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# A New Sparteine Surrogate for Asymmetric Deprotonation of *N*-Boc Pyrrolidine

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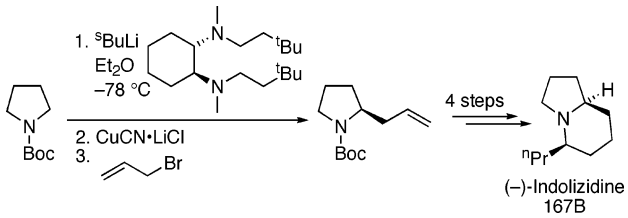
## ABSTRACT




**The *s*-BuLi complex of a cyclohexane-derived diamine is as efficient as *s*-BuLi/(−)-sparteine for the asymmetric deprotonation of *N*-Boc pyrrolidine. This is the first example of high enantioselectivity using a non-sparteine-like diamine in such reactions. The (*S*,*S*)-diamine is a useful (+)-sparteine surrogate and was utilized in short syntheses of (−)-indolizidine 167B and an intermediate for the synthesis of the CCK antagonist (+)-RP 66803.**

Seminal work from the groups of Hoppe[1] and Beak[2] has highlighted the importance and effectiveness of the natural alkaloid (−)-sparteine as a ligand for *s*-butyllithium in asymmetric deprotonation processes.[3] In earlier work, we addressed the limitation of accessing products with (+)-sparteine-derived stereochemistry by introducing a readily available (+)-sparteine surrogate (+)-**1** (Figure 1).[4,5] Diamine (+)-**1** is as efficient as (−)-sparteine in the *s*-BuLi-mediated asymmetric deprotonation of *N*-Boc pyrrolidine and *O*-alkyl carbamates but, importantly, delivers products with opposite enantioselectivity. Diamine (+)-**1** has been adopted by other groups in a range of applications.[6]

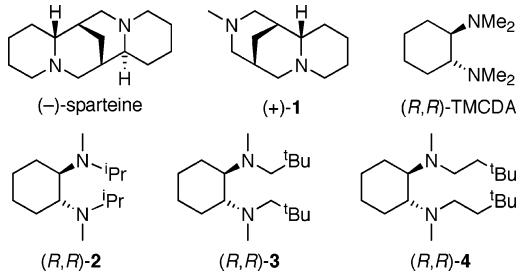



**Figure 1.** Selection of chiral diamines.

Of course, diamine (+)-**1** is only a pseudo-enantiomer of (−)-sparteine and, as such, there will be differences in rates of reactions and enantioselectivity using (−)-sparteine and (+)-**1**. Notwithstanding the success of other pseudo-enantiomeric pairs of ligands (e.g., cinchona alkaloids), enantiomeric ligands are preferred in asymmetric synthesis. Hence, we searched for chiral diamines that would show comparable

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(1) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422.
(2) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
(3) For a review, see: Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.
(4) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870.
(5) For a review, see: O'Brien, P. *Chem. Commun.* **2008**, 655.

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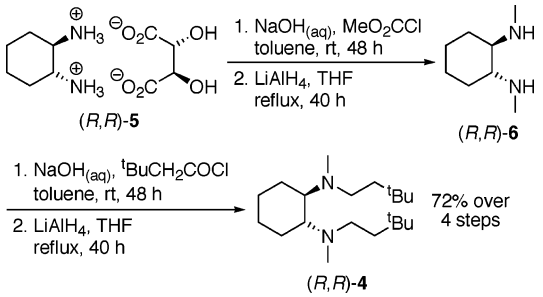
enantioselectivity to (−)-sparteine in *s*-BuLi-mediated deprotonation reactions.

We were attracted to cyclohexane-derived diamines (e.g., TMCDA), which are readily available in both enantiomeric forms. In particular, recent work from the Alexakis group has advocated the use of diamines such as (*R*,*R*)-**2**−**4** that, by way of differently functionalized amino groups, possess stereogenic nitrogen atoms upon complexation to organolithium reagents.[7,8] Hence, we evaluated some asymmetric deprotonation reactions with *s*-BuLi/diamines (*R*,*R*)-**2**−**4**, and herein it is reported that diamine **4** is as effective as (−)-sparteine for the deprotonation of *N*-Boc pyrrolidine. We also describe an efficient multigram scale preparation of diamine (*R*,*R*)-**4** (and (*S*,*S*)-**4**) and two synthetic applications of diamine (*S*,*S*)-**4** where (+)-sparteine-derived stereochemistry is needed to obtain the appropriate enantiomer of the product.

Diamines (*R*,*R*)-**2**−**4** were prepared using routes that involved minor changes to those originally described by Alexakis[7] (see Supporting Information). As a representative example, the synthesis of (*R*,*R*)-**4** is summarized in Scheme 1. First, (±)-*trans*-cyclohexane-1,2-diamine was resolved

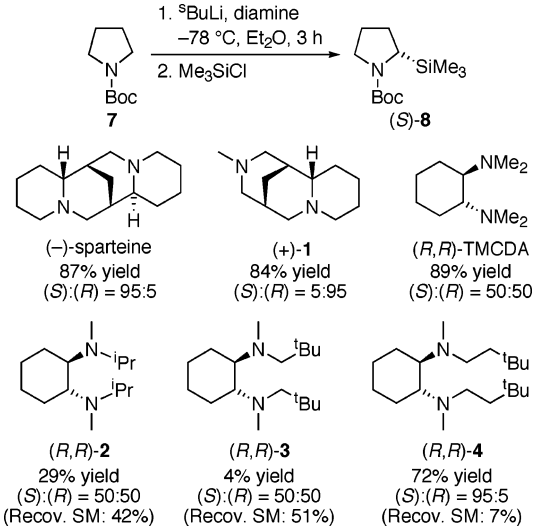
**Scheme 1**




using L- and D-tartaric acid to give both salts (*R*,*R*)-**5** and (*S*,*S*)-**5**.[9] Then, reaction of (*R*,*R*)-**5** with $NaOH_{(aq)}$/$MeO_2CCl$ gave a *bis*-methyl carbamate, which was reduced using $LiAlH_4$[10] to deliver diamine (*R*,*R*)-**6**. Next, acylation of diamine (*R*,*R*)-**6** using *t*-butylacetyl chloride delivered a crude *bis*-amide that was reduced using $LiAlH_4$ to give diamine (*R*,*R*)-**4** in 72% yield after purification by Kugelrohr distillation over 4 steps (Scheme 1). The synthesis was readily achieved on a multigram scale: 10.0 g of salt (*R*,*R*)-**5** produced 8.4 g of diamine (*R*,*R*)-**4** after distillation, the only purification required in the sequence.

With diamines (*R*,*R*)-**2**−**4** in hand, we evaluated them in different asymmetric deprotonation reactions. First, Beak's lithiation-trapping of *N*-Boc pyrrolidine **7** (→ **8**) was used to compare the three ligands. The results are shown in Scheme 2, together with those obtained with (−)-sparteine,

**Scheme 2**




(+)-**1**,[4] and (*R*,*R*)-TMCDA.[11] The sterically hindered diamines (*R*,*R*)-**2** and (*R*,*R*)-**3** produced *s*-BuLi complexes that were unreactive (low yields with significant amounts of recovered starting material) and gave racemic adduct **8**. In contrast, moving the sterically hindered *t*-Bu group in the ligand one atom further along the *N*-alkyl chain relative to (*R*,*R*)-**3** gave a *s*-BuLi complex that delivered (*S*)-**8** of 95:5 er in 72% yield. The difference between diamines (*R*,*R*)-**3** and (*R*,*R*)-**4** is remarkable. Indeed, this is the first example of a non-sparteine-like diamine whose *s*-BuLi complex shows such high enantioselectivity.

Having established that diamine **4** was the optimal cyclohexane-derived ligand, asymmetric deprotonation of an *O*-alkyl carbamate,[1,12] an epoxide,[13] and a phosphine borane[14] were investigated using *s*-BuLi/diamine **4** (Scheme 3). A satisfactory result was obtained with the *O*-alkyl carbamate: deprotonation of **9**, trapping with $CO_2$, and reduction with $BH_3$ gave alcohol (*S*)-**10** of 84:16 er (84% yield). This is slightly worse than a previous result using *s*-BuLi/TMCDA on a sterically hindered O-alkyl carbamate.[12] In contrast, the enantioselectivity with cyclooctene oxide **11** and phosphine borane **13** were significantly worse than those obtained with (−)-sparteine. Apparently, the *s*-BuLi/diamine **4** complex

(6) (a) Johansson, M. J.; Schwartz, M.; Amedjkouh, M.; Kann, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3531. (b) Morita, Y.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2005**, *7*, 4337. (c) Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron* **2006**, *62*, 1833. (d) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7491.

(7) (a) Kizirian, J.-C.; Caille, J.-C.; Alexakis, A. *Tetrahedron. Lett.* **2003**, *44*, 8893. (b) Kizirian, J.-C.; Cabello, N.; Pinchard, L.; Caille, J.-C.; Alexakis, A. *Tetrahedron* **2005**, *61*, 8939. (c) Cabello, N.; Kizirian, J.-C.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J.-C. *Eur. J. Org. Chem.* **2005**, 4835. (d) Gille, S.; Cabello, N.; Kizirian, J.-C.; Alexakis, A. *Tetrahedron: Asymmetry* **2006**, *17*, 1045. (e) Perron, Q.; Alexakis, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2503.

(8) Hoffmann, R. W.; Klute, W.; Dress, R. K.; Wenzel, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1721.

(9) Larrow, J. F.; Jacobsen, E. N. *Org. Synth.* **1997**, *75*, 1.

(10) A long reaction time (48 h) for the $LiAlH_4$ reduction ensured that crude diamine (*R*,*R*)-**6** was of sufficient purity for subsequent reaction.

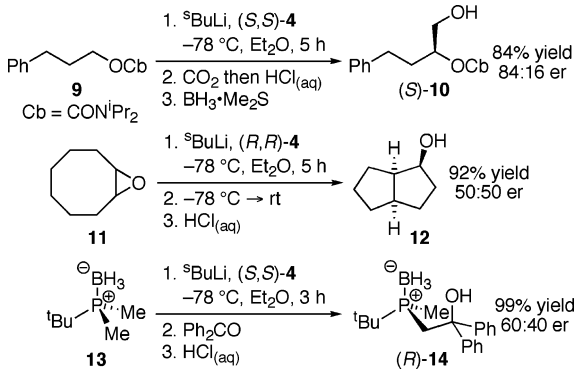
(11) Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092.

(12) Würthwein, E.-U.; Behrens, K.; Hoppe, D. *Chem.−Eur. J.* **1999**, *5*, 3459.

(13) Hodgson, D. M.; Cameron, I. D.; Christlieb, M.; Green, R.; Lee, G. P.; Robinson, L. A. *J. Chem. Soc., Perkin Trans 1* **2001**, 2161.

(14) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.

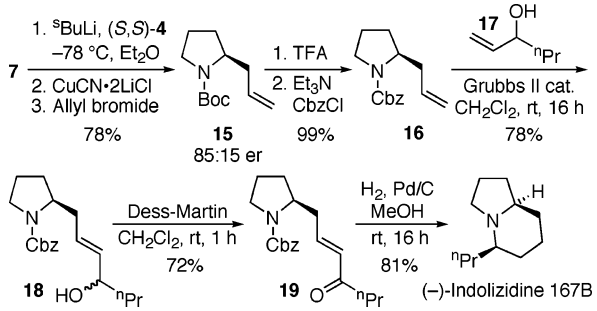
**Scheme 3**




does not show as broad a range of applicability as *s*-BuLi/(−)-sparteine or (+)-**1** although we have recently shown that the *s*-BuLi/diamine **4** complex gives high enantioselectivity in the lithiation-trapping of *N*-Boc piperidine.[15]

Our attention then focused on using *s*-BuLi/diamine **4**-mediated deprotonation of *N*-Boc pyrrolidine **7** in synthesis. In particular, to showcase diamine (*S*,*S*)-**4** as a useful (+)-sparteine surrogate, we used it in two syntheses where the stereochemistry required is opposite to that engendered by (−)-sparteine. Over the last 20 years, there has been considerable interest in the synthesis of indolizidine alkaloids from the *Dendrobates* family of neotropical frogs. We chose indolizidine 167B[16] as a target and optimized a five-step synthesis (Scheme 4).

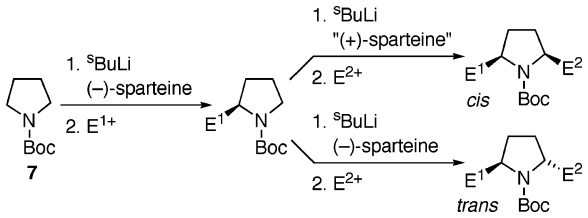
**Scheme 4**




Thus, *N*-Boc pyrrolidine **7** was deprotonated using *s*-BuLi/diamine (*S*,*S*)-**4** and allylated (via transmetallation to Cu) using a protocol developed by Dieter.[17] In this way, allylated pyrrolidine **15** of 85:15 er was produced (78% yield). A slightly reduced enantioselectivity is often encountered during these types of transmetallation-allylation procedures.[17] Next, it was necessary to swap the *N*-protecting group to Cbz,[18] which proceeded uneventfully to give *N*-Cbz protected **16** in 99% yield. Then, cross metathesis of **16** with allylic alcohol **17** gave **18** in 78% yield, which was oxidized with Dess-Martin periodinane to give enone **19** (72% yield), a known intermediate in Lhommet's,[16c] Remuson's,[16d] and Kim's[16e] syntheses. Finally, treatment of enone **19** with $H_2$ and Pd/C gave indolizidine (−)-167B in 81% yield. This is one of the shortest and most efficient syntheses of indolizidine (−)-167B to date (5 steps, 35% overall yield), although the natural product was produced in a presumed 85:15 er.[19]

Diamine (*S*,*S*)-**4** was also utilized in a new strategy for the synthesis of *cis*-2,5-disubstituted pyrrolidines via two sequential lithiation-electrophilic trappings (Scheme 5). Thus,

**Scheme 5**




*cis* relative stereochemistry would be achieved using (−)-sparteine to introduce the $E^1$ substituent and then a (+)-sparteine equivalent (e.g., diamine (*S*,*S*)-**4**) to attach the $E^2$ group.[20] In contrast, use of (−)-sparteine in both steps would produce a *trans*-2,5-disubstituted pyrrolidine, as has been previously reported.[2]

This *cis*-pyrrolidine strategy was used to prepare pyrrolidine *cis*-**22** (Scheme 6), which is a key intermediate in the synthesis of the CCK antagonist (+)-RP 66803.[21] To start with, *s*-BuLi/(−)-sparteine-mediated lithiation-Negishi coupling of *N*-Boc pyrrolidine **7** was used to prepare arylated adduct **20** (81% yield, 95:5 er), according to a protocol recently reported by Campos and co-workers.[22] Then, the second lithiation was carried out using *s*-BuLi/diamine

(15) Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2113.

(16) For previous syntheses, see: (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. (c) Fleurant, A.; Cèlèrier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1992**, *3*, 695. (d) Peroche, S.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron Lett.* **2001**, *42*, 4617. (e) Kim, G.; Lee, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2073. (f) Corvo, M. C.; Pereira, M. M. C. *Tetrahedron Lett.* **2002**, *43*, 455. (g) Amat, M.; Lior, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. (h) Reddy, P. G.; Baskaran, S. *J. Org. Chem.* **2004**, *69*, 3093. (i) Sun, Z.; Shouyun, Y.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300.

(17) Dieter, K. R.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076.

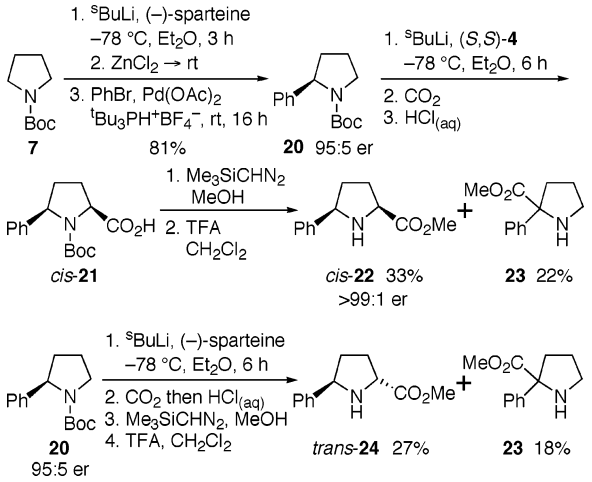
(18) The *N*-Boc analogue of **19** was successfully prepared but Boc deprotection and reaction with $H_2$ and Pd/C gave low yields of impure indolizidine (−)-167B.

(19) Our sample of indolizidine (−)-167B showed $[\alpha]^{24}_D$ −89.5 (*c* 0.2 in $CH_2Cl_2$) (lit. (ref 16c) $[\alpha]^{24}_D$ −115 (*c* 1.17 in $CH_2Cl_2$) for (−)-indolizidine 167B of ≥ 99:1 er), which is consistent with 85:15 er.

(20) For an isolated example of the synthesis of a *cis*-2,5-pyrrolidine via a *s*-BuLi/(−)-sparteine-mediated deprotonation, see: Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.

(21) For previous syntheses, see: (a) Manfré, F.; Pulicanai, J. P. *Terahedron: Asymmetry* **1994**, *5*, 235. (b) Haddad, M.; Imogaï, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680. (c) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599. (d) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305. (e) Rudolph, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895. (f) van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791.

**Scheme 6**




(*S*,*S*)-**4** and subsequent trapping with $CO_2$ afforded acid *cis*-**21** which was not isolated. Instead, the crude carboxylic acid was converted into its methyl ester (using $Me_3SiCHN_2$) and Boc-deprotected to give pyrrolidine *cis*-**22**[21b] (>99:1 er) in 33% isolated yield (after column chromatography). The reagent-controlled *cis*-stereoselectivity was essentially complete as <5% of pyrrolidine *trans*-**24** was produced (as judged by $^1$H NMR spectroscopy of the crude product and comparison with a sample of *trans*-**24** prepared independently, *vide infra*). The efficiency of forming *cis*-**22** was compromised by competitive benzylic deprotonation of **20**,[23] which led to 22% of pyrrolidine **23**.[24] Nonetheless, our two-operation route to pyrrolidine *cis*-**24** from *N*-Boc pyrrolidine **7** is the shortest synthesis reported to date. Interestingly, *cis*-**22** was generated in >99:1 er, which is higher than the 95:5 er of the starting material **20**. Thus, the minor enantiomer of **20** is either not deprotonated by the chiral base or undergoes benzylic lithiation to ultimately give **23**. To demonstrate unequivocally the success of our *cis*-pyrrolidine stratgey, lithiation-carboxylation of **20** using *s*-BuLi/(−)-sparteine and subsequent ester formation and Boc deprotection gave pyrrolidine *trans*-**24**[21c] (27% yield) and optically active pyrrolidine **23** (18% yield, $[\alpha]_D$ −44.5 (*c* 0.05 in $CHCl_3$)).

In summary, we have shown that diamine (*S*,*S*)-**4** is an efficient (+)-sparteine surrogate for the asymmetric deprotonation of *N*-Boc pyrrolidine **7**. It is easy to synthesize multigram quantities of diamine (*S*,*S*)-**4** and we have exemplified the usefulness of diamine (*S*,*S*)-**4** with concise syntheses of indolizidine (−)-167B and pyrrolidine *cis*-**22**. In addition, a convenient strategy for the synthesis of *cis*-2,5-disubstituted pyrrolidines has been disclosed.

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**Supporting Information Available:** Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc*. **2006**, *128*, 3538.

(23) Xiao, D.; Lavey, B. J.; Palani, A.; Wang, C.; Aslanian, R. G.; Kozlowski, J. A.; Shih, N.-Y.; McPhail, A. T.; Randolph, G. P.; Lachowicz, J. E.; Duffy, R. A. *Tetrahedron Lett.* **2005**, *46*, 7653.

(24) Pyrrolidine **23** formed from this reaction was optically active {$[\alpha]_D$ −7.1 (*c* 0.9 in $CHCl_3$)} but we have so far been unable to determine its er or its absolute stereochemistry.