A Convenient and Versatile Synthesis of Chiral Aliphatic and Allylic Amines

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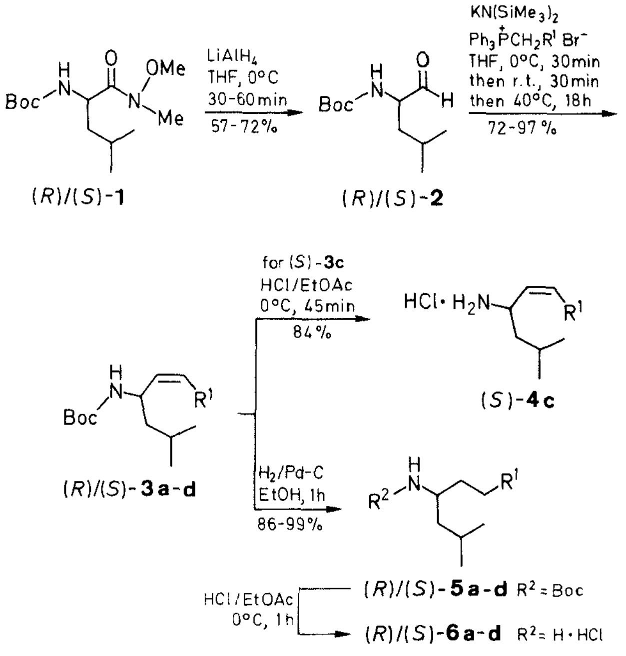
Preparation of optically pure aliphatic and allylic amines from amino acids is described. Wittig olefination of α-Boc-amino aldehydes affords Boc-protected allylic amines which can be deprotected to the corresponding chiral unsaturated amines. Catalytic reduction of the Wittig product prior to deprotection affords aliphatic amines of high optical purity.

Chiral saturated and unsaturated amines in optically pure form are frequently required as synthetic intermediates. One general procedure for the synthesis of these amines is the introduction of the amino function into the desired substrate followed by separation of diastereoisomers or resolution of enantiomers. However, such separations can be difficult and often are not complete or are not applicable to large scale preparations.

We have found that synthesis of chiral aliphatic and allylic amines from optically active amino acids is a convenient and versatile solution to this problem. Conversion of a suitably protected amino acid derivative to the corresponding amino aldehyde followed by Wittig olefination affords Boc-protected allylic amines. Deprotection then yields the unsaturated amines or reduction prior to deprotection gives the saturated amines with high optical purity.

As an example, (*S*)- or (*R*)-Boc-leucinal [(*S*)- or (*R*)-**2**] was obtained from lithium aluminum hydride reduction of the corresponding *N*-methoxy-*N*-methylamide **1** by a modification of the procedure of Fehrentz and Castro.[1] Racemization during these reductions could be avoided by performing the reaction at 0 °C with a small excess of lithium aluminum hydride as recommended by Coy, Hocart and Sasaki.[2] Pure (*S*)-Boc-leucinal [(*S*)-**2**][3] $[\alpha]_D^{22}$ of −51 to −53° ($c = 1$, methanol) was obtained in 65–69% yield after flash chromatography on silica gel.

Following the procedure of Luly and co-workers,[4] a variety of olefins **3** were prepared (Table) by reaction of aldehyde **2** with ylides under Wittig conditions. The olefinic protons of **3** exhibited coupling constants of J = 10 Hz consistent with *Z*-geometry. Deprotection of **3** with anhydrous hydrochloric acid afforded the chiral allylic amines **4**, as exemplied in the case of **3c** while catalytic reduction of **3** prior to deprotection yielded the chiral saturated amines **6**.[5] Enantiomers **6d** and **6e** were determined to be at least 90% optically pure by 376 MHz ^{19}F-NMR of the corresponding α-methoxy-α-(trifluoromethyl)phenylacetamides.[7]



3–6	a	b	c	d
R	Me	Et	Pr	Bu

All melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus using open capillaries and are uncorrected. ^{1}H-NMR spectra were recorded for all intermediates

Table. Compounds 3, 5 and 6 Prepared

Boc Allylic Amine[a]	Yield[b] (%)	$[\alpha]_D$[c]	Boc Amine[a]	Yield[d] (%)	$[\alpha]_D$[c]	Amine[a,e] · HCl	Yield[f] (%)	mp (°C)	$[\alpha]_D$[c]
(*S*)-**3a**	97	+27.5	(*R*)-**5a**	99	− 8.0	(*R*)-**6a**	93	229 (dec)	−5.2
(*R*)-**3a**	90		(*S*)-**5a**	92	+ 8.5	(*S*)-**6a**	91	225 (dec)	+5.2
(*S*)-**3b**	72	+20.7	(*R*)-**5b**	86	−11.9	(*R*)-**6b**	54	211–14 (softens at 203)	−4.5
(*S*)-**3c**	87	+23	(*R*)-**5c**	92	−11.7	(*R*)-**6c**	75	141–44 (softens at 136)	−4.2
(*R*)-**3c**	74	−19.9	(*S*)-**5c**	87	+10.8	(*S*)-**6c**	46	139–42	+4.4
(*S*)-**3d**	90	+23.5	(*R*)-**5d**	95	–	(*R*)-**6d**	65	113–114	−3.7

[a] ^{1}H-NMR consistent with assigned structure. See Experimental Section for typical spectrum.

[b] Yield of isolated product from Wittig reaction.

[c] (c = 1, MeOH), 22 °C.

[d] Yield of isolated saturated amine from reduction.

[e] Satisfactory microanalyses obtained: C ±0.38%, H ±0.40, N ±0.14.

[f] Yield of analytically pure product after removal of Boc group.

and final products on either a Varian XL-300 or a GE NT-360 instrument using TMS as an internal standard and are consistent with assigned structures. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 10 cm cell. TLC were performed on Analtech fluorescent silica gel plates.

(*S*)-N^{α}-(*tert*-Butoxycarbonyl)-*N*-methoxy-*N*-methylleucinamide [(*S*)-1]:

A solution of (*S*)-Boc-leucine hydrate (12.46 g, 50 mmol) in EtOAc (75 mL) is cooled in an ice bath under N_2. A solution of *N*-methylmorpholine (5.5 mL, 50 mmol) in EtOAc (30 mL) is added, followed, by isobutyloxy chloroformate (6.48 mL, 50 mmol). After stirring at ice bath temperature for 15 min, *N,O*-dimethylhydroxylamine (94%, 5.18 g, 50 mmol) is added followed by *N*-methylmorpholine (5.5 mL, 50 mmol). The mixture is stirred at ice bath temperature for 15 min and then at r.t. for 20 h. After washing successively with H_2O (20 mL), 10% citric acid (20 mL), brine (20 mL), sat. $NaHCO_3$ (20 mL), and brine (20 mL), the EtOAc phase is dried (Na_2SO_4), filtered and concentrated to an oil; yield: 13.5 g (99%); homogeneous by TLC, R_f = 0.48 (EtOAc/hexane, 3:7).

^{1}H-NMR ($CDCl_3$): $\delta = 0.94$ [m, 6 H, $CH(C\underline{H}_3)_2$], 1.43 (s, 10 H, *t*-C_4H_9 and CH), 1.72 (m, 2 H, CH_2), 3.20 (s, 3 H, NCH_3), 3.79 (s, 3 H, OCH_3), 4.72 (m, 1 H, CH), 5.07 (d, 1 H, *J* = 9 Hz, NH).

(*R*)-N^{α}(*tert*-Butoxycarbonyl)-*N*-methoxy-*N*-methylleucinamide [(*R*)-1]:

This hydroxamide is prepared from (*R*)-Boc-leucine by the same procedure used to prepare the (*S*)-isomer; yield: 89%; $[\alpha]_D^{22}$ +23.4° (*c* = 1, MeOH).

(*S*)-*N*-(*tert*-Butoxycarbonyl)leucinal [(*S*)-2]:

A 1 M solution of $LiAlH_4$ in THF or Et_2O (3.2 mL, 3.2 mmol) is added over 15 min to a stirred solution of *N*-methoxy-*N*-methylamide (*S*)-1 (1.48 g, 5.39 mmol) in THF (35 mL) cooled in an ice bath under N_2. After stirring at ice bath temperature for 30–60 min, TLC showed that the reaction is complete. A sat. solution of potassium sodium tartrate (10 mL) is added at 0 °C and the mixture is concentrated under reduced pressure at 30 °C. The residue is extracted with Et_2O (50 mL), which is then washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure at 30 °C. Flash chromatography on silica gel using EtOAc/hexane (2:8) as eluent gives (*S*)-2 as an oil; yield: 0.80 g (69%); $[\alpha]_D^{22}$ −51.2° (*c* = 1, MeOH).

^{1}H-NMR ($CDCl_3$): $\delta = 0.97$ [d, 6 H, *J* = 8 Hz, $CH(C\underline{H}_3)_2$] 1.35–1.8 (m, 3 H, CH_2CH), 1.45 (s, 9 H, *t*-C_4H_9), 4.24 (m, 1 H, CH), 4.90 (m, 1 H, NH), 9.60 (s, 1 H, CHO).

This aldehyde may be stored at −20 °C under N_2 for 3–4 d without loss of optical activity.

(*R*)-*N*-(*tert*-Butoxycarbonyl)leucinal [(*R*)-2]:

This aldehyde is prepared from the *N*-methoxy-*N*-methylamide (*R*)-2 by using the same procedure to prepare the (*S*)-isomer; yield: 72%; $[\alpha]_D^{22}$ +47.3° (*c* = 1, MeOH).

(5*S*,3*Z*)-5-(*tert*-Butoxycarbonylamino)-7-methyl-3-octene (3b); Typical Procedure for Wittig Reaction:

A 1.05 M solution of $KN(SiMe_3)_2$ in THF (6.4 mL, 6.69 mmol) is added over 15 min to a stirred mixture of dry propyltriphenylphosphonium bromide (2.58 g, 6.69 mmol) and THF (50 mL) at 0 °C under N_2. After addition is complete, the mixture is stirred at 0 °C for 1 h, and then a solution of (*S*)-Boc-leucinal [(*S*)-2, 1.2 g, 5.57 mmol] in dry toluene (10 mL) is added over 10 min. The mixture is stirred at 0 °C for 30 min, at r.t. for 30 min and then at 40 °C for 18 h. Water (5 mL) is added cautiously and the solvents are removed under reduced pressure at 35 °C. The residue is partitioned between EtOAc (50 mL) and a dilute solution of potassium sodium tartrate (25 mL). The organic phase is washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residue is purified by flash chromatography on silica gel using EtOAc/hexane (1:9) as eluent; yield: 0.96 g (72%); $[\alpha]_D^{22}$ = +20.7° (*c* = 1, MeOH).

^{1}H-NMR ($CDCl_3$): $\delta = 0.92$ [t, 6 H, *J* = 7 Hz, $CH(C\underline{H}_3)_2$], 0.97 (t, 3 H, *J* = 8 Hz, CH_3), 1.23 (m, 2 H, CH_2), 1.42 (s, 9 H, *t*-C_4H_9), 1.60 8m, 1 H, CH), 2.14 (m, 2 H, CH_2), 4.36 (m, 2 H, NH and CH), 5.12 (t, 1 H, *J* = 10 Hz, C=CH), 5.42 (2 t, 1 H, *J* = 8, 10 Hz, HC=C).

(6*S*,4*Z*)-6-Amino-8-methyl-4-nonene Hydrochloride [(*S*)-4c]

A solution of (S)-3c (1.0 g, 3.92 mmol) in EtOAc (50 mL) is cooled in an ice bath under a drierite tube and saturated with anhydrous HCl for 8 min. After stirring in the ice bath for 45 min, solvent is removed under reduced pressure to give the deprotected allylic amine HCl as a waxy solid; yield: 0.63 g (84%).

^{1}H-NMR ($CDCl_3$): $\delta = 0.93$ (m, 9 H, CH_3), 1.3–1.8 (m, 5 H, CH_2 and CH), 2.0–2.2 (m, 2 H, CH_2), 4.06 (m, 1 H, CH), 5.42 (t, 1 H, *J* = 10 Hz, C = CH), 5.72 (2 t, 1 H, *J* = 8, 12 Hz, HC = C), 8.35 (br s, 3 H, NH).

(*R*)-4-(*tert*-Butoxycarbonylamino)-2-methyloctane [(*R*)-5c]; Typical Procedure for the Reduction of Boc-Allylic Amines:

A solution of (*S*)-3b (0.96 g, 3.98 mmol) in absolute EtOH (75 mL) is hydrogenated over a 5% Pd-C catalyst (1.0 g) at 20–25 °C at a pressure of 38 psi in a Parr apparatus. After one equivalent of H_2 has been consumed (1 h), the mixture is filtered and then concentrated under reduced pressure to give the saturated amine (*R*)-5c as an oil; yield: 0.83 g (86%); $[\alpha]_D^{22}$ −11.9° (*c* = 1, MeOH).

^{1}H-NMR ($CDCl_3$): $\delta = 0.90$ (m, 9 H, CH_3), 1.27 (m, 7 H, CH_2), 1.42 (s, 9 H, *t*-C_4H_9), 1.68 (m, 2 H, CH), 3.61 (br m, 1 H, CH), 4.18 (br d, 1 H, *J* = 10 Hz, 1 H, NH).

(*R*)-4-Amino-2-methyloctane Hydrochloride [(*R*)-6*b*]; Typical Procedure for Removal of Boc Protective Group:

A solution of (*R*)-5b (0.80 g, 3.29 mmol) in EtOAc (35 mL) is cooled in an ice bath protected by a drierite tube and saturated with anhydrous HCl for 5 min. After stirring at 0 °C for 1 h, the solvent is removed under reduced pressure and the residue recrystallized from EtOAc/hexane; yield: 0.32 g (54%); mp 211–214 °C (softens at 203 °C); $[\alpha]_D^{22}$ = −4.5° (*c* 1, MeOH).

^{1}H-NMR ($CDCl_3$): $\delta = 0.92$ (m, 9 H, CH_3), 1.3–1.54 (m, 5 H, CH_2), 1.7 (m, 3 H, CH_2), 1.9 (m, 1 H, CH), 3.22 (quint, 1 H, *J* = 7 Hz, CH), 8.34 (br s, 3 H, NH).

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