Enantioselective Deprotonation of Alkyl Carbamates by Means of (*R*,*R*)-1,2-Bis(*N*,*N*-dimethylamino)cyclohexane/*sec*-Butyllithium—Theory and Experiment

Ernst-Ulrich Würthwein,*[a, c] Karin Behrens,[b, d] and Dieter Hoppe*[b, d]

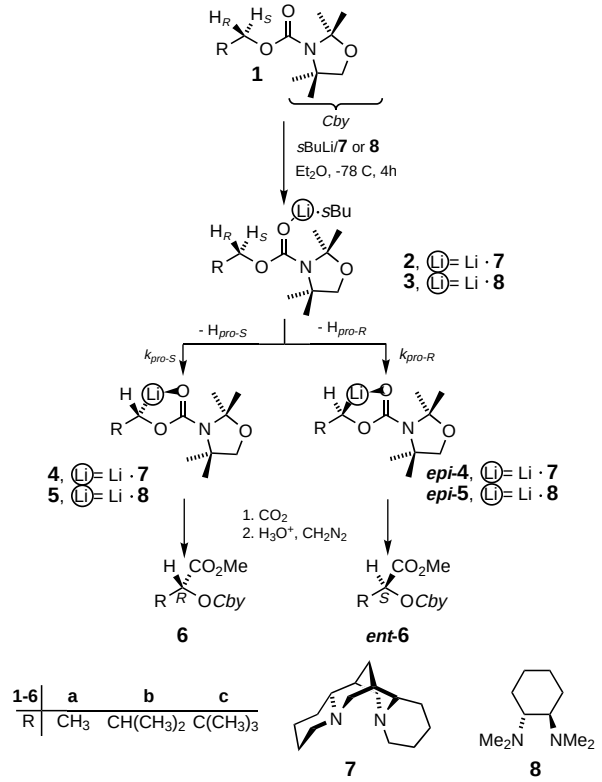
Dedicated to Professor Martin Klessinger on the occasion of his 65th birthday

Abstract: The *O*-ethyl-, *O*-isobutyl-, and *O*-neopentyl carbamates **1a–c** were subjected to the conditions of chiral diamine-assisted deprotonation. The efficiencies were compared for (−)-sparteine (**7**), title compound **8** and (−)-α-isosparteine (**9**). The degree of enantiotopos-differentiation in the deprotonation step was concluded from the enantiomeric ratio in the carboxylation products **6**/*ent*-**6**. The deprotonation of carbamates **1a** and **1b** by *sec*-butyllithium/**7** proceeds with very good selectivity (>95% *ee* in favor for the *pro*-*S*-H), but is not successful with **1c**. (−)-α-Isosparteine (**9**) does not support the deprotonation of alkyl carbamates at all. The medium efficiency of diamine **8** is enhanced by increasing bulk in the β-position (**1a** > **1b** > **1c**). Quantum-chemical calculations (PM3, ab initio methods) on several models for the competing diastereomorphic transition states of the deprotonation under the influence of **8** reflect well the sense and the magnitude of the observed chiral induction and, in addition, give the first insight in the effects which determine the stereochemical outcome of these reactions.

Keywords: chiral diamines · lithiation · quantum-chemical calculations · (−)-sparteine · transition states

Introduction

In 1990, we reported on the first example of a deprotonation reaction proceeding with efficient differentiation between the two enantiotopic protons of the methylene group of very weak carbon acids:[1] Alkyl carbamates of type **1** (Scheme 1, R = *n*-alkyl or heterosubstituted alkyl) are smoothly deprotonated by the chiral base *sec*-butyllithium/(−)-sparteine (**7**) in diethyl ether, pentane or toluene at −78 °C with predominant removal of the *pro*-*S* proton.[2] The enantiomeric ratio in the products **6**/*ent*-**6** which arise from the trapping of intermediate diastereomeric ion pairs **4**/*epi*-**4** usually exceeds 97.5:2.5. Since the ion pairs **4**/*epi*-**4** are configurationally stable under the reaction conditions and the substitution reaction



Scheme 1. Kinetically controlled deprotonation of carbamates **1** with enantiotopic differentiation.

[a] Prof. Dr. E.-U. Würthwein[c]
Organisch-Chemisches Institut
der Westfälischen Wilhelms-Universität
Corrensstrasse 40, D-48149 Münster (Germany)
Fax: (+49) 251-8339772
E-mail: wurthwe@uni-muenster.de

[b] Prof. Dr. D. Hoppe,[d] Dr. K. Behrens[d]
Organisch-Chemisches Institut
der Westfälischen Wilhelms-Universität
Corrensstrasse 40, D-48149 Münster (Germany)
Fax: (+49) 251-8339772
E-mail: dhoppe@uni-muenster.de

[c] Quantum-chemical calculations

[d] Experimental part

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proceeds with complete stereoretention[3] (if R does not interact mesomerically with the carbanionic center) the enantiomeric ratio **6**/*ent*-**6** reflects the ratio of diastereomers **4**/*epi*-**4** which correspond to the relative rate constants $k_{pro\text{-}S}/k_{pro\text{-}R}$ in the deprotonation step. Evidence is accumulating for the rapid formation of an intermediate complex[2, 4] **2** from the alkyl carbamate, *sec*-butyllithium, and (−)-sparteine (**7**), which slowly undergoes intramolecular deprotonation with stereodifferentiation between $H_{pro\text{-}S}$ and $H_{pro\text{-}R}$.

We were trying to understand the structural features determining the differences in $\Delta G^{\neq}$ for the competing transition states by MNDO calculations. These predict a slight preference for the *pro-S* proton, although the high, experimentally observed differences of >1.5 kcal mol^{-1} were not reproduced.[2a, 5, 6] Transition state calculation on lithiodeprotonations,[7] and, particulary on those involving diastereomorphic transition states[8] are scarce. For the sake of simplicity, more sophisticated calculations and, in addition, for meaningful comparison with the experimental results we were seeking for a simpler and, hopefully, a less efficient[9] C_2-symmetric chiral diamine that is capable of supporting the stereoselective deprotonation of the carbamates **1**. It was found finally in (*R*,*R*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane[10] (**8**) (Scheme 1).

Results and Discussion

Experimental results: The carbamates **1a–c**, carrying alkyl groups with increasing bulk, were deprotonated by means of *sec*-butyllithium/**8** (1.45 equivalents diamine, 1.40 equivalents base) in diethyl ether at −78 °C for 4 h. Trapping the mixture of the lithium complexes **4**/*epi*-**4** by gaseous carbon dioxide and methylation of the crude acids furnished the methyl esters **6a–c**/*ent*-**6a–c** with medium enantiomeric ratios (Table 1).

Abstract in German: *Die O-Ethyl-, O-Isobutyl- und O-Neopentylcarbamate **1a–c** wurden in Gegenwart chiraler Diamine deprotoniert. Die Effizienz von (−)-Spartein (**7**), der Titelverbindung **8** und von (−)-α-Isospartein (**9**) wurden verglichen. Das Ausmaß der Enantiotopos-Differenzierung des Deprotonierungsschritts wurde aus den Enantiomerenverhältnissen der Carboxylierungsprodukte **6**/ent-**6** ermittelt. Die Deprotonierung der Carbamate **1a** und **1b** durch sec-Butyllithium/**7** erfolgt hochselektiv (>95 % ee zugunsten des pro-S-H), aber bleibt bei **1c** aus. (−)-α-Isospartein (**9**) ist nicht in der Lage, die Deprotonierung von Alkylcarbamaten zu unterstützen. Die nur mittelmäßige Effizienz des Diamins **8** verbessert sich mit zunehmender Raumerfüllung in β-Stellung (**1a**<**1b**<**1c**). Quantenchemische Rechnungen (PM3, ab initio- und DFT-Methoden) an verschiedenen Modellen für die konkurrierenden diastereomorphen Übergangszustände der Deprotonierung unter dem Einfluß von **8** spiegeln die Richtung und die Größenordnung der beobachteten chiralen Induktion gut wider. Sie geben einen ersten Einblick in die Effekte, welche den sterischen Verlauf dieser Reaktionen bestimmen.*

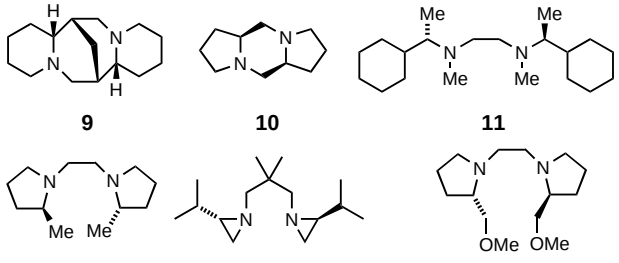
Table 1. Experimental results of the asymmetric deprotonation of carbamates **1a–c**.

Educt	Procedure[a]	Products	Yield [%]	Enantiomeric ratio [% *ee*]	$[\alpha]_D^{22}$[b]
1a	A	**6a**/*ent*-**6a**	81	63:37 (26)	−6.0
	B		73	99:1 (98)	−22.8
1b	A	**6b**/*ent*-**6b**	96	77:23 (54)	−8.4
	B		35	>97.5:2.5 (≥95)	−13.0
1c	A	**6c**/*ent*-**6c**	42	89.5:10.5 (79)	−11.8
	B		0	–	–

[a] Procedure A is mediated by **8**, Procedure B is mediated by **7**. [b] $c = 1.0-1.5$ (CH_2Cl_2).

For comparison, the experiments were repeated with (−)-sparteine (**7**) to provide the esters **6a** and **6b** with enantiomeric ratios of greater than 97.5:2.5. Surprisingly, the neopentyl derivative **1c** was not deprotonated by the (−)-sparteine method, whereas in the presence of the "slimmer" diamine **8** the corresponding ester **6c** was produced with 79 % *ee* (*enantiomeric ratio* **6c**:*ent*-**6c** = 89.5:10.5). The (*R*)-lactic acid derivative **6a** is already known[1b] and the enantiomeric ratios of **6b** and **6c** were determined by ^{1}H NMR shift experiments in the presence of Eu(hfc)$_3$.

From the synthetic point of view, the diamine **8** is superior to (−)-sparteine (**7**) in the deprotonation of bulky alkyl carbamates and, above all, it is easily available in both enantiomeric forms.[10] The results also demonstrate that the delicate balance in the steric demand of the CH-acid and the inducing diamine decides on the success of the deprotonation step. A series of further diamines were tested in the deprotonation of the ethyl carbamate **1a** and were found not capable in supporting the deprotonation at all temperatures between −78 °C and −30 °C: (−)-α-Isosparteine (**9**),[11] perhydro-dipyrrolopyrazine (**10**),[12] (*S*,*S*)-*N*,*N*′-bis(1-cyclohexylethyl)-*N*,*N*′-dimethylethanediamine (**11**), the bis(2-methylpyrrolidine) **12**,[13] bis(aziridine) **13**,[13] and bisprolinol derivative **14**[14] (Scheme 2).



Scheme 2. Chiral diamines which do not support the deprotonation of carbamates **1**.

In a broad study, P. Beak et al. recently investigated the influence of several ligands (including also **7**, **8**, **9**, and **14**) in the asymmetric deprotonation of *N*-Boc-pyrrolidine.[15] Here, the efficiency of (−)-sparteine (**7**) remained unbeaten. Noteably, the cyclohexanediamine **8** did not induce any enantioselectivity.

Theoretical investigations: Based on the fact that the enantioselective deprotonation of the alkyl carbamate is the

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product determining, kinetically controlled step in the electrophilic substitution reactions, we initiated a computational study in order to investigate the performance of modern semiempirical and ab initio methods for such problems.

For steric reasons a 1:1:1 complex of base, diamine and carbamate seems to be most likely for the transition state. Starting from a small transition state model system for the preformed complex of the reaction partners we added stepwise additional sterically and electronically influencing groups in order to get a feeling for the importance of those groups for the enantiomeric excess found in products **6a–c**.

Computational methods: We started with complete geometry optimizations of (*R*,*R*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**8**) with the MMX force field.[16] The resulting geometry was reoptimized by using PM3 as supplied in MOPAC93[17] and several ab initio basis sets (GAUSSIAN94 program package).[18] Then, the lithium cation, complexed with the most simple carbamate $CH_3OC(=O)NH_2$ at the carbonyl oxygen atom, was added. The addition of a methyl group to the lithium cation completed this most simple model for the carbamate/diamine/methyllithium complex. The reaction path technique followed by transition state optimizations (keyword "TS" in MOPAC93) led to two diastereomeric transition states *lk*-TS and *ul*-TS for the proton transfer reaction.[19] These transition state geometries formed the basis for the exchange of the further groups. *i*PrLi instead of MeLi was introduced as a model for the used base *s*Buli, in order to get closer to the experimentally studied system (see Table 2). In several cases, the geometries were reoptimized starting from different starting geometries in order to increase the probability to have localized the energy lowest saddle point on the potential energy hyperface. As a result of the similarity of the diastereomeric transition states an efficient error cancellation of the PM3 heats of formation may be expected which renders relative data which are much more reliable than the heats of formation itself. The same will certainly apply to transition state entropies as well.

Theoretical results: As Table 2 clearly shows simple model transition states with sterically not demanding moieties (entries 1–5) are calculated to possess almost identical heat of formations for the corresponding diastereomeric pairs. However, it seems noteworthy that all systems studied give a preference for the *R*,*R*/*pro-S* (*ul*)[20] transition state, although sometimes to a rather small extent. Thus, neither increasing of the bulkiness of the base (from methyllithium to isopropyllithium, entry 2) nor of that of the carbamate substituent (methyl versus *tert*-butyl, entry 3) leads to a substantial differentiation of the diastereomeric transition states. On the other hand, the nature of the amino group of the carbamate moiety seems to have the most pronounced effect on the enthalpy difference of the transition states. Although NH_2, NMe_2, and pyrrolidinyl for **X** (TS **C**, **D**, **E**) seem to be without influence on the stereodifferentiation, the introduction of a spacious 2,2,5,5-tetramethylpyrrolidinyl group in TS **F** (taken as a model for the experimentally studied, unsymmetrical 2,2,4,4-tetramethyl-1,3-oxazolidine-3-yl group) in compound **3c** leads to a significant kinetic preference for the *R*,*R*/*pro-S* transition state *ul*-**F** (Figure 1). The calculated difference (1.23 kcal mol^{-1}) for this model system **F** is in remarkably good agreement with the experimentally observed one for the produced **6c** (79% *ee* at −78 °C).

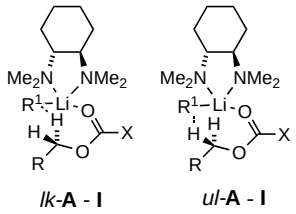

Figure 1. Competing diastereomorphic model transition states **A–I**. For R, R^1 see Table 2.

Figure 2 depicts the calculated transition state structures. Interestingly, the structure *lk*-**F** is more symmetrical with respect to the Li–N complexation and to the C–H–C bond lengths compared with *ul*-**F**, which is lower in energy. However, there is no single, obvious difference in the structure of the two transition states, but rather the sum of several small deviations in different parts of the complexes are responsible for the diastereoselection.

The more spacious base *i*PrLi (TS **F**) gives better results than MeLi (see model system of entry 7, 0.85 kcal mol^{-1} difference). For the corresponding methyl derivatives **H** a much smaller difference of 0.37 kcal mol^{-1} is calculated, which has to be compared with the experimental value of *ee* = 26% for compound **6a**. Here, the nature of the base surprisingly has no effect on the calculated stereodifferentiation (see TS **I**).

We conclude from these data that for the optimization of the enantiomeric excess of the enantiotopos-differentiating

Table 2. Results of the quantum-chemical calculations.

Entry	TS	Base R^{1}Li	R	X	ΔH_f *R*,*R*/*pro-R* *lk*-TS	ΔH_f *R*,*R*/*pro-S* *ul*-TS	$\Delta\Delta H_f$
1	**A**	MeLi	Me	NH_2	−113.77	−113.99	0.22
2	**B**	*i*PrLi	Me	NH_2	−122.88	−122.95	0.07
3	**C**	*i*PrLi	*t*Bu	NH_2	−137.96	−138.05	0.09
4	**D**	*i*PrLi	*t*Bu	NMe_2	−137.91	−137.96	0.05
5	**E**	*i*PrLi	*t*Bu	pyrrolidinyl	−143.03	−143.06	0.03
6	**F**	*i*PrLi	*t*Bu	2,2,5,5-tetramethyl-pyrrolidinyl	−165.08	−166.31	1.23
7	**G**	MeLi	*t*Bu	2,2,5,5-tetramethyl-pyrrolidinyl	−155.39	−156.24	0.85
8	**H**	*i*PrLi	Me	2,2,5,5-tetramethyl-pyrrolidinyl	−142.24	−142.61	0.37
9	**I**	MeLi	Me	2,2,5,5-tetramethyl-pyrrolidinyl	−132.55	−132.89	0.34

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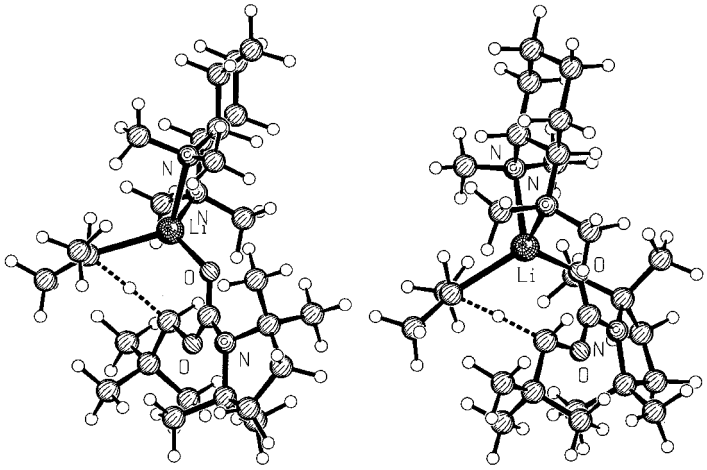

Figure 2. Schakal-plots of the calculated structures for the transition states *lk*-**F** (left) and *ul*-**F** (right); (PM3 results). Characteristic bond lengths [Å]: *lk*-**F** Li–N: 2.2910, 2.2959; Li–C: 2.3466; Li–O: 1.9529; C–H–C: 1.4870, 1.4804; *ul*-**F** Li–N: 2.2373, 2.3100; Li–C: 2.3623; Li–O: 1.9205; C–H–C: 1.4650, 1.5009.

deprotonation reaction, the steric bulkiness of the amino substituent has the most prominent influence on the stereochemical outcome of the reaction. As expected, β-branched alkyl carbamates give better results than *n*-alkyl derivatives. According to these findings, the steric nature of the base has a significant influence only in sterically very crowded systems; nevertheless, for successful deprotonation, the bulkier secondary bases (*s*BuLi in the experiment, or *i*PrLi in the calculations) are essential.

The semiempirical PM3 results have further been checked by comparison with some ab initio data. However, as a result of the size of the system, only relatively small basis sets were applicable. Complete geometry optimization (starting with PM3 geometries) of the two transition states for model system **6** with the RHF/3-21G basis set produces an energy difference $\Delta\Delta H_f$ of 1.21 kcal mol^{-1} in favor of the *R*,*R*/*pro-S* deprotonation pathway, which is in excellent agreement with the PM3 and the experimental results. Geometry optimizations at the RHF/6-31G* level of theory resulted in a energy difference of 0.85 kcal mol^{-1}, MP2/6-31G*//RHF/6-31G* single point calculations give 2.15 kcal mol^{-1}, indicating that the structures are influenced by electron correlation with respect to the energies. Finally, DFT geometry optimizations, which include electron correlation effects, using the B3LYP/6-31G* method, gave a difference in total energy of 1.10 kcal mol^{-1} in favor of the *RR/pro-S* deprotonation, which again is in excellent agreement with the PM3 and 3-21G data.[21]

Conclusion

In conclusion, it is evident from these studies that no simple, easily surveyed model will be available for the prediction of direction and magnitude of the enantiotopos-differentiation in the deprotonation reaction. It is the interplay of steric effects in the chiral auxiliary, in the base, in the alkyl group, and in the amino residue which determines the energetic difference of the competing diastereomorphic transition states. Semiempirical PM3 calculations seem to be a useful tool for the prediction of optimal combinations. However, increasing the overall steric bulk is a tightrope walk: As the experiments with (−)-α-isosparteine (**9**) demonstrate, a situation is reached soon in which a deprotonation of weak carbon acids does not occur at all.

Experimental Section

General: All organometallic reactions were performed under Ar with exclusion of air and moisture. Toluene was dried over Na before use. FC separations were carried out at 0.5–1.5 bar on silica gel 40–63 μm (Merck, Darmstadt). IR: Perkin–Elmer 298. Optical rotations: Perkin–Elmer polarimeter 241. NMR: Bruker WM 300 (300 MHz and 75.5 MHz for ^{1}H and ^{13}C NMR, respectively). For ^{1}H NMR, $CDCl_3$ was used as solvent, TMS as internal standard; for ^{13}C NMR, $CDCl_3$ $\delta_C = 77.0$. The ^{1}H NMR shift experiments were performed by addition of (+)-Eu(hfc)$_3$ (6–21 mg) to a solution of the enantioenriched products (20 mg) in $CDCl_3$ (0.8 mL). Combustion analysis: Perkin–Elmer 240, Organisch-Chemisches Institut der Universität Münster.

Ethyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (**1a**): 2,2,4,4-Tetramethyl-1,3-oxazolidine (12.9 g, 64.2 mmol) was added to ethoxycarbonyl chloride (3.46 g, 32.0 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 16 h, and the mixture was poured into 2 N aq. HCl (80 mL). The aqueous phase was extracted with Et_2O (3 × 40 mL), and the combined ethereal solution neutralized and dried (Na_2SO_4/$NaHCO_3$ 2:1). Evaporation and purification by FC yielded **1a** (8.05 g, 80 %) as a colorless oil. R_f (PE/Et_2O 1:1) = 0.61; IR (film): $\tilde{\nu}$ = 1695 cm^{-1} (NC=O); ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, $J_{2',1'}$ = 7.1 Hz, 2′-H$_3$), 1.37, 1.43 (2 s, 4-CH$_3$), 1.52, 1.57 (2 s, 2-CH$_3$), 3.73 (s, 5-H$_2$), 4.15, 4.19 (2 q, $J_{1',2'}$ = 7.1 Hz, 1′-H$_2$); ^{13}C NMR ($CDCl_3$): δ = 14.51 (C-2′), 24.22, 25.35 (4-CH$_3$), 25.35, 26.55 (2-CH$_3$), 59.68, 60.30 (C-4), 60.30 (C-1′), 76.23, 76.44 (C-5), 94.87, 95.80 (C-2), 152.23, 152.88 (NC=O); $C_{10}H_{19}NO_3$ (201.28): calcd C 59.67, H 9.51; found C 59.71 and H 9.60.

2-Methylpropyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (**1b**): 2-Methylpropanol (2.22 g, 30.0 mmol) was added to a suspension of NaH (60 % in mineral oil; 1.80 g, 45.0 mmol) in THF (50 mL) and the mixture was stirred at room temperature for 30 min. 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carbonyl chloride[1b] (5.75 g, 30.0 mmol), dissolved in THF (25 mL), was added. After the reaction mixture was heated under reflux for 2.5 h, the solution was poured into 2 N aq. HCl/Et_2O (300 mL each). The aqueous phase was extracted with Et_2O (3 × 100 mL), and the combined ethereal solution neutralized and dried (Na_2SO_4/$NaHCO_3$ 2:1). Evaporation and purification by FC (PE/Et_2O 10:1) afforded **1b** (5.74 g, 83 %) as a colorless oil. R_f (PE/Et_2O 2:1) = 0.46; IR (film): $\tilde{\nu}$ = 1700 (C=O), 1400, 1380 cm^{-1} [C(CH$_3$)$_2$]; ^{1}H NMR ($CDCl_3$): δ = 0.97 (d, $J_{3',2'}$ = 6.7 Hz, 3′-H$_3$), 1.39, 1.43, 1.54, 1.56 (4 s, 2-CH$_3$, 4-CH$_3$), 1.98 (m, 1 H, 2′-H), 3.73 (s, 5-H$_2$), 3.89 (d, $J_{1',2'}$ = 6.4 Hz, 1′-H$_2$); ^{13}C NMR ($CDCl_3$): δ = 19.31 (C-3′), 24.09, 25.27, 26.49 (2-CH$_3$, 4-CH$_3$), 27.94 (C-2′), 59.51, 60.45 (C-4), 70.83 (C-1′), 76.09, 76.33 (C-5), 94.69, 95.74 (C-2), 152.21, 152.92 (C=O); $C_{12}H_{23}NO_3$ (229.32): calcd C 62.85; H 10.11, N 6.11; found C 62.85, H 10.32, N 6.29.

Similarly prepared: **2,2-Dimethylpropyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate** (**1c**): 2,2-Dimethylpropanol (1.32 g, 15.0 mmol) and 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl chloride (2.88 g, 15.0 mmol) dissolved in THF (15 mL) were added to NaH (60 % in mineral oil; 900 mg, 22.5 mmol) in THF (30 mL). Aqueous workup and purification by FC (PE/Et_2O 8:1) yielded **1c** (3.02 g, 83 %) as colorless crystals. M.p. = 86 °C; R_f (PE/Et_2O 2:1) = 0.48; IR (film): $\tilde{\nu}$ = 1690 (C=O), 1380, 1360 cm^{-1} [C(CH$_3$)$_2$]; ^{1}H NMR ($CDCl_3$): δ = 0.99 (s, 3′-H$_3$), 1.41, 1.43, 1.57 (3 s, 2-CH$_3$, 4-CH$_3$), 3.74 (s, 5-H$_2$), 3.81 (s, 1′-H$_2$); ^{13}C NMR ($CDCl_3$): δ = 24.16, 25.34, 25.41, 26.66 (2-CH$_3$, 4-CH$_3$), 26.79 (C-3′), 31.44 (C-2′), 59.57, 60.66 (C-4), 74.44 (C-1′), 76.16, 76.42 (C-5), 94.70, 95.94 (C-2), 152.11, 152.98 (C=O); $C_{13}H_{25}NO_3$ (243.35): calcd C 64.17, H 10.35, N 5.76; found C 64.50, H 10.50, N 5.77.

Deprotonation of the alkyl carbamates 1a–c — General Procedure: To a solution of the diamine [Procedure A: 247 mg, 1.45 mmol of (*R*,*R*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**8**), Procedure B: 340 mg, 1.45 mmol of (−)-sparteine (**7**)] in dry diethyl ether (3 mL) kept at −78 °C under argon and, subsequently, *sec*-butyllithium in hexane (1.4 M, 0.99 mL,

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1.40 mmol) was added and, after 10 min, a solution of the carbamate **1** (1.00 mmol) in diethyl ether (3 mL) was slowly introduced through a syringe. The orange colored solution was stirred for 4 h at −78 °C before the gaseous CO_2 (liberated from dry ice) was introduced with a gas inlet. The reaction mixture was stirred for 2 h at −78 °C before a mixture of 2 N aq. HCl (5 mL) and ether (5 mL) was added. The aqueous phase was extracted with Et_2O (3 × 30 mL) and dried over Na_2SO_4. After evaporation of the solvent in vacuum, the residue was dissolved in diethyl ether, and ethereal diazomethane solution was added dropwise until the yellow color remained. The crude ester was purified by flash chromatography (FC) on silica gel.

Methyl (*R*)-2-(2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyloxy)-propanoate (**6a**): Deprotonation of **1a** (201 mg, 1.00 mmol) and addition of CO_2 (in excess) followed by an O-methylation with diazomethane yielded **6a** (Procedure A: 210 mg, 81 %, 26 % *ee*; Procedure B: 189 mg, 73 %, 98 % *ee*) as a colorless oil; shift experiment: 21 mg (+)-Eu(hfc)$_3$, $\Delta\delta$ (2-H) = 0.25; R_f (PE/Et_2O 1:1) = 0.55; IR (film): $\tilde{\nu}$ = 1760 (OC=O), 1705 cm^{-1} (NC=O); ^{1}H NMR ($CDCl_3$): δ = 1.40 (d, 3-H$_3$), 1.45–1.60 (m, 12 H, 2′-CH$_3$, 4′-CH$_3$), 3.75 (s, 5′-H$_2$, OCH$_3$) 5.11, 5.12 (2 q, $J_{2,3}$ = 7.1 Hz, 2-H$_1$); ^{13}C NMR ($CDCl_3$): δ = 17.15 (C-3), 24.08, 25.10 (4′-CH$_3$), 25.34, 25.46, 26.39, 26.62 (2′-CH$_3$), 52.06 (OCH$_3$), 60.11, 60.80 (C-4′), 68.55 (C-2), 76.12, 76.47 (C-5′), 95.26, 95.97 (C-2′), 150.96, 151.72 (NC=O), 171.92 (OC=O); $C_{12}H_{21}NO_5$ (259.30): calcd C 55.59, H 8.16; found C 55.74, H 8.27.

Methyl (*R*)-3-methyl-2-(2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbamoyloxy)-butanoate (**6b**): Deprotonation of **1b** (229 mg, 1.00 mmol) and addition of CO_2 (in excess) followed by an O-methylation with diazomethane yielded **6b** (Procedure A: 277 mg, 96 %, 54 % *ee*; Procedure B: 102 mg, 35 %, ≥ 95 % *ee*) as a colorless oil, shift experiment: 13 mg (+)-Eu(hfc)$_3$, $\Delta\delta$ (2-H) = 0.16; R_f (PE/Et_2O 2:1) = 0.51; IR (film): $\tilde{\nu}$ = 1750 (OC=O), 1700 cm^{-1} (NC=O); ^{1}H NMR ($CDCl_3$): δ = 1.03 (m, 6 H, 4-H$_3$), 1.36, 1.37, 1.50, 1.56, 1.58, 1.67 (6 s, 2′-CH$_3$, 4′-CH$_3$), 2.27 (m, 1 H, 3-H), 3.74, 3.76 (2 s, OCH$_3$, 5′-H$_2$), 4.94 (d, $J_{2,3}$ = 4.3 Hz, 2-H); ^{13}C NMR ($CDCl_3$): δ = 17.66, 17.76, 17.89, 18.97, 23.99, 24.97, 25.34, 25.58, 26.39, 26.69 (C-4, 2′-CH$_3$, 4′-CH$_3$), 30.22 (C-3), 51.76 (OCH$_3$), 60.02, 60.86 (C-4′), 76.09 (C-5′), 76.42 (C-2), 95.13, 96.05 (C-2′), 151.34, 152.17 (NC=O), 170.81 (OC=O); $C_{14}H_{25}NO_5$ (287.36): calcd C 58.52, H 8.77, N 4.87; found C 58.43, H 8.63, N 4.89.

Methyl (*R*)-3,3-dimethyl-2-(2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyloxy)-butanoate (**6c**): Deprotonation of **1c** (243 mg, 1.00 mmol) and addition of CO_2 (in excess) followed by an O-methylation with diazomethane yielded **6c** (Procedure A: 178 mg, 42 %, 79 % *ee*; Procedure B: no yield) as a colorless oil, shift experiment: 6 mg (+)-Eu(hfc)$_3$, $\Delta\delta$ (OCH$_3$) = 0.03; R_f (PE/Et_2O 2:1) = 0.52; IR (film): $\tilde{\nu}$ = 1750 (OC=O), 1700 cm^{-1} (NC=O); ^{1}H NMR ($CDCl_3$): δ = 1.06, 1.07 (2 s, 4-H$_3$), 1.41, 1.44, 1.51, 1.54, 1.56, 1.60, 1.68 (7 s, 2′-CH$_3$, 4′-CH$_3$), 3.73 (s, OCH$_3$), 3.75 (s, 5′-H$_2$), 4.70 (s, 2-H); ^{13}C NMR ($CDCl_3$): δ = 23.99, 24.94, 25.37, 25.75 (2′-CH$_3$, 4′-CH$_3$), 26.59 (C-4), 33.70 (C-3), 51.49 (OCH$_3$), 59.94, 60.96 (C-4′), 76.09 (C-5′), 80.61 (C-2), 95.03, 96.17 (C-2′), 152.41 (NC=O), 170.31 (OC=O); $C_{15}H_{27}NO_5$ (301.38): calcd C 59.78, H 9.03, N 4.65; found C 60.10, H 9.15, N 4.29.

Attempted deprotonation of 1a with (−)-α-isosparteine/*sec*-butyllithium: After treatment of **1a** (201 mg, 1.00 mmol) with *sec*-butyllithium (1.4 M in hexane, 0.99 mL, 1.40 mmol) and (−)-α-isosparteine (**9**, 340 mg, 1.45 mmol) following the general procedure, no product was detected; only the starting material **1a** (170 mg, 85 %) was isolated.

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