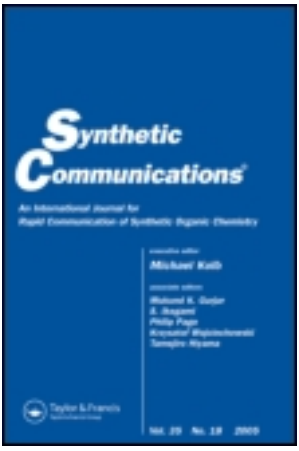


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

ASYMMETRIC SYNTHESIS OF N-SUBSTITUTED (R)-2-[(PYRROLIDIN-1-YL)METHYL]PYRROLIDINES

Justin R. Harrison [a] & Peter O'Brien [b]
[a] Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK
[b] Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK
Published online: 09 Nov 2006.

To cite this article: Justin R. Harrison & Peter O'Brien (2001) ASYMMETRIC SYNTHESIS OF N-SUBSTITUTED (R)-2-[(PYRROLIDIN-1-YL)METHYL]PYRROLIDINES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:8, 1155-1160, DOI: 10.1081/SCC-100103998

To link to this article: http://dx.doi.org/10.1081/SCC-100103998

SYNTHETIC COMMUNICATIONS, 31(8), 1155–1160 (2001)

ASYMMETRIC SYNTHESIS OF *N*-SUBSTITUTED (*R*)-2-[(PYRROLIDIN-1-YL)METHYL]PYRROLIDINES

Justin R. Harrison and Peter O'Brien*

Department of Chemistry, University of York,
Heslington, York YO10 5DD, UK

ABSTRACT

The preparation of (*R*)-2[(pyrrolidin-1-yl)methyl] pyrrolidine and (*R*)-1-methyl-2-[(pyrrolidin-1-yl)methyl]pyrrolidine (both in 85% ee) is reported. The key step in the synthesis involves the sparteine-mediated asymmetric functionalization of *N*-Boc pyrrolidine and subsequent trapping with 1-pyrrolidine-carbonyl chloride.

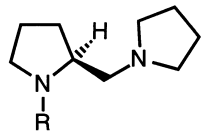
Diamines such as (*S*)-**1-4** prepared in just a few steps from natural (*S*)-proline are extremely useful chiral reagents and ligands for asymmetric synthesis (vide infra). In addition, there is biological interest in the synthesis of structurally related compounds: compounds like **1-4** are prolyl endopeptidase inhibitors[1] and ligands for central nervous system receptors.[2]

The lithium amide of (*S*)-**1**, introduced by Asami,[3–5] is a popular chiral base.[6–8] It can be used to rearrange *meso*-epoxides to enantiomerically enriched allylic alcohols, and asymmetric syntheses of (−)-carbovir[9] and (+)-faranal[10] utilize chiral base (*S*)-**1**. A computational study on the reaction of lithiated (*S*)-**1** with cyclohexene oxide has recently been completed.[11]

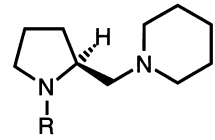
* Corresponding author.

However, since only (*S*)-**1** is readily available, its use in synthesis is limited. Asami addressed this problem by preparing (*S*)-proline-derived diamines that gave, with limited success, enantiocomplementary results to diamine (*S*)-**1**.[12] In contrast, Mori et al. chose to prepare diamine (*R*)-**1** from expensive (*R*)-proline in their synthesis of lasiol.[13]

Diamines (*S*)-**2-4**, introduced by Mukaiyama and Kobayashi,[14] have proven to be very useful reagents for asymmetric Mukaiyama aldol reactions. Recently, such methodology was used on two separate occasions in the total asymmetric synthesis of Taxol reported by Mukaiyama and coworkers.[15] Kobayashi and Horibe have extended the methodology so that, by suitable choice of proline-derived diamine, it is possible to prepare either enantiomer of *syn*-adol products.[16] Nevertheless, ready access to the enantiomeric ligands (*R*)-**2-4** would be advantageous for synthetic chemists.



(*S*)-**1**; R = H
(*S*)-**2**; R = Me

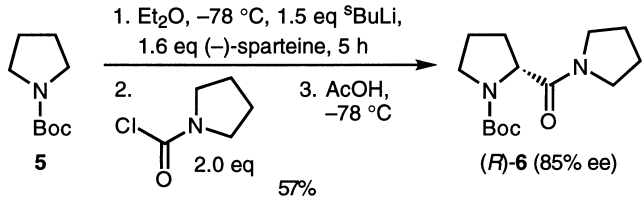


(*S*)-**3**; R = Me
(*S*)-**4**; R = Et

The need for chiral diamines (*R*)-**1-4** prompted us to explore a new approach for their synthesis. We recognized that the required stereochemistry could be set up by asymmetric functionalization of *N*-Boc pyrrolidine **5** using (−)-sparteine as reported by Beak et al.[17–20]. Using this approach, we have completed the synthesis of (*R*)-**1** and (*R*)-**2** and this is the subject of the present communication.

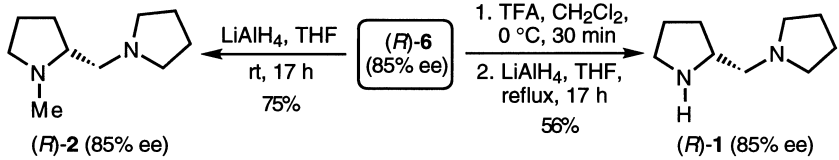
Lithiation of *N*-Boc pyrrolidine **5** at −78°C using s-butyllithium and (−)-sparteine was followed by reaction with commercially available 1-pyrrolidinecarbonyl chloride. The reaction was quenched with acetic acid after just 5–10 min at −78°C. Work-up and purification by chromatography afforded amide (*R*)-**6** {$[\alpha]_D + 36.6$ (*c* 0.9 in MeOH); lit.,[1] $[\alpha]_D + 37.1$ (*c* 1.0 in MeOH)} in 57% yield and 85% ee (established by conversion into diamines (*R*)-**1** and (*R*)-**2** and determination of their enantiomeric excesses, vide infra). If the reaction was left any longer than 10 min before quenching, we observed a compromise in the enantiomeric excess obtained.

Amide (*R*)-**6** was converted into diamine (*R*)-**1** {$[\alpha]_D - 6.0$(*c* 0.8 in EtOH); lit.,[3] $[\alpha]_D + 8.2$ (*c* 2.4 in EtOH) for (*S*)-**1**} by *N*-Boc deprotection using TFA and subsequent lithium aluminium hydride reduction. Diamine (*R*)-**1** generated in this way had 85% ee as shown by conversion into diastereomeric Mosher's amides. Alternatively, diamine (*R*)-**2** {$[\alpha]_D + 66.8$



Scheme 1.

(c 0.8 in EtOH); lit.,[14] $[\alpha]_D$−84.5 (c 0.5 in EtOH) for (*S*)-**2**} was obtained by direct lithium aluminium hydride reduction of amide (*R*)-**6**. The enantiomeric excess (85%) of diamine (*R*)-**2** was verified by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent (*R*)-2,2,2-trifluoro-1-(9-anthryl) ethanol.



Scheme 2.

In summary, we have reported a simple way of preparing diamines (*R*)-**1** and (*R*)-**2** in good enantiomeric excess. Extension of the methodology to include the preparation of other useful diamines such as (*R*)-**3** and (*R*)-**4** and related compounds of biological interest is possible by simple variation of the carbonyl chloride and subsequent synthetic manipulations of the intermediate *N*-Boc amide.

EXPERIMENTAL

THF was dried over sodium-benzophenone and distilled before use. CH_2Cl_2 was dried over calcium hydride and distilled before use. *N*-Butyllithium was titrated against *N*-benzylbenzamide before use.[21] All reactions were carried out under oxygen-free nitrogen using over-dried glassware. For Kugelrohr distillations, the temperatures quoted correspond to the oven temperatures. Melting points were measured on an Electrothermal IA 9100 digital melting point apparatus. Optical rotations were recorded on

a Jasco DIP-370 polarimeter (using the sodium D line; 589 nm) at 20°C and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

(*R*)-1-[*N*-(tert-Butoxycarbonyl)prolinamido]pyrrolidine (*R*)-8

s-Butyllithium (1.8 cm^3 of a 1.28 M solution in cyclohexane, 2.3 mmol) was added dropwise over 5 min to a stirred solution of *N*-Boc pyrrolidine **5** (269 mg, 1.5 mmol) and freshly distilled (−)-sparteine (0.58 cm^3, 2.5 mmol) in Et_2O (10 cm^3) at −78°C under nitrogen. After stirring at −78°C for 5 h, 1-pyrrolidinecarbonyl chloride (Lancaster Synthesis, 0.34 cm^3, 3.0 mmol) was added dropwise over 5 min, followed by the immediate dropwise addition of acetic acid (0.43 cm^3, 7.5 mmol). After allowing to warm to room temperature, water (4 cm^3) was added and the reaction mixture was extracted with EtOAc (3×10 cm^3). The combined organic extracts were washed with 5% phosphoric acid (H_3PO_4; 2 × 4 cm^3) and brine (10 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product as an oil. Purification by flash chromatography with EtOAc as eluent gave amide (*R*)-**8** (235 mg, 57%) as a white solid identical spectroscopically to that previously reported, m.p. 79°–81°C (lit.,[2] 83°–84°C); $[\alpha]_D$+36.6 (*c* 0.9 in MeOH); lit.,[1] $[\alpha]_D$+37.1 (*c* 1.0 in MeOH).

(*R*)-2-[(Pyrrolidin-1-yl)methyl]pyrrolidine (*R*)-1

Trifluoroacetic acid (0.7 cm^3, 9.1 mmol) was added dropwise to a stirred solution of amide (*R*)-**8** (210 mg, 0.8 mmol)in CH_2Cl_2(1.4 cm^3) at 0°C under nitrogen. After stirring at room temperature for 30 min, 10% aqueous sodium hydroxide solution (10 cm^3) was added and the mixture was extracted with CH_2Cl_2 (3×10 cm^3). The combined organic extracts were dried (K_2CO_3) and evaporated under reduced pressure. The residue was dissolved in THF (13 cm^3) under nitrogen. Then lithium aluminium hydride (140 mg, 3.7 mmol) was added and the resulting suspension was heated at reflux for 17 h. After cooling to room temperature, Et_2O (20 cm^3) and excess solid hydrated sodium sulfate were added. The mixture was stirred for 1 h and the solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure to give the crude product as a brown oil. Purification by Kugelrohr distillation gave diamine (*R*)-**1** (68 mg, 56%) as a colorless oil identical spectroscopically to that previously reported, b.p. 95–105°C/14 mm Hg; {$[\alpha]_D - 6.0$ (*c* 0.8 in EtOH); lit.,[3] $[\alpha]_D + 8.2$ (*c* 2.4 in EtOH) for (*S*)-**1**}.

(*R*)-1-Methyl-2-[(pyrrolidin-1-yl)methyl]pyrrolidine (*R*)-2

Lithium aluminium hydride (150 mg, 3.9 mmol) was added dropwise to a stirred solution of amide (*R*)-**8** (213 mg, 0.8 mmol) in THF (8 cm^3) at room temperature under nitrogen. The resulting suspension was stirred at room temperature for 48 h. Then excess solid hydrated sodium sulfate was added. The mixture was stirred for 1 h and the solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure to give the crude product as a brown oil. Purification by Kugelrohr distillation gave diamine (*R*)-**2** (100 mg, 75%) as a colorless oil identical spectroscopically to that previously reported, b.p. 100°–110°C/14 mm Hg; $\{[\alpha]_D + 66.8$. (*c* 0.8 in EtOH); lit.,[14] $\{[\alpha]_D - 84.5$ (*c* 0.5 in EtOH) for (*S*)-**2**$\}$.

ACKNOWLEDGMENTS

We thank The Leverhulme Trust for the award of a fellowship (to JRH).

REFERENCES

1. Arai, H.; Nishioka, H.; Niwa, S.; Yamanaka, T.; Tanaka, Y.; Yoshinaga, K.; Kobayashi, N.; Naoyoshi, M; Ikeda, Y. Chem. Pharm. Bull. **1993**, *41*, 1583.
2. de Coast, B.R.; Dominguez, C.; He, X.-S.; Williams, W.; Radesca, L.; Bowen, W. J. Med. Chem. **1992**, *35*, 4334.
3. Asami, M. Bull. Chem. Soc. Jpn. **1990**, *63*, 721.
4. Asami, M.; Ishizaki, T.; Inoue, S. Tetrahedron: Asymmetry **1994**, *5*, 793.
5. Asami, M.; Inoue, S. Tetrahedron **1995**, *51*, 11725.
6. O′Brien, P. J. Chem. Soc., Perkin Trans.1 **1998**, 1439.
7. Hodgson, D.M.; Gibbs, A.R.; Lee, G.P. Tetrahedron **1996**, *52*, 14361.
8. Asami, M. J. Synth. Org. Chem., Jpn. **1996**, *54*, 188.
9. Asami, M.; Takahashi, J.; Inoue, S. Tetrahedron: Asymmetry **1994**, *5*, 1649–1652.
10. Mori, K.; Murata, N. Liebigs Ann. **1995**, 2089.
11. Nilsson Lill, S.O.; Arvidsson, P.I.; Ahlberg. P. Tetrahedron: Asymmetry **1999**, *10*, 265.
12. Asami, M.; Kirihara, H. Chem. Lett. **1987**, 389.
13. Kasai, T.; Watanabe, H.; Mori, K. Bioorg. Med. Chem. Lett. **1993**, *1*, 67.

14. Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. J. Am. Chem. Soc. **1991**, *113*, 4247.
15. Mukaiyama, T.; Shiina, T.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.-I.; Hasegawa, M.; Yamada, K.; Saitoh, K. Chem. Eur. J. **1999**, *5*, 121.
16. Kobayashi, S.; Horibe, M. Chem. Eur. J. **1997**, *3*, 1472.
17. Beak, P.; Kerrick, S.T.; Wu, S.; Chu, J. J. Am. Chem. Soc. **1994**, *116*, 2131.
18. Nikolic, N.A.; Beak, P. Org. Synth. **1996**, *74*, 23.
19. Hoppe, D.; Hense, T. Angew. Chem. Int. Ed. Engl. **1997**, *36*, 2282.
20. Beak, P.; Basu, A.; Gallagher, D.J.; Park, Y.S.; Thayumanavan, S. Acc. Chem. Res. **1996**, *29*, 552.
21. Burchat, A.F.; Chong, J.M.; Nielson, N. J. Organomet. Chem. **1997**, *542*, 281.

Received May 5, 2000