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A Readily-Accessible (+)-Sparteine Surrogate

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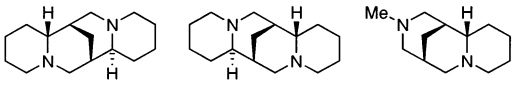
(−)-Sparteine, a naturally occurring and commercially available chiral diamine, has proved to be an extremely useful chiral ligand for a wide range of asymmetric reactions.[1] Following pioneering contributions from the groups of Hoppe and Beak, (−)-sparteine can now be considered unrivalled in its utility as a chiral ligand for lithium in asymmetric deprotonations, substitutions, carbometalations and directed *ortho*-metalations.[2] In addition, new and exciting results on the use of (−)-sparteine as a ligand for *palladium*[3,4] and *magnesium*[5] have recently been disclosed. Given the continued, active research into (−)-sparteine-mediated reactions and the fact that (+)-sparteine is not commercially available, the development of a chiral ligand that behaves as the enantiomer of (−)-sparteine is of paramount importance.

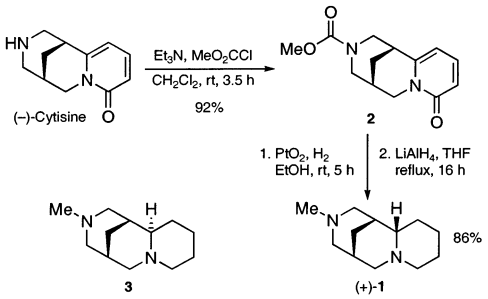
There have been two previous syntheses of (+)-sparteine: Ebner et al. resolved racemic lupanine (isolated from its natural source) and converted it into (+)-sparteine,[6] and most recently, Aubé et al. reported an elegant, multistep total asymmetric synthesis of (+)-sparteine.[7] Over the past few years, other groups[8] have tried to develop (−)-sparteine surrogates that either give enantiocomplementary asymmetric induction to (−)-sparteine or are readily available in *both* enantiomeric forms.[9] However, success has been limited.



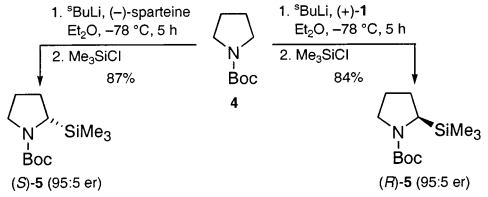
We sought a general solution to the limitation that sparteine is only commercially available as its (−)-antipode by developing a simple and short synthetic sequence that would furnish multigram quantities of a (+)-sparteine equivalent *without recourse to resolution*. Our approach uses the structure of (−)-sparteine as a guide: on inspection of the calculated transition state for lithiation of *N*-Boc pyrrolidine with (−)-sparteine,[10] we reasoned that diamine (+)-**1**, which lacks one of the rings and chiral centers of (+)-sparteine, would be a good (+)-sparteine mimic. Using partially resolved diamine (−)-**1** (er of approximately 78:22), we showed the viability of our concept in one reaction, the lithiation−electrophilic quench of *N*-Boc pyrrolidine.[11] However, there were serious limitations in our synthetic strategy to enantioenriched diamine (−)-**1**. In this work, we report a simple, high-yielding, gram-scale, and short synthesis of diamine (+)-**1** and we demonstrate its use as a (+)-sparteine equivalent in four different reactions.

In developing a synthesis of diamine (+)-**1** (Scheme 1), we recognized that another naturally occurring alkaloid, (−)-cytisine, is equipped with the required bispidine framework and the correct absolute stereochemistry needed for (+)-sparteine mimic **1**. Furthermore, the isolation of (−)-cytisine from *Laburnum anagyroides* seeds has been fully described[12] and is a simple and high-yielding process: Lasne et al. recovered 15−18 g (1.5−1.8% mass yield) of (−)-cytisine from 1 kg of *Laburnum anagyroides* seeds (ca. £35 per kg from Vilmorin, France). In our hands, the (−)-cytisine extraction process was an easy and reproducible procedure. Next, we protected the secondary amine as its methoxy carbamate[12] as a late-stage $LiAlH_4$ reduction would generate the required *N*-methyl substituent. Pyridone **2** was obtained in 92% yield.

Scheme 1



Scheme 2



Hydrogenation of pyridone **2** with Adams' catalyst and subsequent reduction with $LiAlH_4$ in refluxing THF gave diamine (+)-**1** in 86% distilled yield over the two steps (Scheme 1). The diastereomeric system **3** is known,[13] and on examination of the ^1H NMR spectra of (+)-**1**, none of diamine **3** was produced: hydrogenation of **2** had occurred exclusively on the less hindered *exo* face as expected.[14] The er of diamine (+)-**1** {$[\alpha]_D$ +26.5 (*c* 1 in EtOH)} was established as ≥95:5 by chiral shift NMR spectroscopy in comparison with a racemic sample. To summarize, gram-scale quantities of diamine (+)-**1** can be prepared in 79% overall yield via a simple, three-step route from the easily extracted (−)-cytisine (see Supporting Information for full experimental details).

With a convenient synthesis of diamine (+)-**1** in hand, we set about demonstrating that it would behave as a (+)-sparteine equivalent. Beak's lithiation-electrophilic trapping of *N*-Boc pyrrolidine **4**[8a,11,15] to give trimethylsilyl adduct **5** was chosen as an appropriate test reaction. With (−)-sparteine, we obtained an 87% yield of (*S*)-**5** with an er of 95:5 whereas reaction in the presence of diamine (+)-**1** generated an 84% yield of (*R*)-**5** with an identical er of 95:5 (Scheme 2). Thus, (−)-sparteine and diamine (+)-**1** behave in an enantiocomplementary fashion.

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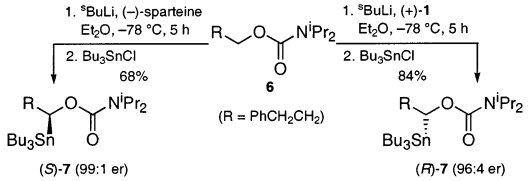
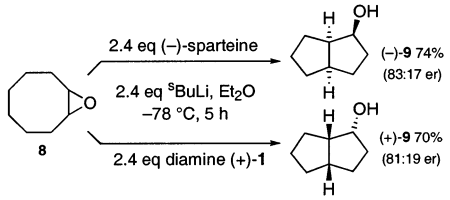
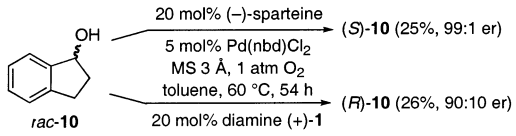
Scheme 3



Scheme 4



Scheme 5



We also compared (−)-sparteine and diamine (+)-**1** in a "Hoppe-style"[16] asymmetric lithiation α to oxygen in an alkyl carbamate. Specifically, we examined the transformation[17] of carbamate **6** into stannylated adduct **7**. In our hands, lithiation of **6** in the presence of (−)-sparteine followed by trapping with Bu_3SnCl gave stannane (*S*)-**7** with an er of 99:1. In contrast, carrying out the same reaction using diamine (+)-**1** as the ligand generated an 84% yield of stannane (*R*)-**7** with a slightly lower er of 96:4 (Scheme 3).

The enantioselective α-lithiation and rearrangement of *cis*-cyclooctene oxide **8** into bicyclic alcohol **9**, a process popularised by Hodgson et al.[2c,18] was also studied. Although optimum results for this reaction typically involve the use of *iso*-propyllithium and (−)-sparteine or (−)-α-isosparteine at −98 °C, we elected to conduct our comparative experiments using commercially available *sec*-butyllithium at −78 °C (for 5 h). Using *sec*-butyllithium/(−)-sparteine, we obtained a 74% yield of alcohol (−)-**9** (er of 83:17). With (+)-**1**, an enantiocomplementary result was observed: alcohol (+)-**9** (er of 81:19) was isolated in 70% yield (Scheme 4).

As a final example, we selected a reaction that uses a sub-stoichiometric amount of (−)-sparteine and does not utilize an organolithium reagent: the oxidative kinetic resolution of racemic 1-indanol **10** using Pd(II), a diamine ligand and molecular oxygen.[4,5] Using conditions reported by Ferraira and Stolz,[4] we obtained a 25% yield of 1-indanol (*S*)-**10** (er of 99:1) with (−)-sparteine (Scheme 5), a result that is consistent with the literature. In contrast, with diamine (+)-**1**, a 26% yield of enantiomeric 1-indanol (*R*)-**10** (er of 90:10) was obtained. These initial results indicate that diamine (+)-**1** is not the optimal ligand for the oxidative kinetic resolution of racemic 1-indanol and further ligand optimization is required to match the enantioselectivity observed with (−)-sparteine.

In summary, we have demonstrated that four different reactions with (−)-sparteine and diamine (+)-**1** proceed with similar enantioselectivity but *in the opposite sense*. This is the first chiral diamine ligand that behaves as a (+)-sparteine surrogate. Significantly, multigram quantities of diamine (+)-**1** can be prepared via a simple, three-step route (79% overall yield), and (+)-**1** can be recovered after acid−base extraction (in 65−80% yield) and reused (after distillation). Furthermore, in contrast to (−)-sparteine, structural modification in chiral bispidines derived from (−)-cytisine can be envisaged to optimize the enantioselectivity for different processes/metals.

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Supporting Information Available: Full experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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