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Asymmetric Transfer Hydrogenation of C=O and C=N Bonds by Tethered Rh^{III} Catalysts

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

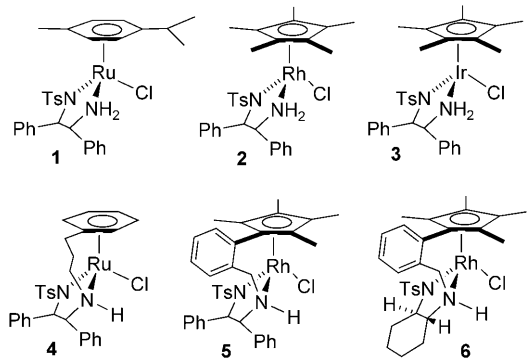
Abstract: Rh^{III} catalysts containing a tetramethylcyclopentadienyl group linked by a 'tether' to a tosylated diamine ligand have previously been reported by our group for the asymmetric transfer hydrogenation (ATH) of ketones. The extension of these catalysts to the asymmetric reduction of imines, as well as to more highly functionalized substrates is reported. In some cases, the catalysts give better *ee* values than other methods for these transformations at lower catalyst loadings. The introduction of a methoxy group into the tethering aryl ring does not negate the performance of the catalyst, thus opening up a route to supported derivatives.

Keywords: asymmetric catalysis · hydrogenation · imines · ketones · reduction

Introduction

Asymmetric transfer hydrogenation (ATH) of ketones and imines provides an efficient approach to the enantioselective synthesis of secondary alcohols and of imines, respectively.[1–10] Research into the development and application of new catalysts for this path has seen a sharp increase in recent years owing to the development of catalysts such as **1–3**, which are based on Ru^{II},[2,4] Rh^{III}, and Ir^{III} [3,4] metals complexed to a monotosylated-1,2-diamine ligand. This ligand is usually *N*-tosyl-1,2-diphenylethane diamine (TsDPEN) or *N*-tosyl-1,2-diaminocyclohexane (TsDAC) and is derived from the enantiomerically pure C2-symmetric diamine.[5] Following the initial reports by Noyori et al.,[2] complexes of this type have been the subject of extensive international research efforts and are now a popular choice for synthetic organic chemists working on total syntheses of complex organic molecules.[6–8] Whilst the combination of formic acid/triethylamine remains a popular one, the use of the catalysts in an aqueous system has also been demonstrated to be highly efficient and enantioselective and is often significantly faster.[9]

In addition to the many synthetic applications which have been reported for the Ru-, Rh-, or Ir-based TsDPEN/TsDAC-containing catalysts, extensive studies have been conducted into the mechanism by which they operate in reduction reactions.[10] These have revealed that the hydrogen-transfer process takes place through a six-atom cyclic transition state in which there is no direct contact between the substrate and the metal centre (i.e., an "outer sphere" mechanism).



Although the Ru^{II}-based catalyst system has been the one to enjoy the greatest level of mechanistic study and synthetic application,[2,4,6,8–10] the isoelectronic Rh^{III}- and Ir^{III}-based catalysts have been found to be efficient and highly enantio-

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selective for several classes of ketones and imines, and in some cases, they also give superior results.[3,4,7,8–10] The Rh^{III} catalyst system has been patented by Avecia and commercialized as the "CATHy" asymmetric transfer hydrogenation system.[3d,7a] Recently, both the Ru^{II}- and Ir^{III}-based catalysts **1** and **3** have also been demonstrated to be effective for asymmetric hydrogenation of ketones when used in methanol rather than isopropanol.[11]

During the course of our studies on asymmetric transfer hydrogenation, we recently reported on the synthesis and applications of a series of "tethered" catalysts related to complexes **1** and **2**. In particular, we have discovered that Ru^{II}-based catalyst **4**[12] and the Rh^{III}-based catalysts **5** and **6**[13] are highly stable, robust, and efficient catalysts for the reduction of a series of ketones with high *ee* values and high conversions. Catalyst **4**, for example, outpaces the non-tethered analogue and completes the reduction of ketones such as acetophenone within 100 min at S/C = 200 (RT), and can be used at S/C of up to 10000. Catalysts **5** and **6** are particularly well suited to the reduction of a range of ketones, including α-chloro ketones and tetralones, and are compatible with use in water. Given these promising results, we have extended our studies into the Rh^{III} catalysts. Herein, we report on the use of catalysts **5** and **6** in the asymmetric transfer hydrogenation of a series of more challenging ketones as well as to imines. We also report on the synthesis of a new derivative of catalyst **6** and on our attempts to prepare an Ir^{III} analogue of **5**.

Results and Discussion

We first elected to study the ability of catalysts (*R*,*R*)-**5** and (*R*,*R*)-**6**[14] in the asymmetric reduction of a representative series of imines. In particular, we selected imines **7**–**11** as representative targets, which have each previously been the subject of enantioselective reduction studies. Each imine was prepared by following established methods from amine starting materials. In the case of **7**, **9**, and **10**, the key synthetic step was the cyclization of the appropriate precursor amide in a Bischler–Napieralski reaction.[8] Imine **8** was formed by a condensation reaction between acetophenone and benzylamine, whilst **11** was prepared in one step by the addition of methyllithium to saccharin.[8j]

Reduction of imines **7**–**11** was studied by using catalysts **5** and **6**, and complete reduction was achieved in a short reaction time (as low as 15 min; Table 1) by using the dropwise formic acid method introduced by Blackmond et al.[8a] Absolute product configurations were established by comparison of the sign of optical rotation to that of known compounds, and the *ee* values were determined by using chiral GC analysis. In the case of **7**, product **12** was formed with rather higher *ee* values by using the TsDPEN catalyst **5** than with the cyclohexyl-based catalyst **6**. This observation was mirrored in the reductions of the related cyclic imines **9** and **10** with an *ee* value of 96% being recorded for product **15**, which compares favorably with other catalysts that have been previously employed in this process.[8] By using the untethered analogue of **5**, product **12** was formed in 90% *ee*.[8c] The reduction of the acyclic imine **8** gave a product of 44% *ee* by using catalyst **6**; although low, this represents an improvement over the result reported (8.4% *ee*) for related catalysts with this challenging substrate.[8c] The reduction of imine **11** was disappointing, however, with the *ee* values of product **16** being just 19 and 8%, respectively, by using catalysts **5** and **6**. This was quite unexpected as the untethered complexes are known to reduce this substrate in 68% *ee*.[8c] The absolute sense of reduction mirrored those achieved by untethered catalysts, and the switch in configuration (and face to which hydrogen is delivered) reflects previous experience and reported results with other ATH catalysts.[8]

We have also extended the ketone reduction capabilities of our catalysts to substrates containing a more complex and challenging set of functional groups. Two examples are reported herein, the first being **17**, which was prepared and re-

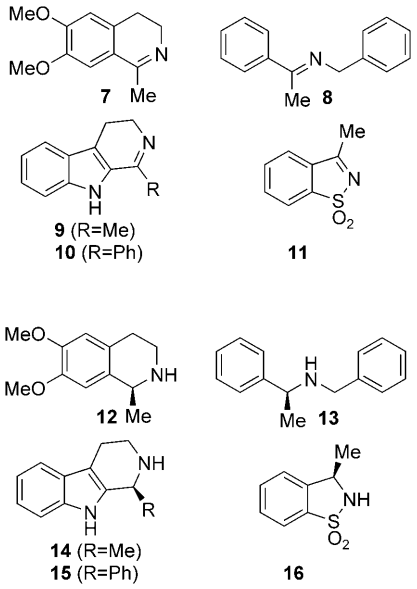


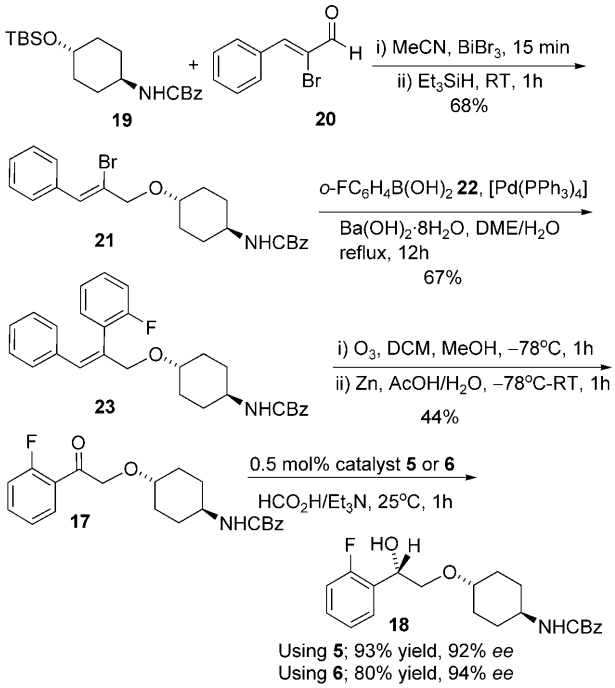
Table 1. Asymmetric transfer hydrogenation of imines **7**–**11** by using Rh^{III} catalysts (*R*,*R*)-**5** and (*R*,*R*)-**6**.[a]

Imine[a]	Catalyst	*t*	Conv. [%]	Yield [%][b]	*ee* [%][c,d]	*R*/*S*[e]
7	**5**	15 min	100	72	87	*S*
7	**6**	15 min	100	71	51	*S*
8	**6**	15 min	100	70	44	*S*
9	**5**	15 min	100	69	88	*S*
9	**6**	15 min	100	65	32	*S*
10	**5**	15 min	100	69	96	*S*
10	**6**	15 min	100	66	79	*S*
11	**5**	1 h	100	74	19	*R*
11	**6**	1 h	100	69	8	*R*

[a] S/C = 200, in HCO_2H/Et_3N (5:2), [imine] = 0.54 M, dichloromethane (DCM), 25 °C. [b] yields of isolated products (no major byproducts formed) [c] *ee* values were determined by chiral HPLC or GC. [d] Racemic standards of each amine product were prepared by using sodium borohydride to reduce the imine. [e] Determined by comparison of sign of optical rotation to a reported example; **12**,[8m] **13**,[8c] **14**,[8m] **15**,[8m] **16**.[8m]

duced to the potential drug development candidate **18** with high *ee* values by Tellers et al.[6e] The screening of several asymmetric hydrogenation (AH) catalysts led to the identification of a ruthenium(phosphinoferrocenyl)oxazoline catalyst that gave **18** in up to 93% *ee*. In their tests on asymmetric transfer hydrogenation catalysts for this application, it was found that the *p*-cymene/Ru catalyst **1** gave a reductive product in up to 86% *ee* (6 mol% catalyst) and the Rh^{III}-based catalyst gave a product of only 64% *ee* (10 mol% catalyst). Our experience suggested that the tethered complexes may show improved activities and we therefore elected to test catalysts (*R*,*R*)-**5** and (*R*,*R*)-**6** for this application.

The synthesis of **17** proved surprisingly elusive and our initial attempts to make it from a combination of the appropriate α-bromoketone and cyclohexanol precursors failed. The successful sequence for the preparation of **17** is shown in Scheme 1 and follows the method reported in a patent.[15]



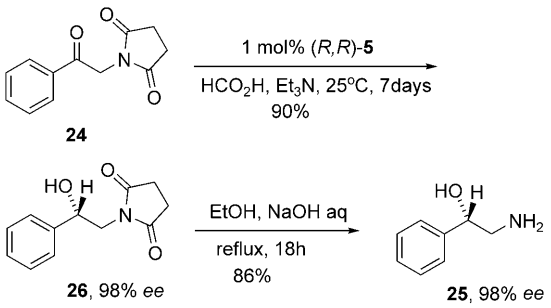
Scheme 1. Preparation and asymmetric transfer hydrogenation of **17**. Bz = benzyl.

The reaction of the benzyloxycarbonyl (CBz)/ *tert*-butyldimethylsilyl (TBS)-protected amino alcohol **19** with aldehyde **20** under reductive conditions (with triethylsilane) resulted in the formation of **21** in 68% yield. The alcohol protecting group is also removed under these conditions. A Suzuki reaction of **21** with **22** gave the 2,3-diaryl-substituted allylic alcohol **23** in 67% yield. This alkene was subsequently converted to **17** upon ozonolysis in 44% yield.

The reduction of **17** by using the tethered Rh catalysts was successful and in each case, full reduction to **18** was achieved in 1 h by using approximately 0.5 mol% catalyst in formic acid/triethylamine (5:2 azeotrope) in 92 and 94% *ee*, respectively (Scheme 1).[6e] The *ee* values were determined in each case by using a supercritical fluid system at Merck.[6e] The enantioselectivities were higher than previously reported for asymmetric transfer hydrogenation catalysts, and were achieved at lower catalyst loadings, thereby providing a viable alternative to pressure hydrogenation for the enantioselective preparation of this substrate.[16]

The asymmetric reduction of a protected α-aminoacetophenone such as **24** is an attractive reaction as it provides a route to 2-amino-1-phenylethanol **25**, which is a useful building block for a variety of pharmaceutically important compounds.[17] Compound **24** may, in principle, be prepared by a number of routes that involve a ketone reduction step; for example, through the asymmetric oxazaborolidine (OAB)-mediated reduction of an α-chloroketone precursor.[17] We, and others, have demonstrated that ATH of α-chloroketones can also be achieved with very high enantioselectivity by using both tethered and untethered Rh^{III}/TsDPEN catalysts.[6r,7b,c,13] However, we were not aware of the application of ATH to the direct reduction of **24** with high *ee* values, which represents perhaps the most conceptually simple approach to the asymmetric synthesis of **25**. This reduction has been successfully achieved through the use of an AH catalyst with *ee* values of >99% in the optimized cases.[17]

We were pleased to find that the increased stability and activity of catalyst **5**, conferred by the tethering group, rendered it capable of catalyzing the full reduction of **24** to the protected alcohol **26** in approximately 98% *ee* (*S*) (Scheme 2). The *ee* of the product was determined by using

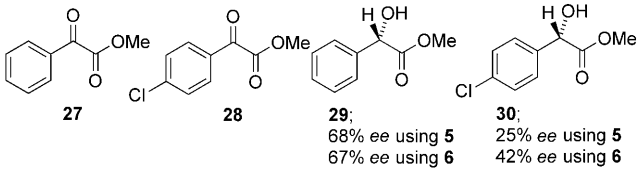


Scheme 2. ATH of **24** by using catalyst (*R*,*R*)-**5**.

an NMR spectroscopic shift reagent. Although the reaction time was long (7 days for full conversion), only 1 mol% of catalyst is required, and the method provides an alternative to hydrogenation under pressure. Completion of the synthesis of **25** was achieved by hydrolysis of **26** with aqueous sodium hydroxide in ethanol (Scheme 2). The comparison of the sign of optical rotation of **26** with the reported value served to confirm the absolute configuration of the product as (*S*).

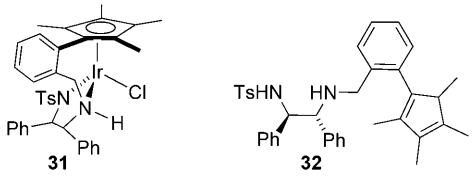
An attempt was also made to develop a highly enantioselective reduction of α-keto esters with Rh^{III} catalysts **5** and **6**

as these catalysts are known to be challenging substrates for ATH. Unfortunately, the reductions of **27** and **28**[18] to alcohols **29** and **30** were achieved in only 67–68% and 25–42% *ee* respectively, depending on the catalyst used.

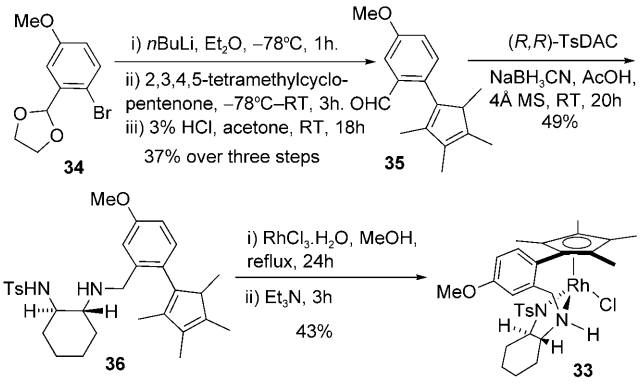


Synthesis and Applications of Novel Catalyst Derivatives

We were interested in preparing the Ir^{III} derivative of catalyst **5**, that is, **31**, as the iridium complexes of TsDPEN (with associated pentamethyl cyclopentadienyl ligands) have been shown to be very effective catalysts for both ATH[7] and, more recently, AH.[11] Unfortunately, we were unable to prepare and isolate **31** despite a number of attempts at complexation of precursor **32** with iridium trichloride.[13] There was evidence, however, of the formation of **31** in situ as the crude product was capable of the asymmetric reduction of a series of ketones. Although the *ee* values were very good in some cases, the conversions were low and results were obtained that indicate some formation of catalyst: acetophenone; 21% yield, 94% *ee* (*R*) after 9 days, α-chloroacetophenone; 63% yield, 97% *ee* (*S*) after 20 h, *p*-trifluoromethylacetophenone; 41% yield, 80% *ee* (*R*) after 6 days, *m*-chloroacetophenone; 43% yield, 75% *ee* (*R*) after 7 days, *p*-chloroacetophenone; 14% yield, 83% *ee* (*R*) after 4 days, α-hydroxyacetophenone; 4% yield, 84% *ee* (*S*) after 2 days. In all cases, reactions were conducted at 28 °C in formic acid/triethylamine (5:2) at S/C = 200.



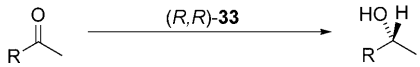
More success was achieved in the synthesis of the Rh^{III} catalyst (*R*,*R*)-**33**, which contains a methoxy group on the tethering aryl ring. This was of interest because it provided an opportunity to establish whether or not this would influence the performance of the catalyst, with a view to creating supported versions (for example, on soluble polymers) through a linkage at this point. The successful[19] route to (*R*,*R*)-**33** is illustrated in Scheme 3 and starts from the bromide **34**,[20] which was converted to **35** through a three step sequence that mirrors that used for **6**. Reductive amination of **35** with (*R*,*R*)-*N*-tosyl-1,2-cyclohexyldiamine resulted in formation of (*R*,*R*)-**36**, which was converted to (*R*,*R*)-**33** by refluxing with rhodium trichloride in methanol in 43% yield.



Scheme 3. Synthesis of catalyst (*R*,*R*)-**33**. TsDAC = 1,2-diaminocyclohexane.

Catalyst (*R*,*R*)-**33** was isolated as a dark-red solid and the proton NMR spectra indicated the formation of a single diastereoisomer of product. Six methyl singlets were present, as well as a clear AB system owing to the benzylic methylene group. Although an X-ray crystallographic structure was not obtained, its relative configuration was assigned by analogy with that of (*R*,*R*)-**6**. Complex (*R*,*R*)-**33** proved to be an effective catalyst for ATH of a series of ketones in formic acid/triethylamine (Table 2), and the product configurations

Table 2. Asymmetric transfer hydrogenation of ketones by using catalyst (*R*,*R*)-**33**.[a]



R[a]	*t* [h]	Conv. [%]	*ee* [%][b]	*R*/*S*[c]	*ee* [%] with **6**[d]
Ph	2.5	99	95	*R*	96 (*R*)
p-BrC_6H_4	3	100	95	*R*	93 (*R*) (aq.)[e]
p-MeC_6H_4	5	100	94	*R*	94 (*R*) (aq.)[e]
o-ClC_6H_4	9	100	85	*R*	85 (*R*)
o-$(CF_3)C_6H_4$	48	37	60	*R*	62 (*R*)
o-$(MeO)C_6H_4$	18	37	94	*R*	94 (*R*)
1-naphthyl	48	99	87	*R*	84 (*R*)
2-furyl	3	100	98	*R*	98 (*R*)
2-thiophenyl	5	100	97	*R*	97 (*R*)
cC_6H_{11}	28	96	87	*S*	87 (*S*)

[a] S/C = 200, in HCO_2H/Et_3N (5:2), [ketone] = approximately 1.0–1.6 M, 25 °C. [b] *ee* values were determined by chiral HPLC or GC. [c] Determined by comparison of the sign of optical rotation to a reported example.[13c] [d] From reference [13a,b]. [e] Reaction in aqueous solution.

matched that which was predicted by using the ligand enantiomers employed, assuming that tethering does not alter its mode of action.

In comparison with catalysts (*R*,*R*)-**5** and (*R*,*R*)-**6**,[13] (*R*,*R*)-**33** exhibited a similar reactivity and selectivity, and the aromatic ketones were reduced in high *ee* values, with the exception of the more sterically hindered compounds that contain an *ortho* substituent. Presumably this arises from an unfavourable steric interaction between this substituent and a group on the catalyst. Acetylcyclohexane was reduced in an acceptable 87% *ee*, which matched that ach-

ieved by using (*R*,*R*)-**6**, again with an absolute configuration which was reversed relative to the aromatic ketones. This reversal of face selectivity has been observed for many of the tethered catalysts that we have prepared,[12,13] and presumably reflects the fact that the aromatic substrates can engage in a CH–π interaction with a part of the catalyst, whilst purely aliphatic substrates cannot.[10]

Conclusions

In conclusion, we have demonstrated that tethered complexes containing a Rh^{III}/cyclopentadienyl/tosylated diamine combination can be used effectively in the asymmetric reduction of imines and of complex functionalized ketones. In the case of **17**, the catalysts give better *ee* values than other methods for this transformation, at lower catalyst loadings. We have demonstrated that the introduction of a methoxy group into the tethering aryl ring does not unfavorably influence the performance of the catalyst, thus opening up a route to supported derivatives. Ir^{III} derivatives have remained elusive.

Experimental Section

General

All reactions, unless otherwise stated, were carried out in vacuum-flame-dried glassware under an atmosphere of nitrogen at ambient temperature (18–22 °C). 0 °C refers to an ice/water slush bath and −78 °C refers to a dry-ice–acetone bath. All reagents were obtained from commercial sources and used without purification unless stated. Distilled solvents (THF, Et_2O) were freshly distilled over sodium. Other dry solvents were supplied by Romil as Hi-Dry solvents, and N,N-dimethylformamide (DMF) and dichloromethane (DCM) were supplied from Fluka/Aldrich as anhydrous in Sure/Seal bottles. All other solvents were from commercial sources and used without further preparation unless otherwise stated. Thin Layer Chromatography was performed on commercially available precoated aluminium-backed silica gel 60 (F_{254}) plates supplied by Merck and visualized by UV_{254} and 2,4-dinitrophenylhydrazine, ninydrin, phosphomolybdic acid, potassium permanganate, and vanillin dips as appropriate. Flash column chromatography was carried out on silica gel 40-63U 60A supplied by Fluorochem Limited. Organic solvents were removed on a Buchi Rotary Evaporator. Melting points were determined by using a Stuart Scientific SMP1 instrument and are uncorrected. Infrared spectra were recorded neat by using a Nicolet Avatar 320 FTIR fitted with a Specac golden gate single reflection diamond attenuated total reflection top plate. Optical rotations were measured using a Perkin–Elmer 241 polarimeter (sodium D line) at room temperature with a 10 cm rotation cell. NMR spectra were recorded on Bruker DPX 300 MHz or Bruker DPX 400 MHz spectrometers. Chemical shift values, quoted in ppm, are relative to the internal standard teramethylsilane (TMS) for ^{1}H NMR, or the middle of the chloroform triplet $\delta = 77$ ppm for ^{13}C NMR. Multiplicities are quoted as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m) and coupling constants (*J*) are quoted in Hz. Mass spectra were recorded on a Kratos analytical MS80 RFAO spectrometer. Transfer hydrogenation conversions and *ee* value determinations were made with GC by using a Cyclodextrin-β-236M-19 (CHROMPAC, 50 m) column or by HPLC by using a Chiralcel OD column supplied by Daicel. The following starting materials have been reported and were prepared by published methods; **7**–**11**,[8] **19**, and[15] **34**.[20] In cases where a substrate was reduced by several catalysts, only the result from one of them is generally listed.

Synthesis

12: A mixture of catalyst (*R*,*R*)-**5** or (*R*,*R*)-**6** (0.014 mmol) in triethylamine (0.95 mL, 6.8 mmol) was stirred at 28 °C for 10 min. A solution of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **7** (0.58 g, 2.81 mmol) in anhydrous DCM (3 mL) was added, followed by the dropwise addition of formic acid (0.65 mL, 17.2 mmol) over 10 min and the reaction mixture was then stirred at 28 °C while the reaction was monitored by TLC. Upon completion of the reaction, the solution was washed with saturated Na_2CO_3 (10 mL) and extracted with DCM (4×20 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure to give a crude brown oil, which was purified by silica gel column chromatography (50→100 % v/v EtOAc/hexane) to afford product **7**[8b] as a pale-orange oil (0.42 g, 2.03 mmol, 72 %). IR (film): $\tilde{\nu} = 3268$, 2930, 2833, 1608, 1511, 1455, 1253, 1222, 1130, 995, 860, 786 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): $\delta = 6.62$ (s, 1H; ArH), 6.57 (s, 1H, ArH), 4.04 (q, $^3J_{HH} = 6.5$ Hz, 1H; CH_3CH), 3.85 (s, 3H; OCH_3), 3.84 (s, 3H; OCH_3), 3.29–3.21 (m, 1H; $NHCH_aH_b$), 3.04–2.95 (m, 1H; $NHCH_aH_b$), 2.84–2.74 (m, 1H; $ArCH_aH_b$), 2.69–2.60 (m, 1H; $ArCH_aH_b$), 1.93 (brs, 1H; NH), 1.44 ppm (d, $^3J_{HH} = 6.5$ Hz, 3H; $CHCH_3$); ^{13}C NMR(100.6 MHz; $CDCl_3$, 25 °C, TMS): $\delta = 147.3$ (ArC_q), 147.3 (ArC_q), 132.4 (ArC_q), 126.8 (ArC_q), 111.8, 109.1 (ArCH), 56.0 (OCH_3), 55.9 (OCH_3), 51.2 (CH), 41.8 (CH_2), 29.5 (CH_2), 22.8 ppm (CH_3); MS (LSIMS): *m*/*z* (%) 208 (MH^+, 100), 192 (56), 154 (18); HRMS (LSIMS): *m*/*z* (%) calcd for $C_{12}H_{17}NO_2$: 208.1338 $[M+H]^+$; found: 208.1344 (3.2 ppm error). Enantiomeric excess determined by HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/propan-2-ol/Et_2NH = 90:10:0.1 (0.5 mL min^{-1}), 254 nm, room temperature, *S* isomer 23.8 min., *R* isomer 32.7 min.); $[\alpha]_D^{26} = -27.1$ (*c* = 1.17, EtOH) 87 % *ee* (*S*); (lit.[8m] $[\alpha]_D^{23} = -51.2$ (*c* = 1.69, EtOH) 95 % *ee* (*S*)). A racemic standard was prepared by reduction of **7** with $NaBH_4$.

13: Following the general procedure described for **12**, from reduction of acetophenone benzylimine **8** (0.68 g, 3.25 mmol), product **13** was obtained as a pale-yellow oil (0.48 g, 2.27 mmol, 70 %).[8c] ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): $\delta = 7.38$–7.20 (m, 10H; ArH), 3.81 (q, 1H, $^3J_{HH} = 6.6$ Hz, 1H; CH), 3.66 (d, 1H, $^3J_{HH} = 13.2$ Hz, 1H; NCH_aH_b), 3.59 (d, $^3J_{HH} = 13.2$ Hz, 1H; NCH_aH_b), 1.66 (brs, 1H; NH), 1.37 ppm (d, $^3J_{HH} = 6.6$ Hz, 3H; CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 145.6 (ArC_q), 140.7 (ArC_q), 128.5, 128.4, 128.2, 127.0, 126.9, 126.7 (ArCH), 57.5 (CH), 51.7 (CH_2), 24.5 ppm (CH_3). Enantiomeric excess determined by HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/propan-2-ol = 99.5:0.5 (0.5 mL min^{-1}), 254 nm, RT, *R* isomer 15.1 min., *S* isomer 17.2 min.); $[\alpha]_D^{26} = -23.9$ (*c* = 1.12, EtOH) 44 % *ee* (*S*); (lit[8c] $[\alpha]_D^{20} = -3.3$ (*c* = 1.0, EtOH) 8.4 % *ee* (*S*)). A racemic standard was prepared by reduction of **8** with $NaBH_4$.

14: Following the general procedure, from reduction of 1-methyl-4,9-dihydro-3*H*-β-carboline **9** (0.52 g, 2.81 mmol), product **14** was obtained as a brown oil (0.36 g, 1.93 mmol, 69 %);[21] IR (film): $\tilde{\nu} = 3396$, 3055, 2842, 1453, 1300, 1158, 1121, 1007, 846, 801, 740 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): $\delta = 8.04$ (brs, 1H; NH), 7.47 (d, $^3J_{HH} = 7.6$ Hz; ArH), 7.28 (d, $^3J_{HH} = 7.6$ Hz, 1H; ArH), 7.16–7.06 (m, 2H; ArH), 4.15 (q, $^3J_{HH} = 6.8$ Hz, 1H; CH), 3.39–3.29 (m, 1H; $NHCH_aH_b$), 3.08–2.98 (m, 1H; $NHCH_aH_b$), 2.81–2.66 (m, 2H; CH_2), 2.41 (brs, 1H; NH), 1.43 (d, $^3J_{HH} = 6.8$ Hz, 3H; CH_3) ppm; ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): $\delta = 136.9$ (ArC_q), 135.7 (ArC_q), 127.5 (ArC_q), 121.6, 119.4, 118.1, 110.8 (ArCH), 108.4 (ArC_q), 48.3 (CH), 42.6 (CH_2), 22.6 (CH_2), 20.7 ppm (CH_3); MS (EI): *m*/*z* (%) 186 (M^+, 51), 171 (100), 157 (50 %), 156 (60), 77 (32), 63 ppm (40); HRMS (EI) *m*/*z* (%) calcd for $C_{12}H_{14}N_2$: 186.1157 $[M]^+$; found: 186.1150 (3.8 ppm error). Enantiomeric excess determined by HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/propan-2-ol/Et_2NH = 80:20:0.1 (1.0 mL min^{-1}), 254 nm, RT, *R* isomer 10.5 min., *S* isomer 15.2 min.); $[\alpha]_D^{32} = -37.1$ (*c* = 0.26, EtOH) 88 % *ee* (*S*); (reference [8m]: $[\alpha]_D^{25} = -62.1$ (*c* = 1.36 EtOH) 99 % *ee* (*S*)). A racemic standard was prepared by reduction of **9** with $NaBH_4$.

15: Following the general procedure, from reduction of 1-phenyl-4,9-dihydro-3*H*-β-carboline **10** (0.69 g, 2.81 mmol), product **15** was obtained as a brown oil (0.48 g, 1.94 mmol, 69 %);[21] IR (film): $\tilde{\nu} = 3394$, 3056, 2845, 1454, 1298, 739, 700 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.91 (brs, 1H; NH), 7.60–7.55 (m, 1H; ArH), 7.38–7.32 (m, 3H; ArH),

7.31–7.26 (m, 2H; ArH), 7.19–7.11 (m, 3H; ArH), 5.11 (s, 1H; CH), 3.38–3.29 (m, 1H; $NHCH_aH_b$), 3.17–3.06 (m, 1H; $NHCH_aH_b$), 2.98–2.78 (m, 2H; CH_2), 1.92 ppm (brs, 1H; NH); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 141.9 (ArC_q), 136.0 (ArC_q), 134.5 (ArC_q), 128.8, 128.6, 128.2 (ArCH), 127.4 (ArC_q), 121.7, 119.4, 118.3, 110.9 (ArCH), 110.2 (ArC_q), 58.1 (CH), 42.8 (CH_2), 22.5 ppm (CH_2); MS (EI): *m/z* (%) 248 $[M]^+$ (86), 247 (55), 219 (76), 218 (100), 217 (42), 171 (44), 78 (25), 69 (45), 63 (29); HRMS (EI): *m/z* (%) calcd for $C_{17}H_{16}N_2$: 248.1313 $[M]^+$, found: 248.1314 (0.3 ppm error). Enantiomeric excess determined by HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/propan-2-ol/Et_2NH = 80:20:0.1 (1.0 mL min^{-1}), 254 nm, RT, *S* isomer 13.0 min., *R* isomer 17.9 min.); $[\alpha]_D^{21}$ = +0.82 (*c* = 0.39, $CHCl_3$) 96% *ee* (*S*); (reference [8m]: $[\alpha]_D^{23}$ = +0.92 (*c* = 0.97, $CHCl_3$) 99% *ee* (*S*)). A racemic standard was prepared by reduction of **10** with $NaBH_4$.

16: Following the general procedure, from **11** (0.51 g, 2.81 mmol), product **16** was obtained as a white solid (0.38 g, 2.08 mmol, 74%);[22] m.p.: 57–59 °C; IR (film): $\tilde{\nu}$ = 3246, 1453, 1396, 1298, 1203, 1165, 1126, 1025, 887, 757 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.75 (d, $^3J_{HH}$ = 7.8 Hz, 1H; ArH), 7.62 (dt, $^3J_{HH}$ = 7.7, 1.0 Hz, 1H; ArH), 7.51 (t, $^3J_{HH}$ = 7.7 Hz, 1H; ArH), 7.39 (d, $^3J_{HH}$ = 7.8 Hz, 1H; ArH), 5.05 (brs, 1H; NH), 4.79 (quin, $^3J_{HH}$ = 6.5 Hz, 1H; CH), 1.60 ppm (d, $^3J_{HH}$ = 6.5 Hz, 3H; CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 141.8 (ArC_q), 135.5 (ArC_q), 133.2, 129.2, 123.9, 121.2 (ArCH), 53.4 (CH), 21.4 ppm (CH_3); MS (EI): *m/z* (%) 184 $[MH]^+$ (21), 168 (100), 150 (16), 104 (14), 77 (20); elemental analysis: calcd (%) for $C_8H_9NO_2S$: C 52.44, H 4.95, N 7.64%; found: C 52.14, H 4.92, N 7.54. Enantiomeric excess determined by HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/propan-2-ol = 85:15 (1.0 mL min^{-1}), 254 nm, RT, *S* isomer 15.1 min., *R* isomer 19.5 min.); $[\alpha]_D^{25}$ = +4.29 (*c* = 1.2, $CHCl_3$) 19% *ee* (*R*); (reference [8m]: $[\alpha]_D^{20}$ = +19.1 (*c* = 1.50, $CHCl_3$) 65% *ee* (*R*)). A racemic standard was prepared by reduction of **11** with $NaBH_4$.

21: To a stirred mixture of benzyl *trans*-(4-*tert*-butyldimethylsilyloxy) cyclohexylcarbamate **19** (17.40 g, 47.9 mmol) and 2-bromocinnamaldehyde **21** (13.66 g, 64.7 mmol) in anhydrous acetonitrile (300 mL) was added bismuth tribromide (1.36 g, 3.02 mmol). After 15 min, triethylsilane (10 g, 13.8 mL, 86.2 mmol) was added dropwise over 15 min. After stirring for 1 hour, the reaction was complete as ascertained by TLC analysis and was quenched with saturated Na_2CO_3 (400 mL), allowed to stir until the black precipitated bismuth metal was consumed and a white precipitate was formed and subsequently extracted with EtOAc (3×400 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (0→20% v/v EtOAc/hexane) to give product **21** as a white solid (14.38 g, 32.5 mmol, 68%); m.p.: 88–90 °C; IR (film): $\tilde{\nu}$ = 3321, 2941, 2857, 1683, 1545, 1525, 1447, 1304, 1265, 1228, 1083, 1052, 749, 741, 692 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.62 (d, $^3J_{HH}$ = 7.3, 1H; ArH), 7.38–7.26 (m, 9H; ArH), 7.06 (s, 1H; vinyl CH), 5.08 (s, 2H; CH_2), 4.65 (brs, 1H; NH), 4.28 (s, 2H; CH_2), 3.60–3.45 (m, 1H; cyclohexyl C*H ortho* to OR), 3.44–3.32 (m, 1H; cyclohexyl C*H ortho* to NH), 2.05 (brd, $^3J_{HH}$ = 10.4 Hz, 4H; 4×cyclohexyl CH), 1.45 (dd, $^3J_{HH}$ = 22.1, 10.4 Hz, 2H; 2×cyclohexyl CH), 1.18 ppm (dd, $^3J_{HH}$ = 22.1, 10.4 Hz, 2H; 2×cyclohexyl CH); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 155.6 (C=O), 136.6 (ArC_q), 135.2 (ArC_q), 129.1, 128.6, 128.2, 128.2, 127.5 (5 overlapping Ar*C*H + vinyl *C*H), 123.1 (C_qBr), 76.7 (CH), 74.2 (CH_2), 66.6 (CH_2), 49.4 (CH), 30.9 (CH_2 of cyclohexyl ring), 30.5 ppm (CH_2 of cyclohexyl ring); MS (EI): *m/z* (%) 446 $[MH(^{81}Br)]^+$ (60), 445 $[M(^{81}Br)]^+$ (38), 444 $[MH(^{79}Br)]^+$ (60), 402 (41), 400 (45), 364 (54), 320 (57), 310 (82), 308 (82), 293 (42), 291 (40), 248 (71), 232 (89), 230 (48), 204 (81), 195 (100), 193 (100), 188 (59), 181 (45), 171 (32), 146 (55), 142 (90), 117 (76), 115 (86); elemental analysis: calcd (%) for $C_{23}H_{26}BrNO_3$: C 62.17, H 5.90, N 3.15%; found: C 62.05, H 5.89, N 3.02. The NMR data is in agreement with the published data for this compound.[15]

23:[15] A stirred mixture of benzyl *trans*-(4-((*Z*)-2-bromo-3-phenylallyloxy) cyclohexyl carbamate **21** (8 g, 18.1 mmol), 2-fluorophenylboronic acid **22** (2.73 g, 19.5 mmol), barium hydroxide octahydrate (8.55 g, 27.1 mmol), tetrakis-triphenylphosphine palladium (0.46 g, 0.4 mmol), DME (110 mL), and water (20 mL) was heated to reflux for 12 h. The mixture was cooled and partitioned between saturated Na_2CO_3 (180 mL) and EtOAc (3×350 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (0→20% v/v EtOAc/hexane) to give product **23** as a white solid (5.6 g, 12.2 mmol, 67%); m.p.: 104–106 °C; IR (film): $\tilde{\nu}$ = 3345, 2942, 2859, 1684, 1532, 1445, 1311, 1265, 1223, 1124, 1103, 1060, 754, 694 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.37–7.24 (m, 6H; ArH), 7.18–6.96 (m, 8H; ArH), 6.80 (s, 1H; vinyl CH), 5.08 (s, 2H; CH_2), 4.57 (brs, 1H, NH), 4.31 (s, 2H; CH_2), 3.57–3.41 (m, 1H; cyclohexyl C*H ortho* to NH), 3.40–3.30 (m, 1H; cyclohexyl C*H ortho* to OR), 2.09–1.94 (m, 4H; 4×cyclohexyl CH), 1.46–1.32 (m, 2H; 2×cyclohexyl CH), 1.23–1.09 ppm (m, 2H; 2×cyclohexyl CH); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 160.0 ($^3J_{FC}$ = 246.1 Hz, ArC–F), 155.6 (C=O), 136.6 (ArC_q), 136.4 (ArC_q), 133.9 (vinyl C_q), 131.4, 129.4, 129.3, 129.2, 128.8, 128.6, 128.1, 128.1, 127.1, 124.4 (9 Ar*C*H + 1 vinyl *C*H), 126.5 ($^3J_{FC}$ = 16.5 Hz, ArC_q adjacent to ArC–F), 115.9 (^3J_F = 21.9 Hz, Ar*C*H adjacent to ArC–F), 76.4 (CH), 72.5 (CH_2), 66.6 (CH_2), 49.5 (CH), 30.9 (CH_2 of cyclohexyl ring), 30.4 ppm (CH_2 of cyclohexyl ring); MS (EI): *m/z* (%) 460 $[MH]^+$ (12), 351 (34), 248 (30), 232 (92), 212 (100), 199 (84), 196 (80), 188 (50), 171 (42), 142 (30), 133 (68), 115 (77); elemental analysis: calcd (%) for $C_{29}H_{30}FNO_3$: C 75.79, H 6.58, N 3.05; found: C 75.94, H 6.67, N 3.04.)

17:[6e] A stream of ozone from an ozone generator was dispersed into a stirred solution of benzyl *trans*-(4-((*E*)-2-(2-fluorophenyl)-3-phenylallyloxy) cyclohexyl carbamate **23** (2.52 g, 5.5 mmol) in DCM (75 mL) and MeOH (25 mL) cooled to −78 °C until a blue color persisted. The excess ozone was purged with nitrogen until the blue color dissipated, and zinc metal (2.51 g, 38.4 mmol) followed by acetic acid/water (15 mL/5 mL) was added to the reaction mixture at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for a further 1 hour before being filtered through celite. The filtrate was washed with saturated $NaHCO_3$ (50 mL) and saturated brine (50 mL). The aqueous layer was extracted with DCM (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (0→30% v/v EtOAc/hexane) to give product **17** as a white solid (0.92 g, 2.39 mmol, 44%); m.p.: 107–108 °C; IR (film): $\tilde{\nu}$ = 3326, 2941, 2867, 1696, 1609, 1524, 1481, 1454, 1316, 1264, 1221, 1122, 1098, 1053, 977, 842, 767, 748, 725, 695 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.94 (1H, dt, $^3J_{HH}$ = 7.5 and 1.8, ArH), 7.58–7.51 (m, 1H; ArH), 7.37–7.24 (m, 6H; ArH), 7.17–7.11 (m, 1H; ArH), 5.08 (s, 2H; CH_2), 4.70 (s, 2H; CH_2), 4.57 (brs, 1H; NH), 3.59–3.47 (m, 1H; cyclohexyl C*H ortho* to NH), 3.42–3.32 (m, 1H; cyclohexyl C*H ortho* to OR), 2.14–2.02 (m, 4H; 4×cyclohexyl CH), 1.54–1.41 (m, 2H; 2×cyclohexyl CH), 1.24–1.11 ppm (m, 2H; 2×cyclohexyl CH); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 195.3 (C=O), 162.0 ($^3J_{FC}$ = 253.8 Hz, ArC–F), 155.6 (C=O), 136.6 (ArC_q), 135.1, 135.0, 130.7, 128.5, 128.1, 124.8 (ArCH), 123.4 ($^3J_{FC}$ = 15.3 Hz, ArC_q adjacent to ArC–F), 116.5 ($^3J_{FC}$ = 23.8 Hz, Ar*C*H adjacent to ArC–F), 77.8 (CH), 74.4 (CH_2), 66.6 (CH_2), 49.4 (CH), 30.9 (CH_2 of cyclohexyl ring), 30.2 ppm (CH_2 of cyclohexyl ring); MS (EI): *m/z* (%) 386 $[MH]^+$ (38), 340 (40), 278 (36), 248 (60), 232 (82), 204 (55), 188 (70), 181 (41), 155 (51), 142 (40), 123 (76), 96 (49), 91 (100), 69 (52); elemental analysis: calcd for $C_{22}H_{24}FNO_4$: C 68.56, H 6.28, N 3.63; found: C 68.61, H 6.24, N 3.69.

Racemic **18**: A stream of ozone from an ozone generator was dispensed into a stirred solution of benzyl *trans*-(4-((*E*)-2-(2-fluorophenyl)-3-phenylallyloxy) cyclohexyl carbamate **23** (0.51 g, 1.11 mmol) in DCM (15 mL) and MeOH (5 mL) cooled to −78 °C until a blue color persisted. The excess ozone was purged with nitrogen until the blue color dissipated, and sodium borohydride (0.084 g, 2.22 mmol) was added to the reaction mixture at −78 °C. After warming the reaction to room temperature over 30 min, the solution was diluted with water (5 mL) and concentrated under reduced pressure. The residue was treated with 3% HCl (10 mL) and extracted with DCM (3×10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (0→30% v/v EtOAc/hexane) to give product **18** as a white solid (0.2 g, 0.52 mmol, 47%); m.p.: 119–121 °C; IR (film): $\tilde{\nu}$ = 3408, 3304, 2935, 2860, 1684, 1534, 1455, 1308, 1267, 1228, 1052, 949, 758, 744, 697 cm^{-1};

^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.55 (dt, $^3J_{HH}$ = 7.5, 1.4 Hz, 1H; ArH), 7.37–7.22 (m, 6H; ArH), 7.16 (dt, $^3J_{HH}$ = 7.5, 1.4 Hz, 1H; ArH), 7.04–6.98 (m, 1H; ArH), 5.16 (dt, $^3J_{HH}$ = 5.8, 2.8 Hz, 1H; C*H*OH), 5.08 (s, 2H; CH_2), 4.57 (brs, 1H; NH), 3.71 (dd, $^3J_{HH}$ = 9.4, 3.1 Hz, 1H; CH_aH_b), 3.58–3.46 (m, 1H; cyclohexyl C*H ortho* to NH), 3.40 (t, $^3J_{HH}$ = 9.4 Hz, 1H; CH_aH_b), 3.35–3.27 (m, 1H; cyclohexyl C*H ortho* to OR), 2.84 (d, $^3J_{HH}$ = 2.8 Hz, 1H; OH), 2.09–1.98 (m, 4H; 4 × cyclohexyl CH), 1.48–1.32 (m, 2H; 2 × cyclohexyl CH), 1.24–1.10 (m, 2H; 2 × cyclohexyl CH) ppm; ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 160.0 ($^3J_{FC}$ = 245.8 Hz, ArC–F), 155.6 (C=O), 136.6 (ArC_q), 129.2, 129.1, 128.6, 128.1, 127.7 (ArCH), 127.4 ($^3J_{FC}$ = 13.4 Hz, ArC_q adjacent to ArC–F), 124.3 (ArCH), 115.1 ($^3J_{FC}$ = 21.5 Hz, Ar*C*H adjacent to ArC–F), 77.5 (CH), 72.4 (CH_2), 67.1 (CH), 66.6 (CH_2), 49.4 (CH), 30.8 (CH_2 of cyclohexyl ring), 30.3 ppm (CH_2 of cyclohexyl ring); MS (EI): *m*/*z* (%) 388 [*M*H]$^+$ (8), 263 (17), 233 (23), 232 (95), 188 (22), 142 (29), 125 (51), 91 (100); elemental analysis: calcd (%) for $C_{22}H_{26}FNO_4$: C 68.20, H 6.76, N 3.62; found: C 68.23, H 6.78, N 3.60.

18 via ATH: A solution of **5** (0.0028 mmol) in formic acid:triethylamine 5:2 azeotrope (1.5 mL) was stirred in a flame dried Schlenk tube at 28 °C for 15 min. Ketone **17** (0.22 g, 0.56 mmol) was added and the reaction mixture was stirred at 25 °C for 1 h, at which point, full conversion had been achieved (ascertained by TLC). The reaction was filtered (silica), washed (50 % EtOAc/50 % hexane), and concentrated under vacuum to afford reduction product **18** as a white solid (0.20 g, 0.52 mmol, 93 %). Enantiomeric excess determined by supercritical fluid chromatography with a Daicel Chemical Industries Chiralpak AD column by using isocratic 30 % (25 mmol *i*BuNH_2 in MeOH)/CO_2 (1.5 mL min^{-1}, 35 °C, 200 psig, 215 nm, room temperature, *R* isomer 9.47 min., *S* isomer 10.04 min); $[\alpha]_D^{23}$ = +22.2 (*c* = 0.3, $CHCl_3$) 92 % *ee* (*S*).[15]

26: Catalyst (*R*,*R*)-**5** (0.005 g, 0.0074 mmol) was dissolved in formic acid (FA)/ triethylamine (TEA) (1 mL) at 28 °C for 30 min with stirring and then a solution of **24** (0.160 g, 0.74 mmol) in FA/TEA (3 mL) was added and the system was stirred at 25 °C. The reaction was followed by H NMR spectroscopy, which indicated full conversion in 7 days. The crude mixture was filtered through a short silica gel column and eluted with $CHCl_3$/MeOH 9:1 and evaporated to afford **26** as a light-yellow solid (0.147 g, 0.67 mmol, 90 %). A sample was recrystalized from hexane/ethyl acetate (0.11 g); m.p.: 185–188 °C (lit[23] 162 °C); $[\alpha]_D^{23}$ = +37.6 (*c* = 0.22, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3360, 2937, 1769, 1678, 1496, 1429, 1402, 1319, 1245, 1165, 1113, 767, 702 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.44–7.28 (m, 5H; ArH), 4.99 (m, 1H; C*H*OH), 3.91 (dd, $^2J_{HH}$ = 10.5, $^3J_{HH}$ = 6.5 Hz, 1H; CH_aH_b), 3.80 (dd, $^2J_{HH}$ = 10.5, $^3J_{HH}$ = 1.5 Hz, 1H; CH_aH_b), 2.94 (brs, 1H; OH), 2.73 ppm (s, 4H; $2CH_2$); ^{13}C NMR (75 MHz; $CDCl_3$, 25 °C, TMS): δ = 178.0 (2C=O), 140.9, 128.5, 128.1, 125.8, (ArC), 71.8 (CH), 46.3 (CH_2), 28.1 ppm ($2CH_2$); HRMS (EI): *m*/*z* (%) calcd for $C_{12}H_{13}NNaO_3$ [*M*+Na]$^+$, 242.0788; found: 242.0778 (4.1 ppm error). The *ee* value was determined on the crude product by using the chiral shift reagent Eu(hfc)$_3$ (hfc = 3-(heptafluoropropylhydroxymethylene)-d-camphorate). Addition of Eu(hfc)$_3$ (10 mg) to a $CDCl_3$ solution of racemic **26** (10 mg) produced a 0.24 ppm shift between the C*H*OH protons, which moved downfield to δ = 8.21 and 7.98 ppm. In the same experiment on enantiomerically pure material, the δ = 8.21 and 7.98 ppm peaks were present in a ratio of approximately 99:1, respectively.

25: Alcohol **26** (0.048 g, 0.22 mmol) was dissolved in 2 mL of 95 % ethanol followed by addition of 2 mL of 20 % aqueous sodium hydroxide. The resulting solution was refluxed for 18 h and then the excess ethanol was evaporated. Methyl *tert*-butyl ether (MTBE; 20 mL) was added to the resulting solution and the mixture was refluxed for one hour to extract the amino alcohol. The mixture was cooled to room temperature and the organic layer was separated, dried over $MgSO_4$, and evaporated, providing crude **25**.[17] The crude compound was filtered on a short silica gel column eluted with chloroform (10 mL) and then 9:1 $CHCl_3$/MeOH (10 mL), providing the pure **25** as a yellow solid (0.026 g, 0.18 mmol, 86 % yield). $[\alpha]_D^{25}$ = +14.3 (*c* = 0.11, EtOH) 98 % *ee* (*S*); (reference [24]: $[\alpha]_D^{24}$ = +43.9 (*c* = 2, EtOH) 99.1 % *ee* (*S*); ^{1}H NMR (300 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.36–7.26 (m, 5H; ArH), 4.63 (m, 1H; α-OH), 3.0 ppm (m, 2H; CH_2); ^{13}C NMR (75 MHz; $CDCl_3$, 25 °C, TMS) δ = 142.5, 128.4, 127.5, 125.8 (ArC), 74.3 (CH), 49.2 ppm (CH_2).

29: Following the general procedure for **17**, by using (*R*,*R*)-**5** (0.016 mmol) and ketone substrate **27** (0.52 g, 3.2 mmol), reduction product **29** was obtained as a white solid (0.35 g, 2.1 mmol, 66 %);[25] m.p.: 56–58 °C; IR (film): $\tilde{\nu}$ = 3438, 2953, 1737, 1433, 1262, 1201, 1186, 1093, 1067, 981, 893, 783, 732, 695 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.43–7.29 (m, 5H; ArH), 5.17 (d, $^3J_{HH}$ = 5.8 Hz, 1H; CH), 3.74 (s, 3H; CH_3) 3.53 ppm (d, $^3J_{HH}$ = 5.8 Hz, 1H; OH); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 174.1 (C=O), 138.3 (ArC_q), 128.6, 128.5, 126.6 (ArCH), 72.9 (*C*H), 53.0 ppm (CH_3); MS (EI): *m*/*z* (%) 167 [*M*H]$^+$ (19), 149 (89), 121 (18), 107 (72), 79 (24); elemental analysis: calcd (%) for $C_9H_{10}O_3$: C 65.05, H 6.07; found: C 64.94, H 6.02. Enantiomeric excess determined by HPLC analysis (Chiralcel OD-H, 250 × 4.6 mm column, hexane/propan-2-ol = 95:5 (0.7 mL min^{-1}), 220 nm, RT, *S* isomer 16.0 min., *R* isomer 29.6 min.); $[\alpha]_D^{26}$ = +86.1 (*c* = 0.68, MeOH) 68 % *ee* (*S*). Assigned by comparison with authentic commercial product; methyl (*R*)-2-hydroxy-2-phenylacetate [20698-91-3], Aldrich, $[\alpha]_D^{20}$ = −144.0 (*c* = 1.00, MeOH) 97 % *ee* (*R*)).

28:[18] 4-Chlorophenylmagnesium bromide (29.0 mL, 1.0 M in Et_2O, 29.1 mmol) was added to a slurry of anhydrous $ZnCl_2$ (5.16 g, 37.0 mmol) in THF (60 mL) at 0 °C. After stirring for 15 min at 0 °C and for 10 min at RT, tetrakis (triphenylphosphine) palladium (1.41 g, 1.22 mmol) was added. The mixture was cooled to 0 °C and methyl chlorooxoacetate (3 g, 2.25 mL, 24.5 mmol) was added quickly. The resulting mixture was stirred at 0 °C for 4 h before being filtered through celite. The filtrate was washed with cold saturated NH_4Cl (50 mL) and saturated brine (50 mL). The aqueous layer was extracted with DCM (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (0→2 % v/v EtOAc/hexane) to give product **28** as a white solid (0.72 g, 3.63 mmol, 12 %); m.p.: 53–55 °C; IR (film): $\tilde{\nu}$ = 3092, 2961, 1726, 1682, 1586, 1441, 1404, 1327, 1206, 1168, 1084, 1002, 910, 845, 825, 782, 712, 667 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.99 (d, $^3J_{HH}$ = 8.5 Hz, 2H; ArH), 7.49 (d, $^3J_{HH}$ = 8.5 Hz, 2H; ArH), 3.98 ppm (s, 3H; CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 184.5 (*C*=O *ortho* to OMe), 163.4 (*C*=O *ortho* to phenyl ring), 141.7 (ArC_q), 131.5 (ArCH), 130.9 (ArC_q), 129.3 (ArCH), 53.0 ppm (CH_3); MS (EI): *m*/*z* (%) 199 [*M*H]$^+$ (53), 141 (40), 139 (100), 111 (36), 75 (22); elemental analysis: calcd (%) for $C_9H_7ClO_3$: C 54.43, H 3.55; found: C 54.77, H 3.58.

30: Following the general procedure for **17**, by using (*R*,*R*)-**5** (0.014 mmol) and ketone substrate **28** (0.56 g, 2.8 mmol), reduction product **30** was obtained as a colorless oil (0.42 g, 2.1 mmol, 75 %); IR (film): $\tilde{\nu}$ = 3325, 3000, 2951, 1732, 1488, 1436, 1215, 1085, 1005, 983, 859, 833, 813, 767 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): δ = 7.38–7.32 (m, 4H; ArH), 5.15 (d, $^3J_{HH}$ = 5.3 Hz, 1H; CH), 3.76 (s, 3H; CH_3) 3.56 ppm (d, $^3J_{HH}$ = 5.3 Hz, 1H; OH); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25 °C, TMS): δ = 173.8 (C=O), 136.7 (ArC_q), 134.4 (ArC_q), 128.8, 128.0 (ArCH), 72.2 (CH), 53.2 ppm (CH_3); *m*/*z* (EI) 200 (*M*$^+$, 12 %), 165 (29 %), 143 (32 %), 141 (100 %), 111 (42 %), 89 (36 %), 77 (49 %); elemental analysis: calcd (%) for $C_9H_9ClO_3$: C 53.88, H 4.52; found: C 54.24, H 4.55. Enantiomeric excess determined by HPLC analysis (Chiralcel OD-H, 250 × 4.6 mm column, hexane/propan-2-ol = 98:2 (0.5 mL min^{-1}), 254 nm, RT, *S* isomer 34.2 min., *R* isomer 41.3 min.); $[\alpha]_D^{26}$ = +0.91 (*c* = 0.5, $CHCl_3$); 25 % *ee* (*S*). Product assumed to be of *S* configuration based on published retention times and analogy with **29**.[26]

35: Under a nitrogen atmosphere, a solution of 2-(2-bromo-5-methoxyphenyl)-1,3-dioxolane **34** (5 g, 19.3 mmol) in freshly distilled Et_2O (35 mL) was cooled to −100 °C and a solution of *n*BuLi (8.11 mL, 2.5 M in hexane, 20.3 mmol) was added dropwise. After maintaining the temperature at −100 °C for 1 hour, a solution of 2,3,4,5-tetramethylcyclopentenone (2.81 g, 3.03 mL, 20.3 mmol) was added dropwise to the mixture. The reaction was allowed to warm to room temperature and stirred for a further 3 h. Toluene (25 mL) and water (25 mL) were added to the reaction mixture and the aqueous layer was removed. The obtained organic layer was washed with saturated brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure give the crude product 2-(1-hydroxy-

2,3,4,5-tetramethylcyclopent-2-enyl)-5-methoxybenzaldehyde (5.92 g). To the obtained crude product (5.92 g) was added THF (120 mL), 3% aqueous HCl solution (50 mL), and acetone (15 mL) and the mixture was stirred at 25°C for 18 h, after which toluene (65 mL) was added to the reaction mixture. The organic layer was washed with water (65 mL), saturated brine (65 mL), and dried ($MgSO_4$). The solvent was removed to give a crude residue, which was purified by silica gel column chromatography (0→5% v/v EtOAc/hexane) to afford product **35** as a bright orange/red oil (1.82 g, 7.11 mmol, 37%); IR (film): $\tilde{\nu}$ = 2962, 2913, 2854, 1684, 1605, 1491, 1385, 1305, 1274, 1224, 1161, 1037, 931, 868, 826, 771, 716 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$, 25°C, TMS): δ = 9.88–9.77 (m, 1H; ArHC=O), 7.45 (d, $^3J_{HH}$ = 2.5 Hz, 1H; ArH), 7.21–7.11 (m, 2H; ArH), 3.87 (s, 3H; OCH_3), 3.27–3.06 (m, 1H; CpH), 1.93 (s, 3H; $CpCH_3$), 1.86 (s, 3H; $CpCH_3$), 1.72 (s, 3H; $CpCH_3$), 0.94 ppm (d, $^3J_{HH}$ = 7.5 Hz, 3H; $CpCH_3$ (next to CpH)); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25°C, TMS): δ = 192.9 (HC=O), 158.4 (ArC_q), 141.8 (ArC_q), 138.3 (ArC_q), 134.5 (CpCH), 132.0, 123.1, 121.8, 118.7, 112.7, 109.0, 106.9 (3 ArCH and 4 CpC), 55.6 (OCH_3); 14.2 ($CpCH_3$), 12.4 ($CpCH_3$), 11.9 ($CpCH_3$), 11.0 ppm ($CpCH_3$); MS (EI): *m/z* (%) 257 $[MH]^+$ (22), 256 (M^+, 100), 162 (7). HRMS (EI): *m/z* (%) calcd for $C_{17}H_{20}0_2$: $[M]^+$, 256.1463; found 256.1471 (3.0 ppm error). Cp = C_5H_5.

36: 5-Methoxy-2-(2,3,4,5-tetramethylcyclopenta-1,4-dienyl) benzaldehyde **35** (1.50 g, 5.86 mmol) was dissolved in dry MeOH (40 mL). To this solution was added (*R,R*)-TsDAC (1.88 g, 7.03 mmol), followed by the addition of 2 g of molecular sieves and 6 drops of glacial acetic acid. After formation of the imine was confirmed by TLC, sodium cyanoborohydride (0.48 g, 7.62 mmol) was added and the reaction left to stir overnight at room temperature. The molecular sieves wereremoved by filteration through filter paper and the solution was concentrated under reduced pressure to remove the MeOH. The residue was redissolved in EtOAc (40 mL). The organic layer was washed with saturated $NaHCO_3$ (40 mL) and saturated brine (40 mL) and then dried ($MgSO_4$). The solvent was removed to give a crude solid, which was purified by silica gel column chromatography (0→30% v/v EtOAc/hexane) to afford product **36** as a yellow solid (1.42 g, 2.8 mmol, 48%); m.p.; 54–56°C; $[\alpha]_D^{24}$ = −33.7 (*c* = 0.3, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3258, 2928, 2857, 1599, 1494, 1446, 1325, 1287, 1232, 1159, 1092, 813, 662 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$, 25°C, TMS): δ = 7.75–7.67 (m, 2H; ArH), 7.26–7.19 (m, 2H; ArH), 7.06–6.85 (m, 2H; ArH), 6.84–6.75 (m, 1H; ArH), 5.39 (brs, 1H; NHTs), 3.87 (s, 3H; OCH_3), 3.74–3.32 (m, 2H; $ArCH_2$), 3.08–2.41 (m, 2H; $NHCH_2$ + Cp*H*), 2.39 (s, 3H; $TsCH_3$), 2.25–0.70 ppm (m, 22H; 4×$CpCH_3$ + *CH*NHTs + *CH*$NHCH_2$ + 8×*CH* of cyclohexyl ring); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25°C, TMS): δ = 143.1 (ArC_q), 140.1 (ArC_q), 138.2 (ArC_q), 136.8 (ArC_q), 136.2 (ArC_q), 131.0, 130.6, 130.2, 129.6, 127.2, 126.9, 123.1, 122.6, 114.2 (5 ArCH and 4 CpC), 60.4 (CH), 58.1 (CH), 57.6 (CH), 55.3 (OCH_3), 46.9 (CH_2), 32.6 (CH_2 of cyclohexyl ring), 31.2 (CH_2 of cyclohexyl ring), 24.6 (CH_2 of cyclohexyl ring), 24.3 (CH_2 of cyclohexyl ring), 21.5 (CH_3), 14.0 ($CpCH_3$), 11.9 ($CpCH_3$), 11.4 ($CpCH_3$), 11.2 ppm ($CpCH_3$); *m/z* (EI) 509 (MH^+, 100%), 241 (49%), 154 (35%). HRMS (EI): *m/z* (%) calcd for $C_{30}H_{40}N_2O_3S$: 508.2760 $[M]^+$; found: 508.2761 (0.2 ppm error).

33: Rhodium(III) chloride hydrate (0.50 g, 2.4 mmol) was added to a stirred solution of 5-methoxy-2-(2,3,4,5-tetramethylcyclopenta-1,4-dienyl)-benzyl-(1*R*,2*R*) toluenesulfonyl cyclohexyldiamine **36** (1.22 g, 2.4 mmol) in MeOH (55 mL). The reaction mixture was heated under reflux and stirred for 24 h. Triethylamine (0.67 mL, 4.8 mmol) was added to the reaction mixture and the reactants were stirred at reflux temperature for a further 24 h. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude residue was triturated with water (30 mL) for 10 min, collected by filtration (filter paper), washed with water (30 mL), and then allowed to dry on the filter paper. The red-brown solid was purified by silica gel column chromatography (50→100% v/v EtOAc/hexane and then 0→5% v/v MeOH/EtOAc) to afford the product (*R,R*)-**33** as a dark-red solid (0.66 g, 1.02 mmol, 43% yield); decomposition temperature 256–258°C; $[\alpha]_D^{24}$ = −218.4 (*c* = 0.3, $CHCl_3$); IR (film): $\tilde{\nu}$ = 2925, 1608, 1447, 1264, 1238, 1127, 1086, 928, 889, 826, 662 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$, 25°C, TMS): δ = 7.93 (d, $^3J_{HH}$ = 8.2 Hz, 2H; ArH), 7.35–7.28 (m, 1H; ArH), 7.16 (d, $^3J_{HH}$ = 8.2 Hz, 2H; ArH), 7.06–6.99 (m, 2H; ArH), 4.33 (brd, $^3J_{HH}$ = 14.1 Hz, 1H; $ArCH_aH_b$), 4.19 (brd, $^3J_{HH}$ = 14.1 Hz, 1H; $ArCH_aH_b$), 4.06 (brs, 1H; NH), 3.88 (s, 3H; OCH_3), 2.40–2.24 (m, 2H; *CH*NTs + $CH_aH_bCH_aH_bCHNTs$), 2.34 (s, 3H; $TsCH_3$), 2.11–1.97 (m, 2H; *CH*$NHCH_2$ + $CH_aH_bCH_aH_bCHNHCH_2$), 1.93 (s, 3H; CpCH_3), 1.86 (s, 3H; $CpCH_3$), 1.57 (s, 3H; $CpCH_3$), 1.55–1.50 (m, 1H; $CH_aH_bCH_aH_bCHNTs$), 1.47 (s, 3H; $CpCH_3$), 1.43–1.34 (m, 1H; $CH_aH_bCH_aH_bCHNHCH_2$), 1.05–0.91 (m, 1H; $CH_aH_bCH_aH_bCHNHCH_2$), 0.90–0.75 ppm (m, 3H; $CH_aH_bCH_aH_bCHNTs$ + $CH_aH_bCH_aH_bCHNTs$ + $CH_aH_bCH_aH_bCHNHCH_2$); ^{13}C NMR (100.6 MHz; $CDCl_3$, 25°C, TMS): δ = 160.3 (ArC_q), 141.3 (ArC_q), 140.1 (ArC_q), 137.1 (ArC_q), 131.2, 128.6, 128.1 (ArCH), 118.3 (ArC_q), 117.2, 114.1 (ArCH), 104.2 ($^3J_{RhC}$ = 6.5 Hz, CpC), 100.7 ($^3J_{RhC}$ = 6.9 Hz, CpC), 97.2 (J_{RhC} = 9.6 Hz, CpC), 87.1 ($^3J_{RhC}$ = 10.0 Hz, CpC), 80.8 ($^3J_{RhC}$ = 8.8 Hz, CpC), 67.7 (CH), 63.5 (CH), 55.6 (OCH_3), 51.0 (CH_2), 35.4 (CH_2 of cyclohexyl ring), 30.2 (CH_2 of cyclohexyl ring), 24.6 (CH_2 of cyclohexyl ring), 24.3 (CH_2 of cyclohexyl ring), 21.4 (CH_3), 10.9 ($CpCH_3$), 9.9 ($CpCH_3$), 9.7 ($CpCH_3$), 7.9 ppm ($CpCH_3$); *m/z* (LSIMS) 609 (M-Cl, 14%), 307 (25%), 154 (100%), 137 (76%). HRMS (LSIMS): *m/z* (%) calcd for $C_{30}H_{38}N_2O_3SRh$ $[M\text{-}Cl]^+$: 609.1658; found: 609.1676 (2.9 ppm error).

Reduction of ketones by using catalyst (*R,R*)-**33**: Reductions were achieved, and *ee* values were determined by following the method previously reported with complex **6**.[13c]

1-Phenylethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 115°C, *P* = 15 psi, ketone 9.6 min, *R* isomer 13.9 min., *S* isomer 14.8 min.); 95% *ee* (*R*).

1-(4′-Bromophenyl)ethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 150°C, *P* = 15 psi, ketone 10.0 min, *R* isomer 15.6 min., *S* isomer 16.5 min.); 95% *ee* (*R*).

1-(4′-Methylphenyl)ethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 125°C, *P* = 15 psi, ketone 11.9 min, *R* isomer 14.3 min., *S* isomer 15.1 min.); 94% *ee* (*R*).

1-(2′-Chlorophenyl)ethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 150°C, *P* = 15 psi, ketone 6.8 min, *R* isomer 10.0 min., *S* isomer 10.7 min.); 85% *ee* (*R*).

1-(2′-Trifluoromethylphenyl)ethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 120°C, *P* = 10 psi, ketone 9.2 min, *R* isomer 15.6 min., *S* isomer 16.5 min.); 60% *ee* (*R*).

1-(2′-Methoxyphenyl)ethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 140°C, *P* = 15 psi, ketone 10.8 min, *S* isomer 13.0 min., *R* isomer 13.5 min.); 94% *ee* (*R*).

1-(1′-Naphthyl)ethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 170°C, *P* = 10 psi, ketone 27.0 min, *S* isomer 41.4 min., *R* isomer 42.9 min.); 87% *ee* (*R*).

2-Furylethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 85°C, *P* = 15 psi, ketone 9.5 min, *R* isomer 14.6 min., *S* isomer 15.7 min.); 98% *ee* (*R*).

2-Thienylethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 125°C, *P* = 9 psi, ketone 11.7 min, *R* isomer 14.0 min., *S* isomer 14.8 min.); 97% *ee* (*R*).

1-Cyclohexylethanol: Enantiomeric excess and conversion determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50 m, *T* = 92°C, *P* = 9 psi, ketone 25.7 min, *R* isomer 41.5 min., *S* isomer 42.0 min.); 87% *ee* (*S*).

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