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Generation and α-hydroxyalkylation of a novel 3-piperidinol *N*-α-carbanion intermediate

ZHENG Xiao†, CHEN Guo, RUAN YuanPing† & HUANG PeiQiang

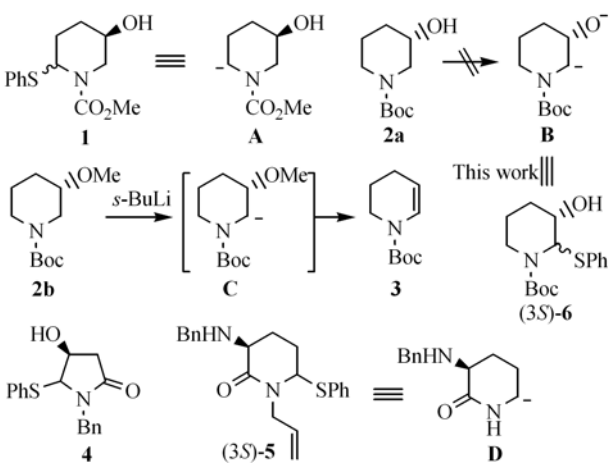
Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China

The (*S*)-sulfide 6 has been synthesized as a synthetic equivalent of novel 3-piperidinol *N*-α-carbanion B via deprotonation and lithium naphthanelide (LN)-mediated reductive lithiation. The reaction of the 3-piperidinol *N*-α-carbanion intermediate B with carbonyl compounds gave, besides some reduced product 2a, the desired α-hydroxyalkylation products 12—17 with excellent 2,3-diastereoselectivity. The reductive α-hydroxyalkylation with unsymmetric carbonyl compounds led to only 50:50 to 77:23 diastereoselectivities at the C-1' carbinol center.

sulfide, *N*-α-carbanion, lithium-naphthanelide, reductive lithiation, carbonyl compounds, α-hydroxyalkylation, diastereoselectivity

1 Introduction

2/6-Substituted 3-piperidinols are characteristic substructures of a number of bioactive natural products, drugs or drug candidates[1−4]. Among a great deal of valuable methods developed for their construction[5−10], those using L-glutamic acid as a chiron have attracted much attention[11−16,17−24]. For the introduction of the required C-2 or C-6 substituents, the methods based on the iminium ion/*N*-acyliminium ion[25−33] intermediates are quite popular. However, the complementary methods[34−43] involving unpoled 3-piperidinol *N*-α/α′-carbanion intermediates are rare[44−46], although several methods for the generation of α-lithiation of 3-pyrrolidinol homologues have been reported[34−43,47−49,50−55]. In 2004, Gallagher and co-workers developed thioether **1** as the first synthetic equivalent of the 3-piperidinol *N*-α′-carbanion **A**, which can react with halides and acyl halides[45]. However, the reductive α-hydroxyalkylation of the sulfide **1** with carbonyl compounds was unsuccessful[45]. In this context, the formation and reaction of the carbanion **B** is even more challenging, as can be seen from the unsuccessful attempted formation of the carbanion **B** from *N*-Boc-3-piperidinol **2** by deprotonation[44,45], and from the exclusive formation of the β-elimination product **3** upon deprotonation of the piperidine derivative **2b** (Scheme 1)[34−43]. Previously



Scheme 1 Reported methods for the generation of 3-hetero-substituted piperidine *N*-α-carbanions.

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†Corresponding author (email: zxiao@xmu.edu.cn; ypruan@xmu.edu.cn)
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we have established a deprotonation-lithium naphthalenide (LN)-mediated reductive lithiation procedure for sulfide **4**[50]. Recently, this procedure was extended to 3-dibenzylamino-2-piperidonyl thioether **5**[46]. However, the 3-dibenzylamino-2-piperidone *N*-α-carbanion **D**, regenerated *in situ* from thioether **5**, can react only with aldehydes without an acidic α-proton. As a continuation of our studies on the chemistry of 3-pyrrolidinol *N*-α-carbanion[50−55] and 3-dibenzylamino-2-piperidone *N*-α-carbanion[46], we report the development of thioether **6** as a synthetic equivalent of the carbanion **B**, and the first flexible reductive α-hydroxyalkylation of 3-piperidinol-2-yl phenyl thioether **6**.

2 Experimental

2.1 General

Melting points were determined on a Yanaco MP-500 micromelting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet technique. ^{1}H NMR spectra were recorded on a Bruker Avance DPX 400 MHz NMR spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton Esquire 3000 plus liquid chromatography-mass spectrum (direct injection) and ABI 3200Q trap liquid chromatography-mass spectrum. Optical rotations were measured with a Perkin-Elmer 341 automatic polarimeter and Rudolph Autopol IV automatic polarimeter. Flash column chromatography was carried out with silica gel (300−400 mesh). THF was distilled over sodium. Dichloromethane was distilled over P_2O_5.

2.2 (*S*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)piperidin-2-one (8)

To an anhydrous CH_2Cl_2 (11 mL) solution of the known lactam **7**[56] (482 mg, 2.1 mmol) and Et_3N (0.64 mL, 4.62 mmol) was added $(Boc)_2O$ (0.97 mL, 4.21 mmol) under nitrogen atmosphere at 0℃. After stirred at room temperature for 96 h, the reaction was quenched with water (5 mL) at 0℃ and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1∶15) to afford **8** (590 mg, yield: 85%) as a pale yellow oil. $[\alpha]_D^{20}$ −18.7 (*c* 1.0, $CHCl_3$); IR (film) *ν*: 2953, 2931, 2886, 2856, 1776, 1721, 1295, 1252, 1150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.08 (s, 3H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.46 (s, 9 H, $OC(CH_3)_3$), 1.72−1.88 (m, 2 H, H-5), 1.90−1.99 (m, 1 H, H-4), 2.00−2.11 (m, 1 H, H-4), 3.57−3.68 (m, 2 H, H-6), 4.16 (dd, *J* = 4.6, 6.6 Hz, 1 H, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.6, −4.7, 18.2, 19.8, 25.7 (3C), 27.9 (3C), 30.4, 45.5, 71.4, 82.6, 152.6, 171.9 ppm; MS (ESI) *m/z* (%): 352 ($M+Na^+$, 100), 368 ($M+K^+$, 58).

2.3 (*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxypiperidin-2-one (9)

To a solution of **8** (265 mg, 0.81 mmol) in anhydrous THF (2 mL) was added a 1 M THF solution of TBAF (1.2 mL, 1.2 mmol) under nitrogen atmosphere at 0℃. The mixture was stirred for 1 h at 0℃ before quenched with water (5 mL). The aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic phases were washed with brine (2 mL), and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1∶2) to afford **9** (146 mg, yield: 84%) as a colorless oil. $[\alpha]_D^{20}$ +5.2 (*c* 0.5, $CHCl_3$); IR (film) *ν*: 3435, 2955, 2929, 2856, 1760, 1724, 1471, 1390, 1368, 1254, 1152, 1074, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (s, 9 H, $C(CH_3)_3$), 1.64−1.72 (m, 1 H, H-4), 1.88−1.95 (m, 2 H, H-5), 2.32−2.40 (m, 1 H, H-4), 3.57−3.64 (m, 1 H, H-6), 3.77−3.83 (m, 1 H, H-6), 4.13 (dd, *J* = 7.17, 11.52 Hz, 1 H, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.0, 27.9, 28.0 (3C), 45.2, 69.2, 83.7, 151.9, 174.5 ppm; MS (ESI) *m/z* (%): 238 ($M+Na^+$, 100).

2.4 (2*S*/*R*,3*S*)-1-(*tert*-Butoxycarbonyl)-2,3-dihydroxypiperidine (10)

To a solution of **9** (53 mg, 0.25 mmol) in MeOH (1.3 mL) was added $NaBH_4$ (23 mg, 0.62 mmol) in one potion at −20 ℃. The mixture was stirred for 30 min, then quenched with saturated aqueous $NaHCO_3$ (1 mL) and brine (1 mL). The aqueous layer was extracted with EtOAc (5 × 4 mL), and the combined organic phases were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1∶2) to afford **10** (53 mg, ratio = 1.09∶1, determined by ^{1}H NMR analysis, yield: 100%) as a white solid. m.p. 137－139℃ (EtOAc/MeOH 3∶1); IR (KBr) ν: 3370, 3262, 2967, 2949, 2930, 2899, 2883, 1674, 1412, 1384, 1367, 1269, 1252, 1171, 1149, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, data of the diastereomeric mixture) δ: 1.33－1.40 (m, 1 H, H-5), 1.46 (s, 9 H, $COC(CH_3)_3$), 1.59－1.65 (m, 1 H, H-4), 1.75－1.94 (m, 2 H, H-4, H-5), 2.98－3.08 (m, 1 H, H-3), 3.72－3.83 (m, 2 H, H-6), 5.46 (s, 1 H, H-2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.4, 24.7, 27.3 (3C), 37.9, 66.7, 77.5, 79.9, 155.9 ppm; MS (ESI) *m/z* (%): 240 (M+Na$^+$, 100).

2.5 (3*S*,4*R*/*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-(phenylthio)piperidine (6)

To a mixture of **10** (64 mg, 0.29 mmol) and PPTS (3 mg, 5% wt) in anhydrous CH_2Cl_2 (1.5 mL) was added thiophenol (0.08 mL, 0.73 mmol) under nitrogen atmosphere. The mixture was stirred at room temperature for 12 h, and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1∶5) to afford **6** as an inseparable diastereomeric mixture in a ratio of 48∶52 (89 mg, combined yield: 98%). The diastereomeric ratio was determined by HPLC analysis employing Shim-pack VP-ODS (150 × 4.6) (CH_3OH/H_2O 70∶30, 1.0 mL/min, λ = 215 nm): t_1) 3.7 min (48%), t_2) 4.7 min (52%). White solid. Data of the diastereomeric mixture: m.p. 84－87℃ (EtOAc/P.E. 1∶1); $[\alpha]_D^{20}$ –54.4 (*c* 1.1, $CHCl_3$); IR (KBr) ν: 3439, 3058, 2976, 2940, 2866, 1697, 1677, 1406, 1366, 1274, 1250, 1171, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02－1.35 (m, 9 H, $COC(CH_3)_3$), 1.42－1.60 (m, 2 H, H-5), 1,60－2.05 (m, 3 H, OH, H-4), 3.01－3.31 (m, 1 H, H-6), 3.78－3.92 (br s, 1 H, H-3), 3.96－4.13 (m, 1 H, H-6), 5.58－6.05 (m, 1 H, H-2), 7.21－7.60 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.0, 23.4, 23.9, 26.3, 27.7 (3C), 28.0, 30.0, 38.0, 69.5 (2C), 74.0, 80.6, 80.8 (2C), 128.4, 129.6 (3C), 134.1, 134.7 (2C), 134.8, 153.2, 154.5 ppm; MS (ESI) *m/z* (%): 332 (M+Na$^+$, 100), 348 (M+K$^+$, 47). Anal. cacld for $C_{16}H_{23}NO_3S$: C 62.11, H 7.49, N 4.53; found: C 62.18, H 7.77, N 4.51.

2.6 General procedure for the one-pot synthesis of compounds 11－17 from 6

To a solution of **6** (0.63 mmol) in 3 mL of dry THF at –78℃ was added *n*-BuLi (2.5 M solution in *n*-hexane, 0.63 mmol) and freshly prepared lithium naphthalenide (1.0 M solution in THF, 2.52 mmol). After stirring for 30 min, an electrophile (3.15 mmol) was added. The mixture was stirred at –78℃ for 1 h, and then allowed to warm to 0℃. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column flash chromatography (eluent: EtOAc/PE = 1∶3) to afford the desired products **11**－**17** and the reduced product **2a** in the cases where carbon electrophiles were used.

2.7 (3*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxypiperidine (2a)

Electrophile used: MeOH; product: **2a** (73% yield). Colorless oil. $[\alpha]_D^{20}$ +7.7 (*c* 2.1, $CHCl_3$); $[\alpha]_D^{28}$ +17.0 (*c* 1.2, EtOH) {Lit[57]. $[\alpha]_D^{25}$ +23.0 (*c* 0.65, EtOH)[58], $[\alpha]_D^{25}$ +23.5 (*c* 1.46, EtOH)}; IR (film) ν: 3434, 2976, 2933, 2860, 1694, 1670, 1427, 1366, 1174, 1149, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (m, 10H, $COC(CH_3)_3$, H-5), 1.50－1.56 (m, 1 H, H-5), 1.72－1.83 (m, 1 H, H-4), 1.84－1.97 (m, 1 H, H-4), 2.97－3.18 (m, 2 H, H-2), 3.46－3.62 (br s, 1 H, H-3), 3.67－3.80 (m, 2 H, H-6) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.5, 28.4 (3C), 32.5, 43.6 (m), 50.6 (m), 66.1, 79.7, 155.2 ppm; MS (ESI) *m/z* (%): 224 (M+Na$^+$, 100), 240 (M+K$^+$, 17).

2.8 (3*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxyl-2-D-piperidine (11)

Electrophile used: MeOD; product: **11** (70% yield). Colorless oil. $[\alpha]_D^{20}$ +8.2 (*c* 1.1, $CHCl_3$); IR (film) ν: 3435, 2976, 2933, 2860, 1693, 1670, 1427, 1366, 1271, 1252, 1157, 1069 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, data of the diastereomeric mixture) δ: 1.39－1.58 (m, 11 H, $SiC(CH_3)_3$, H-5), 1.70－1.93 (m, 3 H, H-4, OH), 3.03－3.19 (m, 1 H, H-2), 3.45－3.58 (br s, 1 H, H-3), 3.67－3.77 (m, 2 H, H-6) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.3, 28.2 (3C), 32.4, 43.3 (m), 50.1 (m), 65.8, 79.5, 155.0 ppm; MS (ESI) *m/z* (%): 203 (M+H$^+$,

21), 225 (M+Na^+, 100).

2.9 (2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-(2-hydroxypropan-2-yl)piperidine (12)

Electrophile used: acetone; product: **12** (28% yield); reduced product: **2a** (24% yield). The diastereomeric homogeneity of **12** was determined by HPLC and ^{1}H and ^{13}C NMR analysis. The conditions used for the HPLC analysis: Shim-pack VP-ODS (150×4.6) (CH_3OH/H_2O 70∶30, 1.0 mL/min, λ = 215 nm): t_1) 4.1 min (100%). **12**: colorless oil. $[\alpha]_D^{20}$ −12.6 (*c* 1.9, $CHCl_3$); IR (film) *ν*: 3390, 2976, 2934, 2867, 1693, 1666, 1421, 1368, 1273, 1151, 1069 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.46 (s, 9 H, $COC(CH_3)_3$), 1.74−1.82 (m, 2 H, H-5), 1.83−1.94 (m, 1 H, H-4), 1.96−2.03 (m, 1 H, H-4), 2.95−3.06 (m, 2 H, H-2, OH), 3.58 (s, 1 H, OH), 3.67−3.74 (m, 1 H, H-6), 3.80−3.92 (br s, 1 H, H-6), 4.33−4.42 (br s, 1 H, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 22.6, 28.4 (3C), 30.1, 30.7, 50.8, 66.2, 72.7, 79.8, 80.3, 157.3 ppm; MS (ESI) *m*/*z* (%): 260 (M+H^+, 29), 282 (M+Na^+, 100). HRMS calcd for [$C_{13}H_{25}NO_4$+Na^+]: 282.1681, found: 282.1688.

2.10 (2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-(1-hydroxycyclopentyl)piperidine (13)

Electrophile used: cyclopentanone; product: **13** (41% yield); reduced product: **2a** (20% yield). The diastereomeric homogeneity of **13** was determined by HPLC and ^{1}H and ^{13}C NMR analysis. The conditions used for the HPLC analysis: Shim-pack VP-ODS (150×4.6)(CH_3-OH/H_2O 80∶20, 1.0 mL/min, λ = 215 nm): t_1) 3.3 min (100%). **13**: colorless oil. $[\alpha]_D^{20}$ −5.5 (*c* 1.3, $CHCl_3$); IR (film) *ν*: 3428, 2966, 2934, 2872, 1665, 1422, 1366, 1273, 1254, 1155, 1064, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36−1.50 (m, 9 H, $C(CH_3)_3$), 1.51−1.66 (m, 4 H, H-3', H-4'), 1.67−1.75 (m, 3 H, H-5, OH), 1.76−2.03 (m, 6 H, H-4, H-2′, H-5′), 2.73−2.89 (br s, 1 H, H-2), 2.90−3.04 (br s, 1 H, H-6), 3.76−3.89 (br s, 1 H, H-6), 3.96−4.10 (br s, 1 H, OH), 4.29 (s, 1 H, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 23.8, 24.0, 28.3(3C), 31.8, 38.6, 39.9, 68.6, 80.2, 83.7, 156.5 ppm; MS (ESI) *m*/*z* (%): 308 (M+Na^+, 100), 324 (M+K^+, 33). HRMS calcd for [$C_{15}H_{27}NO_4$+Na^+]: 308.1838, found: 308.1841.

2.11 (2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-(1-hydroxycyclohexyl)piperidine (14)

Electrophile used: cyclohexanone; product: **14** (34% yield); reduced product: **2a** (32% yield). The diastereomeric homogeneity of **14** was determined by HPLC and ^{1}H and ^{13}C NMR analysis. The conditions used for the HPLC analysis: Shim-pack VP-ODS (150×4.6) (CH_3-OH/H_2O 80∶20, 1.0 mL/min, λ = 215 nm): t_1) 3.7 min (100%). $[\alpha]_D^{20}$ −12.1 (*c* 2.2, $CHCl_3$); IR (film) *ν*: 3399, 2933, 2859, 1682, 1664, 1450, 1418, 1366, 1253, 1154, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23−1.26 (m, 2 H, cyclohexyl), 1.41−1.62 (m, 17 H, $C(CH_3)_3$, cyclohexyl), 1.71−1.84 (m, 2 H, H-5), 1.86−2.04 (m, 2 H, H-4), 2.91−3.04 (br s, 1 H, H-2), 3.12−3.21 (br s, 1 H, H-6), 3.52 (s, 1 H, OH), 3.85−3.92 (br s, 1 H, H-6), 4.38 (s, 1 H, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.7, 21.6 (2C), 22.1, 25.6, 28.4 (3C), 31.3, 35.2 (2C), 36.3, 66.8, 73.5, 80.2, 157.6 ppm; MS (ESI) *m*/*z* (%): 300 (M+H^+, 100).

2.12 (2*R*,3*S*,1′*R*/*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-(1-hydroxybutyl)piperidine (15)

Electrophile used: *n*-butanal; product: **15** (combined yield: 55%, ratio = 77:23 determined by HPLC analysis); reduced product: **2a** (25% yield). The diastereomeric ratio was determined by HPLC analysis employing Shim-pack VP-ODS (150 × 4.6) (CH_3OH/H_2O 70∶30, 1.0 mL/min, λ = 215 nm): t_1) 4.1 min (23%), t_2) 5.4 min (77%). A sample of pure major diastereomer was obtained by chromatography separation as colorless oil. $[\alpha]_D^{20}$ +16.4 (*c* 1.7, $CHCl_3$); IR (film) *ν*: 3413, 2957, 2930, 2871, 1694, 1674, 1417, 1366, 1257, 1153, 1096, 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, data of the major diastereomer) δ: 0.95 (s, 3 H, CH_3), 1.35−1.42 (m, 2 H, H-3'), 1.44 (s, 9 H, $C(CH_3)_3$), 1.50−1.64 (m, 3 H, H-4, H-2'), 1.63−1.84 (m, 2 H, H-5), 1.84−1.96 (m, 1 H, H-4), 3.04−3.12 (m, 1 H, H-6), 3.51−3.67 (m, 2 H, H-6, H-2), 3.99 (br s, 2 H, OH, H-1'), 4.10 (m, 1 H, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 18.2, 19.2, 24.1, 28.4 (3C), 30.7, 35.5, 37.1, 69.8, 79.8, 80.1, 151.2 ppm; MS (ESI) *m*/*z* (%): 296 (M+Na^+, 100). HRMS calcd for [$C_{14}H_{27}NO_4$+Na^+]: 296.1838, found: 296.1840.

2.13 (2*S*,3*S*,1′*R*/*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-(1-hydroxyl-2-methylpropyl)piperidine (16)

Electrophile used: isobutyl aldehyde; product: **16** (com-

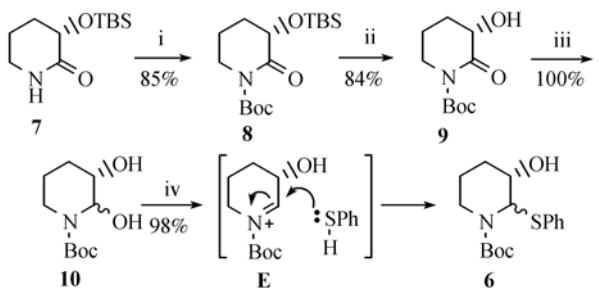
bined yield: 52%, ratio = 43∶57 determined by HPLC analysis); reduced product: **2a** (10% yield). The diastereomeric ratio was determined by HPLC analysis employing Shim-pack VP-ODS (150 × 4.6) (CH_3OH/H_2O 70∶30, 1.0 mL/min, λ=215 nm): t_1) 3.7 min (57%), t_2) 5.5 min (43%). A sample of pure major diastereomer was obtained by chromatography separation as colorless oil. $[\alpha]_D^{20}$ +19.2 (*c* 1.2, $CHCl_3$); IR (film) *v*: 3419, 2965, 2933, 2873, 1682, 1666, 1471, 1418, 1366, 1271, 1253, 1158, 1063, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, data of the major diastereomer) δ: 0.89—0.95 (m, 3 H, CH_3), 0.95—1.04 (m, 3 H, CH_3), 1.45 (s, 9 H, $C(CH_3)_3$), 1.60—1.79 (m, 3 H, H-2', H-5), 1.81—1.99 (m, 2 H, H-4), 2.95—3.14 (m, 1 H, H-2), 3.17—3.32 (m, 1 H, H-6), 3.48 (br s, 1 H, OH), 3.56—3.78 (m, 1 H, H-6), 3.83—3.94 (m, 1 H, H-1'), 4.04 (s, 1 H, OH), 4.11—4.28 (m, 1 H, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, data of the diastereomeric mixture) δ: 13.6, 19.4, 23.5, 27.6(3C), 28.1, 30.7, 54.1, 69.4, 72.2, 79.4, 154.2 ppm; MS (ESI) *m/z* (%): 274 ($M+H^+$, 100), 296 ($M+Na^+$, 36). HRMS calcd for [$C_{14}H_{27}NO_4+H^+$]: 296.1838, found: 296.1842.

2.14 (2*S*,3*S*,1′*R*/*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-(hydroxy(phenyl)methyl)piperidine (17)

Electrophile used: benzaldehyde; product: **17** (combined yield: 71%, ratio = 50∶50 determined by HPLC analysis); reduced product: **2a** (5% yield). The diastereomeric ratio was determined by HPLC analysis employing Shim-pack VP-ODS (150×4.6) (CH_3OH/H_2O 60∶40, 1.0 mL/min, λ = 215 nm): t_1) 4.9 min (50%), t_2) 8.7 min (31%), t_3) 9.7 min (19%). A sample of pure diastereomer was obtained by chromatography separation as colorless oil. $[\alpha]_D^{20}$ −12.3 (*c* 0.9, $CHCl_3$); IR (film) *v*: 3401, 3062, 3029, 2975, 2931, 2864, 1666, 1453, 1423, 1366, 1273, 1252, 1155, 1064, 988 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, data of the pure diastereomer) δ: 1.02—1.40 (m, 9 H, $COC(CH_3)_3$), 1.40—1.56 (m, 2 H, H-5), 1.65—1.88 (m, 2 H, OH, H-4), 1.89—2.10 (m, 1 H, H-4), 3.31 (m, 1 H, H-2), 3.75—3.95 (m, 2 H, H-6), 4.25—4.38 (m, 1 H, H-3), 5.17—5.28 (m, 1 H, H-1'), 7.20—7.41 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7, 27.9, 28.1, 28.4, 28.9, 29.4, 29.9, 38.9, 57.8, 69.3, 72.0, 73.2, 79.7, 79.8, 126.8, 127.0, 127.5, 128.0, 128.1, 128.3, 142.7, 154.1 ppm; MS (ESI) *m/z* (%): 330 ($M+Na^+$, 100).

3 Results and discussion

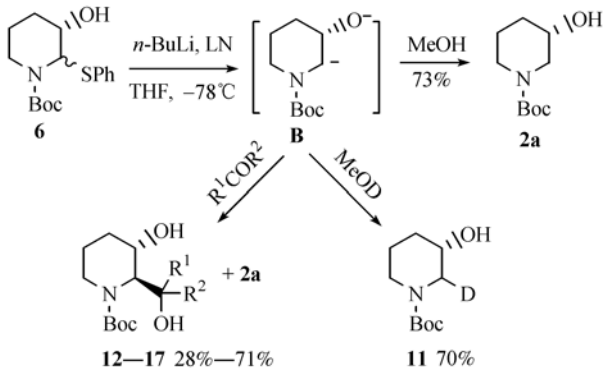
We first focused on the preparation of the synthetic equivalent (**6**) of the 3-piperidinol *N*-α-carbanion **B**. The 3-hydroxypiperidin-2-yl phenyl sulfide **6** was synthesized in four steps from the known 3-silyloxypiperidin-2-one **7** as shown in Scheme 2[56]. The known lactam **7** was converted to imide **9** by treatment with di-*tert*-butyl dicarbonate, followed by desilylation with TBAF. Regioselective partial reduction of imide **9** was achieved with sodium borohydride at –20℃, which afforded the *N*,*O*-acetal **10** as a 52∶48 diastereomeric mixture in quantitative yield. *p*-TsOH-mediated conversion of the diastereomeric mixture of *N*,*O*-acetal **10** with thiophenol gave, *via* the *N*-acyliminium ion intermediate[25−33], the desired thioether **6** in 35% yield, which was improved to 98% by using milder acid PPTS as the promoter. The resulting sulfide **6** is a 52∶48 mixture of two diastereomers as determined by HPLC analysis.



Scheme 2 Synthesis of 3-piperidinol-2-yl phenyl thioether **6**. Reagents and conditions: (i) $(Boc)_2O$, Et_3N, DMAP,CH_2Cl_2, 85%; (ii) TBAF, THF, 0℃, 84%; (iii) $NaBH_4$, MeOH, –20℃, 100%; (iv) PhSH, PPTS, CH_2Cl_2, 98%.

With thioether **6** in hand, we then investigated its reductive lithiation[45,46,50]. Taking into account the previous report on the unsuccessful coupling of the 3-piperidinol *N*-α′-carbanion **A** (generated by reductive lithiation for 2 min) with carbonyl compounds, we reasoned that a complete reductive lithiation of the thioether **6** would be of primordial importance for the success of the coupling with carbonyl compounds. To ensure the complete reductive lithiation, thioether **6** was treated successively with *n*-BuLi (1.0 mol equiv, for the deprotonation of the hydroxyl group) and a freshly prepared lithium naphthalenide (LN, 1.0 M solution in THF, 4.0 mol equiv), and the mixture was stirred for 30 min. The formation of the dianion intermediate **B** was proven by protonation with methanol, which gave the known

N-Boc protected (*S*)-3-hydroxypiperidine **2a**[57,58] in 73% yield (Scheme 3). Capture of the dianion **B** with deuteriomethanol (MeOD) gave the deuterio product **11** in 70% yield. The stereoselectivity of the reaction could not be determined due to the rotamerism arising from the *N*-Boc functional group.



Scheme 3 *In situ* generation and reaction of piperidin-3-oxide *N*-α-carbanions.

Next the stage was set for the investigation on the reaction of the dianion **B** with carbonyl compounds. Thus, the dianion intermediate **B**, generated by reductive lithiation of the thioether **6** (*n*-BuLi, 1.0 mol equiv; LN, 4.0 mol equiv; 30 min.), was reacted with acetone (3 mol equiv), which afforded the desired coupling product **12** as the only observable diastereomer in a yield of 28% (Table 1, entry 3), alongside with the reduced product **2a** (24% yield). Similar results were obtained with cyclopentanone and cyclohexanone (Table 1, entries 4, 5). These results indicate that: (1) the dianion **B** can be trapped by carbonyl compounds; (2) the reaction proceeded with excellent diastereoselectivity at the C-2.

In the same manner, the reaction of transient dianion **B** with *n*-butanal yielded **15** as a mixture of two diastereomers in a ratio of 77∶23 (determined by HPLC analysis) (Table 1, entry 6). Similar reaction with *i*-butanal yielded a diastereomeric mixture of **16** in 43∶57 ratio (Table 1, entry 7).

Because the two diastereomers of both **15** and **16** are inseparable, and rotamerism exists in both **15** and **16** due to the presence of *N*-Boc functional group, their ^{1}H and ^{13}C NMR spectra are quite complex, which prevented a determination of the stereochemistries by NOE technique. However, comparing the results obtained from the reaction with symmetric ketones (only one diastereomer was obtained) and those from the reaction

Table 1 Results of the one-pot synthesis of **11**—**17** from phenyl thioether **6**

Entry	Electrophile	Product (% yield, [a] d.r.)	Side product **2a** (% yield) [a]
1	MeOH	**2a** (73)	
2	MeOD	**11** (70) [b]	
3	MeCOMe	**12** (28, only one diastereomer)	24
4	$(CH_2)_4CO$	**13** (41, only one diastereomer)	20
5	$(CH_2)_5CO$	**14** (34, only one diastereomer)	32
6	*n*-PrCHO	**15** (55, 77:23) [b]	25
7	*i*-PrCHO	**16** (52, 43:57) [b]	10
8	PhCHO	**17** (71, 50:50) [b]	5

a) Isolated yield. b) Combined yield of the diastereomeric mixture; the ratio was determined by HPLC analysis.

with aldehydes (two diastereomers were obtained), we deduced that both **15** and **16** are C′-1 instead of C-2 diastereomeric mixture. The low chemical yields in the α-hydroxyalkylation and the isolation of *N*-Boc-piperidine **2a** might be attributed to the nature of the dianion **B**, that easily abstracts acidic α-proton of the carbonyl compounds. Indeed, reaction of the dianion **B** with benzaldehyde gave the desired coupling products **17** (50∶50 diastereomeric mixture) in a higher yield (71%), alongside with only 5% of the reduced product **2a** (Table 1, entry 8).

4 Conclusions

In summary, we have demonstrated that thioether **6**, easily available from the known lactam **7** in four steps, is a useful synthetic equivalent of novel piperidin-3-hydroxy *N*-α-carbanion synthon **B**, *via* deprotonation and LN-mediated reductive lithiation. Conditions were established for the capture of the 3-piperidinol dianion **B** with a variety of carbonyl compounds, which constitute the first method for α-hydroxyalkylation of 3-piperidinols. The reaction proceeded with high diastereoselectivity at C-2 and mediocre diastereoselectivity at the newly formed carbinolic center when using an aldehyde as electrophile. In view of the rapid development of organocatalysis as a promising field in organic chemistry[59−65], and the value of prolinol derivatives as versatile organocatalysts or chiral ligands, some of the compounds synthesized by the present method may be useful for the development of novel organocatalysts for asymmetric synthesis.

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