Basic instinct: design, synthesis and evaluation of (+)-sparteine surrogates for asymmetric synthesis

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(−)-Sparteine, a naturally occurring lupin alkaloid, is widely used as a chiral ligand for asymmetric synthesis. To address the limitation that sparteine is only available as its (−)-antipode, our group introduced a family of (+)-sparteine surrogates that are structurally similar to (+)-sparteine but lack the D-ring. After briefly summarising the design aspect, this feature article provides an overview of synthetic routes to the sparteine surrogates and a detailed comparison with (−)-sparteine in a range of asymmetric reactions. The main conclusions are: (i) the (+)-sparteine surrogates are most easily prepared starting from (−)-cytisine extracted from *Laburnum anagyroides* seeds; (ii) in nearly all examples, use of the (+)-sparteine surrogates produced essentially equal but opposite enantioselectivity compared to (−)-sparteine and (iii) the *N*-Me-substituted (+)-sparteine surrogate is the most useful and versatile of those investigated.

Introduction

(−)-Sparteine (Fig. 1) is the most well-known naturally occurring chiral diamine used in asymmetric synthesis. The commercial availability of (−)-sparteine reflects its easy isolation by extraction of papilionaceous plants such as Scotch broom (*Cytisus scoparius*).[1] Most frequently, (−)-sparteine is combined with organolithium reagents to produce efficient chiral bases or chiral nucleophiles[2] but (−)-sparteine has also been successfully used in tandem with Mg, Cu, Pd and Zn. As shown in Fig. 1, (−)-sparteine is equipped with an attractive metal-chelating conformation.

Unfortunately, (+)-sparteine is not readily available in significant quantities[3] even though it is a natural product.[4] The lack of availability of (+)-sparteine is a serious limitation in sparteine-mediated asymmetric syntheses as any chiral ligand should ideally be available in *both* enantiomeric forms. In October 1997, our group initiated a programme of research with the specific aim of addressing this "(+)-sparteine problem". To do this, we set out to develop short and efficient syntheses of "sparteine-like" diamines that we hoped would function as (+)-sparteine mimics. This feature article relates our initial design process and summarises the synthesis of all of the known (+)-sparteine surrogates (by ourselves and other groups). In addition, a detailed overview of the use of the (+)-sparteine surrogates in a range of enantioselective transformations is provided.

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Designing the (+)-sparteine surrogates

Our interest in addressing the "(+)-sparteine problem" was initiated by a 1995 paper from the Beak group[5] in which the evaluation of ~20 chiral ligands as substitutes for (−)-sparteine was described. Interestingly, none of the other chiral ligands could match (−)-sparteine in terms of yield/enantioselectivity for the asymmetric deprotonation of *N*-Boc pyrrolidine. In the paper, Beak included Chem3D® space-filling diagrams of TMEDA·Li, (−)-sparteine·Li and (−)-α-isosparteine·Li complexes to exemplify the lower reactivity of the *s*-BuLi/(−)-α-isosparteine complex. On inspection of the Chem3D® space-filling diagram of (−)-sparteine·Li (Fig. 2), we realised that the D-ring of (−)-sparteine was in fact held away from the lithium, the "business end" of the complex.

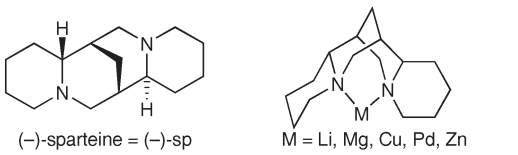


Fig. 1 (−)-Sparteine and its metal-chelating conformation.

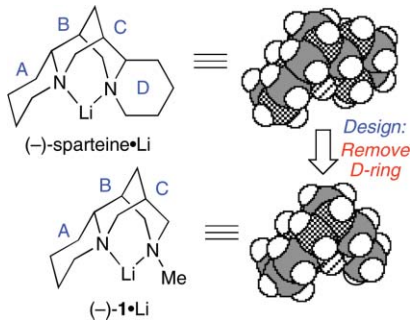


Fig. 2 Designing a sparteine mimic, lacking the D-ring of (−)-sparteine.

Thus, we speculated that this D-ring could be "removed" without especially altering the chiral environment around the lithium. Our initial proposal was that an *N*-Me group (diamine (−)-**1**) would most closely mimic the NCH_2 group of (−)-sparteine's D-ring (Fig. 2).

Of course, since we intended to develop a (+)-sparteine mimic, we needed to remove the D-ring in the mirror image of (−)-sparteine. In this way, diamine (+)-**1** (Fig. 3) was devised as a diamine that could be both synthetically accessible and a good mimic of (+)-sparteine. As well as the parent (+)-sparteine surrogate **1** with an *N*-Me group, it appeared that the *N*-substituent would be a useful handle for "tuning" the steric and electronic properties of the (+)-sparteine-like diamines. Thus, we[6–10] and others[11–16] have synthesised and evaluated eleven (+)-sparteine surrogates **1–11** with a range of *N*-alkyl substituents (Fig. 4).

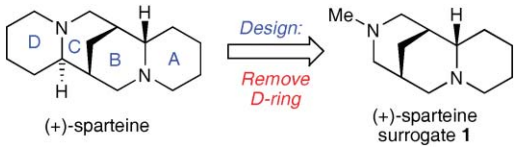


Fig. 3 Designing the original (+)-sparteine surrogate **1**.

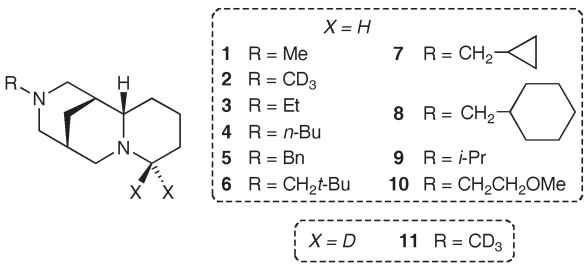
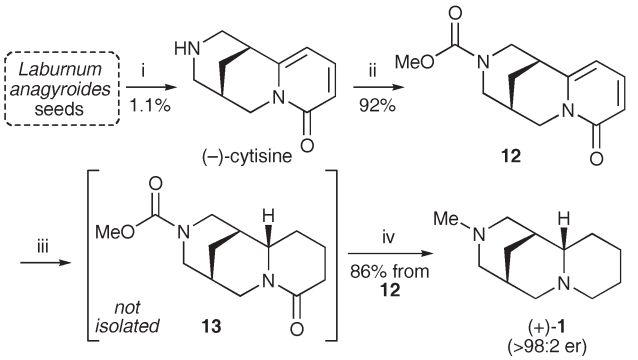


Fig. 4 The (+)-sparteine surrogate family.

Synthesis of (+)-sparteine surrogates

The primary aim of the initial stages of the project was the development of a simple, short and high yielding synthesis of multi-gram quantities of diamine (+)-**1**. It turned out that diamine *rac*-**1** was a known compound and its preparation had been reported by Scheiber and Nemes in 1994.[17] However, no synthesis of (+)- or (−)-**1** had previously been described and our initial exploits were somewhat disappointing.[18–21]

Ultimately, and with some serendipity,[22] we identified (−)-cytisine as a suitable and readily accessible starting material. (−)-Cytisine is a naturally occurring lupin alkaloid and an optimised, large-scale and efficient procedure for extracting it from *Laburnum anagyroides* seeds was reported by Lasne, Rouden and co-workers in 2000.[23] Thus, we adopted this extraction procedure as the first step in the synthesis of (+)-sparteine surrogate **1** (Scheme 1).



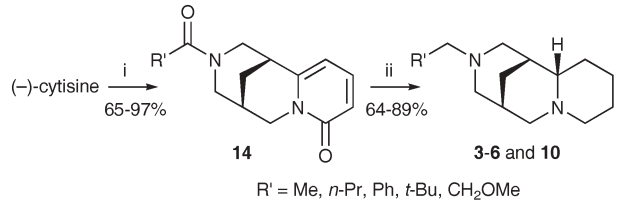
Scheme 1 *Reagents and conditions:* i, (a) $NH_4OH_{(aq)}$, CH_2Cl_2, MeOH, rt, 3 days; (b) 3 M $HCl_{(aq)}$; (c) $NH_4OH_{(aq)}$ then extract into CH_2Cl_2; (d) recrystallise; ii, Et_3N, MeO_2CCl, CH_2Cl_2, rt, 3.5 h; iii, PtO_2, H_2, EtOH, rt, 5 h; iv, $LiAlH_4$, THF, reflux, 16 h.

In our hands, the extraction of (−)-cytisine from *Laburnum anagyroides* seeds was accomplished in 1.1% mass yield using Lasne and Rouden's protocol.[23] Next, (−)-cytisine (>99 : 1 er as shown by chiral HPLC of *N*-Bn cytisine[10]) was converted into methyl carbamate **12** (92% yield) which served as both a convenient *N*-protecting group for the subsequent pyridone hydrogenation and a latent *N*-Me group which would be unmasked upon $LiAlH_4$ reduction. It is preferable to purify methyl carbamate **12** using a plug of silica at this stage as this leads to higher yields for the next two steps which can be carried out without isolation of the intermediate lactam **13**. Thus, pyridone hydrogenation of **12** using PtO_2/H_2 generated a single diastereoisomer of lactam **13** (which was separately fully characterised, including X-ray crystallography[7]). This reaction proceeds *via* exclusive *exo* face attack on the fused bicyclic system. Finally, $LiAlH_4$ reduction of both the lactam and the methyl carbamate of **13** generated the (+)-sparteine surrogate **1** (86% yield over the two steps from methyl carbamate **12**).[6,7] *N*-Me diamine (+)-**1** was obtained as a single diastereoisomer by ^1H and ^{13}C NMR spectroscopy and was shown to be >98 : 2 er by chiral shift NMR spectroscopy.[10]

This three-step synthesis of diamine (+)-**1**, starting from *Laburnum anagyroides* seeds, is the most efficient route and readily delivers multi-gram quantities.[24] We were fortunate that naturally occurring (−)-cytisine possesses the absolute stereochemistry required to prepare (+)-**1** (and not (−)-**1**) and that the pyridone hydrogenation delivered the desired diastereoisomer. Other groups have also successfully used this route to prepare (+)-**1**.[11–16]

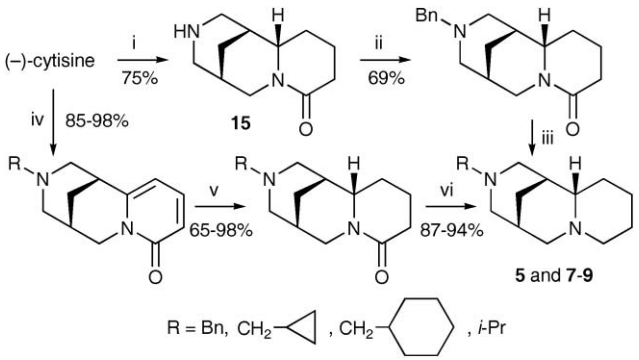
Other (+)-sparteine surrogates **2–11** have been prepared by us,[8–10] Kann[11,12] and Wilkinson[14] using variations of the same approach starting from (−)-cytisine. Diamines possessing

N-CH_2R' groups were easily prepared using the acylation sequence with R′COCl (instead of methyl chloroformate) to give **14**. In this way, diamines **3–6**[8,12] and **10**[14] were prepared in good overall yields (Scheme 2).



Scheme 2 *Reagents and conditions:* i, R′COCl, $NaOH_{(aq)}$, CH_2Cl_2, rt, 5 h or RCOCl, Et_3N (+DMAP), CH_2Cl_2, rt, 3–18 h; ii, (a) PtO_2, H_2, EtOH (or MeOH or AcOH) , rt, 12–18 h; (b) $LiAlH_4$, THF, reflux, 16–20 h.

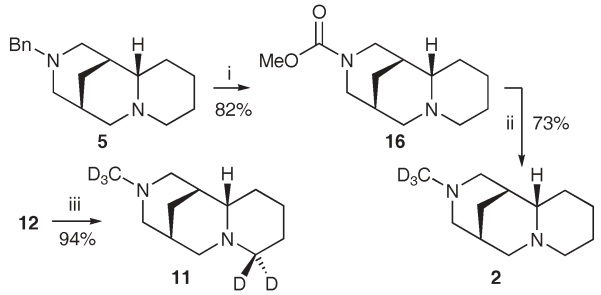
Kann and co-workers[11,12] introduced a slightly different synthetic sequence for the preparation of diamines **5** and **7–9** (Scheme 3). For **5**, (−)-cytisine was first hydrogenated to give lactam **15** (75% yield) and then subjected to reductive amination (using PhCHO/$NaBH(OAc)_3$) before the final $LiAlH_4$ reduction. Alternatively, the order of these steps can be reversed and this was the preferred approach for the synthesis of diamines **7–9**.[12] In contrast to the acylation route, the pyridone hydrogenation in all of the examples in Scheme 3 is best carried out under acidic conditions (AcOH) due to the presence of an unprotected amine.



Scheme 3 *Reagents and conditions:* i, PtO_2, H_2, AcOH, rt, 26 h; ii, PhCHO, $NaBH(OAc)_3$, THF, rt, 18 h; iii, $LiAlH_4$, THF, reflux, 18 h; iv, $NaBH(OAc)_3$, THF, rt, 18 h, *c*-PrCHO (→**7**); *c*-HexCHO (→**8**); acetone (→**9**); v, PtO_2, H_2, AcOH , rt, 26 h; vi, $LiAlH_4$, THF, reflux, 18 h.

We also prepared the deuterated diamines **2** and **11** using the acylation route (Scheme 4).[10] For **2**, *N*-Bn diamine **5** (prepared as in Scheme 2) was first converted into methyl carbamate **16** (by hydrogenolysis and reaction with methyl chloroformate) and then into diamine **2** by $LiAlD_4$ reduction. The synthesis of d_5-diamine **11** was more straightforward as pyridone hydrogenation and $LiAlD_4$ reduction of methyl carbamate **12** (the key intermediate in the synthesis of diamine (+)-**1**) directly produced diamine **11** in 94% yield.

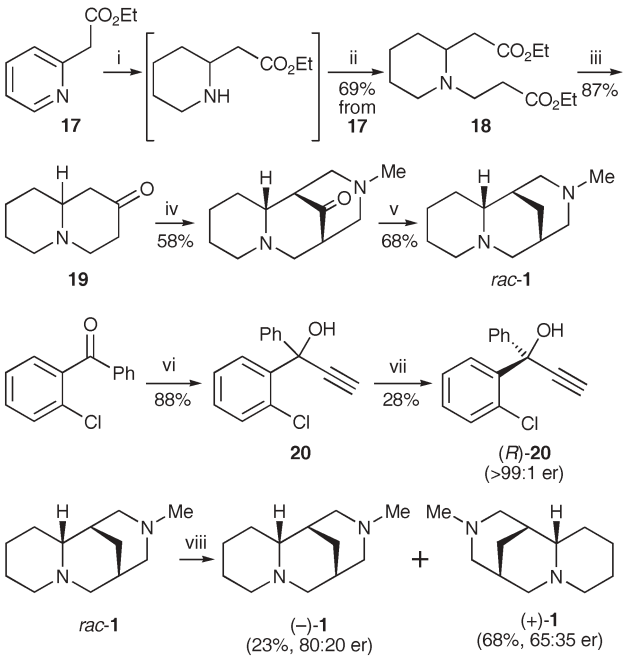
Prior to developing the optimised route to (+)-sparteine surrogates starting from (−)-cytisine, we had developed a



Scheme 4 *Reagents and conditions:* i, (a) $Pd(OH)_2/C$, $NH_4^+HCO_2^-$, EtOH, reflux, 2 h; (b) Et_3N, MeO_2CCl, CH_2Cl_2, rt, 16 h; ii, $LiAlD_4$, THF, reflux, 16 h; iii, (a) PtO_2, H_2, MeOH, rt, 12 h; (b) $LiAlD_4$, THF, reflux, 16 h.

route to diamine *rac*-**1** and a moderately successful resolution method (Scheme 5). Our synthesis of diamine *rac*-**1**[7,21] is an optimised variant of Sheiber and Nemes' original synthesis.[17] Thus, pyridine **17** was hydrogenated to a piperidine which was directly subjected to conjugate addition with ethyl acrylate to give bis ester **18** (69% yield, two steps). High yielding Dieckmann cyclisation was accomplished using LHMDS followed by acidic hydrolysis/decarboxylation to give amino ketone **19**. Finally, double Mannich reaction (which sets up the required relative stereochemistry) and Wolff–Kishner-style reduction (39% yield, two steps) gave diamine *rac*-**1**.

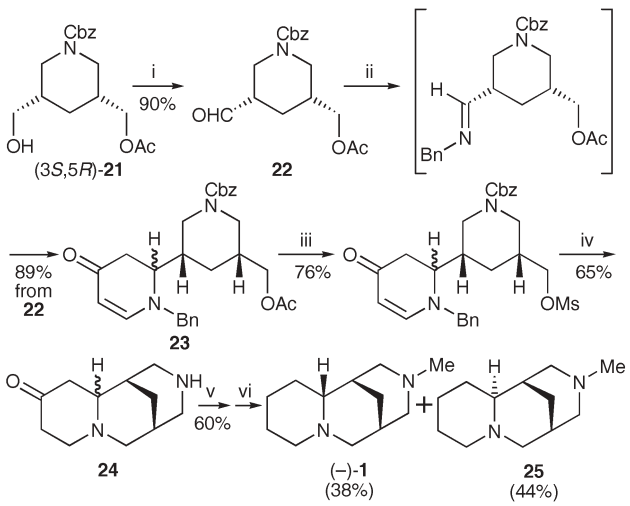
To our disappointment, we could not develop a classical resolution procedure for *rac*-**1**. In the end, we adapted an



Scheme 5 *Reagents and conditions:* i, PtO_2, H_2, $HCl_{(aq)}$, EtOH, rt, 24 h; ii, ethyl acrylate, Et_3N, EtOH, rt, 66 h; iii, (a) LHMDS, THF, −78 °C, 2 h; (b) $HCl_{(aq)}$, reflux, 16 h; iv, $MeNH_2$, $(CH_2O)_n$, AcOH, MeOH, reflux, 16 h; v, $N_2H_4{\cdot}H_2O$, KOH, diethylene glycol, reflux, 2 h; vi, HC≡CMgBr, THF, reflux, 16 h; vii, (a) (−)-sparteine, acetone, rt, 16 h; (b) Filter to collect crystals; (c) Treat crystals with 2 M $HCl_{(aq)}$; (d) Repeat steps (a)–(c); viii, (a) alcohol (*R*)-**20** (>99 : 1 er), acetone, rt, 16 h; (b) Filter to collect crystals; (c) Treat crystals with 2 M $HCl_{(aq)}$.

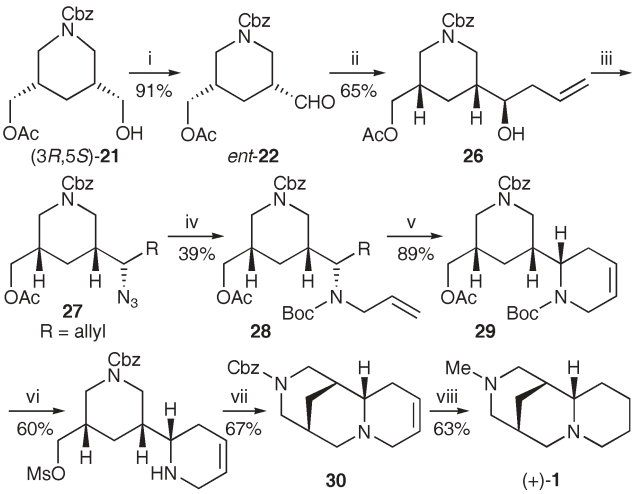
inclusion complex method described by Toda *et al.*[25] First of all, we used the Toda protocol to resolve alcohol **20** by complexation with (−)-sparteine to give (*R*)-**20** of >99 : 1 er in 28% yield (after two complexations). Since diamine **1** had been designed to be "sparteine-like", we hoped that alcohol (*R*)-**20** could now be used to resolve diamine *rac*-**1**. Only one complexation was attempted and this delivered (−)-**1** of 80 : 20 er in 23% yield (from the crystals) and (+)-**1** of 65 : 35 er (68% yield) from the mother-liquor. Further complexation of the enriched diamine (−)-**1** would almost certainly deliver diamine (−)-**1** in >95 : 5 er. Although this resolution route will never compete with the (−)-cytisine route to (+)-sparteine surrogates, it is the best way of synthesising diamine (−)-**1**.

There have been two reports by Lesma and co-workers on the asymmetric synthesis of diamines (−)-**1** and (+)-**1**.[26,27] Both approaches start with *N*-Cbz-protected monoacetate **21** (each enantiomer available by enzymatic desymmetrisation[28]). In Lesma's first approach (Scheme 6),[26] monoacetate (3*S*,5*R*)-**21** was oxidised to aldehyde **22** which was utilised in a one-pot $Sc(OTf)_3$-mediated reaction with Danishefsky's diene to give adducts **23** as a 1 : 1 mixture of diastereoisomers. From **23**, the acetate was converted into a mesylate and then H_2 and Pd/C removed the *N*-protecting groups and the alkene to give a diamine which readily cyclised to ketones **24**. The last two steps involve C=O removal and *N*-methylation and gave a separable mixture of diamine (−)-**1** and its diastereoisomer **25**.



Scheme 6 *Reagents and conditions:* i, DMSO, Et_3N, $(COCl)_2$; ii, $PhCH_2NH_2$, $MgSO_4$, Danishefsky's diene, 10 mol% $Sc(OTf)_3$, MeCN, rt; iii, (a) NaOH, MeOH; (b) Et_3N, MsCl, CH_2Cl_2; iv, (a) H_2, Pd/C, EtOH, $HCl_{(aq)}$; (b) Et_3N, THF, reflux; v, (a) $TsNHNH_2$, EtOH, reflux; (b) $NaBH_4$, THF–water, reflux; vi, $NaBH_3CN$, $CH_2O_{(aq)}$, THF.

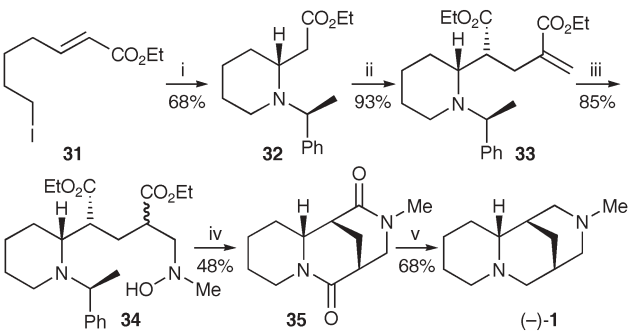
Subsequently, Lesma and co-workers developed a more efficient approach and used this new route to synthesise (+)-sparteine surrogate **1** (Scheme 7).[27] Here, monoacetate (3*R*,5*S*)-**21** was oxidised to aldehyde *ent*-**22** and then subjected to allyl boronation to give **26** with good reagent stereocontrol. Next, **26** was activated and converted into azide **27** before further transformation into diene **28**. Efficient ring closing metathesis then gave **29** which underwent additional manipulations before cyclisation to tricycle **30**. Finally, *N*-Cbz



Scheme 7 *Reagents and conditions:* i, DMSO, Et_3N, $(COCl)_2$; ii, (a) (+)-*B*-methoxyisocampheylborane, allylMgBr, Et_2O, −78 °C; (b) NaOH, H_2O_2; iii, (a) MsCl, CH_2Cl_2; (b) NaN_3, DMF, 80 °C; iv, (a) Ph_3P, THF, water; (b) Et_3N, Boc_2O, CH_2Cl_2; (c) NaH, allylBr, DMF; v, $Ru(PCy_3)_2Cl_2$(=CHPh), CH_2Cl_2, rt; vi, (a) TFA, CH_2Cl_2; (b) $NaOH_{(aq)}$, THF; (c) Et_3N, MsCl, CH_2Cl_2; vii, Et_3N, CH_2Cl_2, reflux; viii, (a) (a) H_2, Pd/C, EtOAc; (b) $NaBH_3CN$, $CH_2O_{(aq)}$, THF.

removal, alkene hydrogenation and *N*-methylation delivered diamine (+)-**1**.

Recent work in our group has led to a new synthesis of diamine (−)-**1** (Scheme 8).[29] Taking the lead from our asymmetric synthesis of (−)-sparteine,[30] we started with iodo ester **31** which underwent a tandem S_N2 substitution-stereoselective cyclisation using (*S*)-α-methylbenzylamine as a chiral auxiliary to give cyclic β-amino ester **32** in 68% yield (3 : 1 stereoselectivity, 23% yield of other diastereoisomer). Then, stereoselective alkylation of the enolate of **32** with ethyl α-(bromomethyl)acrylate furnished ester **33**. Unfortunately, conjugate addition of *N*-methyl hydroxylamine to **33** gave adducts **34** as an inseparable 1 : 1 mixture of diastereoisomers (85% yield). Next, hydrogenolysis of **34** cleaved the benzylic C–N bond and the N–O bond to generate bis lactam **35** (48% yield). $LiAlH_4$ reduction then gave diamine (−)-**1**.



Scheme 8 *Reagents and conditions:* i, (*S*)-α-methylbenzylamine, Et_3N, DMF, rt, 64 h; ii, (a) LHMDS, THF, −78 °C, 1 h; (b) ethyl α-(bromomethyl)acrylate, −78 °C → rt over 4 h then rt, 12 h; iii, Et_3N, MeHN–OH·HCl, THF, rt, 64 h; iv, $Pd(OH)_2$/C, $NH_4^+HCO_2^-$, EtOH, reflux, 16 h; v, $LiAlH_4$, THF, reflux, 16 h.

In summary, the best way of preparing members of the (+)-sparteine surrogate family is to start with (−)-cytisine and either follow an acylation or reductive amination approach. Using the acylation route, multi-gram quantities of the parent (+)-sparteine surrogate **1** (*N*-Me group) can be easily and efficiently produced in three steps from *Laburnum anagyroides* seeds (Scheme 1). Alternatively, the best way of preparing the antipode (−)-**1** is *via* resolution of *rac*-**1** using inclusion complex formation with acetylenic alcohol (*R*)-**20** (Scheme 5) since the three asymmetric approaches are either lengthy or lack stereocontrol at one of the stereogenic centres.

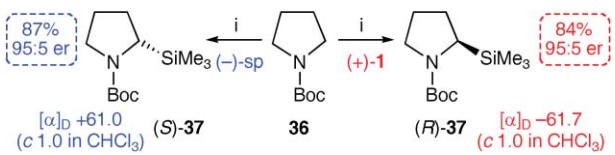
Evaluation of (+)-sparteine surrogates

Evaluation of the *N*-Me (+)-sparteine surrogate

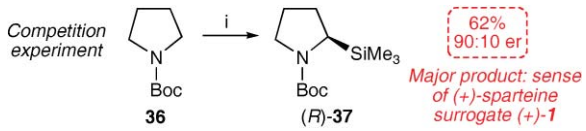
Our originally designed (+)-sparteine surrogate **1** with a *N*-Me substituent was the first diamine that we evaluated and has thus been the most studied both in our group and by other research teams. In this section, a comparison between (−)-sparteine and diamine (+)-**1** in a range of reactions is presented. These reactions comprise different transformations (*e.g.* deprotonation, addition, carbometallation), different metals (*e.g.* Li, Mg, Pd, Cu) and different mechanisms of stereocontrol (*e.g.* asymmetric deprotonation, dynamic thermodynamic resolution and dynamic kinetic resolution).

In October 2001, four years after we had initiated this programme of research, the (−)-cytisine-derived (+)-sparteine surrogate **1** was evaluated for the first time in the asymmetric deprotonation of *N*-Boc pyrrolidine **36** (→**37**). This reaction, originally introduced by Beak and Kerrick in 1991,[31] utilises *s*-BuLi/(−)-sparteine-mediated asymmetric lithiation and proceeds *via* a configurationally stable organolithium that is subsequently trapped by a range of electrophiles.[31,32] In our hands, lithiation of *N*-Boc pyrrolidine **36** using *s*-BuLi/(−)-sparteine in Et_2O at −78 °C and trapping with Me_3SiCl furnished the trimethylsilyl adduct (*S*)-**37** of 95 : 5 er (87% yield) (lit.,[32] 87%, 98 : 2 er). To our delight, an essentially "mirror image" result was obtained using the "near-mirror image" diamine (+)-**1**. Thus, we isolated an 84% yield of adduct (*R*)-**37** of 95 : 5 er using (+)-**1** under identical conditions (Scheme 9).[6] This clearly demonstrated that the D-ring of (−)-sparteine is not required for high enantioselectivity in this asymmetric deprotonation and confirmed our original design hypothesis (Fig. 2 and 3). With the ready availability of diamine (+)-**1** from (−)-cytisine, this initial result suggested that we had found a solution to the "(+)-sparteine problem."

More recently, we have evaluated the relative rates of lithiation of *N*-Boc pyrrolidine **36** using *s*-BuLi/(−)-sparteine and *s*-BuLi/(+)-**1**. This was achieved using a competition



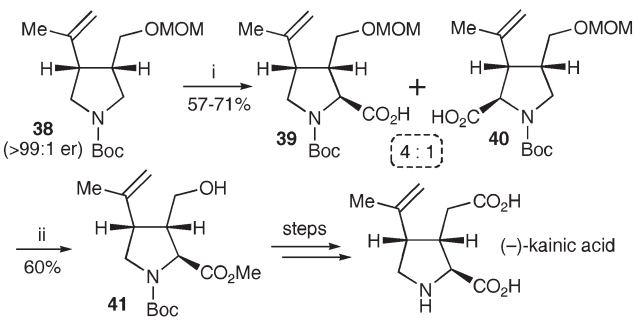
Scheme 9 *Reagents and conditions:* i, (a) 1.3 eq. *s*-BuLi/(−)-sparteine or (+)-**1**, Et_2O, −78 °C, 5 h; (b) Me_3SiCl.



Scheme 10 *Reagents and conditions:* i, (a) 2.6 eq. *s*-BuLi, 1.3 eq. (−)-sparteine, 1.3 eq. (+)-**1**, Et_2O, −78 °C, 5 h; (b) Me_3SiCl.

experiment[33] (Scheme 10). Thus, lithiation of **36** using 2.6 eq. *s*-BuLi and 1.3 eq. of each of (−)-sparteine and (+)-**1** followed by reaction with Me_3SiCl gave adduct (*R*)-**37** (62% yield, 90 : 10 er).[34] This is the same sense of induction shown by (+)-**1** and shows that *s*-BuLi/(+)-**1** lithiates *N*-Boc pyrrolidine **36** faster than *s*-BuLi/(−)-sparteine.

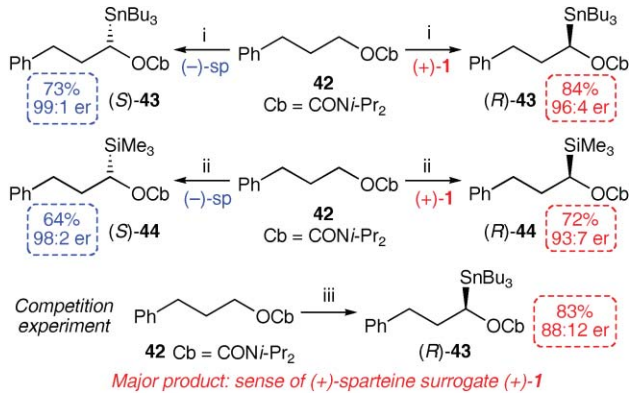
The usefulness of the (+)-sparteine surrogate **1** in a total synthesis of (−)-kainic acid has been shown by Fukuyama and co-workers, in which a Beak-style lithiation-carboxylation of a functionalised *N*-Boc pyrrolidine **38** was the key step.[15] Thus, *N*-Boc pyrrolidine **38** (>99 : 1 er) was prepared in eight steps incorporating an efficient lipase-mediated dynamic kinetic resolution. When **38** was lithiated using *s*-BuLi in THF at −78 °C, poor regio- and stereocontrol resulted after electrophilic trapping. In contrast, under the same conditions, but with (+)-**1** present, a 4 : 1 mixture of regioisomeric carboxylic acids **39** and **40** (both as single diastereoisomers) were generated in good yield (Scheme 11). Use of (−)-sparteine gave the unwanted regioisomer **40** as the major component.[35] The inseparable 4 : 1 mixture of **39** and **40** generated from the (+)-sparteine surrogate reaction was converted into methyl ester **41** which was isolated as a single regio- and stereoisomer and then utilised to complete the synthesis of (−)-kainic acid. It is notable that (+)-**1** was used to control the *regiochemistry* of deprotonation of **38**.



Scheme 11 *Reagents and conditions:* i, (a) 1.5 eq. *s*-BuLi, 3.0 eq. (+)-**1**, THF, −78 °C, 3.5 h; (b) CO_2; (c) water, $NaHCO_3$; ii, (a) K_2CO_3, MeI, DMF, rt; (b) AcCl, MeOH, rt; (c) Boc_2O, $NaHCO_{3(aq)}$, rt.

The first examples of highly enantioselective lithiation-substitution using *s*-BuLi/(−)-sparteine were reported for *O*-alkyl carbamates such as **42** by the Hoppe group in 1990.[36] These reactions proceed *via* asymmetric deprotonation to give a configurationally stable organolithium. Using a reaction originally described by Nakai *et al.*,[37] we subjected *O*-alkyl carbamate **42** to lithiation-Bu_3SnCl trapping with *s*-BuLi/(−)-sparteine and diamine (+)-**1** to give enantiocomplementary results. Thus, stannane (*S*)-**43** of 99 : 1 er was produced (73% yield) with (−)-sparteine whereas use of (+)-**1**

gave an 84% yield of stannane (*R*)-**43** of 96 : 4 er (Scheme 12).[6,10] In a similar fashion, trapping with Me_3SiCl generated the enantiomeric silanes (*S*)-**44** (64%, 98 : 2 er, (−)-sparteine) and (*R*)-**44** (72%, 93 : 7 er, (+)-**1**).[38] A competition experiment between *s*-BuLi/(−)-sparteine and *s*-BuLi/(+)-**1** produced adduct (*R*)-**43** of 88 : 12 er (83% yield) showing that *s*-BuLi/(+)-**1** is the faster lithiator of **42** (Scheme 12).[38]

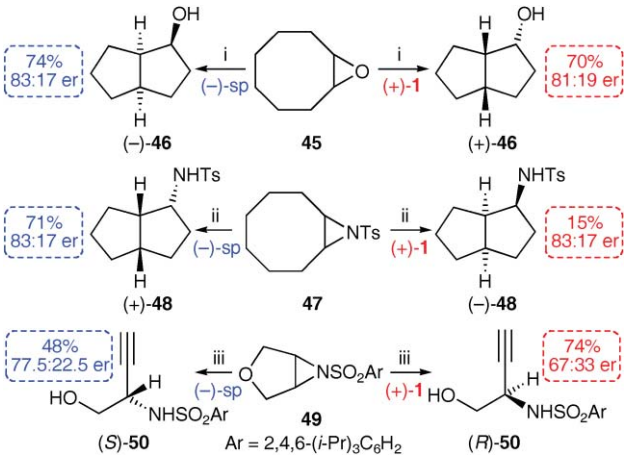


Scheme 12 *Reagents and conditions:* i, (a) 1.4 eq. *s*-BuLi/(−)-sparteine or (+)-**1**, Et_2O, −78 °C, 5 h; (b) Bu_3SnCl; ii, (a) 1.4 eq. *s*-BuLi/(−)-sparteine or (+)-**1**, Et_2O, −78 °C, 5 h; (b) Me_3SiCl; iii, (a) 2.8 eq. *s*-BuLi, 1.4 eq. (−)-sparteine, 1.4 eq. (+)-**1**, Et_2O, −78 °C, 5 h; (b) Bu_3SnCl.

In recent work, Aggarwal and co-workers have described an iterative homologation of boronic esters derived from an *O*-alkyl carbamate. Of note, all four stereoisomers of a simple alcohol equipped with two stereogenic centres were prepared using ligand-controlled reactions with different combinations of (−)-sparteine and the (+)-sparteine surrogate **1**.[16]

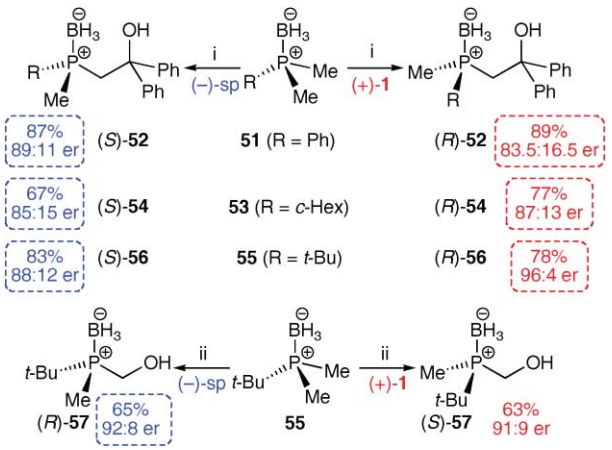
The α-lithiation-rearrangement of epoxides and *N*-tosyl aziridines using *s*-BuLi and diamine (+)-**1** has also been studied in our group. The conversion of epoxides (*e.g.* **45**) into bicyclic alcohols (*e.g.* **46**) using *s*-BuLi/(−)-sparteine was introduced by Hodgson and Lee in 1996.[39,40] In our hands, deprotonation-rearrangement of cyclooctene oxide **45** using *s*-BuLi/(−)-sparteine gave a 74% yield of bicyclic alcohol (−)-**46** of 83 : 17 er. Pleasingly, use of (+)-sparteine surrogate (+)-**1** produced (+)-**46** in similar yield and enantioselectivity (70%, 81 : 19 er) (Scheme 13).[6] We have also investigated the analogous aziridine reaction (**47** → **48**), first reported by Müller and Nury.[41] Thus, reaction of aziridine **47** with *s*-BuLi/(−)-sparteine gave a 71% yield of bicyclic sulfonamide (+)-**48** of 83 : 17 er[42] whereas reaction with *s*-BuLi/(+)-**1** gave (−)-**48** of 83 : 17 er but in only 15% yield (Scheme 13).[43] Recently, we have reported a new transformation of an alkoxy aziridine **49** into an alkyne **50**, mediated by *s*-BuLi and diamines or PMDETA. Use of (−)-sparteine and diamine (+)-**1** in this process gave similar but opposite enantioselectivity allowing access to either (*S*)- or (*R*)-**50** (Scheme 13).[43,44]

Kann and co-workers[11,12] as well as our group[45] have investigated the use of diamine (+)-**1** in asymmetric lithiation-trapping of phosphine boranes. The *s*-BuLi/(−)-sparteine promoted asymmetric functionalisation of phosphine boranes such as **51** was first reported by Evans *et al.* in 1995[46] and then



Scheme 13 *Reagents and conditions:* i, 2.4 eq. *s*-BuLi/(−)-sparteine or (+)-**1**, Et_2O, −78 °C, 5 h; ii, 2.9 eq. *s*-BuLi/(−)-sparteine or (+)-**1**, Et_2O, −78 °C, 4 h then rt, 1 h; iii, 3.0 eq. *s*-BuLi/(−)-sparteine or (+)-**1**, Et_2O, −78 °C, 1 h then rt, 3 h.

further developed by the groups of Imamoto[47] and Livinghouse.[48] It is arguably the most useful sparteine-mediated reaction as it produces enantiopure *P*-stereogenic phosphines and bisphosphines for use in asymmetric catalysis.[49] In Kann's work, three phosphine boranes **51**, **53** and **55** were lithiated using *s*-BuLi/(−)-sparteine or diamine (+)-**1** and trapped with benzophenone to give adducts **52**, **54** and **56** respectively; (−)-sparteine and (+)-**1** gave opposite antipodes in comparable yield and enantioselectivity (Scheme 14). For the phenyl-substituted phosphine borane **51**, (*S*)-**52** (89 : 11 er using (−)-sparteine) was generated in higher enantioselectivity than (*R*)-**52** (83.5 : 16.5 er using (+)-**1**). The opposite trend was observed for the *t*-Bu-substituted phosphine borane **55** : (*R*)-**56** (96 : 4 er using (+)-**1**) and (*S*)-**56** (88 : 12 er with (−)-sparteine) were obtained. Recently, we have studied asymmetric lithiation-oxygenation of **55**. Thus, deprotonation using *s*-BuLi/(−)-sparteine or (+)-**1** and reaction with air gave enantiocomplementary results: (*R*)-**57** (92 : 8 er) and (*S*)-**57** (91 : 9 er)



Scheme 14 *Reagents and conditions:* i, (a) 1.0 eq. *s*-BuLi, 1.1 eq. (−)-sparteine or (+)-**1**, Et_2O, −78 °C, 3 h; (b) Ph_2CO, −20 °C, 4 h; (c) $HCl_{(aq)}$; ii, (a) 1.1 eq. *s*-BuLi, 1.2 eq. (−)-sparteine or (+)-**1**, Et_2O, −78 °C, 3 h; (b) air, −78 °C, 1 h then rt, 16 h.

(Scheme 14).[45] Kann and co-workers have utilised diamine (+)-**1** in the preparation of new chiral phosphine boranes (*S*)-**58–60** (Fig. 5).[50,51] In addition, using an *in situ* deboronation method, **58** was successfully used as a ligand in a Pd-catalysed allylic alkylation reaction.

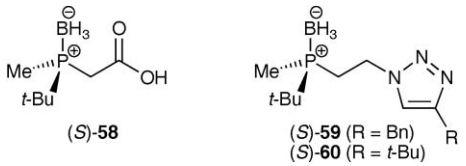
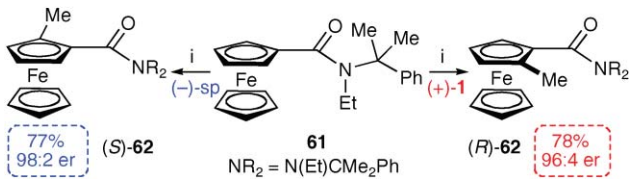


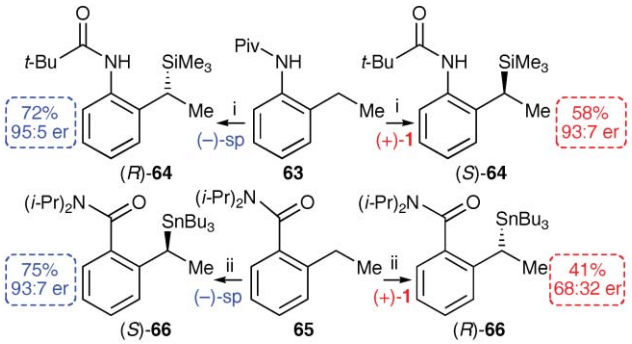
Fig. 5 Phosphine-based ligands synthesised using diamine (+)-**1**.

In a final example of asymmetric deprotonation, we studied the enantioselective *ortho*-lithiation of ferrocene amide **61** using *n*-BuLi/(−)-sparteine and (+)-**1**. The (−)-sparteine-mediated process was originally developed by Snieckus and co-workers and is an efficient way of generating chiral ferrocenes.[52,53] In our hands, lithiation-methylation of ferrocene amide **61** using *n*-BuLi/(−)-sparteine generated ferrocene (*S*)-**62** of 98 : 2 er in 77% yield. An enantiocomplementary result was obtained using diamine (+)-**1** such that ferrocene adduct (*R*)-**62** of 96 : 4 er was produced in 78% yield (Scheme 15).[45]



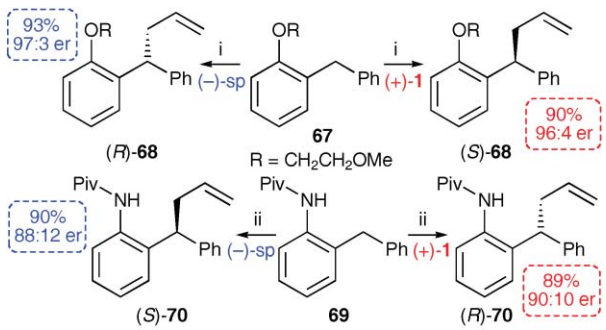
Scheme 15 *Reagents and conditions:* i, (a) 1.2 eq. *n*-BuLi/(−)-sparteine or (+)-**1**, 6 : 1 Et_2O–toluene, −78 °C, 2 h; (b) MeI, −78 °C, 1 h then rt, 16 h.

All of the reactions presented in Schemes 9–15 are organolithium/diamine-mediated asymmetric deprotonations. It was important to show that diamine (+)-**1** also mimicked (+)-sparteine in other types of reactions. With this in mind, some benzylic functionalisation reactions have been studied by us and by Wilkinson *et al.*[13,14] Using detailed mechanistic studies, Beak *et al.* have demonstrated that the benzylic lithiation-trapping of *N*-pivaloyl-*o*-anilide **63** proceeds *via* dynamic thermodynamic resolution. Thus, the dianion derived from **63** was generated using excess *s*-BuLi and then equilibrated in the presence of (−)-sparteine at −25 °C. Rapid cooling to −78 °C and trapping with Me_3SiCl gave a 72% yield of (*R*)-**64** of 95 : 5 er.[54] When we employed (+)-sparteine surrogate (+)-**1**, (*S*)-**64** of 93 : 7 er was generated in 58% yield (Scheme 16).[8] In contrast, the benzylic lithiation-trapping of *N*,*N*-diisopropyl(*o*-ethyl)benzamide **65** proceeds *via* dynamic kinetic resolution of the rapidly equilibrating diastereomeric organolithium species. Using Beak's protocol,[54] lithiation of benzamide **65** using *s*-BuLi/(−)-sparteine in pentane followed by reaction at −78 °C with Bu_3SnCl afforded a 75% yield of stannane (*S*)-**66** of 93 : 7 er. Disappointingly, use of diamine (+)-**1** gave stannane (*S*)-**66** of only 68 : 32 er (41% yield)[55] thus highlighting a limitation of using the (+)-spartene surrogate (+)-**1** in this dynamic kinetic resolution (Scheme 16).



Scheme 16 *Reagents and conditions:* i, (a) 2.4 eq. *s*-BuLi, Et_2O, −25 °C, 2 h; (b) 2.9 eq. (−)-sparteine or (+)-**1**, −25 °C, 45 min; (c) −78 °C, Me_3SiCl; ii, (a) 1.1 eq. *s*-BuLi/(−)-sparteine or (+)-**1**, pentane, −78 °C, 1.5 h; (b) Bu_3SnCl, −78 °C.

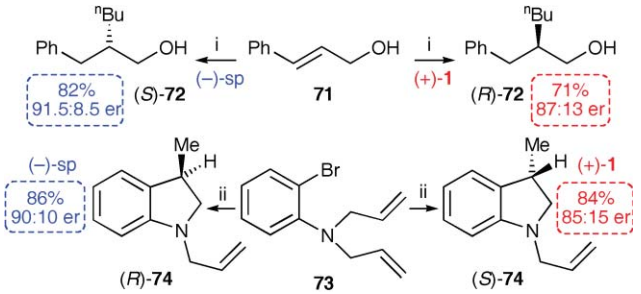
Wilkinson *et al.* have compared (−)-sparteine and diamine (+)-**1** in the asymmetric alkylation of diarylmethanes **67** and **69**. For diarylmethane **67**, lithiation using *s*-BuLi/diamine was followed by a warm-cool protocol and the electrophile was added in two 0.5 eq. portions. In this way, after trapping with allyl tosylate, adduct (*R*)-**68** (93% yield, 97 : 3 er) was obtained using (−)-sparteine and adduct (*S*)-**68** (90% yield, 96 : 4 er) was produced using (+)-**1** (Scheme 17).[14] With diarylmethane **69**, formation of the putative dianion required 3.5 h lithiation with excess *s*-BuLi at 0 °C. Subsequent cooling to −78 °C and addition of (−)-sparteine and then allyl bromide generated adduct (*S*)-**70** of 88 : 12 er (90% yield). Similarly high enantioselectivity was obtained using (+)-**1** whereby (*R*)-**62** of 90 : 10 er (89% yield) was isolated (Scheme 17).[14]



Scheme 17 *Reagents and conditions:* i, (a) 1.1 eq. *s*-BuLi/(−)-sparteine or (+)-**1**, Et_2O, −78 °C; (b) −78 °C → −20 °C over 1 h then −78 °C; (c) 0.5 eq. allyl tosylate; (d) repeat steps (b)–(c); ii, (a) 2.4 eq. *s*-BuLi, Et_2O, 0 °C, 3.5 h; (b) −78 °C, 2.6 eq. (−)-sparteine or (+)-**1**, 2 h; (c) allyl bromide.

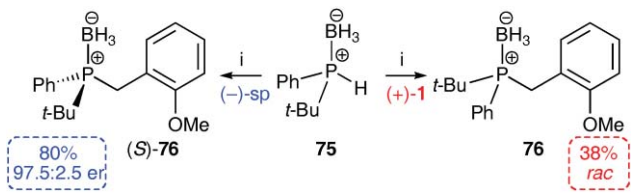
Another area where (−)-sparteine has been employed as a chiral ligand is inter- and intramolecular carbolithiation. A representative intermolecular example is the *n*-BuLi/(−)-sparteine-mediated carbolithiation of cinnamyl alcohol **71**, as developed by Normant and co-workers: reaction of **71** with 3 eq. *n*-BuLi and 1 eq. (−)-sparteine led to the formation of

alcohol (*S*)-**72** of 91.5 : 8.5 er in 82% yield.[56] In our hands, use of (+)-**1** gave a similar degree of enantioselectivity and alcohol (*R*)-**72** of 87 : 13 er (71% yield) was produced (Scheme 18).[8] In a similar way, Bailey's tandem bromine-lithium exchange-intramolecular carbolithiation of *N*,*N*-diallyl-2-bromoaniline (**73** → **74**) also proceeded equally well with (−)-sparteine and diamine (+)-**1**. Using (−)-sparteine, an 86% yield of indoline (*R*)-**74** of 90 : 10 er was generated[57] whereas, with (+)-**1**, (*S*)-**74** of 85 : 15 er (84% yield) was formed (Scheme 18).[58]



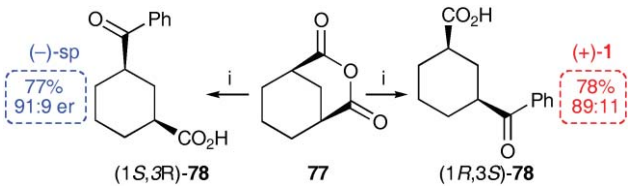
Scheme 18 *Reagents and conditions:* i, 3.0 eq. *n*-BuLi, 1.0 eq. (−)-sparteine or (+)-**1**, cumene, 0 °C, 1 h; ii, (a) 2.2 eq. *t*-BuLi, 9 : 1 pentane–Et_2O, −78 °C, 10 min; (b) 2.2 eq. (−)-sparteine or (+)-**1**, −78 °C; (c) 40 °C, 1.5 h; (d) MeOH.

Use of the (+)-sparteine surrogate (+)-**1** in Livinghouse's dynamic resolution of lithiated *tert*-butylphenylphosphine borane **75**[59] was less successful. As an example, phosphine borane **75** was lithiated with *n*-BuLi/(−)-sparteine in Et_2O at −78 °C and, upon warming to room temperature, a dynamic thermodynamic resolution occurred such that one of the diastereomeric organolithiums precipitated. Rapid cooling to −78 °C and trapping with a benzyl chloride afforded phosphine borane (*S*)-**76** of 97.5 : 2.5 er (80% yield).[59] With (+)-**1**, we did not observe any precipitation upon warming and, after trapping, *racemic* phosphine borane **76** was isolated in a moderate 38% yield (Scheme 19).[8] It is likely that use of (+)-**1** with other solvent/temperature combinations would allow the required crystallisation-driven thermodynamic resolution to occur.



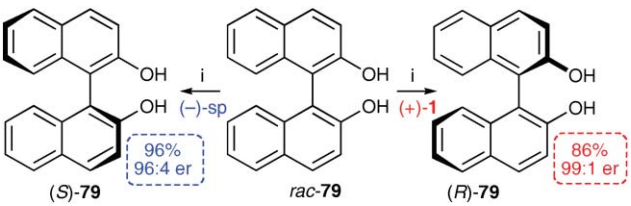
Scheme 19 *Reagents and conditions:* i, (a) 1.0 eq. *n*-BuLi, 1.3 eq. (−)-sparteine or (+)-**1**, Et_2O, −78 °C → rt, 1 h; (b) −78 °C, *o*-$MeOC_6H_4CH_2Cl$, (c) −20 °C, 24 h.

Examples of highly enantioselective (−)-sparteine-mediated Grignard reactions are rare but, in 2002, Fu and Shintani reported the use of such reagents in the desymmetrisation of *meso*-anhydrides. In a typical example, reaction of bicyclic anhydride **77** with PhMgCl/(−)-sparteine in toluene at −78 °C for 20 h generated a 77% yield of keto acid (1*S*,3*R*)-**78** of 91 : 9 er.[60] To our delight, use of this protocol with the (+)-sparteine surrogate (+)-**1** led to the formation of keto acid (1*R*,3*S*)-**78** of 89 : 11 er in 78% yield (Scheme 20).[8]



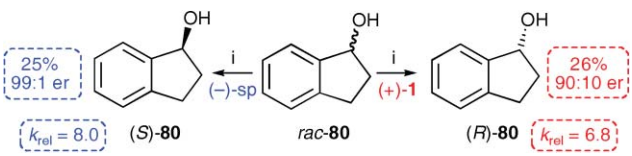
Scheme 20 *Reagents and conditions:* i, 1.3 eq. PhMgCl/(−)-sparteine, toluene, −78 °C, 20 h.

We have also evaluated diamine (+)-**1** in the Cu(II)-mediated resolution of racemic BINOL **79** using a procedure developed by Wulff and co-workers.[61] In their protocol, CuCl was oxidised to Cu(II) using air in the presence of (−)-sparteine and then complexed with BINOL *rac*-**79**. The putative BINOL–Cu(II)–(−)-sparteine complex was allowed to equilibrate to a thermodynamically preferred diastereoisomer which was "trapped" as free BINOL (*S*)-**79** (96%, 96 : 4 er) by treatment with acid at −25 °C.[61] When we used diamine (+)-**1**, an 86% yield of the antipode (*R*)-**79** of 99 : 1 er was isolated (Scheme 21).



Scheme 21 *Reagents and conditions:* i, (a) Air, CuCl, MeOH, 2.8 eq. (−)-sparteine or (+)-**1**, sonicate, 30 min; (b) Ar, sonicate, 1 h; (c) BINOL *rac*-**79**, CH_2Cl_2–MeOH, rt, 2–8 h; (d) −25 °C, 16 h then conc. $HCl_{(aq)}$.

One of the most interesting new developments in synthetic methodology with (−)-sparteine is the Pd(II)-mediated oxidative kinetic resolution of benzylic alcohols. Originally reported by the groups of Stoltz and Sigman,[62–64] the process is notable as it employs sub-stoichiometric amounts of Pd(II) *and* (−)-sparteine. Using Stoltz's original method, we have evaluated (−)-sparteine and diamine (+)-**1** in the kinetic resolution of indanol *rac*-**80**. Thus, reaction of *rac*-**80** with 0.05 eq. $Pd(nbd)Cl_2$ and 0.2 eq. (−)-sparteine under an oxygen atmosphere generated a 25% yield of (*S*)-**80** of 99 : 1 er (k_{rel} = 8.0) after oxidation of the other enantiomer of **80** to indanone. In contrast, use of diamine (+)-**1** produced (*R*)-**80** of 90 : 10 er in 26% yield (k_{rel} = 6.8) (Scheme 22).[6,8]



Scheme 22 *Reagents and conditions:* i, 0.2 eq. (−)-sparteine or (+)-**1**, 0.05 eq. $Pd(nbd)Cl_2$, toluene, O_2, 4 Å molecular sieves, 60 °C, 54 h.

To summarise, the (+)-sparteine surrogate (+)-**1** has been assessed in a wide range of (−)-sparteine-mediated reactions comprising different metals and mechanisms. Diamine (+)-**1**

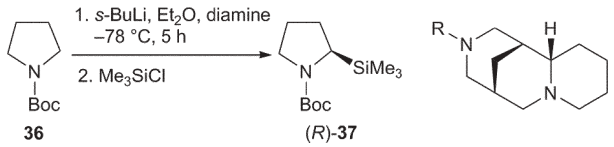
returns the opposite enantiomer to that obtained with (−)-sparteine with similar enantioselectivity in all but two cases.

Comparison of different (+)-sparteine surrogates

Diamine (+)-**1** is the most useful (+)-sparteine surrogate. This is clearly shown when a comparison is made between (+)-**1** and other members of the (+)-sparteine surrogate family **2–11** (with different *N*-alkyl groups). In this section, the effect of different sparteine-like chiral ligands on five of the reactions presented in the previous section are summarised.

From a ligand variation perspective, the most well-studied reaction is the *s*-BuLi/diamine-mediated deprotonation of *N*-Boc pyrrolidine **36** (Table 1 and Fig. 6). For the conversion of **36** into adduct **37**, the highest enantioselectivities (⩾94 : 6 er) were obtained using (−)-sparteine or the *N*-Me diamine (+)-**1** (Table 1, entries 1, 2 and 7, 8).[6,7,9] Increasing the steric hindrance of the *N*-alkyl subsituent to *N*-*t*-BuCH_2 or *N*-*i*-Pr either removes enantioselectivity altogether (with diamine **6**, *N*-*t*-BuCH_2, Table 1, entry 5) or does not produce any product (with diamine **9**, *N*-*i*-Pr, Table 1, entry 6). We are convinced that diamine **9** (*N*-*i*-Pr) forms a complex with *s*-BuLi since high enantioselectivity has been obtained using *s*-BuLi/diamine **9** in other reactions (*vide infra*). Thus, it appears that the *s*-BuLi/diamine **9** complex is too sterically hindered to deprotonate *N*-Boc pyrrolidine **36**. In a similar fashion, the complex of *s*-BuLi and (−)-α-isosparteine is not very reactive (10% lithiation) presumably due to increased steric hindrance compared to (−)-sparteine although adduct **37** was generated in a respectable 80 : 20 er (Table 1, entry 9).

Table 1 Asymmetric lithiation-trapping of *N*-Boc pyrrolidine **36**



36 (*R*)-**37**

Entry	Diamine[a]	R	Yield (%)	Er (*R* : *S*)
1	**1**	Me	84	95 : 5
2	**1**	Me	66[b]	94 : 6[b]
3	**3**	Et	73	90 : 10
4	**4**	*n*-Bu	27	89 : 11
5	**6**	*t*-BuCH_2	35	49 : 51
6	**9**	*i*-Pr	0	—
7	(−)-Sparteine	—	87	5 : 95
8	(−)-Sparteine	—	78[b]	1 : 99[b]
9	(−)-α-Isosparteine[c]	—	10	20 : 80
10	(*S*)-**81**[c]	—	51	12 : 88
11	**25**[d]	—	31	40 : 60
12	**82**[e]	—	45	68 : 32

[a] *Reaction conditions:* (a) 1.3 eq. *s*-BuLi/diamine, Et_2O, −78 °C, 5 h; (b) Me_3SiCl. [b] Reaction carried out with *i*-PrLi in place of *s*-BuLi. [c] Ref. 5. [d] Ref. 26. [e] Ref. 65.

Other sparteine-like diamines (*e.g.* (*S*)-**81**, Beak;[5] **25**, Lesma;[26] **82**, Kozlowski[65]) (Fig. 6) have been investigated but none of these diamines could compete with (−)-sparteine or the *N*-Me diamine (+)-**1** in terms of yield and enantioselectivity (Table 1, entries 10–12). The results obtained with diamines **25** (60 : 40 er) and **82** (68 : 32 er) clearly illustrate the important role of the ABC-rings of (−)-sparteine and fully support our original design conjecture that the D-ring of (−)-sparteine is not required (see Fig. 2).

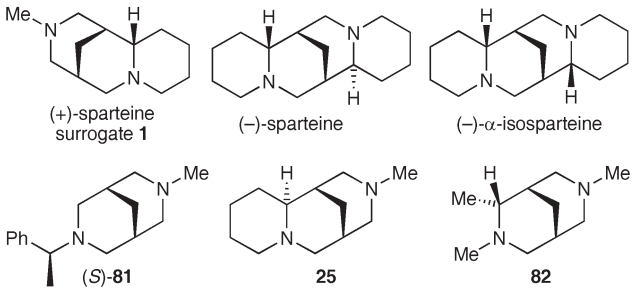
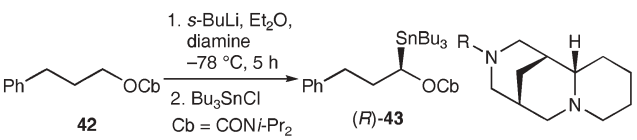


Fig. 6 Sparteine-like diamines investigated in the lithiation-trapping of *N*-Boc pyrrolidine **36**.

In terms of mechanism and the enantioselectivity produced with *s*-BuLi/(−)-sparteine, the lithiation-trapping of *O*-alkyl carbamates (*e.g.* **42** → **43**) is similar to the *N*-Boc pyrrolidine reaction. As depicted in Table 2, ligand variation in the conversion of **42** into adduct **43** follows the same broad trends as observed for *N*-Boc pyrrolidine **36**.[6,10] Thus, *s*-BuLi in combination with (−)-sparteine and the least sterically hindered (+)-sparteine surrogates **1** (*N*-Me), **2** (*N*-CD_3), **3** (*N*-Et) and **11** (*N*-CD_3) all generate adduct **43** in good yield (64–84%) and high enantioselectivity (⩾95 : 5 er) (Table 2, entries 1–4 and 8). However, whilst the use of diamine **6** (*N*-*t*-BuCH_2) led to poor yield and enantioselectivity (Table 2, entry 6) in line with *N*-Boc pyrrolidine **36** (Table 1, entry 5), diamine **9** (*N*-*i*-Pr) behaved rather differently. To our surprise, lithiation-trapping of **42** gave adduct **43** in 55% yield and 86 : 14 er (Table 2, entry 7) whereas the corresponding reaction with *N*-Boc pyrrolidine **36** did not produce any product whatsoever. Importantly, this result clearly shows that an effective complex between *s*-BuLi and the sterically hindered diamine **9** does indeed form.

Table 2 Asymmetric lithiation-trapping of *O*-alkyl carbamate **42**



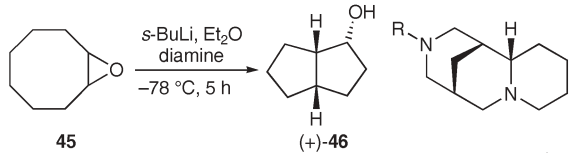
42 (*R*)-**43**

Entry	Diamine[a]	R	Yield (%)	Er (*R* : *S*)
1	**1**	Me	84	96 : 4
2	**2**	CD_3	82	96 : 4
3	**11**	CD_3[b]	68	96 : 4
4	**3**	Et	64	95 : 5
5	**4**	*n*-Bu	72	91 : 9
6	**6**	*t*-BuCH_2	18	54 : 46
7	**9**	*i*-Pr	55	86 : 14
8	(−)-Sparteine	—	73	1 : 99

[a] *Reaction conditions:* (a) 1.4 eq. *s*-BuLi/diamine, Et_2O, −78 °C, 5 h; (b) Bu_3SnCl. [b] Diamine **11** also contains a CD_2 group (see Fig. 4).

A similar set of results was obtained in the deprotonation-rearrangement of cyclooctene oxide **45** using *s*-BuLi and sparteine-like diamines. The results are summarised in Table 3.[6,8] In this case, it was notable that the *N*-Et diamine **3** was the optimal (+)-sparteine-like ligand (82 : 18 er), nearly

Table 3 Asymmetric lithiation-rearrangement of cyclooctene oxide **45**



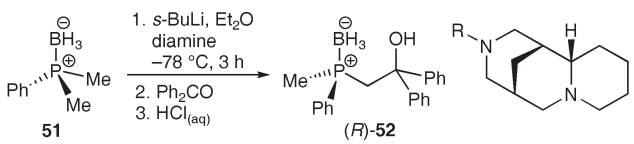
Entry	Diamine[a]	R	Yield (%)	Er[b]
1	**1**	Me	70	81 : 19
2	**3**	Et	72	82 : 18
3	**4**	*n*-Bu	53	73 : 27
4	**6**	*t*-BuCH$_2$	53	66 : 34
5	(−)-Sparteine	—	84	17 : 83

[a] *Reaction conditions:* 2.4 eq. *s*-BuLi/diamine, Et_2O, −78 °C, 5 h. [b] Ratio of (+)-**46** : (−)-**46**.

matching (−)-sparteine for enantioselectivity (83 : 17 er) (Table 3, entries 2 and 5).

Kann and co-workers have carried out a detailed study on ligand variation in the lithiation-trapping of phosphine boranes.[11,12] The results obtained with phosphine boranes **51**, **53** and **55** using a selection of (+)-sparteine surrogates are summarised in Tables 4–6. For all three phosphine boranes, use of (+)-sparteine surrogates **1** (*N*-Me) or **3** (*N*-Et) gave the highest enantioselectivity and the results were comparable to that obtained with (−)-sparteine. In contrast to the *N*-Boc pyrrolidine results, yields were generally high and independent of the steric hindrance of the diamine ligand. Indeed, the formation of an active complex between *s*-BuLi and diamine **9** (*N*-*i*-Pr) was further demonstrated as high yields (72–82%) and good enantioselectivity (⩾81 : 19 er) were obtained with all of the phosphine boranes (Table 4, entry 4; Table 5, entry 4; Table 6, entry 4). The optimum ligand for each phosphine borane was found to be as follows: for phenyl-substituted **51**, diamine (+)-**3** gave (*R*)-**52** of 86.5 : 16.5 er (Table 4, entry 2); for cyclohexyl-substituted **53**, diamine (+)-**1** gave (*R*)-**54** of 87 : 13 er (Table 5, entry 1); for *t*-Bu-substituted **55**, diamine (+)-**1** gave (*R*)-**56** of 96 : 4 er (Table 6, entry 1). Thus, for phosphine

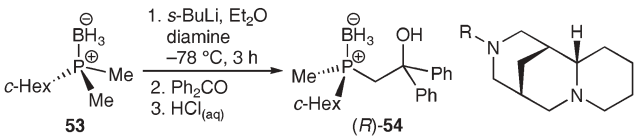
Table 4 Asymmetric lithiation-trapping of phosphine borane **51**



Entry	Diamine[a]	R	Yield (%)	Er (*R* : *S*)
1	**1**	Me	89	83.5 : 16.5
2	**3**	Et	85	86.5 : 13.5
3	**5**	Bn	16	*rac*
4	**9**	*i*-Pr	82	81.5 : 19.5
5	**7**	*c*-PrCH$_2$	63	78 : 22
6	**7**	*c*-PrCH$_2$	48[b]	63 : 37[b]
7	**8**	*c*-HexCH$_2$	93	79.5 : 20.5
8	**8**	*c*-HexCH$_2$	72[b]	80 : 20[b]
9	(−)-sparteine	—	87	11 : 89

[a] *Reaction conditions:* (a) 1.0 eq. *s*-BuLi, 1.1 eq. diamine, Et_2O, −78 °C, 3 h; (b) Ph_2CO, −20 °C, 4 h; (c) $HCl_{(aq)}$. [b] Reaction carried out with *n*-BuLi in place of *s*-BuLi.

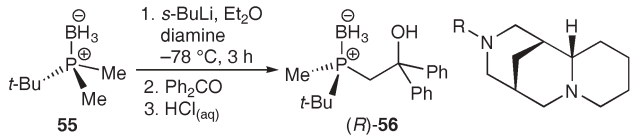
Table 5 Asymmetric lithiation-trapping of phosphine borane **53**



Entry	Diamine[a]	R	Yield (%)	Er (*R* : *S*)
1	**1**	Me	77	87 : 13
2	**3**	Et	62	84 : 16
3	**5**	Bn	24	71 : 29
4	**9**	*i*-Pr	86	81 : 19
5	**7**	*c*-PrCH$_2$	94	83 : 17
6	**8**	*c*-HexCH$_2$	62	80 : 20
7	(−)-Sparteine	—	67	15 : 85

[a] *Reaction conditions:* (a) 1.0 eq. *s*-BuLi, 1.1 eq. diamine, Et_2O, −78 °C, 3 h; (b) Ph_2CO, −20 °C, 4 h; (c) $HCl_{(aq)}$.

Table 6 Asymmetric lithiation-trapping of phosphine borane **55**



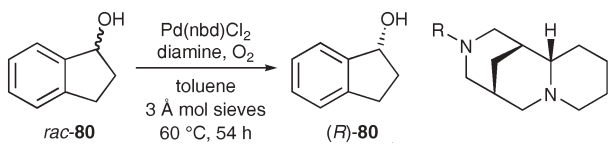
Entry	Diamine[a]	R	Yield (%)	Er (*R* : *S*)
1	**1**	Me	78	96 : 4
2	**3**	Et	82	95 : 5
3	**5**	Bn	35	75 : 25
4	**9**	*i*-Pr	72	87.5 : 12.5
5	**7**	*c*-PrCH$_2$	76	88 : 12
6	**7**	*c*-PrCH$_2$	65[b]	87 : 13[b]
7	**8**	*c*-HexCH$_2$	79	85.5 : 14.5
8	**8**	*c*-HexCH$_2$	73[b]	86.5 : 13.5[b]
9	(−)-Sparteine	—	83	12 : 88

[a] *Reaction conditions*: (a) 1.0 eq. *s*-BuLi, 1.1 eq. diamine, Et_2O, −78 °C, 3 h; (b) Ph_2CO, −20 °C, 4 h; (c) $HCl_{(aq)}$. [b] Reaction carried out with *n*-BuLi in place of *s*-BuLi.

borane deprotonation, it appears that diamine (+)-**1** (*N*-Me) is the ligand of choice.

Our group has also explored ligand variation in the Pd(II)-catalysed oxidative kinetic resolution of indanol *rac*-**80** (Table 7).[8] In this case, increasing the steric hindrance of the

Table 7 Oxidative kinetic resolution of indanol *rac*-**80**



Entry	Diamine[a]	R	C^b (%)	Er (*S* : *R*)	$k_{rel}{}^c$
1	**1**	Me	41	72 : 28	6.8
2	**3**	Et	68	91 : 9	5.3
3	**4**	*n*-Bu	64	79 : 21	3.4
4	**6**	*t*-BuCH$_2$	0	—	—
5	(−)-Sparteine	—	67	4 : 96	8.0

[a] *Reaction conditions*: 0.2 eq. diamine, 0.05 eq. $Pd(nbd)Cl_2$, toluene, O_2, 4 Å molecular sieves, 60 °C, 54 h. [b] *C* = % conversion to corresponding ketone. [c] k_{rel} = relative rate of reaction of each enantiomer of **80**, calculated from the % conversion (*C*) and the enantiomer ratio (er).

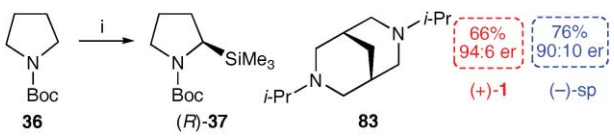
N-alkyl substituent led to a reduction in the efficiency of the kinetic resolution. Furthermore, there was no reaction when the most sterically hindered ligand, diamine **6** (*N*-*t*-BuCH$_2$) was used (Table 7, entry 4). The most effective kinetic resolution was obtained using diamine (+)-**1** (*N*-Me) (Table 7, entry 1).

In all of the cases where a range of (+)-sparteine surrogates has been compared, it is clear that either the *N*-Me or *N*-Et-substituted diamines **1** and **3** are optimal. Increasing the steric hindrance of the *N*-alkyl substituent in the (+)-sparteine surrogates has so far led to significant lowering of yield and/or enantioselectivity.

Catalytic asymmetric deprotonation

Since 2004, our group has been investigating catalytic asymmetric deprotonation reactions using *s*-BuLi and sub-stoichiometric quantities of (−)-sparteine or diamine (+)-**1**. Our first efforts focused on reactions that used a two-ligand system for recycling the chiral diamine (*e.g.* deprotonation of *N*-Boc pyrrolidine **36** and *O*-alkyl carbamate **42**).[34,38,66] However, recent efforts have identified reactions that are successful using one-ligand catalysis (*e.g.* deprotonation of phosphine borane **55** and ferrocene amide **61**).[45]

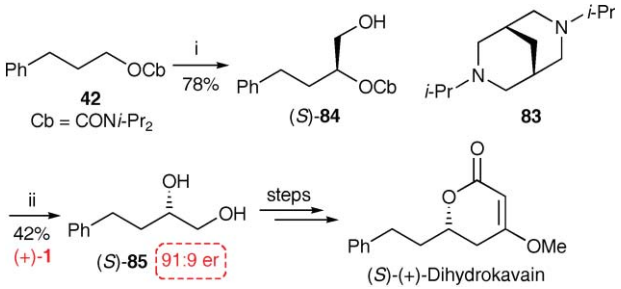
The development of catalytic asymmetric variants of the Beak and Hoppe *s*-BuLi/(−)-sparteine-mediated deprotonation reactions was achieved in our group during 2004–5. As Beak had previously noted for lithiation of *N*-Boc pyrrolidine **36**,[32] use of sub-stoichiometric amounts of (−)-sparteine gave a low yield of (*S*)-**37**. However, if a second ligand, bispidine **83**, was also included, efficient recycling of the chiral diamine was possible. Our optimised catalytic asymmetric lithiation of *N*-Boc pyrrolidine **36** using (−)-sparteine or (+)-**1** and bispidine **83** is shown in Scheme 23.[66]



Scheme 23 *Reagents and conditions:* i, (a) 1.3 eq. *s*-BuLi, 0.2 eq. (−)-sparteine or (+)-**1**, 1.2 eq. **83**, Et$_2$O, −78 °C, 5 h; (b) Me$_3$SiCl.

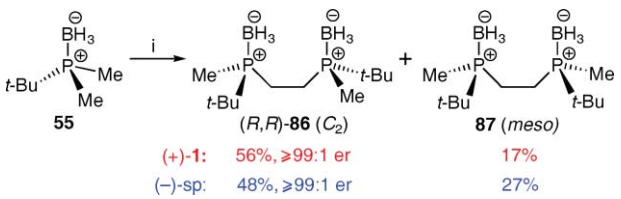
Based on the ligand variation study presented in Table 1 (entry 6, diamine **9**, *N*-*i*-Pr), bispidine **83** was designed with the hope that its *s*-BuLi complex would not deprotonate *N*-Boc pyrrolidine **36** (due to steric hindrance). However, we anticipated that ligand **83** could exchange with (−)-sparteine to allow regeneration of the reactive *s*-BuLi/(−)-sparteine chiral base. To our delight, using 1.3 eq. *s*-BuLi with 0.2 eq. (+)-sparteine surrogate (+)-**1** and 1.2 eq. bispidine **83**, adduct (*R*)-**37** was generated in 66% yield and 94 : 6 er (Scheme 23). This result is notable for two reasons. First, the yield and enantioselectivity are almost identical to those obtained under stoichiometric conditions (84%, 95 : 5 er, Scheme 9). Second, higher enantioselectivity (94 : 6 er) was obtained with (+)-**1** compared to that with (−)-sparteine (90 : 10 er in favour of *S*) (Scheme 23). We speculate that this may be due to a more efficient catalysis as the complex of *s*-BuLi/(+)-**1** is more reactive than *s*-BuLi/(−)-sparteine (Scheme 10).

In a similar fashion, two-ligand catalytic asymmetric deprotonation of *O*-alkyl carbamate **42** was successfully carried out and has been used in a formal synthesis of the natural product (*S*)-(+)-dihydrokavain (Scheme 24).[38] Here, diamine (+)-**1** was required to set up the naturally occurring (*S*)-stereochemistry. Thus, *O*-alkyl carbamate **42** was lithiated using 1.3 eq. *s*-BuLi, 0.2 eq. (+)-**1** and 1.2 eq. **83**, trapped with CO$_2$ and reduced with BH$_3$·Me$_2$S to give adduct (*S*)-**84** in 78% yield. Next, the carbamate group was removed *via* LiAlH$_4$ reduction to generate diol (*S*)-**85** (91 : 9 er) which has previously been converted into (*S*)-(+)-dihydrokavain.[67]



Scheme 24 *Reagents and conditions:* i, (a) 1.3 eq. *s*-BuLi, 0.2 eq. (+)-**1**, 1.2 eq. **83**, Et$_2$O, −78 °C, 5 h; (b) CO$_2$; (c) HCl$_{(aq)}$; (d) BH$_3$·Me$_2$S, THF, rt, 16 h; (e) MeOH, rt, then reflux, 1 h; ii, LiAlH$_4$, THF, reflux, 16 h.

As a final example, we have recently found that one-ligand catalytic asymmetric deprotonation of phosphine borane **55** is possible,[45] as previously noted by Evans.[46] A comparison of the (+)-sparteine surrogate **1** with (−)-sparteine for the lithiation-dimerisation of phosphine borane **55** is shown in Scheme 25. Lithiation of **55** using 1.1 eq. *s*-BuLi/0.2 eq. (+)-**1** was followed by CuCl$_2$-mediated dimerisation to give the C_2 symmetric bisphosphine (*R*,*R*)-**86** in 56% yield and ⩾99 : 1 er.[45] There is asymmetric amplification in the dimerisation as most of the minor enantiomer of the lithiated phosphine borane is converted into *meso*-**87** (17% yield). The catalytic efficiency of the *s*-BuLi/(−)-sparteine complex appears to be less than the *s*-BuLi/(+)-**1** complex as, under identical conditions, a lower yield of (*S*,*S*)-**86** (48%) and an accompanied higher yield of *meso*-**87** (27%) were obtained using (−)-sparteine.



Scheme 25 *Reagents and conditions:* i, (a) 1.1 eq. *s*-BuLi, 0.2 eq. (+)-**1** or (−)-sparteine, Et$_2$O, −78 °C, 3 h; (b) CuCl$_2$, rt, 16 h.

Miscellaneous

In order to provide further information on the (+)-sparteine surrogate family of diamines, X-ray crystallography of the organolithium–diamine complexes has been carried out in

collaboration with Strohmann's group. As a result, solid-state structures of MeLi and PhLi adducts with diamine (+)-**1** have been described.[68] In collaboration with Wiberg and Bailey, we have also carried out a detailed computational study on the asymmetric deprotonation of *N*-Boc pyrrolidine **36** using different (+)-sparteine surrogates.[9] Finally, Hodgson and co-workers have shown that diamine rac-**1** is an optimal ligand for the lithiation-trapping of terminal epoxides.[69]

Conclusions and outlook

In summary, the most useful and widely used (+)-sparteine surrogate is the *N*-Me diamine (+)-**1**, which can be easily prepared from extracted (−)-cytisine. Diamine (+)-**1** has a broad scope and behaves as the mirror image of (−)-sparteine in most of the reactions investigated. Of note, *s*-BuLi/(+)-**1** appears to be more reactive than *s*-BuLi/(−)-sparteine and this has important consequences in deprotonations of less reactive compounds and catalytic asymmetric deprotonation, two areas of current focus in our group. As a result of the enhanced reactivity of *s*-BuLi/(+)-**1**, discovery of an efficient synthesis of the (−)-sparteine surrogate, diamine (−)-**1**, is an important objective for future research in this area.

Acknowledgements

I would especially like to thank each of the following co-workers for their hard work, perseverance and scientific contribution on the "sparteine project" over the last ten years: David Porter, Justin Harrison, Vladimir Tyurin, Jean-Paul Hermet, Tobias Koplin, Jérôme Parmene, Michael Dearden, Matthew McGrath, Cédric Genet, Julia Bilke, Steven Canipa, Darren Stead, Stephen Moore, Jonathan Gammon, Jonathan Wright, Amanda Dixon and Adrian Whitwood. This strand of our research has received generous financial support from EPSRC, BBSRC, AstraZeneca, SmithKline Beechams (as was), Hoffmann-La Roche, Lilly, Celtic Catalysts, The Leverhulme Trust and The Royal Society (NATO). I am also grateful to The Royal Society of Chemistry for the award of a J. W. T. Jones Travelling Fellowship (sabbatical stay at the University of Geneva). Finally, I would like to thank my colleague, Professor Richard J. K. Taylor, who first suggested christening diamine (+)-**1** as the "(+)-sparteine surrogate".

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22 During the summer of 2001, our then Head of Department, Professor Robin Perutz suggested that I consider an overseas lecture tour as a means of raising the group's profile. Hence, I embarked on a lecture tour to France and Belgium in September 2001, funded by a Pfizer travel bursary and it was whilst visiting the Université de Caen–Basse–Normandie that our attention was alerted to the (−)-cytisine extraction procedure, optimised by Jacques Rouden (see ref. 23). We had not previously considered (−)-cytisine as a viable starting material as it is expensive (2007–8 Aldrich price: £502 for 250 mg).

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