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STEREOSELECTIVE GRAM-SCALE SYNTHESIS OF (*S*)-5,5-DIMETHYL-4-PHENYLOXAZOLIDIN-2-ONE

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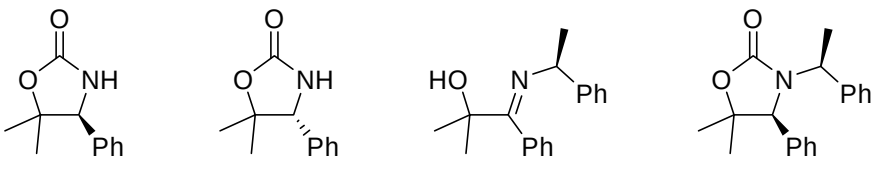
Abstract – A stereoselective gram-scale synthesis of (*S*)-5,5-dimethyl-4-phenyloxazolidin-2-one, SuperQuat [(*S*)-**1**], is described. The key step is the diastereoselective reduction of (*E*)-imine (**2**), which is synthesized from 2-hydroxy-2-methylpropiophenone (**4**) and (*S*)-α-methylbenzylamine using sodium borohydride and acetic acid to give (1*S*,α*S*)-2-methyl-1-(α-methylbenzyl)amino-1-phenylpropan-2-ol (**5**).

SuperQuats [(*S*)-**1** and (*R*)-**1**] (Figure 1) are excellent chiral auxialities developed by Davies *et al*.[1–3] for Evans-type asymmetric reactions and are widely applied to asymmetric α-alkylation,[1,4–6] conjugate addition,[1,3,4,7] cycloaddition,[8] epoxidation,[9] and kinetic resolution.[10] After the asymmetric reactions of *N*-acyl SuperQuats the chiral auxialities are selectively cleaved to afford desired homochiral products.[5] The selectivity of exocyclic cleavage is due to steric interactions between the geminal 5-C dimethyl groups and the nucleophile attacking at the carbonyl of the oxazolidin-2-one.[5] Moreover, reductive cleavage of *N*-(α-substituted) acyl SuperQuats with DIBAH directly affords non-racemic α-substituted aldehydes without loss of stereochemical integrity.[4]



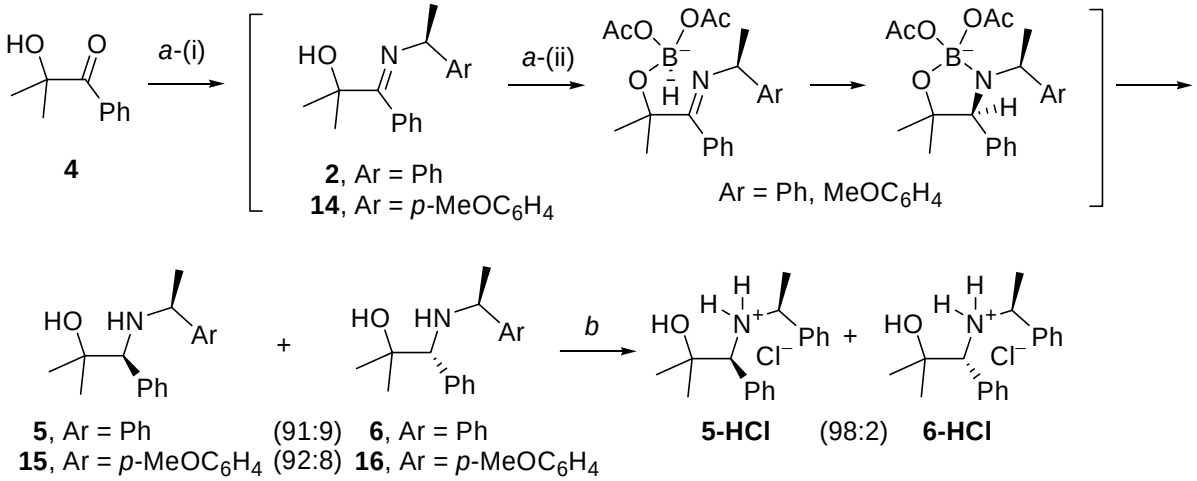
(*S*)-**1** (*R*)-**1** **2** **3**

Figure 1. SuperQuats [(*S*)-**1** and (*R*)-**1**] possessing a phenyl group and intermediates (**2** and **3**) for synthesis of (*S*)-**1**

SuperQuats [(*S*)-**1** and (*R*)-**1**] have been synthesized by two methods. The Grignard reaction of *N*-Boc-L- and *N*-Boc-D-phenylglycine methyl esters following formation of the oxazolidinone rings to give (*S*)-**1**[2] and (*R*)-**1**,[5] respectively. Another method is small-scale synthesis from (4*S*)-4-benzyl-3-(2-phenyl-1-oxo-ethyl)oxazolidin-2-one using the Evans asymmetric alkylation following hydrolysis and the Curtius rearrangement.[11]

We are investigating new synthetic methods of optically active 3-α-methylbenzyloxazolidin-2-ones and their synthetic application.[12–16] We report here a gram-scale asymmetric synthesis of SuperQuat [(*S*)-**1**] from 2-hydroxy-2-methylpropiophenone (**4**). The novel method focuses on the stereoselective hydroxyl-group-mediated reduction[17] of (*E*)-imine (**2**) (Figure 1) and the acidic removal of the α-methylbenzyl groups[12,13] of the 4-phenyloxazolidin-2-one (**3**), whose oxazolidin-2-one ring is cleaved by the Birch reduction.[18]

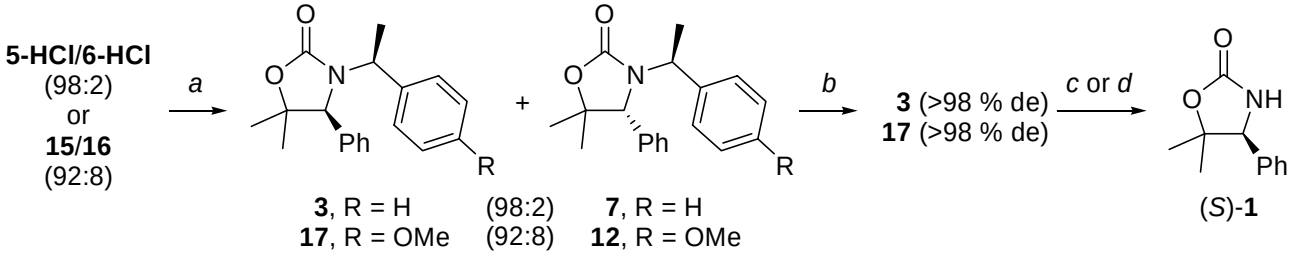
Condensation of 2-hydroxy-2-methylpropiophenone (**4**) with (*S*)-α-methylbenzylamine in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH) in refluxed toluene gave (*E*)-imine (**2**) (Scheme 1). The geometry of the double bond was determined by a comparison of the ^{1}H NMR spectral data of similar imines.[19] After the reaction mixture was diluted with THF, reduction of the imine (**2**) in the reaction mixture *in situ* with sodium borohydride and acetic acid (2 equiv.) gave an oily mixture of amino alcohols (**5** and **6**) (91:9). The good results of the asymmetric reduction of the imine (**2**) would be rationalized by consideration of the possible transition-state geometries.[17] The intramolecular hydride transfer occurred prevalently in the less-hindered *re* face of the imminium function with the formation of



Scheme 1. *Reagents and conditions*: (a) (i) (*S*)-α-methylbenzylamine or (*S*)-α-methyl-4-methoxy-benzylamine, TsOH (catalyst), toluene, reflux, 24 h; (ii) $NaBH_4$, AcOH (2 equiv.), THF (**15** and **16**; 58% from **4** *via* **14**); (b) 4 M HCl in dioxane, hexane (**5-HCl** and **6-HCl**; 66% from **4** *via* **2**).

5. After work-up, the oily mixture of the amino alcohols (**5** and **6**) was dissolved in hexane and treated with a 4 M solution of hydrogen chloride in dioxane to give hydrochloride salts (**5-HCl** and **6-HCl**) (98:2) as fine powder. The powder was not crystalline material; however it was easy to collect by filtration, and the yield was 66% from propiophenone (**4**).

Amino alcohol hydrochloride (**5-HCl**) (96% de) was converted into oxazolidin-2-one (**3**) (96% de) with CDI in refluxing 1,2-dichloroethane (Scheme 2). Oxazolidin-2-one (**3**) was purified by recrystallization from hexane (74% from **5-HCl**, >98% de).



Scheme 2. *Reagents and conditions*: (a) CDI, Et_3N, 1,2-dichloroethane, reflux; (b) Recrystallization (**3**; 74% from **5-HCl**/**6-HCl**, **17**; 39% from **15**/**16**); (c) TfOH, anisole, toluene, 100 °C (84% from **3**); (d) MsOH, anisole, toluene, 100 °C (87% from **17**).

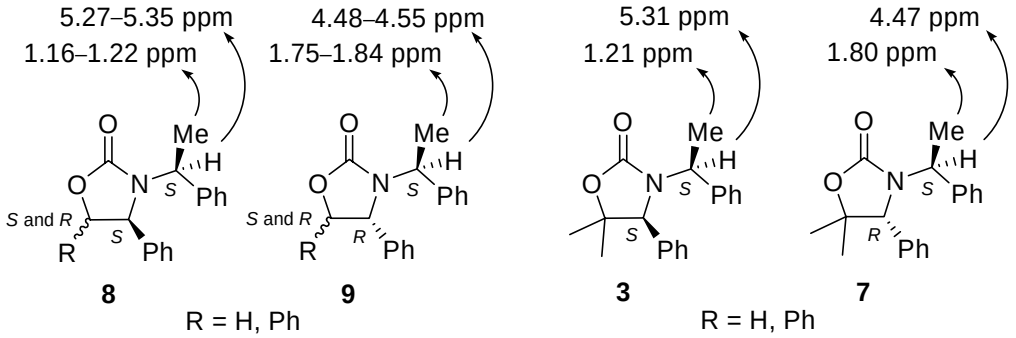


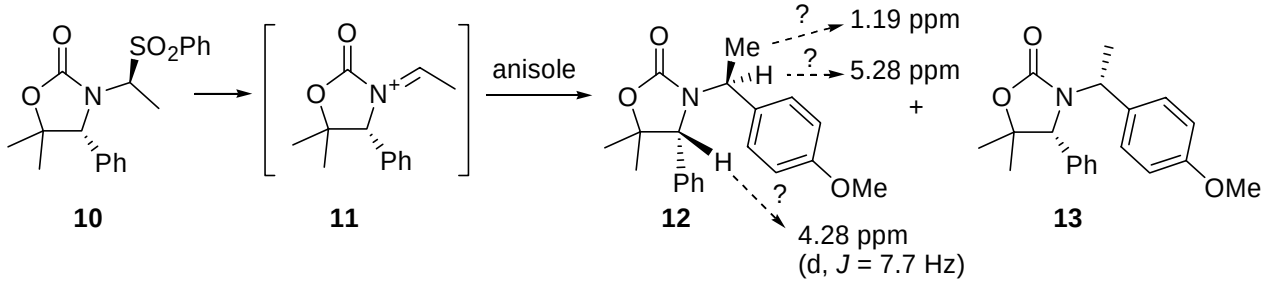
Figure 2. Relationships of shift values on ^{1}H NMR spectrum (in $CDCl_3$)

Absolute configurations of **3** and **7**[20] were deduced by a comparison of the ^{1}H NMR chemical shift values of the α-methylbenzyl moieties based on the empirical rule[13] that methyl protons of (4*S*,α*S*)-3-α-methylbenzyl-4-phenyloxazolidin-2-one derivatives (**8**)[13] resonate at a higher field than the corresponding protons of (4*S*,α*R*)-derivatives (**9**).[13] Furthermore, the benzylic proton of **8** resonates at a lower field than that of **9** (Figure 2). We found identical ^{1}H NMR spectral characters between **3** and **7**. The C-methyl protons of **3** resonated at a higher filed compared to those of **7**, and the benzylic proton of **3** resonated at a lower field compared to that of **7**. Therefore, we predicted that the relative configuration of

3 would be identical to that of **8**.

Finally, the α-methylbenzyl group of **3** was removed with trifluoromethanesulfonic acid (TfOH) and anisole in toluene to afford SuperQuat [(*S*)-**1**] in 84% yield. For easy work-up, we used one equivalent of TfOH instead of ten equivalents of methanesulfonic acid (MsOH).[12,13] The absolute stereochemistry of (*S*)-**1** was determined by a comparison of the specific rotation of reported data,[2,3] and the optical purity of (*S*)-**1** was >99% ee (HPLC analysis using CHIRALCEL OD-H). Thus, our deduction of the relative configuration of **3** was correct.

Recently, a reaction of anisole and an *N*-acyliminium ion (**11**), which was derived from (*R*)-**1** *via* *N*-[1-phenylsulfonylethyl]oxazolidin-2-one (**10**), giving **12** and **13** (80:20) was reported (Scheme 3);[18] however, the reported ^{1}H NMR spectral data of **12** (1.19 ppm, 3H, d, *J* = 7.3 Hz and 5.28 ppm, 1H, q, *J* = 7.3 Hz) were similar with our ^{1}H NMR spectral data of **3** (Figure 2), whose configuration was identical with those of **17** (Scheme 2).



Scheme 3. A reported reaction giving **12** and **13** and ^{1}H NMR spectral data of the major product

To confirm the relative configuration of the products (**12** and **13**) synthesized from **10**, we synthesized oxazolidin-2-one (**17**) according to the synthetic procedure for **3** using (*S*)-α-methyl-4-methoxybenzylamine instead of (*S*)-α-methylbenzylamine (Schemes 1 and 2). A mixture of hydrochloric acid salts (**15-HCl**/**16-HCl**) (92:8) was not a good solid to collect by filtration. Therefore, the aminoalcohols (**15** and **16**) were purified by silica gel column chromatography. After formation of a mixture of oxazolidin-2-ones (**17** and **12**) (92:8), oxazolidin-2-one (**17**) was purified with recrystallization. The α-methyl-4-methoxybenzyl group was removed easily using one equivalent of MsOH and anisole in toluene to afford (*S*)-**1** in 87% yield. The absolute configuration of (*S*)-**1** was also determined by comparison of the specific rotation of reported data[2] and the optical purity of (S)-**1** was >99% ee (HPLC analysis using CHIRALCEL OD-H).

Our ^{1}H NMR data of **17** was identical with the reported data of **12**[18] synthesized from **11**. Thus, the

reported ^{1}H NMR spectral data of **12** indicated that the major product might be **13**, and the reported signal at 4.28 ppm (1H, d, *J* = 7.7 Hz) might be incorrect (Scheme 3).

In conclusion, we developed the stereoselective convenient four-step-synthesis of SuperQuat [(*S*)-**1**] from 2-hydroxy-2-methylpropiophenone (**4**) *via* oxazolidin-2-one (**3**) in 41 % overall yield. TfOH and MsOH were good acids for the removal of the *N*-α-methylbenzyl and *N*-α-methyl-4-methoxybenzyl groups, respectively, from oxazolidin-2-ones. Our method is also a good practical method to synthesize (*S*)-**1** likewise the Davies' four-step synthetic procedure, which gives (*R*)-**1** from D-phenylglycine in 62 % overall yield.[5,21,22] In addition, the empirical rule shown in Figure 2 was useful for presumption of the relative configuration of **3**, **7**, **12**, and **13** (**17**).[24]

EXPERIMENTAL

All commercially available starting materials and solvents were used without further purification. A solution of HCl in dioxane (4 M) was purchased from Kokusan Kagaku Co. Ltd. Melting points were measured with Yanaco MP-3 apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-140 polarimeter. IR spectra were recorded on a Hitachi 215 spectrophotometer. NMR spectra were obtained with JEOL JNM-GSX400 (^{1}H NMR: 400 MHz and ^{13}C NMR: 100 MHz) and JEOL JMS-DX302 (^{1}H NMR: 300 MHz) spectrometers using tetramethylsilane as an internal standard. MS and HR-MS spectra were taken on a JEOL JMS-DX302 spectrometer. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). Analytical TLC was performed on plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} (Merck). All diastereomeric ratios were determined by ^{1}H NMR spectral analysis. Determination of the enatiomeric purities of (*S*)-**1** and (*R*)-**1** was performed using CHIRALCEL OD-H (250 × 4.6 mm) in hexane/2-propanol (7:3) [flow rate 0.5 mL/min, retention time; (*R*)-**1**: 17.5 min, (*S*)-**1**: 29.5 min]

Formation of the imines

A mixture of 2-hydroxy-2-methylpropiophenone (**4**) (16.4 g, 100 mmol) and (*S*)-(–)-α-methylbenzyl-amine (12.2 g, 100 mmol) in toluene (200 mL) was refluxed for 24 h in the presence of catalytic amount of *p*-toluenesulfonic acid monohydrate (190 mg, 1.00 mmol) by using a Dean-Stark device for water separation. After being cooled to rt, this mixture containing (*E*)-imine (**2**) in toluene was used immediately at the next reaction. A trace amount (*ca*. 50 μL) of the reaction mixture was concentrated *in vacuo* to give crude (*E*)-imine (**2**), and this material was used for NMR spectral analysis.

(*E*)-Imine (2): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (3H, m, Ar), 7.19–7.30 (5H, m, Ar), 7.00 (2H, m, Ar), 4.25 (1H, q, *J* = 6.3 Hz, PhC*H*), 1.360 (3H, s, Me), 1.358 (3H, d, *J* = 6.3 Hz, Me), 1.25 (3H, s, Me). ^{13}C

NMR ($CDCl_3$) δ: 174.3 (C=N), 144.8 (C, Ar), 135.1 (C, Ar), 128.3 (CH, Ar), 128.2 (CH × 2, Ar), 128.1 (CH × 2, Ar), 126.9 (CH × 2, Ar), 126.6 (CH, Ar), 126.3 (CH × 2, Ar), 72.9 (HOC), 59.9 (NCH), 27.9 (Me), 27.8 (Me), 25.0 (Me).

(*E*)-Imine (14): According to the procedure described above, a reaction mixture containing (*E*)-imine (**14**) was prepared from **4** (1.09 g, 6.61 mmol) and (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (1.00 g, 6.61 mmol). A trace amount of the reaction mixture was concentrated *in vacuo* to give crude (*E*)-imine (**14**), and this material was used for NMR spectral analysis. Characteristic signals are as follows; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.21 (1H, q, *J* = 6.6 Hz, PhC*H*), 1.35 (3H, s, Me), 1.33 (3H, d, *J* = 6.6 Hz, MeC*H*), 1.25 (3H, s, Me).

Reduction of the imines

The reaction mixture containing (*E*)-imine (**2**) in toluene was diluted with THF (100 mL) and cooled using an ice bath. After sodium borohydride (3.78 g, 100 mmol) was added portionwise to the mixture, acetic acid (12.0 g, 200 mmol) was added dropwise to the mixture over 30 min. The reaction mixture was stirred for 17 h with allowing warm to rt. Water (50 mL) was added dropwise to the reaction mixture over 30 min. The mixture was poured into saturated aqueous sodium hydrogen carbonate (50 mL). The organic layer was separated, and the aqueous layer was extracted twice with toluene (25 mL × 2). The organic layer and extracts were combined, washed with brine, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to give a mixture of amino alcohols (**5** and **6**) (91:9) as a colorless viscous material. The mixture of **5** and **6** was dissolved in hexane (900 mL), and 4 M HCl in dioxane (25 mL) was added dropwise to the solution with stirring. White solids were precipitated, and the mixture was stirred for 4 h using a mechanical stirrer at rt to crush the solids. A mixture of **5-HCl** and **6-HCl** (98:2, 20.2 g, 66%) as a fine powder was collected by filtration using a glass filter.

(1*S*,α*S*)-2-Methyl-1-α-methylbenzylamino-1-phenylpropan-2-ol hydrochloride (5-HCl): Colorless powder, mp 190–193 °C (ethyl acetate). $[\alpha]^{25}_D$ +52.5° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, Py-d_5) δ: 7.74–7.70 (2H, m, Ar), 7.62–7.59 (2H, m, Ar), 7.41–7.34 (3H, m, Ar), 7.23–7.17 (3H, m, Ar), 4.40 (1H, q, *J* = 6.6 Hz, *Ph*CH), 4.39 (1H, s, PhC*H*), 1.80 (3H, d, *J* = 6.6 Hz, Me), 1.52 (3H, s, Me), 1.45 (3H, s, Me). ^{13}C NMR (Py-d_5) δ: 140.3 (C, Ar), 137.0 (C, Ar), 129.4 (CH × 2, Ar), 128.3 (CH × 2, Ar), 128.1 (CH × 2, Ar), 128.0 (CH × 2, Ar), 72.0 (HOC), 71.7 (NCH), 58.2 (NCH), 28.9 (Me), 25.3 (Me), 19.7 (Me). IR (KBr) cm^{-1}: 3210, 3060, 1570, 1432, 1140, 700. MS (FAB) (glycerol) *m/z*: 270 [$(M–Cl)^+$]. HRMS (FAB) (glycerol) Calcd for $C_{18}H_{24}NO$ (M–Cl): 270.1859. Found: 270.1863. *Anal*. Calcd for $C_{18}H_{24}NOCl$: C, 70.00; H, 7.83; N, 4.54. Found: C, 70.28; H, 8.00; N, 4.41.

(1*S*,α*S*)-2-Methyl-1-α-methylbenzylamino-1-phenylpropan-2-ol (5): A small amount of **5-HCl** (96% de, 124 mg, 407 μmol) was distributed between chloroform and aqueous sodium hydrogen carbonate. The

organic layer was dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford **5** as colorless viscous oil (96% de, 105 mg, 96%).

$[\alpha]^{25}_{D}$ –8.1° (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18–7.32 (10H, m, Ar), 3.68 (1H, s, PhC*H*), 3.58 (1H, q, *J* = 6.3 Hz, PhC*H*), 1.31 (3H, d, *J* = 6.6 Hz, *Me*CH), 1.01 (3H, s, Me). ^{13}C NMR ($CDCl_3$) δ: 145.8 (C, Ar), 139.7 (C, Ar), 128.3 (CH × 2, Ar), 128.04 (CH × 2, Ar), 127.96 (CH × 2, Ar), 127.1 (CH, Ar), 127.0 (CH, Ar), 126.5 (CH, Ar), 71.8 (HOC), 69.2 (NCH), 55.0 (NCH), 27.6 (Me), 24.3 (Me), 21.9 (Me). IR (film) cm^{-1}: 2970, 1455, 1380. MS (FAB) (glycerol) *m/z*: 270 [$(M+1)^+$]. HRMS (FAB) (glycerol) Calcd for $C_{18}H_{24}NO$ (M+1): 270.1859. Found: 270.1863.

(1*S*,α*S*)-2-Methyl-(α-methyl-4-methoxybenzyl)amino-1-phenylpropan-2-ol (15): According to the procedure described above except forming the HCl salt, a crude mixture of **15** and **16** was obtained. This crude material was chromatographed on silica gel (hexane/ethyl acetate, 1:1) to afford a mixture of **15** and **16** (92:8, 1.32 g, 58% from **4**) as a colorless oil. $[\alpha]^{23}_{D}$ –36.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26–7.33 (3H, m, Ar), 7.18 (2H, d, *J* = 6.8 Hz, Ar), 7.15 (2H, d, *J* = 8.5 Hz, Ar), 6.81 (2H, d, *J* = 8.5 Hz, Ar), 3.78 (3H, s, OMe), 3.67 (1H, s, PhC*H*), 3.53 (1H, q, *J* = 6.3 Hz, MeC*H*), 1.29 (3H, d, *J* = 6.3 Hz, MeC*H*), 1.18 (3H, s, Me), 1.00 (3H, s, Me). ^{13}C NMR ($CDCl_3$) δ: 158.5 (C, Ar), 139.8 (C, Ar), 138.1 (C, Ar), 128.0 (CH × 2, Ar), 127.9 (CH × 2, Ar), 127.5 (CH × 2, Ar), 127.1 (CH, Ar), 113.7 (CH × 2, Ar), 71.7 (COH), 69.3 (NCH), 55.3 (OMe), 54.3 (NCH), 27.6 (Me), 24.3 (Me), 21.9 (Me). IR (film) cm^{-1}: 3400, 2960, 1515, 1250. MS (FAB) (glycerol) *m/z*: 300 [$(M+1)^+$]. HRMS (FAB) (glycerol) Calcd for $C_{19}H_{26}NO_2$ (M+1): 300.1965. Found: 300.1965.

Formation of the oxazolidin-2-one rings

CDI (11.9 g, 73.2 mmol) was added to a creamy suspension of **5-HCl** (18.7 g, 61.0 mmol) and triethylamine (8.5 mL) in 1,2-dichloroethane (122 mL) at rt, and the mixture was refluxed for 6 h. After being cooled to rt, 5% hydrochloric acid (120 mL) was added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted twice with dichloromethane (60 and 30 mL). The organic layers were combined, washed with half saturated aqueous sodium hydrogen carbonate (60 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a crude **3** as pale yellow solid (16.3 g, 96% de). The solid was recrystallized from hexane/ethyl acetate (10:1, 1.32 L) to afford pure **3** as colorless needles (6.51 g). The residue (9.26 g) from the first filtrate was recrystallized from hexane (500 mL) to afford colorless needles (**3**, 6.91 g, total 13.4 g, 74% yield, >98% de). The residue from the second filtrate (2.34 g) was recrystallized from hexane (50 mL) to give colorless plates (**3**, 0.87 g, 98% de). The residue (1.52 g) from the final filtrate was chromatographed on silica gel (chloroform/methanol, 98:2) to give a diastereomeric mixture of the oxazolidin-2-ones (**3**) and **7** (865 mg, diastereomeric ratio, 53:47).

(4*S*,α*S*)-3-α-Methylbenzyl-5,5-dimethyl-4-phenyloxazolidin-2-one (3): Colorless needles, mp 137–139

^{o}C (hexane). $[\alpha]^{25}_{D}$ +47.6^{o} (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26–7.61 (10H, m, Ar), 5.31 (1H, q, *J* = 7.3 Hz, MeC*H*), 3.86 (1H, s, NCH), 1.209 (3H, s, Me), 1.207 (3H, d, *J* = 7.3 Hz, CH*Me*), 0.86 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3 (C=O), 139.6 (C, Ar), 138.2 (C, Ar), 128.4 (CH × 6, Ar), 127.9 (CH, Ar), 127.4 (CH × 3, Ar), 81.4 (HOC), 66.9 (NCH), 53.1 (NCH), 28.8 (Me), 23.6 (Me), 18.0 (Me). IR (KBr) cm^{-1}: 2980, 2930, 1710, 1420, 1280, 1230, 1085, 1035, 710. MS (FAB) (glycerol) *m/z*: 296 [$(M+1)^{+}$]. HRMS (FAB) (glycerol) Calcd for $C_{19}H_{22}NO_2$ (M+1): 296.1652. Found: 296.1655. *Anal*. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.38; H, 7.36; N, 4.62.

(4*R*,α*S*)-3-α-Methylbenzyl-5,5-dimethyl-4-phenyloxazolidin-2-one (7): Characteristic signals are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.49 (1H, q, *J* = 7.3 Hz, MeC*H*), 4.27 (1H, s, PhC*H*), 1.80 (3H, d, *J* = 7.3 Hz, *Me*CH), 1.44 (3H, s, Me), 0.89 (3H, s, Me). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 157.0 (C=O), 140.4 (C, Ar), 135.8 (C, Ar), 128.2 (CH, Ar), 128.1 (CH, Ar), 127.3 (CH, Ar), 127.2 (CH, Ar), 80.7 (C, Ar), 69.5 (CH), 54.3 (CH), 28.8 (Me), 23.9 (Me), 18.7 (Me).

(4*S*,α*S*)-3-(α-Methyl-4-methoxybenzyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (17): According to the procedure described above, a crude oxazolidin-2-one (**17)** was obtained from a mixture of amino alcohols (**15** and **16**) (92:8, 685 mg, 2.29 mmol). This crude product was chromatographed on silica gel (hexane/ethyl acetate, 7:3) to afford a mixture of oxazolidin-2-ones (**17** and **12**) (92:8, 426 mg, 57%). This mixture (415 mg) was recrystallized from hexane (20 mL) to afford pure **17** (294 mg). Colorless fine needles, mp 113–114 ^{o}C (hexane). $[\alpha]^{23}_{D}$ +68.4^{o} (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (br m, Ar), 7.18 (2H, d, *J* = 8.5 Hz, Ar), 6.88 (2H, d, *J* = 8.5 Hz, Ar), 5.26 (1H, q, *J* = 7.3 Hz, MeC*H*), 3.84 (1H, s, PhC*H*), 3.82 (3H, s, MeO), 1.22 (3H, s, Me), 1.18 (3H, d, *J* = 7.3 Hz, *Me*CH), 0.86 (3H, s, Me). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 159.0 (C), 157.3 (C), 138.2 (C), 131.7 (C), 128.6 (CH × 2), 128.4 (br, CH × 3), 127.7 (br, CH × 2), 113.7 (CH × 2), 81.4 (C), 66.8 (NCH), 55.3 (OMe), 52.6 (NCH), 28.9 (Me), 23.7 (Me), 18.3 (Me). IR (KBr) cm^{-1}: 1730, 1410, 1250. MS (FAB) (glycerol) *m/z*: 326 [$(M+1)^{+}$]. HRMS (FAB) (glycerol) Calcd for $C_{20}H_{24}NO_3$ (M+1): 326.1757. Found: 326.1740. *Anal*. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.87; H, 7.13; N, 4.02.

(4*R*,α*S*)-3-(α-Methyl-4-methoxybenzyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (12): Characteristic signals are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (2H, d, *J* = 8.8 Hz, Ar), 6.70 (2H, d, *J* = 8.8 Hz, Ar), 4.47 (1H, q, *J* = 7.3 Hz, ArC*H*), 3.85 (3H, s, OMe), 3.75 (1H, s, PhC*H*), 1.77 (3H, d, *J* = 7.3 Hz, *Me*CH), 1.43 (3H, s, Me), 0.89 (3H, s, Me). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 158.7 (C), 157.0 (C), 135.9 (C), 132.6 (C), 113.5 (CH × 2), 80.6 (C), 69.4 (NCH), 55.3 (OMe), 53.7 (NCH), 28.8 (Me), 23.9 (Me), 18.8 (Me).

Removal of the α-methylbenzyl group

TfOH (6.39 g, 42.5 mmol) was added to a mixture of oxazolidin-2-one (**3**) (11.4 g, 38.7 mmol) and

anisole (20.9 g, 193 mmol) in toluene (77 mL), and the resulting mixture was stirred for 3 h at 100 °C (bath temperature). After being cooled to rt, the reaction mixture was diluted with ethyl acetate (80 mL) and washed with twice with water (50 mL × 2) and once with saturated sodium hydrogen carbonate (50 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a mixture of brown oil and solid (20.6 g). The mixture was recrystallized from hexane/toluene (1:1, 160 mL) to give (*S*)-**1** as colorless needles (5.55 g, >99% ee, 75%). The filtrate was concentrated *in vacuo* to give a brown oily residue. Hexane (50 mL) was added to the residue. The precipitated brown solid (818 mg) was collected by filtration and purified with a short column (ϕ 4.0 cm × 7.0 cm, SiO_2, hexane/ethyl acetate; 1:1) to afford (*S*)-**1** as colorless crystalline material (653 mg, >99% ee, total 6.20 g, 84%).

(*S*)-5,5-Dimethyl-4-phenyloxazolidin-2-one, SuperQuat [(*S*)-1]. Colorless needles, mp 151–152 °C. $[\alpha]^{28}_D$ +80.3° (*c* 0.5, $CHCl_3$) [lit.,[2] $[\alpha]^{23}_D$ +79.0° (*c* 0.5, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.41 (3H, m, Ar), 7.26–7.29 (2H, m, Ar), 5.76 (1H, s, NH), 4.66 (1H, s, NCH), 1.62 (3H, s, Me), 0.95 (3H, s, Me). ^{13}C NMR (100 Hz, $CDCl_3$) δ: 158.5 (C=O), 136.6 (C, Ar), 128.7 (CH × 2, Ar), 128.5 (CH, Ar), 126.3 (CH × 2, Ar), 84.5 (C), 66.0 (CH), 28.3 (Me), 23.8 (Me). IR (KBr) cm^{-1}: 3550, 2980, 1720, 1270, 995. MS (EI) *m/z*: 191 (M^+, 18%), 133 (91), 105 (73), 105 (73), 104 (95), 59 (100). HRMS (EI) Calcd for $C_{11}H_{13}NO_2$: 191.0947. Found: 191.0946.

A mixture of (*S*)-1 and (*R*)-1. To confirm the structure of **7**, a mixture of the oxazolidin-2-ones (**3** and **7**) (148 mg, 0.502 mmol, diastereomeric ratio, 53:47) was treated with TfOH (49 μL, 0.558 mmol) and anisole (271 mg, 2.51 mmol) in toluene (1.0 mL) according to the procedure described above except purification to afford a crude material, which was purified with silica gel column chromatography (hexane/ethyl acetate, 1:1) to give a mixture of (*S*)-**1** and (*R*)-**1** (49:51, 71 mg, 74%).

Removal of the α-methyl-4-methoxybenzyl group

MsOH (20 mg, 0.21 mmol) was added to a mixture of oxazolidin-2-one (**17**) (60.9 mg, 0.187 mmol) and anisole (101 mg, 0.934 mmol) in toluene (1.0 mL), and the resulting mixture was stirred for 1.5 h at 100 °C (bath temperature). After being cooled to rt, the reaction mixture was diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/ethyl acetate, 1:1) to afford (*S*)-**1** as colorless crystalline material (31.1 mg, >99% ee, 87%).

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20. For NMR analysis of the minor oxazolidin-2-ones (**7**) and (**12**) we measured a mixture of oxazolidin-2-ones (**3**/**7**) (53:47) and **17**/**12** (70:30) obtained from the filtrate of the final recrystallization of **3** and **17**, respectively.
21. In the previous communication,[2] Davies and co-workers reported the synthesis of (*S*)-**1** from *N*-Boc-L-phenylglycine methyl ester in 81 % yield.

22. *N*-Boc-L-phenylglycine methyl ester is obtained from L-phenylglycine methyl ester hydrochloride in 98 % yield.[23] We used this yield for the calculation of overall yield of (*R*)-**1** from D-phenylglycine.
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24. Very recently, we have shown that this empirical rule is applicable to the interemediates of (–)- and (+)-cytoxazones. See: S. Sugiyama, S. Arai, and K. Ishii, *Tetrahedron: Asymmetry*, 2004, **15**, 3149.