On the Stereochemical Course of Self-Replication in Secondary Cycle Sharpless Aminohydroxylation

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Abstract: An investigation on a potential asymmetric self-replication process within the secondary cycle of Sharpless asymmetric aminohydroxylation is discussed. The reaction of two model olefins is investigated within this process and two different models for an asymmetric process are discussed. Analysis of the results on the basis of these models and a mathematical description for development of the enantiomeric excesses as a function of olefin conversion lead to the conclusion that for such processes there is no possibility for any inhibitory effect and that asymmetric self-replication in secondary cycle aminohydroxylation reactions is not a feasible process.

Keywords: amino alcohols; aminohydroxylation; osmium; oxidation; self-replication

Introduction

Asymmetric autocatalytic reactions are among the most fascinating processes in homogeneous catalysis.[1] Apart from the fundamental interest regarding information on the self-replication of chiral enantiopure molecules, explicit knowledge on such processes might ultimately reveal an origin of homochirality and, thus, of the origin of life.[2,3] Certainly, the best studied systems are autocatalytic diisopropylzinc additions to certain aldehydes, a reaction that was pioneered by Soai.[4,5] Due to the fact that autocatalytic reactions produce additional amounts of chiral catalyst continuously, they are characterised by an increase in the overall reaction rate upon conversion. In any event, asymmetric autocatalysis that does not give a 100% ee will inevitably lead to racemic product unless the process is dominated by a chiral amplification.[2a] An initial model to explain the overall reaction course for chiral autocatalytic dialkylzinc additions was described by Soai.[6] Importantly, Soai has also devised autocatalytic reactions which occur with increases in enantioselectivity during the course of catalysis.[7] The exact nature of such systems is not yet fully understood,[8] and work by Blackmond,[9–11] Brown[9,12] and Gridnev[12] suggested dimeric or tetrameric *homo*chiral structures to be the kinetically decisive catalysts. In additional, recent experiments Blackmond has obtained evidence for non-continuous rate increases and for the involvement of *hetero*chiral precipitates.[13] The origin of chiral amplification and thus the general details on the working mode of dimeric catalyst structures in catalytic reactions was uncovered by Noyori.[14] He proved that for diethylzinc additions, homochiral dimers are more reactive than their heterochiral counterparts resulting in an overproportional removal of the minor enantiomer of the catalyst. A variety of other examples of non-linear effects have become available and, as a general feature, a delicate equilibrium between associates of enantiomeric or diastereomeric entities is prerequisite for phenomena of this type.[15] On the other hand, catalytic chiral self-replication can be characterised by a scenario in which a chiral metal-ligand assembly catalyses the formation of a reaction product identical to the chiral ligand. In typical template catalysis,[16] such a reaction releases an enantiomerically enriched product which is identical to the chiral ligand that had been responsible for its asymmetric formation. Unlike in autocatalysis, this product does not complex a metal and thus does not influence subsequent catalytic cycles (Figure 1).

A single example of this type of reaction was reported by Soai in 1997.[17] He described the enantioselective transformation of α-amino ketones employing a chiral reducing agent, which was generated *in situ* from lithium aluminium hydride and chiral 1,2-amino alcohols. In

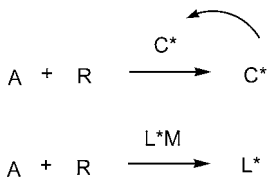

Figure 1. Schematic representation of chiral autocatalysis (*top*) and chiral self-replication (*bottom*).

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these stoichiometric processes, the original ligands were reproduced with as high as 95:5 selectivity ratios.

We here discuss an investigation on the course of a rare example of catalytic asymmetric self-reproduction in oxidation chemistry and prove that the overall stereochemical course of the reaction is influenced by the chiral product.

Results and Discussion

Recently, Sharpless reported the use of certain chiral ligands[18] for efficient osmium-catalysed dihydroxylation (AD) and aminohydroxylation (AA) reactions within the so-called secondary catalytic cycle.[19–21] All these ligands share a free carboxylic acid group as a common prerequisite for product displacement from the osmium complex after olefin functionalisation. In view of such a scenario, aminohydroxylation of acrylates should in principle represent an ideal reaction for chiral, non-racemic self-replication.[22]

Aminohydroxylation Reactions

The expected catalytic cycle for self-replicative aminohydroxylation is depicted in Figure 2 for acrylic acid as the simplest case. *In situ* formation of the azaglycol osmate ester **3** from enantiopure amino alcohol **1** and an osmium(VI) compound such as **2** is followed by oxidation with chloramine-T to furnish the catalyst **4**. Oxidation of an acrylate leads to bis(azaglycolate) **5** which is hydrolysed to give free amino alcohol **1** and regenerate catalyst **4**. Ideally, this sequence leads to a constant reproduction of the initial ligand **1** in enantiopure form.[23] Such a procedure would represent a solution to the so far unknown AA reaction of free acrylates

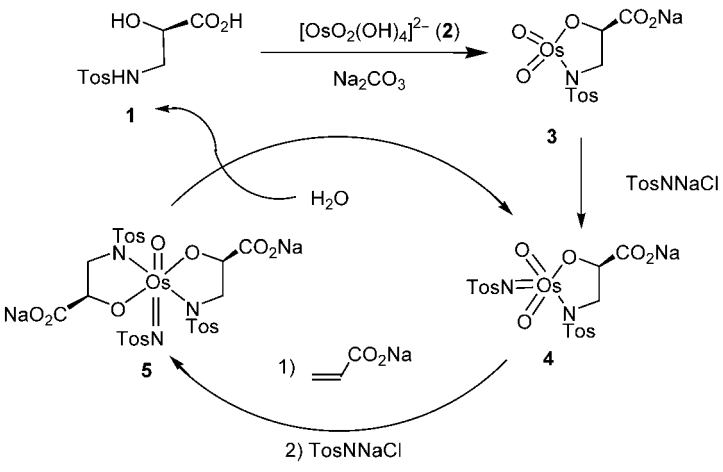


Figure 2. Catalytic cycle for self-replication in asymmetric aminohydroxylation.

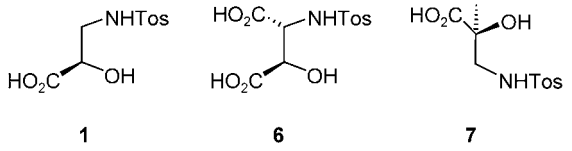


Figure 3. Chiral ligands for self-replication *via* second-cycle AA reaction.

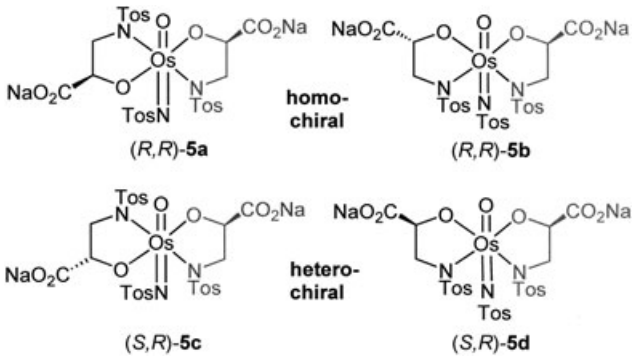


Figure 4. Intermediate bis(azaglycolate) osmium esters.

which is not feasible in the traditional 1st cycle of aminohydroxylation with *Cinchona* alkaloids.[21]

In a first attempt to validate this assumption of asymmetric self-reproduction, aminohydroxylation of sodium acrylate in the presence of **1** after 46 h led only an incomplete isolated yield of 31%. As a consequence, attention was turned towards more elaborate ligands such as **6** and **7**.

Subsequent oxidation reactions of fumarate in the presence of 3-amino-2-hydroxysuccinic acid **6** indeed convinced us of the applicability of the concept. Free succinate **6** was obtained from dimethyl fumarate *via* standard Sharpless first cycle AA reaction (80% yield, 75% ee)[24] followed by alkaline ester cleavage. Esterification of the free diacid was accomplished cleanly with the aid of Meerwein's salt regenerating the original first cycle AA product **8** without any loss in optical purity. This method of esterification was subsequently employed in derivatisation of all the reaction products for their evaluation *via* HPLC analysis.

Thus, when sodium fumarate was submitted to stoichiometric or catalytic reactions, the original chiral ligand **6** was reproduced in good to high yields and with an identical absolute configuration. However, the enantiomeric excesses of the isolated amino alcohol **6** were found to be significantly lower than at the beginning where enantiomerically pure material was employed.

This reaction outcome can be rationalised since chiral catalysts such as **4** are non-perfect and catalyse formation of the undesired enantiomer of the vicinal amino alcohol as well. In case of the present aminohydroxylation, formation of up to six different isomers of the intermediate bis(azaglycolate) osmium ester might be involved (Figure 4).

Table 1. Self-replication of amino alcohol **6**.

S/C	Yield [%][a]	ee [%][b]	ee [%][c]
0.8	88	65	–
2	79	46	44.7
3	77	32	29.5
4	77	17	18.8
6	81	10	7.3

[a] Isolated yield from complete conversion and after reductive work-up.
[b] Combined ee for original and newly formed amino alcohol. Determined after conversion into the corresponding methyl ester. HPLC conditions for **8**: Chiralcel-OG, 2-PrOH/*n*-Hex = 20/80, 1.0 mL/min, 6.8 min, 9.1 min.
[c] Calculated value at quantitative conversion according to Eq. (2) (see below).

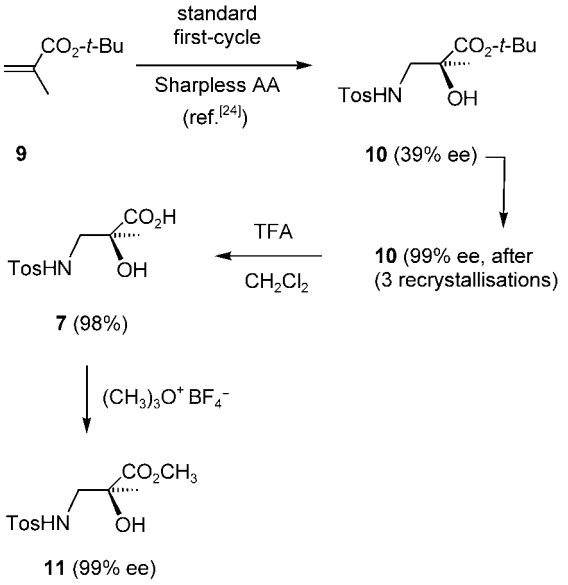
The subsequent hydrolysis of these intermediates is crucial for the overall stereochemical course. For hydrolysis rate, two extreme cases are possible that consist of either exclusive hydrolysis of the homochiral species **5a**,**b** or of their corresponding heterochiral isomers **5c**,**d**. The former case would represent an ideal scenario of asymmetric amplification leading constantly to an exclusive reproduction of enantiopure material while the latter would inevitably give rise to racemic material.

Within this context, it should be noted that these scenarios are unrealistic for high S/C ratios since the amount of active catalyst and thus the overall rate will decrease constantly over time. Still, for the case of preferred hydrolysis of the homochiral intermediates, this pathway devises the simplest model for asymmetric self-reproduction of chiral entities without the previously postulated inhibition through formation of dimeric heterochiral complexes.[14,15]

In order to rationalise the reaction course in the present AA of fumarate, a stoichiometric reaction employing 125 mol % of **6** (S/C = 0.8) was carried out (Table 1, entry 1). The reaction product was treated with sodium sulphite and the combined enantiomeric excess of original and newly formed **6** was determined after conversion into the respective methyl ester **8**. The obtained ee of 65% calculates back to a 21.25% ee for the newly formed product. Thus, the overall process of asymmetric self-replication leads to reproduction of an amino alcohol with identical absolute configuration ($e_r = 0.60625$).

In experiments 2–4, the enantiomeric excess of **6** underwent a significant drop over time, depending on the average turnover number.

A similar trend was observed for self-replication of amino alcohol **7** by oxidation of sodium methacrylate (Table 2). Ligand **7** was obtained from aminohydroxylation of *tert*-butyl methacrylate (**9**) under standard aminohydroxylation conditions (Scheme 1).[24] The respective amino alcohol **10** was isolated in 77% chemical yield with the rather low ee of 39%. Recrystallisation from 2-propanol led to an enantiomerically enriched mother liquor, and after 3 consecutive recrystallisations enantiomerically pure product was obtained. TFA-induced cleavage of the ester group gave then the desired ligand **7** as a single enantiomer. Esterification of **7** with Meerwein's salt gave the enantiopure methyl ester **11** as a standard for HPLC.



Scheme 1. Synthesis of ligand **7**.

Table 2. Self-replication of amino alcohol **7**.

S/C	Yield [%][a]	ee [%][b]	ee [%][c]
0.8	84	69	–
2	83	51	50
3	80	39	35
4	80	27.5	23.8
6	81	11	10.5
10	88	4	2
12	87	<1	0.8

[a] Isolated yield from complete conversion and after reductive work-up.
[b] Combined ee for original and newly formed amino alcohol. Determined after conversion into the corresponding methyl ester. HPLC conditions for **11**: Chiralcel-OG, 2-PrOH/*n*-Hex = 30/70, 1.0 mL/min, 11.7 min, 18.2 min.
[c] Calculated value at quantitative conversion according to Eq. (2) (see below).

As already observed for self-replications with **6**, compound **7** is again reproduced with a significant drop in enantiomeric excess over time. While the enantiomeric excess for the newly formed product in the stoichiometric control reaction was about 30%, all catalytic reactions gave products with a significantly lower ee than the original 100% from the enantiopure starting material.

This investigation on self-replication has so far been restricted to ligands **1**, **6** and **7** since analysis of the reac-

tion course for structurally related olefins is complicated by the inherent regioselectivity problem of Sharpless AA reactions.[21,25]

In view of the observed decrease in amino alcohol ee, one might conclude identical hydrolysis rates for the homochiral intermediates **5a, b** and their heterochiral isomers **5c, d**. Kinetic control experiments indicate that there is indeed no change in reaction rate for reactions from Os(VI)/**7** with methacrylate at S/C = 20 in the range of 10–40% conversion (based on a pseudo-first order rate law). This supports the assumption of identical hydrolysis rates since any difference in hydrolysis regarding the species **5a, b** and **5c, d** must inevitably result in a diminished overall reaction rate.

Mathematical Rationalisation

For any general asymmetric reaction, which involves autocatalytic behaviour without any kinetic differentiation between homo- and heterochiral intermediates whatsoever, the enantiomeric excess ee_n of the product is given by the following expression:

$$ee_n = ee_0\,(e_r)^n \qquad (1)$$

in which ee_0 denotes the enantiomeric excess of the initial ligand, n the number of average turn-overs [at complete conversion, n is given by 100C/S] and e_r the stereochemical reproduction fidelity of the ligand [with 100 e_r : 100 $(1 - e_r)$ representing the enantiomeric ratio for the newly formed product in the stoichiometric control reaction].

For the present case of ligand self-replication, the amino alcohol product arising from hydrolysis is not a catalyst itself and it is only the enantiomeric excess of the chiral catalyst that is of interest for the further stereochemical course. Only on the basis of an identical hydrolysis rate for homo- and heterochiral intermediates **5a, b** and **5c, d**, respectively, there will be release of a product with an identical ee with regard to the previous cycle from the homochiral intermediates **5a, b**, while hydrolysis of **5c, d** releases both enantiomers on a 50% statistical chance, thereby generating 50% of the original chiral catalyst and 50% of its enantiomer. Thus, the respective enantiomeric excesses of released amino alcohol from the n^{th} turn-over and osmium-bound amino alcohol (i.e., the catalyst) after the n^{th} turn-over are identical. Therefore, any value for ee_n can be correlated to ee_{n-1}. Taking into account the different amounts of intermediates **5a, b** and **5c, d**, respectively, which directly result from the stereochemical reproduction fidelity e_r, the enantiomeric excess of all free amino alcohol product after n turn-overs is given by Eq. (1) and the mathematical expression of ee as a function of turn-over is formally identical to the one for simple asymmetric autocatalysis without chirality amplification.

In the case of reductive work-up as applied in the present case, the remaining catalyst is cleaved and additional amounts of amino alcohol are released. As mentioned before, the enantiomeric excess of this additional amount is identical to that of the newly released amino alcohol in the final turn-over prior to reductive work-up. Upon inclusion of this extra amount of amino alcohol, the overall ee is given by:[26]

$$ee_n = \frac{ee_0}{n+1}\left[(n-1)\,e_r^{\,n-1} + 2\,e_r^{\,n}\right] \qquad (2)$$

The observed decrease in ee is the obvious consequence of non-perfect ligand reproduction. Application of Eq. (2) to the respective reactions of aminohydroxylations with catalysts derived from **6** and **7** has been carried out for all entries in Tables 1 and 2. The apparent good agreements between the enantiomeric excesses of the isolated material and the calculated values imply that there is indeed no rate difference in the respective hydrolysis of intermediates **5** and, hence, no inhibitory effect can result. This is not a trivial observation and it should be noted that even without any rate difference in hydrolysis and thus without inhibitory effect, the present reactions demand an insight into the exact stereochemical course of their intermediates.

It is important to note that the decrease in enantiomeric excess in the present self-replicating system proceeds more slowly than for conventional template catalysis models[17,27] since hydrolysis of (*S*,*R*)-complexes such as **5c** and **5d** still results in a 50% reproduction of the original catalyst with correct absolute configuration. This represents an over-proportional reproduction of the original stereochemistry and, for identical reproduction fidelity, the herein discussed asymmetric self-replication processes lead to newly generated catalysts with an ee that is even higher than for related autocatalyses. However, this inherent advantage of the self-replication procedure over any asymmetric autocatalysis regarding newly formed catalyst is lost. This is due to the fact that the original catalyst inevitably does not retain its high initial enantiomeric excess.

The present example thus represents a new, unexplored example for asymmetric catalytic self-replication proceeding *via* an L^*_2M intermediate which, upon release of one L*, regenerates the catalyst L^*_2M (Figure 5). Since the original and the newly formed L* in L^*_2M are no longer distinguishable, any catalytic self-

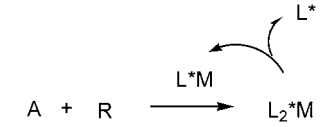


Figure 5. Schematic representation of the present self-replication in asymmetric aminohydroxylation.

replication in such a system without a reproduction fidelity of $e_r = 1$ will inevitably suffer from a decrease in enantiomeric excess as a function of turnover.

Conclusion

We have described the first detailed investigation on the stereochemical course of self-replication in secondary cycle aminohydroxylation reactions. Since the isolation of any intermediate from this catalytic cycle is still lacking, the good agreement between stereochemical outcome and mathematical description suggests that, on the basis of equal hydrolysis rates, the overall catalytic cycle is indeed best described as depicted in Figure 2. More importantly, the stereochemical analysis of the self-reproduction process itself implicitly proofs that *asymmetric* self-replication in this catalytic reaction is not a feasible process. Moreover, the absence of any inhibitory effect enforces an unavoidable decrease of enantiomeric excess over time. Therefore, the search for self-reproduction of other amino alcohols with higher enantioselective reproduction fidelity is of no value.

Experimental Section

General Remarks

Potassium osmate, *tert*-butyl methacrylate, sodium methacrylate, sodium fumarate and chloramine-T were purchased from Aldrich. Dimethyl fumarate and $(DHQD)_2PHAL$ were purchased from Fluka. Dichloromethane was distilled from CaH_2 under argon. All other solvents were reagent grade and used as received. Column chromatography was performed with silica gel (Merck, type 60, 0.063–0.2 mm and Machery Nagel, type 60, 0.015–0.025 mm). Optical rotations were measured on a Perkin Elmer 341 polarimeter. Concentrations are given in g/100 mL as dichloromethane solutions. NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer. All chemical shifts in NMR experiments are reported as ppm downfield from TMS. IR spectra were recorded on a Nicolet Magna 550 FT-IR spectrometer. MS and HRMS experiments, and elemental analysis were performed on a Kratos MS 50 and an Elementar Analysensystem Vario EL, respectively, within the service centres at the Kekulé-Department, Bonn.

General Procedure for Sharpless Aminohydroxylation[24]

A solution of potassium osmate, $K_2[OsO_2(OH)_4]$ (74 mg, 0.2 mmol) and $(DHQD)_2PHAL$ (0.2 g, 0.25 mmol) in 10 mL of a water/*tert*-butyl alcohol solution (1/1, v/v) at room temperature is stirred until both components are completely dissolved. Chloramine-T (4.32 g, 15 mmol, 3.0 equivs.) is added in one portion and the resulting yellow solution is stirred for 20 min before the olefin (5 mmol) is added in one portion. The resulting solution is stirred overnight and then quenched with a 2 M sodium sulphite solution. Extraction with dichloromethane, drying over $MgSO_4$ and evaporation to dryness gives the crude product, which is purified by column chromatography (silica gel, ethyl acetate/*n*-hexane, 1/2, v/v).

General Procedure for Secondary Cycle Aminohydroxylation

A solution of potassium osmate and the respective ligand **6** or **7** (1.1 equivs.) in a mixture of water and *tert*-butyl alcohol (1/1, v/v) is stirred for 2 h at room temperature. Chloramine-T (1.2 equivs. with regard to the substrate plus 1 equiv. with regard to the Os^{VI} source) is added in one portion and the resulting yellow solution is stirred for another 30 min before addition of sodium methycrylate or sodium fumarate, respectively. The reaction is left stirring for a period of up to 36 h and is quenched by addition of solid thiosulphate (1.0 equiv. with respect to chloramine-T). The resulting solution is extracted with dichloromethane, dried over $MgSO_4$ and evaporated to dryness.

All reactions from Tables 1 and 2 were carried out at least three times. The given ee values represent average values and may vary within margins of 5%.

General Procedure for Esterification

A solution of the respective acid in freshly distilled dichloromethane (5 mL per mmol) under argon is cooled to 0 °C and treated slowly with 1.1 equivs. of Meerwein's salt. After stirring for 6 h at room temperature, the reaction is extracted with bicarbonate solution, washed with brine and water and dried over $MgSO_4$ and evaporated to dryness to give the analytically pure methyl esters **8** and **11**, respectively, which were analysed by analytical HPLC on a chiral stationary phase.

3-Tosylamino-2-hydroxy-2-methylpropionic Acid (7)

A solution of the ester **10** (990 mg, 3 mmol) in dichloromethane at room temperature is treated with trifluoroacetic acid/dichloromethane (10 mL, 1/1, v/v) and stirred at room temperature for a period of 3 h. The solvents are removed under reduced pressure to leave the title compound in form of a colourless solid; yield: 800 mg (98%); mp 47 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.28$ (s, 3H), 2.44 (s, 3H), 2.80 (m, 1H), 3.04 (m, 1H), 3.73 (s, 3H), 7.43 (d, $J = 8.3$ Hz, 2H), 7.75 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.23$, 23.27, 51.14, 73.37, 126.98, 129.90, 137.93, 142.93, 175.96; IR (KBr): $\nu = 3358$, 3260, 3031, 2581, 1718, 1421, 1305, 1161, 1097, 908, 817, 704 cm^{-1}; MS (EI, eV): *m/z* (%) = 228 (81), 184 (100), 155 (92), 91 (88), 57 (71); HR-MS: *m/z* calcd. for $C_{10}H_{14}NO_3S$ ($M - CO_2$): 228.0695; found: 228.0699; anal. calcd. for $C_{11}H_{15}NO_5S$: C 48.34, H 5.53, N 5.12, S 11.73; found: C 48.02, H 5.31, N 4.76, S 12.29.

Dimethyl 3-Tosylamino-2-hydroxysuccinate (8)

Synthesised by Sharpless aminohydroxylation according to the general procedure (80% yield, 75% ee). This reaction had been previously described.[24] Enantiomerically pure product (>

99% ee) was obtained through recrystallisation from methanol. HPLC analysis: Chiralcel-OG, 30 °C, 1.0 mL/min, *n*-hexane/2-propanol = 70/30, t_R = 11.7 min, 18.2 min.

tert-Butyl 3-Tosylamino-2-hydroxy-2-methylpropionate (10)

Synthesised by Sharpless aminohydroxylation according to the general procedure (77% yield, 39% ee). Recrystallisation of this sample from 2-propanol gave enantioenriched material from the mother liquor. After three to four recrystallisations, enantiomerically pure material (>99% ee) was obtained. HPLC analysis: Chiralcel-OG, 20 °C, 1.0 mL/min, *n*-hexane/2-propanol = 80/20, t_R = 15.7 min, 19.2 min; mp 68 °C (decomp.); ^{1}H NMR (300 MHz, CD_3OD): δ = 1.32 (s, 3H), 1.53 (s, 9H), 2.46 (s, 3H), 2.86 (d, *J* = 12.3 Hz, 1H), 3.25 (d, *J* = 12.3 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ = 21.72, 24.16, 28.43, 75.62, 83.63, 128.31, 131.02, 139.04, 144.99, 175.29; IR (KBr): ν = 3477, 3361, 3282, 1732, 1461, 1415, 1334, 1284, 1160, 704 cm^{-1}. MS (EI, eV): *m/z* (%) = 329 $[M]^+$ (1), 273 (9), 228 (42), 184 (100), 155 (100), 91 (96), 57 (66); HR-MS: *m/z* calcd. for $C_{15}H_{23}NO_5S$: 329.1297; found: 329.1288.

Methyl 3-Tosylamino-2-hydroxy-2-methylpropionate (11)

Synthesised in optically active form by Sharpless aminohydroxylation according to the general procedure.[24] Alternatively, *rac*-**11** was obtained after secondary cycle aminohydroxylation[18a] and esterification according to the general procedure detailed above. HPLC analysis: Chiralcel-OG, 20 °C, 1.0 mL/min, *n*-hexane/2-propanol = 80/20, t_R = 6.8 min, 9.1 min; mp 92 °C (decomp.); ^{1}H NMR (300 MHz, CD_3OD): δ = 1.36 (s, 3H), 2.46 (s, 3H), 2.98 (d, *J* = 13.0 Hz, 1H), 3.19 (d, *J* = 13.0 Hz, 1H), 3.73 (s, 3H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ = 21.71, 23.89, 52.31, 53.24, 75.77, 128.31, 131.01, 139.14, 145.01, 176.43. IR (KBr): ν = 3520, 3251, 2983, 1726, 1329, 1286, 1240, 1169, 1092, 839, 704 cm^{-1}; MS (EI, eV): *m/z* (%) = 287 $[M]^+$ (2), 228 (12), 184 (93), 155 (100), 104 (47), 91 (98), 65 (37); HR-MS: *m/z* calcd. for $C_{12}H_{17}NO_5S$: 287.0827; found: 287.0832.

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[26] This equation is derived from the observation that the enantiomeric excess for the fraction of all amino alcohol from the (n – 1) turn-overs prior to work-up is calculated to $(n-1)\ ee_0\ e_r^{n-1}$ and the fraction corresponding to the final amount of amino alcohol is $2\ ee_0\ e_r^n$. The sum of both is then the following: $(n-1)\ ee_0\ e_r^{n-1} + 2\ ee_0\ e_r^n$. To arrive at the normalised ee_n, this sum is divided by the total of fractions of amino alcohol which is thus $(n+1)$. Eq. (2) is obtained upon simple transformation.

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