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Fast DKR of Amines Using Isopropyl 2-Methoxyacetate as Acyl Donor

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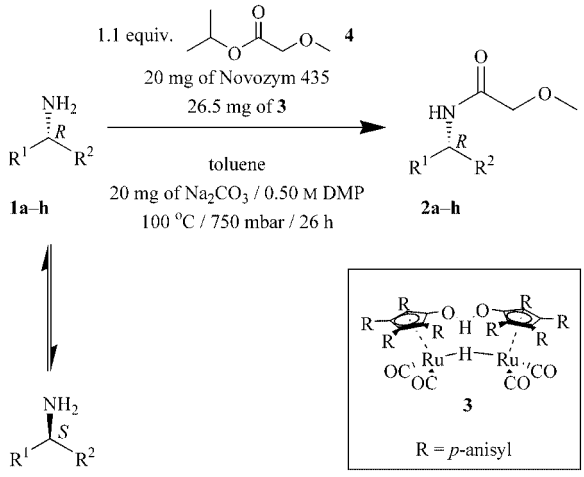
The dynamic kinetic resolution (DKR) of various primary amine substrates was performed using a modified version of the Bäckvall system. A single equivalent of isopropyl 2-methoxyacetate was used as acyl donor in combination with *p*-MeO Shvo complex as the racemization catalyst and Novozym 435 as the acylation catalyst. A reaction temperature of 100 °C was employed to ensure a high racemization rate. Adding 2,4-dimethyl-3-pentanol (DMP) as hydrogen donor at a concentration of 0.5 M successfully suppressed side product formation. Under these modified DKR conditions, complete conversion was observed for most substrates within 26 h showing both high *ee* values and good chemoselectivity, whereas the original system required a reaction time of 72 h.

Introduction

The preparation of enantiomerically pure organic compounds is a major challenge in organic chemistry. The dynamic kinetic resolution (DKR) of racemic starting materials is a particularly attractive method since it allows the synthesis of an optically pure product in theoretically 100% yield from racemic starting material. This immediately shows its advantage over normal, enzyme based, kinetic resolutions having a maximum yield of only 50%. Notably, the DKR of secondary alcohols is applied on industrial scale nowadays because of its immense importance in the field of fine chemistry.[1]

The DKR of amines has been a challenging topic in organic chemistry during the past 10 years. Racemization of amines generally requires relatively harsh reaction conditions and suffers from the formation of side products. During racemization the amine substrate is catalytically oxidized to give a non-chiral imine intermediate, which is subsequently reduced. However, the imine intermediate can react with the amine substrate to generate an aminal that readily looses ammonia, making these side-reactions irreversible.

Initial DKR systems for benzylic amines relied on Pd/C-catalyzed racemization with the disadvantage of moderate selectivity and long reaction times.[2] Over the past years, new racemization methods for amines based on Pd-nanoparticles,[3] alkylsulfanyl radical chemistry[4] and iridium-[5] and ruthenium-based[6,7] organometal complexes have been developed. A very attractive system for the DKR of both aliphatic and benzylic amines was introduced by Bäckvall.[6] They used the *p*-anisyl-modified Shvo catalyst **3** for the racemization step and Novozym 435, *Candida antarctica* Lipase B immobilized on a macro-porous polyacrylic resin, for the catalyst in the kinetic resolution step. Despite the good chemo- and enantioselectivity, this system requires a large excess (7-fold) of acyl donor and relatively long (72 h) reaction times. Given the exciting results, optimisation of this process is of great interest. In a successful DKR system, the asymmetric transformation and the racemization step should have similar rate constants.[8] Improvement of this system should focus both on an increase in the racemization and the acylation rate while keeping high selectivity. Here we like to show an improvement of the Bäckvall system for



Scheme 1. DKR of amine substrates **1a**–**h** (DMP: 2,4-dimethyl-3-pentanol, added as hydrogen donor).

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the DKR of various amines, both in terms of reaction time (26 h) and the required amount of acyl donor (1.1 equiv.), while preserving good selectivity and high *ee* values (Scheme 1).

Results and Discussion

As a start we reproduced the results of Bäckvall et al. (Table 1, entry 1)[6] for the racemization of 1-phenylethanamine (**1a**) with catalyst **3** and investigated if higher racemization rates could be obtained by altering the reaction conditions. We compared the racemization rates at a reaction temperature of 90 and 100 °C at identical catalyst and substrate loading (Table 1, entries 2 and 3). Although k_{rac} indeed increased (to 0.062 h^{-1}), the selectivity towards the substrate was slightly lower (92% after 24 h) compared to the original system (entry 1). At longer reaction times, a further decrease in selectivity was found (86% after 46 h). Reducing the amount of racemization catalyst gave no significant improvement in the selectivity (94% after 24 h, entry 4) and the k_{rac} dropped to 0.029 h^{-1}.

Table 1. Overview of racemization rates and selectivities for optically pure 1-phenylethanamine (96% *ee*) using **3** as racemization catalyst. Racemization of optically pure 1-phenylethanamine (0.50 mmol, 96% *ee*) in toluene (2 mL) using varying amounts of racemization catalyst **3** and reaction temperatures.

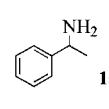
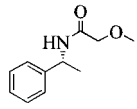
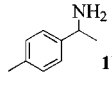
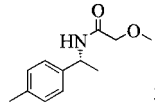
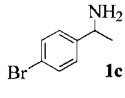
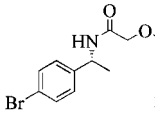
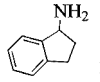
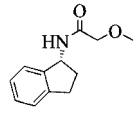
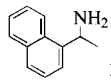
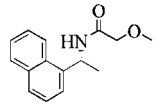
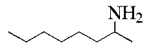
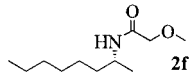
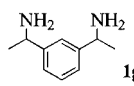
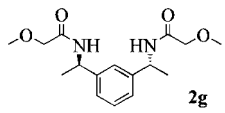
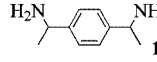
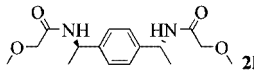
Entry	**3** [mmol]	*T* [°C]	k_{rac} [h^{-1}]	Selectivity[a] [%]/time [h]
1[b]	0.02	90	0.025	95/24
2	0.02	90	0.020	92/20
3	0.02	100	0.062	92/24, 86/47
4	0.01	100	0.029	94/24, 74/47
5[c]	0.01	100	0.022	99/24, 98/47

[a] Selectivity based on GC measurements vs. internal standard. [b] Data calculated from literature.[6] [c] 2,4-Dimethyl-3-pentanol (0.50 M) was added as hydrogen donor.

To increase the selectivity towards the substrate, we added 0.50 M 2,4-dimethyl-3-pentanol (DMP) as hydrogen donor to more effectively reduce the imine intermediate. DMP was selected since it has been established that this alcohol is not accepted as a substrate by Novozym 435 due to its steric bulkiness.[9] The addition of DMP resulted in a major improvement in selectivity (99% after 24 h) and a small decrease of k_{rac} to 0.022 h^{-1} (entries 4 and 5). To have a sufficiently high racemization rate and good selectivity in the DKR experiments, a catalyst loading of 0.04 mmol of **3** per mmol of amine substrate was selected in combination with a temperature of 100 °C and the addition of 0.5 M DMP.

To increase the acylation rate during DKR, we evaluated the effect of changing the acyl donor from isopropyl acetate into isopropyl 2-methoxyacetate (**4**). Alkyl 2-methoxyacetates emerged as very effective acyl donors for the enzymatic acylation of amine substrates. In lipase-catalyzed kinetic resolution of 1-phenylethanamine rate increases up to 200 times have been observed by using methyl 2-methoxyacetate instead of methyl butyrate as acyl donor.[10] The DKR of *rac*-1-phenylethanamine (**1a**) using 1.25 equiv. of **4** or the same amount of isopropyl butyrate as acyl donor was performed and both reactions were followed in time by chiral GC analysis (see electronic supporting information). All DKR experiments were performed under reduced pressure to remove the isopropyl alcohol from the reaction mixture. The latter can be oxidized to acetone by the racemization catalyst and subsequent reaction with the amine substrates followed by reduction results in the undesirable formation of secondary isopropylamines. The use of **4** as acyl donor results in a complete acylation of (*R*)-1-phenylethanamine within 2 h. For this reason, the racemization of the residual amine substrate is more effective, resulting in a faster overall DKR process. However, at 100 °C spontane-

Table 2. Results for the DKR of amine substrates **1a**–**h** (0.50 mmol amine groups) using *p*-MeO Shvo catalyst (**3**) (26.5 mg, 0.02 mmol), isopropyl 2-methoxyactate (**4**) (68 μL, 1.0 equiv.), Novozym 435 (20 mg), Na_2CO_3 (20.0 mg, 0.20 mmol) in toluene (8 mL) containing 0.5 M DMP at 100 °C and 750 mbar for 26 h. After 24 h an additional amount of **4** (7 μL, 0.1 equiv.) was added to complete the reaction.

Entry	Substrate	Product	Yield[a] [%]	*ee*[b] [%]
1	 **1a**	 **2a**	68	98
2	 **1b**	 **2b**	73	99
3	 **1c**	 **2c**	59	97
4	 **1d**	 **2d**	80	96
5[c]	 **1e**	 **2e**	56	99[d]
6	 **1f**	 **2f**	66	95
7	 **1g**	 **2g**	70[e]	chiral:*meso* 1:0.21 86 % *ee*[f]
8	 **1h**	 **2h**	55	chiral:*meso* 1:0.09 / 99 % *ee*[f]

[a] Isolated yields with greater than 95% purity according to ^{1}H NMR. [b] The *ee* value of purified 2-methoxyacetamide was determined by chiral GC unless otherwise noted. [c] Total reaction time 42.5 h. instead of 26 h. [d] The *ee* value was determined by chiral GC on hydrolyzed 2-methoxyacetamide after Ac_2O derivatization. [e] Purity over 90% according to ^{1}H NMR. [f] *ee* determined by chiral HPLC on hydrolyzed methoxyacetamide.

ous acylation of the amine substrate by **4** was observed, resulting in a lower *ee* of the desired reaction product. To limit this chemical background reaction, a single equivalent of acyl donor was used in all further experiments. In case of isopropyl butyrate as acyl donor, the complete initial acylation of all (*R*)-1-phenylethanamine was not observed and the *ee* of the residual amine substrate stays relatively low, indicating similar acylation and racemization rates.

Further optimization showed that a DMP concentration of 0.5 M in combination with a substrate concentration of 62.5 μM and the addition of 1 equiv. of acyl donor were found to give highest selectivity for the DKR process of 1-phenylethanamine. These reaction conditions were subsequently used for the DKR of seven other (di)amine substrates (see Table 2).

After 23.5 h a small sample of the reaction mixture was analyzed by ^{1}H NMR spectroscopy. Complete conversion of the amine groups was observed in all cases except for substrate **1e** (conversion 63%). To complete the reaction, another 0.1 equiv. of **4** was added and the reaction was continued for 2 more hours. All crude products were obtained in quantitative yield and ^{1}H NMR analysis revealed a chemoselectivity of $> 90\%$ for all substrates investigated. The isolated yields of the pure products, however, are 10–20% lower than those reported by Bäckvall for the corresponding acetamide, which is mainly due to separation problems during column chromatography. Chiral GC or HPLC analysis of the isolated products showed *ee* values which were directly comparable to those reported for the original amine DKR system. Formation of *meso*-bis(methoxyacetamides) was observed for both substrates **1g** and **1h**. In case of substrate **1h**, an excellent *ee* value of 99% and a low amount of the *meso* product were observed after hydrolysis as determined by chiral HPLC analysis. The results described here show that chiral primary amides can be obtained within 26 h and with high *ee*, and that this improved method is also applicable to produce primary diamides with high *ee* values.

Conclusions

The use of a single equivalent of isopropyl 2-methoxyacetate (**4**) as acyl donor combined with the addition of 0.5 M DMP as hydrogen donor and a reaction temperature of 100 °C results in a reaction time of less than 26 h for the DKR of various amine substrates. Complete conversions and high selectivities were observed for most substrates and the obtained *ee* values are directly comparable to those described for the original system, although isolated yields are somewhat lower due to isolation problems. Additionally, the first successful DKR of phenylene bis(ethanamine) substrates **1g** and **1h** was shown. Especially the DKR of **1h** showed excellent enantioselectivity for the enzymatic acylation step resulting in high *ee* values and limited amounts of *meso* product. In future research, those two substrates will be combined with a diacyl donor under DKR conditions with the intended formation of chiral polyamides.

Experimental Section

General: Column chromatography was performed over flash silica gel (40–63 μm; purchased from Grace Division). ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400, 300 or 200 MHz and at 100, 75 or 50 MHz respectively. Peaks are notated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qui.) or heptet (h), broadened peaks are notated as (br.). Chemical shifts are reported in ppm and are with respect to TMS (δ = 0 ppm) or the solvent peak ($CDCl_3$, $\delta = 77.16 \pm 0.32$ ppm). Chiral GC analysis was performed on a Shimadzu GC-17A equipped with a FID, an AOC-20i autosampler and a CP-Chiralcel-Dex-CB column (25 m, i.d. 0.25 mm) using helium as carrier gas. Unless otherwise stated, the following settings were used: T_{inj} = 250 °C, T_{det} = 300 °C. The separation of the 2-methoxyacetamides was optimized using the racemic compounds, which were prepared as described below. Chiral HPLC measurements were performed by Syncom B.V. (Groningen, the Netherlands) using an Agilent 1100 HPLC system (G1322A degasser, G1311A Quatpump, G1313A Autosampler) equipped with a Daicel Crownpak CR(-) 150 × 4 mm column and using aqueous $HClO_4$ (pH =1) as eluent. A G3115 DAD-detector at a wavelength of 208 (+/–4) nm was used for detection.

Formamide, 1,3,5-tri-*tert*-butylbenzene, 1,3-diacetylbenzene, 1,4-diacetylbenzene, 1-(1-naphthyl)ethylamine, 1-*p*-tolylethylamine, 2-octylamine, were purchased from Sigma–Aldrich. 4,4′-Dimethoxybenzil, 2-(4-methoxyphenyl)acetic acid, formic acid, isopropyl acetate, 2-methoxyacetic acid, 4-bromo-α-phenethylamine and 1-aminoindan were obtained from Acros. *rac*-1-Phenylethanamine was purchased from Merck, (*R*)-1-phenylethanamine and (*S*)-1-phenylethanamine were obtained from Jansen Chimica. Novozym 435 was obtained from Novozymes. Tetracarbonylruthenium was purchased from Strem. All used solvents were purchased from Biosolve (The Netherlands).

rac-1-Phenylethanamine, (*R*)-1-phenylethanamine, (*S*)-1-phenylethanamine and 2-octylamine were distilled over KOH and stored over 4 Å molecular sieves under an Argon atmosphere. Toluene was stored over 4 Å molecular sieves. Na_2CO_3 was dried under vacuum for 3 h at 300 °C and kept in a well closed vial afterwards. All other chemicals were used as received. The prepared racemization catalyst (**3**) was weighed out in the air and put under an Argon atmosphere afterwards. Novozym 435 was used as received.

General Methods for Racemization and DKR Experiments

All glassware for the racemization and DKR experiments was dried for at least 2 h at 120 °C.

Racemization Experiments and DKR Optimization Experiments: A stock solution containing 1-phenylethanamine (606 mg, 5.00 mmol) and 1,3,5-tri-*tert*-butylbenzene (internal standard) (123 mg, 0.50 mmol) in dry toluene (10 mL) was prepared. Racemization catalyst (**3**) (26.5 mg, 0.020 mmol) and dry Na_2CO_3 (20 mg) were weighed into a dry Schlenk tube. The Schlenk tube was evacuated and backfilled with Argon 3 times. Toluene (6.4 mL), 2,4-dimethyl-3-pentanol (560 μL) and stock solution (1.0 mL) were added by syringe. The Schlenk tube was evacuated to 200 mbar and backfilled with argon 3 times and heated to the desired temperature. Small samples (0.05 mL) were withdrawn from the reaction mixture at regular time intervals, filtered over a piece of cotton in a pipette and diluted with DCM (ca. 1.5 mL). The underivatized samples were directly analyzed by means of GC-FID. To determine the *ee* of the substrate, acetic anhydride (2–3 drops) was added to the sample and all volatiles were evaporated under reduced pressure after which the residue was redissolved and measured again on GC-FID.

For the optimization of the DKR of 1-phenylethanamine, Novozym 435 (20 mg) was weighed into the Schlenk tube together with the racemization catalyst (26.5 mg, 0.020 mmol) and Na_2CO_3 (20 mg) and acyl donor (typically 1 mol-equiv.) was added by syringe after the addition of the stock solution. GC-FID Temperature Program: 105 °C | 9 min → 180 °C, 40 °C/min | 10 min.

For the racemization experiments, selectivity was defined as the residual substrate area divided by the initial substrate area (data normalized to internal standard area). For the DKR experiments, the amount of substrate conversion was determined with respect to the initial substrate area (data normalized to internal standard area) and the selectivity was defined as follows:

$$S = \frac{A_{\text{product}}}{A_{\text{product}} + \Sigma A_{\text{side poducts}}}$$

Dynamic Kinetic Resolution (DKR) Experiments. General Procedure: Novozym 435 (20.0 mg), Na_2CO_3 (20.0 mg, 0.20 mmol), racemization catalyst (26.5 mg, 0.020 mmol) were weighed into a dry Schlenk tube. The Schlenk tube was evacuated and backfilled with Argon 3 times. The amine substrates (0.50 mmol amine groups) were weighed into a sample vial and put under an Argon atmosphere. Toluene (7.4 mL in total) was added portion wise to this vial and the amine was transferred quantitively into the Schlenk tube after which 2,4-dimethyl-3-pentanol (560 μL, 4.0 mmol) and isopropyl methoxyacetate (**4**) (68 μL, 0.50 mmol, 1 equiv.) were added. The Schlenk tube was evacuated to a pressure of 200 mbar and backfilled with Argon to atmospheric pressure 3 times. After this procedure, the reaction vessels were immediately heated to 100 °C at a pressure of 750 mbar under an Argon atmosphere. After 23.5 h reaction time, a sample (0.10 mL) was withdrawn, filtered over a piece of cotton in a pipette, diluted with $CDCl_3$ and analyzed by ^{1}H NMR to check the conversion. 24 h after the start of the reaction more isopropyl methoxyacetate (7 μL, 0.050 mmol, 0.1 equiv.) was added and stirring was continued at 100 °C and 750 mbar for 2 h. After cooling to room temp., the reaction mixture was filtered over a paper filter and the Schlenk tube was rinsed with DCM (3 × 20 mL) after which all volatiles were removed in vacuo. The residue was co-evaporated with toluene (2 × 5 mL), after which the crude product was purified by column chromatography over silica gel to give the 2-methoxyacetamide. For t_R values see Table 3.

Table 3. Overview of retention times for compounds in DKR and racemization experiments.

Compound	t_R [min]
(*R*)-1-Phenylethanamine	8.08
(*S*)-1-Phenylethanamine	8.29
1,3,5-Tri-*tert*-butylbenzene	11.88
(*S*)-*N*-(1-Phenylethyl)-2-acetamide	13.51
(*R*)-*N*-(1-Phenylethyl)-2-acetamide	13.68
(*S*)-*N*-(1-Phenylethyl)-2-methoxyacetamide	14.70
(*R*)-*N*-(1-Phenylethyl)-2-methoxyacetamide	14.87
(*S*)-*N*-(1-Phenylethyl)-2-butyramide	15.61
(*R*)-*N*-(1-Phenylethyl)-2-butyramide	16.14

General Procedure for the Synthesis of *rac*-2-Methoxyacetamides 2a–g: 0.10 mmol of the desired amine was put in a dry 5 mL vial equiped with a stirring bar and flushed with Argon. A solution of DIPEA (0.15 mmol/mL) in dry dichloromethane (1.0 mL) was added to the vial, followed by the addition of in-situ prepared methoxy acetylchloride (**15**) (200 μL, 0.51 mmol/mL, 1 equiv.). The vial was flushed with Argon and stirred overnight at room temperature. The contents of the vial were filtered over a pipette containing a piece of cotton and normal silica gel (ca. 2 cm). The vial was rinsed with DCM (2 × 5 mL) and the solvent was removed under reduced pressure. The racemic methoxy acetamides were isolated in sufficient purity (> 90%) according to ^{1}H NMR and directly used without further purification to optimize the GC-FID temperature programs.

(*R*)-2-Methoxy-*N*-(1-phenylethyl)acetamide (2a): Compound **2a** was synthesized from 1-phenylethanamine (61.0 mg, 0.50 mmol) following the general procedure described above. After column chromatography (pentane/EtOAc, 1:4), **2a** was isolated as a white solid (66 mg, 68%, 98% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.06 (m, 4 H, Ar*H*), 6.88–6.60 (br. s, 1 H, -N*H*), 5.18 (dq, *J* = 13.9, *J* = 6.9 Hz, 1 H, -C*H*CH$_3$), 3.91 (d, *J* = 15.0 Hz, 1 H, H$_\alpha$ -CH_2OCH$_3$), 3.88 (d, *J* = 15.0 Hz, 1 H, H$_\beta$ -CH_2OCH$_3$), 3.40 (s, 3 H, -CH$_2$OCH_3), 1.52 (d, *J* = 6.9 Hz, 3 H, -CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 143.1, 128.8, 127.5, 126.2, 72.07, 59.2, 48.1, 22.0 ppm. GC-FID temperature program: 105 °C | 9 min → 180 °C, 40 °C/min | 10 min. t_R(S): 14.43 min, t_R(R): 14.58 min. $C_{11}H_{15}NO_2$ (193.24): calcd. C 68.3, H 7.82, N 7.25; found C 67.96, H 7.89, N 7.05.

(*R*)-*N*-(1-*p*-Tolylethyl)-2-methoxyacetamide (2b): Compound **2b** was synthesized from 1-*p*-tolylethanamine (67.0 mg, 0.50 mmol) following the general procedure described above. After column chromatography (pentane/EtOAc, 1:1), **2b** was isolated as a white solid (75 mg, 73%, 99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 7.14 (d, *J* = 8.1 Hz, 2 H, Ar*H*), (br. d, *J* = 5.8 Hz, 1 H, -N*H*), 5.15 (dq, *J* = 7.5, *J* = 7.0 Hz, 1 H, -C*H*CH$_3$), 3.89 (d, *J* = 15.0 Hz, 1 H, H$_\alpha$ -CH_2OCH$_3$), 3.86 (d, *J* = 15.0 Hz, 1 H, H$_\beta$ -CH_2OCH$_3$), 3.38 (s, 3 H, -CH$_2$OCH_3), 2.33 (s, 3 H, ArCH_3), 1.50 (d, *J* = 6.9 Hz, 3 H, -CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 140.1, 137.1, 129.4, 126.1, 72.0, 59.1, 47.8, 21.9, 21.1 ppm. GC-FID temperature program: 120 °C | 5 min → 180 °C, 10 °C/min | 5 min. t_R(*S*): 14.71 min, t_R(*R*): 14.92 min. $C_{12}H_{17}NO_2$ (207.27): calcd. C 69.54, H 8.27, N 6.76; found C 68.95, H 8.02, N 6.55.

(*R*)-*N*-[1-(4-Bromophenyl)ethyl]-2-methoxyacetamide (2c): Compound **2c** was synthesized from 1-(4-bromophenyl)ethanamine (100.0 mg, 0.50 mmol) following the general procedure described above. After column chromatography (pentane/EtOAc, 1:4), **2c** was isolated as a white solid (81 mg, 59%, 97% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.20 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 6.73 (br. d, *J* = 6.4 Hz, 1 H, -N*H*), 5.12 (dq, *J* = 8.2, *J* = 7.0 Hz, 1 H, -C*H*CH$_3$), 3.90 (d, *J* = 15.0 Hz, 1 H, H$_\alpha$ -CH_2OCH$_3$), 3.87 (d, *J* = 15.0 Hz, 1 H, H$_\beta$ -CH_2OCH$_3$), 3.41 (s, 3 H, -CH$_2$OCH_3), 1.49 (d, *J* = 7.0 Hz, 3 H, -CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 142.3, 131.9, 128.0, 121.3, 72.0, 59.25, 47.65, 21.89 ppm. GC-FID temperature program: 110 °C | 5 min → 200 °C, 5 °C/min | 20 min. t_R(*S*): 24.61 min, t_R(*R*): 24.80 min. $C_{11}H_{14}BrNO_2$ (272.14): calcd. C 48.55, H 5.19, N 5.15; found C 48.59, H 5.09, N 5.13.

(*R*)-*N*-(2,3-Dihydro-1*H*-inden-1-yl)-2-methoxyacetamide (2d): Compound **2d** was synthesized from 1-aminoindan (66.7 mg, 0.50 mmol) following the general procedure described above. After column chromatography (pentane/EtOAc, 1:4), **2d** was isolated as an off-white solid (82 mg, 80%, 96% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.14 (m, 4 H, ArH), 6.76 (br. d, *J* = 6.8 Hz, 1 H, -N*H*), 5.53 (q, *J* = 7.8 Hz, 1 H, -C*H*CH$_2$CH$_2$), 3.94 (s, 2 H, -CH_2OCH$_3$), 3.39 (s, 3 H, -CH$_2$OCH_3), 3.04-2.93 (m, 1 H, H$_\alpha$ -CHCH_2CH$_2$), 2.93–2.81 (m, 1 H, H$_\beta$ -CHCH_2CH$_2$), 2.68–2.52 (m, 1 H, H$_\alpha$ CHCH$_2$CH_2), 1.90–1.76 (m, 1 H, H$_\beta$ -CHCH$_2$CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 143.5, 143.0, 128.1, 126.9, 124.9, 124.1, 72.1, 59.2, 54.0, 34.1, 30.3 ppm. GC-FID temperature

program: 130 °C | 5 min → 160 °C, 2 °C/min → 190 °C, 1 °C/min | 10 min. $t_R(S)$: 29.00 min, $t_R(R)$: 29.34 min. $C_{12}H_{15}NO_2$ (205.25): calcd. C 70.22, H 7.37, N 6.82; found C 69.56, H 7.31, N 6.77.

(*R*)-2-Methoxy-*N*-[1-(naphthalen-1-yl)ethyl]acetamide (2e): Compound **2e** was synthesized from 1-(1-naphthyl)ethanamine (85.6 mg, 0.50 mmol) following the general procedure described above. After 23.5 h, incomplete conversion of the substrate was observed, for this reason the reaction mixture was stirred for a total time of 42.5 h. After column chromatography (pentane/EtOAc, 1:4), **2e** was isolated as a white solid (69 mg, 57%, 99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, J = 8.5 Hz, 1 H, Ar*H*), 7.86 (dd, J = 8.4, 1.1 Hz, 1 H, Ar*H*), 7.79 (d, J = 8.1 Hz, 1 H, Ar*H*), 7.57–7.42 (m, 4 H, Ar*H*), 6.78 (br. d, J = 7.8 Hz, 1 H, -N*H*), (dq, J = 15.5, J = 6.8 Hz, 1 H, -C*H*CH$_3$), 3.93 (d, J = 15.2 Hz, 1 H, H$_\alpha$ -CH_2OCH$_3$), 3.87 (d, J = 15.2 Hz, 1 H, H$_\beta$ CH_2OCH$_3$), 3.31 (s, 3 H, -CH$_2$OCH_3), 1.68 (d, J = 6.8 Hz, 3 H, -CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 138.2, 134.0, 131.2, 128.9, 128.5, 126.6, 125.9, 125.3, 123.5, 122.7, 72.0, 59.1, 44.0, 21.1 ppm. GC-FID analysis of compound **2e** was not directly possible, this compound was hydrolyzed as described below for compounds **2g** and **2h**. The *ee* was determined by means of GC-FID after derivatization with acetic anhydride. GC-FID temperature program for *N*-[1-(naphthalen-2-yl)ethyl]acetamide: 140 °C | 1 min → 200 °C 1 °C/min | 10 min. $t_R(S)$: 45.26 min, $t_R(R)$: 45.86 min. $C_{15}H_{17}NO_2$ (243.3): calcd. C 74.05, H 7.04, N 5.76; found C 73.71, H 6.93, N 5.77.

(*R*)-2-Methoxy-*N*-(octan-2-yl)acetamide (2f): Compound **2f** was synthesized from 2-octylamine (64.6 mg, 0.50 mmol) following the general procedure described above. After column chromatography (pentane/EtOAc, 1:1), **2f** was isolated as a white solid (66 mg, 66%, 94% *ee*). $KMnO_4$ staining followed by gentle heating was required for analysis of the TLC plates. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.29 (br. d, J = 6.8 Hz, 1 H, -N*H*), 4.08–3.95 (m, 1 H, -C*H*CH$_3$), 3.87 (s, 2 H, -CH_2OCH$_3$), 3.41 (s, 3 H, -CH$_2$OCH_3), 1.50–1.40 (m, 2 H, -CHCH_2CH$_2$-) 1.37–1.20 (m, 6 H, CHCH_2CH_2CH_2-), 1.15 (d, J = 6.6 Hz, 3 H, -CHCH_3), 0.88 (t, J = 6.8 Hz, 3 H, -CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 72.1, 59.2, 44.7, 37.0, 31.8, 29.2, 26.0, 22.7, 21.0, 14.1 ppm. GC-FID temperature program: 150 °C | 5 min → 180 °C, 10 °C/min. $t_R(S)$: 6.88 min, $t_R(R)$: 6.99 min. $C_{11}H_{23}NO_2$ (201.31): calcd. C 65.63, H 11.52, N 6.96; found C 65.62, H 11.55, N 6.91.

(1*R*,1′*R*)-*N*,*N*′-(1,3-Phenylene)bis(ethane-1,1′-diyl)bis(2-methoxyacetamide) (2g): Compound **2g** was synthesized from 1,1′-(1,3-phenylene)bis(ethanamine) (**1g**) (41.0 mg, 0.25 mmol) following the general procedure described above. After column chromatography (pentane/EtOAc, 1:4), **2g** was isolated as a light yellow solid (53 mg, 70%, 86% *ee*, ratio chiral/*meso* = 1:0.21). According to ^{1}H NMR residues of the racemization catalyst were still present, resulting in a purity of approximately 90 mol-%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.36 (m, 4 H, Ar*H*), 6.80–6.70 (br. s, 2 H, -N*H*), 5.18 (dq, J = 14.4, J = 7.1 Hz, 2 H, -C*H*CH$_3$), 3.91 (d, J = 15.0 Hz, 2 H, H$_\alpha$ -CH_2OCH$_3$), 3.88 (d, J = 15.0 Hz, 2 H, H$_\beta$ -CH_2OCH$_3$), 3.41 (s, 6 H, -CH$_2$OCH_3), (d, J = 6.9 Hz, 6 H, -CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 143.5, 129.2, 125.2, 124.3, 72.0, 59.2, 48.1, 22.0 ppm. GC-FID analysis of compound **2g** was not possible, this compound was hydrolyzed as described below and the *ee* was determined by means of chiral HPLC using the method described above. Racemic **1g** was used as reference for the determination of the *ee*, $t_R(R,R)$: 45.17 min, t_R(*meso*): 63.13 min, $t_R(S,S)$: 71.74 min, ratio chiral/*meso* = 1:0.21, *ee*(chiral): 86%. $C_{16}H_{24}N_2O_4$ (308.37): calcd. C 62.32, H 7.84, N 9.08; found C 62.43, H 7.21, N 7.16.

(1*R*,1′*R*)-*N*,*N*′-(1,4-Phenylene)bis(ethane-1,1′-diyl)bis(2-methoxyacetamide) (2h): Compound **2h** was synthesized from 1,1′-(1,4-phenylene)bis(ethanamine) (**1h**) (41.0 mg, 0.25 mmol) following the general procedure described above. After column chromatography (pentane/EtOAc, 1:4), **2h** was isolated as a off-white solid (42 mg, 55%, 99% *ee*, ratio chiral/*meso* = 1:0.09). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (s, 4 H, Ar*H*), 6.74 (br. d, 2 H, -N*H*), 5.15 (dq, J = 13.9, J = 7.0 Hz, 2 H, -C*H*CH$_3$), 3.90 (d, J = 15.0 Hz, 2 H, H$_\alpha$ -CH_2OCH$_3$), 3.89 (d, J = 15.0 Hz, 2 H, H$_\beta$ -CH_2OCH$_3$), 3.40 (s, 6 H, -CH$_2$OCH_3), 1.50 (d, J = 6.9 Hz, 6 H, -CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.6, 142.3, 126.6, 72.1, 59.2, 47.9, 21.9 ppm. GC-FID analysis of compound **2g** was not possible, this compound was hydrolyzed as described below and the *ee* was determined by means of chiral HPLC using the method described above. Racemic **1h** was used as reference for the determination of the *ee*, $t_R(R,R)$: 46.57 min, t_R(*meso*): 76.34 min, $t_R(S,S)$: 93.46 min, ratio chiral/*meso* = 1:0.09, *ee*(chiral): 99%. Elemental analysis is not available for this compound.

Determination of *ee* Values for 2e, 2g, and 2h: No direct chiral GC analysis of compounds **2e**, **2g**, **2h** and was possible. These methoxy acetamides were hydrolyzed and the *ee* was determined by means of chiral HPLC (**2g**–**h**) or by GC-FID after derivatization with Ac_2O.

General Hydrolysis Procedure for the Hydrolysis of 2-Methoxyacetmides 2a–g: Compound **2g** or **2h** (typically 40 mg, 0.13 mmol) was put in a 25 mL flask and aqueous HCL was added (5 mL, 3 M). The resulting solution was refluxed under an Argon atmosphere for a period of 4 h. After cooling to room temp., the reaction mixture was diluted with water (5 mL) and extracted with Et_2O (2 × 5 mL). The pH of the aqueous layer was adjusted to >10 by careful addition of concentrated NaOH (4 M), followed by extraction with Et_2O (3 × 15 mL). The combined organic layers were washed with 4 M NaOH (5 mL) and dried with Na_2SO_4. After removal of the solvent under reduced pressure, the free amines were obtained as a yellow colored liquid in typically 50% yield. ^{1}H NMR showed a purity of at least 80% for hydrolyzed **2g** and at least 90% for hydrolyzed **2h**.

In a reference experiment in which **2a** was hydrolyzed and derivatized with Ac_2O under identical conditions, no significant amount of racemization was observed (97.4% *ee* after hydrolysis vs. 98.3% before).

Derivatization of Hydrolyzed 2e: Ac_2O (+/– 10 mg) was added to 1 mL of the Et_2O extract containing hydrolyzed **2e**. All volatiles were evaporated under reduced pressure for 30 min at 50 °C. The obtained crude white solid was directly used for chiral GC analysis to determine the *ee* values.

Supporting Information (see also the footnote on the first page of this article): Procedures for the preparation of starting materials, analytical data, comparison between the use of isopropyl butyrate and isopropyl 2-methoxyacetate as acyl donor in the DKR of 1-phenylethanamine and the optimisation of the DKR of 1-phenylethanamine.

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