Diastereoselective Lithiation and Substitution of (*S*)-*N*-Benzylprolinol and *rac*-*N*-Benzylpiperidine-2-methanol via the Carbamate Esters: Kinetic Resolution by Means of (–)-Sparteine-Mediated Deprotonation

B. Weber,[a] J. Schwerdtfeger,[a] R. Fröhlich[a], A. Göhrt,[b] D. Hoppe*[a]

[a]Institut für Organische Chemie der Westfälischen Wilhelms-Universität Münster, Corrensstraße 40, D-48149 Münster, Germany
Fax +49(251)8339772

[b]Bayer AG, D-51368 Leverkusen, Germany

Received 7 June 1999

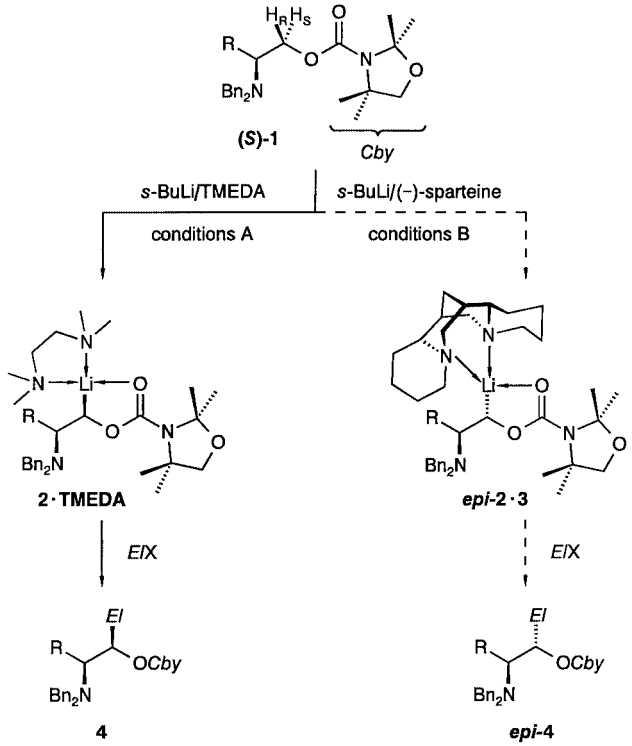
Abstract: The (*S*)-*N*-benzylprolinol carbamate (*S*)-**8** is deprotonated by *sec*-butyllithium with the removal of the *pro*-*R*-H and the intermediate lithium compound **10** is trapped by several electrophiles. Complete *ul*-diastereotopos-differentation is achieved irrespective of the supporting additive [TMEDA, (−)-sparteine, or ether]. For the homologous piperidine derivative *rac*-**9**, the substrate-directed diastereoselectivity is less pronounced (~6:1). Thus, an efficient kinetic resolution is observed by means of *sec*-butyllithium/(−)-sparteine, leading to the preferential consumption of the (+)-(*R*)-**9** with abstraction of the *pro*-*S*-H, followed by its substitution by electrophiles. Enantioenriched (−)-(*S*)-**9** remains unchanged.

Key words: β-amino alcohols, β-amino-α-oxy carbanions, diastereoselective deprotonation, (−)-sparteine, kinetic resolution, carbanions, lithiation, Mosher esters

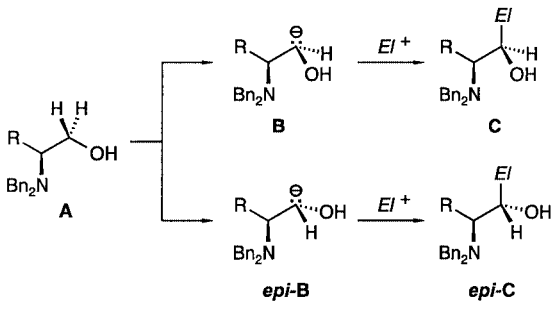
Introduction

As we have recently reported, carbamate esters of 2-(*N*,*N*-dibenzylamino)alkan-1-ols **1** are deprotonated in the α-position by means of *sec*-butyllithium/tertiary diamine reagents (Scheme 1).[1–4]

The selection between the diastereotopic protons *pro*-*R*-H_1 and *pro*-*S*-H_1 is greatly influenced by the nature of the complexing diamine. The achiral additive *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA, conditions A) usually supports the substrate-directed removal of the *ul*-proton[5] [*pro*-*R*-H in (*S*)-**1**, *pro*-*S*-H in (*R*)-**1**] to form preferentially **2**·TMEDA [or *ent*-**2**·TMEDA from (*R*)-**1**]. The base *sec*-butyllithium/(−)-sparteine (conditions B), due to its high preference for *pro*-*S*-protons in alkyl carbamates, reacts with (*S*)-**1** in a mismatched situation[6] slowly leading to the lithium intermediate *epi*-**2**·**3**.[7] Trapping of the mixtures by electrophiles *El*X gives rise to the main products **4** or *epi*-**4**, respectively, in a substitution reaction with complete retention of the configuration.[3a] Consequently, with substrates (*R*)-**1** under (−)-sparteine conditions B, the matched pair[6] results in a very rapid deprotonation and, therefore, could be utilized for the kinetic resolution of a racemic amino alcohol.[8] The accumulated experimental evidence led to the conclusion, that the dibenzylamino group does not support the deprotonation step by complexation of the lithium cation.[2–4] The method provides a flexible solution for generating synthetic equivalents for the synthons **B**, *epi*-**B**, and their enantiomers. It is an umpoled version of the usual route consisting in the addition of nucleophiles to *N*-protected α-amino aldehydes (Scheme 2).[9]



Scheme 1



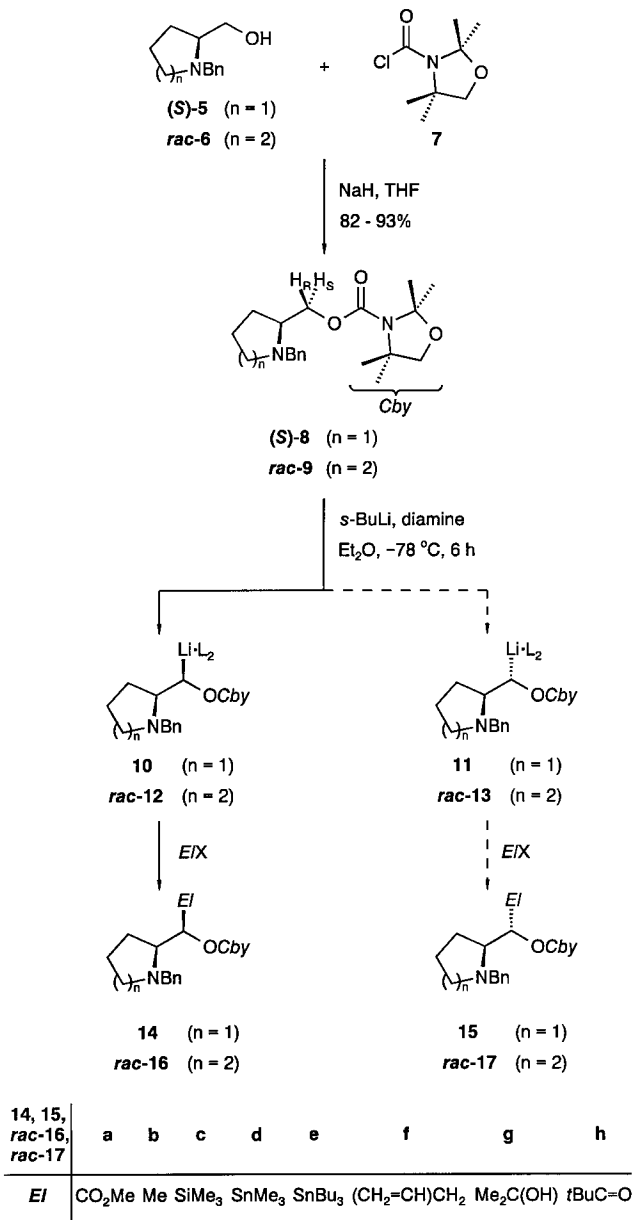
Scheme 2

In this work, we investigated the carbamates (*S*)-**8**[1] and *rac*-**9**, derived from the cyclic amino alcohols (*S*)-*N*-benzylprolinol [(*S*)-**5**] and *rac*-*N*-benzylpiperidine-2-methanol (*rac*-**6**), which, surprisingly, exhibit a different stereochemical reactivity pattern, deviating from that of the open-chain counterparts **1**.

Results and Discussion

Deprotonation and Substitution

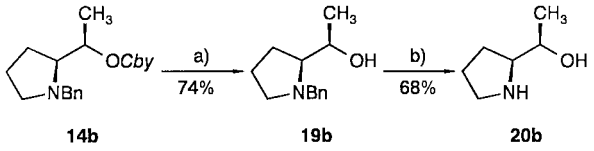
The carbamates (*S*)-**8** and *rac*-**9** were prepared from the corresponding *N*-benzylamino alcohols (*S*)-**5**[10] or *rac*-**6**[10] and the oxazolidinecarbonyl chloride **7** by the sodium hydride method (Scheme 3).[11]



Scheme 3

Compound (*S*)-**8** was allowed to react with 2.0 equivalents of *sec*-butyllithium (approx. 1.3 M in cyclohexane/hexane, 92:8) in diethyl ether in the presence of TMEDA (2.0 equiv) at −78°C for 3 hours (conditions A) and the reaction mixture was quenched with methyl chloroformate. Workup afforded the methyl ester **14a**, arising from the substitution of the *pro-R*-H, via the lithiated diastereomer **10** as a single diastereomer (Table 1, Entry 1). The same result was obtained (Entry 3) when (−)-sparteine (**3**) was used as the additive (conditions B), and - even in a higher yield (Entry 4) - in the absence of any diamine ligand (conditions C). Unlike the *N*,*N*-dibenzylaminoalkyl carbamates **1**, for efficient deprotonation of (*S*)-**8**, no bidentate diamine is required. The same turned out to be true for the next homologue *rac*-**9** (Entry 14). For a possible explanation see below.

The reaction of (*S*)-**8** via **10** with methyl iodide, chlorotrimethylsilane, chlorotributyltin, and acetone also yielded the expected compounds **14** with high diastereoselectivity (for spectroscopic data, see Table 3). As we had already observed in related cases,[12] no stereospecifity with respect to the former carbanionic center was achieved in the reaction with allyl bromide (Table 1, Entry 11). In all other cases, deprotonation and substitution - as found for all sp^3-carbamoyloxy-substituted carbanions - proceeded with complete stereoretention. The expected configuration [2*S*,2(1*R*)] for the methylation product **14b** was confirmed by transformation into the known amino alcohol **20b**[11,13] (Scheme 4). The stereostructure of the acetone addition product **14g** was established by an X-ray crystal structure analysis (Figure 1).[14]



Reagents and conditions: a) i. $MeSO_3H$/MeOH, reflux; ii $Ba(OH)_2 \cdot 8H_2O$/MeOH, reflux; b) Pd black, MeOH/HCO_2H (95:5).

Scheme 4

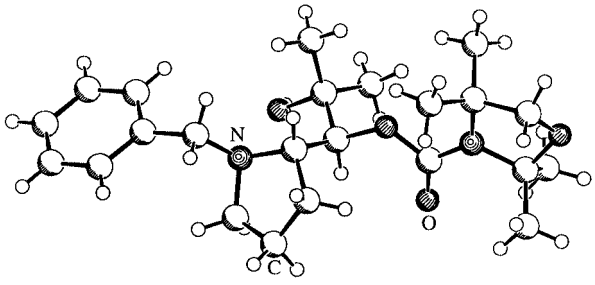


Figure 1 X-ray structure of **14g**[14]

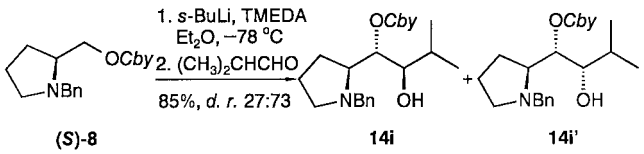
2-Methylpropanal as a prochiral electrophile led to the diastereomers **14i** and **14i'** (dr = 27:73) arising from

Table 1 Yields and Diastereomeric Ratios in the Reaction of (*S*)-**8** and *rac*-**9** with Various Electrophiles

Entry	Substrate	*El*X	Product	Diamine	Yield (%)[a,b]	mp (°C) (solvent)	Ratio (dr)	$[\alpha]_D^{20}$ [c,d,e]
1	(*S*)-**8**	$ClCO_2CH_3$	**14a**	TMEDA	59[a]	oil	>95:<5	–19.6[c]
2		CO_2/CH_2N_2	**14a**	TMEDA	40[b]		>95:<5	–19.2[c]
3		$ClCO_2CH_3$	**14a**	(–)-sparteine	66[a]		>95:<5	–18.9[c]
4		$ClCO_2OMe$	**14a**	–	84[a]		>95:<5	–19.3[c]
5	(*S*)-**8**	MeI	**14b**	TMEDA	71[b]	52 (E/P)	>95:<5	–51.0[d]
6		MeI	**14b**	(–)-sparteine	56[b]		>95:<5	–51.4[d]
7		MeI	**14b**	–	73[a]		>95:<5	–51.8[d]
8	(*S*)-**8**	Me_3SiCl	**14c**	TMEDA	33[b]	45 (E/P)	>95:<5	–54.8[e]
9	(*S*)-**8**	Bu_3SnCl	**14e**	TMEDA	71[b]	oil	>95:<5	–69.6[c]
10	(*S*)-**8**	Me_2CO	**14g**	TMEDA	33[b]	102 (E/P)	>95:<5	– 7.4[c]
11	(*S*)-**8**	$(CH_2{=}CH)CH_2Br$	**14f**[f] + **15f**[g]	TMEDA	49[a] 33[a]	oil oil	60:40	–47.6[c] –54.1[c]
12	(*S*)-**8**	Me_2CHCHO	**14i**[g] + **14i'**[f]	TMEDA	23[b] 62[b]	64 (E/P) oil	27:73	– 8.1[c] – 1.3[c]
13	*rac*-**9**	$ClCO_2Me$	*rac*-**16a**[g] + *rac*-**17a**[h]	TMEDA	80[a]	oil –[h]	85:15	
14	*rac*-**9**	$ClCO_2Me$	*rac*-**16a**[g] + *rac*-**17a**[h]	–	49[a]		92:8	
15	*rac*-**9**	MeI	*rac*-**16b** + *rac*-**17b**	TMEDA	86[a]	–[i]	84:16	
16	*rac*-**9**	MeI	*rac*-**16b** + *rac*-**17b**	–	50[a]		94:6	
17	*rac*-**9**	Me_3SiCl	*rac*-**16c**	TMEDA	66[a]	95-97 (E/P)	>95:<5[j]	
18	*rac*-**9**	Me_3SnCl	*rac*-**16d** + *rac*-**17d**	TMEDA	72[k]	oil[i]	79:21	
19	*rac*-**9**	Me_3SnCl	*rac*-**16d** + *rac*-**17d**	–	34[k]		87:13	
20	*rac*-**9**	Me_3COCl	*rac*-**16h** + *rac*-**17h**	TMEDA	84[a]	oil[i]	85:15	
21	*rac*-**9**	Me_3COCl	*rac*-**16h** + *rac*-**17h**	–	52[a]		95:5	

[a] Flash chromatography on silica gel.
[b] Flash chromatography on aluminium oxide.
[c] $c = 1.0$ in $CHCl_3$.
[d] $c = 0.5$ in $CHCl_3$.
[e] $c = 1.5$ in $CHCl_3$.
[f] More polar diastereomer on Al_2O_3.
[g] Less polar diastereomer on Al_2O_3.
[h] Mixture of *rac*-**17** and educt *rac*-**9**, which is not separable by flash chromatography.
[i] Diastereomeric mixture of *rac*-**16** and *rac*-**17**, which is not separable by flash chromatography.
[j] No evidence was found for the other diastereomer by TLC or ^1H and ^{13}C NMR spectra.
[k] Purified by flash chromatography with Et_2O/pentane (1:5) and 3% Et_3N on silica gel.

diminished facial selectivity at the carbonyl group (Table 1, Entry 12). We assume the following relative configurations for **14i** and **14i'** by comparison of their polarities on silica gel and their OH-proton shifts in $CDCl_3$ in analogy to former results (Scheme 5).[3a]



Scheme 5

The deprotonation of the piperidine derivative *rac*-**9** under conditions A (TMEDA) and trapping with different electrophiles occurred with lower diastereotopic selectivity affording *rac*-**16** and *rac*-**17** in a ratio of roughly 6:1 (Table 1). When applying conditions C (no additive), the diastereomeric ratio increased to 95:5 (e.g., see Entries 20 and 21), but the yields are lower due to a slower deprotonation. Both facts are the reasons for a successful kinetic resolution of *rac*-**9** (see below).

Why the lithiation of the *N*,*N*-dibenzylaminoalkyl carbamates **1** requires the presence of a bidentate external ligand whereas for the cyclic carbamates **8** and **9** a weak donor solvent such as diethyl ether is sufficient? In the cyclic *N*-benzyl compounds **8** and **9**, a more rigid conformation and a less shielded lone pair at the nitrogen atom are

given. This led us to the speculation that tricyclic chelate complexes such as **10A** and **12A**, containing one molecule of diethyl ether (Figure 2), are the energetically most preferred arrangements in the systems. Four membered-ring lithium structures[15] are numerous.[16] We encountered several cases, where donor-ligands being attached to stereogenic centers cause extremely high and reliable diastereoselectivities.[4,17,18] Obviously, all important features, stabilizing the particular transition states of diastereomeric deprotonation reactions, are also reflected in the ground state energies of bi- or tricyclic chelate complexes.

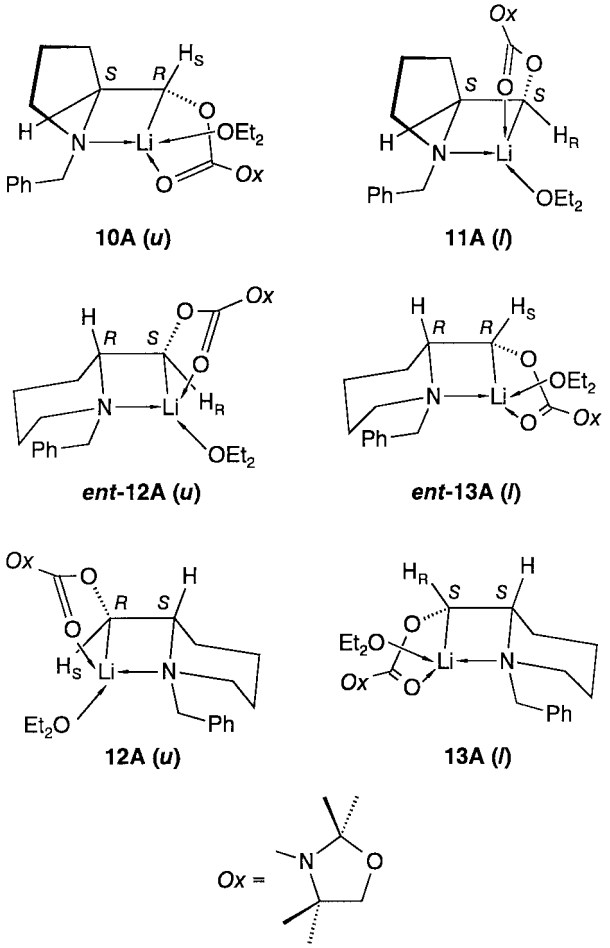


Figure 2 Chelate complex structures of **10–13**

When comparing the diastereomeric chelate complexes *u*-**10A** and *l*-**11A** one expects the first one, bearing *anti*-fused five-membered rings connected at the azalithiocyclobutane ring and arising from an *ul*-deprotonation, to be the more stable one. In the *syn*-fused tricycle **11A** severe steric interactions between the two five-membered rings are expected to occur. Similar arguments may count for the preferential formation of **12A** in the annulated 6,4,5-tricyclic intermediates, although to a lesser extent, since a decreased diastereotopic selection is observed in the experiment (Table 1, e.g. Entries 14 and 16). In addition, it must be concluded that the (−)-sparteine complex **11·3** [L_2 = (−)-sparteine] is largely disfavoured in competition with **10A**.

Kinetic Resolution

Fortunately, *sec*-BuLi/(−)-sparteine reacts more rapidly than *sec*-BuLi/Et_2O with *rac*-**9**, when applying deprotonation conditions B (varying ratios of substrate/base/ligand; see Scheme 6, Table 2). Methoxycarbonylation or trimethylsilylation of the lithium intermediates furnishes the optically active products (+)-*ent*-**16a** and (+)-*ent*-**16c**, which were produced besides some recovered, partially enantiomerically enriched starting material consisting in excess of (−)-(*S*)-**9**.

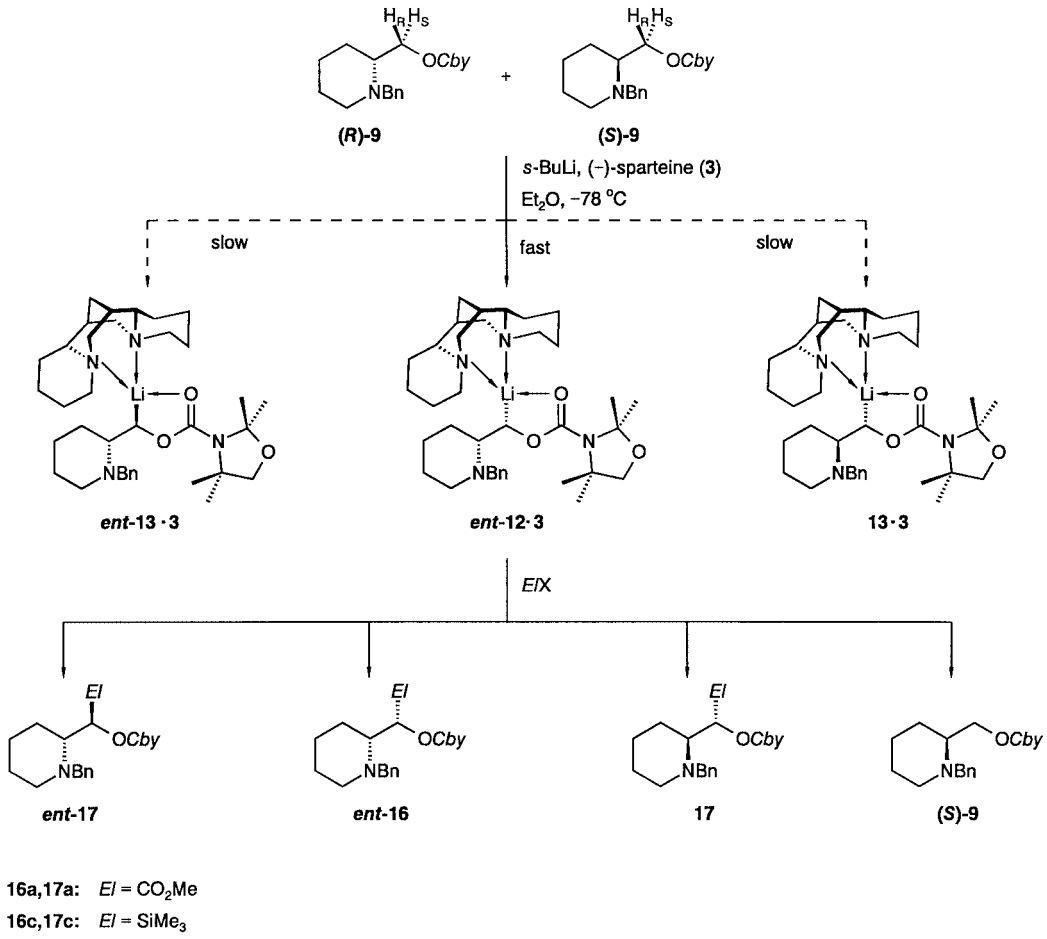
The best results were achieved when 0.6–0.7 equivalents of *sec*-BuLi and 0.8 equivalent of (−)-sparteine **(3)** (based on *rac*-**9**) were applied: The methyl carboxylate *ent*-**16a** and the silane *ent*-**16c** were produced with high diastereoselectivity (dr >96:4) and in high enantiomeric excess (up to er = 97:3, 94% ee). The relative and absolute configuration of (+)-*ent*-**16c** [2*R*,2(1*S*)], was confirmed by an X-ray crystal structure analysis[19] employing anomalous dispersion (Figure 3), the enantiopole parameter of 0.00(3) for (+)-*ent*-**16c** accounts for a high reliability.

Since the stereochemistry is determined on the deprotonation step, it is certain that the silane (+)-*ent*-**16c** and the ester (+)-*ent*-**16a** have the equal topicity, which is [2*R*,2(1*R*)] for the latter one due to a change in the CIP priorities. The same stereochemical reaction course was found for a carbolithiation reaction applying a related *N*-cinnamyl derivative (*rac*-**9**, $CH_2CH{=}CHPh$ for Bn).[20] Thus (+)-(*R*)-**9** is consumed preferentially by abstraction of the *pro*-*S*-H and (−)-(*S*)-**9** remains behind. This is also

Table 2 Kinetic Resolution of (*S*)-**9** and (*R*)-**9**

Entry	Product	*El*X	(–)-Sparteine (equiv)	*s*-BuLi (equiv)	Yield (product)	Ratio (dr)	[α] (% ee *ent*-**16**) [a,b]
1	*ent*-**16a** + *ent*-**17a**	$ClCO_2Me$	0.60	0.55	39 (56)	98:2	+ 9.8
2	*ent*-**16a** + *ent*-**17a**	$ClCO_2Me$	0.80	0.65	38 (53)	96:4	+ 9.4 (86)[c]
3	*ent*-**16a** + *ent*-**17a**	$ClCO_2Me$	0.80	0.60	41 (43)	>98:<2	+10.4 (94)
4	*ent*-**16c**	Me_3SiCl	0.80	0.70	40 (40)	>98:<2	+22.1

[a] *c* = 1.0 in CH_2Cl_2.
[b] Determined by Mosher ester method (see Scheme 7).
[c] 80% ee for enantioenriched educt (*S*)-**9**, determined by Mosher ester method (see Scheme 8).



Scheme 6

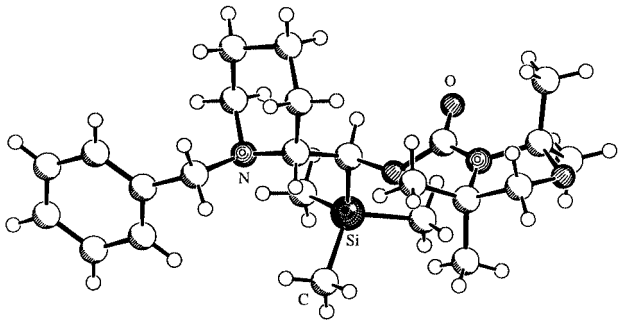
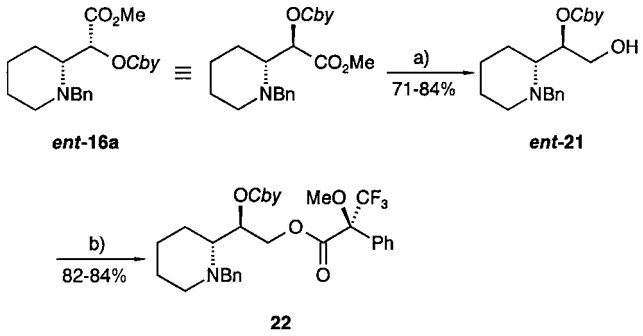


Figure 3 X-ray structure of (+)-*ent*-**16c**[19]



Reagents and conditions: a) $LiEt_3BH$/THF, 0°C. b) (*R*)-(−)-α-Methoxy-α-trifluoromethylphenylacetyl chloride/pyridine/CH_2Cl_2

Scheme 7

predicted from the considerations (see Scheme 3) since only in (*R*)-**9** both the substrate- and the reagent-directed preferences match.

The enantiomeric ratios in *ent*-**16a**, *ent*-**16c**, and (*S*)-**9** could not be determined directly by applying optically active NMR shift reagents. The enantioenriched ester *ent*-**16a** was partially reduced with $LiEt_3BH$[21] to the mono protected diol *ent*-**21**, which was converted to the Mosher ester[22] **22** and its epimer[23] (Scheme 7); their diastereomeric ratio was analyzed by ^1H NMR spectroscopy (Table 2, Entries 2 and 3).

The recovered starting material (***S***)-**9** and the silane ***ent*-16c** were deprotected to the alcohols (*S*)-**6** and *ent*-**24c** by the standard method (Scheme 8). The enantioenriched **(*S*)-6** was converted to the Mosher ester[22] **23** and its epimer;[23] their diastereomeric ratio was determined by ^1H NMR spectroscopy (Table 2, Entry 2).

Table 3a Selected Data of C-1'-Substituted Carbamates[a]

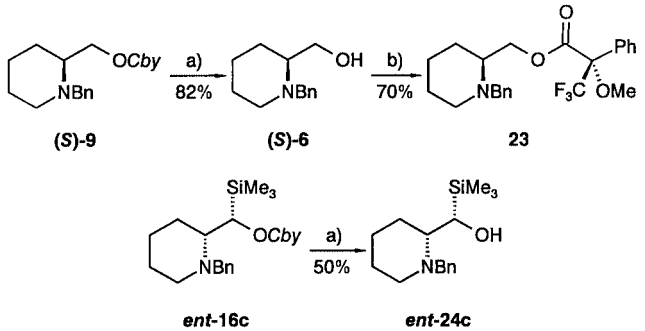
Product	IR (KBr/film)	^{1}H NMR (300 MHz, $CDCl_3$), δ, *J* (Hz)			
	ν (cm^{-1})	2-(1-H)	2-H	NCH_2Ph	
14a	1755, 1700	5.29 (d, $^3J_{2,2\text{-}1}$ = 3.3)	2.85-2.95 (m)	3.28, 4.16/4.17 (2 d, $^2J_{Bn}$ = 13.0)	1.64–1.71 (m, 4-H_2), 1.84–2.02 (m, 3-H_2), 2.10–2.23 (m, 5-H_a), 2.99–3.11 (m, 5-H_b), 3.75 (s, CO_2CH_3)
14b	1700, 1680	5.14 (dq, $^3J_{2,2\text{-}1}$ = 3.4, $^3J_{2\text{-}1,2\text{-}2}$ = 6.5)	2.55-2.66 (m)	3.17, 4.22/4.23 (2 d, $^2J_{Bn}$ = 12.8)	1.30 [2-(2-H_3)], 1.55–1.97[b] (m, 3-H_2, 4-H_2), 2.03–2.18 (5-H_a), 2.83–2.92 (5-H_b), 3.75 (s, CO_2CH_3)
14c	1690	5.26 (d, $^3J_{2,2\text{-}1}$ = 2.1)	2.55 (dt, $^3J_{2,3}$ = 8.3)	2.92, 4.32 (2 d, $^2J_{Bn}$ = 12.6)	0.13 [Si(CH_3)$_3$], 1.44–1.70[b] (m, 4-H_2), 1.84–2.05 (m, 3-H_2, 5-H_a), 2.79–2.88 (m, 5-H_b)
14e	1685, 1675	5.12/5.16 (d, $^3J_{2,2\text{-}1}$ = 2.0)	2.65-2.73 (m)	3.01/3.04, 4.21/4.25 (2 d, $^2J_{Bn}$ = 12.9)	0.85–2.12[b] [m, 3-H_2, 4-H_2, 5-H_a, Sn(C_4H_9)$_3$], 2.84–2.94 (m, 5-H_b)
14f	1695, 1640	5.22 (dd, $^3J_{2,2\text{-}1}$ = 3.3, $^3J_{2\text{-}1,2\text{-}2}$ = 7.7)	2.86 (dt, $^3J_{2,3}$ = –[c])	3.11, 4.23/4.24 (2 d, $^2J_{Bn}$ = 13.0)	1.30–1.98[b] (m, 3-H_2, 4-H_2), 2.04-2.13, 2.61–2.72 (m, 5-H_a, 5-H_b), 2.37–2.50 [m, 2-(2-H_2)], 5.05, 5.10 [2 ddt, $^2J_{2\text{-}4,2\text{-}4}$ = 2.0, $^3J_{2\text{-}3,2\text{-}4}$ = 10.2, $^4J_{2\text{-}2,2\text{-}4}$ = 1.1, 1.8, 2-(4-H_2)], 5.84 [ddt, 2-(3-H)]
15f	1690, 1640	5.00-5.16[b] (m)	2.87-3.00[b] (m)	3.36, 4.15 (2 d, $^2J_{Bn}$ = 13.4)	1.35–1.91[b] (m, 3-H_2, 4-H_2), 2.04–2.41 (m, 5-H_a, 5-H_b), 2.73 [dddt, $^2J_{2\text{-}2a,2\text{-}2b}$ = 14.8, $^3J_{2\text{-}1,2\text{-}2}$ = 3.0, $^3J_{2\text{-}2,2\text{-}3}$ = 6.0, $^4J_{2\text{-}2,2\text{-}4}$ = 1.7, 2-(2-H)], 2.87–3.00[b] [m, 2-(2-H_b)], 5.00–5.16[b] [m, 2-(4-H_2)]
14g	3180, 1685	4.74 (d, $^3J_{2,2\text{-}1}$ = 9.8)	3.26-3.38 (m)	3.50, 3.90/3.91 (2 d, $^2J_{Bn}$ = 12.7)	1.17–2.00[b] [m, 3-H_2, 4-H_2, 2-(3-H_3), 2-(2-CH_3)], 2.62, 2.92 (2 dt, $^2J_{5a,5b}$ = 12.0, $^3J_{4,5}$ = 5.9, 7.6)
14i'	3400, 1690, 1680	4.85 (dd, $^3J_{2,2\text{-}1}$ = 7.0, $^3J_{2\text{-}1,2\text{-}2}$ = 8.8)	2.77-2.98 (m)	3.29-3.50, 4.10-4.30 (2 m)	0.95, 1.04 [2 d, $^3J_{2\text{-}3,2\text{-}4}$ = 6.8, $^3J_{2\text{-}3,2\text{-}3\text{-}CH3}$ = 7.0, 2-(4-H_3), 2-(3-CH_3)], 1.68–1.93 [m, 3-H_2, 4-H_2, 2-(3-H)], 1.93–2.17, 2.38–2.48 (2 m, 5-H_a, 5-H_b); 3.11 (br s, OH), 3.78 (dd, $^3J_{2\text{-}2,2\text{-}3}$ = 2.9, 2-(3-H)]
14i	3240, 1685, 1680	4.85 (dd, $^3J_{2,2\text{-}1}$ = 1.2, $^3J_{2\text{-}1,2\text{-}2}$ = 2.2)	3.57 (dt, $^3J_{2,3}$ = 8.9)	3.28/3.29, 4.30/4.34 (2 d, $^2J_{Bn}$ = 12.6)	0.86/0.87, 1.08/1.09 [2 d, $^3J_{2\text{-}3,2\text{-}4}$ = $^3J_{2\text{-}3,2\text{-}3\text{-}CH3}$ = 6.6, 2-(4-H_3), 2-(3-CH_3)], 1.31–2.30 [m, 3-H_2, 4-H_2, 2-(3-H)], 2.82-2.92, 3.42–3.54 (2 m, 5-H_a, 5-H_b), 3.73 [dd, $^3J_{2\text{-}2,2\text{-}3}$ = 1.2, 2-(3-H)], 6.88–7.28[b] (m, OH)
rac-**16a**	1750, 1690	5.63 (bs)	2.74-2.93[b] (m)	3.18/3.20, 4.17/4.19 (2 d, $^2J_{Bn}$ = 13.2)	1.25–1.85[b] (m, 3-H_2, 4-H_2, 5-H_2), 1.93–2.05 (m, 6-H_a); 2.74–2.93[b] (m, 6-H_b), 3.76 (s, CO_2CH_3)
rac-**17a**[d]	–[c]	5.52 (d, $^3J_{2,2\text{-}1}$ = 4.5)		3.32/3.37, 4.18 (2 d, $^2J_{Bn}$ = 13.1)	3.77 (s, CO_2CH_3)
rac-**16b**	1680	5.25-5.36 (m)	2.25-2.43 (m)	3.15, 4.27 (2 d, $^2J_{Bn}$ = 13.4)	1.24–1.86[b] [m, 3-H_2, 4-H_2, 5-H_2, 2-(2-H_3)], 1.90–2.06 (m, 6-H_a), 2.82 (d, $^2J_{6a,6b}$ = 11.4, 6-H_b)
rac-**17b**[d]	–[c]	5.45-5.55 (m)			
rac-**16c**	1680	5.36 (d, $^3J_{2,2\text{-}1}$ = 6.7)	2.60-2.80[b] (m)	3.25-3.40, 4.14 (m and d, $^2J_{Bn}$ = 13.1)	0.11 [s, Si(CH_3)$_3$], 1.15–1.88[b] (m, 3-H_2, 4-H_2, 5-H_2), 2.01–2.16 (m, 6-H_a), 2.60–2.80[b] (m, 6-H_b)
rac-**16d**	1680	5.15 (d, $^3J_{2,2\text{-}1}$ = 5.2)	2.65-2.80[b] (m)	3.38, 4.16 (2 d, $^2J_{Bn}$ = 13.0)	0.16 [s, Sn(CH_3)$_3$], 1.00–1.75 (m, 3-H_2, 4-H_2, 5-H_2), 1.75–1.90 (m, 6-H_a), 2.65–2.80[b] (m, 6-H_b)
rac-**17d**[d]	–[c]	5.36 (d, $^3J_{2,2\text{-}1}$ = 5.5)		3.21/4.05 (2 d, $^2J_{Bn}$ = 13.4)	
rac-**16h**	1690, 1680	6.05 (d, $^3J_{2,2\text{-}1}$ = 4.3)	2.81-2.97[b] (m)	3.31/3.34, 4.09 (2 d, $^2J_{Bn}$ = 13.1)	1.10–1.85[b] (m, 3-H_2, 4-H_2, 5-H_2), 1.23 [s, C(CH_3)$_3$], 2.07–2.22 (m, 6-H_a), 2.81–2.97[b] (m, 6-H_b)
rac-**17h**[e]	–[c]	6.03 (d, $^3J_{2,2\text{-}1}$ = 9.1)			

[a] NMR data of the *Cby* group and the aromatic rings are omitted. NMR data carrying the symbol * are interchangeable.
[b] As part of a multiplet; [c] Not recorded.
[d] Recorded from the mixture of diastereomers; [e] Recorded from the mixture with the starting material *rac*-**7**.

Table 3b Selected Data of C-1'-Substituted Carbamates

Product	^{13}C NMR (75 MHz, $CDCl_3$), δ			
	2-(C-1)	C-2	NCH_2Ph	
14a	72.6/72.7	64.6	58.8	22.9 (C-4), 26.6 (C-3), 52.0 (CO_2CH_3), 53.8 (C-5), 170.5 (CO_2CH_3)
14b	70.2	67.6	59.3	17.3 [2-(C-2)], 22.6 (C-4), 26.9 (C-3), 54.4 (C-5)
14c	66.0*	65.8*	57.9	–2.18 [$Si(CH_3)_3$], 22.0 (C-4), 29.1 (C-3), 53.7 (C-5)
14e	70.4	68.3	58.6	10.4, 13.7, 28.1, 29.2 [$Sn(C_4H_9)_3$], 22.2 (C-4); 27.6 (C-3), 54.2 (C-5)
14f	72.1	66.3	58.9	22.5 (C-4), 25.9 (C-3), 37.0 [2-(C-2)], 54.2 (C-5), 117.0 [2-(C-4)], 134.6 [2-(C-3)]
15f	74.5	64.8	59.4	23.8 (C-4), 26.0 (C-3), 33.4 [2-(C-2)], 54.3 (C-5), 116.6 [2-(C-4)], 135.7 [2-(C-3)]
14g	76.0	66.2	60.4	22.6 [2-(C-3), 2-(2-CH_3)] 26.2 (C-4), 27.9 (C-3), 51.3 (C-5), 72.7 [2-(C-2)]
14i'	72.4	68.6	61.0	15.1, 20.1 [2-(C-4), 2-(3-CH_3)], 22.4 (C-4), 27.5 (C-3), 29.8 [2-(C-3)], 52.8 (C-5), 68.6 [2-(C-2)]
14i	74.7	66.4	61.3	18.8, 19.5 [2-(C-4), 2-(3-CH_3)], 23.9 (C-4), 28.6 (C-3), 30.8 [2-(C-3)], 54.6 (C-5), 66.4 [2-(C-2)]
rac-**16a**	72.4/72.6	62.5	58.3	24.0, 24.6, 26.8 (C-3, C-4, C-5), 52.0 (CO_2CH_3), 52.2 (C-6), 170.4 (CO_2CH_3)
rac-**17a**[d]	73.3	62.8	57.9	51.9 (CO_2CH_3), 51.0 (C-6)
rac-**16b**	71.0/71.2	64.8	57.9	16.6 [2-(C-2)], 24.0, 24.2, 25.9 (C-3, C-4, C-5), 52.0 (C-6)
rac-**16c**	67.7	62.2	57.9	–1.9 [$Si(CH_3)_3$], 22.2, 22.7, 24.9 (C-3, C-4, C-5), 49.0 (C-6)
rac-**16d**	74.2	64.3	58.7	–7.9 [$Sn(CH_3)_3$], 23.3, 24.8, 26.7 (C-3, C-4, C-5), 50.0 (C-6)
rac-**16h**	72.4/72.6	60.7	58.1	23.7, 24.0, 24.8 (C-3, C-4, C-5), 26.9 [$C(CH_3)_3$], 43.6 [$C(CH_3)_3$], 51.9 (C-6), 211.5 (C=O)

[a]NMR data of the *Cby* group and the aromatic rings are omitted. NMR data carrying the symbol * are interchangeable.
[b]As part of a multiplet.
[c]Not recorded.
[d]Recorded from the mixture of diastereomers.
[e]Recorded from the mixture with the starting material *rac*-**7**.



Reagents and conditions: a) i. $MeSO_3H$/MeOH, reflux; ii. $Ba(OH)_2 \cdot 8H_2O$/ MeOH, reflux. b) (*S*)-(-)-α-Methoxy-α-trifluoromethylphenylacetic acid/ DCC/DMAP/CH_2Cl_2

Scheme 8

Conclusions

As we have demonstrated, the carbamates of 2-pyrrolidinyl- and 2-piperidinylmethanols react with alkyllithium bases with strong selection between the diastereotopic protons adjacent to the carbamate group. As a result, in the presence of a chiral ligand, such as (−)-sparteine, efficient kinetic resolution is achievable, which is coupled with a highly diastereoselective electrophilic substitution.

All experiments involving organometallic reagents were carried out under argon in dried glasswares. All solvents were purified by distillation and dried, if necessary, prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM300 or U600 spectrometer. Optical rotations were recorded on a Perkin-Elmer polarimeter 241. Mps were obtained on Gallenkamp melting point apparatus MFB-595 and are uncorrected. Products were purified by flash column

chromatography on silica gel (40–63 μm) or aluminium oxide (activity = 0).

rac-*N*-Benzylpiperidine-2-methanol (*rac*-6)[10]

rac-Piperidine-2-methanol (4.61 g, 40 mmol) was dissolved in toluene (40 mL) and K_2CO_3 (5.53 g, 40 mmol) was added. The suspension was heated under reflux for 30 min and BnBr (4.75 mL, 6.84 g, 42 mmol) was added dropwise. After refluxing for 16 h the inorganic salts were filtered off and washed with Et_2O (30 mL). The solvents were evaporated in vacuo and the residue was purified by flash chromatography (silica gel, Et_2O/pentane 1:1, 3 vol% Et_3N) to afford the pure alcohol *rac*-**6** (6.63 g, 81%); R_f 0.15 (Et_2O/pentane, 1:2, silica gel); colorless oil.

IR (film): ν = 3430 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.25–1.80 (m, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.15 (ddd, 1 H, $^2J_{6a,6b}$ = 12.4 Hz, $^3J_{5a,6a}$, $^3J_{5b,6a}$ = 3.1, 10.3 Hz, 6-H_a), 2.45 (dddd, 1H, $^3J_{2,2\text{-}1a}$ = $^3J_{2,2\text{-}1b}$ = 4.3 Hz, $^3J_{2,3a}$, $^3J_{2,3b}$ = 4.3, 8.1 Hz, 2-H), 2.58 (br s, 1 H, OH), 2.87 (ddd, 1 H, $^3J_{5a,6b}$ = $^3J_{5b,6b}$ = 3.8, 5.2 Hz, 6 H_b), 3.32, 4.06 (2 d, 2 H, $^2J_{Bn}$ = 13.4 Hz, NCH_2Ph), 3.52 [dd, 1 H, $^2J_{2\text{-}1a,2\text{-}1b}$ = 11.0 Hz, 2-(1-H_a)], 3.85 [dd, 1 H, 2-(1-H_b)], 7.15–7.35 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.4, 24.1, 27.3 (C-3, C-4, C-5), 50.9 (C-6), 57.7 (2C, NCH_2Ph), 60.5 (C-2), 62.3 [2-(C-1)], 126.9, 128.3,128.8, 139.1 (6 C, C_6H_5).

Anal. Calcd. for $C_{13}H_{19}NO$ (205.3): C, 76.06; H, 9.33; Found C, 75.87; H, 9.52.

Carbamates (*S*)-8 and *rac*-9; General Procedure[11]

A solution of the monobenzylated alcohol (*S*)-**5** or *rac*-**6** (15 mmol) in anhyd THF (12 mL) was added dropwise to a suspension of NaH (880 mg, 22 mmol, 60% in mineral oil) in THF (12 mL). The mixture was refluxed for 30 min, before 2,2,4,4-tetramethyloxazolidine-3-carbonyl chloride[11a] (*Cby*Cl, **7**, 3.23 g, 17 mmol) in THF (8 mL) was added. After heating under reflux for 2 h and cooling to r.t., H_2O (15 mL) and Et_2O (30 mL) were added carefully to the mixture. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined extracts were dried ($MgSO_4$). The solvents were evaporated in vacuo and the crude products were purified by flash chromatography (silica gel, Et_2O/pentane, 1:6 to 1:3) to yield pure carbamate (*S*)-**8** (4.26 g, 82%) or *rac*-**9** (5.02 g, 93%).

(*S*)-**8**

R_f 0.37 (Et_2O/pentane, 1:1, silica gel); yellow oil; $[\alpha]_D^{20}$ −60.2 (*c* = 2, $CHCl_3$).

IR (film): ν = 1705, 1690 (NC=O), 1095, 1070 cm^{-1} (COC).

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.38/1.40, 1.43/1.44, 1.54/1.56, 1.58 (4 s, 12 H, *Cby*-CH_3), 1.65–2.26 (m, 5 H, 3-H_2, 4-H_2, 5-H_a), 2.70–2.85 (m, 1 H, 2-H), 2.85–2.98 (m, 1 H, 5-H_b), 3.34, 4.10 (2 d, 2H, $^2J_{Bn}$ = 13.0 Hz, NCH_2Ph), 3.74 (s, 2 H, *Cby*-CH_2), 3.97 [dd, 1 H, $^2J_{2\text{-}1a,2\text{-}1b}$ = 10.8 Hz, $^3J_{2,2\text{-}1a}$ = 1.7 Hz, 2-(1-H_a)], 4.27 [dd, 1 H, $^3J_{2,2\text{-}1b}$ = 3.9 Hz, 2-(1-H_b)], 7.18–7.36 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.8, 28.9 (C-3, C-4), 24.2, 25.3, 26.6 (4 C, *Cby*-CH_3); 54.2 (C-5); 59.2 (2 C, NCH_2Ph), 59.7/60.5

[NC$(CH_3)_2CH_2$], 62.5 (C-2), 66.5 [2-(C-1)], 75.1/75.4 (*Cby*-CH_2), 94.8/95.8 [OC$(CH_3)_2$N], 126.7, 128.0, 128.6, 139.6 (6 C, C_6H_5), 152.0/152.7 (NC=O).

Anal. Calcd. for $C_{20}H_{30}N_2O_3$ (346.5): C, 69.33; H, 8.72; Found C, 69.33; H, 8.77.

rac-**9**

R_f 0.38 (Et_2O/pentane, 1:2, silica gel); pale yellow oil.

IR (film): ν = 1690, 1680 (NC=O), 1090, 1060 cm^{-1} (COC).

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.30–1.65 (m, 4 H, 3-H_2, 5-H_2), 1.41, 1.56 (2 s, 12 H, *Cby*-CH_3), 1.65–1.82 (m, 2 H, 4-H_2), 2.02 (ddd, 1 H, $^2J_{6a,6b}$ = 11.9 Hz, $^3J_{5a,6a}$, $^3J_{5b,6a}$ = 3.3, 9.5 Hz, 6-H_a), 2.48–2.62 (m, 1 H, 2-H), 2.76 (ddd, 1 H, $^3J_{5a,6b}$ = $^3J_{5b,6b}$ = 3.9 Hz, 6-H_b), 3.27, 4.10 (2 d, 2 H, $^2J_{Bn}$ = 13.4 Hz, NCH_2Ph), 3.73 (s, 2 H, *Cby*-CH_2), 4.29 [d, 2 H, $^2J_{2\text{-}1a,2\text{-}1b}$ = 5.0 Hz, 2-(1-H_2)], 7.10–7.35 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.4, 25.3, 29.5 (C-3, C-4, C-5), 24.1/25.3, 25.3/26.6 (4 C, *Cby*-CH_3), 51.7 (C-6), 58.8 (2 C, NCH_2Ph), 59.7/60.5 [NC$(CH_3)_2CH_2$], 60.5 (C-2), 66.7 [2-(C-1)], 76.1/76.4 (*Cby*-CH_2), 94.9/96.0 [OC$(CH_3)_2$N], 126.7, 128.1, 128.7, 139.5 (6 C, C_6H_5), 152.1/152.8 (NC=O).

Anal. Calcd. for $C_{21}H_{32}N_2O_3$ (360.50): C, 69.97; H, 8.95; Found C, 69.57; H, 9.14.

Deprotonation of Carbamates (*S*)-8 and *rac*-9 with *s*-BuLi/Diamine and Preparation of Substituted Products; General Procedures

Method A: Carbamate (*S*)-**8** or *rac*-**9** (1.00 mmol) and TMEDA (232 mg, 2.00 mmol) were dissolved in anhyd Et_2O (15 mL) under argon in a dry ice/acetone bath and a 1.3 M solution of *s*-BuLi in cyclohexane/hexane (1.5 mL, 2.00 mmol) was added to the solution dropwise.

After stirring for 3 h [(*S*)-**8**] or 6 h (*rac*-**9**), the electrophile (3.00 mmol) was slowly introduced via a syringe.

Method B: In Method B, TMEDA was replaced by (−)-sparteine (469 mg, 2.00 mmol) for the deprotonation of carbamate (***S***)-**8**.

Method C: In Method C, no diamine was used as complex ligand in the deprotonation step of carbamate (*S*)-**8** or *rac*-**9**.

Carboxylation

After stirring at −78°C for 3 h, a stream of dry CO_2 was introduced into the solution of the deprotonated carbamate (*S*)-**8** via a syringe for 30 min. After warming to r.t. and hydrolysis with H_2O (10 mL), 2 N HCl was added until pH 5. The organic layer was separated and the aqueous solution was extracted with Et_2O (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and the solvents were evaporated in vacuo. The crude product was dissolved in Et_2O (10 mL) and treated with ethereal CH_2N_2 solution until the color of the solution remain yellow. After stirring for 1 h, silica gel (50 mg) was added and the mixture was stirred for 15 min in order to destroy the excess of CH_2N_2.

Subsequent flash chromatographic purification (Et_2O/pentane, 1:4, Al_2O_3) yielded the methyl ester **14a**.

Other Electrophiles

After stirring at −78°C for 3 h [(*S*)-**8]** or 6 h (*rac*-**9**), the electrophile was slowly introduced with a syringe. The mixture was allowed to warm up to r. t. for 12 h and H_2O (10 mL) was added. The Et_2O layer was separated and the aqueous phase was extracted with Et_2O (3 × 10 mL).

The combined Et_2O extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (Et_2O/pentane, 1:1 to 1:8) to afford the substituted carbamates **14**, **16**, and **17**. For yields and physical data of substituted carbamates **14**, **16**, and **17**, see Tables 1 and 3.

Kinetic Resolution of (*S*)-9 and (*R*)-9; General Procedure

Carbamate *rac*-**9** (1.00 mmol) and (−)-sparteine (amounts, see Table 2) were dissolved in anhyd Et_2O (15 mL) under argon and a 1.3 M solution of *s*-BuLi in cyclohexane/hexane (amounts, see Table 2) was added to the solution dropwise at −78°C. Stirring was continued for 6 h at this temperature and, finally, the electrophile (3.00 mmol) was slowly introduced via a syringe. Work up was accomplished in the same manner as described above.

Decarbamoylation of 14b, *ent*-16c, and (*S*)-9; Preparation of 19b, *ent*-24c, and (*S*)-6; General Procedure[11]

The substituted carbamate **14b** (Table 1, Entry 5), *ent*-**16c** (Table 2, Entry 4) or (*S*)-**9** (Table 2, Entry 2) (1.00 mmol) and $MeSO_3H$ (324 mL, 480 mg, 5.00 mmol) were dissolved in MeOH (10 mL) and the solution was refluxed for 5 h. After the addition of $Ba(OH)_2 \cdot 8H_2O$ (3.15 g, 10 mmol), the mixture was refluxed for further 4 h. The salts were filtered off and washed with MeOH (30 mL). The solvent was evaporated in vacuo and the residue was purified by flash chromatography to give the pure alcohol **19b**, *ent*-**24c** or **(*S*)-6**.

[1*R*,1(1*S*)]-1-(*N*-Benzylpyrrolidin-2-yl)ethanol (19b)

135 mg (66%); yellow oil; R_f 0.56 (Et_2O/pentane, 1:1, Al_2O_3); $[\alpha]_D^{20}$ −85.0 (*c* = 0.7, $CHCl_3$).

IR (film): ν = 3450 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.15 [d, $^3J_{2\text{-}1,2\text{-}2}$ = 6.4, 2-(2-H_3)], 1.53–1.93 (m, 3-H_2, 4-H_2), 2.20–2.29 (m, 5-H_a), 2.45–2.51 (m, 5-H_b); 2.93–2.99 (m, 2-H), 3.10 (br s, OH), 3.28, 4.04 (2 d, $^2J_{Bn}$ = 13.0, *N*-CH_2Ph), 3.95 [dq, $^3J_{2,2\text{-}1}$ = 2.6, 2-(1-H)], 7.187.36 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.5 [2-(C-2)], 23.2, 23.3 (C-3, C-4), 54.6 (C-5), 58.3 (2 C, NCH_2Ph), 64.3 (C-2); 68.8 [2-(C-1)], 127.0, 128.3, 128.7, 139.4 (6 C, C_6H_5).

MS (CI, isobutane): *m*/*z* Calcd for $C_{13}H_{19}NO$ (205.30); Found M^+ + 1 = 206.

1-(*N*-Benzylpiperidin-2-yl)-1-(trimethylsilyl)methanol (*ent*-24c)

Yield: 136 mg (50%); colorless oil; R_f 0.78 (Et_2O/pentane, 4:1, 3% Et_3N, silica gel); $[\alpha]_D^{20}$ + 49.1 (*c* = 1, CH_2Cl_2).

IR (film): ν = 3430 cm^{-1} (OH).

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.09 [s, 9 H, $Si(CH_3)_3$], 1.15–1.85 (m, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.00 (ddd, 1 H, $^2J_{6a,6b}$ = 11.6, $^3J_{5a,6a}$, $^3J_{5b,6a}$ = 2.9, 11.4, 6-H_a), 2.31 (ddd, 1 H, $^3J_{2,2\text{-}1}$ = 3.1, $^3J_{2,3a}$, $^3J_{2,3b}$ = 3.6, 10.6, 2-H), 2.81 (br s, 1 H, OH), 2.89 (ddd, 1 H, $^3J_{5a,6b}$ = $^3J_{5b,6b}$ = 3.3, 6 H_b), 3.04, 4.23 (2 d, 2 H, $^2J_{Bn}$ = 13.4, NCH_2Ph), 3.85 [d, 1 H, 2-(1-H)], 7.05–7.25 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = −1.9 [$Si(CH_3)_3$], 24.4, 25.5, 27.6 (C-3, C-4, C-5), 53.1 (C-6), 57.6 (2C, NCH_2Ph), 63.8, 64.1[C-2, 2-(C-1)], 126.9, 128.3, 128.9, 139.1 (6 C, C_6H_5).

Anal. Calcd for $C_{16}H_{27}NOSi$ (277.5): C, 69.26; H, 9.81; Found C, 68.89; H, 10.05.

(*S*)-**6**

Yield: 207 mg (82%); $[\alpha]_D^{20}$ −35.0 (*c* = 1, CH_2Cl_2).

Reduction of *rac*-16a and *ent*-16a with $LiEt_3BH$; 2-(*N*-Benzylpiperidin-2-yl)-2-(2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyloxy)ethanol[21]

$LiEt_3BH$ (1.00 mL, 1 M in THF) was added to the substituted carbamate *rac*-**16a** (Table 1, Entry 13) or *ent*-**16a** (Table 2, Entries 2 and 3) (0.25 mmol) in anhyd THF (4 mL) at 0°C and the stirring was continued for 90 min. After hydrolysis with H_2O (5 mL) at this temperature Et_2O (10 mL) was added and the two layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (Et_2O/pentane, 1:4, 1% Et_3N, silica gel) to yield the pure alcohol as a pale yellow oil.

rac-[2*R**,2(2*R**)]-**21**

Yield: 83 mg (83%); colorless oil; R_f 0.11 (Et_2O/pentane, 1:2, silica gel).

IR (film): ν = 3460 (OH), 1660 cm^{-1} (NC=O).

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.25–1.92 (m, 18 H, 3-H_2, 4-H_2, 5-H_2, *Cby*-CH_3), 2.28–2.42 (m, 1 H, 6-H_a), 2.74–2.88 (m, 1 H, 2-H), 2.95 (ddd, 1 H, $^2J_{6a,6b}$ = 12.5, $^3J_{5a,6b}$, $^3J_{5b,6b}$ = 3.2, 6.8, 6-H_b), 3.57/3.59, 4.11 (2 d, 2 H, $^2J_{Bn}$ = 13.1, NCH_2Ph), 3.72 (s, 2 H, *Cby*-CH_2), 3.65–3.80 [m, 1 H, 2-(2-H_a)], 3.87 [dd, 1 H, $^2J_{2a,2b}$ = 11.4, 2-(2-H_b)], 5.26 [ddd, 1 H, $^3J_{2,2\text{-}1}$, $^3J_{2\text{-}1,2\text{-}2a}$, $^3J_{2\text{-}1,2\text{-}2b}$ = 5.5, 5.5, 6.9, 2-(1-H)], 7.15–7.35 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.2, 22.0, 23.0 (C-3, C-4, C-5), 24.0/24.2, 25.0/25.2, 25.4/25.6 26.6/26.8 (4,C, *Cby*-CH_3), 49.2 (C-6), 57.9 (2,C, NCH_2Ph), 59.8/60.9 [NC$(CH_3)_2CH_2$], 62.1 (C-2); 65.0 [2-(C-2)], 72.5 [2-(C-1)], 76.1/76.4 (*Cby*-CH_2), 94.9/96.1 [OC$(CH_3)_2$N], 127.2, 128.5, 128.8, 138.7 (6 C, C_6H_5) 151.8/152.5 (NC=O).

Anal. Calcd for $C_{22}H_{34}N_2O_4$ (390.5): C, 67.66; H, 8.78; Found C, 67.46; H, 8.52.

ent-[2*R*,2(2*R*)]-**21**

Yield: 71 mg (72%); $[\alpha]_D^{20}$ +9.8 (*c* = 1.0, CH_2Cl_2; from *ent*-**16a**, Table 2, Entry 2).

Yield: 84 mg (88%); $[\alpha]_D^{20}$ +10.8 (*c* = 1.3, CH_2Cl_2; from *ent*-**16a**; Table 2, Entry 3).

Mosher Ester 22 and its Epimer from *rac*-21 or *ent*-21[22a]

To a solution of *rac*-**21** or *ent*-**21** (Table 2, Entries 2 and 3) (38 mg, 0.10 mmol) in CH_2Cl_2 (0.3 mL) and pyridine (0.2 mL) was added (*R*) (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride (21 μL, 28 mg, 0.11 mmol). The suspension was stirred for 24 h at r.t. The salts were filtered off and washed with CH_2Cl_2 (5 mL). After evaporation of the solvents, the residue was purified by flash chromatography (Et_2O/pentane, 1:5, silica gel) to give **22** and its epimer as a diastereomeric mixture, which could not be separated by flash chromatography.

In the ^1H NMR spectrum (600 MHz, $CDCl_3$, TMS) the 2-(2-H_a) protons of **22** (δ = 4.43) and of its epimer (δ = 4.47) could be detected separately.

From *rac*-[2*R**,2(2*R**)]-**21**; yield: 51 mg (84%); dr = 50:50.

From *ent*-[2*R*,2(2*R*)]-**21** (Table 2, Entry 2); yield: 49 mg (82%); dr = 93:7 or 86% ee.

From *ent*-[2*R*,2(2*R*)]-**21** (Table 2, Entry 3); yield: 51 mg (84%); dr = 97:3 or 94% ee.

Mosher Ester 23 and its Epimer from *rac*-6 or (*S*)-6[22b]

To a solution of *rac*-**6** or (*S*)-**6** (Table 2, Entry 2) (20 mg, 0.10 mmol), dicyclohexyl carbodiimide (DCC, 25 mg, 0.12 mmol), and (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (23 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was added 4-(dimethylamino)pyridine (0.6 mg, 5 μmol). The suspension was stirred for 24 h at r.t. The salts were filtered off and washed with CH_2Cl_2 (5 mL). After evaporation of the solvents the residue was purified by flash chromatography (Et_2O/pentane, 1:5, silica gel) to give **23** and its epimer as a diastereomeric mixture, which could not be separated by flash chromatography.

In the ^1H NMR spectrum (600 MHz, D_8-toluene) the 2-(1-H_a) protons of **23** (δ = 3.37) and of its epimer (δ = 3.40) could be detected separately.

From *rac*-**6**; yield: 25 mg (60%); dr = 50:50.

From (*S*)-**6** (Table 2, Entry 2); yield: 29 mg (70%); dr = 90:10 or 80% ee.

Debenzylation of 19b; Preparation of [1*R*,1(1*S*)]-1-(Pyrrolidin-2-yl)ethanol (20b)[13]

A suspension of $PdCl_2$ (163 mg, 0.90 mmol, 40 mol%) in MeOH (20 mL) was reduced with H_2 for 30 min at r.t. The solvent was decanted and the residue was washed with MeOH (2 × 5 mL). The freshly prepared Pd was suspended in MeOH/HCOOH (10 mL,

95:5) and a solution of **19b** (471 mg, 2.30 mmol) in MeOH/HCO_2H (5 mL, 95:5) was added dropwise. After stirring for 12 h at r.t., the solid materials were filtered off and washed with MeOH (2 × 5 mL). The solvents were removed in vacuo. Purification of the residue by flash chromatography (EtOAc/pentane, 2:1, silica gel) afforded the amino alcohol **20b** (180 mg, 68%) as air-sensitive crystals; mp 86°C (Et_2O/pentane); $[\alpha]_D^{20}$ −36.4 (*c* = 1, MeOH).

Acknowledgement

Generous support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Bayer AG is gratefully acknowledged.

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Article Identifier:
1437-210X,E;1999,0,11,1915,1924,ftx,en;P03599SS.pdf