Stereoselective Synthesis of Enantiopure β-Amino Alcohols via Nucleophilic β-Amino-α-hydroxyalkylation by Means of 1-Lithiated 2-[*N*-(Diphenylmethyleneamino)]alkyl Carbamates

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Dedicated to Professor Burchard Franck on the occasion of his 70th birthday

2-[*N*-(Diphenylmethyleneamino)]alkyl carbamates are deprotonated by means of *sec*-butyllithium in the presence of TMEDA or (−)-sparteine and the diastereomeric ion pairs of α-oxycarbanions formed are substituted by several electrophiles. Deprotection proceeds smoothly to yield chain-elongated β-amino alcohols. Problems arise due to nucleophilic attack of the alkyllithium at one aryl ring of the benzophenone imines under certain reaction conditions.

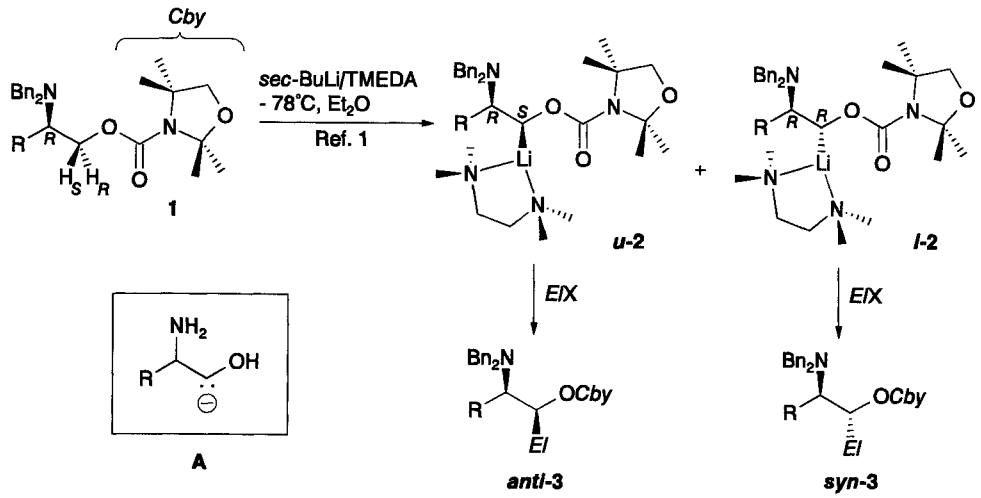
Recently, we reported on the first and so far the only known method for the deprotonation and electrophilic α-substitution of 2-aminoalkan-1-ols, which are devoid of carbanion-stabilizing substituents.[1-3] Optically active 2-(*N*,*N*-dibenzylamino)alkyl carbamates of type **1**, derived from the appropriate amino alcohols, are smoothly converted to the lithium derivatives **2** by deprotonation with *sec*-butyllithium/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). The deprotonation step proceeds with a good, substrate-directed diastereotopic selection between H_S and H_R, forming the configurationally stable diastereomeric ion pairs *u*-**2** (1*S*,2*R* or 1*R*,2*S*, respectively)[4] and *l*-**2** (1*S*,2*S* or 1*R*,2*R*) with a ratio of ~ 9:1. The reaction with several electrophiles takes place with retention of the configuration yielding the 1-substituted, protected amino alcohols *syn*- and *anti*-**3**[5] in moderate to high yields (Scheme 1). Hence, the lithium compounds **2** constitute the synthetic equivalents for the β-amino-α-hydroxyalkyl synthon **A**. However, deprotection of the amino group in larger scale by catalytic hydrogenolysis is an inconvenient step, since it usually requires the expensive platinum catalyst in large amounts.[6]

We were thus searching for further amino protecting groups, which

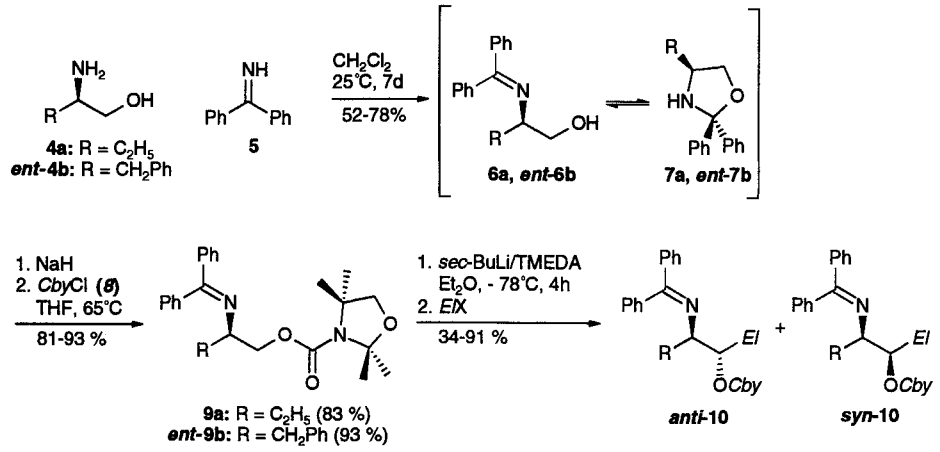
- tolerate alkyllithium,
- should not support β-elimination of lithium amide, and
- should not compete with the chelating ligand.[7]

To our great surprise, the *N*,*N*-diphenylmethylene group, established by O'Donnell,[8] who also demonstrated the ease of its introduction and removal, turned out to be compatible with these requirements, when applied to amino groups in secondary position. (*R*)-2-Aminobutan-1-ol (**4a**) or (*S*)-phenylalaninol (*ent*-**4b**[9]), on transimination with benzophenone imine[8] (**5**), afforded tautomeric mixtures of the *N*-alkylideneamino alcohols (**6a**, *ent*-**6b**) and the corresponding 1,3-oxazolidines[10] (**7a**, *ent*-**7b**), which were *O*-acylated with 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl chloride[11] (**8**) by the sodium hydride method. The carbamate esters **9a** and *ent*-**9b** can be purified chromatographically on silica gel, deactivated by diethylamine. The deprotonation of the carbamates **9** proceeds smoothly under the usual conditions (1.5 equiv *sec*-butyllithium/TMEDA, Et_2O, 4 h at −78 °C) and the lithiated intermediates were trapped with excess of the electrophile (Scheme 2, Table 1) to yield the diastereomeric products *anti*- and *syn*-**10**.

The observed diastereomeric ratios *anti*-**10**/*syn*-**10** range between 62:38 and 79:21, and are decreased in comparison to the reactions with the appropriate *N*,*N*-dibenzyl derivatives (~90:10).[2,12] Interestingly, the alkylation of the lithium intermediates by primary alkyl iodides, such as propyl and hexyl iodide, does not cause problems, in contrast to the reactions of the *N*,*N*-dibenzylated analogues **2**.[12] Separation was possible for the diastereomers **10d–f** or, in most cases, at the stage of the benzamides **15** and **16**.



Scheme 1



Scheme 2

anti/syn-**10**	R	*El*	*anti/syn*-**10**	R	*El*
a	Et	D	**g**	Et	$CH_2C_6H_5$
b	Et	$SiMe_3$	**h**	Et	CH_2CHCH_2
c	Et	$SnMe_3$	**i**	Et	CO_2Me
d	Et	CH_3	**k**	Et	$COC(CH_3)_3$
e	Et	*n*-C_3H_7	**l**	CH_2Ph	D
f	Et	*n*-C_6H_{13}	**m**	CH_2Ph	CH_3

Table 1. Compounds **9** and **10** Prepared

Starting Material	Product[a]	Yield (%)	*anti/syn*[b] Ratio	$[\alpha]_D^{20}$[c]	IR (KBr/film) ν (cm^{-1})	^1H NMR (300 MHz, $CDCl_3$)[d] δ, J (Hz)	^{13}C NMR (300 MHz, $CDCl_3$)[d] δ
4a	**9a**	83		+15.9	1680, 1610	0.85 (t, 3H, J = 7.4, 4-H), 1.30–1.80 (m, 2H, 3-H), 3.63 (br s, 1H, 2-H), 4.18 (t, 1H, J = 7.0, 1-H_A), 4.33 (br s, 1H, 1-H_B)	10.5 (C-4), 26.4 (C-3), 62.1 (C-2), 68.2 (C-1), 152.1/152.8 (NC=O), 168.1 (C=N)
ent-**3b**	*ent*-**9b**	93		−102.0	1670, 1610	3.13 (br s, 3H, 3-H), 4.12 (br s, 2H, 2-H), 4.45 (dd, 1H, J = 6.9, 10.7, 1-H_A), 4.55 (br s, 1H, 1-H_B)	39.8 (C-3), 62.7 (C-2), 68.1 (C-1), 151.9/152.6 (NC=O), 168.7 (C=N)
9a	*anti/syn*-**10a**[e]	91[f]	73 : 27[g]	–[e]	1680, 1610	0.85 (t, J = 7.4, 4-H), 1.30–1.80 (m, 3-H), 3.63 (br s, 2-H), 4.18 (br s, 1-H_A), 4.33 (br s, 1-H_B)	10.5 (C-4), 26.4 (C-3), 62.1 (C-2), 68.2 (C-1), 152.1/152.8 (NC=O), 168.1 (C=N)
9a	*anti/syn*-**10b**[e]	66[h]	78 : 22	–[e]	1675, 1610	*anti*: 0.11 [s, $Si(CH_3)_3$], 0.76 (t, J = 7.4, 4-H), 1.34–1.70 (m, 3-H), 3.67 (br s, 2-H), 4.77 (br s, 1-H) *syn*: 0.04 [s, $Si(CH_3)_3$], 0.75 (t, J = 7.4, 4-H), 1.34–1.70 (m, 3-H), 3.48 (br s, 2-H), 4.90 (d, J = 8.7, 1-H)	*anti*: −1.3 [$Si(CH_3)_3$], 11.1 (C-4), 26.8 (C-3), 65.6 (C-2), 73.7 (C-1), 152.7/153.4 (NC=O), 166.3 (C=N) *syn*: −1.8 [$Si(CH_3)_3$], 10.9 (C-4), 26.8 (C-3), 69.6 (C-2), 73.7 (C-1), 152.7/153.4 (NC=O), 166.0 (C=N)
9a	*anti/syn*-**10c**[e]	70[i]	71 : 29	–[e]	1670, 1610	*anti*: 0.18 [s, $Sn(CH_3)_3$], 0.79 (t, J = 7.4, 4-H), 1.25–1.63 (m, 3-H), 3.81 (br s, 2-H), 4.83 (br s, 1-H) *syn*: 0.13 [s, $Sn(CH_3)_3$], 0.75 (t, J = 7.4, 4-H), 1.25–1.63 (m, 3-H), 3.69 (br s, 2-H), 4.72 (d, J = 6.7, 1-H)	*anti*: −7.4 [$Sn(CH_3)_3$], 11.1 (C-4), 26.9 (C-3), 66.6 (C-2), 78.9 (C-1), 152.8/153.5 (NC=O), 166.7 (C=N) *syn*: −7.5 [$Sn(CH_3)_3$], 10.9 (C-4), 26.9 (C-3), 65.8 (C-2), 74.9 (C-1), 152.8/153.5 (NC=O), 166.3 (C=N)
9a	*anti/syn*-**10d**[j]	83	78 : 22	−14.6[j]	1670, 1610	*anti*: 0.80 (t, J = 7.4, 5-H), 1.28 (d, J = 6.3, 1-H), 1.32–1.78 (m, 4-H), 3.52 (m, 3-H), 5.05 (dq, J = 6.3, 6.4, 2-H) *syn*: 0.89 (t, J = 6.7, 5-H), 1.19 (d, J = 6.4, 1-H), 1.32–1.78 (m, 4-H), 3.30 (m, 3-H), 5.05 (dq, J = 6.3, 6.4, 2-H)	*anti*: 10.8 (C-5), 15.9 (C-1), 25.6 (C-4), 65.7 (C-3), 73.7 (C-2), 151.7/152.4 (NC=O), 167.5 (C=N) *syn*: 10.8 (C-5), 15.9 (C-1), 25.6 (C-4), 65.7 (C-3), 73.7 (C-2), 151.7/152.4 (NC=O), 167.5 (C=N)

Table 1. (continued)

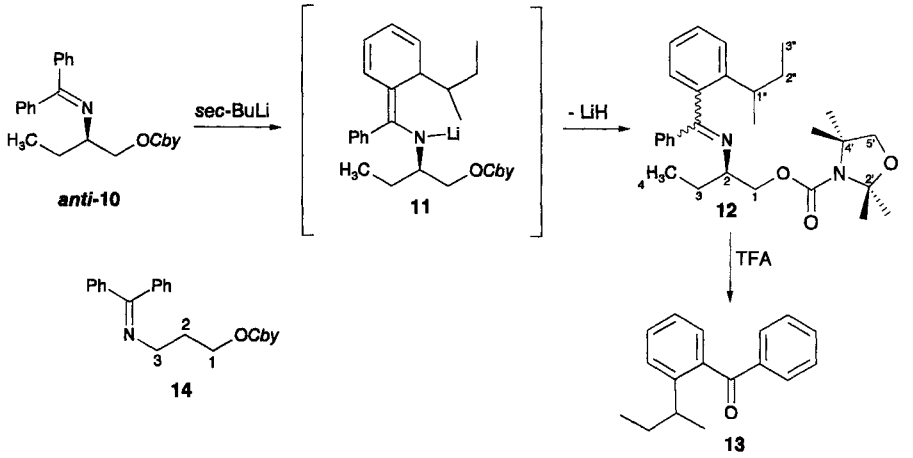
Starting Material	Product[a]	Yield (%)	*anti*/*syn*[b] Ratio	$[\alpha]_D^{20}$ [c]	IR (KBr/film) ν (cm^{-1})	^1H NMR (300 MHz, $CDCl_3$)[d] δ, J (Hz)	^{13}C NMR (300 MHz, $CDCl_3$)[d] δ
9a	*anti*/*syn*-**10e**	65[k]	78 : 22	−18.6[j]	1680, 1610	*anti*: 0.79/0.91 (t, J = 7.5, 1-H, 7-H), 1.20–1.80 (m, 2-H, 5-H, 6-H), 3.48 (m, 3-H), 4.99 (dt, J = 4.5, 8.6, 4-H) *syn*: 0.79/0.91 (t, J = 7.5, 1-H, 7-H), 1.20–1.80 (m, 2-H, 5-H, 6-H), 3.48 (m, 3-H), 4.84 (dt, J = 3.3, 4-H)	*anti*: 10.8 (C-1), 14.1 (C-7), 19.2 (C-5), 25.5 (C-2), 33.1 (C-6), 65.3 (C-3), 76.9 (C-4), 152.8/153.5 (NC=O), 167.3 (C=N) *syn*: 10.8 (C-1), 14.1 (C-7), 19.2 (C-5), 25.5 (C-2), 33.1 (C-6), 65.3 (C-3), 76.9 (C-4), 152.8/153.5 (NC=O), 167.3 (C=N)
9a	*anti*/*syn*-**10f**	55	79 : 21	−11.2[j]	1670, 1615	*anti*: 0.77/0.85 (t, J = 7.4, 1-H, 1-H, 10-H), 1.12–1.72 (m, 2-H, 5-H, 6-H, 7-H, 8-H, 9-H), 3.46 (m, 3-H), 4.95 (dt, J = 4.8, 8.1, 4-H) *syn*: 0.77/0.85 (t, J = 7.4, 1-H, 1-H, 10-H), 1.12–1.72 (m, 2-H, 5-H, 6-H, 7-H, 8-H, 9-H), 3.39 (m, 3-H), 4.95 (dt, J = 4.8, 8.1, 4-H)	*anti*: 10.8 (C-1), 13.9 (C-10), 25.9 (C-2), 22.5/29.1/30.8/31.7 (C-5, C-6, C-7, C-8, C-9), 65.3 (C-3), 77.1 (C-4), 152.6/153.6 (NC=O), 167.2 (C=N) *syn*: 10.8 (C-1), 13.9 (C-10), 25.9 (C-2), 22.5/29.1/30.8/31.7 (C-5, C-6, C-7, C-8, C-9), 65.3 (C-3), 77.1 (C-4), 152.6/153.6 (NC=O), 167.2 (C=N)
9a	*anti*-**10g**/*syn*-**10g**[e]	34	67 : 33	–[e]	1680, 1610	*anti*/*syn*: 0.85 (t, J = 7.4, 4-H), 1.68 (m, 3-H), 3.15 (d, J = 6.2, 1-CH_2Ph), 3.82 (m, 2-H), 5.31 (br s, 1-H)	*anti*/*syn*: 10.8 (C-4), 26.4 (C-3), 36.9 (CH_2Ph), 64.8 (C-2), 77.0 (C-1), 151.1/151.5 (NC=O), 167.7 (C=N)
9a	*anti*-**10h**/*syn*-**10h**[e]	45	62 : 38	–[e]	1680, 1610	*anti*/*syn*: 0.79 (t, J = 7.5, 7-H), 1.63 (m, 6-H), 2.52 (br s, 3-H), 3.53 (br s, 5-H), 5.03 (m, 1-H, 4-H), 5.75 (m, 2-H)	*anti*/*syn*: 10.6 (C-7), 25.4 (C-6), 35.4 (C-3), 64.5 (C-5), 76.3 (C-4), 116.8 (C-1), 135.2 (C-2), 151.0/151.9 (NC=O), 167.6 (C=N)
9a	*anti*/*syn*-**10i**[e]	36	62 : 38	–[e]	1790, 1680, 1610	*anti*: 0.87 (t, J = 6.6, 4-H), 1.33–1.85 (m, 3-H), 3.64 (s, OCH_3), 3.80 (br s, 2-H), 5.14 (br s, 1-H) *syn*: 0.87 (t, J = 6.6, 4-H), 1.33–1.85 (m, 3-H), 3.73 (s, OCH_3), 3.75 (br s, 2-H), 5.21 (d, J = 2.9, 1-H)	*anti*: 10.4 (C-4), 24.9 (C-3), 51.8 (OCH_3), 64.2 (C-2), 75.5 (C-1), 151.8/152.7 (NC=O), 168.6 (C=N), 169.8 (OC=O) *syn*: 10.7 (C-4), 24.9 (C-3), 51.8 (OCH_3), 63.6 (C-2), 73.8 (C-1), 151.8/152.7 (NC=O), 168.5 (C=N), 170.2 (OC=O)
9a	*anti*/*syn*-**10k**[e]	73	75 : 25	–[e]	1690, 1680, 1615	*anti*: 0.77 (t, J = 7.6, 4-H), 1.02 (s, *t*-C_4H_9), 1.25–1.65 (m, 3-H), 3.83 (br s, 2-H), 5.71 (d, J = 7.6, 1-H) *syn*: 0.82 (t, J = 7.4, 4-H), 0.91 (s, *t*-C_4H_9), 1.25–1.65 (m, 3-H), 4.00 (br s, 2-H), 5.65 (d, J = 2.9, 1-H)	*anti*: 10.5 (C-4), 26.5 (C-3), 26.1 [$C(CH_3)_3$], 43.7 [$C(CH_3)_3$], 63.2 (C-2), 76.1 (C-1), 151.9/152.4 (NC=O), 168.5 (C=N), 213.0 (OC=O) *syn*: 10.6 (C-4), 26.5 (C-3), 26.1 [$C(CH_3)_3$], 43.7 [$C(CH_3)_3$], 63.6 (C-2), 76.1 (C-1), 151.9/152.4 (NC=O), 168.1 (C=O), 213.0 (OC=O)
ent-**9b**	*ent*-*anti*/*syn*-**10l**[e]	85	78 : 22	–[e]	1670, 1610	*anti*/*syn*: 3.13 (br s, 3-H), 4.12 (br s, 2-H), 4.45 (dd, J = 6.9, 10.7, 1-H_A), 4.55 (br s, 1-H_B)	*anti*/*syn*: 39.8 (C-3), 62.7 (C-2), 68.1 (C-1), 151.9/152.6 (NC=O), 168.7 (C=N)
ent-**9b**	*ent*-*anti*/*syn*-**10m**	80	75 : 25	−78.2[j]	1680, 1615	*anti*: 1.28 (d, J = 6.4, 1-H), 2.84 (m, 4-H), 3.61 (m, 3-H), 5.02 (quint, J = 6.4, 2-H) *syn*: 1.28 (d, J = 6.4, 1-H), 2.84 (m, 4-H), 3.61 (m, 3-H), 4.96 (dq, J = 2.1, 2-H)	*anti*: 16.7 (C-1), 39.2 (C-4), 66.8 (C-3), 73.8 (C-2), 163.6/164.4 (NC=O), 168.1 (C=N) *syn*: 16.7 (C-1), 39.2 (C-4), 66.8 (C-3), 73.8 (C-2), 163.6/164.4 (NC=O), 168.1 (C=N)

[a] Satisfactory elemental analyses obtained (C ± 0.39, H ± 0.29, N ± 0.39, except for **10c** and **10f**). All products, **9a**, *ent*-**9b** and *anti*/*syn*-**10** are oils.
[b] Determined by GC.
[c] c = 0.8–1.8 (acetone).
[d] NMR data of the *Cby* group and the aromatic ring are omitted.
[e] Not separated.
[f] Yield: 21% with (−)-sparteine, *anti*/*syn* > 95 : 5.
[g] Determined by ^1H NMR spectroscopy.
[h] Yield: 28% with (−)-sparteine, *anti*/*syn* = 96 : 4.
[i] Yield: 23% with (−)-sparteine, *anti*/*syn* > 95 : 5.
[j] For pure *anti*-**10**, mp of pure *anti*-**10d** 98 °C (PE/Et_2O).
[k] Yield: 20% with (−)-sparteine, *anti*/*syn* > 95 : 5.

Table 2. Products **15** and **16** Prepared

Starting Material (*anti*/*syn*)	Product[a] (Method)	Yield (%) (*anti*/*syn*)	$[\alpha]_D^{20}$ [b]	mp (°C) (Et_2O/cyclohexane)	IR (KBr/film) ν (cm^{-1})	^1H NMR (300 MHz) δ, J (Hz)[c]	^{13}C NMR (300 MHz)[c] δ
10d (75 : 25)	*anti*-**15d** A	82 (81 : 19)	+13.6	oil	3500, 3300, 1680, 1630	0.96 (t, J = 7.4, 5-H), 1.31 (m, 4-H_A), 1.55 (d, J = 6.9, 1-H), 1.73 (m, 4-H_B), 4.26 (m, 3-H), 4.92 (dq, J = 3.6, 6.9, 2-H), 6.85 (d, J = 9.0, NH)[d]	10.7 (C-5), 17.2 (C-1), 23.7 (C-4), 54.6 (C-3), 73.7 (C-2), 151.8/152.7 (NC=O), 167.0 (NHC=O)[d]
	syn-**15d**		−7.40	oil	3300, 1680, 1630	0.96 (t, J = 7.4, 5-H), 1.13–1.49 (m, 1-H, 4-H_A), 1.76 (m, 4-H_B), 4.19 (m, 3-H), 5.03 (dq, J = 6.4, 6.4, 2-H), 6.55 (d, J = 8.1, NH)[d]	9.6 (C-5), 17.9 (C-1), 25.3 (C-4), 55.6 (C-3), 74.1 (C-2), 152.0/152.8 (NC=O), 167.1 (NHC=O)[d]
10h (35 : 65)	*anti*-**15h** A	64 (67 : 33)	−6.7	oil	3300, 1680, 1640	0.96 (t, J = 7.4, 7-H), 1.34–1.55 (m, 6-H_A), 1.73 (m, 6-H_B), 2.46 (br s, 3-H), 4.32 (br s, 5-H), 4.93 (dt, J = 3.6, 6.7, 4-H), 5.07 (dd, J = 1.7, 5.9, 1-H_A), 5.12 (dd, J = 1.7, 12.9, 1-H_B), 5.82 (m, 2-H), 6.95 (br s, NH)[d]	10.7 (C-7), 25.4 (C-6), 36.7 (C-3), 53.6 (C-5), 76.8 (C-4), 117.9 (C-1), 133.8 (C-2), 152.0/152.8 (NC=O), 166.0 (NHC=O)[d]
	syn-**15h**		−13.2	oil	3300, 1680, 1640	0.97 (t, J = 7.4, 7-H), 1.17–1.57 (m, 6-H_A), 1.75 (m, 6-H_B), 2.46 (br s, 3-H), 4.30 (br s, 5-H), 5.02 (br q, 4-H), 5.09 (m, 1-H_A), 5.13 (dd, J = 1.4, 8.1, 1-H_B), 5.82 (m, 2-H), 6.43 (br s, NH)[d]	9.7 (C-7), 25.5 (C-6), 36.3 (C-3), 53.5 (C-5), 74.2 (C-4), 118.3 (C-1), 133.2 (C-2), 152.0/152.8 (NC=O), 166.9 (NHC=O)[d]
10k (75 : 25)	*anti*-**15k** A	32 (80 : 20)	−28.3	oil	3300, 1710, 1680, 1640	0.97 (t, J = 7.4, 5-H), 1.21–1.45 (m, 4-H, t-C_4H_9), 4.58 (br s, 3-H), 5.73 (d, J = 2.9, 2-H), 7.10 (m, NH)[e]	10.8 (C-5), 26.3 [C($\underline{C}H_3)_3$], 26.8 (C-4), 44.2 [$\underline{C}(CH_3)_3$], 51.6 (C-3), 72.7 (C-2), 150.4/152.2 (NC=O), 167.0 (NHC=O), 212.1 (t-BuCO)[e]
	syn-**15k**		+53.0	oil	3300, 1710, 1680, 1640	1.04 (t, J = 7.4, 5-H), 1.22–1.60 (m, 4-H, t-C_4H_9), 4.60 (dt, J = 3.1, 7.2, 3-H), 5.67 (d, J = 3.1, 2-H)	10.5 (C-5), 26.0 (C-4), 26.7 [C($\underline{C}H_3)_3$], 43.6 [$\underline{C}(CH_3)_3$], 50.7 (C-3), 73.4 (C-2), 150.4/152.2 (NC=O), 166.9 (NHC=O), 210.6 (t-BuCO)[e]
10d (78 : 22)	*anti*-**16d** B	82 (78 : 22)	+28.1	175	3340, 3260, 1615	0.96 (t, J = 7.4, 5-H), 1.20 (d, J = 6.0, 1-H), 1.52 (ddq, J = 10.2, 14.1, 7.4, 4-H_A), 1.84 (ddq, J = 3.5, 14.1, 7.4, 4-H_B), 3.79 (ddd, J = 6.3, 10.2, 3.5, 3-H), 3.88 (m, 2-H)[e]	12.3 (C-5), 21.3 (C-1), 24.9 (C-4), 59.9 (C-3), 72.0 (C-2), 171.9 (NHC=O)[e]
	syn-**16d**		+21.4	101	3340, 3265, 1620	0.97 (t, J = 7.4, 5-H), 1.16 (d, J = 6.0, 1-H), 1.67 (m, 4-H), 3.89 (br s, 2-H, 3-H)[e]	11.6 (C-5), 20.7 (C-1), 25.6 (C-4), 58.5 (C-3), 69.9 (C-2), 171.1 (NHC=O)[e]
10f (79 : 21)	*anti*-**16f**[f] B	79 (84 : 16)	+8.6	172	3320, 3260, 1640	0.86 (t, J = 7.4, 10-H), 0.96 (t, J = 7.4, 1-H), 1.14–1.62 (m, 2-H_A, 5-H, 6-H, 7-H, 8-H, 9-H), 1.82 (m, 2-H_B), 3.57 (m, 3-H), 3.89 (ddd, J = 3.3, 6.1, 10.2, 4-H)[e]	12.3 (C-1), 15.5 (C-10), 24.6, 24.8, 28.1, 31.5, 34.1 (C-2, C-6, C-7, C-8, C-9), 36.1 (C-5), 58.9 (C-3), 76.0 (C-4), 171.4 (NHC=O)[e]
10k (75 : 25)	*anti*/*syn*-**16k** B	37 (78 : 22)	–[g]	121	3350, 1700, 1630	*anti*: 0.94 (t, J = 7.4, 4-H), 1.22 (s, t-C_4H_9), 1.50–1.82 (m, 3-H), 4.38 (m, 2-H), 4.73 (d, J = 4.8, 1-H)[e] *syn*: 1.02 (t, J = 7.4, 4-H), 1.21 (s, t-C_4H_9), 1.50–1.82 (m, 3-H), 4.38 (m, 2-H), 4.83 (d, J = 2.4, 1-H)[e]	*anti*: 8.4 (C-4), 20.0 (C-3), 24.3 [C($\underline{C}H_3)_3$], 42.1 [$\underline{C}(CH_3)_3$], 52.4 (C-2), 72.4 (C-1), 167.7 (NC=O), 214.0 (NHC=O)[e] *syn*: 8.5 (C-4), 20.0 (C-3), 24.9 [C($\underline{C}H_3)_3$], 42.1 [$\underline{C}(CH_3)_3$], 51.9 (C-2), 71.0 (C-1), 167.7 (NC=O), 211.9 (NHC=O)[e]

[a] Satisfactory elemental analyses obtained (C ± 0.20, H ± 0.07, N ± 0.22, except for **15k**).
[b] c = 0.6–1.7 (acetone).
[c] NMR Data of the *Cby* group and the aromatic ring are omitted.
[d] Solvent: $CDCl_3$.
[e] Solvent: CD_3OD.
[f] *syn*-**16f** could not be detected.
[g] The diastereomers could not be separated.



Scheme 3

Diastereomerically pure products such as *anti*-**10b–d**, which arise from the substitution of the *pro-S*-H in **9a**, are obtained in 20–28% yield, when in the deprotonation step the achiral diamine TMEDA is exchanged for (−)-sparteine.[1,11,13] As a side product (12–21%), the imine **12**, which bears an *O-sec*-butyl group in one of the phenyl residues, was isolated as an *E*/*Z*-mixture of diastereomers (Scheme 3). The constitution of **12** was elucidated by acid-catalyzed hydrolysis to afford 2-*sec*-butylphenyl phenyl ketone **(13)**. Compound **12** was also obtained in 33% yield when **9a** was subjected to the action of *sec*-butyllithium without addition of a chelating diamine.

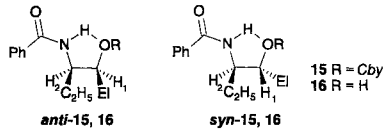
Compound **12** arises from the addition of alkyllithium to one of the *ortho*-positions of the imine **9a** followed by reductive elimination of lithium hydride from intermediate **11**. Similar reactions of benzophenone imines with Grignard reagents are known.[14] This clearly demonstrates the limitation of the *N*-(diphenylmethylene)amino group under less solvating reaction conditions. The nucleophilic addition of *sec*-butyllithium becomes even more severe in the attempt to deprotonate the protected primary amines such as **14**.[15]

The ease of deprotection was demonstrated with four selected examples (Scheme 4, Table 2). Treatment of *anti*/*syn*-**10** with trifluoroacetic acid in aqueous THF[8] leads to the liberation of the amino group, whereas refluxing **10** in 6 N HCl effected also the removal of the *Cby* group. In order to facilitate isolation, the crude free amines were benzoylated to yield the benzamides **15** and **16**, respectively. The *anti*- and *syn*-diastereomers **15** and **16** were easily separated in most cases by chromatography on silica gel.

In solution **15** and **16** exist as an equilibrium of the open chain and the hydrogen-bridged cyclic form. As expected from the observations made for the $^3J_{1,2}$ coupling constants of 1,2-diols ($J_{syn} > J_{anti}$),[12,16,17] the *anti*-diastereomers of **15** show a smaller $^3J_{1,2}$ coupling constant (2.9–3.7 Hz) than the corresponding *syn*-diastereomers (5.0–5.7 Hz). Because of the steric strain for the cyclic structure of *anti*-**15**, the acyclic form should be preferred in solution, which results in a higher polarity and therefore a lower R_f value for *anti*-**15** (0.10–0.17, PE/Et_2O, 2:1) compared to *syn*-**15** (0.13–0.34).[16] This is also displayed in the R_f values for *anti*/*syn*-**16d** (Table 3).

Table 3. Analytical and ^{1}H NMR Spectral Distinction of *anti*/*syn*-**15** and **16**[a]

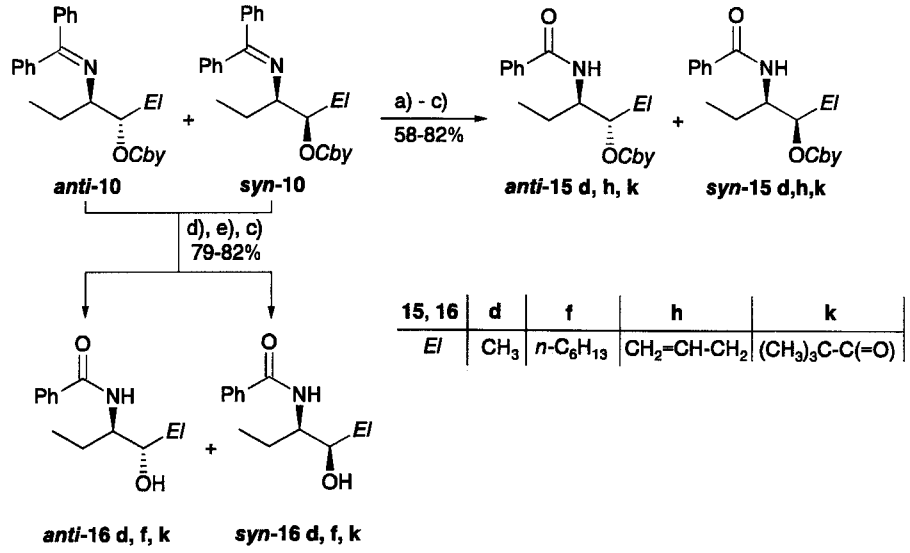
Product	*anti*-Isomer			*syn*-Isomer		
	R_f (TLC)[b]	^{1}H NMR[c]		R_f (TLC)[b]	^{1}H NMR[c]	
		$\delta_{1\text{-H}}$	$^3J_{1,2}$ (Hz)		$\delta_{1\text{-H}}$	$^3J_{1,2}$ (Hz)
15d	0.11	4.92	3.6	0.34	5.0	6.4
15h	0.10	4.93	3.6	0.13	5.0	7.1
15k	0.19	5.73	2.9	0.24	5.7	3.1
16d	0.17	3.88	6.3	0.20	3.9	–[d]
16f	0.44	3.89	6.1	–[e]	–[e]	–[e]
16k	0.42	4.73	4.8	0.42[f]	4.8	2.4

[a] 

[b] Silica gel; PE/Et_2O (2:1).
[c] Solvent for **15d, h**: $CDCl_3$; **15k, 16d, f, k**: CD_3OD.
[d] Signal appears as a broad singlet.
[e] Compound *syn*-**16f** could not be detected by ^{1}H NMR or TLC.
[f] The diastereomers *anti*- and *syn*-**16k** could not be separated.

The *anti*/*syn*-mixtures of compounds **10b** and *ent*-**10l** were converted to the corresponding *N*,*N*-dibenzylamines **2**, which are stereochemically assigned.[12] It turned out that by means of both protecting techniques the same major and the minor diastereomers are produced.

Experiments involving metal-organic intermediates were carried out under Ar atmosphere with oven-dried glassware. 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 AM 300 spectrometer. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Optical rotations were recorded on a Perkin-Elmer polarimeter 241. Melting points were obtained on a Mettler melting point apparatus FP 61 and are uncorrected. Products were purified by flash column chromatography on silica gel (60–200 mesh) or by recrystallization. The NMR signals of the ring-chain tautomers of **6a** and *ent*-**6b** and of the *E*/*Z* isomers of **12** are separated by diagonal strokes. Petroleum ether (PE) refers to the fraction with a boiling range of 40–60 °C.



15, 16	d	f	h	k
El	CH_3	n-C_6H_{13}	CH_2=CH-CH_2	$(CH_3)_3$C-C(=O)

a) 2 eq. TFA, THF, H_2O, 25°C, 1 h; b) $NaHCO_3$, pH 8; c) 3 eq. PhCOCl, 0°C → 25°C, 4 h; d) 6N HCl, THF, 65°C, 1 h; e) NaOH, pH 12.

Scheme 4

(*R*)-2-[-*N*-(Diphenylmethylidene)amino]butan-1-ol (6a); Typical Procedure:

To a stirred solution of (*R*)-**4a** (2.45 g, 27.6 mmol) in CH_2Cl_2 (50 mL) was added *N*-(diphenylmethylidene)amine[18] (**5**; 5.0 g, 27.6 mmol). The reaction vessel was topped with a $CaCl_2$ tube. After stirring for 7 d, the solvent was evaporated and the remaining residue recrystallized from Et_2O/PE, yielding the imine **6a** (5.44 g, 78%), R_f 0.08 (Et_2O/PE 1:2), $[\alpha]_D^{20}$ + 68.9 (*c* = 1.38, acetone), mp 93°C (Et_2O/PE).

IR (KBr): ν = 3200 (OH/NH), 1590 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.77/0.95 (t, *J* = 7.4 Hz, CH_2CH_3, 4-H), 1.55 (m, CH_2CH_3), 2.20 (br s, OH/NH), 3.21/3.45 (m, 2-H), 3.45/3.65 (t, *J* = 6.6, 10.7/7.1, 7.6 Hz, 1-H_A), 3.75/3.98 (t, *J* = 10.7/7.6 Hz, 1-H_B), 7.00–7.80 (m, C_6H_5).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 10.7/11.3 (C-4), 25.5/26.6 (C-3), 60.3/64.8 (C-2), 66.3/70.8 (C-1), 99.3/169.0 [O*C*(Ph)$_2$N/C=N], 125.4, 126.3, 127.2, 127.4, 128.0, 129.9, 137.1, 139.9, 144.6, 144.7 (Ar–C).

Anal. Calcd for $C_{19}H_{19}NO$: C, 80.63; H, 7.51; N, 5.53. Found: C, 80.76; H, 7.51; N, 5.78.

(S)-2-[-N-(Diphenylmethylidene)amino]-3-phenylpropan-1-ol (*ent*-**6b**):

This compound was obtained similarly in 52% yield; R_f 0.12 (Et_2O/PE, 1:2); $[\alpha]_D^{20}$ −217.8 (*c* = 1.78, acetone); mp 132°C (Et_2O).

IR (KBr): ν = 3200 (OH/NH), 1610 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.15/2.23 (br s, OH/NH), 2.65/2.80/2.94 (dd/d, *J* = 7.3, 13.8/6.2 Hz, 2 H), 3.48–3.90 (m, 1-H, 2-H), 6.60–6.72 (m, C_6H_5).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 39.6/39.0 (C-3), 59.4/65.4 (C-2), 66.1/70.4 (C-1), 99.9/169.7 [O*C*(Ph)$_2$N/C=N], 125.7/125.9, 126.2/126.4, 127.2/127.5, 127.7, 127.9, 128.5/128.7, 129.7/130.0, 136.6, 138.4/138.8, 139.6, 144.2 (Ar–C).

Anal. Calcd for $C_{22}H_{21}NO$: C, 83.80; H, 6.67; N, 4.44. Found: C, 83.46; H, 6.72; N, 4.62.

(*R*)-2-[*N*-(Diphenylmethylidene)amino]butyl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (9a); Typical Procedure:

To a refluxing suspension of NaH (1.10 g, 60% in paraffin, 27 mmol) in anhyd THF (20 mL) was added the imine **9b** (6.25 g, 25.0 mmol) in THF (20 mL) in one portion, and the mixture was refluxed for 1 h. After the evolution of H_2 had ceased, a solution of carbamoyl chloride[11] **8** (5.20 g, 27.0 mmol) in anhyd THF (20 mL) was added and the stirring was continued for 3 h under reflux. The mixture was cooled and treated with H_2O (30 mL). The Et_2O layer was separated and the aqueous layer extracted with Et_2O (2 × 30 mL). The combined Et_2O solutions were dried ($MgSO_4$), evaporated in vacuum and the residue was purified by chromatography on silica gel, deactivated with diethylamine (PE/Et_2O/Et_2NH, 20:4:1), with pentane/Et_2O (5:1) as eluent to afford the carbamate ester **9a** (Table 1).

(S)-2-[N-(Diphenylmethylidene)amino]-3-phenylpropyl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (*ent*-**9b**) was obtained similarly in 93% yield (Table 1).

Deprotonation of 9 and Synthesis of 10 by Electrophilic Substitution; General Procedure:

Using TMEDA: To a stirred of **9a** (or *ent*-**9b**) (1.0 mmol) and TMEDA (193 mg, 1.65 mmol) in Et_2O (10 mL) under Ar in a dry ice/acetone bath was introduced a 1.2–1.4 M solution of *s*-BuLi in cyclohexane/isopentane (1.5 mmol) with a syringe within ca 2 min. Stirring was continued for 4 h before the electrophile (3.0 mmol) (Scheme 2) was added. The mixture was stirred for further 90 min at −78°C and allowed to warm up to r.t. After adding MeOH (2 mL), the precipitate formed was filtered. The Et_2O layer was evaporated in vacuo and the residue purified by flash chromatography (silica gel, Et_2O/PE, 1:5) to yield the substituted carbamates **10a–m** (Table 1).

Using(−)-sparteine: To a stirred solution of **9a** (or *ent*-**9b**) (1.0 mmol) and (−)-sparteine (386 mg, 1.65 mmol) in Et_2O (10 mL) under Ar in a dry ice/acetone bath was introduced a 1.2–1.4 M solution of *s*-BuLi in cyclohexane/isopentane (1.5 mmol) with a syringe within ca 2 min. Stirring was continued for 4 h before the electrophile (3.0 mmol) (Scheme 2) was added. The mixture was stirred for further 90 min at −78°C allowed to warm up to r.t., and worked up as described above (Table 1).

Formation and Characterization of the Imine 12:

To a stirred solution of **9a** (430 mg, 1.05 mmol) in Et_2O (10 mL) under Ar in a dry ice/acetone bath, was introduced a 1.4 M solution of *s*-BuLi in cyclohexane/isopentane (1.13 mL, 1.58 mmol) with a syringe within ca 2 min. Stirring was continued for 4 h before MeOD (0.13 mL, 104 mg, 3.15 mmol) was added. The mixture was stirred for an additional 90 min at −78°C and allowed to warm up to r.t.. After adding MeOH (2 mL), the precipitate formed was filtered. The Et_2O layer was evaporated in vacuum and the residue purified by flash chromatography (silica gel, Et_2O/PE, 1:5) to yield an *E*/*Z*-mixture (73:23) of **12** (160 mg, 33%), which could not be

separated, and 32 mg (7%) of the educt **9a**, *E*/*Z*-**12**: R_f 0.41/0.49 (Et_2O/PE, 1:2).

IR (film): $\nu = 1670$ (C=O), 1610 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.42/0.82$ (t, $J = 6.3$ Hz, 3″-H), 0.85/0.88 (t, $J = 6.7$ Hz, 4-H), 0.92/1.10 (d, $J =$ Hz, 1″-CH_3), 1.30–1.80 (m, 2′-CH_3, 4′-CH_3, 2″-H), 2.38 (m, 1″-H), 3.35/3.45 (br s, 2-H), 3.69/3.72 (s, 5′-H), 4.00–4.27 (m, 1-H), 7.00–6.61 (m, Ar-H).

^{13}C NMR ($CDCl_3$, 300 MHz): $\delta = 9.8/10.4$ (C-3″), 11.9/12.1 (C-4), 20.9/21.4 (1″-CH_3), 24.1/25.3/26.2 (2′-CH_3, 4′-CH_3), 26.1/26.4 (C-3), 30.2/30.5 (C-2″), 37.2/37.6 (C-1″), 59.8/60.5 (C-4′), 62.1/62.4 (C-2), 66.7/66.8 (C-1), 76.1 (C-5′), 94.8/95.8 (C-2′), 125.4/125.6, 126.1/126.4, 127.8, 128.0/128.1, 128.3, 128.7, 129.7/129.8, 135.3/135.6, 140.0/140.4, 145.3/145.7 (Ar-C), 152.2/152.9 (C=O), 167.8/168.0 (C=N).

Anal. Calcd for $C_{29}H_{40}N_2O_3$: C, 75.00; H, 8.62; N, 6.03. Found: C, 74.97; H, 8.37; N, 5.88.

2-(1-Methylpropyl)benzophenone (13):
To a solution of imine **12** (50 mg, 0.11 mmol) in THF (2 mL) and water (0.5 mL) was added CF_3CO_2H (0.22 mL). After refluxing for 1 h, the mixture was cooled to r.t. and extracted with Et_2O (5 mL) and the organic layer separated. The aqueous layer was extracted with Et_2O (3 × 5 mL), the combined Et_2O layers were washed with satd. $NaHCO_3$, dried ($MgSO_4$), and the solvent evaporated in vacuum. The residue was purified by flash chromatography (silica gel, Et_2O/PE, 1:10) to give 21 mg (88%) of **13**, R_f 0.62 (Et_2O/PE, 1:2).

IR (film): $\nu = 1655$ cm^{-1} (C=O).

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.72$ (t, 3H, $J = 7.4$ Hz, CH_2CH_3), 1.17 (d, 3H, $J = 6.9$, $CHCH_3$), 1.56 (m, 2H, CH_2CH_3), 2.74 (sext, 1H, $CHCH_3$), 7.18–7.82 (m, 9H, Ar-H).

^{13}C NMR ($CDCl_3$, 300 MHz): $\delta = 12.1$ (CH_2CH_3), 22.1 ($CHCH_3$), 30.9 (C-2), 37.3 (C-1), 125.1, 126.4, 127.5, 128.4, 130.1, 133.2, 137.9, 139.1, 146.1, 199.0 (C=O).

HRMS (FAB) (Calc. for $C_{17}H_{18}O$): $m/z = 238.1357$ (M^+). Found: 238.1362.

2-(*N*-Benzoylamino)alkyl Carbamates 15, General Procedure:
To a solution of **10** (1.00 mmol) in THF (5 mL) and water (1 mL), was added CF_3CO_2H (2.00 mL). After stirring for 1 h at r.t., satd. aq $NaHCO_3$ was added until the solution reached pH 8. The mixture was cooled to 0°C with an ice bath, benzoyl chloride (421 mg, 3.00 mmol) was added, and allowed to warm up to r.t. within 4 h. After adding water (5 mL), the organic layer was separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined Et_2O layers were dried ($MgSO_4$), evaporated in vacuum and the residue was purified by flash chromatography (silica gel, Et_2O/PE, 1:5 to 1:2) to afford the 2-(benzoylamino)alkyl carbamates **15** (Table 2).

2-(*N*-Benzoylamino)alkan-1-ols 16, General Procedure:
A solution of **10** (1.00 mmol) in THF (3 mL) and 6 N HCl (5 mL) was refluxed for 1 h. The mixture was cooled and solid NaOH (1.3 g, 0.033 mmol) was added until the solution reached pH 12 and refluxed for 12 h. The mixture was cooled to 0°C with an ice bath, benzoyl chloride (421 mg, 3.00 mmol) introduced, and then warmed up to r.t. within 4 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined Et_2O solutions were dried ($MgSO_4$), evaporated in vacuum and the residue purified by flash chromatography (silica gel, EtOAc/cyclohexane, 1:8 to 1:2) to give the 2-(benzoylamino)alkanols **16** (Table 2).

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