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Efficient Enantioselective Synthesis of the NMDA 2B Receptor Antagonist Ro 67-8867

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Abstract:

An efficient, enantioselective, and scalable eight-step synthesis for the NMDA 2B receptor antagonist Ro 67-8867 (*S*,*S*)-1 selected for the treatment of acute ischemic stroke is described based on the coupling reaction of the amino alcohol (*S*,*S*)-6 with the sulfone building block 7. The synthesis of the amino alcohol (*S*,*S*)-6 was achieved by the highly selective asymmetric hydrogenation of the piperidinone 4*HCl proceeding with concomitant dynamic kinetic resolution to (*S*,*S*)-5. Subsequent debenzylation afforded the enantiomerically pure amino alcohol (*S*,*S*)-6 after ee-enhancement by simple crystallization in good yield. The hydrogenation substrate 4*HCl was prepared as a stable hydrochloride in two steps from ethyl *N*-benzyl-3-oxo-4-piperidinecarboxylate hydrochloride (2) for which a new, short, efficient, and cheap synthesis was developed. To bypass a mutagenic intermediate, a revised safe protocol for the sulfone building block 7 was established. The new synthesis allows the access to Ro 67-8867 (*S*,*S*)-1 in an overall yield of 53% compared to 3.5% of the Discovery Chemistry approach.

Introduction

Ro 67-8867 (*S*,*S*)-**1** is a high affinity, selective, and activity-dependent antagonist of the *N*-methyl-D-aspartate (NMDA) receptor. NMDA receptor subtypes with different pharmacological properties are formed by heteromeric assembly of different subunits. It is proposed that by selectively blocking an NMDA receptor subtype (containing NR2B subunits) in brain regions vulnerable to ischemic damage, neuroprotection will be achieved without the unwanted side-effects of nonselective NMDA receptor antagonists (e.g., hallucinations, hypertension[1]).

Although the Discovery Chemistry synthesis to (*S*,*S*)-**1** is short (nine steps, six steps in the linear sequence, Scheme 1), it proved unsuitable for large-scale production due to (a) the commercial availability of the (expensive!) starting material **2** in only gram amounts, (b) the instability of the piperidinone intermediate **4**, (c) the poor efficiency of the optical resolution step of rac-**5**, and (d) the limited stability and high mutagenicity of 4-(2-chloro-ethylsulfanyl)phenol **14**, an intermediate in the synthesis of the sulfone building block **7**. Finally, after several chromatographic purifications the six-step linear sequence afforded (*S*,*S*)-**1** in only 3.5% overall yield. To allow a first multikilogram production of GMP material of (*S*,*S*)-**1** in the Kilolab within 6 months an alternative synthesis without the drawbacks mentioned had to be established and evaluated. In the following we present an efficient, technically feasible and scalable synthesis which proved suitable for the production of 50 kg of (*S*,*S*)-**1**.

Synthesis of β-Keto Ester 2. The procurement of the starting β-keto ester **2** was critical since only one reliable external supplier offered **2** in kilogram amounts but with a lead-time of 8 months at a high price. Since a literature search revealed only two low-yielding syntheses[2] of **2**, we designed a new, simple two-step sequence (Scheme 2). The reaction of ethyl-4-bromobutyrate **8**, *N*-benzylglycine ethylester **9**, and NEt_3 in DMF afforded **10** in virtually quantitative yield. Subsequent treatment of **10** under Dieckmann conditions and subsequent hydrochloride formation led directly to **2** in an overall yield of 90% over both steps (Scheme 2). Using this straightforward procedure the external supplier was able to produce 40 kg of **2** within 6 weeks at a considerably lower price.

Synthesis of Racemic Piperidinone 4*HCl. With **2** at hand we embarked on circumventing the original alkylation conditions to **3** (NaH/DMF, benzyl bromide) because of safety reasons such as the generation of hydrogen and the use of NaH as a suspension in mineral oil on a large scale. Various bases were tested for the transformation of **2** to **3**, whereby best results were obtained using potassium *tert*-butylate in THF at room temperature. Incomplete conversion and formation of side products (e.g. due to benzylation at C2) were observed with K_2CO_3 in DMF, NaOEt in EtOH or potassium *tert*-butylate in *tert*-butyl alcohol. Since piperidinone **4** was insufficiently stable (it decomposes at room temperature overnight), a stable form of **4** was required for scale-up. We found that the corresponding hydrochloride is stable at room temperature for several weeks. Therefore the crude **3** was hydrolyzed and decarboxylated in a mixture of 37% aqueous HCl and EtOH 4:1 for 19 h at reflux. Crystallization from EtOAc afforded the stable hydrochloride **4*HCl** in 78% yield over two steps (based on **2**). The conversion of **4** to the amino alcohol (*S*,*S*)-**6** by reduction with potassium selectride, optical resolution of rac-**5** with derivatives of tartaric acid (including four to five crystallizations), and subsequent debenzylation was achieved according to the conditions of the original Discovery Chemistry

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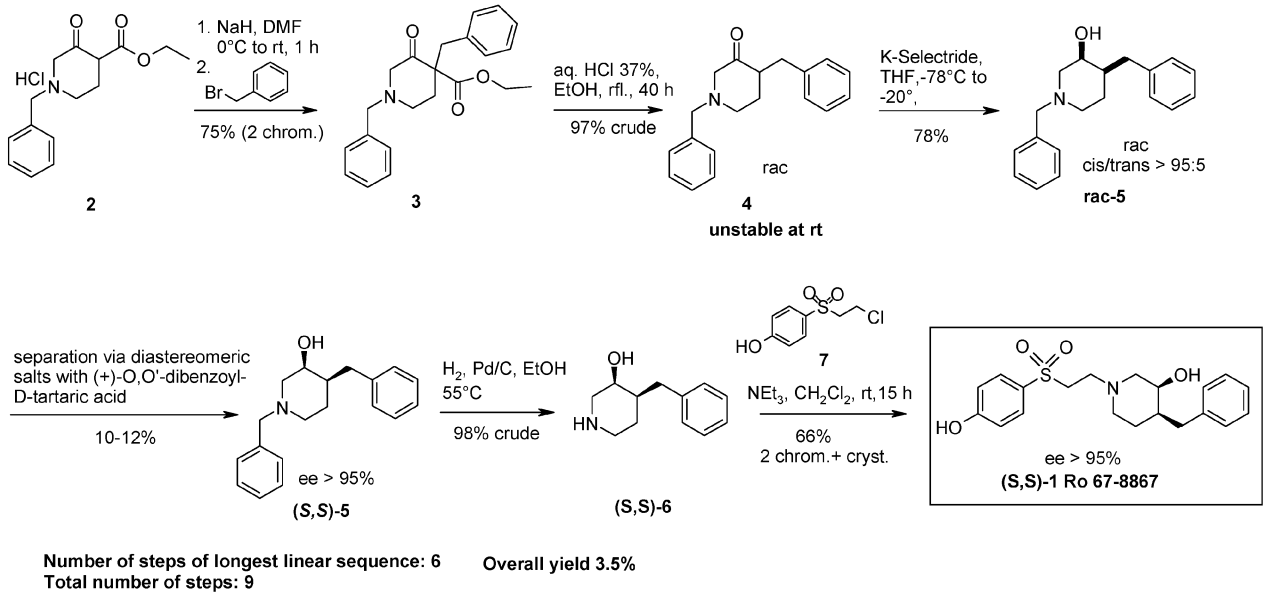
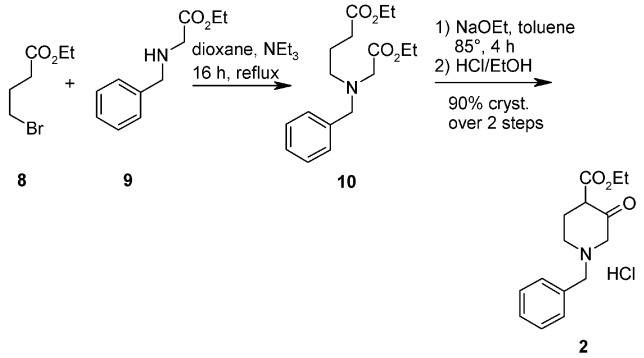
Scheme 1. **Discovery chemistry synthesis of (*S,S*)-1**



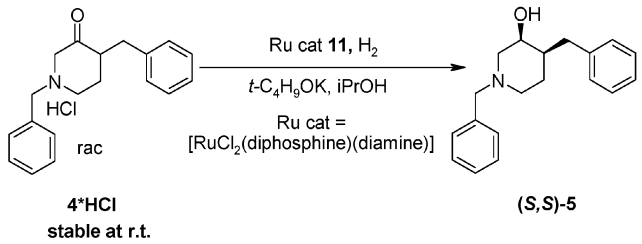
Scheme 2. **New synthesis of the starting *β*-keto ester 2**



synthesis with only 9% yield over three steps. Attempts to replace the flammable potassium selectride in the reduction step by safer reducing agents such as $NaBH_4$ or $NaBH_3CN$ in THF failed due to the increased formation of the trans isomer of rac-**5** ($NaBH_3CN$ in THF gave up to 60% trans isomer of rac-**5**). The optical resolution of rac-**5** and rac-**6** via diastereomeric salts was tested with up to 60 resolving agents. Although the original procedure was considerably improved concerning reproducibility and scalability, the best results were again achieved with derivatives of tartaric acid, but the yield of enantiomerically pure (*S,S*)-**6** was still only 10−15% yield after three to four crystallizations. Whereas enzymatic reduction methods tested on **4** failed,[3] asymmetric hydrogenation of the piperidinone **4*HCl** under conditions of simultaneous dynamic−kinetic racemization[4] was successful.

Synthesis of Piperidinol *(S,S)*-5 by Asymmetric Hydrogenation. After a short series of exploratory experiments Noyori's ruthenium precatalysts of type [$RuCl_2$(chiral diphosphine)(chiral diamine)] **11**[5] proved to be most suitable for the desired conversion (Scheme 3).

Scheme 3. **Asymmetric hydrogenation of 4*HCl via dynamic kinetic resolution**



Both chiral components in the ruthenium precatalysts, the chiral diphosphine, and the chiral diamine (Tables 1 and 2, respectively) were varied. All chiral diphosphines belong to the MeOBIPHEP family and are easily accessible in analogy to the parent compound MeOBIPHEP which is present in **11a**.[6] In agreement with previous reports on the enantioselective hydrogenation of cyclohexanone[7] and acetophenone[8] derivatives, the *ul* combination[9] of the configuration of the diphosphine and the diamine afforded higher diastereo- and enantioselectivity than the *l* combination. The introduction of substituents in the 3- and 5-positions of the aryl moieties at phosphorus led to a substantial ee improvement, the highest value of 96−97% being obtained when two isopropyl groups were present (Table 1, entry 6). The existence of a (usually positive) "3,5-dialkyl meta-effect" in enantioselective homogeneous catalysis has already been described. Its origin has been attributed to mostly steric[10] or mostly

(3) Wirz, B. *Biotechnology*, Hoffmann-La Roche Basel, personal communication.
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(5) Ohkuma, T.; Ooka, H.; Shoei, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675.
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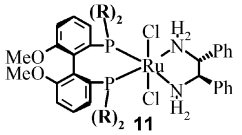
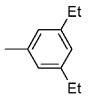
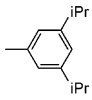
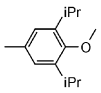
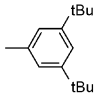
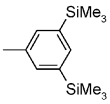
(9) a) Prelog, V.; Helmchen, G. *Helv. Chim. Acta* **1972**, *55*, 2581. b) Seebach, D.; Prelog, V. *Angew. Int. Ed. Engl.* **1982**, *21*, 654. c) Brewster, J. H. *J. Org. Chem.* **1986**, *51*, 4751.
(10) Selvakumar, K.; Valentini, M.; Pregosin, P. S.; Albinati, A.; Eisenträger, F. *Organometallics* **2000**, *19*, 1299 and references therein.

Table 1. **Influence of chiral diphosphine**[a]

Entry			%conv./h	cis/trans	%ee (*S,S*)
	 **11**				
1	R = 	*(S)-(R,R)*-**11a**	100 / 2	98:2	77
2		*(R)-(R,R)*-**11a**	100 / 19	93:7	15
3		*(S)-(R,R)*-**11b**	100 / 4	99:1	90
4		*(S)-(R,R)*-**11c**	100 / 3	>99:1	90
5		*(S)-(R,R)*-**11d**	100 / 2	99:1	95
6		*(S)-(R,R)*-**11e**	100 / 3	>99:1	96
7		*(S)-(R,R)*-**11f**	57 / 3	>99:1	40
8		*(S)-(R,R)*-**11g**	100 / 21	88:12	36
9		*(S)-(R,R)*-**11h**	27 / 2	83:17	71
10		*(S)-(R,R)*-**11i**	100 / 3	>99:1	52

[a] Conditions: 1.26 g (4.0 mmol) of **4*HCl** in 30 mL of ^{i}PrOH, [$RuCl_2$((*S*)-diphosphine) ((*R,R*)-DPEN)] molar S/C 1,000−2,000, ^{t}BuOK (5.6 mmol) (cf. ref 12), 20 °C, 40 bar H_2.

electronic[11] factors, although the influence of the combination of both factors is by far not yet understood. If an additional substituent was present in the para position or if the meta substituents were bulkier, the ee and in two instances also the cis/trans ratio decreased remarkably (entries 7−9). Replacement of the aryl moieties on phosphorus by an alkyl group such as isopropyl, thereby increasing strongly the electron density at the site of chelation, also led to a strong decrease of the ee (entry 10). Among the chiral diamines tested, DPEN afforded always the best results in terms of both cis/trans ratio and ee (Table 2).

It is well documented that the ruthenium complexes of type **11** require activation by addition of a base.[5] Among the various bases tested (^{t}BuOLi, $KOSiMe_3$, KOMe, Cs_2CO_3, K_2CO_3, Rb_2CO_3, KOH), potassium *tert*-butylate as well as its sodium analogue gave the catalysts with the highest enantioselectivity. The amount of base employed determines the activity of the catalyst, whereby the highest activity was obtained with a substrate/base ratio of 5:10.[12] Under these conditions the asymmetric hydrogenation of the racemic piperidinone **4*HCl** reached complete conversion within few hours even in the presence of very small amounts of catalyst, i.e., substrate-to-catalyst molar ratio (S/C) of 800,000 with (*S*)-3,5-Xyl-MeOBIPHEP and 200,000 with (*S*)-3,5-^{i}Pr-MeOBIPHEP (Table 3).

Preliminary experiments revealed that for the asymmetric hydrogenation of **4*HCl** the quality of the solvent (^{i}PrOH) and of the hydrogen used were not critical, such that technical qualities were employed. The presence of traces of water was not tolerated. With 0.05 equiv of water the conversion dropped to 11% (instead of 74%) after 4 h, the cis/trans ratio was reduced to 93/7 (99/1), and the ee value dropped to 94% (97%). By using the optimum conditions (cf. Scheme 5) 9 kg of (*S,S*)-**5** were produced in a joint effort of the Catalysis Lab and the Kilolab.

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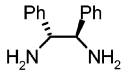
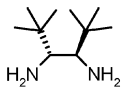
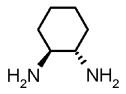
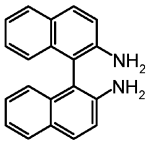
(12) Since the substrate **4** is employed as its stable hydrochloride **4*HCl**, one molar equivalent of base is added additionally to neutralize the hydrogen chloride.

Table 2. **Influence of chiral diamine**[a]

Entry	Diamine		%conv./h	cis/trans	%ee (*S,S*)
1		**DPEN** *(R,R)*	100 / 4	>99:1	90
		(S,S)	100 / 3	93:7	48
2		**DTBEN** *(R,R)*	100 / 4	99:1	73
3		**DACH** *(R,R)*	100 / 3	>99:1	87
		(S,S)	100 / 3	96:4	28
4		**DABN** *(R)*	44 / 2	80:20	50
		(S)	61 / 2	81:19	38

[a] Conditions: cf. footnote in Table 1, substrate/base = 5 (cf. ref 12), precatalyst is [$RuCl_2$((*S*)-3,5-Xyl-MeOBIPHEP)-(diamine)], i.e., **11b** and analogues.

Scheme 4. **Modified synthesis of the sulfone building block 7**

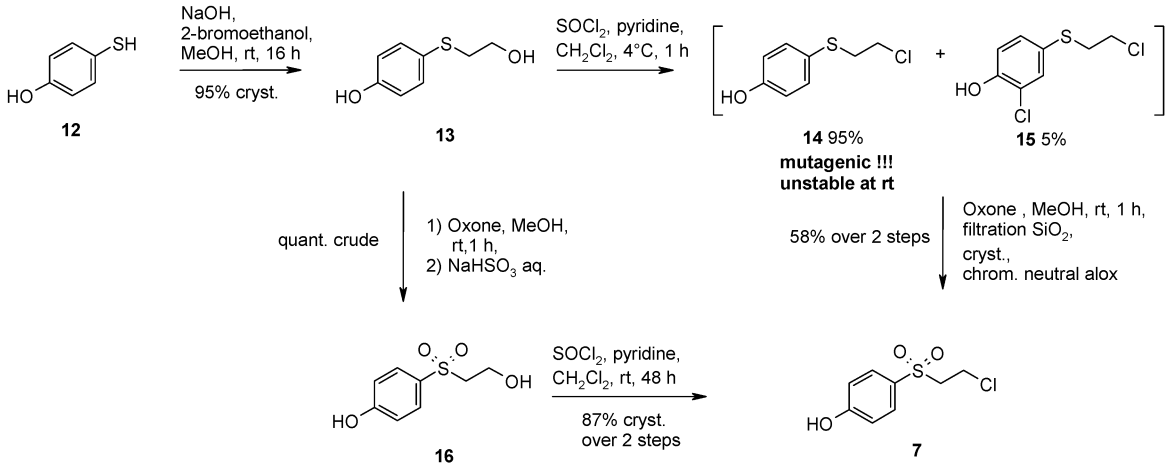


Table 3. **Performance of the ruthenium precatalysts**[a]

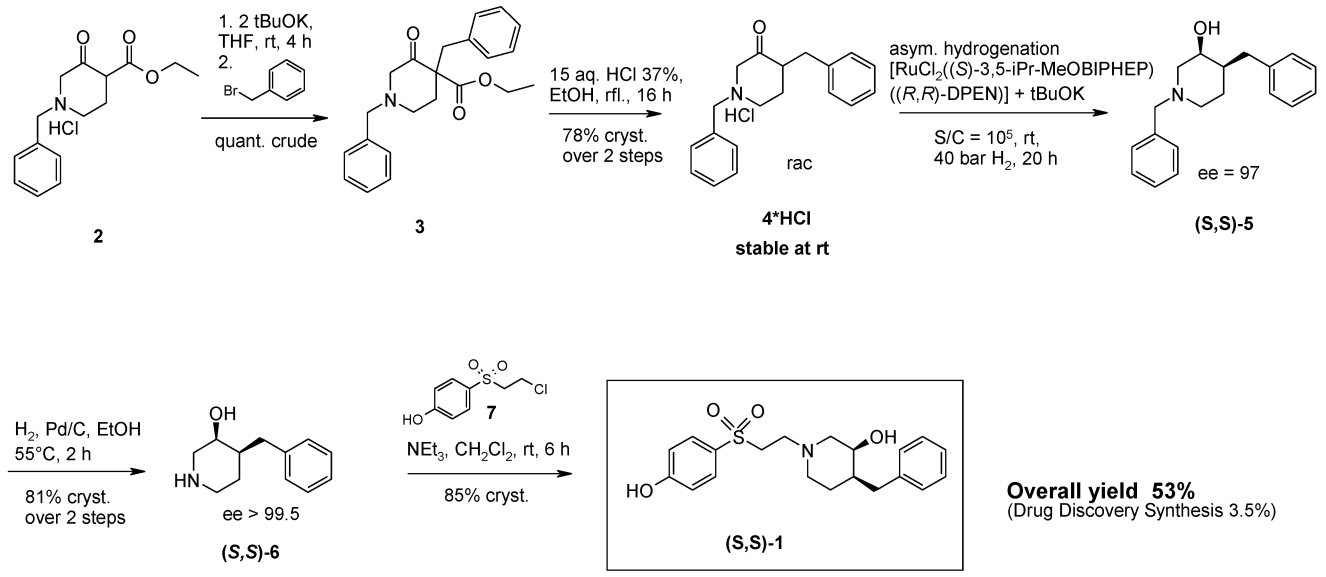
entry	precatalyst	S/C	*p* [bar]	% conv. 4 h	20 h	cis/trans	% ee (*S,S*)
1	**11b**	50,000	40	100	–	>99:1	90
2	"	400,000	40	98	100	99:1	90
3	"	800,000	40	44	99	98:2	87
4	"	800,000	200	100	–	99:1	89
5	"	1,000,000	40	55	91	95:5	79
6	**11e**	50,000	40	74	100	99:1	97
7	"	200,000	40	–	100	99:1	96

[a] Conditions: cf. footnote in Table 1, 30 mmol of **4*HCl** in 48 mL of ^{i}PrOH, substrate/base = 5−10 (cf. ref 12).

Synthesis of Sulfone Building Block 7 and Final Steps. Hydrogenolysis of the benzylic protecting group of (*S,S*)-**5** (ee ≥ 90%) with H_2 and Pd/C in EtOH and subsequent crystallization from toluene/hexane provided the enantiomerically pure amino alcohol (*S,S*)-**6** (ee ≥ 99.5%) in 81% yield over two steps (based on **4**). In a previous protocol debenzylation of (*S,S*)-**5** (ee = 48%) followed by crystallization with (+)-di-*O,O*′-*p*-toluyl-tartaric acid yielded (*S,S*)-**6** after two recrystallizations in 42% (ee = 99.8%) based on **4**.

To complete the scalable synthesis of (*S,S*)-**1**, the synthesis of the building block **7** had to be revised. The chlorosulfone **7** had been synthesized by Discovery Chemistry starting with the coupling of the commercially available 4-mercatophenol **12** with 2-bromoethanol in the presence of a base. The subsequent reaction of **13** with $SOCl_2$ and pyridine in CH_2Cl_2 led to a mixture of the unstable, highly mutagenic intermediate **14** and the byproduct **15**, which were not separable at this stage (Scheme 4). The oxidation of this mixture with oxone in MeOH led after two chromatographies and one crystallization to **7** in 58% yield over two steps. We simply inverted the chlorination/oxidation sequence and not only obtained a more efficient synthesis of **7** but also bypassed the unstable and highly mutagenic intermediate **14**. To this end, **13** was first oxidized with oxone in MeOH to afford the crude crystalline **16** in quantitative yield. Subsequent treatment of **16** with $SOCl_2$ and pyridine in CH_2Cl_2 provided **7** in 87% over two steps. With this procedure no **14** or chlorinated byproduct **15** was detected in the sulfone **7**.

Scheme 5. **Scalable enantioselective synthesis of (*S,S*)-1**



The final coupling step was carried out stepwise, whereby the chlorosulfone **7** was first treated with NEt_3 in CH_2Cl_2 to generate the corresponding vinyl sulfone (Caution! Causes skin irritation!). The subsequent addition of the crystalline amino alcohol (*S,S*)-**6** afforded the final product (*S,S*)-**1** after workup and crystallization from MeOH/toluene, in 85% yield. No filtration over SiO_2 was required to eliminate the excess of the toxic vinyl sulfone to below 0.1% area HPLC in the final product (*S,S*)-**1**.

Conclusions

In conclusion an efficient and scalable enantioselective synthesis for the NMDA 2B receptor antagonist (*S,S*)-**1** was created by taking advantage of a highly selective asymmetric hydrogenation of the piperidinone **4*HCl** to (*S,S*)-**5** as the key step, followed by debenzylation to (*S,S*)-**6** and the final coupling with the chlorosulfone **7**. Together with the short new approach to the starting piperidinone **2** and the revised, safe access to the sulfone **7**, this synthesis with 53% overall yield compares very favorably with the Discovery Chemistry synthesis (3.5% yield) and is now suitable for large-scale production.

Experimental Section

Reagents and solvent were used as received from commercial suppliers. Melting points were measured in glass capillaries using a Büchi 510 apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker AMX 400 instrument with chemical shifts given in ppm relative to TMS at $\delta = 0$. The precatalysts [$RuCl_2$(chiral diphosphine)(chiral diamine)] were prepared as isolated compounds according to ref 13 or in situ according to ref 14.

4-(Benzyl-ethoxycarbonylmethylamino)butyric Acid Ethyl Ester 10. To a solution of 2.57 L (17.25 mol) of ethyl-4-bromobutyrate (**8**) in 10 L of dioxane was added at 100 °C 1.72 kg (8.54 mol) of *N*-benzylglycine ethyl ester (**9**). The yellow reaction mixture was treated under reflux over a period of 6 h with 3.10 L (22.24 mol) of NEt_3 and subsequently stirred under reflux for 16 h. The resulting suspension was cooled to 50 °C, treated with 10 L of toluene, stirred at 0 °C for 1 h, and filtered. The filtrate was evaporated to dryness to yield 3.08 kg of crude product **10**. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.36-7.20$ (m, ArH, 5H), 4.19−4.05 (m, 2 × OCH_2, 4H), 3.77 (s, CH_2, 2H), 3.29 (s, CH_2, 2H), 2.67 (t, CH_2, 2H, $J = 7.2$), 2.35 (t, CH_2, 2H, $J = 7.2$), 1.85−1.74 (m, CH_2, 2H), 1.29−1.19 (m, 2 × CH_3, 6H). IR (MIR) selected cm^{-1}: 2980, 1729, 1452, 1370, 1246, 1177, 1139, 1075, 1027, 956, 913, 855, 736, 698. MS (ISP): 308 (100%, $[M + H]^+$).

Ethyl *N*-Benzyl-3-oxo-4-piperidinecarboxylate Hydrochloride 2. A solution of 2.02 kg (5.60 mol) of 4-(benzyl-ethoxycarbonylmethylamino)butyric acid ethyl ester (**10**) in 10 L of toluene was treated at room temperature with 0.79 kg (11.03 mol) of sodium ethoxide (exothermic). The reaction mixture was heated to 85 °C and stirred for 3.5 h. The formed suspension was cooled to room temperature and treated with 5 L of toluene and 0.5 kg of dicalite speedex. After neutralization by slow addition of 0.7 L of acetic acid, the suspension was filtered. The filtrate was concentrated to a volume of 9 L and treated with 1.4 L (6.86 mol) of HCl in ethanol (4.9 M). After formation of crystals, ethanol was exchanged under reduced pressure by addition of 8 L of toluene. The formed suspension was treated with 5 L of toluene, stirred at 0 °C for 16 h, and subsequently filtered. The crystals were dried to yield 1.62 kg (94% over two steps) of product. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.68$ (s, OH, 1H), 7.72−7.62 (m, ArH, 2H), 7.49−7.43 (m, ArH, 3H), 4.46−4.33 (m, CH_2Ar, 2H), 4.23 (q, $COOCH_2$, 2 H, $J = 8.0$), 3.96−3.80 (m, CH_2, 1H), 3.72−3.28 (m, 2 × CH_2, 3H), 3.15−2.98 (m, CH_2, 1H), 2.69−2.54 (m, CH_2, 1H), 1.25 (t, CH_3, 3H, $J = 8.0$). IR (Nujol) selected cm^{-1}: 3403, 2922, 2853, 2479, 1673, 1630, 1455, 1415, 1373, 1321, 1301, 1225,

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1139, 1094, 1058, 1021, 984, 796, 753, 704. EA: calculated C: 60.50, H: 6.77, N: 4.70, Cl: 11.91, found: C: 60.02, H: 6.94, N: 4.71, Cl: 11.81. MS (ISP): 262 (100%, $[M + H]^+$).

1,4-Dibenzyl-3-oxo-piperidine-4-carboxylic Acid Ethyl Ester 3. A mixture of 38.3 g (341.0 mmol) of potassium *tert*-butoxide and 625 mL of absolute tetrahydrofuran was stirred at room temperature for 0.5 h. The resulting milky solution was cooled to 0 °C, and then 50.0 g (168.0 mmol) of *N*-benzyl-3-oxo-4-piperidine carboxylate hydrochloride (**2**) was added via a powder dropping funnel whereby the temperature was kept below 5 °C. The mixture was then warmed to room temperature and further stirred for 1 h, resulting in a yellow solution. After cooling to 0 °C, a solution of 30.2 g (176.0 mmol) of benzyl bromide in 20.0 mL of absolute tetrahydrofuran was added dropwise within 0.5 h. A maximum temperature of 2 °C was observed. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction solution was cooled to 0 °C, and 200 mL of saturated NH_4Cl solution was added. After extraction and phase separation, the aqueous phase was extracted twice with 100 mL of ethyl acetate. The combined organic phases were washed twice with 100 mL of saturated NaCl solution and dried over Na_2SO_4; the solvent was evaporated under reduced pressure and the residue dried to yield 58.3 g (99%) of crude ester **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31−7.09 (m, 2 × ArH, 10H), 4.06 (q, $COOCH_2$, 2 H, J = 7.2), 3.53 (d, CH_2ArH, 1H, J = 13.2), 3.48 (d, CH_2ArH, 1H, J = 13.2), 3.25 (d, NCH_2CO, 1H, J = 14.0), 3.14 (d, CH_2ArH, 1H, J = 15.6), 3.02 (d, CH_2ArH, 1H, J = 16.0), 2.91 (d, NCH_2CO, 1H, J = 13.6), 2.74−2.65 (m, CH_2, 1H), 2.60−2.44 (m, CH_2, 2H), 1.69−1.60 (m, CH_2, 1H), 1.10 (t, CH_3, 3H, J = 7.2). IR (film) selected cm^{-1}: 3029, 2931, 2801, 1722, 1604, 1584, 1495, 1454, 1367, 1297, 1237, 1194, 1095, 1028, 917, 860, 776, 743, 702. MS (ISP): 352 (100%, $[M + H]^+$), 174 (15).

1,4-Dibenzyl-3-oxo-piperidine Hydrochloride 4*HCl. A solution of 118.0 g (0.34 mol) of crude 1,4-dibenzyl-3-oxo-piperidine-4-carboxylic acid ethyl ester (**3**) in 118.0 mL of absolute ethanol was cooled to 0 °C, and subsequently 405 mL (4.9 mol) of 37% hydrochloric acid was cautiously added. The reaction temperature was kept below 7 °C. Finally the mixture was heated under reflux for 19 h. To the dark-brown solution was added some crystals of 1,4-dibenzyl-3-oxo-piperidine hydrochloride, and then the mixture was allowed to cooled to room temperature and was further stirred for 2 h. The resulting crystals were isolated on a Buchner funnel, washed twice with 60 mL of deionized water, and dried to yield 102.2 g of crude product **4*HCl**. Then 400 mL of ethyl acetate was added to the crude product, and the mixture refluxed for 2 h and cooled to room temperature. The resulting beige suspension was filtered, and the crystals were washed twice with 50 mL of ethyl acetate and dried to yield 82.2 g (78% over two steps) of **4*HCl**. ^{1}H NMR (400 MHz, $CDCl_3$) E/Z isomers of the salt, very broad peaks δ = 11.48, 11.75 (2s, HCl, 1H), 7.65−7.40 (m, ArH, 5H), 7.32−7.11 (m, ArH, 5H), 4.49−4.28 (m, CH_2ArH, 2H), 3.97−3.75 (m, CH_2, 2H), 3.60−3.45 (m, CH_2ArH, 2H), 3.22−3.11 (m, CH, 1H), 2.96−2.81 (m, CH_2, 1H), 2.41−2.32 (m, CH_2, 1H), 2.07−1.85 (m, CH_2, 2H). IR (Nujol) selected cm^{-1}: 2925, 2854, 2459, 2361, 1720, 1454, 1342, 1074, 971, 921, 755, 727, 700. EA: calculated C: 72.25, H: 7.02, N: 4.43, Cl: 11.23, found: C: 72.01, H: 6.83, N: 4.53, Cl: 11.27. MS (ISP): 280 (100%, $[M + H]^+$), 262 (9). Mp 202−203 °C.

(3*S*, 4*S*)-1,4-Dibenzyl-piperidin-3-ol (*S*,*S*)-5. In a glovebox (O_2 content ≤ 2 ppm) 16.9 mg of [$RuCl_2$((*S*)-3,5-^{i}Pr-MeOBIPHEP)((*R*,*R*)-DPEN)] **11e** (0.013 mmol) were dissolved in 20.0 mL of 2-propanol. The clear, yellow catalyst solution was stirred for 20 min at room temperature. In the glovebox a glass flask was charged with 41.0 g of **4*HCl** (128.8 mmol), 205.0 mL of 2-propanol, and 17.5 g (156.0 mmol) of potassium *tert*-butylate. The resulting suspension was stirred for 10 min (exothermic up to 30 °C) and transferred into a 380-mL stainless steel, glass-lined autoclave and treated with 4.0 mL of catalyst solution (2.6 μmol → S/C 50,000). The autoclave was then sealed and connected to a hydrogenation line. The hydrogenation was carried out under stirring at room temperature and at a pressure of 40 bar. After 2 h the reaction was completed as determined by hydrogen absorption. The reaction mixture (yellow suspension) was removed from the autoclave with the aid 50 mL of 2-propanol and treated under vigorous stirring with 300 mL of ethyl acetate, 170 mL of water, 50 mL of aqueous NH_4Cl 5% solution, and 50 g of solid NaCl. After phase separation, the aqueous phase was extracted twice with 100 mL of ethyl acetate, and the combined organic phases were washed with 150 mL of brine. The combined organic phase was dried over Na_2SO_4, the solvent was evaporated under reduced pressure to yield 35.6 g of crude (*S*,S)-**5** as light-yellow crystals (ee = 96%). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.37−7.13 (m, ArH, 10H), 3.59 (s, C*H*OH, 1H), 3.50 (s, CH_2ArH, 2H), 3.00−2.90 (m, CH_2, 1H), 2.89−2.71 (m, OH, CH_2, 3H), 2.61−2.49 (m, CH_2, 1H), 2.13−2.04 (m, CH_2, 1H), 2.00−1.86 (m, CH_2, 1H), 1.68−1.38 (m, CH, CH_2, 3H).

(3*S*, 4*S*)-4-Benzyl-piperidin-3-ol (*S*,*S*)-6. A solution of 35.6 g of crude (*S*,*S*)-**5** (126.6 mmol) in 400.0 mL of ethanol was treated at room temperature with 6.7 g of Pd/C 10% (6.3 mmol). The black suspension was stirred under H_2 for 2 h at 55 °C. Subsequent filtration and evaporation of the solvent yielded 25.3 g of the crude product (*S*,*S*)-**6** as amorphous material. This material was dissolved at 100 °C in 100 mL of toluene, cooled to 65 °C, and treated with 125 mL of hexane. The so-formed suspension was cooled to 35 °C and treated again with 125 mL of hexane. The suspension was stirred for 48 h at 0 °C and filtered to yield 10.0 g of product (*S*,*S*)-**6** as white crystals. The mother liquor was dissolved at 90 °C in 45 mL of toluene, treated at 55 °C with 55 mL of hexane, cooled to 45 °C, and 55 mL of hexane was again added. The suspension was stirred for 16 h at room temperature and for 3 h at 0 °C and filtered to yield 9.7 g of product (*S*,*S*)-**6** as white crystals. Yield: 81% over two steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31−7.14 (2m, ArH, 5H), 3.58 (s, C*H*OH, 1H), 3.09−2.98 (m, CH_2, 2H), 2.79−2.71 (m, CH_2, 1H), 2.65−2.49 (m, OH, NH, CH_2 (1H), CH_2, 5H), 1.71−1.61 (m, CH, 1H), 1.61−1.48 (m, CH_2, 1H), 1.46−

1.36 (m, CH_2, 1H). IR (Nujol) selected cm^{-1}: 3298, 2922, 2854, 2739, 1601, 1495, 1471, 1450, 1106, 1094, 1065, 946, 854, 736, 698. MS (EI): 191 (100%, [M]), 118 (76), 91 (44), 30 (100). Mp 91.5−92.5 °C.

(3*S*,4*S*)-4-Benzyl-1-[2-(4-hydroxybenzenesulfonyl)ethyl]piperidin-3-ol (*S*,*S*)-1. To a solution of 5.9 g of chlorosulfone **7** (26.1 mmol) in 50.0 mL of dichloromethane was added at 37 °C 3.9 mL of triethylamine (27.5 mmol). The clear solution was stirred for 3.5 h at this temperature. A solution of 5.0 g of (*S*,*S*)-**6** (26.1 mmol) in 50.0 mL of dichloromethane was added over a time period of 30 min. The reaction mixture was stirred for 2 h at 37 °C, and the reaction was monitored by TLC and HPLC. The reaction mixture was cooled to room temperature, treated with 80 mL of water and with 20 g of solid NaCl. After extraction and phase separation the water phases were extracted twice with 70 mL of dichloromethane. The combined organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was dried (room temperature, 0.1 mbar, 2 h) to yield 10.7 g of crude (*S*,*S*)-**1** as white foam. The crude (*S*,*S*)-**1** (10.5 g) was dissolved in 10 mL of dichloromethane/TBME = 19/1 and filtered over 110 g of SiO_2 (0.043−0.060 mm) with 1.5 L of dichloromethane/TBME = 19/1, 1.0 L of dichloromethane/TBME = 2/1, and 1.0 L of dichloromethane/TBME = 1/1. The samples with the pure product were collected, and the solvent was evaporated to yield 8.5 g of (*S*,*S*)-**1** as a white powder. (*S*,*S*)-**1** (8.3.g) was dissolved at 40 °C in 7 mL of methanol. The volume of the solution was reduced via evaporation of the solvent to 35 mL. The residue was treated dropwise with 175 mL of toluene and with some crystals of (*S*,*S*)-**1**. The volume of the so-formed suspension was reduced to 90 mL. The thick suspension was filtered, and the crystals were washed with 60 mL of toluene. The crystals were dried (room temperature, 0.1 mbar, 15 h) to yield 8.0 g of (*S*,*S*)-**1** as white crystals. Yield: 85%. ^{1}H NMR (400 MHz, DMSO) δ = 10.60 (s, OH, 1H), 7.71 (d, ArH, 2H, J = 8.8), 7.29−7.09 (2m, ArH, 5H), 6.95 (d, ArH, 2H, J = 8.8), 3.90 (s, OH, 1H), 3.46−3.29 (2m, SO_2CH_2, CH−O, 3H), 2.69−2.35 (2m, CH_2ArH, 2 × CH_2, 5H), 2.06−1.96 (m, CH_2, 1H), 1.93−1.82 (m, CH_2, 1H), 1.54−1.35 (2m, CH, CH_2, 2H), 1.21−1.12 (m, CH_2, 1H). IR (Nujol) selected cm^{-1}: 3582, 2924, 2855, 1601, 1580, 1454, 1378, 1303, 1247, 1140, 1091, 1022, 837, 759, 743, 698. EA: calculated C: 63.98, H: 6.71, N: 3.73, S: 8.54, found: C: 63.96, H: 6.86, N: 3.82, S: 8.72. MS (ISP): 398 (8%, $[M + Na]^+$), 376 (100, $[M + H]^+$), 358 (12). Mp 155.5−156.2 °C.

4-(2-Hydroxyethylsulfanyl)phenol 13. A solution of 5.0 g (35.7 mmol) of 4-mercaptophenol (**12**) in 50 mL of methyl alcohol was treated at −5 °C dropwise over a period of 30 min with 39.2 mL (39.2 mmol) of aqueous NaOH 1 N and stirred 1 h at −5 °C. A solution of 5.2 mL (39.2 mmol) of 2-bromoethanol in 16.5 mL of methyl alcohol was added dropwise at −5 °C over a period of 15 min. The reaction mixture was stirred for 21 h at room temperature and concentrated, and the residue was treated with 10 mL of water and 30 mL of TBME. After extraction and phase separation, the organic phase was washed with 20 mL of saturated $NaHCO_3$ and 20 mL of brine. The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure to yield 6.03 g of crude product **13**. This crude product was dissolved in 18 mL of TBME at 40 °C and subsequently treated dropwise with 25 mL of hexane. The so-formed suspension was stirred 16 h at room temperature and 1 h at 4 °C. The crystals were separated on a filter funnel and washed with 5 mL of hexane (4 °C) to yield 4.8 g (78%) of product **13** as white crystals. ^{1}H NMR (250 MHz, DMSO) δ = 9.55 (s, OH, 1H), 7.23 (d, ArH, 2H, J = 8.6), 6.73 (d, ArH, 2H, J = 8.6), 4.82 (s, OH, 1H), 3.52−3.40 (m, CH_2, 2H), 2.84 (t, CH_2, 2H, J = 7.0). MS (ISN): 229 (100%, $[M + OAc]^-$), 169 (29, $[M - H]^-$). Mp 71.5−72.0 °C.

4-(2-Hydroxyethansulfonyl)phenol 16. A solution of 5.0 g (28.5 mmol) of 4-(2-hydroxyethylsulfanyl)phenol (**13**) in 25 mL of methyl alcohol was treated at 10 °C in parts over 20 min with 26.3 g (42.8 mmol) of oxone. The suspension was stirred at room temperature (exothermic reaction) for 2 h and filtered, and the filtrate was treated with 1 mL of aqueous sodium hydrogen sulfite solution (38−40%). The pH of the reaction mixture was adjusted to 7 with 2 mL of aqueous NaOH (28%), the suspension was filtered, and the filtrate was evaporated. The residue was treated with 20 mL of toluene, and subsequently the solvent was evaporated. This procedure was repeated two times to yield 6.81 g of crude product **16** as white crystals. ^{1}H NMR (400, DMSO) δ = 10.54 (s, OH, 1H), 7.69 (d, ArH, 2H, J = 8.8), 6.94 (d, ArH, 2H, J = 8.8), 4.83 (s, OH, 1H), 3.69−3.59 (m, CH_2, 2H), 3.33 (t, CH_2, 2H, J = 6.4). IR (Nujol) selected cm^{-1}: 3168, 1604, 1588, 1500, 1465, 1315, 1133, 1073, 1020, 841, 736. MS (EI): 202 (9%, [M]), 174 (13), 157 (30), 109 (32), 94 (100). Mp 125.9−127.6 °C.

4-(2-Chloroethansulfonyl)phenol 7. A solution of 6.81 g of crude 4-(2-hydroxyethansulfonyl)phenol (**16**) in 35 mL of CH_2Cl_2 was treated at room temperature with 5.3 mL (65.9 mmol) of pyridine. To the reaction mixture at 0 °C was added dropwise over 15 min a solution of 4.2 mL (57.1 mmol) of thionyl chloride in 10 mL of CH_2Cl_2. After 20 h at room temperature the reaction mixture was treated with 35 mL of brine and extracted, and the organic phases were washed twice with a total of 100 mL of aqueous half-saturated NaCl. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield 6.77 g of crude product **7**. The crude product was dissolved in 2.5 mL of CH_2Cl_2 and 25 mL of toluene, stirred for 24 h at 50 °C, 24 h at room temperature, and 48 h at 0 °C. The so-formed suspension was filtered to yield 5.44 g (87% over two steps) of product **7** as white crystals. ^{1}H NMR (400 MHz, DMSO) δ = 10.65 (s, OH, 1H), 7.73 (d, ArH, 2H, J = 8.8), 6.97 (d, ArH, 2H, J = 8.8), 3.79−3.68 (m, 2 × CH_2, 4H). IR (Nujol) selected cm^{-1}: 3310, 2934, 2855, 1605, 1591, 1445, 1319, 1298, 1138, 1085, 845, 838, 758. EA: calculated C: 43.54, H: 4.11, Cl: 16.07, S: 14.53, found: C: 43.57, H: 4.03, Cl: 16.09, S: 14.39. MS (EI): 220 (17%, [M]), 157 (100), 109 (18), 94 (17), 93 (60), 65 (41). Mp 72.5−73.5 °C.

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