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Solvent and in situ catalyst preparation impacts upon Noyori reductions of aryl-chloromethyl ketones: application to syntheses of chiral 2-amino-1-aryl-ethanols

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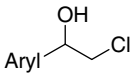
Abstract—As part of medicinal chemistry efforts we found it necessary to develop general syntheses of highly enantiomerically enriched 1-aryl-2-chloroethanols and 1-aryl-2-methylaminoethanols. A survey of literature methods suggested that a truly general approach had not yet been reported, encouraging us to undertake the development of such a methodology. This study describes the design, development, and reduction to practice of a general synthesis of chiral 1-aryl-2-chloroethanols and the transformation of these entities to highly enantiomerically enriched 1-aryl-2-methylaminoethanols. Of particular importance were observations of the impact of solvent and the method of catalyst preparation on the yield and enantiomerical excess of chlorohydrins prepared via Noyori transfer hydrogenations of aryl-chloromethyl ketones.

1. Introduction

As part of two medicinal chemistry campaigns we found it necessary to consider the preparation of highly enantiomerically enriched 1-aryl-2-chloroethanols **1** and highly enantiomerically enriched 1-aryl-2-methylaminoethanols **2**. It was our desire to develop a single method for the introduction of asymmetry and derive the target 1-aryl-2-methylaminoethanols from precursor 1-aryl-2-chloroethanols for the sake of simplicity. Aryl groups of interest included phenyl-, 2-pyridyl, 3-pyridyl, pyrazinyl, 2-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, and benzofuranyl. Therefore any method selected or developed would be required to accept this cross-section of substrates and provide 1-aryl-2-chloroethanols in good to excellent yields with high ee's:



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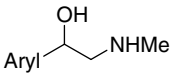

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A survey of the literature led us to consider enzymatic/microbial resolution of racemic halohydrins and enzymatic/microbial reduction of aryl-chloromethyl ketones, as well as asymmetric chemical reduction (DIP-Cl, oxazaborolidine, Noyori) of aryl-chloromethyl ketones. We elected not to pursue enzymatic/microbial resolution/

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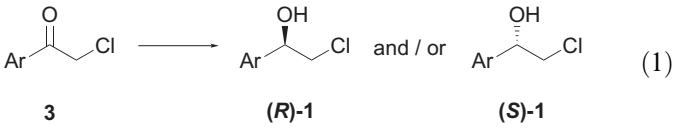
reduction as substrate generality within a limited number of enzymes/microorganisms was not apparent.[1]

Within the realm of chemical reduction methods (Eq. 1), Brown's DIP-Cl[2a] has seen limited use in the reduction of aryl-chloromethyl ketones **3**, causing us to question the generality of this stoichiometric reagent for our applications, but has been reported to afford good ee's where employed:[2]



(1)

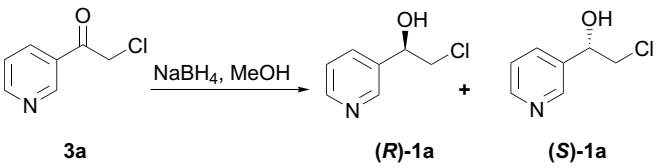
The Corey[3]–Itsuno[4] oxazaborolidine based catalytic asymmetric reduction[5] has been utilized for the synthesis of 1-aryl-2-chloroethanols **1** and **2**, providing good yields and enantiomeric excesses for those cases where Ar = non-coordinating phenyl derivatives. The paucity of examples wherein the aryl possesses a Lewis basic coordinating group[5a] is a concern as many of the substrates of interest to us bear coordinating groups.

Noyori-type reductions[6–8] have been widely applied to achieve asymmetric reductions of aryl-chloromethyl ketones **3**. A selection of metals (e.g., Ir, Rh, Ru), a diversity of chiral ligands, and a variety of conditions (solvent, *source* of H_2) have been employed to achieve good to excellent levels of asymmetric induction. However, the cross-section of aryl moieties of interest to us (phenyl-, 2-pyridyl, 3-pyridyl, pyrazinyl, 2-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, benzofuranyl) in the chloromethyl framework had not been examined in a single metal/ligand/H_2 source combination. Therefore we elected to examine the basic Noyori reduction[6] ([RuCl-*p*-cymene]$_2$/(1*R*,2*S* or 1*S*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine/HCOOH–Et_3N) for its generality and utility in the preparation of highly enantiomerically enriched 1-aryl-2-chloroethanols **1**.

2. Results and discussion

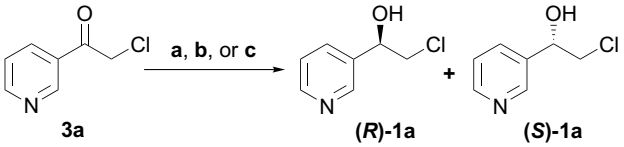
2.1. Asymmetric reduction development

As a representative aryl-chloromethyl ketone, we selected 3-chloroacetylpyridine[2d] **3a** to begin our studies. Ketone **3a** was smoothly reduced with sodium borohydride (Scheme 1) to provide racemic 2-chloro-1-(3-pyridyl)-ethanol (***RS***)-**1a** for analytical purposes. The mixture was easily separated/analyzed[9] and the 2-chloro-1-(3-pyridyl)-ethanol (***RS***)-**1a** was readily purified and handled, setting the stage



Scheme 1. Racemic halohydrin synthesis, chiral separation, and analysis.

for method development. Asymmetric reduction attempts began with a comparison of the Brown (+)-DIP-Cl reduction[2a] of 3-chloroacetylpyridine **3a** as reported by Fisher et al.,[2d] with the Corey–Itsuno oxazaborolidine (derived from L-proline),[3] prepared by the method of Mathre et al.,[3] and the Noyori protocol.[6] Our first attempts to perform chiral reductions are presented in Scheme 2.

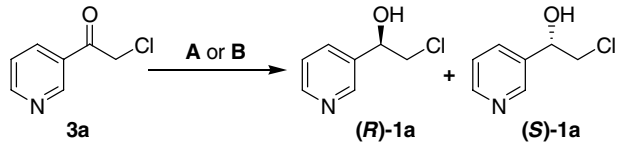


	Conditions	Yield	Ratio (*R*)-1a/(*S*)-1a
a	(+)-DIP-Cl, Et_3N, THF, -20°C, 4 days	27%	3:97
b	L-prolinol derived oxazaboroladine, BH_3-SMe_2	90%	30:70
c	RuCl[(1*S*,2*S*)-pTsNCH(Ph)-CH(Ph)NH_2](η^6-*p*-cymene), HCO_2H / Et_3N (5:2), 72 h	27%	80:20

Scheme 2. Chiral reductions—initial attempts.

The (+)-DIP-Cl reaction provides excellent enantiomeric excess for the anticipated major (*S*)-enantiomer, however the poor conversion, stoichiometric use of the reagent, and the extended reaction time at low temperature render this approach to be of low utility. By comparison, the L-prolinol derived oxazaboroladine, BH_3–SMe_2 reduction proceeds rapidly and in high yield, but unfortunately the chiral selectivity is far below what we required. The Noyori reduction afforded modest ee's at low conversion, but the catalytic nature of the process when combined with the modest level of asymmetric induction led us to focus on this method as one, which might be optimizable for the substrates at hand. An observation by Vedejs,[10] that the simple expedient of venting the reaction vessel during a Noyori asymmetric catalytic reduction of dihydroisoquinolines, presumably to allow H_2 and CO_2 to exit, enabled reactions that had stalled at ca. 25% conversion to proceed nearly to completion. We had vented our reaction vessels during the course of performing the reactions cited in Scheme 2, and therefore additional alterations were needed. Perhaps the utilization of a solvent, which would lower the viscosity of the medium, coupled with reaction vessel venting would facilitate greater conversion. Entries 1 and 2 (Table 1) represent baseline experiments with the (1*S*,2*S*)-*p*TsNHCH(Ph)–CH(Ph)NH_2 and (1*R*,2*R*)-*p*TsNHCH(Ph)–CH(Ph)NH_2 ligands, respectively. Solvent effects were examined beginning with entries 3–5. The addition of CH_2Cl_2 (entry 3) to the reduction milieu led to an increased conversion (39% vs ca. 25%) with a shorter reaction time (16 h vs 48 h) and a modest improvement in ee (70% vs 60%). Conducting the Noyori reduction in THF (entry 4) resulted in an outcome that was nearly identical to that obtained in CH_2Cl_2, a modest improvement over

Table 1. Chiral reductions—method development



3a **(*R*)-1a** **(*S*)-1a**

Entry	Conditions	Yield (%)	Ratio (***R***)-**1a**/(***S***)-**1a**	ee (%)
1	**A**, 48 h, rt	27	80:20	60
2	**B**, 48 h, rt	24	19:81	62
3	**A**, CH_2Cl_2, 16 h, rt	39	85:15	70
4	**A**, THF, 16 h, rt,	37	83:17	66
5	**A**, DMF, 16 h, rt	67	95:5	90
6	**A**, DMF, 90 min, rt	73	98:2	96
7	**A**, DMF, 16 h, −15 °C	59	96:4	92
8	**A**, DMF, 45 min, rt, house vacuum	71	98:2	96
9	**B**, DMF, 45 min, rt, house vacuum	64	2:98	96

A: RuCl[(1*S*,2*S*)-*p*-TsNCH(Ph)–CH(Ph)NH_2] (η^6-*p*-cymene), HCO_2H/Et_3N (5:2); **B**: RuCl[(1*R*,2*R*)-*p*-TsNCH(Ph)–CH(Ph)NH_2] (η^6-*p*-cymene), HCO_2H/Et_3N (5:2).

the standard HCO_2H/Et_3N conditions. DMF was the next solvent selected for this study and the effects of this solvent were dramatic. As can be seen from the data presented in Table 1, entry 5, the reaction time was shortened to ⩽16 h (first time point measured), giving a 67% isolated yield of halohydrins as a 95:5 mixture (*R*:*S*, 90% ee). The dramatic improvement in relative reaction rate, overall conversion, and enantioselectivity suggested an important role for DMF in the reduction.

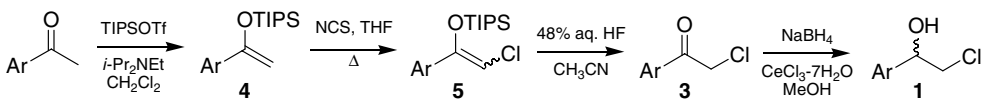
Given the lack of data points pre-16 h in the reaction course and the rapid pace of the reaction, we needed to study the time course of the reduction and examine the impact of temperature on the reduction. It was observed that the reduction was complete in 90 min (entry 6) to furnish a 73% isolated yield of halohydrins with an excellent 98:2 ratio (96% ee) favoring the expected (*R*)-enantiomer. Lowering the temperature of the reaction mixture to −15 °C (Table 1, entry 7) slowed the reaction, requiring 16 h to be complete under these conditions, unfortunately we did not observe an increase in the selectivity of the reduction (96:4). Similarly, the application of modest vacuum (ca. 30 mmHg) to the reaction vessel had an impact on the relative rate of reaction (45 min to completion) but did not alter the selectivity (entries 8 and 9).

The data of Table 1 support a large solvent effect in the Noyori asymmetric transfer hydrogenation of 3-chloroacetylpyridine **3a** and implicate a solvent role in the transition state of the reduction. The next phase of our investigations centered upon demonstrating the breadth of the reduction across a representative set of aryl-chloromethyl ketones. Toward that end, we felt it necessary to consider alternatives to the direct halogenation of aryl acetophenones, as sensitive π-rich heterocycles and electron rich acetophenones may suffer halogenation on the acetyl and the aryl nucleus. Penning et al. have described[11] the facile chlorination (NCS, THF) of the TMS-enol ether of a 2,4-dialkoxy-3-alkyl-acetophenone to furnish an unisolated chloro-enol ether, which, after $(n\text{-Bu})_4NF$ treatment, leads to the target chloromethyl ketone in modest yield (58%). To facilitate possible purification at chloro-enol ether stage we elected to examine the conversion of starting ketones to the more stable TIPS-enol ether [$(i\text{-Pr})_3Si$], as described by Katz.[12] Further modification of the Penning sequence was considered for the desilylation step where we planned to replace the relatively basic $(n\text{-Bu})_4NF$ deblocking with an HF desilylation.[13]

2-Acetyl pyridine was exposed to TIPSOTf and $i\text{-Pr}_2NEt$ (CH_2Cl_2) to give the desired TIPS-enol ether (Table 2, entry 1) **4b** in 99% yield. Chlorination was realized upon treatment of **4b** with NCS (1.1 equiv) in THF at reflux to furnish a mixture of geometric chloro enol ether isomers **5b** in 92% yield. The desired chloromethyl ketone **3b** was isolated in 85% yield after desilylation with 48% aq HF in acetonitrile. Likewise, treatment of 2-acetylfuran, 2-acetylthiophene, 3-acetylthiophene, 2-acetylthiazole, 2-acetylpyrazine, and 2-acetylbenzofuran as outlined in Table 2 led to the related chloromethyl ketones **3c**–**h** in good overall yields. Racemic halohydrins **1b**–**h**, required for the development of chiral chromatographic analytical methods, could be easily prepared from **3b**–**h** via the Luche protocol.[14] By comparison, standard $NaBH_4$/MeOH reductions of **3b**–**h** provided **1b**–**h** contaminated with the corresponding epoxide, an outcome not observed with the slightly acidic Luche paradigm.

With a cross-section of aryl-chloromethyl ketones in hand, we examined the reduction protocol for potential problems

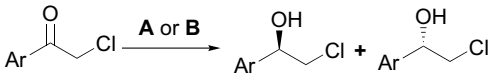
Table 2. Aryl-chloromethyl ketone synthesis and racemic reduction



Entry	Ar	Yield **4** (%)	Yield **5** (%)	Yield **3** (%)	Yield **1** (%)
1	**b** 2-Pyridyl	99	92	85	75
2	**c** 2-Furyl	98	99	67	65
3	**d** 2-Thienyl	99	98	77	75
4	**e** 3-Thienyl	99	95	85	71
5	**f** 2-Benzofuranyl	99	99	60	73
6	**g** 2-Thiazolyl	96	98	95	77
7	**h** 2-Pyrazinyl	99	98	87	56

and possible further improvements. Noyori has reported[6] a simple catalyst preparation and a crystallization, which may be accompanied by decomposition. We were concerned, as was Vedejs,[11] as to the impact of catalyst variability on a reaction survey such as that proposed herein. It was our desire to develop a catalyst preparation that might reduce the variability that can accompany batch catalyst preparation and disparate storage time. An in situ catalyst preparation was viewed as the most obvious first pass solution to this potential development problem.

Attempted in situ catalyst preparation was initiated by combining $RuCl_2(\eta^6$-*p*-cymene) and the selected *p*-TsNCH(Ph)–CH(Ph)NH_2 (1 and 2 mol %, respectively) in the reaction vessel selected for the reduction and the mixture was covered with *i*-PrOH (7.7 mL/ mmol *p*-TsNCH(Ph)–CH(Ph)NH_2), Et_3N (2 mmol/ mmol *p*-TsNCH(Ph)–CH(Ph)NH_2) was added. The resulting solution was refluxed for 1 h, then the solvent was removed and the reduction was conducted as usual. Scheme 3 provides our optimization/in situ catalyst preparation studies with three representative aryl-chloromethyl ketones 2-pyridyl **3b**, 2-furyl **3c**, and the commercially available phenacyl chloride **3i**. The in situ catalyst generation afforded a rust red/brown powdery material and a red-brown solution upon the addition of DMF and 2-chloroacetylpyridine **3b** (Scheme 3). The first indication of a difference in the reduction sequence was observed almost immediately after the addition of the HCO_2H/Et_3N 5:2 azeotrope. During the conduct of the reactions of Table 1, we noted an induction period of 15–30 min after the addition of the HCO_2H/Et_3N 5:2 azeotrope before gas evolution (believed to be CO_2, H_2) was observed. In the case of Scheme 3 entry 1, gas evolution was almost immediate and HPLC analysis of the reaction mixture indicated completion of the reduction after only 45 min. The halving of the reaction time (vs Table 1, run 6) was accompanied also by an improvement in the reduction enantioselectivity, giving (***R***)-**1b** in 80% yield and >99% ee (vs 73% and 96% ee). The reduction of **3b** with the (*R*,*R*)-based catalyst was similarly rapid and high yielding, giving a 77% yield of (***S***)-**1b** in >99% ee. The reduction of 2-chloroacetylfuran **3c** was similarly facile, giving (***R***)-**1c** (77%, 98% ee) and (***S***)-**1c** (72%, 98% ee) selectively (Scheme 3, entries 3 and 4) in 90 min (2 mol % catalyst). The final substrate examined in our optimization study was phenacyl chloride **3i** that selectively gave (***R***)-**1i** [entry 5, (*S*,*S*) ligand, 83%, 98% ee] and (***S***)-**1i** [entry 6, (*R*,*R*) ligand, 81%, 98% ee] within 45 min. A comparison of the rotations of (***R***)-**1i** and (***S***)-**1i** with commercially available chiral material (Aldrich, Cat. #36,356-1 and 36,358-8) further secured the absolute stereochemistry assigned.



3b (Ar = 2-pyridyl) **c** (Ar = 2-furyl) **i** (Ar = phenyl) — (***R***)-**1b** **c** **i** — (***S***)-**1b** **c** **i**

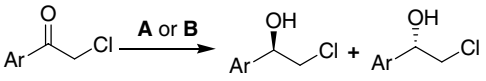
Entry	Aryl	Condition	Yield (%)	Ratio (*R*/*S*)	ee (%)
1	**3b**	**A**, 45 min	80	100:0	>99
2	**3b**	**B**, 45 min	77	0:100	>99
3	**3c**	**A**, 90 min	77	99:1	98
4	**3c**	**B**, 90 min	72	1:99	98
5	**3i**	**A**, 45 min	83	99:1	98
6	**3i**	**B**, 45 min	81	1:99	98

A: RuCl[(1*S*,2*S*)-*p*TsNCH(Ph)-CH(Ph)NH_2](η^6-*p*-cymene), HCO_2H, / Et_3N (5:2), DMF, RT **B**: RuCl[(1*R*,2*R*)-*p*TsNCH(Ph)-CH(Ph)NH_2](η^6-*p*-cymene), HCO_2H, / Et_3N (5:2), DMF, RT

Scheme 3. Chiral reductions—optimization—in situ catalyst preparation.

The results presented in Table 1 suggest a fundamental role for the solvent DMF in the transition state of the reaction, reflected in relative reaction rate and enantioselectivity. In addition, the data of Scheme 3 indicate that the method of catalyst preparation has an impact on the relative rate of the reduction as well as the enantioselectivity of the process suggesting some modification in the catalyst, either in structure or in the percentage of catalytically competent material contained therein. With what appears to be a robust and reasonably well optimized chiral transfer hydrogenation system in hand, we turned our attention to performing reductions on a reasonable scale (10–43 g) for the complete cross-section of substrates represented by **3b–i** (Table 3).

Table 3. Chiral reductions—scale-up



3 (***R***)-**1** (***S***)-**1**

Entry	Aryl	Catalyst	Yield (%)	Ratio (*R*/*S*)	ee (%)
1	**b** 2-Pyridyl	**A**	61	98:2	96
2	**b** 2-Pyridyl	**B**	68	0:100	>99
3	**c** 2-Furyl	**A**	71	99:1	98
4	**c** 2-Furyl	**B**	76	1:99	98
5	**d** 2-Thienyl	**A**	74	99:1	98
6	**d** 2-Thienyl	**B**	68	1:99	98
7	**e** 3-Thienyl	**A**	66	98:2	96
8	**e** 3-Thienyl	**B**	63	1:99	98
9	**f** 2-Benzofuranyl	**A**	93	99:1	98
10	**f** 2-Benzofuranyl	**B**	92	1:99	98
11	**g** 2-Thiazolyl	**A**	81	98.5:1.5	97
12	**g** 2-Thiazolyl	**B**	68	1.5:98.5	97
13	**h** 2-Pyrazinyl	**A**	70	88:12	76
14	**h** 2-Pyrazinyl	**B**	88	11:89	78
15	**i** Phenyl	**A**	88	100:0	>99
16	**i** Phenyl	**B**	85	0.6:99.4	98.8

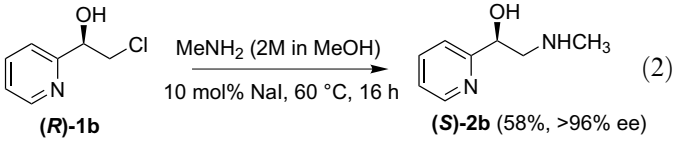
A: RuCl[(1*S*,2*S*)-*p*-TsNCH(Ph)–CH(Ph)NH_2] (η^6-*p*-cymene), HCO_2H/ Et_3N (5:2), DMF; **B**: RuCl[(1*R*,2*R*)-*p*-TsNCH(Ph)–CH(Ph)NH_2] (η^6-*p*-cymene), HCO_2H/Et_3N (5:2), DMF.

Seven of the eight aryl-chloromethyl ketones examined in this study suffered reduction in good to excellent yields and excellent ee's, as measured by chiral HPLC analysis. The reductions of Table 3 were carried out with in situ generated catalyst with a catalyst loading of $\leqslant$2 mol %. Previously, we demonstrated good yields and ee's for the 2-pyridyl system **3b**, 2-furyl chloromethyl ketone **3c**, and phenacyl chloride **3i** in small scale reductions (Scheme 3).

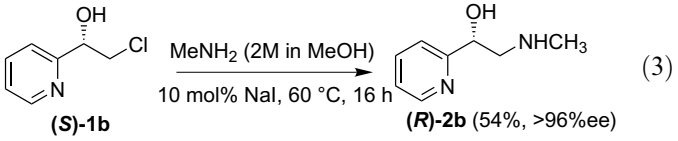
On large scale, these compounds were similarly well behaved. On identical 24 g scale reductions, **3b** afforded (***R***)-**1b** (61%, 96% ee) and (***S***)-**1b** (68%, >99% ee) upon exposure to catalysts **A** (*S*,*S*) and **B** (*R*,*R*), respectively (Table 3, entries 1 and 2). The less polar, π-rich heterocycles 2-chloroacetylfuran **3c**, 2-chloroacetylthiophene **3d**, 3-chloroacetylthiophene **3e**, and 2-chloroacetylbenzofuran **3f** behave similarly when exposed to catalysts **A** (*S*,*S*) (Table 3, entries 3, 5, 7, and 9) giving the expected halohydrins (***R***)-**1c–f** in 66–93% yield and 96–98% ee. The reduction of **3c**, **3d**, **3e**, and **3f** under the influence of catalyst **B** (*R*,*R*) was also successful, leading to halohydrins (***S***)-**1c–f** (entries 4, 6, 8, and 10) in 63–92% yield and 98% ee for each substrate. The bis-heteroaromatics 2-chloroacetylthiazole **3g** and 2-chloroacetylpyrazine **3h** provide an interesting contrast, to each other and to the entities subjected to asymmetric reduction until this point. The 2-thiazolyl chloromethylketone **3g** is smoothly reduced with the (*S*,*S*) catalyst (entry 11) to give alcohol (***R***)-**1g** in 81% yield and 97% ee. The reduction of **3g** with catalyst **B** (*R*,*R*) gave alcohol (***S***)-**1g** in a reduced 68% yield, but equally good 97% ee. We were taken aback by the results obtained upon reduction of 2-chloroacetylpyrazine **3h**. Ketone **3h** was reduced with the (*S*,*S*) catalyst **A**, in the usual way, to provide (***R***)-**1h** in 70% yield with a much reduced 76% ee. A similarly disappointing result was obtained upon reduction of **3h** with the (*R*,*R*) catalyst **B**, to furnish (***S***)-**1h** in 88% yield and 78% ee. Repeated reductions, and manipulation of the reduction temperature did not improve the enantiomeric excess of the **1h** product halohydrins. These results were unexpected, as both 3-chloroacetylpyridine **3a** and 2-chloroacetylpyridine **3b** had been reduced in good yield and excellent ee's, and we considered 2-chloroacetylpyrazine **3h** to be a hybrid of these structures. Clearly there are factors, as yet not fully understood, that can lead to an erosion in the chiral integrity of the reduction process. The final examples of Table 3, the reduction of commercially available phenacyl chloride **3i** to afford (***R***)-**2i** (88%, >99% ee) and (***S***)-**2i** (85%, 98.6% ee) proceeded in high yield and % ee, and have also been conducted on >100 g scale without an impact on enantioselectivity.

2.2. The synthesis of highly enantiomerically enriched *N*-methyl-2-amino-1-aryl-ethanols

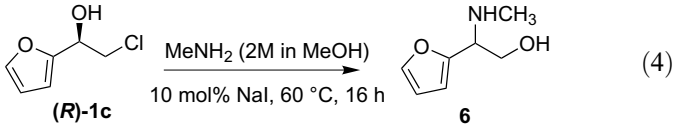
With a general method for the production of highly enantiomerically enriched 1-aryl-2-chloroethanols in hand, we turned our attention to the conversion of these molecules to the target 1-aryl-2-methylaminoethanols. The direct conversion of a 1-aryl-2-chloroethanol to the related 1-aryl-2-methylaminoethanol was envisioned to occur by direct amine displacement as described by Ehlers.[15] Our initial attempt to prepare a chiral 1-aryl-2-methylaminoethanol utilized the 2-pyridylhalohydrin (***R***)-**1b**. Treatment of this substrate with methylamine (10 equiv, 2 M in MeOH) at 60 °C in a thick-walled, sealed glass bottle resulted in ca. 40% conversion after 24 h. The introduction of 10 mol % NaI into the reaction medium (Eq. 2) led to smooth conversion to the aminoethanol, affording (*S*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***S***)-**2b** in 58% yield (>96% ee, Eq. 2). In a similar fashion, 2-pyridyl halohydrin (***S***)-**1b** was reacted with methyl amine (10 equiv, 2 M in MeOH), in the presence of 10 mol % NaI, at 60 °C, in a thick-walled, sealed glass bottle, to give (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***R***)-**2b** in 54% yield (>96% ee, Eq. 3). The measured enantiomeric excesses for both (***S***)-**2b** and (***R***)-**2b** were difficult to ascertain with great precision as the chromatographic characteristics of these aminoethanols were less than ideal. A similar displacement was next examined for the 2-furyl halohydrin (***R***)-**1c** as shown in Eq. 4. The reaction produced a number of products, the major entity isolated was relatively unstable unlike reports of the racemic *N*-methyl-1-(2-furyl)-2-aminoethanol,[16] and it provided 1H-chemical shifts and multiplicities outside of those expected after the syntheses of (***S***)-**2b** and (***R***)-**2b**. Further support for the assigned structure came from long-range ^{1}H–^{13}C heteronuclear shift correlation (HMBC).[17] These data caused us to assign the 2-(2-furyl)-2-amino ethanol structure **6** to this compound and surmise that its origin might be derived from the related epoxide.[18] The result of Eq. 4 predicts difficulties for other π-rich heterocycles, a trait possessed by many of the chiral halohydrins of Table 3. It was necessary to examine an alternative to direct amine displacement that would obviate the styrene-*like*-oxide as a putative intermediate:



(2)

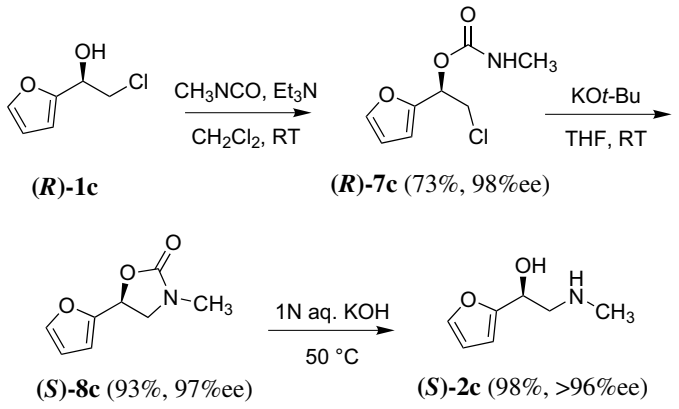


(3)



(4)

The failure of an intermolecular nitrogen introduction, either due to formation of the epoxide or via –OH ionization, suggested that we examine an intramolecular delivery of the nascent methylamino group using the halohydrin-OH as the tether. The work of Das[19] provided the framework for the chemistry illustrated in Scheme 4. 2-Furyl-halohydrin (*R*)-**2c** was reacted with methyl isocyanate and Et_3N, in methylene chloride at room temperature, to provide (*R*)-1-(2-furyl)-2-chloroethyl *N*-methylcarbamate (***R***)-**7c** in 73% yield (98% ee). Cyclization of the carbamate with KO-*t*-Bu in THF smoothly led to the stable intermediate (5*R*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c** (93%, 97% ee), which was easily and quickly analyzed by chiral HPLC suggesting an oxazolidinone as an ideal intermediate for analysis and/or chiral chromatographic upgrade. A number of hydrolytic paradigms were examined to unravel the oxazolidinone and reveal the desired aminoethanol. Ultimately, we settled upon a simple treatment of (***S***)-**8c** with 1 N aq KOH at 50 °C. The two phase mixture gave way, over 3 h, to a homogenous solution. Analysis of the mixture by analytical HPLC at this time



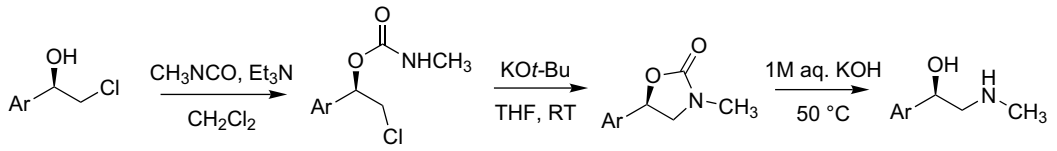
Scheme 4. Oxazolidinone approach to *N*-methyl (*S*)-1-(2-furyl)-2-aminoethanol (***S***)-**2c**.

point indicated complete conversion to a single entity. Saturation of the solution with salt and extraction with Et_2O/CH_2Cl_2 (95:5), followed by drying (Na_2SO_4) led directly to analytically pure *N*-methyl *S*-1-(2-furyl)-2-aminoethanol (***S***)-**2c** (98%, >96% ee).

The oxazolidinone approach, shown in Scheme 4, has attributes that make it quite attractive despite its length. Molecules, which resist conversion to the desired aminoethanols might be accessed via this route providing two approaches to these target molecules. The facility with which the penultimate oxazolidinone might be assessed for enantiomeric excess and upgraded through preparative chiral chromatography, or even recrystallization, is noteworthy and must be contrasted to the long retention times and broadened peaks observed for the aminoethanols (***S***)-**2b** and (***R***)-**2b**. This suggests the utility of both routes, wherein the chemistry of Scheme 4 will be our preferred approach, with failure leading to direct displacement. The direct displacement of Eqs. 2 and 3 can then benefit from aminoethanol to oxazolidinone conversion for analysis of enantiomeric excess and/or chiral upgradation. The application of the chemistry of Scheme 4 to the remaining chiral halohydrins of Table 3 is shown in Tables 4 and 5.

The (*R*)-halohydrins **1a** and **1d**–**i** are very well behaved (Table 4, shown with data for **1c** from Scheme 4), furnishing good yields and high enantiomeric excess of related carbamates (***R***)-**7** upon treatment with methyl isocyanate. The cyclization reaction, to oxazolidinones **8** proved to be less general. The 3-pyridyl-, 2-thienyl-, 3-thienyl-, 2-benzofuranyl-, and phenyl-(*R*)-carbamates **7** were readily cyclized with 1 M KO-*t*-Bu in THF at room temperature to give oxazolidinones **8** in 56–96% yields with very good to excellent ee's. The demarcation between good performance and failure for the oxazolidone route to amino ethanols is obvious when one inspects the results obtained for the cyclizations of the 2-thiazolyl carbamate (***R***)-**7g** and the 2-pyrazinyl carbamate (***R***)-**7h**. The addition of 1 M KO-*t*-Bu in THF to (***R***)-**7g** at room temperature resulted in the immediate development of a red-black color. Quickly quenching the reaction provided oxazolidinone **8g** in a much reduced 35% yield. In addition to the low yield of cyclization observed for (***R***)-**7g**, we discovered that **8g** was racemic. Repeating the cyclization with KO-*t*-Bu, NaH, or $NaN(SiMe_3)_2$ at temperatures from −78 °C to room temperature did not result in an improved outcome. The 2-pyrazinylcarbamate (***R***)-**7h** also behaved poorly. The reaction of (***R***)-**7h** with KO-*t*-Bu at room temperature led to a red-black solution and the destruction of the starting material. Lowering the reaction temperature to −78 °C afforded oxazolidinone (***S***)-**8h** in a poor 15%, and an inexplicably improved 92% ee. The data of Table 4 suggest that the conversion of chiral halohydrins **1** to chiral aminomethanols **2** should not be attempted via the oxazolidinone route for 2-azaaryl-carbamates **7** such as 2-thiazolyl-**7g** and 2-pyrazinyl-**7h**. The rapid development of color, much diminished yields, and altered ee's suggest the possibility of a deprotonation/elimination event as the root cause of the difficulties for these substrates. The sequence was completed by treating oxazolidinones (***R***)-**8a**, (***S***)-**8d**, (***R***)-**8e**, (***S***)-**8f**, and (***R***)-**8i** with 1 N aq KOH (50 °C) to furnish aminoethanols (***R***)-**2a** (68%, >96% ee), (***S***)-**2d** (85%, >98% ee), (***R***)-**2e** (93%, >99% ee), (***S***)-**2f** (93%, 92% ee), and (***R***)-**2i** (98%, >98% ee). A comparison of the specific rotation determined for (***R***)-**2i** ($[\alpha]_D^{25} = -41$ (*c* 0.97, EtOH) with a literature value for (***R***)-**2i** (*R*)-halostachine,

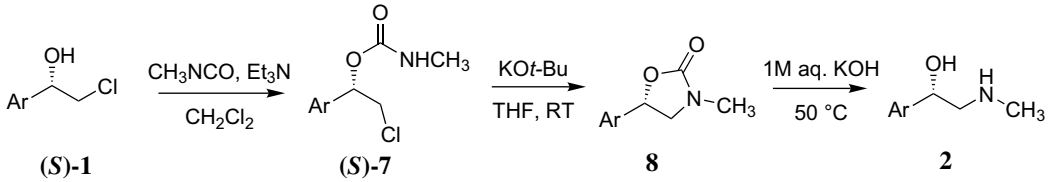
Table 4. Oxazolidinone route to aminoethanols from chiral halohydrins (***R***)-**2**



(***R***)-**1** (***R***)-**7** **8** **2**

Entry	Ar	Yield **7** (%)	ee (%)	Yield **8** (%)	(*R*)/(*S*)	ee (%)	Yield **2** (%)	(*R*)/(*S*)	ee (%)
1a	3-Pyridyl	89	94.6	71	*R*	97.6	68	*R*	>96
1c	2-Furyl	73	98	93	*S*	97	98	*S*	>96
1d	2-Thienyl	91	92.4	91	*S*	98.4	85	*S*	>98
1e	3-Thienyl	88	92.8	81	*R*	>99	93	*R*	>99
1f	2-Benzofuranyl	89	98	56	*S*	92	93	*S*	92
1g	2-Thiazolyl	77	>99	35	—	0	—	—	—
1h	2-Pyrazinyl	85	82	15	*S*	92	—	—	—
1i	Phenyl	89	98	96	*R*	>98	95	*R*	>98

Table 5. Oxazolidinone route to aminoethanols from chiral halohydrins (*S*)-**2**



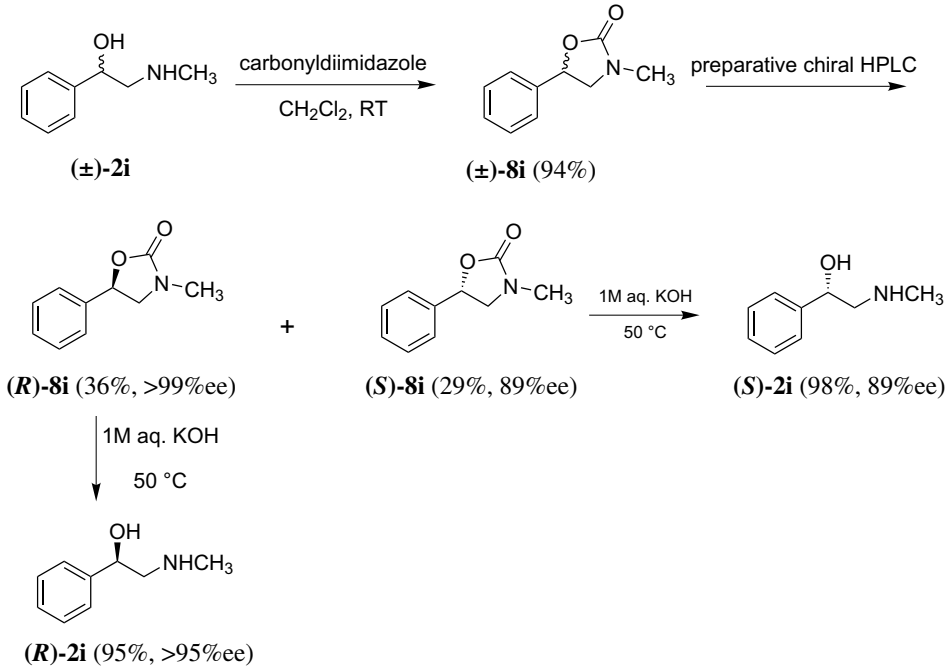
(*S*)-**1** (*S*)-**7** **8** **2**

Entry	Ar	Yield **7** (%)	ee (%)	Yield **8** (%)	(*R*)/(*S*)	ee (%)	Yield **2** (%)	(*R*)/(*S*)	ee (%)
1a	3-Pyridyl	90	96.6	83	*S*	96.6	68	*S*	97.4
1c	2-Furyl	65	98	93	*R*	98	96	*R*	>96
1d	2-Thienyl	92	97	91	*R*	>98	90	*R*	>98
1e	3-Thienyl	88	97	83	*S*	97	93	*S*	>99
1f	2-Benzofuranyl	89	98	61	*R*	92	92	*R*	92
1i	Phenyl	85	>98	83	*S*	96	91	*S*	97

$[\alpha]_D^{25} = -40.7$ (*c* 1.3, EtOH))[20] supports the assigned absolute stereochemistry and demonstrates the stereochemical fidelity of the oxazolidinone process.

The experience gained in the conduct of the chemistry presented in Table 4 resulted in a reduction in the (*S*)-halohydrins selected for reaction via the oxazolidinone route (Table 5). The results of Table 5 for substrates **1a**, **1c**–**f**, and **1i** are nearly identical to those illustrated in Table 4. For this series, the only erosion of enantiomeric excess occurred during the cyclization of the 2-benzofuranylcarbamate (***S***)-**1f**, a decrease in % ee from 98% to 92% ee for oxazolidinone (***R***)-**8f**, which leads to (***R***)-**2f** in 92% ee. The close concordance of these data with the benzofuran results of Table 4, and the lack of ee erosion in the reactions of **1a**, **1c**–**e**, and **1i** (Table 5), as well as **1a**, **1c**–**e**, and **1i** in Table 4 support a base sensitivity for this substrate as do the diminished yields of oxazolidinones (***S***)-**8f** (56%, Table 4) and (***R***)-**8f** (61%, Table 5). Again in the case of Table 5 substrates, the sequence was completed by treating oxazolidinones (***S***)-**8a**, (***R***)-**8c**, (***R***)-**8d**, (***S***)-**8e**, (***R***)-**8f**, and (***S***)-**8i** with 1 M aq KOH (50 °C) to furnish aminoethanols (***S***)-**2a** (68%, 97.4% ee), (***R***)-**2c** (96%, >96% ee), (***R***)-**2d** (90%, >98% ee), (***S***)-**2e** (93%, >99% ee), (***R***)-**2f** (92%, 92% ee), and (***S***)-**2i** (91%, 97% ee). A comparison of the specific rotation determined for (***S***)-**2i** ($[\alpha]_D^{25} = +39$ (*c* 0.83, EtOH) with a literature value for (***S***)-**5h** (*S*)-halostachine, $[\alpha]_D^{25} = 40.4$ (*c* 1.89, EtOH))[1f] again supported the assigned absolute stereochemistry and provided further proof of the stereochemical fidelity of the oxazolidinone process.

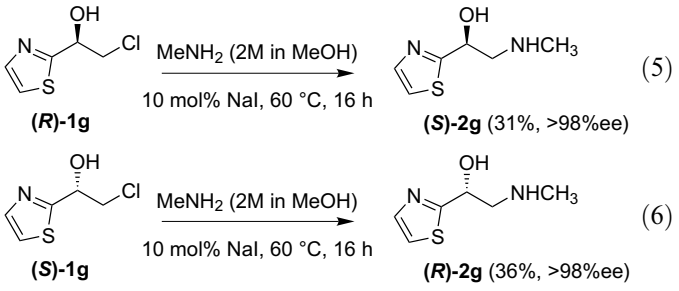
The failed substrates from Table 4, and those withdrawn from Table 5, namely 2-thiazolyl-(***R***)-**1g**, 2-pyrazinyl-(***R***)-**1h**, 2-thiazolyl-(***S***)-**1g**, and 2-pyrazinyl-(***S***)-**1h** halohydrins might be converted to their respective aminoethanols by the direct displacement used in Eqs. 2 and 3. Should that



Scheme 5. Chiral upgrading via the oxazolidinone route.

succeed, we would examine an oxazolidinone formation, chiral chromatographic upgrade, unmasking for the modestly enantiomerically pure 2-pyrazinyl-halohydrins (***R***)-**1h** and (***S***)-**1h**.

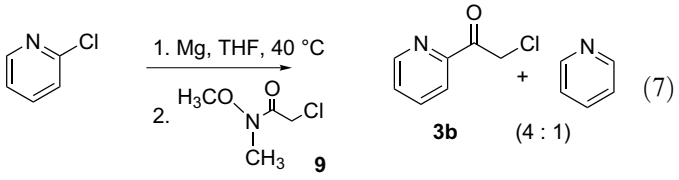
The 2-thiazolylhalohydrins (***R***)-**1g** and (***S***)-**1g** were converted in modest yield to the related 2-thiazolylaminoethanols (***S***)-**2g** (31%, >98% ee, Eq. 5) and (***R***)-**2g** (36%, >98% ee, Eq. 6), in these cases isolation was difficult due to the high water solubility of the aminoethanols. As a test case for chiral upgrading we elected to examine the conversion of commercially available, racemic halostachine (±)-**2i** (Aldrich #20,984-8) to (±)-**8i** and attempted to achieve a preparative chiral chromatographic separation. In the event (Scheme 5), (±)-**2i** was treated with carbonyldiimidazole (CH_2Cl_2, rt) to give (±)-**8i** in 94% yield. Single pass preparative chiral chromatographic separation on a >50 g scale (Chirobiotic T column—ethanol mobile phase) gave (***R***)-**8i** (36%, >99% ee) and (***S***)-**8i** (29%, 89% ee) as well as some mixed fractions. Oxazolidinone hydrolysis in the usual way led to (***R***)-**2i** (95%, >95% ee) and (***S***)-**2i** (98%, 89% ee), respectively:

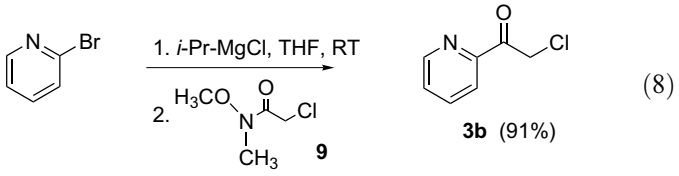


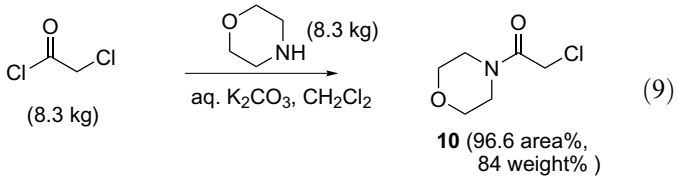
Armed with reasonable methodology for the preparative chiral chromatographic upgrade of 1-aryl-2-methylaminoethanols, we selected an antipode of the pyrazinyl system for conversion/upgrade as shown in Scheme 6. 2-Pyrazinyl-chlorohydrin (***S***)-**1h** (76% ee) smoothly suffered displacement with methyl amine in methanol to give (*R*)-2-methylamino-1-pyrazin-2-ylethanol (***R***)-**2h** in 72% yield and 76% ee. A reasonable yield of this material was only realized upon the elimination of an aqueous reaction work-up and placement of the crude reaction mixture (after solvent removal) directly onto a chromatography column. The upgrade substrate, pyrazinyl oxazolidinone (***R***)-**8h** was obtained in 88% yield (77% ee) and subsequent preparative chiral HPLC separation (Chirobiotic T column—ethanol mobile phase) provided (***R***)-**8h** in 55% yield and a much improved >96% ee. Finally, oxazolidinone cleavage (1 N aq KOH) led to pyrazinyl aminoethanol (***R***)-**2h** in 79% yield and >93% ee.

2.3. Transition to the pilot plant

The route outlined above (Table 2, Scheme 3, Eq. 2) was to be used to prepare multi-kilogram quantities of amino alcohol (***R***)-**1b**. From a large scale operational point of view, the principle issues with this route were associated with the preparation of the chloroketone **3b** and not the subsequent modified Noyori reduction and amine displacement. Therefore we set out to develop a more process friendly chloroketone preparation. Process chemists at Merck previously reported a route to chloroketones using the corresponding Weinreb amide, reporting yields of 80–95% for a variety of substrates.[21] Thus, the Weinreb reagent *N*-methoxy-*N*-methylchloroacetamide **9** was prepared by the Merck procedure and the work-up modified to allow the isolation of the product **9** as a white crystalline solid in 95% yield. The desired 2-pyridyl Grignard reagent was prepared as a black solution by treating 2-chloropyridine with magnesium in THF at 40 °C. Adding this Grignard reagent to 0.9 equiv of Weinreb amide **9** gave a 4:1 mixture of desired chloroketone **3b** to pyridine along with a number of small impurities by HPLC (Eq. 7):

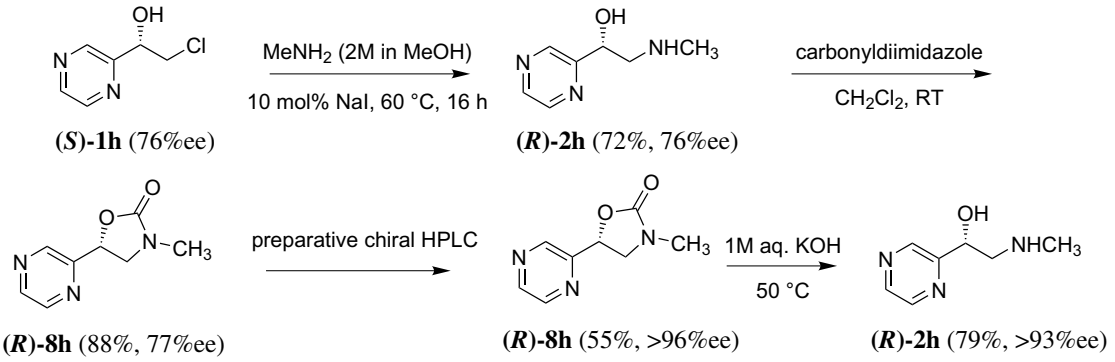






It was previously shown that reaction of 2-iodopyridine with ethylmagnesium bromide smoothly afforded the 2-pyridyl Grignard,[22] however, only research quantities of 2-iodopyridine are commercially available, whereas 2-bromopyridine is a bulk article of commerce. It was then found that high purity 2-pyridyl magnesium halide could be conveniently prepared by adding 2-bromopyridine to commercially available 2 M isopropyl magnesium chloride in THF and by reacting at room temperature for 2–3 h. With the desired 2-pyridyl organometallic in hand, it was reacted with **9** and cleanly gave the desired chloroketone, **3b** (90%, Eq. 8).

As we prepared to transition the chemistry of Eq. 8 to larger scale we identified a serious safety issue, which caused us to alter our course. The Weinreb amide reagent **9**, was identified as a high energy intermediate (1920 J/g) and although the decomposition temperature for the pure compound is over 198 °C the nature of the N–O bond cleavage and the large amount of potential energy warranted closer examination. In addition, we had planned to isolate, the *N*,*O*-dimethylhydroxylamine free base by-product, which is also reported to have high energy and a much lower thermal onset (~50 °C), similar to hydroxylamine. For these reasons we elected to use morpholine amide, **10** in place of **9** for our pilot run. Amide **10** was prepared under Schotten–Bauman conditions (Eq. 9, 96.6 area %) using methylene chloride and aqueous potassium carbonate with

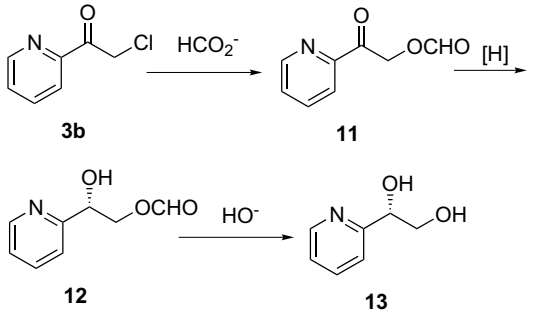


Scheme 6. Chiral upgrading in the pyrazinyl manifold via an oxazolidinone.

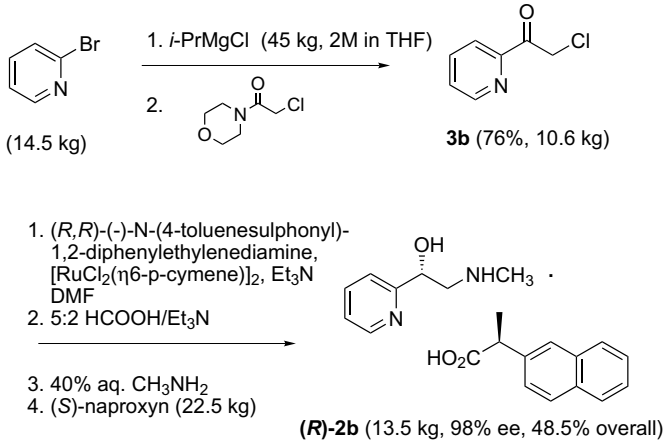
morpholine and chloroacetyl chloride. The product partitioned efficiently into the organic phase and was crystallized in the laboratory by replacing the methylene chloride with octanes. However, the solid **10** had a melting point of 26–30 °C and it was impractical to isolate this intermediate in the pilot plant. We instead chose to exchange the methylene chloride for THF and use the solution of **10** directly in the next step.

While reaction of 2-pyridyl Grignard reagent with **9** gave the desired **3b** with no significant by-product formation, the same is not true for **10**. In our first attempt at the reaction, we found a new impurity formed in about 15% yield. HPLC MS confirmed that this impurity is the result of morpholine addition to **3b**. Running the reaction at −20 °C for 4–6 h instead of 5–10 °C reduced the amount of this impurity, affording **3b** as an MTBE solution without removal of the impurity. In order to avoid isolation of **3b**, which is low melting and a lachrymator, it was found that the crude oil (97–98 area % purity) (with or without small amounts of MTBE) from the Grignard coupling could be carried directly into the modified Noyori reduction without crystallization. However, in order to achieve the same rate of reduction, 1.27 mol % of the catalyst was required, as opposed to 0.85 mol % with crystallized **3b**. A fast reduction (<4 h) is preferred in order to minimize formation of the diol, **13** observed after the aminolysis, which we speculate might be the result of nucleophilic attack of formate on the chlorohydrin intermediate as shown in Scheme 7. Recently, Noyori reported the formate as the exclusive product in low catalyst loading reductions of aryl alkyl chloroketones.[6c] More of the putative formate ester intermediates are observed to form in slow reductions by HPLC. Interestingly, the chlorohydrin **1b** does not appear to degrade upon extended reaction, suggesting that displacement of the chloroketone is the primary mechanism for diol formation

Also during the scale-up we discovered an additional alteration to the in situ catalyst preparation outlined above (Scheme 3). For large scale operations we have found that it is preferable to form the catalyst complex in situ without the solvent swap. In the event, stirring the ruthenium dimer with the ligand in DMF and Et_3N at room temperature for 1 h, followed by the addition of **3b** and the 5:2 mixture of $HCOOH/Et_3N$ gives an equivalent catalyst, which affords (***S***)-**1b** in >98% ee in 90 min on a >10 kg scale. Despite this success at reproducing the high ee of (***S***)-**1b** from the laboratory scale to pilot plant scale, isolation remained somewhat problematic. Extractive isolation of the chlorohydrin intermediate is inefficient due to its hydrophilic nature. Therefore, it was postulated that we could avoid these isolations by quenching the reduction mixture into a solution of sodium hydroxide and methylamine to yield the desired amino alcohol (***R***)-**2b** directly. Happily, this was found to be the case, which allowed for the rapid development of a scalable procedure. The salts formed from neutralizing the formic acid and neutralizing the chlorohydrin were easily removed by filtration after distilling off the DMF solvent for the reduction and water from



Scheme 7. Diol formation in the reduction of ketone **3b**.



Scheme 8. Pilot plant preparation of (***R***)-**2b**.

the commercial methylamine and sodium hydroxide under reduced pressure and solvent exchange to ethanol. The product (***R***)-**2b** was then isolated in >98% ee (13.5 kg) by addition of (*S*)-Naproxen cooling and filtering in 49% yield from 2-bromopyridine as the (*S*)-Naproxen salt (Scheme 8).

3. Conclusion

As a direct result of our efforts in another area, we realized that we required a general method to access a wide variety of 1-aryl-2-methylaminoethanols. Our analysis of the situation suggested that the ideal penultimate aminoethanol precursor, for maximum utility, should be a chiral 1-aryl-2-chloroethanol. Using the Noyori transfer asymmetric reduction [RuCl[(1*S*,2*S* or 1*R*,2*R*)-*p*-TsNCH(Ph)–CH(Ph)NH_2/HCOOH–Et_3N] of aryl-chloromethyl ketones as the starting point for methodological manipulation, a number of seminal alterations/observations have been made. First, there is a profound solvent effect in the reduction step, wherein DMF as the solvent results in a sizeable increase in the relative rate of the reduction (Table 1; entry 1—48 h to entry 6—1.5 h), an increase in the yield of reduced materials (Table 1; entry 1—27%, entry 6—73%), and a dramatic improvement in the % ee of the product halohydrin (Table 1; entry 1—60% ee, entry 6—96% ee). These data implicate a solvent role in the transition state of the reduction, a role, which is as yet unknown. Further modification to the reduction catalyst was driven by the anticipated need for consistent (over time) reduction, and readily scaled reduction with a catalyst that was known to suffer some degradation in conversion and enantioselectivity as a function of age/handling. Toward that end, we have developed an in situ catalyst preparation, which has an impact on the relative rate of the reduction as well as the enantioselectivity of the process suggesting some modification in the catalyst, either in structure or in the percentage of catalytically competent material contained therein (Scheme 3, Table 3). These alterations have provided us with a robust, general, scaleable reduction paradigm. The scalability of this route is well demonstrated in the transition to the pilot plant setting, where reduction on a >10 kg scale proceeds rapidly (90 min) in good yield (Scheme 8) and in excellent ee (>98%). Further improvements in the catalyst generation paradigm were made in the pilot plant setting where component admixing in the presence of Et_3N and DMF afforded the results alluded to above. Aminoethanol synthesis is readily accomplished, but has proven to be less general with respect to the path chosen. Two methods allow the synthesis of the target aminoethanols, the direct displacement (Eqs. 2 and 3), and the oxazolidinone route (Scheme 4) wherein displacement is realized from an intramolecularly held carbamate nitrogen. The oxazolidinone route is preferred for ease of handling, ease of chiral analysis, and oxazolidinones have resulted in facile chiral upgrade (Schemes 5 and 6) in hybrid displacement/oxazolidinone formation sequences. Direct amine displacement can be the method of choice in those instances where the aryl moiety exhibits a N at the position adjacent to chloroethanol attachment (viz Table 4 entries **1g** and **1h**; Eqs. 5 and 6, Scheme 8), in these instances attempted intramolecular oxazolidinone formation leads to degradation and/or partial racemization. Direct displacement has allowed the preparation of >10 kg of (***R***)-**2b** in a single pilot plant run. The chiral halohydrins and chiral aminoethanols reported herein, produced in good to excellent yields, with high ee's and with predictable chiral selectivity (directly correlated to literature entities and items of commerce) have been of great utility.

4. Experimental

All reagents were used as received unless otherwise stated. All reactions were performed under a blanket of nitrogen, in oven (150 °C) dried glassware with rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned. Melting points were determined on a Fisher–Johns hot stage melting point apparatus and are uncorrected. Proton magnetic resonance spectra (^1H NMR) were recorded on a Bruker AVANCE-DPX-300 spectrometer at 300 MHz or a Bruker AVANCE 400 spectrometer at 400 MHz as indicated, in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million (δ scale) from internal tetramethylsilane. Data are reported as follows: chemical shifts [multiplicity (s = singlet, br s = broad singlet, dd = doublet of doublets, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration]. ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer at 100.6 MHz in the solvent mentioned. Chemical shifts are reported in parts per million (δ scale) from the internal solvent reference. Data for mass spectra analysis are reported in the form *m*/*z* (intensity relative to base = 100). Thin layer chromatography (TLC) was performed on EMerck silica gel GF254 plates. Spots were made visible with UV light, and/or exposure to I_2 vapors, and/or dipping into a solution of ammonium molybdate (75 g) and ceric sulfate (2.5 g) in water and concd sulfuric acid (500 mL; 9:1, v/v) followed by heating. Flash column chromatography was performed according to the procedure of Still[23] and eluted with the solvents mentioned, or via the use of the Biotage™ system using either 40S, 40M, or 40L Biotage KP-Sil™ silica prepacked cartridges and eluted with the solvents mentioned. Solvents for extraction and chromatography were of HPLC grade. All the intermediates and final compounds demonstrated >95% purity by HPLC (254 nm, C_{18} column, gradient from 10% MeCN/buffered aqueous to 85% MeCN/buffered aqueous, where 4 L of high purity water was buffered by adding 5.22 g Na_2HPO_4 and 0.76 mL H_3PO_4).

4.1. (±)-2-Chloro-1-(3-pyridyl)-ethanol (±)-1a

3-(2-Chloroacetyl)-pyridine[2d] **3a** (86.40 g, 0.45 mol) was dissolved in MeOH (0.6 L) and the resulting solution was cooled to −10 °C (internal) under nitrogen. To this chilled solution was added $NaBH_4$ (25.92 g, 0.685 mol) in six portions over the course of 1 h. The solution was allowed to warm slowly to room temperature and was stirred at room temperature for 18 h. The reaction was quenched by the addition of water (0.5 L) and the methanol was removed by rotary evaporator at reduced pressure (25 °C). The pH

of the resulting solution was adjusted to ca. 7.0 by the addition of acetic acid and the solution was extracted with EtOAc (4×0.5 L) and the combined organic phases were dried (Na_2SO_4). Filtration and concentration in vacuo afforded crude (±)-2-chloro-1-(3-pyridyl)-ethanol **(±)-1a** as a yellow oil, which was purified by chromatography on a column of silica gel (70 mm OD, 450 g, 230–400 mesh; packed and eluted EtOAc/hexanes 10:90, 500 mL fractions) using the flash technique. Fractions 4–10 were combined and concentrated in vacuo to give 57.5 g (81%) of (±)-**1a** as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.41$ (s, 1), 8.31 (d, $J = 5.0$ Hz, 1), 7.74 (m, 1), 7.24 (m, 1), 4.89 (m, 1), 3.62 (d, $J = 6.0$ Hz, 2).

4.2. (*S*)-2-Chloro-1-(3-pyridyl)-ethanol (*S*)-1a

To RuCl[(1*R*,2*R*)-*p*-TsNCH(Ph)–CH(Ph)NH_2] (η^6-*p*-cymene) (2.5 mg, 0.004 mmol),[6] in a 5 mL 1-neck round bottom flask, was added anhydrous DMF (Aldrich Sure Seal, 2 mL), followed in order by 3-chloroacetylpyridine **3a**[2d] (0.075 g, 0.48 mmol) and HCOOH/Et_3N (5:2, Fluka, 0.18 mL). The red-black solution was placed under house vacuum and the reaction progress was monitored by reverse phase analytical HPLC. After 45 min of stirring, the starting material had been consumed (95:5 NaH_2PO_4/H_3PO_4 buffered water/CH_3CN to 5:95, 17 min; retention time of starting chloroketone **3a**: 7.39 min, retention time of halohydrin 2.66 min). The reaction was quenched by adding MeOH (0.25 mL), stirred for 5 min and then the DMF, etc. were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O/CH_2Cl_2 (4:1, 25 mL), placed in a 100 mL separatory funnel, washed with saturated aq $NaHCO_3$ (25 mL), brine (25 mL), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a red-orange oil, which was purified by chromatography (Biotage® 40S, compound applied in CH_2CL_2/hexanes 60:40; eluted with hexanes/Et_2O 75:25 0.25 L; 65:35 0.25 L; 55:45 0.25 L; 20 mL fractions) using the flash technique. Fractions 21–22 were combined to afford (0.049 g, 64%) of the target (*S*)-3-(1-hydroxy-2-chloroethyl)-pyridine (***S*)-1a** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.53$ (m, 2), 7.79 (m, 1), 7.32 (m, 1), 4.97 (m, 1), 3.88 (br s, 1), 3.72 (m, 2); IR (liq.) 3166 (s, b), 2956 (s), 2856 (s, b), 2096 (w), 1940 (b), 1597 (s), 1582 (s), 1481 (s), 1428 (s), 1082 (s), 1045 (s), 1030 (s), 745 (s), 711 (s), 645 (s) cm^{-1}; % Water (KF titration): 0.59; $[\alpha]_D^{25} = +42$ (*c* 0.81, methanol); Anal. Calcd for C_7H_8ClNO: C, 53.35; H, 5.12; N, 8.89. Found: C, 53.19; H, 5.20; N, 8.65; Chiral HPLC (Chirobiotic T): 2:98; 96% ee.

4.3. [[1-(2-Pyridyl)ethenyl]oxy]tri-isopropylsilane 4b

2-Acetylpyridine (50 g, 0.413 mol) was placed in a 2 L 1 N round bottom flask and anhydrous CH_2Cl_2 (Alrdich Sure Seal®, 0.65 L) was added, followed by the addition of *i*-Pr_2NEt (160.27 g, 1.24 mol, 3 equiv, 216 mL). The flask was equipped with a 125 mL pressure equalized dropping funnel, and the mixture was placed under nitrogen and cooled in an ice-water bath. To the chilled ketone/amine mixture was added TIPSOTf (139.7 g, 0.456 mol, 1.1 equiv, 122.6 mL) over 1.5 h. The mixture was allowed to warm to room temperature overnight. The reaction mixture was concentrated in vacuo on a rotary evaporator ($T \leqslant 25$ °C) to give a yellow oil and a white solid. The flask contents were transferred to a 2 L separatory funnel with ether (1.2 L) resulting in the formation of an additional white solid material (likely *i*-$Pr_2(Et)NH^+$ $^-$OTf, which might be removed by filtration but was not in this experiment) and the mixture was washed with saturated aq $NaHCO_3$ (2×0.65 L). The organic phase was separated, dried over Na_2SO_4, and then was concentrated in vacuo to furnish the crude 2-[1-tri-isopropylsilyloxy-vinyl]-pyridine **4b** (131.5 g) as a yellow-orange oil. This crude material was not further purified, but was immediately carried to the chlorination step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.57$ (m, 1), 7.71 (m, 2), 7.21 (m, 1), 5.65 (br s, 1), 4.58 (br s, 1), 1.36 (heptet, $J = 7.2$ Hz, 3), 1.15 (d, $J = 7.21$ Hz, 18).

4.4. [[2-Chloro-1-(2-pyridyl)ethenyl]oxy]tri-isopropylsilane 5b

Crude 2-[1-tri-isopropylsilyloxy-vinyl]-pyridine **4b** (131.5 g, assumed 0.413 mmol) was placed in a 2 L, 1 N round bottom flask and dissolved in anhydrous THF (Aldrich Sure Seal, 0.6 L). The flask was equipped with a reflux condenser and the apparatus was placed under nitrogen. NCS (60.66 g, 0.454 mol, 1.1 equiv) was added and the mixture was heated to reflux and maintained at reflux for 2 h. The reaction mixture was cooled to room temperature, poured into a 4 L separatory funnel containing ether (1.5 L), and was washed with saturated aq $NaHCO_3$ (2×0.7 L). The organic phase was separated, dried (Na_2SO_4), and concentrated in vacuo to afford the target 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-pyridine **5b** (117.5 g, 91%) as a yellow-orange oil. The crude material was not further purified, but was immediately carried into the next step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.53$ (d, $J = 4.7$ Hz, 1), 7.71 (td, $J = 7.7$, 1.8 Hz, 1), 7.52 (d, $J = 7.7$ Hz, 1), 7.22 (dd, $J = 4.7$, 1.8 Hz, 1), 6.58 (s, 1), 1.21 (heptet, $J = 7.4$ Hz, 3), 1.13 (d, $J = 7.4$ Hz, 18).

4.5. 2-(Chloroacetyl)-pyridine 3b

Crude 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-pyridine **5b** (117.3 g, 0.376 mol) was placed in a 4 L plastic bottle and was dissolved in acetonitrile (0.4 L). To the stirring solution was added 48% aqueous HF (170 mL, 0.45 mL/ mmol) and the progress of the reaction was monitored by reverse phase analytical HPLC. After ca. 2 h the reaction was judged to be complete, and the pH of the solution was carefully adjusted to ca. 8 with saturated aq $NaHCO_3$. The mixture was poured into a separatory funnel containing CH_2Cl_2 (1.5 L). The organic phase was removed and the aq layer was extracted with CH_2Cl_2 (2×1.0 L). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo to afford crude 2-chloroacetyl pyridine **3b** (49.5 g, 85%) as a tan solid (after cooling). The crude material was judged to be quite pure by ^{1}H NMR and HPLC and was used *as is* in the Noyori asymmetric reduction. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.66$ (d, $J = 4.7$ Hz, 1), 8.09 (d, $J = 7.9$ Hz, 1), 7.88 (td, $J = 7.9$, 1.6 Hz, 1), 7.54 (m, 1), 5.12 (s, 2).

4.6. [[1-(2-Furyl)ethenyl]oxy]tri-isopropylsilane 4c

2-Acetylfuran (50 g, 0.454 mol) was placed in a 2 L 1 N round bottom flask and anhydrous CH_2Cl_2 (Alrdich Sure Seal, 0.70 L) was added, followed by the addition of *i*-Pr_2NEt (176 g, 1.36 mol, 3 equiv, 237 mL). The flask was equipped with a 125 mL pressure equalized dropping funnel, and the mixture was placed under nitrogen and cooled in an ice-water bath. To the chilled ketone/amine mixture was added TIPSOTf (153.2 g, 0.5 mol, 1.1 equiv, 134.3 mL) over 1.5 h. The mixture was allowed to warm to room temperature overnight. The reaction mixture was concentrated in vacuo on a rotary evaporator ($T \leqslant 25$ °C) to give a yellow oil and a white solid. The flask contents were transferred to a 2 L separatory funnel with ether (1.2 L) resulting in the formation of an additional white solid material (likely *i*-$Pr_2(Et)NH^+{}^-OTf$, which might be removed by filtration but was not in this experiment) and the mixture was washed with saturated aq $NaHCO_3$ (2×0.70 L). The organic phase was separated, dried over Na_2SO_4, and then was concentrated in vacuo to furnish the crude 2-[1-tri-isopropylsilyloxy-vinyl]-furan **4c** (118.3 g, 98%) as a yellow-orange oil. This crude material was not further purified, but was immediately carried to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (br s, 1), 6.49 (d, $J = 3.2$ Hz, 1), 6.40 (m, 1), 4.86 (d, $J = 1.7$ Hz, 1), 4.37 (d, $J = 1.7$ Hz, 1), 1.32 (heptet, $J = 7.2$ Hz, 3), 1.14 (d, $J = 7.2$ Hz, 18).

4.7. [[2-Chloro-1-(2-furyl)ethenyl]oxy]tri-isopropylsilane 5c

Crude 2-[1-tri-isopropylsilyloxy-vinyl]-furan **4c** (116.3 g, assumed 0.436 mmol) was placed in a 2 L, 1 N round bottom flask and dissolved in anhydrous THF (Aldrich Sure Seal, 0.6 L). The flask was placed under nitrogen, cooled in a −10 °C bath, then NCS (64.11 g, 0.48 mol, 1.1 equiv) was added and the mixture was stirred for 1 h, after which time the reaction was judged to be complete by analytical reverse phase HPLC. The reaction mixture was warmed to room temperature, poured into a 4 L separatory funnel containing ether (1.5 L), and was washed with saturated aq $NaHCO_3$ (2×0.7 L). The organic phase was separated, dried (Na_2SO_4), and concentrated in vacuo to afford the target chloro-enol ether 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-furan **5c** (129.9 g, 99%) as a yellow-orange oil. The crude material was not further purified, but was immediately carried into the next step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 1.8$ Hz, 1), 6.43 (m, 1), 6.40 (m, 1), 5.95 (s, 1), 1.30 (heptet, $J = 7.2$ Hz, 3), 1.11 (d, $J = 7.2$ Hz, 18).

4.8. 2-(Chloroacetyl)-furan 3c

2-[1-Tri-isopropylsilyloxy-2-chloro-vinyl]-furan **5c** (129.9 g, 0.431 mol) was placed in a 4 L plastic bottle and was dissolved in acetonitrile (0.6 L). To the stirring solution was added 48% aqueous HF (65 mL, 0.15 mL/ mmol) and the progress of the reaction was monitored by reverse phase analytical HPLC. After ca. 2 h, the reaction was judged to be complete, and the pH of the solution was carefully adjusted to ca. pH 7 with saturated aq $NaHCO_3$. The mixture was poured into a separatory funnel containing CH_2Cl_2 (1.5 L). The organic phase was removed and the aq layer was extracted with CH_2Cl_2 (2×1.0 L). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo to afford crude 2-chloroacetyl furan (41.9 g, 67%) **3c** as a yellow oil. The crude material was judged to be quite pure by ^{1}H NMR and HPLC and was used *as is* in the Noyori asymmetric reduction. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$ (m, 1), 7.33 (d, $J = 2.7$ Hz, 1), 6.59 (m, 1), 4.57 (s, 2); MS (ES+): 145.4 ($M+H^+$).

4.9. [[1-(2-Thienyl)ethenyl]oxy]tri-isopropylsilane 4d

As described for the preparation of [[1-(2-furyl)ethenyl]oxy]tri-isopropylsilane **4c**, 2-acetylthiophene (50 g, 0.396 mol) was treated with (*i*-Pr)$_3$SiOTf (133.6 g, 0.436 mol, 117 mL) and (*i*-Pr)$_2$NEt (153.6 g, 0.59 mol, 207 mL) in CH_2Cl_2 (0.7 L) to give 2-[1-tri-isopropylsilyl-oxy-vinyl]-thiophene **4d** (111.9 g, 100%) as a golden yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$ (m, 1), 7.22 (m, 1), 6.99 (m, 1), 4.79 (d, $J = 2.0$ Hz, 1), 4.33 (d, $J = 2.0$ Hz, 1), 1.32 (heptet, $J = 7.2$ Hz, 3), 1.16 (d, $J = 7.2$ Hz 18); MS (ES+): 283.2 (M+H).

4.10. [[2-Chloro-1-(2-thienyl)ethenyl]oxy]tri-isopropylsilane 5d

As described for the preparation of [[2-chloro-1-(2-furyl)ethenyl]oxy]tri-isopropylsilane **5c**, 2-[1-tri-isopropylsilyloxy-vinyl]-thiophene **3c** (111.19 g, 0.396 mol) was treated with NCS (58.2 g, 0.426 mol) in THF (0.6 L) to afford 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-thiophene **5d** (140 g, 98%) as a viscous orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 1.9$ Hz, 1), 6.33 (m, 1), 6.30 (m, 1), 5.92 (s, 1), 1.32 (heptet, $J = 7.2$ Hz, 3), 1.14 (d, $J = 7.2$ Hz, 18).

4.11. 2-(Chloroacetyl)-thiophene 3d

As described for the preparation of 2-chloroacetyl furan **3c**, [1-tri-isopropylsilyloxy-2-chloro-vinyl]-thiophene **4c** (140 g, 0.389 mol), in CH_3CN (0.4 L) was treated with 48% aq HF (58 mL), in acetonitrile, to give 2-chloroacetylthiophene **3d** (48 g, 77%) as a light brown solid. The crude material was judged to be quite pure by ^{1}H NMR and HPLC and was used *as is* in the Noyori asymmetric reduction. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.81$ (m, 1), 7.76 (m, 1), 7.19 (m, 1), 4.62 (s, 2).

4.12. [[1-(3-Thienyl)ethenyl]oxy]tri-isopropylsilane 4e

As described for the preparation of [[1-(2-furyl)ethenyl]oxy]tri-isopropylsilane **4c**, 3-acetylthiophene (50 g, 0.396 mol) in anhydrous CH_2Cl_2 (Alrdich Sure Seal®, 600 mL) was treated with *i*-Pr_2NEt (1.18 mol, 3 equiv, 207 mL), TIPSOTf (0.436 mol, 1.1 equiv, 117.2 mL) to give the crude enol ether, 3-[1-tri-isopropylsilyloxy-vinyl]-thiophene **4e** (117 g) as a brown oil. This crude material was not further purified, but was immediately carried to the next step. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$ (m, 1), 7.20 (dd, $J = 4.8$, 1.6 Hz, 1), 6.99 (dd, $J = 6.7$, 4.9 Hz, 1), 4.79 (d, $J = 2.7$ Hz, 1), 4.33 (d, $J = 2.7$ Hz, 1), 1.31 (heptet, $J = 7.6$ Hz, 3), 1.20 (d, $J = 7.6$ Hz, 18).

4.13. [[2-Chloro-1-(3-thienyl)ethenyl]oxy]tri-isopropylsilane 5e

As described for the preparation of [[2-chloro-1-(2-furyl)ethenyl]oxy]tri-isopropylsilane **5c**, 3-[1-tri-isopropylsilyloxy-vinyl]-thiophene, **4e** (117 g, assumed 0.396 mol) was treated with NCS (52.87 g, 0.396 mol) to give 138 g of crude 3-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-thiophene **5e**. This crude material was not further purified, but was immediately carried to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.27$ (m, 1), 7.22 (m, 1), 7.01 (m, 1), 5.83–5.92 (1), 1.23–1.35 (m, 3), 1.10–1.22 (m, 18).

4.14. 3-(Chloroacetyl)-thiophene 3e

As described for the preparation of 2-chloroacetyl furan **3c**, 3-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-thiophene **5e** (138 g, assumed 0.396 mol) was treated with 48% aq HF (59 mL) in acetonitrile (0.5 L) to give 3-chloroacetylthiophene **3e** (54.6 g, 0.34 mol, 85%) as an amorphous pale yellow solid. The crude material was judged to be quite pure by ^{1}H NMR and HPLC and was used *as is* in the Noyori asymmetric reduction. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.18$ (m, 1), 7.60 (m, 1), 7.40 (m, 1), 4.61 (s, 2).

4.15. [[1-(2-Benzofuranyl)ethenyl]oxy]tri-isopropylsilane 4f

As described for the preparation of [[1-(2-furyl)ethenyl]oxy]tri-isopropylsilane **4c**, 2-acetyl benzofuran (32.03 g, 0.200 mol) was treated with (*i*-Pr)$_3$SiOTf (80 mL, 91.93 g, 0.30 mol) and (*i*-Pr)$_2$NEt (104 mL, 77.55 g, 0.60 mol) in CH_2Cl_2 (0.3 L) to give 2-[1-tri-isopropylsilyloxy-vinyl]-benzofuran **4f** (72.52 g, 100%) as an orange oil. This crude material was not further purified, but was immediately carried to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$ (d, $J = 7.6$ Hz, 1), 7.47 (d, $J = 8.1$ Hz, 1), 7.30 (m, 1), 7.23 (m, 1), 5.18 (d, $J = 1.7$ Hz, 1), 4.58 (d, $J = 1.7$ Hz, 1), 1.23–1.42 (3), 1.18 (d, $J = 7.3$ Hz, 18).

4.16. [[2-Chloro-1-(2-benzofuranyl)ethenyl]oxy]tri-isopropylsilane 5f

As described for the preparation of [[2-chloro-1-(2-furyl)ethenyl]oxy]tri-isopropylsilane **5c**, 2-[1-tri-isopropylsilyloxy-vinyl]-benzofuran **4f** (79.52 g, 0.2 mol) was treated with NCS (29.4 g, 0.22 mol) in THF (0.4 L) to afford 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-benzofuran **5f** (79.52 g, 100%) as a viscous yellow oil. This crude material was not further purified, but was immediately carried to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.62$ (m, 1), 7.52 (m, 1), 7.28 (m, 1), 7.27 (m, 1), 5.99 (s, 1), 1.20–1.36 (m, 3), 1.10–1.22 (18).

4.17. 2-(Chloroacetyl)-benzofuran 3f

As described for the preparation of 2-chloroacetyl furan **3c**, 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-benzofuran **5f** (79.52 g, 0.20 mol) was treated with 48% aq HF (40 mL) in CH_3CN to give 2-chloroacetylbenzofuran **3f** (23.32 g, 60%) as a powdery, tan solid. The crude material was judged to be quite pure by ^{1}H NMR and HPLC and was used *as is* in the Noyori asymmetric reduction. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 7.9$ Hz, 1), 7.68 (s, 1), 7.61 (d, $J = 8.4$ Hz, 1), 7.54 (m, 1), 7.37 (m, 1), 4.73 (s, 2); IR (diffuse reflectance) 2479 (w), 2412 (w), 2360 (w), 2338 (w), 2306 (w), 1694 (s), 1550 (s), 1271 (s), 1263 (s), 1255 (s), 1164 (s), 1023 (s), 752 (s), 743 (s), 716 (s) cm^{-1}; Anal. Calcd for $C_{10}H_7ClO_2$: C, 61.72; H, 3.63. Found: C, 61.92; H, 3.68.

4.18. [[1-(2-Thiazolyl)ethenyl]oxy]tri-isopropylsilane 4g

As described for the preparation of [[1-(2-furyl)ethenyl]oxy]tri-isopropylsilane **4c**, 2-acetyl thiazole (25 g, 0.196 mol) was treated with (*i*-Pr)$_3$SiOTf (66.26 g, 0.216 mol, 58.12 mL) and (*i*-Pr)$_2$NEt (76.22 g, 0.59 mol, 102.7 mL) in CH_2Cl_2 (0.35 L) to give 2-[1-tri-isopropylsilyloxy-vinyl]-thiazole **4g** (59.45 g) as a golden yellow liquid. This crude material was not further purified, but was immediately carried to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.80$ (d, $J = 3.2$ Hz, 1), 7.32 (d, $J = 3.2$ Hz, 1), 5.50 (d, $J = 1.9$ Hz, 1), 4.52 (d, $J = 1.9$ Hz, 1), 1.35 (heptet, $J = 7.2$ Hz, 3), 1.17 (d, $J = 7.2$ Hz, 18).

4.19. [[2-Chloro-1-(2-thiazolyl)ethenyl]oxy]tri-isopropylsilane 5g

As described for the preparation of [[2-chloro-1-(2-furyl)ethenyl]oxy]tri-isopropylsilane **5c**, 2-[1-tri-isopropylsilyloxy-vinyl]-thiazole **4g** (59.45 g, assumed 0.196 mol) was treated with NCS (29.37 g, 0.22 mol) in THF (0.35 L) to give 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-thiazole **5g** (69.61 g) as a yellow-orange semi-solid. This crude material was not further purified, but was immediately carried to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 3.2$ Hz, 1), 7.32 (d, $J = 3.2$ Hz, 1), 6.57 (s, 1), 1.37 (m, 3), 1.10–1.22 (18).

4.20. 2-(Chloroacetyl)-thiazole 3g

As described for the preparation of 2-chloroacetyl furan **3c**, 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-thiazole **5g** (69.61 g, assumed 0.196 mol) was treated with 48% aq HF (29 mL) in CH_3CN (0.3 L) to give 2-chloroacetylthiazole **3g** (32.95 g, 100%) as a light brown liquid, which solidified to a tan solid upon cooling. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.06$ (d, $J = 3.0$ Hz, 1), 7.79 (d, $J = 3.0$ Hz, 1), 5.00 (s, 2); IR (diffuse reflectance) 2476 (w), 2453 (w), 2430 (w), 2391 (w), 2371 (w), 1372, 1225, 957, 897, 793, 773, 710 (s), 704 (s), 655 (s), 630 (s) cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 161 (M^+, 33), 133 (15), 112 (base), 99 (15), 86 (61), 84 (86), 58 (33), 57 (34), 51 (37); HRMS (ESI) calcd for C_5H_4ClNOS+H 161.9780, found 161.9779; Anal. Calcd for C_5H_4ClNOS: C, 37.16; H, 2.49; N, 8.67. Found: C, 37.17; H, 2.51; N, 8.62.

4.21. [[1-(2-Pyrazinyl)ethenyl]oxy]tri-isopropylsilane 4h

As described for the preparation of [[1-(2-furyl)-ethenyl]oxy]tri-isopropylsilane **4c**, 2-acetylpyrazine (53.9 g, 0.441 mol) in CH_2Cl_2 (700 mL) was treated with *i*-Pr_2NEt (171.0 g, 1.32 mol, 3 equiv, 231 mL), and TIPSOTf

(148.6 g, 0.4851 mol, 1.1 equiv, 130.4 mL) to give the crude enol ether, 2-[1-tri-isopropylsilyloxy-vinyl]-pyrazine, **4h** (132.9 g) as a brown oil. This crude material was not further purified, but was immediately carried to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.97$ (s, 1H), 8.49 (s, 2), 5.66 (s, 1), 4.65 (s, 1), 1.36 (heptet, $J = 7.0$ Hz, 3), 1.14 (d, $J = 7.0$ Hz, 18); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 153.0$, 150.0, 143.8, 143.5, 141.1, 94.1, 18.1, 12.7; IR (liq.) 2945, 2892, 2867, 1619, 1471, 1329, 1151, 1019, 1006, 883, 847, 812, 742, 689, 682 cm^{-1}; MS (EI) *m/z* (rel. intensity) 278 (M^+, 8), 237 (13), 236 (43), 235 (base), 207 (12), 165 (9), 149 (42), 105 (21), 84 (10), 75 (8); HRMS (FAB) calcd for $C_{15}H_{26}N_2OSi+H_1$ 279.1892, found 279.1891.

4.22. [[2-Chloro-1-(2-pyrazinyl)ethenyl]oxy]tri-isopropylsilane 5h

As described for the preparation of [[2-chloro-1-(2-furyl)ethenyl]oxy]tri-isopropylsilane **5c**, 2-[1-tri-isopropylsilyloxy-vinyl]-pyrazine **4h** (132.9 g, assumed 0.441 mmol) in anhydrous THF (640 mL) was chlorinated with NCS (64.78 g, 0.485 mol, 1.1 equiv) to give the target chloroenol ether, 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-pyrazine, **5h** (169.45 g) as a brown oil. The crude material was not further purified, but was immediately carried into the next step. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.82$ (br s, 1), 8.51 (br s, 1), 8.49 (s, 1), 6.62 (s, 1), 1.33 (heptet, $J = 7.0$ Hz, 3), 1.13 (d, $J = 7.0$ Hz, 18); MS (CI) *m/z* (rel. intensity) 315 (22), 314 (15), 313 (MH^+, 74), 279 (53), 277 (23), 96 (13), 75 (9), 58 (14), 53 (10), 52 (base); HRMS (FAB) calcd for $C_{15}H_{25}ClN_2OSi+H_1$ 313.1503, found 313.1511.

4.23. 2-(Chloroacetyl)-pyrazine 3h

As described for the preparation of 2-chloroacetyl furan **3c**, 2-[1-tri-isopropylsilyloxy-2-chloro-vinyl]-pyrazine **5h** (169.45 g, assume 0.441 mol) was dissolved in acetonitrile (470 mL) and treated with 48% aqueous HF (73.54 mL, 4 equiv) to give 2-chloroacetylpyrazine **3h** (60.1 g, 0.384 mol, 87%) as a very light yellow solid. Mp: 82.6–83.8 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 9.23$ (s, 1), 8.80 (d, $J = 1.0$ Hz, 1), 8.64 (d, $J = 1.0$ Hz, 1), 5.01 (s, 2); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 191.4$, 148.4, 145.6, 143.5, 143.3, 46.4; IR (diffuse reflectance) 2944, 1716, 1400, 1390, 1318, 1226, 1170, 1163, 1053, 1019, 1000, 851, 807, 790, 685 cm^{-1}; MS (EI) *m/z* (rel. intensity) 156 (M^+, base), 128 (4), 122 (4), 108 (4), 107 (47), 88 (4), 87 (5), 86 (12).

4.24. Representative in situ catalyst preparation of [*S*,*S*]-ligand

$[RuCl_2(\eta^6$-*p*-cymene$)]_2$ (0.84 g, 1.37 mmol) and (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.0 g, 2.72 mmol) are combined in a 500 mL 1 N round bottom flask. Isopropanol (25 mL) and Et_3N (0.67 g, 6.66 mmol, 0.93 mL) are added, a reflux condenser is attached and the mixture is warmed under reflux for 1 h. The mixture is cooled to room temperature and concentrated in vacuo to furnish the catalyst as a brown powdery solid.

4.25. (*R*)-2-(1-Hydroxy-2-chloroethyl)-pyridine (*R*)-1b

To the catalyst prepared as described in the representative in situ catalyst preparation of [*S*,*S*]-ligand using $[RuCl_2(\eta^6$-*p*-cymene$)]_2$ (0.84 g, 1.37 mmol) and (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.0 g, 2.72 mmol, 1.78 mol % based upon ketone), isopropanol (25 mL), and Et_3N (0.67 g, 6.66 mmol, 0.93 mL), was added anhydrous DMF (225 mL), followed in order by 2-chloroacetylpyridine **3b** (23.88 g, 0.153 mol) and HCOOH/Et_3N (5:2, 55 mL). After ca. 2–3 min of stirring (room temperature) bubbles were apparent, emanating from the stirring vortex of the red-black solution. Reaction progress was monitored by reverse phase analytical HPLC, and after 75 min of stirring, the starting material had been consumed (95:5 NaH_2PO_4/H_3PO_4 buffered water/CH_3CN to 5:95, 17 min; retention time of starting chloroketone: 7.39 min, retention time of halohydrin 2.66 min). The reaction was quenched by adding MeOH (25 mL) and stirred for 5 min. The solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O/CH_2Cl_2 (4:1, 1.25 L), placed in a 3 L separatory funnel, washed with saturated aq $NaHCO_3$ (1.0 L), brine (1.0 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a red-orange oil, which was purified by chromatography on a column of silica gel (70 mm OD, 250 g 230–400 mesh, packed hexanes; compound applied in CH_2Cl_2/hexanes 60:40; eluted with hexanes/Et_2O 75:25 2 L; 65:35 2 L; 55:45 2 L; 350 mL fractions) using the flash technique. Fractions 9–16 were combined to afford 14.72 g (61%) of the halohydrin (*R*)-2-(1-hydroxy-2-chloroethyl)-pyridine (***R***)-**1b** as a pale yellow solid. Mp: 47–48 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.60$ (d, $J = 4.6$ Hz, 1), 7.77 (dt, $J = 7.6$, 1.6 Hz, 1), 7.58 (d, $J = 7.6$ Hz, 1), 7.30 (m, 1), 5.00 (t, $J = 5.4$ Hz, 1), 4.20 (br s, 1), 3.85 (m, 2); IR (neat): 3138, 3074, 3029, 3014, 2974, 2964, 2955, 2895, 2862, 2848, 2472, 2350, 2328, 2305, 2261 (w) cm^{-1}; EI-MS (70 eV): 160 (M^+, 35), 158 (M^+, 90), 122 (90), 106 (base); Anal. Calcd for C_7H_8ClNO: C, 53.35; H, 5.12; N, 8.89. Found: C, 53.23; H, 5.12; N, 8.82; $[\alpha]_D^{25} = -39$ (*c* 0.94, CH_2Cl_2). Chiral HPLC Analysis (Chiracel OJ): 98:2; 96% ee.

4.26. (*S*)-2-(1-Hydroxy-2-chloroethyl)-pyridine (*S*)-1b

As described for the preparation of (*R*)-2-(1-hydroxy-2-chloroethyl)-pyridine (***R***)-**1b**, the catalyst prepared from $[RuCl_2(\eta^6$-*p*-cymene$)]_2$ (0.84 g, 1.37 mmol), Et_3N (0.67 g, 6.66 mmol, 0.93 mL), and (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.0 g, 2.72 mmol, 1.78 mol % based upon ketone) and 2-chloroacetylpyridine **3b** (23.88 g, 0.153 mol), HCOOH/Et_3N (5:2, Fluka, 55 mL) in DMF (225 mL) gave a red-black viscous oil. The crude material was taken up in Et_2O/CH_2Cl_2 (4:1, 1.25 L), washed with saturated aq $NaHCO_3$ (1.0 L), brine (1.0 L), and dried over Na_2SO_4. Filtration and concentration in vacuo afforded the crude product as a red-orange oil, which was purified by chromatography on a column of silica gel (70 mm OD, 250 g 230–400 mesh, packed hexanes; compound applied in CH_2Cl_2/hexanes 60:40; eluted with hexanes/Et_2O 75:25 2 L; 65:35 2 L; 55:45 2 L; 350 mL fractions) using the flash technique. Fractions 11–17 were combined to afford

16.41 g (68%) of the target (*S*)-2-(1-hydroxy-2-chloroethyl)-pyridine (***S***)-**1b** as a pale yellow solid. Mp: 49–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.60$ (d, $J = 4.6$ Hz, 1), 7.77 (dt, $J = 7.6$, 1.58 Hz, 1), 7.58 (d, $J = 7.6$ Hz, 1), 7.30 (m, 1), 5.00 (t, $J = 5.4$ Hz, 1), 4.20 (br s, 1), 3.85 (m, 2); EI-MS (70 eV): 160 (M^+, 35), 158 (M^+, 90), 122 (90), 106 (base); IR (neat): 3085, 3075 (b), 2470 (w), 2350 (w), 2328 (w), 2305 (w), 2260 (w), 1109, 1077, 1006 (s), 783 (s), 762 (s), 720 (s), 640, 624 (s) cm^{-1}; Anal. Calcd for C_7H_8ClNO: C, 53.35; H, 5.12; N, 8.89; Cl, 22.50. Found: C, 53.27; H, 5.19; N, 8.81, Cl, 22.29; $[\alpha]_D^{25} = +62$ (*c* 0.94, methanol); Chiral HPLC Analysis (Chiracel OJ): 100:0; >99% ee.

4.27. (*R*)-2-(1-Hydroxy-2-chloroethyl)-furan (*R*)-1c

As described for the preparation of (*R*)-2-(1-hydroxy-2-chloroethyl)-pyridine (***R***)-**1b**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.99 g, 1.61 mmol), (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.18 g, 3.22 mmol, 2.10 mol % based upon ketone), *i*-PrOH (25 mL), and Et_3N (0.67 g, 6.66 mmol, 0.93 mL) was combined with 2-chloroacetylfuran **3c** (22.3 g, 0.154 mol) and HCOOH/Et_3N (5:2, 55 mL) in DMF (250 mL) to give the crude product as a red-orange oil (22.7 g) that was triturated with ether/pentane (10:90, 4 × 100 mL). The combined triturates were concentrated in vacuo (warning: the halohydrin is volatile) to furnish the desired halohydrin (*R*)-1-(2-furyl)-2-chloroethanol (***R***)-**1c** (16.03 g, 71%) as a pale yellow oil, in good purity as determined by HPLC and ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$ (m, 1), 6.37 (m, 2), 4.95 (br dd, $J = 11.8$, 5.4 Hz, 1), 3.85 (m, 2), 2.58 (d, $J = 5.0$ Hz, 1); IR (liq.) 3373, 2475, 2084, 2023, 1940, 1505, 1226, 1151, 1142, 1089, 1068, 1012, 884, 818, 742 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 146 (13), 148 (4), 146 (13), 98 (4), 97 (base), 95 (4), 94 (2), 69 (6), 65 (2), 41 (7), 39 (3); HRMS (EI) calcd for $C_6H_7ClO_2$ 146.0135, found 146.0133; $[\alpha]_D^{25} = -18$ (*c* 0.97, methanol); Chiral HPLC Analysis (Chiracel OJ): 99:1; 98% ee.

4.28. (*S*)-2-(1-Hydroxy-2-chloroethyl)-furan (*S*)-1c

As described for the preparation of (*S*)-2-(1-hydroxy-2-chloroethyl)-furan (***S***)-**1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.99 g, 1.61 mmol), (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.18 g, 3.22 mmol, 2.25 mol % based upon ketone), *i*-PrOH (25 mL), and Et_3N (0.67 g, 6.66 mmol, 0.93 mL) was combined with 2-chloroacetylfuran **3c** (20.6 g, 0.143 mol) and HCOOH/Et_3N (5:2, 51 mL) in DMF (250 mL). After 75 min, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min, then the reaction mixture was poured into ice-water (1 L) and the aqueous phase was saturated with salt. The mixture was extracted with ether (3 × 500 mL), and the combined organic layers were washed with saturated aq $NaHCO_3$ (0.5 L), brine (4 × 250 mL), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a red-orange oil (20.5 g) that was triturated with ether/pentane (10:90, 4 × 100 mL). The combined triturates were concentrated in vacuo (the halohydrin is volatile) to furnish the desired halohydrin (*S*)-1-(2-furyl)-2-chloroethanol (***S***)-**1c** (15.97 g, 76%) in good purity as determined by HPLC and ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$ (m, 1), 6.37 (m, 2), 4.95 (br dd, $J = 11.8$, 5.4 Hz, 1), 3.85 (m, 2), 2.58 (d, $J = 5.4$ Hz, 1); IR (diffuse reflectance) 1428 (b), 1422 (b), 1221 (b), 1205 (b), 1198 (b), 1166, 1096, 1021 (s), 953, 924, 883, 789 (s), 738, 714, 666 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 146 (M^+, 17), 129 (2), 98 (6), 97 (base), 95 (3), 94 (1), 69 (3), 41 (2); HRMS (EI) calcd for $C_6H_7ClO_2$ 146.0135, found 146.0136; $[\alpha]_D^{25} = +17$ (*c* 0.97, methanol); Chiral HPLC Analysis (Chiracel OJ): 1:99; 98% ee.

4.29. (*R*)-2-(1-Hydroxy-2-chloroethyl)-thiophene (*R*)-1d

As described for the preparation of (*R*)-2-(1-hydroxy-2-chloroethyl)-furan (***R***)-**1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.99 g, 1.61 mmol), (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.18 g, 3.22 mmol, 2.10 mol % based upon ketone), *i*-PrOH (25 mL), and Et_3N (0.67 g, 6.66 mmol, 0.93 mL) was combined with 2-chloroacetylthiophene **3d** (26 g, 0.16 mol) and HCOOH/Et_3N (5:2, 58 mL) in DMF (250 mL). After 75 min, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min and then the solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O (1.25 L), washed with saturated aq $NaHCO_3$ (1.0 L), brine (1.0 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a red-orange oil that was triturated with ether/pentane (10:90, 4 × 100 mL). The combined triturates were concentrated in vacuo to give a light brown oil (26 g), which was purified by chromatography on a 40 L Biotage® column (gradient from pentane to 5% ether/pentane, 50 mL fractions) to give 19.53 g (74%) of (***R***)-**1d** as a colorless, viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.30$ (dd, $J = 5.0$, 1.0 Hz, 1), 7.05 (m, 1), 7.01 (dd, $J = 5.0$, 1.0 Hz, 1), 5.17 (m, 1), 3.77 (m, 2), 2.79 (d, $J = 4.0$ Hz, 1); IR (liq.) 3384 (s, b), 2290 (w), 2161 (w), 2068 (w), 1996 (w), 1929 (w), 1426, 1257, 1069 (s), 1042, 852, 771, 706 (s), 677, 635 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 162 (M^+, 12), 113 (base), 110 (12), 109 (12), 97 (11), 88 (12), 86 (66), 85 (62), 84 (87), 51 (49); HRMS (EI) calcd for C_6H_7ClOS 161.9906, found 161.9904; % Water (KF): 0.60; Anal. Calcd for C_6H_7ClOS: C, 44.31; H, 4.34; Cl, 21.80; S, 19.71. Found: C, 43.94; H, 4.39; N, 0.20; Cl, 21.78; S, 19.42; Specific rotation $[\alpha]_D^{25} = -31$ (*c* 0.91, methylene chloride); Chiral HPLC (Chiracel OJ): 99:1; 98% ee.

4.30. (*S*)-2-(1-Hydroxy-2-chloroethyl)-thiophene (*S*)-1d

As described for the preparation of (*S*)-2-(1-hydroxy-2-chloroethyl)-furan (***S***)-**1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.99 g, 1.61 mmol), (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.18 g, 3.22 mmol, 2.10 mol % based upon ketone), *i*-PrOH (25 mL), and Et_3N (0.67 g, 6.66 mmol, 0.93 mL) was combined with 2-chloroacetylthiophene **3d** (26 g, 0.16 mol) and HCOOH/Et_3N (5:2, 58 mL) in DMF (250 mL). After 75 min, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min, then the reaction mixture was poured into ice-water (1 L) and the aqueous phase was saturated with salt. The mixture was extracted with ether

(3 × 500 mL), and the combined organic layers were washed with saturated aq $NaHCO_3$ (0.5 L), brine (4 × 250 mL), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a red-orange oil that was triturated with ether/pentane (10:90, 4 × 100 mL). The combined triturates were concentrated in vacuo to give a light brown oil (23 g), which was purified by chromatography on a 40 L Biotage® column (gradient from pentane to 5% ether/pentane, 50 mL fractions) to give 17.8 (68%) of (***S***)-**1d** as a colorless, viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.30$ (dd, $J = 5.0$, 1.0 Hz, 1), 7.05 (m, 1), 7.01 (dd, $J = 5.0$, 1.0 Hz, 1), 5.17 (m, 1), 3.76 (m, 2), 2.81 (d, $J = 4.0$ Hz, 1); IR (liq.) 3393 (s, b), 2290 (w), 2160 (w), 2080 (w), 1996 (w), 1426, 1257, 1069 (s), 1043, 852, 771, 738, 706 (s), 677, 635 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 162 (M^+, 10), 113 (94), 111 (10), 97 (12), 88 (23), 86 (87), 85 (76), 84 (base), 83 (14), 51 (65), 50 (21); HRMS (EI) calcd for C_6H_7ClOS 161.9906, found 161.9908; % Water (KF): 0.44; Specific rotation $[\alpha]_D^{25} = +30$ (*c* 0.90, methylene chloride); Chiral HPLC (Chiracel OJ): 1:99; 98% ee.

4.31. (*R*)-3-(1-Hydroxy-2-chloroethyl)-thiophene (*R*)-1e

As described for the preparation of (*R*)-2-(1-hydroxy-2-chloroethyl)-furan (***R***)-**1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (1.15 g, 1.87 mmol), (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.37 g, 3.74 mmol, 2.0 mol % based upon ketone), *i*-PrOH (25 mL), and Et_3N (0.67 g, 6.66 mmol, 0.93 mL) was combined with 3-chloroacetylthiophene **3e** (30 g, 0.187 mol) and HCOOH/Et_3N (5:2, 68 mL) in DMF (250 mL). After 2.5 h, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min, and the solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O/CH_2Cl_2 (4:1, 1.25 L), placed in a 3 L separatory funnel, washed with saturated aq $NaHCO_3$ (1.0 L), brine (1.0 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a red-orange oil that was triturated with ether/pentane (10:90, 4 × 100 mL). The combined triturates were concentrated in vacuo to give 20 g (66%) of (*R*)-3-(1-hydroxy-2-chloroethyl)-thiophene (***R***)-**1e** as a pale yellow, waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.26$ (m, 1), 7.22 (m, 1), 7.13 (m, 1), 5.01 (dd, $J = 8.2$, 3.5 Hz, 1), 3.80 (dd, $J = 13.2$, 3.5 Hz, 1), 3.71 (dd, $J = 13.2$, 8.2 Hz, 1); IR (diffuse reflectance) 2431 (w), 2394 (w), 2376 (w), 2354 (w), 2326 (w), 1420 (s), 1335 (s), 1251 (s), 1073 (s), 835 (s), 802 (s), 758 (s), 704 (s), 682 (s), 624 (s) cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 164 (3), 162 (M^+, 10), 115 (4), 114 (5), 113 (base), 111 (5), 109 (1), 86 (2), 85 (45), 45 (6); HRMS (EI) C_6H_7ClOS 161.9906, found 161.9901; $[\alpha]_D^{25} = -40$ (*c* 0.85, methylene chloride); Chiral HPLC (Chiracel OJ): 98:2, 96% ee.

4.32. (*S*)-3-(1-Hydroxy-2-chloroethyl)-thiophene (*S*)-1e

As described for the preparation of (*S*)-2-(1-hydroxy-2-chloroethyl)-furan (***S***)-**1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (1.15 g, 1.87 mmol), Et_3N (0.72 g, 7.16 mmol, 1.0 mL), (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.37 g, 3.74 mmol, 2.0 mol % based upon ketone), and *i*-PrOH (25 mL) was combined with 3-chloroacetylthiophene **3e** (30 g, 0.187 mol) and HCOOH/Et_3N (5:2, 68 mL) in DMF (250 mL). After 2.5 h, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min and the solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O/CH_2Cl_2 (4:1, 1.25 L), placed in a 3 L separatory funnel, washed with saturated aq $NaHCO_3$ (1.0 L), brine (1.0 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a red-orange oil that was triturated with ether/pentane (10:90, 4 × 100 mL). The combined triturates were concentrated in vacuo to give (*S*)-1-(3-thienyl)-2-chloroethanol (***S***)-**1e** (27.4 g, 63%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.26$ (m, 1), 7.22 (m, 1), 7.13 (m, 1), 5.01 (dd, $J = 8.2$, 3.5 Hz, 1), 3.80 (dd, $J = 13.2$, 3.5 Hz, 1), 3.71 (dd, $J = 13.2$, 8.2 Hz, 1); IR (liq.) 3393 (s, b), 2289 (w), 2163 (w), 2084 (w), 1933 (w), 1425, 1256, 1072 (s), 1017, 853 (s), 794 (s), 757 (s), 689 (s), 656, 646 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 164 (4), 162 (M^+, 10), 115 (4), 114 (6), 113 (base), 111 (3), 109 (2), 85 (57), 45 (16), 39 (5); HRMS (EI) calcd for C_6H_7ClOS 161.9906, found 161.9905; $[\alpha]_D^{25} = +40$ (*c* 1.01, methylene chloride); Chiral HPLC Analysis (Chiracel OJ): 1:99, 98% ee.

4.33. (*R*)-2-(1-Hydroxy-2-chloroethyl)-benzofuran (*R*)-1f

As described for the preparation of (*R*)-2-(1-hydroxy-2-chloroethyl)-furan (***R***)-**1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.57 g, 0.925 mmol), (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (0.56 g, 1.54 mmol, 3.0 mol % based upon ketone), *i*-PrOH (20 mL), and Et_3N (0.34 g, 3.33 mmol, 0.47 mL) was combined with 2-chloroacetylbenzofuran **3f** (10.0 g, 51.4 mmol) and HCOOH/Et_3N (5:2, 16 mL) in DMF (250 mL). After 2.5 h, the reaction was quenched by adding MeOH (15 mL), stirred for 5 min, then cast into water/ice (0.5 L), saturated with salt, and extracted with Et_2O (3 × 0.375 L). The combined organic phases were washed with saturated aq $NaHCO_3$ (0.75 L), dried (Na_2SO_4), and concentrated in vacuo to give the crude product as a brown oil that was triturated with ether/pentane (10:90, 4 × 100 mL). The combined triturates were concentrated in vacuo to give (*R*)-2-(1-hydroxy-2-chloroethyl)-benzofuran (***R***)-**1f** (9.42 g, 93%) as a light tan oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.58$ (d, $J = 8.2$ Hz, 1), 7.48 (d, $J = 8.2$ Hz, 1), 7.22–7.34 (2), 6.79 (s, 1), 5.11 (m, 1), 3.98 (m, 2); IR (liq.) 3371 (s, b), 2496, 2357 (w), 2336 (w), 2259 (w), 2135 (w), 1660 (s), 1453 (s), 1253 (s), 1172 (s), 1106 (s), 1092 (s), 1011 (s), 752 (s), 744 (s) cm^{-1}; HRMS (EI) calcd for $C_{10}H_9ClO_2$ 196.0291, found 196.0291; $[\alpha]_D^{25} = -31$ (*c* 1.03, chloroform); Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 60.83; H, 5.19; Chiral HPLC Analysis (Chiracel OJ): 99:1, 98% ee.

4.34. (*S*)-2-(1-Hydroxy-2-chloroethyl)-benzofuran (*S*)-1f

As described for the preparation of (*S*)-2-(1-hydroxy-2-chloroethyl)-furan (***S***)-**1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.57 g, 0.925 mmol), (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (0.56 g,

1.54 mmol, 3.0 mol % based upon ketone), *i*-PrOH (20 mL), and Et_3N (0.34 g, 3.33 mmol, 0.47 mL) was combined with 2-chloroacetylbenzofuran **3f** (10.0 g, 51.4 mmol) and HCOOH/Et_3N (5:2, 16 mL) in DMF (250 mL). After 2.5 h, the reaction was quenched by adding MeOH (15 mL), stirred for 5 min then cast into water/ice (0.5 L), saturated with salt, and extracted with Et_2O (3×0.375 L). The combined organic phases were washed with saturated aq $NaHCO_3$ (0.75 L), dried (Na_2SO_4), and concentrated in vacuo to give the crude product as a brown oil that was triturated with ether/pentane (10:90, 4×100 mL). The combined triturates were concentrated in vacuo to give (*S*)-2-(1-hydroxy-2-chloroethyl)-benzofuran (***S*)-1f** (9.26 g, 92%) as a light tan oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.58$ (d, $J = 8.2$ Hz, 1), 7.48 (d, $J = 8.2$ Hz, 1), 7.22–7.34 (2), 6.79 (s, 1), 5.10 (m, 1), 3.98 (m, 2); IR (liq.) 3367 (b), 1663 (s), 1454 (s), 1437, 1414, 1388, 1254 (s), 1171, 1095, 1011, 881, 808, 775, 753 (s), 664 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9ClO_2$ 196.0291, found 196.0295; $[\alpha]_D^{25} = +31$ (*c* 1.05, chloroform); Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 60.83; H, 5.19; Chiral HPLC Analysis (Chiracel OJ): 1:99, 98% ee.

4.35. (*R*)-2-(1-Hydroxy-2-chloroethyl)-thiazole (*R*)-1g

As described for the preparation of (*R*)-2-(1-hydroxy-2-chloroethyl)-furan (***R*)-1c**, the catalyst prepared from [$RuCl_2(\eta^6$-*p*-cymene)]$_2$ (1.15 g, 1.87 mmol), (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.38 g, 3.76 mmol, 2.0 mol % based upon ketone), *i*-PrOH (25 mL), and Et_3N (0.77 g, 7.72 mmol, 1.08 mL) was combined with 2-chloroacetylthiazole **3g** (30.42 g, 0.188 mol) and HCOOH/Et_3N (5:2, 68 mL) in DMF (250 mL). After 2.5 h, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min, and the solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O/CH_2Cl_2 (4:1, 1.25 L), washed with saturated aq $NaHCO_3$ (1.0 L), brine (1.0 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product (23.87 g) as a cream colored solid. Recrystallization from Et_2O gave 24.7 g (81%) (*R*)-2-(1-hydroxy-2-chloroethyl)-thiazole (***R*)-1g** as white needles. Mp: 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.8$ (d, $J = 3.0$ Hz, 1), 7.38 (d, $J = 3.0$ Hz, 1), 5.26 (m, 1), 4.08 (dd, $J = 11.0$, 4.0 Hz, 1), 3.90 (dd, $J = 11.0$, 4.0 Hz, 1), 3.63 (m, 1H); IR (diffuse reflectance) 3122 (s), 3103 (s), 2460 (w), 2387 (w), 2350 (w), 2306 (w), 2270 (w), 1507, 1195, 1151, 1088, 776 (s), 739 (s), 733 (s), 690 (s) cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 163 (M^+, 7), 163 (7), 115 (6), 114 (base), 86 (49), 85 (5), 84 (33), 59 (41), 58 (40), 57 (11), 51 (16); % Water (KF): 0.08; $[\alpha]_D^{25} = -33$ (*c* 0.92, methylene chloride); Anal. Calcd for C_5H_6ClNOS: C, 36.70; H, 3.70; N, 8.56; Cl, 21.67; S, 19.59. Found: C, 36.75; H, 3.64; N, 8.51; Cl, 21.22; S, 19.31; Chiral HPLC Analysis (Chiracel OJ): 98.5:1.5, 97% ee.

4.36. (*S*)-2-(1-Hydroxy-2-chloroethyl)-thiazole (*S*)-1g

As described for the preparation of (*S*)-2-(1-hydroxy-2-chloroethyl)-furan (***S*)-1c**, the catalyst prepared from [$RuCl_2(\eta^6$-*p*-cymene)]$_2$ (0.99 g, 1.50 mmol), (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.18 g, 3.00 mmol, 1.875 mol % based upon ketone), *i*-PrOH (25 mL), and Et_3N (0.66 g, 6.66 mmol, 0.93 mL) was combined with 2-chloroacetylthiazole **3g** (26.0 g, 0.16 mol) and HCOOH/Et_3N (5:2, 58 mL) in DMF (250 mL). After 2.5 h, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min, and the solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O/CH_2Cl_2 (4:1, 1.25 L), washed with saturated aq $NaHCO_3$ (1.0 L), brine (1.0 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a cream colored semi-solid. Trituration with ether/pentane (10:90, 4×100 mL) gave (*S*)-2-(1-hydroxy-2-chloroethyl)-thiazole (***S*)-1g** (17.8 g, 68%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.30$ (dd, $J = 5.0$, 1.0, Hz, 1), 7.05 (m, 1), 7.01 (dd, $J = 5.0$, 4.0 Hz, 1), 5.17 (m, 1), 3.76 (m, 2), 2.81 (d, $J = 4.0$ Hz, 1); IR (liq.) 3393 (s, b), 2290 (w), 2160 (w), 2080 (w), 1996 (w), 1426, 1257, 1069 (s), 1043, 852, 771, 738, 706 (s), 677, 635 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 162 (M^+, 10), 113 (94), 111 (10), 97 (12), 88 (23), 86 (87), 85 (76), 84 (base), 83 (14), 51 (65), 50 (21); HRMS (EI) calcd for C_6H_7ClOS 161.9906, found 161.9908; % Water (KF): 0.44; $[\alpha]_D^{25} = +30$ (*c* 0.90, methylene chloride); Chiral HPLC Analysis (Chiracel OJ): 1.5:98.5, 97% ee.

4.37. (*R*)-2-(1-Hydroxy-2-chloroethyl)-pyrazine (*R*)-1h

As described for the preparation of (*R*)-2-(1-hydroxy-2-chloroethyl)-furan (***R*)-1c**, the catalyst prepared from [$RuCl_2(\eta^6$-*p*-cymene)]$_2$ (0.245 g, 0.398 mmol), (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (0.292 g, 0.796 mmol, 2.5 mol % based upon ketone), *i*-PrOH (10 mL), and Et_3N (0.166 g, 1.64 mmol, 0.23 mL) was combined with 2-chloroacetylpyrazine **3h** (5.0 g, 31.9 mmol) and HCOOH/Et_3N (5:2, 13.75 mL) in DMF (55 mL). After 1 h, the reaction was quenched by adding MeOH (5 mL), stirred for 5 min, and the solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O/CH_2Cl_2 (4:1, 0.5 L), washed with saturated aq $NaHCO_3$ (0.5 L), brine (1.0 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a brown oil. The crude product was purified by chromatography on a Biotage® 40M column (ether/hexanes 3:1, 1 L; ether 1 L, 50 mL fractions). Fractions 9–23 were combined to afford (*R*)-2-(1-hydroxy-2-chloroethyl)-pyrazine (***R*)-1h** (3.55 g, 70%) as a pale yellow, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.80$ (s, 1), 8.56 (s, 2), 5.07 (t, $J = 5.0$ Hz, 1), 3.93 (dd, $J = 10.9$, 5.0 Hz, 1), 3.88 (dd, $J = 10.9$, 5.0 Hz, 1); IR (liq.) 3280 (s, b), 3064 (b), 2183 (w), 1996 (w), 1949 (w), 1405 (s), 1308, 1154 (s), 1092 (s), 1059 (s), 1019 (s), 856, 775, 663 (s), 649 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 161 (7), 159 (MH^+, 23), 124 (13), 123 (88), 122 (12), 109 (17), 108 (12), 107 (37), 106 (27), 96 (10), 52 (base); Specific rotation $[\alpha]_D^{25} = -40$ (*c* 1.16, methylene chloride); Anal. Calcd for $C_6H_7ClN_2O$: C, 45.44; H, 4.45; N, 17.66; Cl, 22.36. Found: C, 45.21; H, 4.48; N, 17.76; Cl, 22.00; Chiral HPLC Analysis (Chiralpak AD): 88:12, 76% ee.

4.38. (*S*)-2-(1-Hydroxy-2-chloroethyl)-pyrazine (*S*)-1h

As described for the preparation of (*S*)-2-(1-hydroxy-2-chloroethyl)-furan (***S*)-1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.98 g, 1.60 mmol), (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.17 g, 3.20 mmol 2.0 mol % based upon ketone), *i*-PrOH (24.7 mL), and Et_3N (0.664 g, 0.041 equiv, 6.56 mmol, 0.914 mL) was combined with 2-chloroacetylpyrazine **3h** (25.0 g, 0.16 mol) and HCOOH/Et_3N (5:2, 57.3 mL) in DMF (250 mL). After 3 h, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min, and the solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in CH_2Cl_2 (1.25 L), washed with saturated aq $NaHCO_3$ (1.0 L), brine (1.0 L), and dried ($MgSO_4$). Filtration through silica gel (pre-wet with diethyl ether), rinsing with diethyl ether, and concentration in vacuo afforded (1*S*)-2-chloro-1-pyrazin-2-ylethanol (***S*)-1h** (22.5 g, 88%) as a pale brown oil. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.80$ (s, 1), 8.56 (s, 2), 5.07 (t, $J = 5.0$ Hz, 1), 3.93 (dd, $J = 11.0$, 5.0 Hz, 1), 3.87 (dd, $J = 11.0$, 5.0 Hz, 1); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 154.2$, 144.2, 143.5, 143.3, 71.7, 48.9; IR (liq.) 3275, 3064, 2959, 2869, 1474, 1405, 1308, 1154, 1091, 1059, 1019, 856, 775, 663, 649 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 159 (MH^+, 22), 161 (7), 159 (22), 140 (13), 126 (5), 124 (14), 123 (20), 109 (11), 107 (24), 52 (base); HRMS (FAB) calcd for $C_6H_7ClN_2O+H_1$ 159.0325, found 159.0323; $[\alpha]_D^{25} = +40$ (*c* 0.61, ethanol); Anal. Calcd for $C_6H_7ClN_2O$: C, 45.44; H, 4.45; N, 17.66. Found: C, 45.23; H, 4.60; N, 17.38; Chiral HPLC Analysis (Chiralpak AD) 11:89, 78% ee.

4.39. (*R*)-2-Chloro-1-phenylethanol (*R*)-1i

As described for the preparation of (*R*)-2-(1-hydroxy-2-chloroethyl)-furan (***R*)-1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.99 g, 1.617 mmol), (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.18 g, 3.234 mmol, 2.0 mol % based upon ketone), *i*-PrOH (25 mL), and Et_3N (0.674 g, 6.66 mmol, 0.93 mL) was combined with 2-chloroacetophenone **3i** (25.0 g, 0.167 mol) and HCOOH/Et_3N (5:2, 58 mL) in DMF (250 mL). After 90 min, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min, and the solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O (1.25 L), washed with saturated aq $NaHCO_3$ (2×0.65 L), brine (0.65 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a brown oil. The crude product was purified by chromatography on a column of silica gel (70 mm OD; 250 g, 230–400 mesh, ether/hexanes 40:60, 1 L; 250 mL fractions) using the flash technique. Fractions 3–5 were combined to afford (*R*)-2-chloro-1-phenylethanol (***R*)-1i** (22.32 g, 88%) as a pale yellow, semi-solid. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.20$–7.50 (5), 4.92 (dd, $J = 8.7$, 3.5 Hz, 1), 3.77 (dd, $J = 11.2$, 3.5 Hz, 1), 3.67 (dd, $J = 11.2$, 8.7 Hz, 1), 2.49 (br s, 1); IR (diffuse reflectance) 3430 (b), 3419 (b), 3410 (b), 3390, 2497 (w), 2423 (w), 2351 (w), 2335 (w), 2312 (w), 1450, 1062 (s), 768, 750, 723 (s), 698 (s) cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 158 (14), 156 (M^+, 43), 108 (72), 107 (base), 88 (74), 86 (88), 84 (89), 79 (88), 78 (77), 77 (90), 51 (80), 50 (72); HRMS (ESI) calcd for $C_8H_9ClO+H_1$ 157.0420, found 157.0418; $[\alpha]_D^{25} = -50$ (*c* 0.87, methylene chloride) {lit.[24] $[\alpha]_D^{25} = -56.2$ (*c* 1.1, $CHCl_3$)}; Chiral HPLC Analysis (Chiracel OJ): 100:0, >99% ee.

4.40. (*S*)-2-Chloro-1-phenylethanol (*S*)-1i

As described for the preparation of (*S*)-2-(1-hydroxy-2-chloroethyl)-furan (***S*)-1c**, the catalyst prepared from $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.99 g, 1.617 mmol), (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.18 g, 3.234 mmol, 2.0 mol % based upon ketone), *i*-PrOH (25 mL), and Et_3N (0.674 g, 6.66 mmol, 0.93 mL) was combined with 2-chloroacetophenone **3i** (25.0 g, 0.167 mol) and HCOOH/Et_3N (5:2, 58 mL) in DMF (250 mL). After 90 min, the reaction was quenched by adding MeOH (25 mL), stirred for 5 min, and the solvents were removed in vacuo (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material was taken up in Et_2O (1.25 L), washed with saturated aq $NaHCO_3$ (2×0.65 L), brine (0.65 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a brown oil. The crude product was purified by chromatography on a column of silica gel (70 mm OD; 250 g, 230–400 mesh, ether/hexanes 40:60, 1 L; 250 mL fractions) using the flash technique. Fractions 3–5 were combined to afford (*S*)-2-chloro-1-phenylethanol (***S*)-1i** (21.55 g, 85%) as a pale yellow, semi-solid. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.20$–7.50 (5), 4.92 (dd, $J = 8.7$, 3.5 Hz, 1), 3.77 (dd, $J = 11.2$, 3.5 Hz, 1), 3.67 (dd, $J = 11.2$, 8.7 Hz, 1), 2.49 (br s, 1); IR (liq.) 3397 (b), 2337 (w), 1995 (w), 1956 (w), 1495, 1454, 1427, 1086, 1065 (s), 1029, 1013, 771, 723 (s), 698 (s), 615 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 158 (4), 156 (M^+, 13), 108 (24), 107 (base), 105 (23), 103 (16), 91 (20), 79 (83), 78 (36), 77 (79), 51 (48), 50 (21). HRMS (ESI) calcd for $C_8H_9ClO+H_1$ 157.0420, found 157.0419; $[\alpha]_D^{25} = +44$ (*c* 0.93, methanol) [lit.[25] $[\alpha]_D^{25} = +47$ (*c* 1.84, *c*-C_6H_{12})]; Chiral HPLC Analysis (Chiracel OJ): 0.6:99.4, 98.8% ee.

4.41. (*S*)-2-(1-Hydroxy-2-*N*-methylamino-ethyl)-pyridine (*S*)-2b

(*R*)-2-(1-Hydroxy-2-chloroethyl)-pyridine (***R*)-1b** (6.0 g, 38 mmol) and NaI (0.57 g, 3.8 mmol) were combined in a 500 mL, plastic coated, thick-walled bottle and covered with 2 M $MeNH_2$ in MeOH (0.19 L). The Teflon® stopper was wrapped in Teflon® tape and the bottle was sealed. Stirring was started, and the bottle was immersed in a 60 °C oil bath for 16 h. The yellow-brown mixture was cooled to room temperature and analyzed by analytical reverse phase HPLC, which indicated that the reaction was complete (retention time starting material = 2.66 min; retention time product = 1.22 min). Concentration in vacuo afforded the crude product as a yellow oil, which was treated with CH_2Cl_2/THF (0.25 L, 10:90) to give a yellow solution and a white precipitate. The precipitate was removed by filtration, rinsed with CH_2Cl_2/THF (10:90) and the combined filtrates were concentrated in vacuo to give a yellow-brown oil. The crude product was

purified by chromatography on a column of silica gel (70 mm OD, 250 g, 230–400 mesh; packed with CH_2Cl_2/MeOH 90:10; eluted with CH_2Cl_2/MeOH 90:10, 2 L, 500 mL fractions; CH_2Cl_2/MeOH/NH_4OH 89:10:1, 8 L, 500 mL fractions) using the flash technique. Fractions 10–18 were combined to provide 3.34 g (58%) of (*S*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***S*)-2b** as an amber oil. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.48$ (d, $J = 4.8$ Hz, 1), 7.78 (td, $J = 7.7$, 1.7 Hz, 1), 7.50 (d, $J = 7.7$ Hz, 1), 7.25 (dd, $J = 4.8$, 1.7 Hz, 1), 4.70 (dd, $J = 8.2$, 3.8 Hz, 1), 2.85 (dd, $J = 12.1$, 3.8 Hz, 1), 2.67 (dd, $J = 12.1$, 8.2 Hz, 1), 2.34 (s, 3); IR (liq.) 3291 (s, b), 3090 (s, b), 3066 (s, b), 2942 (s, b), 2890 (s, b), 2853 (s, b), 2799 (s), 1996 (w), 1918 (w), 1591 (s), 1473 (s), 1436 (s), 1070 (s), 772 (s), 751 (s) cm^{-1}; MS (CI) *m*/*z* (rel. intensity): 153 (MH^+, base), 151 (18), 137 (23), 135 (12), 122 (26), 110 (14), 108 (36), 106 (25), 80 (19), 52 (49). HRMS (ESI) calcd for $C_8H_{12}N_2O+H_1$ 153.1028, found 153.1046; Specific rotation $[\alpha]_D^{25} = -46$ (*c* 0.37, methylene chloride); Chiral HPLC Analysis (Chiralpak AD): >98:<2, >96% ee.

4.42. (*R*)-2-(1-Hydroxy-2-*N*-methylamino-ethyl)-pyridine (*R*)-2b

As described for the preparation of (*S*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***S*)-2b**, (*S*)-2-(1-hydroxy-2-chloroethyl)-pyridine (***S*)-1b** (6.0 g, 38 mmol) was treated with NaI (0.57 g, 3.8 mmol) and 2 M $MeNH_2$ in MeOH (0.19 L) in a sealed, thick-walled glass bottle at 60 °C to give (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***R*)-2b** (3.18 g, 54%) as an amber oil after flash chromatography. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.49$ (d, $J = 4.8$ Hz, 1), 7.79 (dt, $J = 7.7$, 1.7 Hz, 1), 7.52 (d, $J = 7.7$ Hz, 1), 7.25 (dd, $J = 4.8$, 1.7 Hz, 1), 4.75 (dd, $J = 8.4$, 3.67 Hz, 1), 2.90 (dd, $J = 12.1$, 3.7 Hz, 1), 2.67 (dd, $J = 12.1$, 8.4 Hz, 1), 2.32 (s, 3); IR (neat): 3279 (s, b), 3090 (s, b), 3064 (s, b), 3012 (s), 2943 (s, b), 2890 (s, b), 2851 (s, b), 2799 (s), 1996 (w), 1591 (s), 1473 (s), 1436 (s), 1070 (s), 772 (s), 751 (s) cm^{-1}; EI-MS (70 eV): 153 (M^+, base), 135 (18), 122 (20), 108 (62); HRMS (FAB): calcd for $C_8H_{12}N_2O+H$ 153.1028, found 153.1009; $[\alpha]_D^{25} = +49$ (*c* 0.36, CH_2Cl_2); Chiral HPLC Analysis (Chiralpak AD): <2:>98, >96% ee.

4.43. (*R*)-1-(2-Furyl)-2-chloroethanol–*N*-methylcarbamate (*R*)-7c

To (*R*)-1-(2-furyl)-2-chloroethanol (***R*)-1c** (5.0 g, 34.2 mmol) in dry CH_2Cl_2 (75 mL), cooled in an ice-water bath under nitrogen, was added Et_3N (1.38 g, 13.7 mmol, 0.4 equiv, 1.9 mL). The solution was allowed to stir for 5 min, then methylisocyanate (3.32 g, 58.21 mmol, 1.7 equiv, 3.46 mL) was added via syringe over 2 min. The ice was allowed to melt and the mixture to stir overnight, HPLC at 16 h indicated that the reaction was complete. The mixture was cast into Et_2O (0.3 L) and brine (0.3 L). The organic phase was reserved, the aq layer was extracted with Et_2O (2 × 0.2 L), then the combined organic phases were washed with brine (0.4 L), and dried (Na_2SO_4). Concentration in vacuo afforded the crude carbamate as a brown viscous oil that was purified by chromatography (Biotage® 40S column, EtOAc/hexanes 10:90 1 L, EtOAc/hexanes 20:80 1 L, 50 mL fractions). Fractions 25–42 afforded 4.56 g (65%) of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R*)-7c**, as a clear, pale yellow oil, which solidified to an ivory solid upon cooling. Mp: 26–27 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$ (m, 1), 6.45 (m, 1), 6.39 (m, 1), 5.97 (t, $J = 6.3$ Hz, 1), 4.79 (br s, 1), 3.89 (m, 2), 2.82 (d, $J = 4.9$ Hz, 3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.2$, 150.3, 143.3, 110.8, 109.9, 69.1, 44.0, 28.0. IR (liq.) 3352 (b), 2481 (w), 2192 (w), 1721 (s), 1537 (s, b), 1504, 1267 (s), 1252 (s), 1176, 1151 (s), 1131 (s), 1015, 1003, 772, 745 cm^{-1}; MS (EI) *m*/*z* (rel. intensity): 129 (96), 110 (base), 97 (83), 95 (65), 94 (89), 93 (57), 84 (58), 66 (61), 65 (85), 58 (80); MS (FAB) *m*/*z* (rel. intensity) 206 (1), 204 (MH^+, 6), 168 (9), 167 (12), 133 (12), 131 (33), 130 (8), 129 (base), 110 (29), 95 (8), 94 (25), 65 (8); HRMS (FAB) calcd for $C_8H_{10}ClNO_3+H_1$ 204.0427, found 204.0421; $[\alpha]_D^{25} = -102$ (*c* 0.98, chloroform); Chiral HPLC Analysis (Chiracel OJ): 1:99, 98% ee.

4.44. 5*S*-3-Methyl-5-(2-furyl)-2-oxazoldinone (*S*)-8c

To (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R*)-7c** (3.00 g, 14.77 mmol) in dry THF (25 mL), cooled in an ice-water bath under nitrogen, was added a solution of KO-*t*-Bu in THF (15 mL, 1 M, 15 mmol) over 15 min. The mixture was allowed to stir after the addition was complete and HPLC analysis suggested that the reaction was complete within 15 min. The mixture was cast into Et_2O (125 mL) and brine (125 mL) containing 1 N aq HCl (5 mL). The organic phase was separated and the aqueous layer was extracted with Et_2O (125 mL). The combined organic phases were washed with saturated aq $NaHCO_3$ (125 mL) and dried (Na_2SO_4). Concentration in vacuo afforded the crude oxazolidinone as a yellow oil. The crude material was purified by chromatography on a 40M Biotage® column (CH_2Cl_2, 1 L; Et_2O/CH_2Cl_2 2:98, 1 L; Et_2O/CH_2Cl_2 4:96, 1 L; Et_2O/CH_2Cl_2 6:94, 1 L; 50 mL fractions). Fractions 23–57 were combined to afford 2.29 g (93%) of 5*S*-3-methyl-5-(2-furyl)-2-oxazoldinone (***S*)-8c** as a pale yellow oil, which furnished an ivory solid upon cooling. Mp: 54–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.47$ (m, 1), 6.49 (m, 1), 6.41 (m, 1), 5.46 (m, 1), 3.78 (m, 2), 2.97 (s, 3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.9$, 148.1, 142.1, 109.0, 108.4, 65.9, 48.8, 29.4; IR (diffuse reflectance): 2491, 2464, 2436, 2402, 2351, 1743, 1503, 1439, 1344, 1307, 1267, 1154, 1138, 1029, 748 cm^{-1}; MS (EI) *m*/*z* (rel. intensity): 167 (M^+, 57), 123 (69), 108 (44), 95 (26), 94 (37), 86 (67), 84 (base), 81 (43), 53 (20), 51 (57); $[\alpha]_D^{25} = +109$ (*c* 0.97, CH_2Cl_2); Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.42; H, 5.48; N, 8.38.; Chiral HPLC Analysis (Chiracel OJ): 98.5:1.5; 97% ee.

4.45. *N*-Methyl (*S*)-1-(2-furyl)-2-aminoethanol (*S*)-2c

To (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S*)-8c** (8.0 g, 47.8 mmol) in a 500 mL 1 N RB flask was added 1 N aq KOH (240 mL, 0.24 mol, 5 equiv). The flask was equipped with a reflux condenser, placed under nitrogen, and then was immersed in a preheated (50 °C) oil bath. The mixture was allowed to stir and the (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S*)-8b** suspension slowly gave way to a clear

solution. After stirring for 3 h at 50 °C, HPLC analysis indicated that the reaction was complete. The mixture was cooled to room temperature and was cast into Et_2O/CH_2Cl_2 (95:5, 0.5 L) and the aq layer was saturated with salt. The organic phase was removed, the aq phase was extracted with Et_2O/CH_2Cl_2 (95:5, 2 × 0.5 L) and the combined organic phases were dried (Na_2SO_4). Concentration in vacuo afforded the desired *N*-methyl *S*-1-(2-furyl)-2-aminoethanol (***S***)-**2c** (6.64 g, 98%) as a pale orange oil that solidifies at freezer (-20 °C) temperatures. This material was determined to be analytically pure and was utilized without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.55$ (m, 1), 6.37 (m, 1), 6.25 (d, $J = 3.2$ Hz, 1), 4.59 (m, 1), 2.70 (m, 2), 2.25 (s, 3); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 157.3$, 141.9, 110.5, 105.9, 65.5, 56.5, 36.5; IR (liq.) 3318 (s, b), 3116 (s), 2945 (s, b), 2852 (s, b), 2801 (s), 2086 (b), 2019 (b), 1474 (s), 1453 (s), 1151 (s), 1065 (s), 1010 (s), 884 (s), 738 (s), 600 (s) cm^{-1}; MS (CI) *m*/*z* (rel. intensity): 142 (MH^+, base), 140 (13), 128 (4), 126 (18), 124 (20), 110 (3), 95 (4), 61 (11), 52 (13); HRMS (FAB) calcd for $C_7H_{11}NO_2$+H_1 142.0868, found 142.0871; % Water (KF titration): 0.64; $[\alpha]_D^{25} = -32$ (*c* 0.91, ethanol); Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.28; H, 7.98; N, 9.80; Chiral HPLC Analysis Chiral HPLC (Chirobiotic TAG): >98:<2, >96% ee.

4.46. (*R*)-1-(3-Pyridyl)-2-chloroethanol–*N*-methylcarbamate (*R*)-7a

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*R*)-2-chloro-1-(3-pyridyl)-ethanol **1a** (5 g, 31.7 mmol) was treated with Et_3N (1.27 g, 12.8 mmol, 1.76 mL) and methyl isocyanate (3.08 g, 54 mmol, 3.21 mL) to give 6.08 g (89%) of *R*-1-(3-pyridyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7a** as an amorphous white solid after chromatographic purification (Biotage® 40M, CH_2Cl_2, 1 L; CH_2Cl_2/MeOH 95:5, 1 L; 50 mL fractions). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.65$ (d, $J = 2.0$ Hz, 1), 8.59 (m, 1), 7.69 (d, $J = 8.0$ Hz, 1), 7.32 (m, 1), 5.93 (t, $J = 6.0$ Hz, 1), 5.16 (s, 1H), 3.79 (m, 2H), 2.81 (d, $J = 5.0$ Hz, 3); IR (diffuse reflectance) 3323 (s), 3311 (s, b), 2496 (w), 2413 (w), 2276 (w), 2229 (w), 2148 (w), 1722 (s), 1550 (s), 1284 (s), 1275 (s), 1256 (s), 1144 (s), 1010 (s), 746 (s) cm^{-1}; $[\alpha]_D^{25} = -33$ (*c* 0.92, chloroform); Anal. Calcd for $C_9H_{11}ClN_2O_2$: C, 50.36; H, 5.16; N, 13.05. Found: 50.33; H, 5.15; N, 12.96; Chiral HPLC Analysis (Chiracel OJ) 2.7:97.3, 94.6% ee.

4.47. 5*R*-3-Methyl-5-(3-pyridyl)-2-oxazoldinone (*R*)-8a

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, (*R*)-1-(3-pyridyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7a** (6.15 g, 28.7 mmol) was treated with KO-*t*-Bu (29 mL, 1.0 M in THF, 29 mmol) to give (5*R*)-3-methyl-5-(3-pyridyl)-2-oxazoldinone (***R***)-**8a** (3.62 g, 71%) as an ivory solid after chromatography (Biotage® 40M, gradient CH_2Cl_2 to CH_2Cl_2/MeOH 2:98, 50 mL fractions). Mp: 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.64$ (m, 2), 7.76 (m, 1), 7.38 (m, 1), 5.55 (t, $J = 8.0$ Hz, 1), 3.99 (t, $J = 9.0$ Hz, 1), 3.49 (m, 1), 2.96 (s, 3); IR (diffuse reflectance) 2477 (w), 2455 (w), 2401 (w), 2369 (w), 2353 (w), 1744 (s), 1728 (s), 1436 (s), 1263 (s), 1031 (s), 958 (s), 804 (s), 758 (s), 718 (s), 662 (s) cm^{-1}; MS (ES+): *m*/*z* (rel. intensity) 179 ($M+H^+$, 23); $[\alpha]_D^{25} = -39$ (*c* 1.00, chloroform); Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.66; N, 15.72. Found: C, 60.50; H, 5.73; N, 15.72; Chiral HPLC Analysis (Chirobiotic T, 98.8:1.2, 97.6% ee).

4.48. (*R*)-*N*-Methyl-1-(3-pyridyl)-2-aminoethanol (*R*)-2a

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, (5*R*)-3-methyl-5-(3-pyridyl)-2-oxazoldinone (***R***)-**8a** 3.62 g (20.3 mmol), and 1 N aq KOH (120 mL) were warmed in a 50 °C oil bath to give (*R*)-*N*-methyl-1-(3-pyridyl)-2-aminoethanol (***R***)-**2a** (2.11 g, 68%) as an amber oil. ^{1}H NMR (400 MHz, DMSO) $\delta = 8.53$ (d, $J = 2.0$ Hz, 1), 8.44 (m, 1), 7.73 (m, 1), 7.34 (m, 1), 5.42 (s, 1), 4.68 (m, 1), 2.61 (m, 2), 2.29 (s, 3); IR (diffuse reflectance) 3295 (s), 3086 (s, b), 3053 (s, b), 3034 (s), 2977 (s), 2888 (s, b), 2837 (s, b), 2793 (s), 2312 (b), 2264 (w), 2179 (w), 2115 (w), 2092 (w), 815 (s), 713 (s) cm^{-1}; MS (ESI, ES+): *m*/*z* (rel. intensity) 153 ($M+H^+$, 45); HRMS (ESI) calcd for $C_8H_{12}N_2O$+H_1 153.1028, found 153.1017; $[\alpha]_D^{25} = -67$ (*c* 0.93, methylene chloride); Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.77; H, 7.96; N, 18.18; Chiral HPLC Analysis (Chirobiotic T): <2:>98, >96% ee.

4.49. (*R*)-1-(2-Thienyl)-2-chloroethanol–*N*-methylcarbamate (*R*)-7d

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*R*)-2-chloro-1-(2-thienyl)-ethanol (***R***)-**1d** (5.54 g, 0.034 mol) was treated with Et_3N (1.37 g, 13.8 mmol, 1.9 mL) and methyl isocyanate (3.36 g, 59 mmol, 3.5 mL) to give 6.8 g (91%) of (*R*)-1-(2-thienyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7d** as a colorless oil after chromatographic purification (Biotage® 40L, gradient from 5% to 60% methylene chloride/pentane, 50 mL fractions). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.30$ (m, 1), 7.11 (m, 1), 7.00 (m, 1), 6.17 (m, 1), 4.77 (br s, 1), 3.82 (m, 2), 2.81 (d, $J = 4.9$ Hz, 3); IR (liq.) 3427, 3347 (b), 2270 (w), 2080 (w), 1713 (s), 1525, 1436, 1421, 1265 (s), 1250 (s), 1131, 948, 772, 707, 632 cm^{-1}; MS (CI) *m*/*z* (rel. intensity): 179 (42), 164 (23), 162 (59), 145 (18), 111 (77), 110 (31), 93 (68), 52 (27); HRMS (FAB) calcd for $C_8H_{10}ClNO_2S$+H 220.0199, found 220.0212; % Water (KF): 0.18; $[\alpha]_D^{25} = -61$ (*c* 0.73, methylene chloride); Anal. Calcd for $C_8H_{10}ClNO_2S$: C, 43.74; H, 4.59; N, 6.38. Found: C, 43.58; H, 4.43; N, 6.30; Chiral HPLC Analysis (Chiracel OJ): 3.8:96.2, 92.4% ee.

4.50. 5*S*-3-Methyl-5-(2-thienyl)-2-oxazoldinone (*S*)-8d

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, (*R*)-1-(2-thienyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7d** (6.4 g, 29 mmol) was treated with KO-*t*-Bu (30 mL, 1.0 M in THF, 30 mmol) to give (5*S*)-3-methyl-5-(2-thienyl)-2-oxazoldinone (***S***)-**8d** (4.9 g, 91%) as an ivory amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.36$ (dd, $J = 5.0$, 1.0 Hz, 1), 7.14 (m, 1), 7.01 (dd, $J = 5.0$, 4.0 Hz, 1), 5.70 (t, $J = 8.0$ Hz,

1H), 3.90 (m, 1), 3.61 (m, 1), 2.95 (s, 3); IR (diffuse reflectance) 2458 (w), 2428 (w), 2387 (w), 2320 (w), 2286 (w), 1748 (s), 1732 (s), 1504, 1436, 1289 (s), 1255 (s), 1130 (s), 1026 (s), 852 (s), 712 (s) cm^{-1}; MS (EI) *m/z* (rel. intensity) 183 (M^+, 90), 139 (64), 138 (base), 124 (19), 113 (16), 111 (29), 97 (59), 86 (17), 84 (24), 51 (15); HRMS (ESI) calcd for $C_8H_9NO_2S+H$ 184.0432, found 184.0430; $[\alpha]_D^{25} = +90$ (*c* 0.96, methylene chloride); Chiral HPLC Analysis (Chiracel OJ): 0.8:99.2, 98.4% ee.

4.51. (*S*)-*N*-Methyl-1-(2-thienyl)-2-aminoethanol (*S*)-2d

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, (5*S*)-3-methyl-5-(2-thienyl)-2-oxazoldinone (***S***)-**8d** (4.41 g, 24 mmol), and 1 N aq KOH (50 mL) were warmed in a 50 °C oil bath to give (*S*)-*N*-methyl-1-(2-thienyl)-2-aminoethanol (***S***)-**2d** (2.94 g, 85%) as an ivory, waxy, solid after trituration with pentane/ether (80:20, 100 mL). ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.26$ (m, 1), 6.98 (m, 2), 4.99 (m, 1), 2.89 (m, 2), 2.48 (s, 3); IR (diffuse reflectance) 3109 (s), 3095 (s), 3064 (s), 2985 (s), 2958 (s), 2938 (s), 2876 (s), 2835 (s), 2807 (s), 2735 (s, b), 2358, 2342 (b), 2328 (b), 2169 (w), 2117 (w) cm^{-1}; MS (EI) *m/z* (rel. intensity): 139 (74), 138 (33), 113 (42), 111 (62), 98 (50), 97 (base), 86 (64), 85 (86), 84 (73), 51 (51); % Water (KF): 0.18; $[\alpha]_D^{25} = -24$ (*c* 1.06, methylene chloride); Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.08; H, 7.09; N, 8.81; Chiral HPLC Analysis (Chirobiotic TAG): >99:<1, >98% ee.

4.52. (*R*)-1-(3-Thienyl)-2-chloroethanol–*N*-methylcarbamate (*R*)-7e

As described for the preparation of *R*-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*R*)-2-chloro-1-(3-thienyl)-ethanol (***R***)-**1e** (5.00 g, 30.7 mmol) was treated with Et_3N (1.24 g, 12.3 mmol) and methyl isocyanate (2.98 g, 52.3 mmol) to give 5.91 g (88%) of *R*-1-(3-thienyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7e** as a colorless oil after chromatographic purification (Biotage® 40M, gradient from CH_2Cl_2 to CH_2Cl_2/Et_2O 20:80, 45 mL fractions). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.40 (2), 7.09 (m, 1), 6.03 (m, 1), 4.82 (br s, 1), 3.82 (m, 2), 2.82 (d, $J = 4.9$ Hz, 3); IR (liq.) 3429, 3348 (b), 1711 (s), 1527 (s), 1420, 1263 (s), 1248 (s), 1135 (s), 1098, 796, 772, 693, 660, 646, 626 cm^{-1}; MS (CI) *m/z* (rel. intensity) 220 (MH^+, 5), 162 (23), 128 (13), 126 (10), 111 (14), 110 (15), 96 (20), 93 (65), 52 (base); $[\alpha]_D^{25} = -59$ (*c* 0.86, methylene chloride); Anal. Calcd for $C_8H_{10}ClNO_2S$: C, 43.74; H, 4.59; N, 6.38; Cl, 16.14; S, 14.59. Found: C, 43.81; H, 4.71; N, 6.37; Cl, 15.30; S, 14.48; Chiral HPLC Analysis (Chiracel OJ): 3.6:96.3, 92.8% ee.

4.53. (5*R*)-3-Methyl-5-(3-thienyl)-2-oxazoldinone (*R*)-8e

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, (*R*)-1-(3-thienyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7e** (5.39 g, 24.9 mmol) was treated with KO-*t*-Bu (25.5 mL, 1.0 M in THF, 25.5 mmol) to give (5*R*)-3-methyl-5-(3-thienyl)-2-oxazoldinone (***R***)-**8e** (3.69 g, 81%) as a pale yellow solid. Mp: 68–69 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (m, 1), 7.26 (m, 1), 7.00 (dd, $J = 5.0$, 1.3 Hz, 1), 5.47 (t, $J = 8.0$ Hz, 1), 3.81 (t, $J = 8.6$ Hz, 1), 3.42 (dd, $J = 8.6$, 7.2 Hz, 1), 2.85 (s, 3); IR (diffuse reflectance) 3096, 1749 (s), 1743 (s, b), 1501, 1435, 1408, 1307, 1264 (s), 1249, 1137 (s), 1030, 988, 856, 789, 761 cm^{-1}; MS (EI) *m/z* (rel. intensity) 183 (M^+, 84), 139 (base), 138 (48), 113 (42), 111 (69), 98 (64), 97 (86), 94 (51), 86 (44), 84 (57); HRMS (FAB) calcd for $C_8H_9NO_2S+H_1$ 184.0432, found 184.0426; $[\alpha]_D^{25} = +13$ (*c* 0.99, chloroform); Anal. Calcd for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.64; S, 17.50. Found: C, 52.33; H, 4.93; N, 7.60; S, 17.29; Chiral HPLC analysis (Chirobiotic T): 0:100, >99% ee.

4.54. (*R*)-*N*-Methyl-1-(3-thienyl)-2-aminoethanol (*R*)-2e

As described for the preparation of *N*-methyl *S*-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, 5*R*-3-methyl-5-(3-thienyl)-2-oxazoldinone (***R***)-**8e** (3.32 g, 18.1 mmol) and 1 N aq KOH (95 mL) were warmed in a 50 °C oil bath to give (*R*)-*N*-methyl-1-(3-thienyl)-2-aminoethanol (***R***)-**2e** (2.66 g, 93%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.31$ (m, 1), 7.24 (m, 1), 7.08 (dd, $J = 4.9$, 1.3 Hz, 1), 4.85 (dd, $J = 8.1$, 4.1 Hz, 1), 2.75–2.95 (2), 2.66 (br s, 3), 2.47 (s, 3); IR (liq.) 3315 (s, b), 3102 (s, b), 2973 (s), 2940 (s, b), 2887 (s, b), 2855 (s, b), 2799 (s), 1472 (s), 1450 (s), 1112 (s), 1066 (s), 853 (s), 836 (s), 787 (s), 652 (s) cm^{-1}; MS (CI) *m/z* (rel. intensity) 158 (MH^+, 81), 156 (7), 142 (5), 140 (7), 108 (6), 61 (9), 52 (base); HRMS (FAB) calcd for $C_7H_{11}NOS+H_1$ 158.0640, found 158.0636; $[\alpha]_D^{25} = -48$ (*c* 1.07, chloroform); Chiral HPLC analysis (Chirosil CH): 0:100, >99% ee.

4.55. (*R*)-1-(2-Benzofuranyl)-2-chloroethanol–*N*-methylcarbamate (*R*)-7f

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*R*)-2-(1-hydroxy-2-chloroethyl)-benzofuran (***R***)-**1f** (9.20 g, 46.8 mmol) was treated with Et_3N (1.89 g, 18.7 mmol) and methyl isocyanate (4.54 g, 79.5 mmol) to give 10.56 g (89%) of (*R*)-1-(2-benzofuranyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7f** as a white solid after chromatographic purification (Biotage® 40S, EtOAc/hexanes 20:80, 45 mL fractions). Mp: 75–77 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.57$ (d, $J = 7.8$ Hz, 1), 7.50 (d, $J = 8.2$ Hz, 1), 7.23–7.35 (2), 6.83 (s, 1), 6.11 (t, $J = 6.2$ Hz, 1), 4.85 (br s, 1), 3.99 (m, 2), 2.85 (d, $J = 4.9$ Hz, 3); IR (diffuse reflectance) 3374, 2495 (w), 2466 (w), 2367 (w), 2257 (w), 2240 (w), 1699, 1535 (s), 1251 (s), 1134 (s), 975 (s), 821 (s), 771 (s), 748 (s), 676 (s) cm^{-1}; $[\alpha]_D^{25} = -110$ (*c* 0.95, chloroform); Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52; Cl, 13.98. Found: C, 57,19.; H, 4.68; N, 5.61; Cl, 13.79; Chiral HPLC Analysis (Chiracel OJ): 1:99, 98% ee.

4.56. (5*S*)-3-Methyl-5-(2-benzofuranyl)-2-oxazoldinone (*S*)-8f

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, (*R*)-1-(2-benzofuranyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7f** (10.15 g, 40.0 mmol) was treated with KO-*t*-Bu (41 mL, 1.0 M in THF, 41 mmol) to give (5*S*)-3-methyl-5-(2-benzofuranyl)-2-oxazoldinone (***S***)-**8f** (4.86 g, 56%) as a tan solid after chromato-

graphic purification (flash, 70 mm OD; 400 g, 230–400 mesh, CH_2Cl_2 and gradient to CH_2Cl_2/EtOAc, 10:90, 325 mL fractions). Mp: 72–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 7.6$ Hz, 1), 7.50 (d, $J = 8.0$ Hz, 1), 7.35 (m, 1), 7.28 (m, 1), 6.83 (s, 1), 5.62 (m, 1), 3.87 (m, 2), 3.00 (s, 3); IR (diffuse reflectance) 2494 (w), 2463 (w), 2421 (w), 2388 (w), 2350 (w), 1754 (s), 1358 (s), 1255 (s), 1136 (s), 1018 (s), 966 (s), 919 (s), 806 (s), 765 (s), 757 (s) cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}NO_3$+H_1 218.0817, found 218.0816, $[\alpha]_D^{25} = +37$ (*c* 1.00, chloroform); Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.29; H, 5.15; N, 6.43; Chiral HPLC Analysis (Chiracel OJ): 4:96, 92% ee.

4.57. (*S*)-*N*-Methyl-1-(2-benzofuranyl)-2-aminoethanol (*S*)-2f

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, 5*S*-3-methyl-5-(2-benzofuranyl)-2-oxazoldinone (***S***)-**8f** (5.10 g, 23.5 mmol) and 1 N aq KOH (10 mL) in ethanol (75 mL) were warmed in a 50 °C oil bath to give (*S*)-*N*-methyl-1-(2-benzofuranyl)-2-aminoethanol (***S***)-**2f** (2.66 g, 93%) as a light tan solid. Mp: 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J = 7.6$ Hz, 1), 7.47 (d, $J = 8.2$ Hz, 1), 7.20–7.31 (2), 6.70 (s, 1), 4.93 (m, 1), 3.11 (dd, $J = 12.2$, 7.6 Hz, 1), 3.02 (dd, $J = 12.2$, 4.2 Hz, 1), 2.52 (s, 3); IR (diffuse reflectance) 3291 (s), 3061 (s), 3034 (s), 2943 (s), 2875 (s, b), 2852 (s, b), 2836 (s, b), 2802 (s), 2715 (s, b), 2700 (s, b), 2364 (b), 2342 (b), 2056 (w), 1983 (w), 1939 (w) cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{13}NO_2$+H_1 192.1024, found 192.1026; $[\alpha]_D^{25} = -30$ (*c* 1.02, chloroform); Chiral HPLC Analysis (Chirosil CH): 4:96, 92% ee.

4.58. (*R*)-1-(2-Thiazolyl)-2-chloroethanol–*N*-methylcarbamate (*R*)-7g

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*R*)-2-(1-hydroxy-2-chloroethyl)-thiazole (***R***)-**1g** (9.20 g, 46.8 mmol) was treated with Et_3N (1.31 g, 13 mmol) and methyl isocyanate (3.31 g, 58 mmol) to give 5.8 g (77%) of (*R*)-1-(2-thiazolyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7g** as a white solid, which was purified by recrystallization from ether/pentane. Mp: 74–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.82$ (m, 1), 7.37 (m, 1), 6.28 (m, 1), 4.97 (br s, 1), 4.11 (dd, $J = 11.8$, 4.1 Hz, 1), 4.02 (dd, $J = 11.8$, 6.3 Hz, 1), 2.88 (d, $J = 4.9$ Hz, 3); IR (diffuse reflectance) 3322 (s), 2403 (w), 2286 (w), 2214 (w), 2158 (w), 2099 (w), 1705 (s), 1556 (s), 1273 (s), 1142 (s), 955, 767, 738, 684 (s), 667 cm^{-1}; MS (CI) *m*/*z* (rel. intensity): 221 (MH^+, base), 164 (10), 129 (30), 114 (12), 112 (59), 66 (11), 52 (6); $[\alpha]_D^{25} = -17$ (*c* 1.10, methylene chloride); Anal. Calcd for $C_7H_9ClN_2O_2S$: C, 38.10; H, 4.11; N, 12.69. Found: C, 38.36; H, 4.12; N, 12.67; Chiral HPLC analysis (Chiracel OJ) 0:100, >99% ee.

4.59. *R*-1-(2-Pyrazinyl)-2-chloroethanol–*N*-methylcarbamate (*R*)-7h

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*R*)-2-(1-hydroxy-2-chloroethyl)-pyrazine (***R***)-**1h** (8.50 g, 53.6 mmol) was treated with Et_3N (2.17 g, 21.44 mmol) and methyl isocyanate (5.20 g, 91.11 mmol) to give 9.78 g (85%) of (*R*)-1-(2-pyrazinyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7h** as an ivory solid after chromatographic purification (Biotage® 40L, EtOAc/hexanes 50:75 and EtOAc/hexanes 40:60, 350 mL fractions). Mp: 55–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.69$ (br s, 1), 8.57 (m, 2), 6.06 (t, $J = 5.2$ Hz, 1), 4.90 (br s, 1), 4.02 (m, 2), 2.83 (d, $J = 4.9$ Hz, 3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.9$, 152.6, 144.8, 144.4, 144.0, 72.1, 45.7, 28.1; IR (diffuse reflectance) 3350 (s), 2495 (w), 2387 (w), 2351 (w), 2326 (w), 2211 (w), 1699 (s), 1550 (s), 1545 (s), 1419, 1269 (s), 1257 (s), 1186, 1133, 1019 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 216 (MH^+, 24), 159 (8), 141 (9), 140 (12), 124 (20), 123 (35), 109 (15), 108 (5), 107 (base); HRMS (ESI) calcd for $C_8H_{10}ClN_3O_2$+H_1 216.0540, found 216.0537; $[\alpha]_D^{25} = -29$ (*c* 1.01, methylene chloride); Anal. Calcd for $C_8H_{10}ClN_3O_2$: C, 44.56; H, 4.67; N, 19.49. Found: C, 44.81; H, 4.66; N, 19.32; Chiral HPLC analysis (Chiralpak AD): 91:9, 82% ee.

4.60. (*R*)-1-Phenyl-2-chloroethanol–*N*-methylcarbamate (*R*)-7i

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*R*)-2-(1-hydroxy-2-chloroethyl)-benzene (***R***)-**1i** (5.00 g, 31.9 mmol) was treated with Et_3N (1.27 g, 12.8 mmol) and methyl isocyanate (3.10 g, 54.2 mmol) to give 6.06 g (89%) of (*R*)-1-phenyl-2-chloroethanol–*N*-methylcarbamate (***R***)-**7i** as an ivory solid after chromatographic purification (Biotage® 40M, EtOAc/hexanes 5:95, 10:90, 15:85 and EtOAc/hexanes 40:60, 45 mL fractions). Mp: 75–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.15$–7.50 (5), 5.80 (m, 1), 3.72–4.10 (2), 2.56 (d, $J = 4.5$ Hz, 3); IR (diffuse reflectance): 3369 (s), 2486 (w), 2405 (w), 2339 (w), 2318 (w), 2287 (w), 1715 (s), 1532 (s), 1265 (s), 1246 (s), 1140 (s), 1018 (s), 953 (s), 728 (s), 627 (s) cm^{-1}; MS (CI) *m*/*z* (rel. intensity): 214 (MH^+, 16), 138 (4), 120 (5), 104 (5), 93 (18); $[\alpha]_D^{25} = -15$ (*c* 0.93, methylene chloride); Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.55. Found: C, 56.10; H, 5.57; N, 6.55; Chiral HPLC analysis (Chiracel OJ): 1:99, 98% ee.

4.61. (5*R*)-3-Methyl-5-phenyl-2-oxazoldinone (*R*)-8i

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, (*R*)-1-phenyl-2-chloroethanol–*N*-methylcarbamate (***R***)-**7i** (5.11 g, 23.9 mmol) was treated with KO-*t*-Bu (24.5 mL, 1.0 M in THF, 24.5 mmol) to give (5*R*)-3-methyl-5-phenyl-2-oxazoldinone (***R***)-**8i** (4.05 g, 96%) as an ivory solid after chromatographic purification (Biotage® 40M, CH_2Cl_2; CH_2Cl_2/EtOAc 98:2; CH_2Cl_2/EtOAc 90:10; 45 mL fractions). Mp: 75–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.50 (5), 5.49 (t, $J = 8.4$ Hz, 1), 3.93 (t, $J = 8.7$ Hz, 1), 3.46 (dd, $J = 8.7$, 7.5 Hz, 1), 2.94 (s, 3); IR (diffuse reflectance) 2960 (s), 2909 (s), 2499 (w), 2423 (w), 2400 (w), 2350 (w), 2342 (w), 1743 (s), 1729 (s), 1702 (s), 1433 (s), 1404 (s), 1026 (s), 951 (s), 703 (s) cm^{-1} MS (EI) *m*/*z* (rel. intensity): 177 (M^+, base), 133 (26), 132 (77), 117 (7), 105 (10), 91 (15), 84 (10), 77 (10),

51 (8); $[\alpha]_D^{25} = -41$ (*c* 0.90, chloroform); Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.66; H, 6.22; N, 7.87; Chiral HPLC analysis (Chirobiotic T): <1:>99, >98% ee.

4.62. (*R*)-*N*-Methyl-1-phenyl-2-aminoethanol (*R*)-2i

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, *R*-3-methyl-5-phenyl-2-oxazoldinone (***R***)-**8i** (3.32 g, 18.7 mmol) and 1 N aq KOH (95 mL) were warmed in a 50 °C oil bath to give (*R*)-*N*-methyl-1-phenyl-2-aminoethanol (***R***)-**2i** (2.70 g, 95%) as a colorless oil, which slowly crystallized. Mp: 47–48 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.41$–7.27 (m, 5H), 4.76 (dd, $J = 9.0$, 4.0 Hz, 1), 2.85 (dd, $J = 12.0$, 4.0 Hz, 1), 2.74 (dd, $J = 12.0$, 9.0 Hz, 1), 2.60 (br s, 2), 2.48 (s, 3); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 142.7$, 128.3, 127.4, 125.8, 71.4, 59.1, 35.8; IR (diffuse reflectance): 3317 (s), 3121 (s, b), 3105 (s, b), 3061 (s), 3037 (s), 2975 (s), 2953 (s), 2937 (s), 2904 (s), 2864 (s), 2839 (s), 2803 (s), 2779 (s, b), 756 (s), 701 (s) cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 152 (MH^+, base), 150 (13), 136 (6), 134 (15), 74 (3), 61 (4), 52 (7); HRMS (ESI) calcd for $C_9H_{13}NO+H_1$ 152.1075, found 152.1083; $[\alpha]_D^{25} = -38$ (*c* 0.66, EtOH); lit.[16] $[\alpha]_D^{25} = -40.7$ (*c* 1.3, EtOH); Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.45; H, 8.74; N, 9.23.

4.63. (*S*)-1-(3-Pyridyl)-2-chloroethanol–*N*-methylcarbamate (*S*)-7a

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*S*)-2-chloro-1-(3-pyridyl)-ethanol (***S***)-**1a** (5 g, 31.7 mmol) was treated with Et_3N (1.27 g, 12.8 mmol, 1.76 mL) and methyl isocyanate (3.08 g, 54 mmol, 3.21 mL) to give 6.10 g (90%) of (*S*)-1-(3-pyridyl)-2-chloroethanol–*N*-methylcarbamate (***S***)-**7a** as an amorphous white solid after chromatographic purification (Biotage® 40M, CH_2Cl_2, 1 L; CH_2Cl_2/MeOH 95:5, 1 L; 50 mL fractions). Mp: 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.65$ (m, 1), 8.59 (m, 1), 7.69 (m, 1), 7.32 (m, 1), 5.93 (m, 1), 5.16 (br s, 1), 3.79 (m, 2), 2.81 (d, $J = 5.2$ Hz, 3); IR (diffuse reflectance) 3323 (s), 3311 (s, b), 2496 (w), 2413 (w), 2276 (w), 2229 (w), 2148 (w), 1722 (s), 1550 (s), 1284 (s), 1275 (s), 1256 (s), 1144 (s), 1010 (s), 746 (s) cm^{-1}; MS (ESI+) *m*/*z* (rel. intensity): 215.1 (MH^+, base); $[\alpha]_D^{25} = +33$ (*c* 0.96, chloroform); Anal. Calcd for $C_9H_{11}ClN_2O_2$: C, 50.36; H, 5.16; N, 13.05. Found: C, 50.29; H, 5.18; N, 12.96; Chiral HPLC Analysis (Chiracel OJ): 98.3:1.7, 96.6% ee.

4.64. (5*S*)-3-Methyl-5-(3-pyridyl)-2-oxazoldinone (*S*)-8a

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, (*S*)-1-(3-pyridyl)-2-chloroethanol–*N*-methylcarbamate (***S***)-**7a** (6.15 g, 28.7 mmol) was treated with KO-*t*-Bu (29 mL, 1.0 M in THF, 29 mmol) to give (5*S*)-3-methyl-5-(3-pyridyl)-2-oxazoldinone (***S***)-**8a** (4.19 g, 83%) as an ivory solid after chromatography (Biotage® 40M, gradient CH_2Cl_2 to CH_2Cl_2/MeOH 2:98, 50 mL fractions). Mp: 84–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.64$ (m, 2), 7.76 (m, 1), 7.39 (m, 1), 5.55 (t, $J = 8.0$ Hz, 1), 3.99 (t, $J = 9.0$ Hz, 1), 3.48 (m, 1), 2.96 (s, 3); IR (diffuse reflectance) 2479 (w), 2455 (w), 2401 (w), 2369 (w), 2315 (w), 1748 (s), 1728 (s), 1436 (s), 1263 (s), 1031 (s), 958 (s), 804 (s), 758 (s), 718 (s), 662 (s) cm^{-1}; MS (ESI+): *m*/*z* (rel. intensity) 179 ($M+H^+$, 37); $[\alpha]_D^{25} = +40$ (*c* 0.91, chloroform); Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.66; N, 15.72. Found: C, 60.50; H, 5.73; N, 15.72; Chiral HPLC Analysis (Chirobiotic T): 1.7:98.3, 96.6% ee.

4.65. (*S*)-*N*-Methyl-1-(3-pyridyl)-2-aminoethanol (*S*)-2a

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, (5*S*)-3-methyl-5-(3-pyridyl)-2-oxazoldinone (***S***)-**8a** (4.19 g, 23.5 mmol) and 1 N aq KOH (120 mL) were warmed in a 50 °C oil bath to give *N*-methyl (*S*)-1-(3-pyridyl)-2-aminoethanol (***S***)-**2a** (2.43 g, 68%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.53$ (d, $J = 2.0$ Hz, 1), 8.44 (m, 1), 7.73 (m, 1), 7.34 (m, 1), 4.68 (m, 1), 2.61 (m, 2), 2.29 (s, 3); IR (diffuse reflectance) 3303 (s), 3295 (s), 3087 (s, b), 3053 (s), 3035 (s), 2977 (s), 2889 (s, b), 2840 (s, b), 2793 (s), 2311 (w), 2265 (w), 2178 (w), 2114 (w), 2092 (w), 713 (s) cm^{-1}; MS (ESI, ES+): *m*/*z* (rel. intensity) 153 ($M+H^+$, 39); HRMS (ESI) calcd for $C_8H_{12}N_2O+H_1$ 153.1028, found 153.1019; $[\alpha]_D^{25} = +39$ (*c* 0.83, EtOH, lit.,[17] $[\alpha]_D^{25} = +40.4$ (*c* 1.89 EtOH)); Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.39; H, 7.93; N, 18.00; Chiral HPLC Analysis (Chirobiotic T): 98.7:1.3, 97.4% ee.

4.66. (*S*)-1-(2-Furyl)-2-chloroethanol–*N*-methylcarbamate (*S*)-7c

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*S*)-2-chloro-1-(2-furyl)-ethanol (***S***)-**1c** (5.0 g, 34.2 mmol) was treated with Et_3N (1.38 g, 13.7 mmol, 0.4 equiv, 1.9 mL) and methyl isocyanate (3.32 g, 58.21 mmol, 1.7 equiv, 3.46 mL) to give 4.56 g (65%) of (*S*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***S***)-**7c** as a clear, pale yellow oil, which solidified to an ivory solid upon cooling, after chromatographic purification (Biotage® 40S, EtOAc/hexanes 10:90 1 L, EtOAc/hexanes 20:80 1 L, 50 mL fractions). Mp: 26–27 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$ (m, 1), 6.45 (m, 1), 6.39 (m, 1), 5.97 (t, $J = 6.3$ Hz, 1), 4.79 (br s, 1), 3.89 (m, 2), 2.82 (d, $J = 4.9$ Hz, 3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.2$, 150.3, 143.3, 110.8, 109.9, 69.1, 44.0, 28.0; IR (diffuse reflectance): 3365 (s), 3355 (s), 3344 (s, b), 3333 (s), 2477 (w), 2392 (w), 2197 (w), 2088 (w), 1727 (s), 1694 (s), 1550 (s), 1531 (s), 1518 (s), 1253 (s), 1248 (s) cm^{-1}; MS (CI) *m*/*z* (rel. intensity): 221 ($M+NH_4^+$, 3), 146 (7), 129 (6), 113 (5), 96 (base), 79 (53), 52 (33); % Water (KF): 0.13%; $[\alpha]_D^{25} = +94$ (*c* 1.02, CH_2Cl_2); Anal. Calcd for $C_8H_{10}ClNO_3$: C, 47.19; H, 4.95; N, 6.88; Cl, 17.41. Found: C, 46.99; H, 4.89; N, 6.85; Cl, 17.31; Chiral HPLC Analysis (Chiracel OJ): 99:1, 98% ee.

4.67. (5*R*)-3-Methyl-5-(2-furyl)-2-oxazoldinone (*R*)-8c

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, (*S*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***S***)-**7c** (3.00 g, 14.77 mmol) was treated with KO-*t*-Bu (15.5 mL, 1.0 M in THF, 15.5 mmol)

to give (5*R*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***R*)-8c** (2.29 g, 93%) as a pale yellow oil, which solidified to fine, pale yellow needles, after chromatography (Biotage® 40M, gradient CH_2Cl_2 to CH_2Cl_2/Et_2O 6:94, 50 mL fractions). Mp: 54–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.47$ (m, 1), 6.49 (m, 1), 6.41 (m, 1), 5.46 (m, 1), 3.78 (m, 2), 2.97 (s, 3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.9$, 148.1, 142.1, 109.0, 108.4, 65.9, 48.8, 29.4; IR (diffuse reflectance): 2492 (w), 2436 (w), 2402 (w), 2351 (w), 2304 (w), 1759 (s), 1743 (s), 1503 (s), 1439 (s), 1307, 1267 (s), 1154 (s), 1138 (s), 1029, 747 (s) cm^{-1}; MS (EI) *m*/*z* (rel. intensity): 167 (M^+, 71), 123 (base), 108 (76), 95 (43), 94 (59), 86 (45), 84 (64), 81 (70), 53 (28), 51 (50); $[\alpha]_D^{25} = +106$ (*c* 1.01, CH_2Cl_2); % Water (KF): 0.07%; Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.46; H, 5.39; N, 8.36; Chiral HPLC Analysis (Chiracel OJ): 1:99; 98% ee.

4.68. (*R*)-*N*-Methyl-1-(2-furyl)-2-aminoethanol (*R*)-2c

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S*)-2c**, (5*R*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***R*)-8c** (8.0 g, 47.8 mmol), and 1 N aq KOH (240 mL) were warmed in a 50 °C oil bath to give (*R*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***R*)-2c** (6.50 g, 96%) as a pale yellow oil, which solidified upon cooling. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.55$ (m, 1), 6.37 (m, 1), 6.25 (d, $J = 3.2$ Hz, 1), 4.59 (m, 1), 2.70 (m, 2), 2.25 (s, 3); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 157.3$, 141.9, 110.5, 105.9, 65.5, 56.5, 36.5; IR (liq.) 3318 (s, b), 3116 (s, b), 2945 (s, b), 2853 (s, b), 2801 (s), 2085 (b), 2019 (b), 1474 (s), 1452 (s), 1151 (s), 1065 (s), 1010 (s), 884 (s), 738 (s), 600 (s) cm^{-1}; MS (CI) *m*/*z* (rel. intensity): 142 (MH^+, base), 140 (13), 128 (4), 126 (18), 124 (20), 110 (3), 95 (4), 61 (11), 52 (13); MS (CI) *m*/*z* (rel. intensity): 159 ($M+NH_4^+$, 14), 142 (M+H, base), 126 (15), 124 (8), 112 (4), 74 (7), 69 (6), 61 (18); % Water (KF titration): 0.83%; $[\alpha]_D^{25} = +32$ (*c* 0.96, EtOH); Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.90; H, 7.83; N, 9.68; Chiral HPLC Analysis Chiral HPLC (Chirobiotic TAG): <2:>98, >96% ee.

4.69. (*S*)-1-(2-Thienyl)-2-chloroethanol–*N*-methylcarbamate (*S*)-7d

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R*)-7c**, (*S*)-2-chloro-1-(2-thienyl)-ethanol (***S*)-1d** (5.54 g, 34 mmol) was treated with Et_3N (1.38 g, 13.7 mmol, 0.4 equiv, 1.9 mL) and methyl isocyanate (3.36 g, 59 mmol, 3.5 mL) to give 6.87 g (92%) of (*S*)-1-(2-thienyl)-2-chloroethanol–*N*-methylcarbamate (***S*)-7d** as a clear, colorless oil, after chromatographic purification (Biotage® 40S, EtOAc/hexanes 10:90 1 L, EtOAc/hexanes 20:80 1 L, 50 mL fractions). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (m, 1), 7.11 (m, 1), 7.00 (m, 1), 6.17 (m, 1), 4.77 (br s, 1), 3.82 (m, 2), 2.81 (d, $J = 4.9$ Hz, 3); IR (diffuse reflectance): 3428, 3348 (b), 2954, 2193 (w), 1713 (s), 1526 (s), 1436, 1421, 1265 (s), 1250 (s), 1131 (s), 1095, 948, 772, 707 cm^{-1}; MS (CI) *m*/*z* (rel. intensity): 220 (MH^+, 1), 179 (39), 164 (27), 162 (75), 144 (22), 111 (93), 110 (28), 96 (25), 93 (75); HRMS (FAB) calcd for $C_8H_{10}ClNO_2S$+H 220.0199, found 220.0208; % Water (KF): 0.25%; $[\alpha]_D^{25} = +58$ (*c* 0.97, CH_2Cl_2); Anal. Calcd for $C_8H_{10}ClNO_2S$: C, 43.74; H, 4.59; N, 6.38. Found: C, 43.59; H, 4.39; N, 6.32; Chiral HPLC Analysis (Chiracel OJ): 98.5:1.5, 97% ee.

4.70. (5*R*)-3-Methyl-5-(2-thienyl)-2-oxazoldinone (*R*)-8d

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S*)-8c**, (*S*)-1-(2-thienyl)-2-chloroethanol–*N*-methylcarbamate (***S*)-7d** (6.4 g, 29 mmol) was treated with KO-*t*-Bu (30 mL, 1.0 M in THF, 30 mmol) to give (5*R*)-3-methyl-5-(2-thienyl)-2-oxazoldinone (***R*)-8d** (4.94 g, 91%) as an ivory amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.36$ (dd, $J = 5.0$, 1.0 Hz, 1), 7.14 (m, 1), 7.01 (dd, $J = 5.0$, 4.0 Hz, 1), 5.70 (t, $J = 8.0$ Hz, 1), 3.90 (m, 1), 3.61 (m, 1), 2.95 (s, 3); IR (diffuse reflectance) 2458 (w), 2428 (w), 2387 (w), 2320 (w), 2264 (w), 1732 (s), 1504, 1437, 1289, 1255 (s), 1129, 1026 (s), 950, 852, 712 (s) cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 183 (M^+, base), 139 (74), 138 (81), 124 (18), 113 (19), 111 (33), 98 (18), 97 (base), 86 (18), 84 (40); HRMS (ESI) calcd for $C_8H_9NO_2S$+H 184.0432, found 184.0435; $[\alpha]_D^{25} = -94$ (*c* 1.04, methylene chloride); Chiral HPLC Analysis (Chiracel OJ): >99:<1, >98% ee.

4.71. (*R*)-*N*-Methyl-1-(2-thienyl)-2-aminoethanol (*R*)-2d

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S*)-2c**, (5*R*)-3-methyl-5-(2-thienyl)-2-oxazoldinone (***R*)-8d** (4.63 g, 25 mmol), and 1 M aq KOH (100 mL) were warmed in a 50 °C oil bath to give (*S*)-*N*-methyl-1-(2-thienyl)-2-aminoethanol (***R*)-2d** (3.28 g, 90%) as an ivory, waxy, solid after trituration with pentane/ether (80:20, 100 mL). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.26$ (m, 1), 6.98 (m, 2), 4.99 (m, 1), 2.89 (m, 2), 2.48 (s, 3); IR (diffuse reflectance) 3319 (s), 3094 (s), 3074 (s), 3063 (s, b), 2980 (s), 2956 (s), 2909 (s), 2844 (s, b), 2809 (s), 2723 (s, b), 2359, 2169 (w), 2119 (w), 2069 (w), 1940 (w) cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 157 (M^+, 6), 139 (29), 138 (17), 113 (16), 111 (29), 97 (44), 88 (25), 86 (89), 85 (33), 84 (base), 51 (51); % Water (KF): 0.00; $[\alpha]_D^{25} = +26$ (*c* 1.05, methylene chloride); Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.31; H, 7.13; N, 8.84; Chiral HPLC Analysis (Chirobiotic TAG): <1:>99, >98% ee.

4.72. (*S*)-1-(3-Thienyl)-2-chloroethanol–*N*-methylcarbamate (*S*)-7e

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R*)-7c**, (*S*)-2-chloro-1-(3-thienyl)-ethanol (***S*)-1e** (5.00 g, 30.7 mmol) was treated with Et_3N (1.24 g, 12.3 mmol) and methyl isocyanate (2.98 g, 52.3 mmol) to give 5.91 g (88%) of (*S*)-1-(3-thienyl)-2-chloroethanol–*N*-methylcarbamate (***S*)-7e** as a colorless oil after chromatographic purification (Biotage® 40M, gradient from CH_2Cl_2 to CH_2Cl_2/Et_2O 20:80, 45 mL fractions). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.40 (2), 7.09 (m, 1), 6.03 (m, 1), 4.82 (br s, 1), 3.82 (m, 2), 2.82 (d, $J = 4.9$ Hz, 3); IR (liq.) 3430, 3349 (b), 2398 (w), 2192 (w), 1996 (w), 1713 (s, b), 1528 (s), 1420, 1264 (s), 1248 (s), 1135 (s), 796, 772, 660, 646 cm^{-1}; MS (CI) *m*/*z* (rel.

intensity) 220 (MH^+, 5), 162 (20), 128 (10), 126 (10), 111 (12), 110 (15), 93 (59), 89 (10), 52 (86); $[\alpha]_D^{25} = +57$ (*c* 0.73, methylene chloride); Anal. Calcd for $C_8H_{10}ClNO_2S$: C, 43.74; H, 4.59; N, 6.38; Cl, 16.14; S, 14.59. Found: C, 43.70; H, 4.68; N, 6.38; Cl, 15.53; S, 14.47; Chiral HPLC Analysis (Chiracel OJ): 98.5:1.5, 97% ee.

4.73. (5*S*)-3-Methyl-5-(3-thienyl)-2-oxazoldinone (*S*)-8e

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, (*S*)-1-(2-thienyl)-2-chloroethanol–*N*-methylcarbamate (***S***)-**7e** (5.39 g, 24.9 mmol) was treated with KO-*t*-Bu (25.5 mL, 1.0 M in THF, 25.5 mmol) to give (5*S*)-3-methyl-5-(3-thienyl)-2-oxazoldinone (***S***)-**8e** (3.80 g, 83%) as a pale yellow solid. Mp: 68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (m, 1), 7.26 (m, 1), 7.00 (dd, $J = 5.0$, 1.3 Hz, 1), 5.47 (t, $J = 8.0$ Hz, 1), 3.81 (t, $J = 8.6$ Hz, 1), 3.42 (dd, $J = 8.6$, 7.2 Hz, 1), 2.85 (s, 3); IR (diffuse reflectance) 3096 (s), 2483 (w), 2408 (w), 2350 (w), 2328 (w), 2253 (w), 1755 (s), 1733 (s), 1501 (s), 1439 (s), 1408 (s), 1264 (s), 1249 (s), 1137 (s), 1030 (s) cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 183 (M^+, 91), 139 (base), 138 (30), 113 (28), 111 (61), 98 (50), 97 (74), 94 (28), 86 (34), 84 (62); HRMS (ESI) calcd for $C_8H_9NO_2S+H_1$ 184.0432, found 184.0432; $[\alpha]_D^{25} = -14$ (*c* 1.05, chloroform); Anal. Calcd for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.64; S, 17.50. Found: C, 52.38; H, 5.05; N, 7.60; S, 17.33; Chiral HPLC analysis (Chirobiotic T): 98.5:1.5, 97% ee.

4.74. (*S*)-*N*-Methyl-1-(3-thienyl)-2-aminoethanol (*S*)-2e

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, 5*S*-3-methyl-5-(3-thienyl)-2-oxazoldinone (***S***)-**8e** (3.35 g, 18.2 mmol), and 1 N aq KOH (95 mL) were warmed in a 50 °C oil bath to give *N*-methyl *S*-1-(3-thienyl)-2-aminoethanol (***S***)-**2e** (2.79 g, 97%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.31$ (m, 1), 7.24 (m, 1), 7.09 (dd, $J = 4.9$, 1.3 Hz, 1), 4.85 (dd, $J = 8.1$, 4.1 Hz, 1), 2.75–2.95 (2), 2.66 (br s, 3), 2.47 (s, 3); IR (liq.) 3315 (s, b), 3102 (s, b), 2972 (s), 2941 (s, b), 2890 (s, b), 2857 (s, b), 2800 (s), 1996 (w), 1473 (s), 1451, 1066 (s), 853 (s), 836 (s), 787 (s), 652 (s) cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 158 (MH^+, base), 156 (9), 142 (8), 140 (19), 110 (10), 108 (18), 61 (43), 52 (75); HRMS (FAB) calcd for $C_7H_{11}NOS+H_1$ 158.0640, found 158.0628; $[\alpha]_D^{25} = +48$ (*c* 0.86, chloroform); Chiral HPLC analysis (Chirosil CH): 100:0, >99% ee.

4.75. (*S*)-1-(2-Benzofuranyl)-2-chloroethanol–*N*-methylcarbamate (*S*)-7f

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*R*)-2-(1-hydroxy-2-chloroethyl)-benzofuran (***S***)-**1f** (8.45 g, 43 mmol) was treated with Et_3N (1.74 g, 17.2 mmol) and methyl isocyanate (4.17 g, 73.1 mmol) to give 9.75 g (89%) of *S*-1-(2-benzofuranyl)-2-chloroethanol–*N*-methylcarbamate (***S***)-**7f** as a white solid after chromatographic purification (Biotage® 40S, EtOAc/hexanes 20:80, 45 mL fractions). Mp: 77–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$ (d, $J = 7.8$ Hz, 1), 7.49 (d, $J = 8.2$ Hz, 1), 7.23–7.35 (2), 6.83 (s, 1), 6.11 (t, $J = 6.2$ Hz, 1), 4.58 (br s, 1), 3.99 (m, 2), 2.85 (d, $J = 4.9$ Hz, 3); IR (diffuse reflectance) 3374, 1699, 1535 (s), 1251 (s), 1134 (s), 975 (s), 924, 821 (s), 814, 771 (s), 748 (s), 733, 676 (s), 626, 613 cm^{-1}; Specific rotation $[\alpha]_D^{25} = +101$ (*c* 0.85, chloroform); Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52; Cl, 13.98. Found: C, 57.04; H, 4.77; N, 5.55; Cl, 13.53; Chiral HPLC Analysis (Chiracel OJ): 99:1, 98% ee.

4.76. 5*R*-3-Methyl-5-(2-benzofuranyl)-2-oxazoldinone (*R*)-8f

As described for the preparation of 5*S*-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, *R*-1-(2-benzofuranyl)-2-chloroethanol–*N*-methylcarbamate (***S***)-**7f** (9.67 g, 38.1 mmol) was treated with KO-*t*-Bu (38.5 mL, 1.0 M in THF, 38.5 mmol) to give 5*R*-3-methyl-5-(2-benzofuranyl)-2-oxazoldinone (***R***)-**8f** 5.05 g (61%) as a tan solid after chromatographic purification (flash, 70 mm OD; 400 g, 230–400 mesh, CH_2Cl_2 and gradient to CH_2Cl_2/EtOAc, 10:90, 325 mL fractions). Mp: 68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 7.6$ Hz, 1), 7.50 (d, $J = 8.0$ Hz, 1), 7.35 (m, 1), 7.28 (m, 1), 6.83 (s, 1), 5.62 (m, 1), 3.87 (m, 2), 3.00 (s, 3); IR (diffuse reflectance) 1755 (s), 1495 (s), 1451 (s), 1410 (s), 1358 (s), 1340 (s), 1325 (s), 1255 (s), 1204 (s), 1135 (s), 1006 (s), 967 (s), 817 (s), 766 (s), 758 (s) cm^{-1}; $[\alpha]_D^{25} = -38$ (*c* 0.95, chloroform); Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.14; H, 5.07; N, 6.30; Chiral HPLC Analysis (Chiracel OJ): 96:4, 92% ee.

4.77. (*R*)-*N*-Methyl-1-(2-benzofuranyl)-2-aminoethanol (*R*)-2f

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, (5*R*)-3-methyl-5-(2-benzofuranyl)-2-oxazoldinone (***R***)-**8f** (4.89 g, 22.5 mmol), and 1 N aq KOH (10 mL) in ethanol (75 mL) were warmed in a 50 °C oil bath to give (*R*)-*N*-methyl-1-(2-benzofuranyl)-2-aminoethanol (***R***)-**2f** (3.97 g, 92%) as a light tan solid. Mp: 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.56$ (d, $J = 8.4$ Hz, 1), 7.47 (d, $J = 8.2$ Hz, 1), 7.20–7.31 (2), 6.70 (s, 1), 4.92 (m, 1), 3.10 (dd, $J = 12.2$, 7.6 Hz, 1), 3.02 (dd, $J = 12.2$, 4.2 Hz, 1), 2.51 (s, 3); IR (diffuse reflectance) 3291 (s), 3063 (s), 3051 (s), 2945 (s), 2932 (s), 2892 (s, b), 2877 (s, b), 2852 (s, b), 2840 (s, b), 2801 (s), 2721 (s, b), 2341 (w), 2119 (w), 2049 (w), 1939 (w) cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{13}NO_2+H_1$ 192.1024, found 192.1026; $[\alpha]_D^{25} = +31$ (*c* 1.05, chloroform); Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.71; H, 6.98; N, 7.16; Chiral HPLC Analysis (Chirosil CH): 96:4, 92% ee.

4.78. (*S*)-1-Phenyl-2-chloroethanol–*N*-methylcarbamate (*S*)-7i

As described for the preparation of (*R*)-1-(2-furyl)-2-chloroethanol–*N*-methylcarbamate (***R***)-**7c**, (*S*)-2-(1-hydroxy-2-chloroethyl)-benzene (***S***)-**1i** (5.00 g, 31.9 mmol) was treated with Et_3N (1.27 g, 12.8 mmol) and methyl isocyanate (3.10 g, 54.2 mmol) to give 6.06 g (89%) of (*S*)-1-phenyl-2-chloroethanol–*N*-methylcarbamate (***S***)-**7i** as an ivory solid after chromatographic purification (Biotage® 40M, EtOAc/hexanes 5:95, 10:90, 15:85 and EtOAc/hexanes

40:60, 45 mL fractions). Mp: 74–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.15$–7.50 (5), 5.80 (m, 1), 3.72–4.10 (2), 2.56 (d, $J = 4.5$ Hz, 3); IR (diffuse reflectance) 3370 (s), 1715 (s), 1693 (s), 1532 (s), 1264 (s), 1246 (s), 1140 (s), 1018 (s), 953 (s), 779, 773 (s), 731 (s), 697 (s), 628 (s), 617 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 214 (MH^+, 20), 120 (5), 104 (5), 102 (7), 93 (21), 89 (10); HRMS (FAB) calcd for $C_{10}H_{12}ClNO_2+H_1$ 214.0635, found 214.0636; $[\alpha]_D^{25} = +13$ (*c* 1.01, methylene chloride); Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.55. Found: C, 56.10; H, 5.57; N, 6.55; Chiral HPLC analysis (Chiracel OJ): 98.5:1.5, 97% ee.

4.79. (5*S*)-3-Methyl-5-phenyl-2-oxazoldinone (*S*)-8i

As described for the preparation of (5*S*)-3-methyl-5-(2-furyl)-2-oxazoldinone (***S***)-**8c**, (*S*)-1-phenyl-2-chloroethanol–*N*-methylcarbamate (***S***)-**7i** (5.06 g, 23.7 mmol) was treated with KO-*t*-Bu (24.2 mL, 1.0 M in THF, 24.2 mmol) to give (5*S*)-3-methyl-5-phenyl-2-oxazoldinone (***S***)-**8i** (3.49 g, 83%) as an ivory solid after chromatographic purification (Biotage® 40M, CH_2Cl_2; CH_2Cl_2/EtOAc 98:2; CH_2Cl_2/EtOAc 90:10; 45 mL fractions). Mp: 72–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.50 (5), 5.49 (t, $J = 8.4$ Hz, 1), 3.93 (t, $J = 8.7$ Hz, 1), 3.46 (dd, $J = 8.7$, 7.5 Hz, 1), 2.94 (s, 3); IR (diffuse reflectance) 2960 (s), 2907 (s), 1727 (s), 1702 (s), 1495 (s), 1433 (s), 1404 (s), 1337 (s), 1252 (s), 1026 (s), 1001 (s), 951 (s), 760 (s), 702 (s), 660 (s) cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 177 (M^+, 50), 133 (38), 132 (base), 105 (20), 91 (48), 86 (26), 84 (38), 78 (21), 77 (37), 51 (37). HRMS (ESI) calcd for $C_{10}H_{11}NO_2+H_1$ 178.0868, found 178.0880; Specific rotation $[\alpha]_D^{25} = +39$ (*c* 1.03, chloroform); Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.65; H, 6.25; N, 7.87; Chiral HPLC analysis (Chirobiotic T): 98:2, 96% ee.

4.80. (*S*)-*N*-Methyl-1-phenyl-2-aminoethanol (*S*)-2i

As described for the preparation of *N*-methyl *S*-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, (5*S*)-3-methyl-5-phenyl-2-oxazoldinone (***S***)-**8i** (3.32 g, 18.7 mmol) and 1 N aq KOH (95 mL) were warmed in a 50 °C oil bath to give (*R*)-*N*-methyl-1-phenyl-2-aminoethanol (***S***)-**2i** (2.59 g, 91%) as a colorless oil, which slowly crystallized. Mp: 45–46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.39$–7.27 (m, 5), 4.76 (dd, $J = 9.0$, 4.0 Hz, 1), 2.84 (dd, $J = 12.0$, 4.0 Hz, 1), 2.74 (dd, $J = 12.0$, 9.0 Hz, 1), 2.57 (br s, 2), 2.48 (s, 3); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 142.6$, 128.3, 127.5, 125.8, 71.3, 59.0, 35.8; IR (diffuse reflectance) 3316 (s), 3121 (s, b), 3105 (s, b), 3086 (s, b), 3061 (s, b), 3037 (s), 3003 (s, b), 2975 (s), 2951 (s), 2937 (s), 2905 (s, b), 2889 (s, b), 2864 (s, b), 2839 (s, b), 2804 (s) cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 152 (MH^+, base), 150 (13), 136 (6), 134 (15), 74 (3), 61 (4), 52 (7); HRMS (ESI) calcd for $C_9H_{13}NO+H_1$ 152.1075, found 152.1080; $[\alpha]_D^{25} = +39$ (*c* 0.83, EtOH; lit.,[17] $[\alpha]_D^{25} = +40.4$ (*c* 1.89 EtOH)); Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.34; H, 8.78; N, 9.21.

4.81. (*S*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-thiazole (*S*)-2g

As described for the preparation of (*S*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***S***)-**2b**, (*R*)-2-(1-hydroxy-2-chloroethyl)-thiazole (***R***)-**1g** (3.0 g, 18 mmol) was treated with NaI (0.28 g, 1.9 mmol) and 2 M $MeNH_2$ in MeOH (75 mL) in a sealed, thick-walled glass bottle at 60 °C to give (*S*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-thiazole (***S***)-**2g** (0.90 g, 31%) as an ivory oil, which solidified upon cooling to afford an ivory amorphous solid, after flash chromatography (50 mm OD; 100 g, 230–400 mesh, CH_2Cl_2; CH_2Cl_2/MeOH 95:5; CH_2Cl_2/MeOH saturated with NH_3 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.74$ (d, $J = 3.0$ Hz, 1), 7.29 (d, $J = 3.0$ Hz, 1), 5.02 (m, 1), 3.06 (m, 2), 2.46 (s, 3); IR (diffuse reflectance) 3270 (s), 3130 (s), 3079 (s), 2945 (s), 2925 (s), 2899 (s), 2865 (s), 2844 (s), 2677 (s, b), 2659 (s, b), 2364 (b), 2354, 2343, 2158 (b), 2086 (b) cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 159 (MH^+, base), 145 (16), 143 (28), 141 (13), 112 (18), 91 (17), 86 (27), 74 (16), 69 (18), 61 (58); HRMS (ESI) calcd for $C_6H_{10}N_2OS+H_1$ 159.0592, found 159.0589; % Water (KF): 0.18; $[\alpha]_D^{25} = -19$ (*c* 1.02, methylene chloride); Anal. Calcd for $C_6H_{10}N_2OS$: C, 45.55; H, 6.37; N, 17.70. Found: C, 45.39; H, 6.42; N, 17.40; Chiral HPLC Analysis (Chiracel OJ): >99: < 1, >98% ee.

4.82. (*R*)-2-(1-Hydroxy-2-*N*-methylamino-ethyl)-thiazole (*R*)-2g

As described for the preparation of (*S*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***S***)-**2b**, (*S*)-2-(1-hydroxy-2-chloroethyl)-thiazole (***S***)-**1g** (6.02 g, 36.8 mmol) was treated with NaI (0.56 g, 3.8 mmol) and 2 M $MeNH_2$ in MeOH (75 mL) in a sealed, thick-walled glass bottle at 60 °C to give (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-thiazole (***R***)-**2g** (2.08 g, 36%) as an ivory oil, which solidified upon cooling to afford an ivory amorphous solid, after flash chromatography (50 mm OD; 100 g, 230–400 mesh, CH_2Cl_2; CH_2Cl_2/MeOH 95:5; CH_2Cl_2/MeOH saturated with NH_3 95:5, 45 mL fractions). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.73$ (d, $J = 3.3$ Hz, 1), 7.32 (d, $J = 3.3$ Hz, 1), 5.31 (dd, $J = 8.0$, 3.8 Hz, 1), 4.46 (br s, 3), 3.31 (dd, $J = 12.3$, 3.8 Hz, 1), 3.16 (dd, $J = 12.3$, 8.0 Hz, 1), 2.64 (s, 3); IR (diffuse reflectance) 3270 (s), 3130 (s), 3079 (s), 2945 (s), 2925 (s), 2899 (s), 2865 (s), 2844 (s), 2677 (s, b), 2659 (s, b), 2364 (b), 2354, 2343, 2158 (b), 2086 (b) cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 159 (MH^+, base), 145 (20), 143 (29), 141 (15), 112 (11), 91 (17), 86 (27), 74 (16), 69 (18), 61 (58); HRMS (ESI) calcd for $C_6H_{10}N_2OS+H_1$ 159.0592, found 159.0582; Specific rotation $[\alpha]_D^{25} = 31$ (*c* 1.02, DMSO); Chiral HPLC Analysis (Chiracel OJ): <1:>99, >98% ee.

4.83. (5*R*)-3-Methyl-5-phenyl-2-oxazoldinone (*R*)-8h and (5*S*)-3-methyl-5-phenyl-2-oxazoldinone (*S*)-8i

To a solution of (±)-**1i** (38.9 g, 0.191 mol) in dichloromethane (700 mL) was added a suspension of carbonyldiimidazole (31.0 g, 0.191 mol) in dichloromethane (100 mL). The sides of the flask were washed down with dichloromethane (50 mL) and after 0.5 h, the reaction was determined to be complete by TLC analysis. The organic layer was extracted with saturated citric acid followed by H_2O. The dichloromethane layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The racemic material obtained (31.90 g, 0.180 mol, 94% yield)

required no further purification. A total of 53 g of racemic material was separated by chiral HPLC (Chirobiotic T column—7.5 cm × 50 cm) resulting in the isolation of 19.0 g of (***R***)-**8i** (>99% ee by chiral HPLC) and 15.6 g of (***S***)-**8i** (89% ee by chiral HPLC).

4.84. (*R*)-2-(1-Hydroxy-2-*N*-methylamino-ethyl)-pyrazine (*R*)-2h

As described for the preparation of (*S*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***S***)-**2b**, (*S*)-2-(1-hydroxy-2-chloroethyl)-pyrazine (***S***)-**1h** (11.8 g, 74.4 mmol, 76% ee) was treated with NaI (1.12 g, 7.44 mmol) and 2 M $MeNH_2$ in MeOH (375 mL) in a sealed, thick-walled glass bottle at 60 °C to give *N*-methyl (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyrazine (***R***)-**2h** (8.18 g, 72%) as a pale orange oil, which solidified upon cooling to afford a pale orange solid, after flash chromatography (70 mm OD; 500 g, 230–400 mesh, CH_2Cl_2; gradient to MeOH, 350 mL fractions). Mp: 78–81 °C; ^{1}H NMR (400 MHz, CD_3OD) $\delta = 8.79$ (s, 1), 8.58 (s, 1), 8.53 (s, 1), 5.00 (dd, $J = 8.0$, 4.0 Hz, 1), 3.15 (dd, $J = 12.0$, 4.0 Hz, 1), 3.05 (dd, $J = 12.0$, 8.0 Hz, 1), 2.55 (s, 3); ^{13}C NMR (75 MHz, CD_3OD) $\delta = 159.1$, 145.1, 144.6, 143.9, 71.5, 57.5, 35.6; IR (diffuse reflectance) 3270, 3195, 3183, 3165, 3056, 3014, 2984, 2946, 2903, 2876, 2852, 2796, 2695, 1398, 1020 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 154 (MH^+, 73), 138 (62), 136 (57), 124 (24), 111 (32), 109 (31), 107 (87), 95 (56), 61 (41), 52 (base); HRMS (FAB) calcd for $C_7H_{11}N_3O+H_1$ 154.0980, found 154.0973; $[\alpha]_D^{25} = +58$ (*c* 1.02, methanol); Chiral HPLC Analysis (Chiralpak AD): 11.5:88.5, 77% ee.

4.85. (5*R*)-3-Methyl-5-(2-pyrazinyl)-2-oxazoldinone (*R*)-8h

As described for the preparation of (5*R*)-3-methyl-5-phenyl-2-oxazoldinone (***R***)-**8i** and (5*S*)-3-methyl-5-phenyl-2-oxazoldinone (***S***)-**8i**, (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyrazine (***R***)-**2h** (3.66 g, 23.9 mmol) was treated with carbonyldiimidazole (4.26 g, 1.1 equiv, 26.2 mmol) to give (5*R*)-3-methyl-5-(2-pyrazinyl)-2-oxazoldinone (***R***)-**8h** (3.77 g, 88%) as a white solid after chromatographic purification using the flash technique (70 mm OD; 500 g 230–400 mesh, 98:2 dichloromethane, 250 mL fractions). This material was upgraded by chiral preparative HPLC (Chiralpak AD, 7.5 cm × 50 cm) to give 2.07 g (55%) of 5*R*-3-methyl-5-(2-pyrazinyl)-2-oxazoldinone (***R***)-**8h** with >96% ee. Mp: 113.5–114.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.84$ (s, 1), 8.62 (s, 1), 8.58 (s, 1), 5.62 (dd, $J = 9.0$, 6.9 Hz, 1), 4.02 (t, $J = 9.0$ Hz, 1), 3.80 (dd, $J = 9.0$, 6.0 Hz, 1), 2.94 (s, 3); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 157.4$, 153.2, 144.8, 144.1, 142.7, 72.2, 51.6, 31.1; IR (diffuse reflectance) 1749, 1420, 1409, 1362, 1255, 1247, 1136, 1059, 1052, 1027, 1017, 962, 871, 841, 759 cm^{-1}; MS (CI) *m*/*z* (rel. intensity) 180 (MH^+, 12), 197 (45), 180 (12), 138 (35), 137 (17), 136 (base), 122 (11), 107 (24), 96 (14), 95 (10), 58 (11); HRMS (FAB) calcd for $C_8H_9N_3O_2+H_1$ 180.0773, found 180.0781; $[\alpha]_D^{25} = +20$ (*c* 0.95, methylene chloride); Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.38; H, 5.03; N, 23.35; Chiral HPLC analysis (Chirobiotic T): <2:>98, >96% ee.

4.86. (*R*)-2-(1-Hydroxy-2-*N*-methylamino-ethyl)-pyrazine (*R*)-2h

As described for the preparation of (*S*)-*N*-methyl-1-(2-furyl)-2-aminoethanol (***S***)-**2c**, (5*R*)-3-methyl-5-(2-pyrazinyl)-2-oxazoldinone (***R***)-**8h** (1.51 g, 8.43 mmol), and 1 N aq KOH (95 mL) were warmed in a 50 °C oil bath to give *R*-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyrazine (***R***)-**2h** (1.02 g, 79%) as a colorless oil, which slowly crystallized. Mp: 84–85 °C; Specific rotation $[\alpha]_D^{25} = +66$ (*c* 0.95, methanol); Chiral HPLC analysis (Chiralpak AD): <3.5:96.5, >93% ee.

4.87. Pilot plant preparation of 4-(chloroacetyl)morpholine 10

A 400 L reactor was charged with 30 L water followed by 27.9 kg of 47% aqueous potassium carbonate and the line rinsed with 10 L of water while maintaining the temperature at less than 30 °C. The potassium carbonate solution was cooled to maintain the temperature between 0 and 5 °C. Morpholine (8.3 kg) was charged to the tank. The line was rinsed with 20 L of methylene chloride and a further 30 L of methylene chloride was added. The mixture was cooled to maintain the temperature between −2 and −6 °C. Chloroacetyl chloride (8.3 kg) was charged to a 200 L reactor and the line was rinsed in with 20 L of methylene chloride. With *vigorous* agitation and while maintaining −6 to 0 °C, using nitrogen pressure, the chloroacetyl chloride solution was transferred to the 100 L reactor over about 45 min. After the addition was complete the reaction mixture was warmed to 15 °C and stirred for 2 h at that temperature. The agitation was stopped and the phases allowed to settle for at least 30 min. The lower methylene chloride phase was transferred to a 200 L reactor. The aqueous phase was washed with 35 L of methylene chloride. The combined product solutions were concentrated to ~25 L volume using vacuum distillation. To this mixture was added 100 L of THF and the solution concentrated to ~30 L volume under vacuum. An additional 100 L of THF was added and the solution concentrated to ~40 L volume. The solution was cooled to maintain the temperature between 20 and 23 °C and packaged in a drum. GC indicated 96.6 area % **10** (rt = 9.56 min, column HP-1 30 m, Injector 250 °C, detector 250 °C, initial temp 40 °C, initial time 2 min, ramp 15 °C/min, final temp 275 °C); an analytical sample was prepared by concentrating the extracts from a similar reaction to dryness (103% yield); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 3.49$ (s, 2), 3.58 (m, 2), 3.67 (m, 4), 4.03 (s, 2). Sample for solids determination and GC showed an 84% weight yield of 10 corrected for purity.

4.88. Pilot plant preparation of 2-(chloroacetyl)-pyridine 3b

4.88.1. Grignard preparation. Isopropyl magnesium chloride (45 kg) in THF was charged to a 400 L reactor. The line was rinsed with 10 L of THF from a carboy and a further 15 L of THF was added. The solution was cooled to maintain the temperature between 20 and 23 °C. 2-Bromopyridine (14.5 kg) was charged to a 200 L reactor and the line rinsed with 10 L of THF from a carboy. The solution

of 2-bromopyridine was transferred to the Grignard solution in the 400 L reactor maintaining the temperature at less than 25 °C and rinsed with 10 L of THF. The mixture was stirred at 20–23 °C for at least 12 h, sampled for HPLC and repeated every 2 h until less than 3% 2-bromopyridine remained.

4.88.2. Adduct formation. All of the THF solution of **10** from the previous step was charged to a 200 L reactor and the mixture was cooled to −25 °C. The Grignard slurry from the 400 L reactor was transferred into the THF solution of 10 while maintaining the temperature at −25 to −20 °C. The Grignard slurry was rinsed with THF (10 L). The resultant slurry was stirred at −20 to −25 °C until the reaction was judged to be complete by HPLC.

4.88.3. Quench. Water (40 L) was charged to the 400 L reactor. Acetic acid (8.5 kg) was added to the water and rinsed with 10 L of water. MTBE (50 L) was then charged to the 400 L reactor and the mixture cooled to maintain the temperature between 0 and 5 °C. Using nitrogen pressure, the reaction was transferred from the 200 L reactor to the 400 L reactor while keeping the temperature at less than 10 °C. The phases were separated and the aqueous solution was washed with 50 L of MTBE. The organic phase was then washed with 50 L of 10% aq NaCl solution. Using vacuum distillation, the combined organics were concentrated to about 25 L volume, and 125 L of MTBE was added. The solution was concentrated to about 30 L and held for the next reaction. The solution was stored cold. Sampled solid determination showed 10.6 kg of **3b** in this solution. This was a 76% yield, while the expected yield was about 85%. No correction was made for the low yield in the reduction/aminolysis or salt formation steps.

4.89. Pilot plant preparation of (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (*R*)-2b

4.89.1. Reduction. To a 200 L reactor was charged 14.9 kg of formic acid, then 13.5 kg of triethylamine was slowly added to the formic acid, while maintaining the temperature from 5 to 30 °C. When the addition was complete, the cooling was adjusted to maintain at temperature at 15–25 °C.

To a 400 L reactor was charged 300 g of (1*R*,2*R*)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine, 250 g dichloro-(*p*-cymene)-ruthenium(II) dimer, and using a funnel 370 mL of TEA was charged. DMF (20 L) was added and the mixture stirred at 20–25 °C for 30 min. The solution of **3b** from above was added and rinsed in with 4 L MTBE. The 5:2 formic acid/triethylamine solution was transferred from the 200 L reactor to the 400 L reactor keeping the temperature less than 30 °C. By cooling the temperature was maintained at 20–30 °C and stirred for 1.5 h. HPLC (three drops reaction diluted in 1 mL methanol) showed no detectable **3b** (rt = 5.4 min) and 90.5 area % *S*-2-(1-hydroxy-2-chloroethyl)-pyridine (***S***)-**1b** (rt = 3.40 min) (Agilent HPLC 50:50 acetonitrile/0.1 M NH_4OAc, 1 mL/min, detection at 254 nm, 250 × 4.6 mm Zorbax RX-C8).

4.89.2. Aminolysis. Forty percent aqueous methylamine (116 kg) was charged to the 400 L reactor. The solution was cooled to maintain the temperature between 0 and 10 °C and 25.9 kg of 50% w/w sodium hydroxide was added while maintaining the temperature at 0–10 °C (minimal exotherm).

When the reduction was complete by HPLC the mixture was transferred into the aminolysis mixture while maintaining the temperature at −5 to 20 °C with full cooling and rinsed with 20 L of ethanol. The mixture was warmed to 10–20 °C and stirred for more than 12 h. Silica gel TLC (direct spot 475:35:4.8 CH_2Cl_2/MeOH/NH_4OH) showed complete conversion to (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***R***)-**2b** ($R_f = 0.30$). The reaction mixture was vacuum distilled to 25 L volume, then 25 L of ethanol was added and the solution concentrated to 25 L volume (repeated four more times). Then 25 L ethanol was added and the reaction mixture was cooled to maintain the temperature between 20 and 25 °C. The salts were filtered and washed with 15 L of ethanol. *S*-Naproxen (22.5 kg) was charged to the 400 L reactor and the ethanol solution was transferred onto the Naproxen. The mixture was stirred at a temperature of 20–25 °C until all turned into solution. The solution was seeded with 100 g and stirred at a temperature of 20–25 °C for 4–6 h and then cool to −25 to −20 °C for at least 18 h. The slurry was filtered and washed with −10 to 5 °C ethanol (20 L). The product was dried with heated nitrogen (50–70 °C) to give 13.5 kg of (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***R***)-**2b** (*S*)-Naproxen salt as a beige solid. Yield (49%) was based on 2-bromopyridine. HPLC rt = 6.4 min (enantiomer at rt = 1.44) (isocratic 900:100:1:1 heptane/ethanol/trifluoroacetic acid/triethylamine, 1 mL/min, 250 × 4.6 mm Chiralcel OD-H, detection at 254 nm); ee >98%. (Note: dissolved (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***R***)-**2b** *S*-Naproxen salt at 2 mg/mL in 90:10 ethanol/triethylamine for injection on HPLC to give rt (*S*-Naproxen) = 1.08; without triethylamine, (*S*)-Naproxen coelutes with (*R*)-2-(1-hydroxy-2-*N*-methylamino-ethyl)-pyridine (***R***)-**2b**.) ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.47$ (d, $J = 2.0$ Hz, 1), 7.73–7.78 (m, 3), 7.67 (s, 1), 7.50 (d, $J = 8.0$ Hz, 1), 7.41 (d, $J = 8.0$ Hz, 1), 7.25 (s, 2), 7.12 (dd, $J = 9.0$, 2.0 Hz, 1), 4.76 (dd, $J = 9.0$, 4.0 Hz, 1), 3.85 (s, 3), 3.68 (q, $J = 7.0$ Hz, 1), 2.97 (dd, $J = 12.0$, 4.0 Hz, 1), 2.74 (dd, $J = 12.0$, 9.0 Hz, 1), 2.49 (s, 1), 2.37 (s, 3), 1.40 (d, $J = 7.0$ Hz, 3); ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 176.72$, 162.59, 156.92, 148.34, 137.91, 136.66, 133.04, 129.04, 128.47, 126.79, 126.51, 125.36, 122.23, 120.29, 118.45, 105.72, 70.98, 56.57, 55.16, 45.99, 34.74, 19.03; $[\alpha]_D^{25} = +60$ (*c* 1.02, DMSO); Anal. Calcd for $C_8H_{12}N_2O{\cdot}C_{14}H_{14}O_3$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.06; H, 6.93; N, 7.28.

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