Dynamic Kinetic and Kinetic Resolution of *N*-Boc-2-lithiopiperidine

Iain Coldham,*[a] Jignesh J. Patel,[a] Sophie Raimbault[a] and David Whittaker[b]

[a] Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, UK.
Fax: (+44) 114 222 9346; Tel: (+44) 114 222 9428; E-mail: i.coldham@sheffield.ac.uk
[b] AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK.

Electronic Supplementary Information

Experimental procedures and spectroscopic data:

The ligand **5** [(–)-sparteine] was obtained from commercial sources.
The ligand **6** was prepared by addition of 1,4-dibromobutane to cyclohexane-1,2-diamine according to the literature (D. Zhao, C. Chen, F. Xu, L. Tan and R. Tillyer, Organic Syntheses, Eds.; Wiley: New York, 2000, **77**, 12).
The ligands **7**–**9** and *ent*-**9** were prepared according to the literature (T. Mukaiyama, *Tetrahedron*, 1981, **37**, 4111; D.J. Gallagher, S. Wu, N.A. Nikolic and P. Beak, *J. Org. Chem.,* 1995, **60**, 8148).

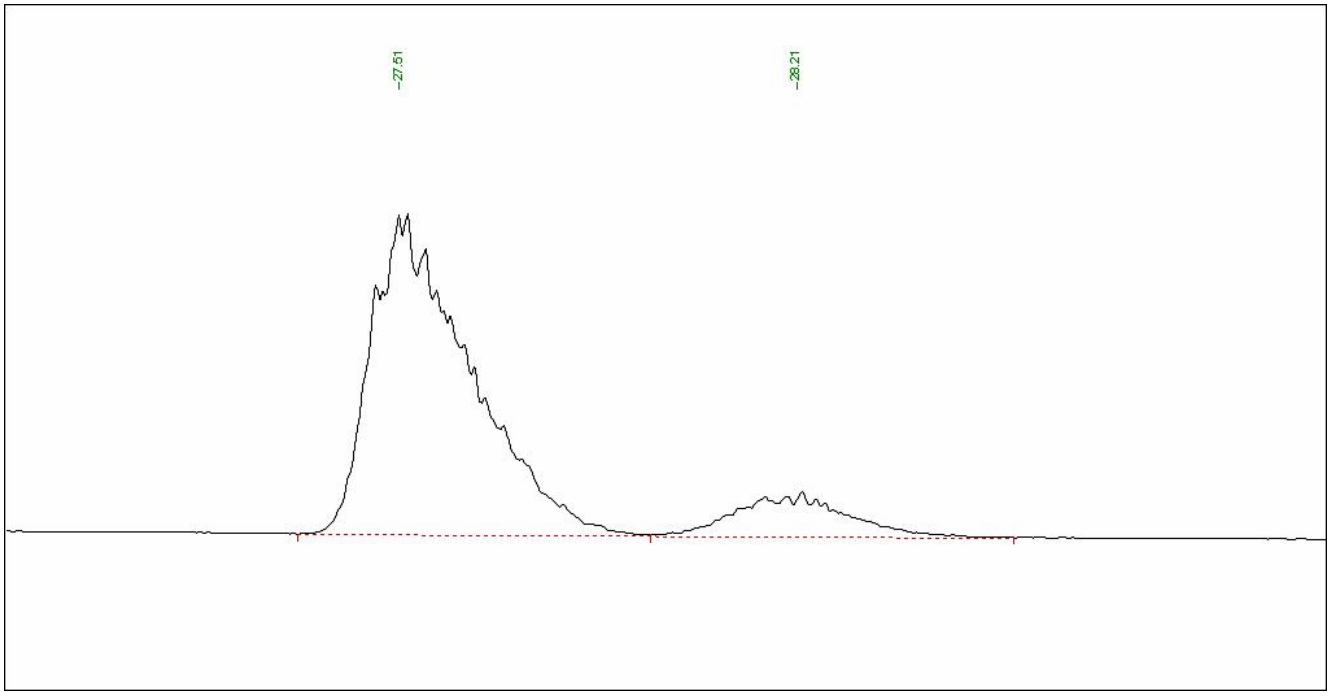
For the formation of (*S*)-**4** (60% yield, er 95:5) by dynamic kinetic resolution, see the main paper: Notes and references section. The same procedure was used for the formation of (*R*)-**4**, using ligand *ent*-**9**.
An authentic sample of (*S*)-**4** was prepared according to the literature (W.F. Bailey, P. Beak, S.T. Kerrick, S. Ma and K.B. Wiberg, *J. Am. Chem. Soc.*, 2002, **124**, 1889); this was converted to the *p*-bromobenzoate derivative as reported and the er (87:13) was determined by chiral HPLC as reported [(Chiracel OD column, hexane–^{i}PrOH 99.5:0.5, flow rate 0.5 mL per min, detection at 254 nm, retention times: 22.8 min (major) and 24.9 min (minor)] and by GC [β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 27.5 min (major) and 28.2 min (minor) (at 85 °C)]. The absolute configuration was verified by X-ray crystal structure analysis of the *p*-bromobenzoate derivative and was in line with that reported (W.F. Bailey, P. Beak, S.T. Kerrick, S. Ma and K.B. Wiberg, *J. Am. Chem. Soc.*, 2002, **124**, 1889).

Procedure for the kinetic resolution to give the piperidine (*R*)-**2**:
N-Boc-piperidine **1** (0.293 g, 1.58 mmol) and TMEDA (0.26 mL, 1.74 mmol) in THF (1.6 mL) were treated with *sec*-BuLi (1.24 mL, 1.74 mmol, 1.4 M in hexanes) at –78 °C. After 3 h, the deprotonated ligand **9** [prepared by adding *n*-BuLi (0.95 mL, 2.38 mmol, 2.5 M in hexanes) to **9** (0.471 g, 2.38 mmol) in THF (1.6 mL) at 0 °C] was added. The electrophile TMSCl (0.4 mL, 3.17 mmol) was added slowly over approximately 1 h. After a further 1 h, the electrophile Bu_3SnCl (0.26 mL, 0.95 mmol) was added. The mixture was allowed to warm to room temperature over 18 h and was quenched with MeOH (1.5 mL). The solvent was evaporated and the residue was purified by column chromatography on silica, eluting with light petroleum (b.p. 40–60 °C)–EtOAc (98:2) to give the piperidine (*S*)-**4** (120 mg, 30%), er 75:25 determined by chiral stationary phase GC (as above) and the piperidine (*R*)-**2** (90 mg, 12%), er 99:1 determined by conversion to the naphthamide derivative (by treatment with *B*-bromocatechol borane then 1-naphthoyl chloride) followed by chiral HPLC [Chiracel OD column, hexane–^{i}PrOH 99.6:0.4, flow rate 0.5 mL per min, detection at 254 nm, retention times: 20.0 min (major) and 28.2 min (minor)]; absolute configuration of the major enantiomer (major peak by chiral HPLC) of the stannane **2** determined by conversion of a sample of enantioenriched stannane **2** to the silane **4** (using *n*-BuLi, Et_2O, TMEDA, –78 °C then TMSCl); data for piperidine (*R*)-**2**: $[\alpha]_D^{24}$ –42.2 (1.8, $CHCl_3$); R_f 0.61 [petrol–EtOAc (96:4)]; HMRS (ES^+) Found: MNa^+ = 498.2348. $C_{22}H_{45}NO_2NaSn$ requires MNa^+ = 498.2370; Data in accordance with the literature (P. Beak and W.K. Lee, *J. Org. Chem.*, 1993, **58**, 1109).

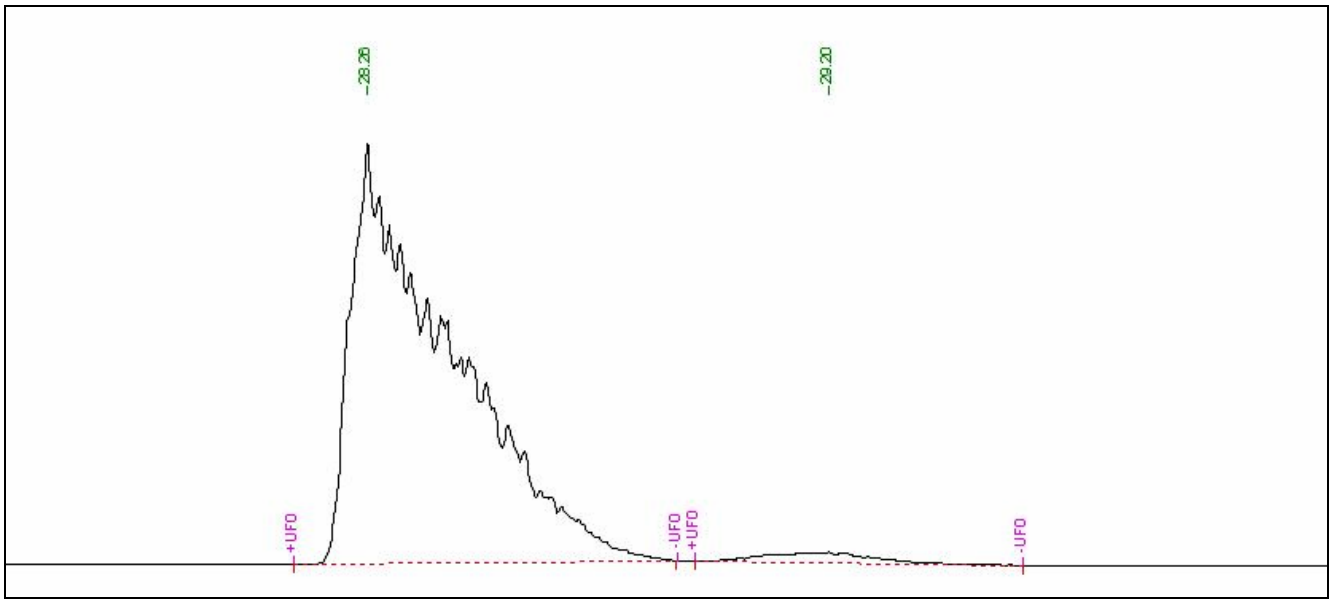
Procedure for the kinetic resolution to give the piperidine (*R*)-**10**:
In the same way as the stannane (*R*)-**2**, *N*-Boc-piperidine **1** (0.163 g, 0.88 mmol), TMEDA (0.15 mL, 0.97 mmol), *sec*-BuLi (0.73 mL, 0.97 mmol, 1.33 M in hexanes) in THF (0.88 mL) and the deprotonated ligand **9** [prepared by adding *n*-BuLi (0.48 mL, 1.14 mmol, 2.4 M in hexanes) to **9** (0.209 g, 1.06 mmol) in THF (0.88 mL) at 0 °C], the electrophile TMSCl (0.22 mL, 1.76 mmol) and the electrophile Me_2SO_4 (0.17 mL, 1.76 mmol) gave, after purification by column chromatography on silica, eluting with light petroleum (b.p. 40–60 °C)–EtOAc (98:2) the piperidine (*S*)-**4** (83 mg, 37%), er 80:20 determined by chiral stationary phase GC as above and the piperidine (*R*)-**10** (34 mg, 19%), er 95:5 determined by chiral stationary phase GC [β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 16.8 min (major) and 17.8 min (minor) (at 85 °C)]. Data for piperidine (*R*)-**10** as a mixture with **1** (**10**:**1** 1:3) $[\alpha]_D^{24}$ –12.0 (0.25, $CHCl_3$), lit. for (*R*)-**10**, er 100:0, $[\alpha]_D$ –46.4 (0.83, $CHCl_3$) (D. Doller, R. Davies and S. Chackalamannil, *Tetrahedron: Asym.*, 1997, **8**, 1275), other data as reported.

GC and HPLC traces:

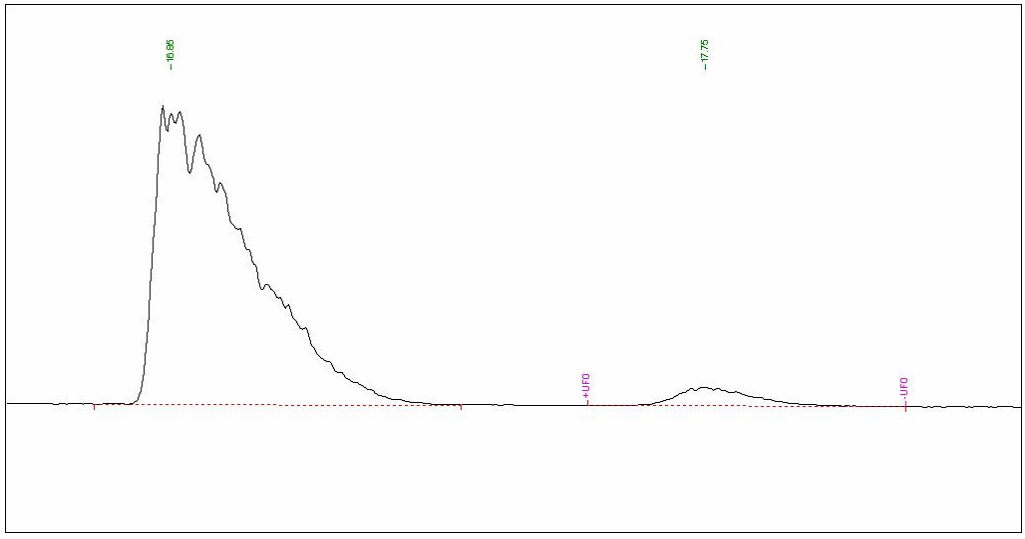
Piperidine (*S*)-**4** (er 87:13) prepared by asymmetric deprotonation using (−)-sparteine.
GC column: β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 27.5 min (major) and 28.2 min (minor) (at 85 °C)



Piperidine (*S*)-**4** (60% yield, er 95:5) by dynamic kinetic resolution



Piperidine (*R*)-**10**: er 95:5
GC column: β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 16.8 min (major) and 17.8 min (minor) (at 85 °C)



Piperidine (*R*)-**2**: er 99:1
HPLC column: Chiracel OD column, hexane–^{i}PrOH 99.6:0.4, flow rate 0.5 mL per min, detection at 254 nm, retention times: 20.0 min (major) and 28.2 min (minor)