well as the β-amino alcohols, which are readily accessible by reduction of α-amino acids, allows the introduction of a considerable degree of structural diversity following a very short reaction sequence. The reagents and the reaction conditions, which have been applied in the synthesis of **2**, are depicted in Scheme 3.



Scheme 3 *Reagents and conditions*: (a) AcCl, 2 h, r.t. (**1** → **6**), then $SOCl_2$, reflux, 3 h, 100%; (b) β-amino alcohol (1.0 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C to r.t., 17 h, 59–78%; (c) MsCl (3.0 equiv), DMAP (10 mol%), Et_3N–CH_2Cl_2 (3:1), 0 °C to r.t., 17 h, 62–67%; (d) DAST (1.1 equiv), CH_2Cl_2, –78 °C, 1 h, 56–71%; (e) LiOH (3.0 equiv), MeOH, 0 °C, 3 h, 62–94%.

First, mandelic acid (**1**) was converted into acetyl-protected intermediate **6**[18] by treatment of **1** with acetyl chloride at room temperature. Subsequent addition of $SOCl_2$ to **6** afforded **7** in quantitative yield. The reactions were performed with both enantiomers of mandelic acid to give (*R*)-**7** and (*S*)-**7**, respectively. In the following step, enantiopure **7** was treated with one equivalent of an amino alcohol in the presence of triethylamine as base to give condensation products **8** as single diastereomers in good yields (up to 78%). Formation of the oxazoline was then achieved by treatment of amides **8** with mesyl chloride in the presence of an excess of triethylamine. Starting from either (*R*,*S*)-**8b** or (*S*,*S*)-**8b** [derived from both enantiomers of **1** and (*S*)-*tert*-leucinol] this protocol led to α-acetoxy-2-oxazolines (*R*,*S*)-**9b** and (*S*,*S*)-**9b**, respectively, as single diastereoisomers. Unfortunately, however, the attempted stereospecific ring-closures of the other four amides [(*R*,*R*)-**8a**, (*S*,*R*)-**8a**, (*R*,*R*)-**8c** and (*S*,*R*)-**8c** derived from both enantiomers of **1** and (*R*)-valinol or (*R*)-phenylglycinol, respectively] occured with partial epimerization leading to diastereomeric mixtures of **9a** and **9c**. The difficulties encountered in the chromatographic separation of these diastereoisomers required the employment of an alternative method for the oxazoline formation. After screening of various protocols, the diethylaminosulfur trifluoride (DAST)-mediated cyclization[19] was identified as a method, which preserved the stereochemical features of the starting materials and products. Thus with DAST, α-acetoxy-2-oxazolines (*R*,*R*)-**9a**, (*S*,*R*)-**9a**, (*R*,*R*)-**9c** and (*S*,*R*)-**9c** were obtained from the corresponding amides **8a** and **8c** in diastereomerically pure form. In comparison to the MsCl–Et_3N method a minor decrease in yield had to be accepted. Finally, the syntheses of all diastereomers of target compounds **2a**–**c** were completed by hydrolyses of the ester groups of **8a**–**c** under basic conditions, employing an excess of lithium hydroxide in methanol. In Figure 1 the structures of all compounds are depicted and the overall yields (after four steps, referring to the initial amount of mandelic acid) are given.

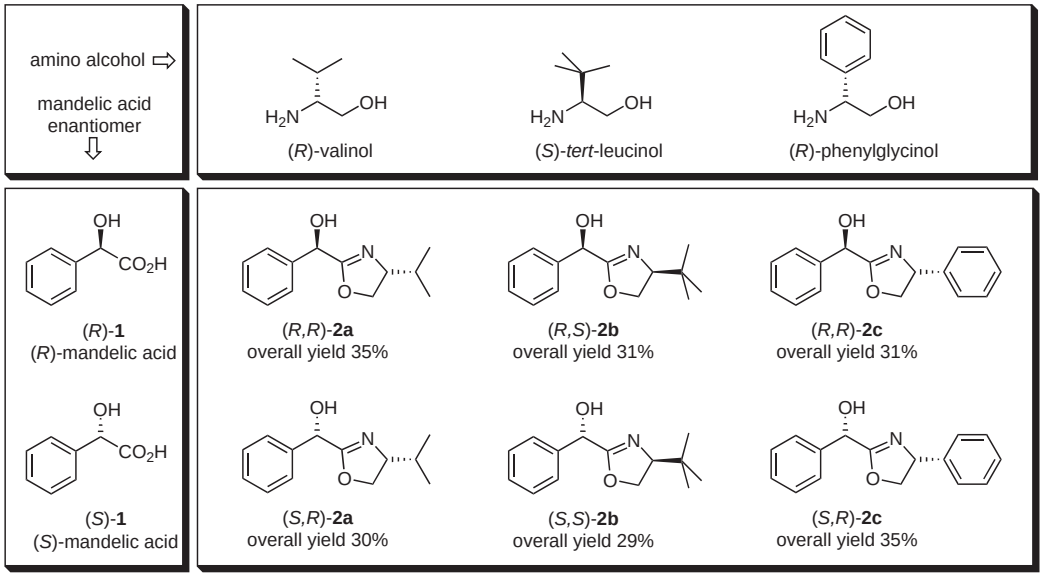
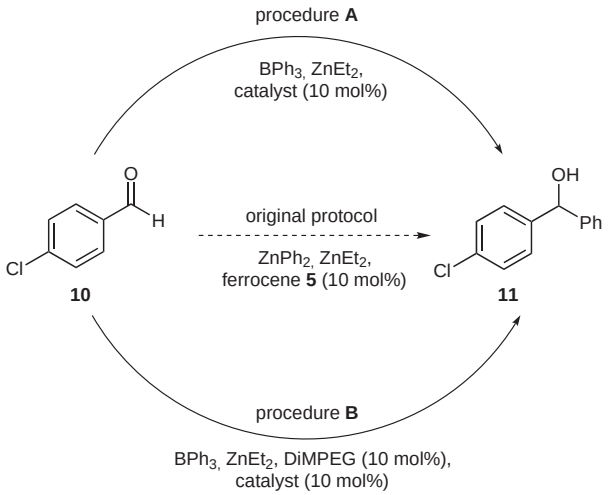


Figure 1 Diastereomerically pure α-hydroxy-2-oxazolines **2a**–**c** prepared by the combination of (*R*)- and (*S*)-mandelic acid with three enantiopure amino alcohols.

Next, the diastereomerically pure α-hydroxy-2-oxazolines **2a**–**c** were employed in the catalytic enantioselective phenyl transfer reaction towards aromatic aldehydes. Notably, as a consequence of the chosen synthetic pathway, it was possible to easily modify the structural features of the ligand, either by changing the substituent on the oxazoline ring or by adjusting the configurations of the two stereogenic centers. Moreover, the six α-hydroxy-2-oxazolines were prepared as couples of diastereoisomers, thus allowing an evaluation of possible 'match–mismatch' effects to be displayed during the catalytic reactions.

Asymmetric Aryl Transfer Reaction

In order to evaluate the capability of the α-hydroxy-2-oxazolines to serve as chiral ligands in the phenyl transfer reaction to aldehydes, two different protocols were followed. In both, 4-chlorobenzaldehyde (**10**) was the test substrate (Scheme 4). Procedure **A** involved mixtures of diethylzinc and triphenylborane as the phenyl source.[20] Procedure **B** made use of the recent discovery that the presence of small quantities of DiMPEG had beneficial effects on the enantioselectivity of the catalyzed aryl transfer.[12,21] Thus in procedure **B** a reagent combination consisting of BPh_3, $ZnEt_2$ and DiMPEG was applied. Table 1 summarizes the results.



Scheme 4 *Reagents and conditions*: BPh_3 (1.0 equiv), $ZnEt_2$ (4.3 equiv), **2** (10 mol%), toluene, 12 h, 10 °C; work-up (procedure **A**); BPh_3 (1.0 equiv), $ZnEt_2$ (4.3 equiv), **2** (10 mol%), DiMPEG (10 mol%; MW = 2500 g mol^{-1}), toluene, 12 h, 10 °C, work-up (procedure **B**).

Gratifyingly, most α-hydroxy-2-oxazolines led to catalytically active systems giving diarylmethanol **11** with up to 76% yield. Unfortunately, however, neither the enantioselectivity in the formation of **11** nor the activity of the catalysts exceeded those of the known systems.[11,12] The highest ee-values (ranging between 30 and 35%) were achieved with catalysts originating from α-hydroxy-2-oxazoline **2b** (Table 1, entries 3 and 4). Both diastereomers

Table 1 Catalyzed Asymmetric Phenyl Transfer to 4-Chlorobenzaldehyde (**10**) to Give Diarylmethanol **11**

Entry	α-Hydroxy-2-oxazoline	Procedure **A**		Procedure **B**	
		Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	(*R*,*R*)-**2a**	33	16 (*R*)	26	21 (*R*)
2	(*S*,*R*)-**2a**	76	9 (*S*)	<5	n.d.[c]
3	(*R*,*S*)-**2b**	72	32 (*S*)	54	30 (*S*)
4	(*S*,*S*)-**2b**	19	32 (*S*)	20	35 (*S*)
5[d]	(*R*,*R*)-**2c**	74	*rac*	74	3 (*R*)
6[d]	(*S*,*R*)-**2c**	50	24 (*S*)	35	26 (*S*)

[a] After column chromatography.
[b] The enantiomer ratios of **11** were determined by HPLC using a chiral Chiralcel OB-H column.
[c] Not determined.
[d] Use of the original protocol with mixtures of $ZnPh_2$ and $ZnEt_2$ gave irreproducible results.

afforded *S*-configured **11** indicating that the absolute configuration of the product was determined by the stereogenic center at the oxazoline group. In terms of catalytic activity (*R*,*S*)-**2b** proved superior over (*S*,*S*)-**2b** as revealed by the yield of **11**. Catalysts based on α-hydroxy-2-oxazolines **2a** and **2c** were less enantioselective [ee_{max} = 26% with (*S*,*R*)-**2c**; Table 1, entry 6] than those derived of **2b**. The yields were comparable and reached up to 76% (Table 1, entry 2). We assume that the differences in the enantioselectivities of catalysts stemming from **2a** and **2c** on one side and **2b** on the other originate from the chemical properties of the corresponding α-hydroxy-2-oxazolines. To our surprise, **2a** and **2c** showed a rather limited solubility in toluene, which is the solvent of choice for the catalyzed aryl transfer reactions. Probably, the sterically bulky *tert*-butyl substituent at the oxazoline group of **2b** eases the dissolution of the α-hydroxy-2-oxazolines in the reaction medium and facilitates their conversions into the corresponding catalytically active species. Due to partial or full decomposition during the catalysis, none of the α-hydroxy-2-oxazolines **2** could be recovered and reused.

A benefical effect of a small quantity of DiMPEG in the reaction mixture on the enantioselectivity of the aryl transfer reaction had been revealed in previous studies.[12,21] Although the cause of this 'MPEG-effect' still needs to be fully elucidated, it is assumed that the increase in ee originates from a polyether-based deactivation of catalytically active but achiral species, which otherwise lower the enantioselectivity of the overall process by producing racemic product.[21] A similar trend was observed here. Thus, compared to procedure **A**, the ee-values increased slightly (with one exception) when the catalyses were performed with DiMPEG as additive according to procedure **B** (Table 1).

In summary, six α-hydroxy-2-oxazolines have been prepared from mandelic acid in a straightforward manner following an easy to perform four-step reaction sequence. The absolute and the relative stereochemistry of the products is dictated by the starting materials, which all stem from the chiral pool. With the optimized protocol, neither racemization nor epimerization was detected during the synthesis, which allows a specific access of all stereoisomers. The reaction sequence appears to be general and should also be applicable to other hydroxy acid–amino alcohol combinations allowing the preparation of large α-hydroxy-2-oxazoline libraries. The capability of such compounds to serve as ligands in asymmetric catalysis was demonstrated in the enantioselective phenyl transfer to an aromatic aldehyde from a mixture of BPh_3 and $ZnEt_2$ in the presence of DiMPEG, which afforded an optically active diarylmethanol. Although the enantioselectivity in this process remained moderate (35% ee), improvements are expected to result from ligand optimizations and an extensive library screening.

Air sensitive manipulations were carried out under an inert atmosphere of Ar using standard Schlenk techniques. Triphenyl borane and diethylzinc were donated by Bayer AG and Crompton Corp. (previously Witco), respectively. D-valine, L-*tert*-leucine, D-phenylglycine were provided by Degussa AG. Toluene was distilled from sodium–benzophenone ketyl radical, and CH_2Cl_2 from calcium hydride prior to use. EtOAc, petroleum ether (PE, boiling fraction 40–70 °C), pentane, and Et_2O for column chromatograpy were distilled before use. MeOH was HPLC grade and was used as received. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer (300 and 75 MHz, respectively) and on a Varian Inova 400 spectrometer (400 and 100 MHz, respectively). IR spectra were measured on a Perkin-Elmer PE 1760 FT instrument as KBr pellets or neat (in the case of liquid compounds); absorptions are given in wavenumbers (cm^{-1}). MS spectra were recorded on a Varian MAT 212 or on a Finnigan MAT 95 spectrometer with EI ionization. Optical rotation measurements were conducted at r.t. with a Perkin-Elmer PE 241 polarimeter at a wavelength of 589 nm. HPLC measurements were performed on a Dionex HPLC system (previously Gynkotek) with autosampler Gina 50, UV-detector UVD 170S, degasser DG 503 and gradient pump M480G. The HPLC columns with chiral stationary phases were from Chiral Technologies. Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument. Mps were measured in open capillaries with a Buechi B-540 apparatus and are uncorrected. All experiments were conducted at least twice to ensure reproducibilty.

O-Acetylmandelic Acid Chloride (7); General Procedure

In a flame-dried, round-bottomed flask (*R*)- or (*S*)-mandelic acid (22.82 g, 0.15 mol) was dissolved in acetyl chloride (175 mL). After stirring the solution at r.t. for 2 h, the excess of acetyl chloride was removed under high vacuum to give **6**. Thionyl chloride (100 mL) was added to the oily residue. The resulting solution was stirred and heated at reflux for an additional 3 h. After this time, the reaction mixture was cooled to r.t., and excess thionyl chloride was removed under high vacuum, to furnish pure *O*-acetyl mandelic acid chloride (**7**) which was successively been used without further purification.

(*R*)-*O*-Acetylmandelic Acid Chloride [(*R*)-7][18]

Yield: 31.9 g (100%); yellow oil; $[\alpha]^{20}_D$ –184.0 (*c* 1.96 in $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, CH_3), 6.08 (s, 1 H, CH), 7.37–7.52 (m, 5 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 (CH_3), 81.0 (CH), 128.4, 129.2, 130.3, 130.8 (aryl), 169.9 (CO), 170.7 (CO).

(*S*)-*O*-Acetylmandelic Acid Chloride [(*S*)-7][18]

Yield: 31.9 g (100%); yellow oil; $[\alpha]^{20}_D$ +183.2 (*c* 1.94 in $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3 H, CH_3), 6.08 (s, 1 H, CH), 7.38–7.53 (m, 5 H, H_{ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (CH_3), 80.9 (CH), 128.4, 129.2, 130.3, 130.8 (aryl), 169.9 (CO), 170.8 (CO).

Condensation of Acid Chlorides 7 with Amino Alcohols to Give Amides 8; General Procedure

In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, the appropriate amino alcohol (50 mmol, 1.0 equiv) and Et_3N (10.12 g, 100 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (80 mL). The mixture was cooled to 0 °C and a solution of *O*-acetylmandelic acid chloride (**7**) (10.63 g, 50 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (70 mL) was added dropwise over 10 min. The resulting reaction mixture was allowed to warm to r.t., stirred for 17 h and then washed with aq HCl (1 M; 2 × 100 mL). The combined aq phases were extracted with CH_2Cl_2 (100 mL) and the combined organic layers washed with sat. aq NaCl (2 × 100 mL). Drying ($MgSO_4$) followed by removal of the solvent in vacuo afforded **8** as crude product. Pure **8** was obtained by recrystallization.

(*R*,*R*)-*O*-Acetylmandelic Acid (1-Hydroxymethyl-2-methyl)propylamide [(*R*,*R*)-8a]

Prepared starting from (*R*)-**7** and (*R*)-valinol (5.19 g, 50 mmol, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*R*,*R*)-**8a**.

Yield: 8.36 g (30 mmol, 60%); white solid; mp 91–92 °C; $[\alpha]^{20}_D$ –41.4 (*c* 0.82 in $CHCl_3$).

IR (KBr): 1052, 1238, 1563, 1663, 1747, 2962, 3284 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, 3 H, *J* = 6.8 Hz, CH_3), 0.93 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.90 (sept, 1 H, *J* = 6.8 Hz, CH), 2.17 (s, 3 H, CH_3), 2.92 (br s, 1 H, OH), 3.56–3.73 (m, 3 H, CH_2CH), 6.06 (s, 1 H, CH), 6.57–6.61 (m, 1 H, NH), 7.32–7.48 (m, 5 H, H_{ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 (CH_3), 19.6 (CH_3), 21.0 (CH_3), 29.0 (CH), 56.9 (CH), 62.9 (CH_2), 75.8 (CH), 127.4, 128.8, 129.0, 135.6 (aryl), 169.0 (CO), 169.5 (CO).

MS (EI, 70 eV): *m*/*z* = 280 (M^+ + 1), 149, 130, 108, 107, 77, 69.

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.70; H, 7.59; N, 5.21.

(*S*,*R*)-*O*-Acetylmandelic Acid (1-Hydroxymethyl-2-methyl)propylamide [(*S*,*R*)-8a]

Prepared starting from (*S*)-**7** and (*R*)-valinol (5.19 g, 50 mmol, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*S*,*R*)-**8a**.

Yield: 8.62 g (31 mmol, 62%); white solid; mp 88–89 °C; $[\alpha]^{20}_D$ +118.6 (*c* 1.00 in $CHCl_3$).

IR (KBr): 1068, 1238, 1373, 1549, 1655, 1734, 3300, 3471 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, 3 H, *J* = 6.8 Hz, CH_3), 0.88 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.84 (sept, 1 H, *J* = 6.8 Hz, CH), 2.17 (s, 3 H, CH_3), 3.59–3.78 (m, 3 H, CH_2CH), 6.05 (s, 1 H, CH), 6.44 (br s, 1 H, NH), 7.32–7.40 (m, 3 H, H_{ar}), 7.42–7.50 (m, 2 H, H_{ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6 (CH_3), 19.6 (CH_3), 21.0 (CH_3), 29.0 (CH), 56.9 (CH), 63.2 (CH_2), 75.8 (CH), 127.6, 128.8, 129.1, 135.4, (aryl) 169.2 (CO), 169.8 (CO).

MS (EI, 70 eV): *m*/*z* = 279 (M^+), 149, 130, 108, 107, 91, 77, 69.

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.15; H, 7.37; N, 4.99.

(*R*,*S*)-*O*-Acetylmandelic Acid (1-Hydroxymethyl-2,2-dimethyl)propylamide [(*R*,*S*)-8b]

Prepared starting from (*R*)-**7** and (*S*)-*tert*-leucinol (5.86 g, 50 mmol, 1.0 equiv). Purification by recrystallization from EtOAc furnished pure (*R*,*S*)-**8b**.

Yield: 11.44 g (39 mmol, 78%); white solid; mp 151–152 °C; $[\alpha]^{20}_D$ –84.1 (*c* 0.84 in $CHCl_3$).

IR (KBr): 1052, 1233, 1370, 1576, 1659, 1742, 2968, 3079, 3297 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 9 H, CH_3), 2.17 (s, 3 H, CH_3), 2.83 (br s, 1 H, OH), 3.52–3.60 (m, 1 H, CH), 3.77–3.87 (m, 2 H, CH_2), 6.07 (s, 1 H, CH), 6.47–6.51 (m, 1 H, NH), 7.32–7.37 (m, 3 H, H_{ar}) 7.46–7.52 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 26.9 (CH_3), 33.9 (C_q), 59.4 (CH), 62.3 (CH_2), 76.0 (CH), 127.6, 128.8, 129.1, 135.4 (aryl), 169.3 (CO), 170.0 (CO).

MS (EI, 70 eV): *m*/*z* = 294 (M^+ + 1), 262, 177, 174, 149, 144, 107, 91, 77, 57.

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.41; H, 7.95; N, 4.74.

(*S*,*S*)-*O*-Acetylmandelic Acid (1-Hydroxymethyl-2,2-dimethyl)propylamide [(*S*,*S*)-8b]

Prepared starting from (*S*)-**7** and (*S*)-*tert*-leucinol (5.86 g, 50 mmol, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*S*,*S*)-**8b**.

Yield: 9.33 g (32 mmol, 64%); white solid; mp 93–94 °C; $[\alpha]^{20}_D$ +46.4 (*c* 1.00 in $CHCl_3$).

IR (KBr): 1050, 1229, 1373, 1560, 1661, 1749, 2959, 3337, 3444 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 9 H, CH_3), 2.20 (s, 3 H, CH_3), 2.45 (br s, 1 H, OH), 3.53–3.62 (m, 1 H, CH), 3.75–3.84 (m, 2 H, CH_2), 6.10 (s, 1 H, CH), 6.43 (br s, 1 H, NH), 7.32–7.41 (m, 3 H, H_{ar}), 7.42–7.48 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (CH_3), 26.7 (CH_3), 33.8 (C_q), 59.2 (CH), 62.4 (CH_2), 75.8 (CH), 127.1, 128.6, 128.8, 135.4 (aryl), 169.0 (CO), 169.0 (CO).

MS (EI, 70 eV): *m*/*z* = 278, 262, 177, 149, 144, 118, 107, 86, 77, 57.

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.67; H, 7.92; N, 4.65.

(*R*,*R*)-*O*-Acetylmandelic Acid (2-Hydroxymethyl-1-phenyl)ethylamide [(*R*,*R*)-8c]

Prepared starting from (*R*)-**7** and (*R*)-phenylglycinol (6.86 g, 50 mmol, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*R*,*R*)-**8c**.

Yield: 9.49 g (30.5 mmol, 61%); white solid; mp 126–127 °C; $[\alpha]^{20}_D$ –107.0 (*c* 1.00 in $CHCl_3$).

IR (KBr): 1030, 1249, 1294, 1375, 1557, 1705, 3325, 3469 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, CH_3), 2.67 (br s, 1 H, OH), 3.78–3.82 (m, 2 H, CH_2), 5.02 (dt, 1 H, *J* = 4.7, 7.3 Hz, CH), 6.10 (s, 1 H, CH), 7.01–7.18 (m, 1 H, NH), 7.20–7.44 (m, 10 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9 (CH_3), 55.3 (CH), 65.7 (CH_2), 75.5 (CH), 126.4, 127.1, 127.6, 128.6, 128.8, 135.1, 138.4, (aryl), 168.5 (CO), 169.2 (CO).

MS (EI, 70 eV): *m*/*z* = 314 (M^+ + 1), 282, 223, 194, 165, 164, 149, 107, 91, 77.

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47 Found: C, 68.63; H, 6.18; N, 4.41.

(*S*,*R*)-*O*-Acetylmandelic Acid (2-Hydroxymethyl-1-phenyl)ethylamide [(*S*,*R*)-8c]

Prepared starting from (*S*)-**7** and (*R*)-phenylglycinol (6.86 g, 50 mmol, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*S*,*R*)-**8c**.

Yield: 9.24 g (29.5 mmol, 59%); white solid; mp 123–124 °C; $[\alpha]^{20}_D$ +31.5 (*c* 1.00 in $CHCl_3$).

IR (KBr): 1074, 1241, 1372, 1540, 1661, 1725, 3337, 3548 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, CH_3), 2.75 (br s, 1 H, OH), 3.75–3.84 (m, 2 H, CH_2), 5.00–5.06 (m, 1 H, CH), 6.07 (s, 1 H, CH), 6.96–7.02 (m, 1 H, NH), 7.10–7.15 (m, 2 H, H_{ar}), 7.26–7.32 (m, 3 H, H_{ar}), 7.32–7.37 (m, 3 H, H_{ar}), 7.40–7.47 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9 (CH_3), 55.3 (CH), 65.7 (CH_2) 75.5 (CH), 126.3, 127.4, 127.6, 128.5, 128.6, 128.9, 135.0, 138.4 (aryl), 168.5 (CO), 169.5 (CO).

MS (EI, 70 eV): *m*/*z* = 314 (M^+ + 1), 282, 255, 254, 226, 164, 91, 77.

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.94; H, 6.24; N, 4.40.

Formation of the Oxazoline Ring; General Procedure

Method A

In a flame-dried, round-bottomed Schlenk flask under an inert atmosphere of argon, the appropriate *O*-acetylmandelic acid amide **8** (10.0 mmol) was dissolved in a mixture of anhyd CH_2Cl_2–Et_3N (3:1; 160 mL). To this solution, DMAP (0.122 g, 1.0 mmol, 0.1 equiv) was added, and the reaction mixture was cooled to 0 °C. Subsequently, mesyl chloride (3.44 g, 30 mmol, 3.0 equiv), dissolved in anhyd CH_2Cl_2 (10 mL), was added dropwise, and the reaction was stirred at r.t. overnight. The solvent was then removed by rotary evaporation and replaced by a mixture of EtOAc and H_2O (4:1; 150 mL). The aq phase was extracted with EtOAc (150 mL), and the combined organic layers were washed with H_2O (2 × 150 mL). After drying ($MgSO_4$), removal of the solvent in vacuo afforded crude **9** as a yellow-brown oil.

Method B

In a flame-dried, round-bottomed Schlenk flask under an inert atmosphere of argon, the appropriate *O*-acetylmandelic acid amide **8** (10.0 mmol) was dissolved in anhyd CH_2Cl_2 (100 mL). The solution was cooled to –78 °C and diethylaminosulfur trifluoride (DAST) was added dropwise (1.44 mL, 11.0 mmol, 1.1 equiv) over 5 min. After the addition, the reaction mixture was stirred at –78 °C for 1 h. Then, K_2CO_3 (2.07 g, 15 mmol, 1.5 equiv) was added in one portion and the reaction was allowed to warm to r.t. Subsequently, the reaction mixture was poured into sat. aq $NaHCO_3$ (200 mL) and the organic layer was collected. The aq layer was extracted once more with CH_2Cl_2 (200 mL) and the combined organic layers were dried ($MgSO_4$). Removal of the solvent in vacuo afforded crude **9** as a brown or yellow oil.

(*R*,*R*)-2-Acetoxyphenylmethyl-4-isopropyl-4,5-dihydro-oxazole [(*R*,*R*)-9a]

According to method B, the title compound was prepared starting from (*R*,*R*)-**8a** (2.79 g, 10.0 mmol). Purification by flash column chromatography (EtOAc–PE, 1:2) afforded pure (*R*,*R*)-**9a**.

Yield: 1.86 g (7.1 mmol, 71%); colorless oil; $[\alpha]^{20}_D$ +71.7 (*c* 0.47 in $CHCl_3$).

IR (neat): 1044, 1230, 1372, 1673, 1747, 2962 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, 3 H, *J* = 6.8 Hz, CH_3), 0.90 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.77 (dsept, 1 H, *J* = 1.1, 6.8 Hz, CH), 2.18 (s, 3 H, CH_3), 3.93–4.07 (m, 2 H, CH_2), 4.21 (dd, 1 H, *J* = 7.7, 9.4 Hz, CH), 6.28 (s, 1 H, CH), 7.31–7.42 (m, 3 H, H_{ar}), 7.45–7.53 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (CH_3), 18.5 (CH_3), 20.9 (CH_3), 32.4 (CH), 70.6 (CH), 70.9 (CH), 71.8 (CH_2), 127.6, 128.7, 129.0, 135.3 (aryl), 163.8 (NCO), 169.8 (CO).

MS (EI, 70 eV): *m*/*z* = 261 (M^+), 218, 176, 158, 149, 107, 91, 77.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.60; H, 7.38; N, 5.30.

(*S*,*R*)-2-Acetoxyphenylmethyl-4-isopropyl-4,5-dihydro-oxazole [(*S*,*R*)-9a]

According to method B, the title compound was prepared starting from (*S*,*R*)-**8a** (2.79 g, 10.0 mmol). Purification by flash column chromatography (EtOAc–PE, 1:2) afforded pure (*S*,*R*)-**9a**.

Yield: 1.46 g (5.6 mmol, 56%); colorless oil; $[\alpha]^{20}_D$ +89.1 (*c* 2.12 in $CHCl_3$).

IR (neat): 1043, 1231, 1372, 1677, 1747, 2962, 3340 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, 3 H, *J* = 6.9 Hz, CH_3), 0.93 (d, 3 H, *J* = 6.9 Hz, CH_3), 1.84 (dsept, 1 H, *J* = 1.1, 6.9 Hz, CH), 2.17 (s, 3 H, CH_3), 3.93–4.01 (m, 2 H, CH_2), 4.18–4.31 (m, 1 H, CH), 6.29 (s, 1 H, CH), 7.32–7.41 (m, 3 H, H_{ar}), 7.47–7.53 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 18.8 (CH_3), 21.0 (CH_3), 32.1 (CH), 70.1 (CH_2), 70.9 (CH), 71.8 (CH), 127.4, 128.4, 128.8, 135.3 (aryl), 163.5 (NCO), 169.6 (CO).

MS (EI, 70 eV): *m*/*z* = 261 (M^+), 246, 218, 176, 158, 105, 91, 77.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.84; H, 7.19; N, 5.69.

(*R*,*S*)-2-Acetoxyphenylmethyl-4-*tert*-butyl-4,5-dihydro-oxazole [(*R*,*R*)-9b]

According to method A, the title compound was prepared starting from (*R*,*S*)-**8b** (2.93 g, 10.0 mmol). Purification by flash column chromatography (EtOAc–PE, 2:3 + 5% Et_3N) afforded pure (*R*,*S*)-**9b**.

Yield: 1.71 g (6.2 mol, 62%); yellow oil; $[\alpha]^{20}_D$ –94.0 (*c* 1.01 in $CHCl_3$).

IR (neat): 1046, 1230, 1570, 1678, 1748, 2957 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 9 H, CH_3), 2.15 (s, 3 H, CH_3), 3.88 (ddd, 1 H, *J* = 1.1, 8.3, 10.1 Hz, CH), 4.03 (t, 1 H, *J* = 8.3 Hz, CH_2), 4.20 (dd, 1 H, *J* = 8.7, 10.1 Hz, CH_2), 6.30 (s, 1 H, CH), 7.29–7.41 (m, 3 H, H_{ar}), 7.45–7.54 (m, 2 H, H_{ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_3), 25.9 (CH_3), 33.8 (C_q), 69.2 (CH), 71.1 (CH), 75.7 (CH_2), 127.6, 128.6, 129.0, 135.6 (aryl) 163.5 (NCO), 169.8 (CO).

MS (EI, 70 eV): *m*/*z* = 275 (M^+), 218, 176, 159, 105, 77.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{21}NO_3$: 275.15214; found: 275.15209.

(*S*,*S*)-2-Acetoxyphenylmethyl-4-*tert*-butyl-4,5-dihydro-oxazole [(*S*,*S*)-9b]

According to method A, the title compound was prepared starting from (*S*,*S*)-**8b** (2.93 g, 10 mmol). Purification by flash column chromatography (EtOAc–PE, 4:5) afforded (*S*,*S*)-**9b**.

Yield: 1.85 g (6.7 mmol, 67%); pale yellow oil; $[\alpha]^{20}_D$ +6.0 (*c* 1.07 in $CHCl_3$).

IR (neat): 1048, 1232, 1678, 1747, 2956 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 9 H, CH_3), 2.18 (s, 3 H, CH_3), 3.90 (dd, *J* = 9.9, 7.4 Hz, 1 H, CH), 4.11–4.18 (m, 2 H, CH_2), 6.29 (s, 1 H, CH), 7.32–7.42 (m, 3 H, H_{ar}), 7.46–7.52 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9 (CH_3), 25.6 (CH_3), 33.8 (C_q), 69.4 (CH), 70.9 (CH), 75.4 (CH_2), 127.4, 128.4, 128.8, 135.0 (aryl), 163.5 (NCO), 169.6 (CO).

MS (EI, 70 eV): *m*/*z* = 275 (M^+), 176, 159, 105, 77, 57.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{21}NO_3$: 275.15214; found: 275.15213.

(*R*,*R*)-2-Acetoxyphenylmethyl-4-phenyl-4,5-dihydro-oxazole [(*R*,*R*)-9c]

According to method B, the title compound was prepared starting from (*R*,*R*)-**8c** (3.13 g, 10 mmol). Purification by flash column chromatography (EtOAc–PE, 1:2) afforded (*R*,*R*)-**9c**.

Yield: 1.61 g (6.5 mmol, 65%); yellow oil; $[\alpha]^{20}_D$ –31.3 (*c* 0.78 in $CHCl_3$).

IR (neat): 1045, 1229, 1373, 1672, 1748, 3032, 2903 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, CH_3), 4.08 (t, 1 H, *J* = 8.4 Hz, CH_2), 4.66 (dd, 1 H, *J* = 8.4, 10.1 Hz, CH_2), 5.18–5.27 (m, 1 H, CH), 6.37 (s, 1 H, CH), 7.14–7.46 (m, 8 H, H_{ar}), 7.53–7.61 (m, 2 H, H_{ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_3), 69.6 (CH), 71.0 (CH), 75.4 (CH_2), 126.7, 127.6, 127.7, 128.7, 128.8, 129.2, 135.2, 141.7 (aryl), 165.4 (NCO), 170.0 (CO).

MS (EI, 70 eV): *m*/*z* = 295 (M^+), 280, 252, 236, 174, 118, 91, 77.

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.94; H, 6.00; N, 4.67.

(*S*,*R*)-2-Acetoxyphenylmethyl-4-phenyl-4,5-dihydro-oxazole [(*S*,*R*)-9c]

According to method B, the title compound was prepared starting from (*S*,*R*)-**8c** (3.13 g, 10 mmol). Purification by flash column chromatography (EtOAc–PE, 1:2) afforded (*S*,*R*)-**9c**.

Yield: 1.89 g (6.4 mmol, 64%); white solid; mp 113–114 °C; $[\alpha]^{20}_D$ +134.3 (*c* 1.03 in $CHCl_3$).

IR (KBr): 1047, 1182, 1233, 1371, 1676, 1741, 2969, 3460 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 4.07 (t, 1 H, *J* = 8.4 Hz, CH_2), 4.65 (dd, 1 H, *J* = 8.4, 10.3 Hz, CH_2), 5.17–5.25 (m, 1 H, CH), 6.35 (s, 1 H, CH), 7.15–7.21 (m, 2 H, H_{ar}), 7.23–7.47 (m, 6 H, H_{ar}), 7.53–7.60 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9 (CH_3), 69.5 (CH), 70.9 (CH), 75.3 (CH_2), 126.5, 127.4, 127.5, 128.5, 128.6, 129.0, 135.0, 141.5 (aryl), 165.1 (NCO), 169.7 (CO).

MS (EI, 70 eV): *m*/*z* = 295 (M^+), 280, 252, 236, 175, 118, 105, 91, 77.

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.86; H, 5.94; N, 4.61.

α-Hydroxy-2-oxazolines 2; General Procedure

In a round-bottomed flask, the appropriate acetoxyoxazoline **9** (5.0 mmol) was dissolved in MeOH (30 mL). The solution was cooled to 0 °C and aq LiOH solution (1 M; 15 mL, 3.0 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h and allowed to warm to r.t. The mixture was then extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with sat. aq NaCl (2 × 50 mL). After drying ($MgSO_4$) and evaporation of the solvent crude α-hydroxy-2-oxazoline **2** was obtained as a yellow solid or oil. Recrystallization afforded pure product.

(*R*,*R*)-2-Hydroxyphenylmethyl-4-isopropyl-4,5-dihydro-oxazole [(*R*,*R*)-2a]

Prepared starting from (*R*,*R*)-**9a** (1.31 g, 5.0 mmol). Recrystallization from EtOAc gave pure (*R*,*R*)-**2a**.

Yield: 898 mg (4.1 mmol, 82%); white crystalline solid; mp 73–74 °C; $[\alpha]^{20}_D$ +7.4 (*c* 1.00 in $CHCl_3$).

IR (KBr): 1089, 1200, 1266, 1673, 1741, 2909, 3174 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, 3 H, *J* = 6.7 Hz, CH_3), 0.94 (d, 3 H, *J* = 6.7 Hz, CH_3), 1.74 (sept, 1 H, *J* = 6.7 Hz, CH), 3.78–3.88 (m, 1 H, CH), 4.05 (t, 1 H, *J* = 8.5 Hz, CH_2), 4.25 (dd, 1 H, *J* = 8.5, 9.6 Hz, CH_2), 4.57 (br s, 1 H, OH), 5.32 (s, 1 H, CH), 7.27–7.40 (m, 3 H, H_{ar}), 7.42–7.49 (m, 2 H, H_{ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1 (CH_3), 18.7 (CH_3), 32.5 (CH), 69.7 (CH), 71.2 (CH), 71.8 (CH_2), 126.7, 128.3, 128.5, 139.3 (aryl), 168.5 (NCO).

MS (EI, 70 eV): *m*/*z* = 219 (M^+), 176, 146, 107, 91, 77.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.03; H, 7.82; N, 6.36.

(*S*,*R*)-2-Hydroxyphenylmethyl-4-isopropyl-4,5-dihydro-oxazole [(*S*,*R*)-2a]

Prepared starting from (*S*,*R*)-**9a** (1.31 g, 5.0 mmol). Recrystallization from EtOAc gave pure (*S*,*R*)-**9a**.

Yield: 918 mg (4.2 mmol, 84%); white crystalline solid; mp 85–86 °C; $[\alpha]^{20}_D$ +152.5 (*c* 0.97 in $CHCl_3$).

IR (KBr): 1090, 1198, 1462, 1670, 2754, 2971, 3148 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, 3 H, *J* = 6.8 Hz, CH_3), 0.93 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.74 (sept, 1 H, *J* = 6.8 Hz, CH), 3.90–4.01 (m, 1 H, CH_2), 4.24–4.36 (m, 2 H, CH + OH), 5.26 (s, 1 H, CH), 7.28–7.38 (m, 3 H, H_{ar}), 7.41–7.47 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (CH_3), 18.7 (CH_3), 32.4 (CH), 69.7 (CH), 71.1 (CH), 71.6 (CH_2), 126.6, 128.2, 128.3, 139.1 (aryl), 168.2 (NCO).

MS (EI, 70 eV): *m*/*z* = 219 (M^+), 176, 146, 107, 91, 77.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.25; H, 7.86; N, 6.33.

(*R*,*S*)-2-Hydroxyphenylmethyl-4-*tert*-butyl-4,5-dihydro-oxazole [(*R*,*S*)-2b]

Prepared starting from (*R*,*S*)-**9b** (1.40 g, 5.0 mmol). Recrystallization from EtOAc gave pure (*R*,*S*)-**2b**.

Yield: 769 mg (3.3 mmol, 65%); white solid; mp 123–124 °C; $[\alpha]^{20}_D$ +1.5 (*c* 0.84 in $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 9 H, CH_3), 3.75–3.83 (m, 1 H, CH), 4.11–4.23 (m, 2 H, CH_2), 4.49 (br s, 1 H, OH), 5.33 (s, 1 H, CH), 7.27–7.39 (m, 3 H, H_{ar}), 7.40–7.48 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (CH_3), 33.8 (C_q), 69.7 (CH), 70.5 (CH_2), 74.8 (CH), 126.6, 128.3, 128.5, 139.3 (aryl), 168.4 (NCO).

MS (EI, 70 eV): *m*/*z* = 233 (M^+), 219, 177, 146, 107, 91, 77.

IR (KBr): 1029, 1101, 1411, 1671, 2869, 3195 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.95; H, 8.50; N, 5.99.

(*S*,*S*)-2-Hydroxyphenylmethyl-4-*tert*-butyl-4,5-dihydro-oxazole [(*S*,*S*)-2b]

Prepared starting from (*S*,*S*)-**9b** (1.31 g, 5.0 mmol). Recrystallization from EtOAc gave pure (*S*,*S*)-**9b**.

Yield: 718 mg (3.1 mmol, 62%); white solid; mp 104–105 °C; $[\alpha]^{20}_D$ –1.7 (*c* 1.05 in $CHCl_3$).

IR (KBr): 1089, 1197, 1673, 2957, 3163 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 9 H, CH_3), 3.82 (dd, 1 H, *J* = 8.0, 9.9 Hz, CH), 4.12–4.24 (m, 3 H, CH_2 + OH), 5.32 (s, 1 H, CH), 7.28–7.39 (m, 3 H, H_{ar}), 7.42–7.48 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9 (CH_3), 33.8 (C_q), 69.7 (CH), 70.6 (CH_2), 74.8 (CH), 126.6, 128.3, 128.5, 139.2 (aryl), 168.3 (NCO).

MS (EI, 70 eV): *m*/*z* = 234, 233 (M^+), 177, 146, 107, 91, 77.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.80; H, 7.88; N, 6.00.

(*R*,*R*)-2-Hydroxyphenylmethyl-4-phenyl-4,5-dihydro-oxazole [(*R*,*R*)-2c]

Prepared starting from (*R*,*R*)-**9c** (1.48 g, 5.0 mmol). Recrystallization from EtOAc gave pure (*R*,*R*)-**2c**.

Yield: 997 mg (3.9 mmol, 79% yield); white crystalline solid; mp 108–109 °C; $[\alpha]^{20}_D$ –29.1 (*c* 1.01 in $CHCl_3$).

IR (KBr): 1080, 1177, 1454, 1664, 2871, 2967, 3138, 3390 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.20 (t, 1 H, *J* = 8.7 Hz, CH_2), 4.60 (dd, 1 H, *J* = 8.7, 10.0 Hz, CH_2), 4.95 (br s, 1 H, OH), 5.09–5.17 (m, 1 H, CH), 5.14 (s, 1 H, CH), 7.21–7.27 (m, 2 H, H_{ar}), 7.29–7.41 (m, 6 H, H_{ar}), 7.42–7.47 (m, 2 H, H_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.6 (CH), 69.4 (CH), 75.9 (CH_2), 126.5, 126.6, 127.7, 128.2, 128.3, 128.6, 138.8, 141.3 (aryl), 169.8 (NCO).

MS (EI, 70 eV): *m*/*z* = 255 (M^+), 254, 236, 176, 120, 91, 77.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.67; H, 6.07; N, 5.48.

(*S*,*R*)-2-Hydroxyphenylmethyl-4-phenyl-4,5-dihydrooxazole [(*S*,*R*)-2c]

Prepared starting from (*S*,*R*)-**2c** (1.48 g, 5.0 mmol). Recrystallization from EtOAc gave pure (*S*,*R*)-**9c**.

Yield: 1.11 g (4.7 mmol, 94%); white crystalline solid; mp 124–125 °C; $[\alpha]^{20}_D$ +175.3 (*c* 0.99 in $CHCl_3$).

IR (KBr): 1056, 1241, 1455, 1651, 2905, 2970, 3164 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.09 (t, 1 H, *J* = 8.4 Hz, CH_2), 4.25 (br s, 1 H, OH), 4.68 (dd, 1 H, *J* = 8.4, 10.0 Hz, CH_2), 5.15–5.25 (m, 1 H, CH), 5.35 (s, 1 H, CH), 7.12–7.18 (m, 2 H, H_{ar}), 7.23–7.40 (m, 6 H, H_{ar}), 7.43–7.50 (m, 2 H, H_{ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.7 (CH), 69.9 (CH), 74.0 (CH_2), 126.5, 126.7, 127.8, 128.5, 128.6, 128.8, 139.2, 141.6 (aryl), 169.9 (NCO).

MS (EI, 70 eV): *m*/*z* = 255, 254 (M^+), 236, 208, 176, 120, 107, 91, 77.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.70; H, 6.03; N, 5.51.

Performed Catalysis; General Procedures

General Procedure A

In a glovebox under inert atmosphere, BPh_3 (60 mg, 0.25 mmol) was sealed in a flame-dried reaction vessel (18 × 50 mm). Toluene (3 mL) was added, and the resulting solution was treated with $ZnEt_2$ (110 μL, 1.075 mmol). After stirring for 15 min at r.t., α-hydroxy-2-oxazoline **2** (0.025 mmol) was added as toluene solution (0.5 mL) and stirring was continued for 30 min. at r.t. The resulting clear solution was cooled to 10 °C, and 4-chlorobenzaldehyde (**11**) (35 mg, 0.25 mmol) in toluene (0.5 mL) was added in one portion. After stirring at 10 °C for 12 h, the reaction mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and the solvents were removed under reduced pressure. The resulting oil was submitted to flash chromatography (pentane–Et_2O, 85:15) to give pure **12**. The enantiomeric excess was determined by HPLC using a chiral column [Chiralcel OB-H, 30 °C, 230 nm; heptane–*i*-PrOH, 90:10; 0.5 mL/min; t_R = 25.7 min (*R*), 33.6 min (*S*)].

General Procedure B

In a glovebox under inert atmosphere, BPh_3 (60 mg, 0.25 mmol) and DiMPEG (M = 2500 g/mol, 63 mg, 0.025 mmol) were sealed in a flame dried reaction vessel (18 × 50 mm). Toluene (3 mL) was added, and the resulting mixture was treated with $ZnEt_2$ (110 μL, 1.075 mmol) to give a clear solution containing small amouts of a white precipitate. After stirring for 15 min at r.t., α-hydroxy-2-oxazoline **2** (0.025 mmol) was added as a toluene solution (0.5 mL) and stirring was continued for 30 min. at r.t. The resulting solution was cooled to 10 °C, and 4-chlorobenzaldehyde (**11**) (35 mg, 0.25 mmol) in toluene (0.5 mL) was added in one portion. From here on the protocol followed general procedure A.

(4-Chlorophenyl)phenylmethanol

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (br s, 1 H, OH), 5.80 (s, 1 H, CH), 7.27–7.36 (m, 9 H, H_{ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.91 (CH), 126.74, 128.08, 128.81, 128.86, 133.48, 142.39, 143.62 (aryl).

All other analytical data are in agreement with those reported in the literature.[21,22]

Acknowledgment

The Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft within the SFB 380 and the Graduiertenkolleg 440 are gratefully acknowledged for financial support. We also thank Degussa AG and Bayer AG for the generous gift of chemicals.

References

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**. (b) *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, **1998**. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfalz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**. (d) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, **2000**.

(2) Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle and Sauerländer: Frankfurt, **1980**, 91.

(3) Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935.

(4) (a) Meyers, A. I.; Gant, T. G. *Tetrahedron* **1994**, *50*, 2297. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*; Wiley: New York, **1999**.

(5) (a) Bolm, C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 542. (b) Pfalz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (c) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991. (d) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (f) Braunstein, P.; Naud, F. *Angew. Chem. Int. Ed.* **2001**, *40*, 680.

(6) (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfalz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**, 911. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

(7) (a) Meguro, K.; Aizawa, M.; Sohda, T.; Kawamatsu, Y.; Nagaoka, A. *Chem. Pharm. Bull.* **1985**, *33*, 3787. (b) Toda, F.; Tanaka, K.; Koshiro, K. *Tetrahedron: Asymmetry* **1991**, *2*, 873. (c) Stanev, S.; Rakovska, R.; Berova, N.; Snatzke, G. *Tetrahedron: Asymmetry* **1995**, *6*, 183. (d) Botta, M.; Summa, V.; Corelli, F.; Di Pietro, G.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263. (e) See also: Bolshan, Y.; Chen, C.-Y.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111.

(8) Soai, K.; Kawase, Y.; Oshio, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1613.

(9) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444.

(10) (a) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940. (b) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145.

(11) (a) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295. (b) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3465. (c) Bolm, C.; Kesselgruber, M.; Grenz, A.; Hermanns, N.; Hildebrand, J. P. *New J. Chem.* **2001**, *25*, 13. (d) Bolm, C.; Hermanns, N.; Kesselgruber, M.; Hildebrand, J. P. *J. Organomet. Chem.* **2001**, *624*, 157. (e) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 1488. (f) For a theoretical study on the competition between phenyl and ethyl transfer in this reaction, see: Rudolph, J.; Rasmussen, T.; Bolm, C.; Norrby, P.-O. *Angew. Chem. Int. Ed.* **2003**, *42*, 3002. (g) For a recent application of this protocol, see: Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532.

(12) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850.

(13) (a) Non-asymmetric: Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450. (b) Non-asymmetric: Fürstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *343*, 343. (c) Enantioselective: Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 3279.

(14) Oi, S.; Moro, M.; Inoue, Y. *Chem. Commun.* **1997**, 1621.

(15) (a) Oi, S.; Moro, M.; Inoue, Y. *Organometallics* **2001**, *20*, 1036. (b) Murata, M.; Shimazaki, R.; Ishikura, M.; Watanabe, S.; Masuda, Y. *Synthesis* **2002**, 717.

(16) Braga, A. L.; Rubim, R. M.; Schrekker, H. S.; Wessjohann, L. A.; de Bolster, M. W. G.; Zeni, G.; Sehnem, J. A. *Tetrahedron: Asymmetry* **2003**, *14*, 3291.

(17) Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Yu, K.-B. *J. Org. Chem.* **2003**, *68*, 6474.

(18) (a) Schmidlin, T.; Wallach, D.; Tamm, C. *Helv. Chim. Acta* **1984**, *67*, 1998. (b) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1999**, *55*, 2431.

(19) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.

(20) Rudolph, J.; Schmidt, F.; Bolm, C. *Adv. Synth. Catal.*, accepted for publication.

(21) Rudolph, J.; Hermanns, N.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 3997.

(22) (a) Wu, B.; Mosher, H. S. *J. Org. Chem.* **1986**, *51*, 1904. (b) Lee, J.-S.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428.