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Chemoenzymatic Dynamic Kinetic Resolution of Primary Amines Catalyzed by CAL-B at 38−40 °C

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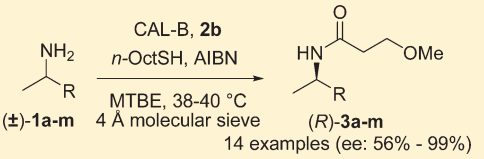
Supporting Information

ABSTRACT: The (*R*)-selective chemoenzymatic dynamic kinetic resolution of primary amines was performed at 38−40 °C in MTBE, in good to high yields and with high enantiomeric excesses. These reactions associating CAL-B to octanethiol as radical racemizing agent were carried out in the presence of methyl β-methoxy propanoate as acyl donor, under photochemical irradiation at 350 nm in glassware.



The advantages of dynamic kinetic resolution (DKR) over a simple kinetic resolution (KR) are well-known and have been exemplified in numerous reviews.[1] Over the past few years, we have devoted research work to the performance of metal-free chemoenzymatic DKR of primary amines. Contrary to most other groups involved in this field, we have discarded homogeneous and heterogeneous metal catalysts as racemizing agents.[2] We opted for a radical racemization procedure mediated by the intermediacy of sulfanyl radicals. After having optimized both the racemization procedure[3] and the enzymatic resolution conditions,[4] we were able to propose the first DKR methodology that could be adapted to the synthesis of either (*R*)- or (*S*)-amides by changing the nature of the enzyme, i.e., moving from a lipase to a protease.[5]

Most racemization procedures associated with enzymatic resolutions are carried out at temperatures higher than 70 °C.[2,6] Owing to the lack of thermostability of lipases, most investigations are limited to the thermally stable supported lipase B of *Candida antartica* (CAL-B), i.e., Novozym 435. It has been pointed out that two routes could be envisaged to circumvent this problem in DKR processes. One could either carry out racemization at a lower temperature or increase the thermostability of the enzyme. Bäckvall and co-workers, who used ruthenium-based catalysts to racemize amines at 90 °C, selected the second route and opted for increasing the thermal stability of the enzyme through its immobilization in silica-based mesocellular foam.[7] We rather selected the alternative pathway, that is, the decrease of the temperature of racemization,[3c] which we successfully realized for the DKR of amines mediated with proteases.[5c] The performance of racemization at low temperature was made possible by initiating the formation of sulfanyl radical at 38−40 °C upon irradiation at 350 nm in glassware. Blank experiments having demonstrated that CAL-B was not denaturated in the presence of the thiol and the acyl donor under these conditions, we had to adapt the CAL-B-catalyzed KR at 40 °C to make it kinetically compatible with the new racemization conditions.

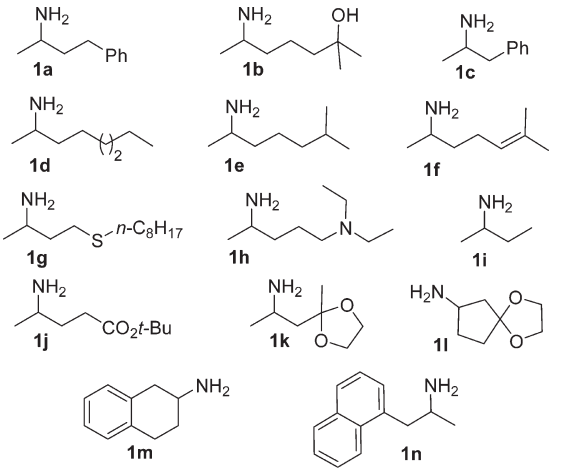


Figure 1. Amine structures.

Amine **1a** (Figure 1) was used as model substrate in these optimization experiments.

The selection of the acyl donor was restricted to three candidates (Figure 2):

- Ethyl laurate (**2a**), which gave the best results in KR catalyzed by CAL-B at 80 °C and was taken as reference.
- Methyl β-methoxypropionate (**2b**), which has scarcely been used as acyl donor. It reacts 11 times faster than ethyl butyrate and 18 times slower than ethyl α-methoxyacetate in the BCL-catalyzed acylation of 1-phenethanamine.[8] Even though the use of ethyl α-methoxyacetate is widespread because it leads to very fast kinetic resolutions, this donor proved to be incompatible with the racemization conditions.[9]

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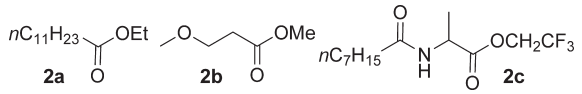


Figure 2. Acyl donors.

- The trifluoroethyl ester of racemic *N*-octanoyl alanine (**2c**), because it led to very good results in KR achieved at 30 °C with proteases.[4c,5c] Moreover, it had never been tested with any lipase.

Test reactions were carried out by monitoring the enantiomeric excess of the amine during the KR performed at 38−40 °C in toluene. The amine reached an ee of >99% in 4 h, when using 1.5 equiv of **2c**. After the same time of reaction, the amine ee was 70% when using **2b**, whereas it was only 20% with **2a**.

However, **2c** had to be discarded for two reasons. It led to a significant amount of noncatalyzed acylation (10% in 24 h),[10] and in addition, the racemization reaction was inhibited by the release of trifluoroethanol in the reaction medium. Thus, further experiments were conducted with **2b**. A significant practical advantage is that, compared to **2a**, **2b** is volatile and can easily be removed from the reaction medium.

A rapid screening of solvents led us to select MTBE (methyl *tert*-butyl ether) rather than toluene or even THF. In this solvent, a 50% conversion, together with a 95% amine ee, was reached in 2 h in the presence of 4 Å molecular sieves. In the absence of the dehydrating agent, the conversion was only 20%, and the amine ee was 45% within the same time of reaction. The molecular sieve is likely to trap both traces of water and methanol released from the acyl donor.[11]

The results of the acylation of amines **1a**−**n** (Figure 1) are reported in Table 1.

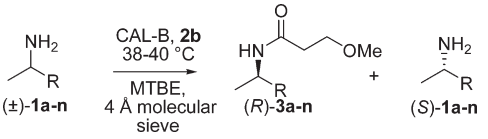
The enantioselectivity factors are high in most cases. They are at least similar or even superior to those observed for the KR performed at 80 °C with **2a** as acyl donor.[4a] The amines can roughly be separated into three classes: those for which *E* values are excellent, i.e. *E* >200, those which give mean *E* values (**1j**, **1h**, and **1m**), and those for which *E* values are very low (**1i**, **1l**). The latter are amines with little stereodifferentiation between the two alkyl substituents.

For the radical racemization to be efficient, the time of reaction must not exceed 3−5 h. Thus another important parameter to take into account is the rate of KR, which must be as close as possible to that of racemization. Time of KR ranges between 2.5 and 24 h. Substrates for which KR is particularly slow (**1j**, **1k**, **1m**, **1n**) will be good probes to evaluate the efficiency of the DKR process.

The DKR experiments are reported in Table 2. Most reactions were carried out by running a DKR period over 3.75 h (AIBN, overall 20 mol % was added portion-wise each 45 min) followed by an additional KR period of 4 h (after stopping the racemization process by switching off the UV lamps of the Rayonet apparatus).

In some cases (very slow KR), it was found even more advantageous to perform a preliminary KR period, before starting the DKR and the subsequent KR. A few data, which allowed us to evaluate the significant gain in the overall yield by applying this procedure are given in Table 2 (**1a**, **1b**, **1h**, **1k**, **1l**, **1m**, **1n**). It is worth noting that in all cases where comparative data were available, isolated yields were superior to those obtained in the DKR performed at 80 °C,[5a] and the enantiomeric excesses were similar or superior. In the cases of amines **1h** and **1l**, method B made it possible to reach enantiomeric excesses higher than with the KR alone.

Table 1. KR of Amines (±)-1a−n



amine[a]	time, h	*C*, %[b]	amine ee, %[c]	amide ee, %[d]	*E*
1a	2.5	50	>98	>99	>200
1b	6	40	67	>99	>200
1c	6	44	77	>99	>200
1d	2.5	47	88	>99	>200
1e	3	45	81	>99	>200
	20		>99		
1f	5	48	92	>99	>200
1g	1	50	>99	>99	>200
1h	6	49	83	85	30
	18		>99		
1i	3	50	74	75	15
1j	3	38	60	95	70
	24		>99		
1k	24	42	71	>98	>200
1l	6	45	45	53	5
	24		>99		
1m	20	45	79	95	90
1n	20	42	71	>99	>200

[a] Standard protocol: amine (0.25 mmol, 0.1 M solution), **2b** (0.75 mmol, 1.5 equiv), MTBE (2.5 mL), 4 Å molecular sieve (250 mg), CAL-B (50 mg), temperature 38−40 °C. [b] Enantioselectivity factors were calculated according to $E = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$.[12] [c] Determined by GC after derivatization. [d] Determined by HPLC.

Amine **1n** gave the slowest KR of the series. Method B enabled 81% yield and 99% ee for the corresponding (*R*)-amide. This result can be compared to the result obtained by Gotor,[13] who used Shvo's catalyst as racemizing agent and α-methoxyacetate as acyl donor at 100 °C (50% yield and 97% ee).

The benefit of carrying out the DKR experiments at 38−40 °C instead of 80 °C is well demonstrated by the cases of amines **1c** and **1j**. Amine **1c**, which was degraded under racemization conditions at 80 °C, led to amide **3c** in 82% yield and an ee >99% under these new conditions. The DKR of amine **1j** could not be achieved at 80 °C because lactamization proceeded faster than the enzymatic resolution. 5-Methylpyrrolidin-2-one was formed in 67% yield with no ee. This means that performing DKR at a lower temperature opens access to the formation of optically pure amides from substrates that are unstable or undergo competitive reactions at 80 °C.

In conclusion, performing the radical racemization at 38−40 °C under photochemical initiation enabled us to carry out CAL-B-catalyzed DKR of a wide series of non benzylic amines, bearing different functional groups. Under standard experimental conditions, optimized for amine **1a**, high yields and excellent enantiomeric excesses were reached in most cases. This procedure might open the route to the use of other lipases in further work.

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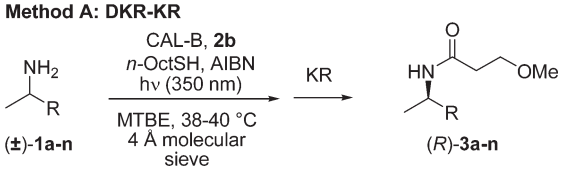
Table 2. DKR of Amines (±)-1a−n



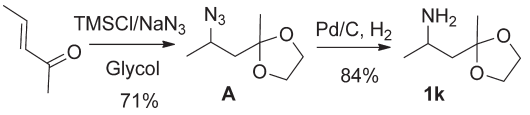
amine	procedure[a,b]	amide isolated yield, % (ee, %)[c]
1a	DKR + KR	81 (>99)
	KR + DKR + KR	89 (>99)
1b	DKR + KR	61 (>99)
	KR + DKR + KR	74 (>99)
1c	DKR + KR	82 (98)
1d	DKR + KR	84 (>99)
1e	DKR + KR	75 (>99)
1f	DKR + KR	81 (>99)
1g	DKR + KR	72 (>99)
1h	DKR + KR	57 (85)
	KR + DKR + KR	62 (90)
1i	DKR + KR	84 (70)
1j	DKR + KR	85 (95)
1k	DKR + KR	58 (98)[d]
	KR + DKR + KR	66 (98)
1l	DKR + KR	55 (56)
	KR + DKR + KR	71 (75)
1m	DKR + KR	68 (74)
	KR + DKR + KR	71 (75)
1n	DKR + KR	37 (>99)
	KR + DKR + KR	81 (>99)

[a] Standard protocol for direct DKR: amine (1 mmol, 0.1 M solution), **2b** (1.5 mmol, 1.5 equiv), MTBE (10 mL), 4 Å molecular sieve (1 g), CAL-B (200 mg), *n*-OctSH (1.2 mmol, 208 μL), AIBN (1 g, 0.76 mmol added portion-wise 5 times, i.e., 20 mg each 45 min), temperature 38−40 °C. [b] See Experimental Section. [c] Determined by HPLC. [d] Determined by GC.

EXPERIMENTAL SECTION

General. The ^{1}H and ^{13}C NMR spectra were recorded at 400 and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are given in Hz. Enantiomeric excesses (ee's) of amides were determined by analytical chiral HPLC. The solvents for chiral chromatography (*n*-hexane, *i*-PrOH, EtOH) were HPLC grade. They were degassed and filtered on a 0.45 μm membrane before use. The chiral HPLC analyses were performed with UV detection on Chiralcel OD-H or OD-3 (250 × 4.6 mm, cellulose tris(3,5-dimethylphenylcarbamate)), Chiralpak AD (250 × 4.6 mm, amylose tris(3,5-dimethylphenylcarbamate)) and Chiralpak AS-3 (amylose tris-[(*S*)-α-phenethyl]carbamate) from Chiral Technologies Europe (Illkirch, France), Lux-Cellulose-2 (cellulose tris(3-chloro-4-methylphenylcarbamate)), Lux-Cellulose-4 (cellulose tris(4-chloro-3-methylphenylcarbamate)) from Phenomenex, and TCI chiral BP-S from Tokyo Chemical Industry. The retention times t_R are given in minutes for each enantiomer, the retention factor $k = (t_R - t_0)/t_0$ (t_0 is the retention time for an unretained peak determined by injection of tritertiobutylbenzene), the enantioselectivity factor $\alpha = k_2/k_1$, and the resolution Rs are given to characterize the chiral separations. The enantiomeric excesses of the primary amines were determined, after derivatization in trifluoroacetamide with 1.5 equiv of *N*-methyl-bis-trifluoroacetamide, by gas chromatography (GC) analysis on a chromatograph fitted with a Lipodex D column or a Crompack column with flame ionization detector (FID), using the derivatized racemic compounds as reference (see Supporting Information). Octanethiol, ethyl laurate (**2a**), methyl 3-methoxypropanoate (**2b**), and amines (**1a**, **1b**, **1d**, **1e**, **1h**, **1i** and **1m**) are commercially available; they were used without further purification. Compounds **1c**,[4a,14] **1f**,[3a] **1g**,[3c] **1j**,[15] **1n**,[16] and **2c**[5c] were prepared according to literature procedures.

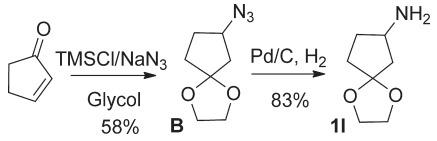
Synthesis of Amine 1k.



2-(2-Azidopropyl)-2-methyl-1,3-dioxolane (A)[17]**.** To a solution of 3-penten-2-one (1.68 g, 20 mmol) in dichloromethane (50 mL) were added sodium azide (1.56 g, 23 mmol) and trimethylsilyl chloride (3.04 mL, 23 mmol). This mixture was stirred for 15 min at rt, and then ethylene glycol (1.338 mL, 23 mmol) was added. The solution was refluxed for 8 h, cooled to rt, and diluted with water. The aqueous solution was extracted twice with dichloromethane and dried under $MgSO_4$. After concentration, the crude material was subjected to flash column chromatography on silica gel (0/100 to 50/50 Et_2O/pentane) to give **A** (1.21 g, 14 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): 3.96 (m, 4H), 3.63 (m, 1H), 1.94 (dd, J = 14.7, 7.8, 1H), 1.77 (dd, J = 14.7, 4.5, 1H), 1.36 (s, 3H), 1.29 (d, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 108.6 (C), 64.6 (CH_2), 64.5 (CH_2), 53.9 (CH), 44.6 (CH_2), 24.2 (CH_3), 20.9 (CH_3). HRMS ([M + H]$^+$, ESI): m/z calcd for $C_7H_{14}N_3O_2$ 172.1081, found 172.1082.

1-(2-Methyl-1,3-dioxolan-2-yl)propan-2-amine (1k). A solution of **A** (1.05 g, 6.14 mmol) and Pd/C (5 wt %) (50 mg) in a mixture of Et_2O/MeOH (20 mL/0.5 mL) was stirred overnight under H_2 (1 atm). After filtration and concentration, the crude product was distilled with a Kugelrohr apparatus (150 °C/20 mbar) leading to **1k** (750 mg, 5.16 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): 3.89 (m, 4H), 3.13 (m, 1H), 2.00 (broad s, 2H), 1.70−1.57 (m, 2H), 1.27 (s, 3H), 1.02 (d, J = 6.4, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 109.9 (C), 64.5 (CH_2), 64.1 (CH_2), 47.6 (CH_2), 43.2 (CH), 24.6 (CH_3), 24.1 (CH_3). HRMS ([M + H]$^+$, ESI): m/z calcd for $C_7H_{16}NO_2$ 146.1176, found 146.1170.

Synthesis of Amine 1l.



7-Azido-1,4-dioxaspiro[4.4]nonane (B). To a solution of 2-cyclopenten-1-one (1.64 g, 20 mmol) in dichloromethane (50 mL) were added sodium azide (1.56 g, 23 mmol) and trimethylsilyl chloride (3.04 mL, 23 mmol). This mixture was stirred for 15 min at rt, and then ethylene glycol (1.338 mL, 23 mmol) was added. The solution was refluxed for 8 h, cooled to rt, and diluted with water. The aqueous solution was extracted twice with dichloromethane and dried under $MgSO_4$. After concentration, the crude material was subjected to flash column chromatography on silica gel (0/100 to 50/50 Et_2O/pentane) to give **B** (1.645 g, 11.6 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): 3.98 (broad quint, J = 7.0, 1H), 3.94−3.87 (m, 4H), 2.16 (dd, J = 14.2, 7.3, 1H), 2.07−1.97 (m, 2H), 1.90 (dd, J = 14.2, 5.7, 1H), 1.85−1.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 116.05 (C), 64.4 (CH_2), 64.1

(CH_2), 59.8 (CH), 42.0 (CH_2), 34.5 (CH_2), 30.0 (CH_2). HRMS ([M + Li]$^+$, ESI): m/z calcd for $C_7H_{11}N_3O_2Li$ 176.1006, found 176.1008.

1,4-Dioxaspiro[4.4]nonan-7-amine (1l). A solution of **B** (569 mg, 3.37 mmol) and Pd/C (5 wt %) (50 mg) in a mixture of Et_2O/MeOH (20 mL/1 mL) was stirred overnight under H_2 (1 atm). After filtration and concentration, the crude product was distilled with a Kugelrohr apparatus (150 °C/50 mbar) leading to **1l** (400 mg, 2.79 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): 3.84 (m, 4H), 3.34 (quint, J = 6.7, 1H), 2.06 (dd, J = 13.6, 7.2, 1H), 2.02 (broad s, 2H), 1.99−1.90 (m, 2H), 1.78−1.70 (m, 1H), 1.54 (dd, J = 13.6, 6.8, 1H), 1.43−1.34 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 116.8 (C), 64.1 (CH_2), 64.0 (CH_2), 50.7 (CH), 45.7 (CH_2), 35.0 (CH_2), 34.0 (CH_2). HRMS ([M + H]$^+$, ESI): m/z calcd for $C_7H_{14}NO_2$: 144.1019, found 144.1021.

General Procedure for the Kinetic Resolution of Amines. In a glass tube (diameter 1.8 cm), the amine (0.5 mmol) was added to a solution of methyl 3-methoxypropanoate (**2b**) (0.75 mmol), molecular sieves 4 Å (0.5 g), and CAL-B (100 mg) in MTBE (5 mL). The resulting mixture was stirred at rt, and the reaction was monitored by chiral GC and/or chiral HPLC.

General Procedure for the Dynamic Kinetic Resolution of Amines. *Method A (DKR + KR Sequence).* To a solution of methyl 3-methoxypropanoate (**2b**) (1.5 mmol) in MTBE (10 mL) were added amine (**1a**−**n**) (1 mmol), CAL-B (200 mg), octanethiol (1.2 mmol), and molecular sieves 4 Å (1 g). The mixture was irradiated at 38−40 °C in a glass tube (diameter 1.8 cm) in a Rayonet apparatus (RPR-200, 16 UV lamps Sylvania Blacklight 351 F15W/T5/BL350) for 3.75 h, and AIBN (75 mg, 0.55 mmol) was added portion-wise every 45 min (5 × 15 mg). After the irradiation was switched off, the resulting mixture was stirred at 38 °C for 5 h. The enzyme was filtered out from the solution and washed with dichloromethane (5 mL). The combined organic phases were then evaporated, and the crude material was purified by flash chromatography on silica gel (dichloromethane/methanol; gradient from 0 to 5%) to give pure amide.

Method B (KR + DKR + KR Sequence). In a glass tube (diameter 1.8 cm), the amine (1 mmol) was added to a solution of methyl 3-methoxypropanoate (**2b**) (1.5 mmol), molecular sieves 4 Å (1 g), and CAL-B (200 mg) in MTBE (10 mL). The resulting mixture was stirred at rt for 2.5 to 20 h depending on the substrate (see Table 1). Then octanethiol (1.2 mmol) was added. The mixture was irradiated at 38−40 °C in a Rayonet apparatus (RPR-200, 16 UV lamps Sylvania Blacklight 351 F15W/T5/BL350) for 3.75 h, and AIBN (75 mg, 0.55 mmol) was added portion-wise every 45 min (5 × 15 mg). After the irradiation was switched off, the resulting mixture was stirred at 38 °C for 5 h. The enzyme was filtered out from the solution and washed with dichloromethane (5 mL). The combined organic phases were then evaporated, and the crude material was purified by flash chromatography on silica gel (dichloromethane/methanol; gradient from 0 to 5%) to give pure amide.

3-Methoxy-*N*-(4-phenylbutan-2-yl)propanamide (3a). Amide **3a** was prepared in 81% yield from amine **1a** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 7.30 (m, 2H), 7.20 (m, 3H), 5.98 (broad d, J = 6.6, 1H), 4.08 (pseudo sept, J = 6.7, 1H), 3.65 (t, J = 5.8, 2H), 3.40 (s, 3H), 2.66 (m, 2H), 2.44 (t, J = 5.8, 2H), 1.77 (pseudo q, J = 7.8, 2H), 1.08 (d, J = 6.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.8 (CO), 144.9 (C), 128.4 (CH), 128.3 (CH), 125.9 (CH), 68.9 (CH_2), 58.7 (CH_3), 44.9 (CH), 38.7 (CH_2), 37.2 (CH_2), 32.4 (CH_2), 21.0 (CH_3). HPLC conditions: Chiralcel OD-H, *n*-hexane/ethanol 95:5, flow rate = 1 mL/min, UV 254 nm, t_R (*S*) = 19 min, t_R (*R*) = 23.5 min, k (*S*) = 5.13, k (*R*) = 6.60, α = 1.28, Rs = 3. ee > 99%. $[\alpha]^{25}_D$ = +20.8 (*c* 1.0, $CHCl_3$). HRMS ([M + H]$^+$, ESI): m/z calcd for $C_{14}H_{22}NO_2$ 236.1645, found 236.1648.

***N*-(6-Hydroxy-6-methylheptan-2-yl)-3-methoxypropanamide (3b).** Amide **3b** was prepared in 61% yield from amine **1b** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 5.97 (broad s, 1H), 4.00 (pseudo sept, J = 6.6, 1H), 3.62 (t, J = 5.7, 2H), 3.35 (s, 3H), 2.41 (t, J = 5.7, 2H), 1.84 (br s, 1H), 1.51−1.35 (m, 6H), 1.19 (s, 3H), 1.18 (s, 3H), 1.12 (d, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.8 (CO), 70.6 (C), 68.8 (CH_2), 58.6 (CH_3), 44.7 (CH), 43.3 (CH_2), 37.2 (CH_2), 37.1 (CH_2), 29.4 (CH_3), 28.9 (CH_3), 21.0 (CH_3), 20.5 (CH_2). HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*-PrOH 95:5, flow rate = 1 mL/min, UV 220 nm, t_R (*R*) = 15.05 min, t_R (*S*) = 16.83 min, k (*R*) = 4.02, k (*S*) = 4.61, α = 1.42. ee >99%. $[\alpha]^{25}_D$ = +6.2 (*c* 5.6, MeOH). HRMS ([M + H]$^+$, ESI): m/z calcd for $C_{12}H_{26}NO_3$ 232.1907, found 232.1909.

3-Methoxy-*N*-(1-phenylpropan-2-yl)propanamide (3c). Amide **3c** was prepared in 82% yield from amine **1c** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 7.33−7.30 (m, 2H), 7.26−7.20 (m, 3H), 6.07 (broad s, 1H), 4.29 (m, 1H), 3.59 (m, 2H), 3.33 (s, 3H), 2.80 (AB part of an ABX spectrum, 2H, J_{AB} = 13.5, Δν = 23.7), 2.42 (AB part of an ABX_2 spectrum, 2H), 1.14 (d, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.7 (CO), 138.1 (C), 129.5 (CH), 128.3 (CH), 126.4 (CH), 68.7 (CH_2), 58.6 (CH_3), 45.9 (CH), 42.4 (CH_2), 37.0 (CH_2), 20.0 (CH_3). HPLC conditions: Chiralcel OD-H, *n*-hexane/*i*-PrOH 95:5, flow rate = 1 mL/min, UV 220 nm, t_R (*R*) = 16.15 min, t_R (*S*) = 19 min, k (*R*) = 4.4, k (*S*) = 5.3, α = 1.20, Rs = 2.3. ee 98%. $[\alpha]^{25}_D$ = +15.4 (*c* 1.5, $CHCl_3$). HRMS ([M + H]$^+$, ESI): m/z calcd for $C_{13}H_{20}NO_2$ 222.1489, found 222.1485.

3-Methoxy-*N*-(octan-2-yl)propanamide (3d). Amide **3d** was prepared in 84% yield from amine **1d** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 6.00 (broad s, 1H), 3.94 (m, 1H), 3.60 (t, J = 5.8, 2H), 3.34 (s, 3H), 2.41 (t, J = 5.8, 2H), 1.39 (m, 2H), 1.24 (m, 8H), 1.09 (d, J = 6.6, 3H), 0.85 (t, J = 7.1, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.4 (CO), 68.8 (CH_2), 58.5 (CH_3), 45.0 (CH), 37.1 (CH_2), 36.8 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 25.8 (CH_2), 22.4 (CH_2), 20.7 (CH_3), 13.8 (CH_3). HPLC conditions: Chiralpak AS-3, *n*-hexane/ethanol 95:5, flow rate = 1 mL/min, UV 220 nm, t_R (*S*) = 14 min, t_R (*R*) = 15.6 min, k (*S*) = 3.7, k (*R*) = 4.2, α = 1.13, Rs = 1.5. ee >99%. $[\alpha]^{25}_D$ = +1.1 (*c* 1.4, $CHCl_3$). HRMS ([M + H]$^+$, ESI): m/z calcd for $C_{12}H_{26}NO_2$ 216.1958, found 216.1961.

3-Methoxy-*N*-(6-methylheptan-2-yl)propanamide (3e). Amide **3e** was prepared in 75% yield from amine **1e** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 5.87 (broad s, 1H), 3.89 (m, 1H), 3.56 (t, J = 5.8, 2H), 3.30 (s, 3H), 2.35 (t, J = 5.8, 2H), 1.45 (nonet, J = 6.7, 1H), 1.31 (m, 2H), 1.23 (m, 2H), 1.10 (m, 2H), 1.05 (d, J = 6.6, 3H), 0.79 (d, J = 6.6, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.5 (CO), 68.8 (CH_2), 58.5 (CH_3), 44.9 (CH), 38.7 (CH_2), 37.1 (CH_2), 37.0 (CH_2), 27.8 (CH), 23.6 (CH_2), 22.5 (2 x CH_3), 20.8 (CH_3). HPLC conditions: Chiralpak AS-3, *n*-hexane/*i*-PrOH 95:5, flow rate = 1 mL/min, UV 220 nm, t_R (*S*) = 12.8 min, t_R (*R*) = 14.5 min, k (*S*) = 3.28, k (*R*) = 3.85, α = 1.17, Rs = 1.73. ee >99%. $[\alpha]^{25}_D$ = +1.2 (*c* 1.4, $CHCl_3$). HRMS ([M + H]$^+$, ESI): m/z calcd for $C_{12}H_{26}NO_2$ 216.1958, found 216.1959.

3-Methoxy-*N*-(7-methyloct-6-en-2-yl)propanamide (3f). Amide **3f** was prepared in 81% yield from amine **1f** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 6.00 (broad d, J = 5.9, 1H), 5.09 (broad t, J = 7.2, 1H), 3.97 (pseudo sept, J = 6.7, 1H), 3.62 (t, J = 5.8, 2H), 3.37 (s, 3H), 2.43 (t, J = 5.8, 2H), 1.99 (broad q, J = 7.3, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.44 (q, J = 7.0, 2H), 1.12 (d, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.3 (CO), 131.2 (C=), 123.4 (HC=), 68.4 (CH_2), 58.1 (CH_3), 44.4 (CH), 36.6 (CH_2), 36.3 (CH_2), 25.2 (CH_3), 24.2 (CH_2), 20.4 (CH_3), 17.1 (CH_3). HPLC conditions: Chiralcel OD-H, *n*-hexane/*i*-PrOH 95:5, flow rate = 1 mL/min, UV 220 nm, t_R (*R*) = 27.3 min, t_R (*S*) = 29 min, k (*R*) = 8.1, k (*S*) = 8.7, α = 1.07, Rs = 1.9. ee >99%. $[\alpha]^{25}_D$ = +7.5 (*c* 1.3, $CHCl_3$). HRMS ([M + H]$^+$, ESI): m/z calcd for $C_{12}H_{24}NO_2$ 214.1802, found 214.1803.

3-Methoxy-*N*-(4-(octylthio)butan-2-yl)propanamide (3g). Amide **3g** was prepared in 72% yield from amine **3g** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 6.11 (broad s, 1H), 4.08 (pseudo sept, J = 6.7, 1H), 3.63 (t, J = 5.6, 2H), 3.37 (s, 3H), 2.53−2.48 (m, 4H), 2.47−2.43 (m, 2H), 1.77−64 (m, 2H), 1.56 (quint, J = 7.7, 2H), 1.36 (pseudo quint, J = 6.6, 2H), 1.24 (m, 8H), 1.06 (d, J = 6.7, 3H), 0.88 (t, J = 7.0, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.8 (CO), 68.7 (CH_2), 58.6 (CH_3), 44.6 (CH), 37.1 (CH_2), 36.9 (CH_2), 32.2 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 22.6 (CH_2), 20.8 (CH_3), 14.0 (CH_3). HPLC conditions: Chiralpak AD, *n*-hexane/*i*-PrOH (95/5), 1 mL/min. Detectors: UV (220 nm). t_R (*S*) = 10.2 min, t_R (*R*) = 11.35 min, k (*S*) = 2.4, k (*R*) = 2.8, α = 1.16, Rs = 2.9. ee >99%. $[\alpha]^{25}_D$ = +13.5 (*c* 1.5, $CHCl_3$). HRMS ($[M + H]^+$, ESI): *m*/*z* calcd for $C_{16}H_{34}NO_2S$ 304.2305, found 304.2302. The assignment of the absolute configuration is based on the selectivity of the lipase.

***N*-(5-(Diethylamino)pentan-2-yl)-3-methoxypropanamide (3h).** Amide **3h** was prepared in 57% yield from amine **1h** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 6.28 (broad d, J = 7.3, 1H), 3.99 (pseudo sept, J = 6.6, 1H), 3.63 (m, 2H), 3.35 (s, 3H), 2.66 (q, J = 7.2, 4H), 2.56 (m, 2H), 2.42 (t, J = 5.9, 2H), 1.63−1.54 (m, 2H), 1.50−1.44 (m, 2H), 1.13 (d, J = 6.6, 3H), 1.10 (t, J = 7.2, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.6 (CO), 68.7 (CH_2), 58.5 (CH_3), 52.4 (CH_2), 46.5 (2 x CH_2), 44.6 (CH), 37.0 (CH_2), 34.5 (CH_2), 22.8 (CH_2), 20.8 (CH_3), 10.9 (2 x CH_3). HPLC conditions: TCI chiral BP-S, *n*-hexane/ethanol (90/10), 1 mL/min. Detectors: DAD. t_R (*R*) = 6.75 min, t_R (*S*) = 8.33 min, k (*R*) = 1.25, k (*S*) = 1.78, α = 1.42, Rs = 2.53. ee 90%. $[\alpha]^{25}_D$ = +37.8 (*c* 1.2, $CHCl_3$). HRMS ($[M + H]^+$, ESI): *m*/*z* calcd for $C_{13}H_{29}N_2O_2$ 245.2224, found 245.2216. The assignment of the absolute configuration is based on the selectivity of the lipase.

***N*-*sec*-Butyl-3-methoxypropanamide (3i).** Amide **3i** was prepared in 84% yield from amine **1i** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 5.96 (s, 1H), 3.91 (m, 1H), 3.63 (t, J = 5.8, 2H), 3.37 (s, 3H), 2.43 (t, J = 5.8, 2H), 1.42−1.47 (m, 2H), 1.11 (d, J = 6.6, 3H), 0.90 (t, J = 7.3, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.7 (CO), 68.8 (CH_2), 58.6 (CH_3), 46.3 (CH), 37.1 (CH_2), 29.5 (CH_2), 20.3 (CH_3), 10.2 (CH_3). HPLC conditions: Lux-Cellulose-2, *n*-hexane/ethanol 95:5, flow rate = 1 mL/min, UV 220 nm, t_R (*R*) = 19.91 min, t_R (*S*) = 20.53 min, k (*R*) = 5.64, k (*S*) = 5.84, α = 1.08, Rs = 2.6. ee 70%. $[\alpha]^{25}_D$ = −8.6 (*c* 1.3, $CHCl_3$). HRMS ($[M + H]^+$, ESI): *m*/*z* calcd for $C_8H_{18}NO_2$ 160.1332, found 160.1331.

***tert*-Butyl 5-(3-Methoxypropanamido)hexanoate (3j).** Amide **3j** was prepared in 85% yield from amine **1j** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 6.03 (broad d, J = 8.1, 1H), 4.08−3.95 (m, 1H), 3.64 (t, J = 5.8, 2H), 3.38 (s, 3H), 2.42 (t, J = 5.8, 2H), 2.29 (m, 2H), 1.81−1.67 (m, 4H), 1.46 (s, 9H), 1.16 (d, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 172.7 (CO), 170.6 (CO), 80.1 (C), 68.6 (CH_2), 58.4 (CH_3), 44.5 (CH), 36.9 (CH_2), 36.8 (CH_2), 32.1 (CH_2), 31.4 (CH_2), 27.8 (3xCH_3), 20.7 (CH_3). HPLC conditions: TCI chiral BP-S, *n*-hexane/*i*-PrOH 80:20, flow rate = 1 mL/min, DAD and polarimeter, t_R (*S*) = 4.77 min, t_R (*R*) = 7.40 min, k (*S*) = 0.59, k (*R*) = 1.47, α = 2.5, Rs = 5.01. ee 95%. $[\alpha]^{25}_D$ = +7.0 (*c* 1.2, $CHCl_3$). HRMS ($[M + H]^+$, ESI): *m*/*z* calcd for $C_{13}H_{26}NO_4$ 260.1856, found 260.1857. The assignment of the absolute configuration is based on the selectivity of the lipase.

3-Methoxy-*N*-(1-(2-methyl-1,3-dioxolan-2-yl)propan-2-yl)propanamide (3k). Amide **3k** was prepared in 66% yield from amine **1k** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 6.48 (broad s, 1H), 4.08 (m, 1H), 3.97−3.88 (m, 4H), 3.62 (m, 2H), 3.35 (s, 3H), 2.40 (t, J = 5.8, 2H), 1.80 (m, 2H), 1.30 (s, 3H), 1.18 (d, J = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.5 (CO), 109.2 (C), 68.6 (CH_2), 64.6 (CH_2), 64.1 (CH_2), 58.6 (CH_3), 44.5 (CH_2), 42.3 (CH), 37.2 (CH_2), 23.8 (CH_3), 21.8 (CH_3). GC analysis for the racemic mixture: Lipodex D column, injector 250 °C, program: 20 min/120 °C then 3 °C/min from 120 to 180 °C and 20 min/180 °C. Detector: FID. t_R (*R*) = 42.37 min, t_R (*S*) = 42.98 min, k (*R*) = 15.94, k (*S*) = 16.19, α = 0.99, Rs = 2.92. ee 98%. $[\alpha]^{25}_D$ = −2.4 (*c* 1.2, $CHCl_3$). HRMS ($[M + H]^+$, ESI): *m*/*z* calcd for $C_{11}H_{22}NO_4$ 232.1543, found 232.1540. The assignment of the absolute configuration is based on the selectivity of the lipase.

***N*-(1,4-Dioxaspiro(4,4)nonan-7-yl)-3-methoxypropanamide (3l).** Amide **3l** was prepared in 55% yield from amine **1l** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 6.53 (broad s, 1H), 4.43−4.35 (m, 1H), 3.91 (m, 4H), 3.62 (t, J = 5.8, 2H), 3.36 (s, 3H), 2.41 (t, J = 5.8, 2H), 2.18−2.08 (m, 2H), 1.97−1.80 (m, 2H), 1.69−1.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.5 (CO), 116.5 (C), 68.5 (CH_2), 64.2 (CH_2), 63.9 (CH_2), 58.5 (CH_3), 47.9 (CH), 42.2 (CH_2), 36.7 (CH_2), 34.2 (CH_2), 30.9 (CH_2). HPLC conditions: Lux-Cellulose-4, *n*-hexane/*i*-PrOH 70:30, flow rate = 1 mL/min, UV 220 nm, t_R (*R*) = 11.27 min, t_R (*S*) = 20.59 min, k (*R*) = 2.76, k (*S*) = 5.86, α = 1.83, Rs = 10.5. ee 75%. $[\alpha]^{25}_D$ = −7.6 (*c* 1.4, $CHCl_3$). HRMS ($[M + H]^+$, ESI): *m*/*z* calcd for $C_{11}H_{20}NO_4$ 230.1387, found 230.1388. The assignment of the absolute configuration is based on the selectivity of the lipase.

***N*-(1,2,3,4-Tetrahydronaphthalen-3-yl)-3-methoxypropanamide (3m).** Amide **3m** was prepared in 68% yield from amine **1m** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 7.13−7.05 (m, 4H), 6.30 (broad s, 1H), 4.31 (m, 1H), 3.61 (t, J = 5.7, 2H), 3.28 (s, 3H), 3.11 (dd, J = 16.2, 5.0, 1H), 2.95−2.81 (m, 2H), 2.65 (dd, J = 16.2, 7.7, 1H), 2.44 (t, J = 5.7, 2H), 2.08−2.01 (m, 1H), 1.84−1.75 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.9 (CO), 135.5 (C), 134.3 (C), 129.4 (HC=), 128.8 (HC=), 126.0 (HC=), 125.8 (HC=), 68.8 (CH_2), 58.6 (CH_3), 45.0 (CH), 37.0 (CH_2), 35.6 (CH_2), 28.7 (CH_2), 27.3 (CH_2). HPLC conditions: Lux-Cellulose-4, *n*-hexane/*i*-PrOH 80:20, flow rate = 1 mL/min, UV 220 nm, t_R (*R*) = 9.23 min, t_R (*S*) = 16.49 min, k (*R*) = 7.6, k (*S*) = 7.8, α = 0.5, Rs = 2.58. ee 75%. $[\alpha]^{25}_D$ = +13.7 (*c* 1.6, $CHCl_3$). HRMS ($[M + H]^+$, ESI): *m*/*z* calcd for $C_{14}H_{20}NO_2$ 234.1489, found 234.1485.

3-Methoxy-*N*-(1-(naphthalen-8-yl)propan-2-yl)propanamide (3n). Amide **3n** was prepared in 37% yield from amine **1n** according to the general procedures for dynamic kinetic resolutions. ^{1}H NMR (400 MHz, $CDCl_3$): 8.31 (d, J = 8.5, 1H), 7.84 (d, J = 8.0, 1H), 7.74 (d, J = 8.2, 1H), 7.56 (m, 1H), 7.47 (m, 1H), 7.39 (t, J = 7.0, 1H), 7.30 (d, J = 6.7, 1H), 6.16 (broad d, J = 6.5, 1H), 4.40 (sept, J = 6.5, 1H), 3.62−3.52 (m, 2H), 3.51 (dd, J = 13.6, 5.5, 1H), 3.30 (s, 3H), 2.96 (dd, J = 13.6, 8.3, 1H), 2.43−2.39 (m, 2H), 1.13 (d, J = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 171.0 (CO), 134.7 (C=), 133.9 (C=), 132.4 (C=), 128.6 (HC=), 127.6 (HC=), 127.3 (HC=), 126.2 (HC=), 125.7 (HC=), 125.2 (HC=), 124.4 (HC=), 68.7 (CH_2), 58.6 (CH_3), 45.9 (CH), 40.0 (CH_2), 37.0 (CH_2), 20.0 (CH_3). HPLC conditions: Chiralcel OD-H, *n*-hexane/*i*-PrOH 95:5, flow rate = 1 mL/min, UV 220 nm, t_R (*S*) = 19.96 min, t_R (*R*) = 24.1 min, k (*S*) = 5.53, k (*R*) = 6.7, α = 1.2, Rs = 4.9. ee >99%. $[\alpha]^{25}_D$ = −17.3 (*c* 1.2, $CHCl_3$). HRMS ($[M + H]^+$, ESI): *m*/*z* calcd for $C_{17}H_{22}NO_2$ 272.1645, found 272.1643.

■ ASSOCIATED CONTENT

Supporting Information. Amine analysis procedures and NMR spectra for compounds **1c**, **1f**, **1g**, **1j**, **1k**, **1l**, **1n**, **A**, **B**, **2c**, and **3a**−**3n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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