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Evaluation of a sparteine-like diamine for asymmetric synthesis

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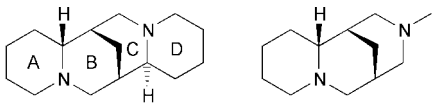
Evaluation of a sparteine-like diamine indicates that only the ABC rings of sparteine are required for high enantioselectivity in the lithiation–substitution of *N*-Boc pyrrolidine.

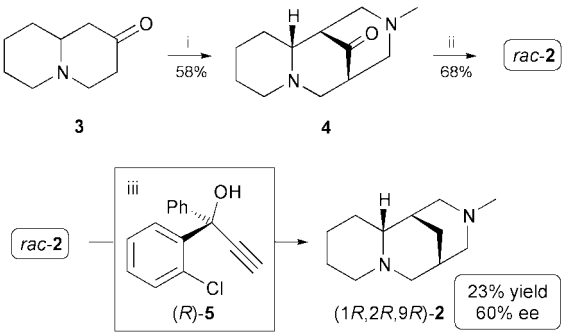
Sparteine **1** is a naturally occurring alkaloid extracted from plants such as Scotch Broom. It is commercially available and has been widely used as a chiral diamine ligand in asymmetric synthesis over the last 30 years.[1] For example, asymmetric lithiation–electrophilic quench using the combination of sparteine and alkyllithiums on a wide range of substrates occurs routinely with > 90% enantioselectivity. The groups of Hoppe[2] and Beak[3] have led the way with pioneering contributions in the applications of sparteine in synthesis. More recently, Hoppe *et al.*[4] and Wiberg and Bailey[5] have carried out theoretical calculations of transition state energies aimed at elucidating how sparteine exerts such high levels of enantiodifferentiation.



One of the main limitations of using sparteine in synthesis is that it is only commercially available in one enantiomeric form. Attempts to find other chiral diamine ligands capable of matching the enantioselectivity of sparteine have been moderately successful.[6,7] With the long term aim of developing a ligand that will function as the enantiomer of sparteine, we have investigated whether diamine **2**, which lacks the D-ring of sparteine as well as one of the chiral centres, mimicks sparteine sufficiently to give high enantioselectivity. Structural comparisons of diamines **1** and **2** complexed to lithium together with a recent calculated transition state for reaction[5] suggested that the D-ring of sparteine was not a key element in the enantiodiscriminating process. In this communication, we provide experimental evidence in support of this conjecture.

Although racemic diamine **2** is a known compound[8] and has found recent application in the functionalisation of terminal epoxides,[9] there have been no reports on the preparation of enantiomerically enriched diamines like **2**. An approach from amino acids investigated in our laboratory[10] was unsuccessful due to unavoidable racemisation in one of the steps. Thus, we resorted to resolution as a means of preparing non-racemic diamine **2** as outlined in Scheme 1.

Racemic diamine **2** was prepared using a published route:[8] double Mannich reaction of ketone **3** gave a single diastereoisomer of **4** (58% yield) which was converted into the required diamine **2** (68% yield) using Wolff–Kishner reduction. Unfortunately, we were unable to develop a resolution protocol for racemic **2** using commercial chiral acids (*e.g.* tartaric acid and derivatives, malic acid and camphorsulfonic acid). However, we had more success with resolution by inclusion complex formation using a method previously described by Toda *et al.*[11] Toda had discovered that it was possible to use naturally ocurring sparteine **1** to resolve racemic acetylinic alcohols such as **5**. Since diamine **2** is structurally similar to sparteine, we speculated that enantiomerically pure **5** could be used for resolution.

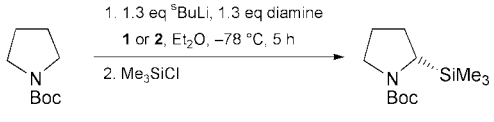


Scheme 1 *Reagents and conditions*: i, $MeNH_2$, $(CH_2O)_n$, AcOH, MeOH, reflux, 16 h; ii, N_2H_4, H_2O, KOH, diethylene glycol, reflux, 2 h; iii, acetone, evaporation over 64 h.†

Thus, Toda's method was employed to synthesise alcohol (*R*)-**5** of 98% ee (by chiral HPLC on an Astec Cyclobond I 2000-RSP column) and it was used in turn to partially resolve diamine **2**. In this way, we obtained a 23% yield of enantiomerically enriched diamine **2**† ($[\alpha]_D$ −15.7 (*c* 0.5 in EtOH); ~60% ee by chiral shift NMR). This resolution was reproducible in the 50–60% ee range and after repeating it a few times, we obtained a sufficient quantity of diamine **2** of ~55% ee. Since alcohol (*R*)-**5** had been obtained *via* crystal formation with sparteine **1**, it seemed likely that resolved diamine **2** (isolated *via* crystal formation with (*R*)-**5**) would have the same *absolute* stereochemistry as the ABC rings of sparteine.

With diamine **2** of ~55% ee in hand, we elected to directly compare it with sparteine **1** using lithiation of *N*-Boc pyrrolidine **6** and subsequent trapping with Me_3SiCl.[6,12] The results are presented in Table 1. Using sparteine **1**, we obtained a 73% isolated yield of silylated pyrrolidine (*S*)-**7** of 95% ee (by chiral GC). Under the same conditions, use of diamine **2** of ~55% ee gave an unoptimised 41% yield of silylated pyrrolidine (*S*)-**7** of 53% ee (by chiral GC).‡ The sense of asymmetric induction was

Table 1 Lithiation–substitution of *N*-Boc pyrrolidine using diamines **1** and **2**



Diamine	Yield of (*S*)-**7** (%)[a]	ee (%)[b]
Sparteine **1**	73	95
(1*R*,2*R*,9*R*)-**2** (~55% ee)	41	53

[a] Isolated yield after column chromatography; [b] Enantiomeric excess determinined by chiral GC on a Chiraldex G-PN 20 m × 0.25 mm id (γ-cyclodextrin, propionyl derivative in the 3-position) column.

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the same in both reactions indicating that resolved diamine **2** does indeed possess the same absolute stereochemistry as the ABC rings of sparteine. More importantly, however, the results presented in Table 1 provide the first experimental evidence that only the ABC rings of sparteine **1** are required for high enantioselectivity in the lithiation of *N*-Boc pyrrolidine **6**.

In summary, our results indicate that diamine **2** exhibits essentially the same level of enantioselectivity as sparteine **1** in the lithiation of *N*-Boc pyrrolidine **6**. Thus, we conclude that the sparteine D-ring is superfluous and is not a prerequisite for high enantioselectivity.

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Notes and references

† *Resolution of diamine rac*-**2**: A solution of freshly distilled diamine *rac*-**2**[8] (742 mg, 3.8 mmol) in acetone (3 cm^3) was added dropwise to a solution of alcohol (*R*)-**5** (929 mg, 3.8 mmol; 98% ee by chiral HPLC on an Astec Cyclobond I 2000-RSP column) in acetone (3 cm^3) at rt. The solvent was allowed to evaporate slowly by standing at rt for 64 h and pale yellow crystals formed. Petrol (5 cm^3) was added and the crystals were collected by filtration and washed well with petrol (3 × 5 cm^3). The crystals were dissolved in Et_2O (15 cm^3) and 2 M $HCl_{(aq)}$ (10 cm^3), the layers were separated and the organic layer was extracted with 2 M $HCl_{(aq)}$ (2 × 10 cm^3). Then, 20% $NaOH_{(aq)}$ was added to the combined aqueous layers until pH 9 and the solution was extracted with Et_2O (3 × 10 cm^3), dried (K_2CO_3) and evaporated under reduced pressure to give diamine (1*R*,2*R*,9*R*)-**2** (171 mg, 23%; ~60% ee by ^1H NMR spectroscopy in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) as a colourless oil, $[\alpha]_D$ −15.7 (*c* 0.5 in EtOH). Treatment of the petrol washings in the same way as described above for the crystals gave diamine (1*S*,2*S*,9*S*)-**2** (503 mg, 68%; ~30% ee by ^1H NMR spectroscopy in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) as a colourless oil, $[\alpha]_D$ +6.1 (*c* 0.6 in EtOH).

‡ In theory, silylated pyrrolidine (*S*)-**7** of >55% ee could have been generated if a non-linear effect was occurring. Our results clearly indicate the absence of a non-linear effect and are in line with the calculated transition state for reaction[5] which invokes deprotonation by a monomeric complex.

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