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On the Two-Ligand Catalytic Asymmetric Deprotonation of *N*-Boc Pyrrolidine: Probing the Effect of the Stoichiometric Ligand†

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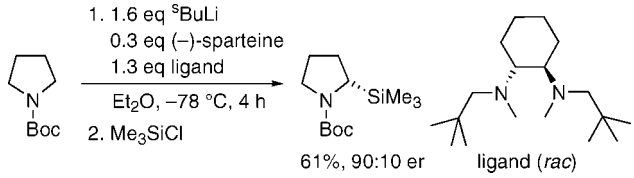
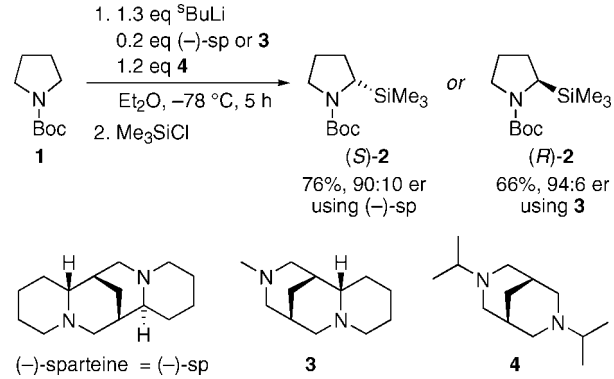


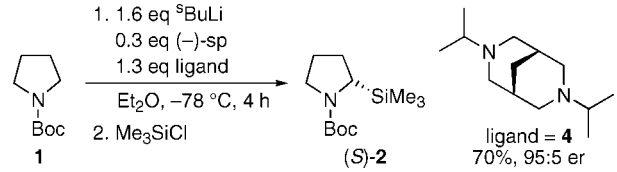
To map out the stoichiometric ligand requirements in the two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine, 24 different ligands have been evaluated; the highest enantioselectivity (90:10 er) was obtained by using *s*-BuLi in the presence of 0.3 equiv of (−)-sparteine and 1.3 equiv of a cyclohexanediamine-derived ligand.

The asymmetric deprotonation of *N*-Boc pyrrolidine **1** with *s*-BuLi/(−)-sparteine, first reported by Kerrick and Beak in 1991,[1] is not only a landmark achievement in chiral base methodology but has also proved to be a very useful approach for the direct synthesis of chiral pyrrolidines.[1b,2] Our group has a long-standing interest in Beak's *N*-Boc pyrrolidine methodology: we have used it to evaluate the efficacy of (+)-sparteine surrogates[3–6] and in total synthesis.[6] Recently, we reported a two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1**.[7,8] Thus, deprotonation of **1** was achieved by using 1.3 equiv of *s*-BuLi, 0.2 equiv of (−)-sparteine, and 1.2 equiv of bispidine **4**; subsequent trapping with Me_3SiCl gave a 76% yield of silylated adduct (*S*)-**2** of 90:10 er (Scheme 1).[7] A similar result, with the opposite sense of induction, was obtained by using the (+)-sparteine surrogate **3**. If bispidine **4** was omitted, there was no turnover of the (−)-sparteine and low yield and reduced enantioselectivity resulted. This two-ligand strategy was also successful in Hoppe's *O*-alkyl carbamate methodology.[9]

SCHEME 1. Two-Ligand Catalytic Asymmetric Deprotonation of *N*-Boc Pyrrolidine 1, using *s*-BuLi/(−)-Sparteine or (+)-Sparteine Surrogate 3



SCHEME 2. Two-Ligand Catalytic Asymmetric Deprotonation of *N*-Boc Pyrrolidine 1



Bispidine **4** was designed with steric hindrance on the amines so that its *s*-BuLi complex would have a low reactivity thus minimizing background racemic deprotonation.[8] To establish whether such a design criteria was important and to map out the structural requirements of the stoichiometric ligand, we have now carried out an extensive ligand variation study. For the synthesis of the ligands, our criteria were that the synthesis should be no more than three steps, it must allow multigram quantities to be prepared, and there should be only one purification at the end of the synthesis. Herein, we report the results of an investigation of 24 different stoichiometric ligands in the *s*-BuLi-mediated two-ligand asymmetric deprotonation of *N*-Boc pyrrolidine **1**.

To evaluate the different stoichiometric ligands, the following conditions were adopted for the deprotonation of *N*-Boc pyrrolidine **1**: 1.6 equiv of *s*-BuLi, 0.3 equiv of (−)-sparteine, and 1.3 equiv of the stoichiometric ligand (either achiral or racemic). Using bispidine **4** under these conditions gave a 70% yield of silylated adduct (*S*)-**2** of 95:5 er (Scheme 2), the same enantioselectivity as we routinely obtain using stoichiometric (−)-sparteine. This was the benchmark result and we hoped to identify other ligands that would produce such high enantioselectivity. We designed a series of more sterically hindered analogues of commonly encountered ligands for organolithium-mediated deprotonation reactions.

† This paper is dedicated to the memory of Professor A. I. Meyers for his numerous pioneering contributions to organolithium-mediated deprotonation reactions.

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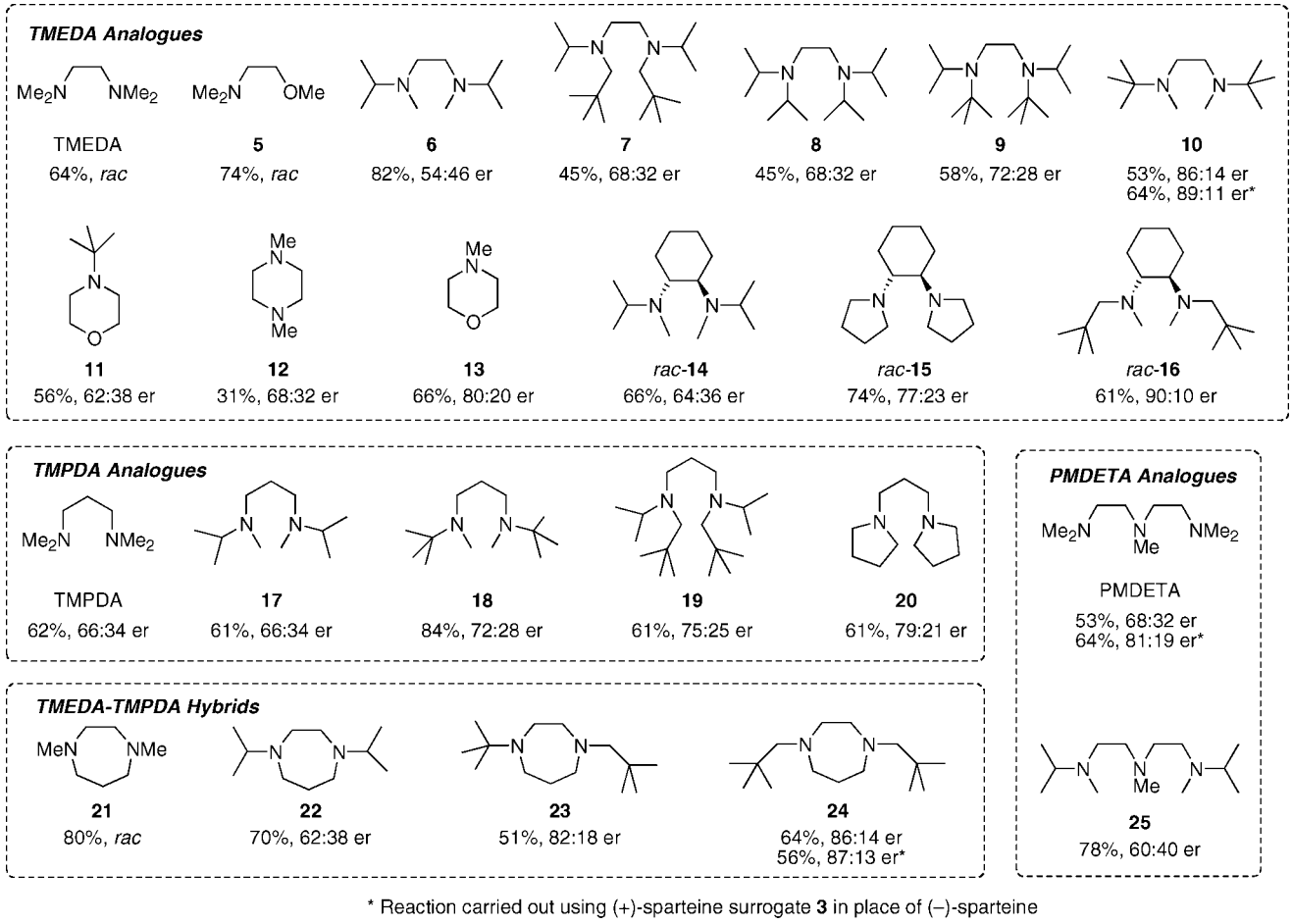

FIGURE 1. Results for the two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1**.

These included analogues of tetramethylethylenediamine (TMEDA), tetramethyl-1,3-propanediamine (TMPDA), and pentamethyldiethylenetriamine (PMDETA) as well as TMEDA-TMPDA hybrid ligands containing a homopiperazine motif (Figure 1). The syntheses of all of the ligands **5**−**25** are described in the Supporting Information. The ligands were evaluated by using the conditions shown in Scheme 2 (1.3 equiv of ligand in place of bispidine **4**) and the full results are shown in Figure 1. The yields are those obtained after purification by chromatography and the er values were determined by using chiral GC. In three examples, we also carried out the catalytic reactions using the (+)-sparteine surrogate **3**.

By using TMEDA and amino ether **5**, *racemic* silylated adduct **2** was generated and this reflects the rapid lithiation of *N*-Boc pyrrolidine **1** by their *s*-BuLi complexes.[10] Beak had previously noted a similar result using TMEDA and substoichiometric amounts of (−)-sparteine.[1b] By increasing the steric hindrance of the *N*-substituents (ligands **6**−**10**), better enantioselectivity was obtained (up to 86:14 er with (−)-sparteine). Broadly speaking, the degree of enantioselectivity mirrored the steric hindrance of the ligand but, perhaps surprisingly, the highest er (86:14 er of (*S*)-**2** with ligand **10**) was not obtained with the most sterically hindered ligands **7**−**9**. Similarly, with morpholines **11** and **13**, better results were obtained with the less sterically hindered ligand **13** (80:20 er). The 80:20 er observed with ligand **13** is the highest enantioselectivity we have obtained with a commercially available ligand. In contrast, *N*,*N*′-dimethylpiperazine **12** was a poor stoichiometric ligand, giving low yield (31%) and enantioselectivity (68:32 er). Investigations into the use of diamines based on a racemic *trans*-cyclohexanediamine scaffold **14**−**16** led to the discovery of our best stoichiometric ligand: *rac*-**16** gave (*S*)-**2** of 90:10 er in 61% yield.

Collum and co-workers had previously reported that *n*-BuLi/TMPDA was less reactive than *n*-BuLi/TMEDA in the α-lithiation of an imine.[11] Our catalytic results with *s*-BuLi/TMPDA are consistent with a similar rate difference for the deprotonation of *N*-Boc pyrrolidine **1**: using TMPDA, (*S*)-**2** of 66:34 er was obtained (compared to *rac*-**2** with TMEDA). Therefore, we explored more sterically hindered TMPDA analogues **17**−**20** with moderate success (up to 79:21 er with ligand **20**) and TMEDA-TMPDA hybrids **21**−**24** with more success. The catalytic results with *N*,*N*′-dimethylhomopiperazine ligand **21** led to the generation of *rac*-**2** suggesting that it is more TMEDA-like than TMPDA-like. In line with this, increasing the steric hindrance in the homopiperazines **22**−**24** did lead to improved catalytic results (up to 86:14 er with (−)-sparteine).

Finally, we briefly investigated the use of the triamines PMDETA and ligand **25**, a more sterically encumbered analogue. In these cases, the (−)-sparteine catalytic results were somewhat disappointing and the best enantioselectivity was 68:32 er with (−)-sparteine. For three of the ligands *rac*-**16**, **24**, and PMDETA, the (+)-sparteine surrogate **3** was compared with

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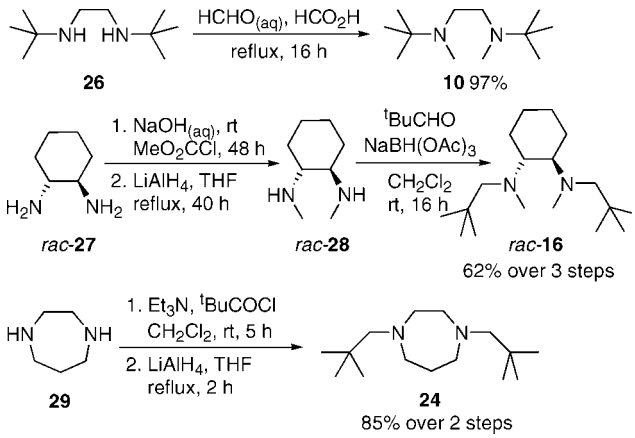
SCHEME 3. Synthesis of the Optimum Stoichiometric Ligands 10, *rac*-16, and 24



(−)-sparteine in the catalytic reactions. In each case, higher enantioselectivity was obtained with diamine **3** and the largest difference was noted with PMDETA: 68:32 er with (−)-sparteine and 81:19 er with diamine **3**. These results fit our previous suggestion[8] that the higher reactivity of the *s*-BuLi/diamine **3** complex facilitates more efficient turnover in the two-ligand catalytic process and hence results in improved enantioselectivity compared to (−)-sparteine.

Our studies have revealed that diamine ligands **10** (86:14 er), *rac*-**16** (90:10 er), and **24** (86:14 er) are the optimum TMEDA-like stochiometric ligands for the two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1**. These diamines are easy to synthesize and their synthetic routes are summarized in Scheme 3. Diamine **10**[12] (97% yield) was prepared in one step from diamine **26** via Eschweiler−Clarke methylation. For the synthesis of diamine *rac*-**16**, *trans*-cyclohexanediamine *rac*-**27** was first converted into diamine *rac*-**28** (via bis-methyl carbamate formation and $LiAlH_4$ reduction). Then, reductive amination generated diamine *rac*-**16**[13] in 62% yield over 3 steps. A two-step route comprising acylation and $LiAlH_4$ reduction was used to synthesize diamine **24** from homopiperazine **29** (85% yield over 2 steps).

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In summary, a study of 24 different stoichiometric ligands in the two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1** has identified three satisfactory TMEDA-like diamine ligands: **10**, *rac*-**16**, and **24**. These ligands are easy to synthesize on a multigram scale and the best result (61% yield, 90:10 er) was obtained with cyclohexanediamine-derived ligand *rac*-**16**. Surprisingly, use of the most sterically hindered ligands such as **7**, **8**, **9**, **19**, and **23** did not lead to the highest enantioselectivity indicating the subtle and unpredictable nature of steric effects in organolithium-mediated deprotonation processes.

Experimental Section

General Procedure for the Catalytic Asymmetric Deprotonation of *N*-Boc Pyrrolidine 1. A solution of (−)-sparteine or the (+)-sparteine surrogate **3** (0.6 mmol, 0.3 equiv) in Et_2O (1 mL) was added dropwise to a stirred solution of *s*-BuLi (2.7 mL of a 1.2 M solution in cyclohexane, 3.2 mmol, 1.6 equiv) in Et_2O (5 mL) at −78 °C under Ar. Then, a solution of the stoichiometric ligand (TMEDA, TMPDA, PMDETA or ligands **4**−**25**) (2.6 mmol, 1.3 equiv) in Et_2O (1 mL) was added dropwise. After being stirred for 10 min, a solution of *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv) in Et_2O (1 mL) was added dropwise via a cannula over 10 min. The resulting solution was stirred at −78 °C for 4 h. Then, Me_3SiCl (0.4 mL, 3.2 mmol, 1.6 equiv) was added dropwise and the reaction mixture was allowed to warm to rt over 4 h and stirred at rt for 12 h. $H_3PO_{4(aq)}$ (5%, 10 mL) was added and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 19:1 petrol−Et_2O as eluent gave the pure adduct (*S*)- or (*R*)-**2** as a colorless oil (chiral GC 30 m × 0.25 mm i.d. (β-cyclodextrin), T = 91 °C isothermal, He carrier gas at 12 psi constant pressure). Spectroscopic data are consistent with those reported in the literature.[1b]

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Supporting Information Available: Full experimental procedures, characterization data, and copies of $^1H/^{13}C$ NMR spectra of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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