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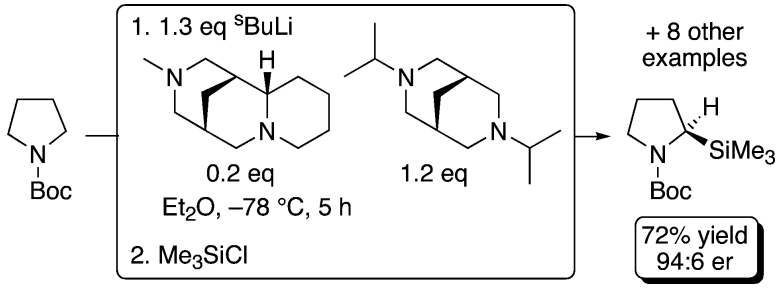

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Catalytic Asymmetric Deprotonation Using a Ligand Exchange Approach

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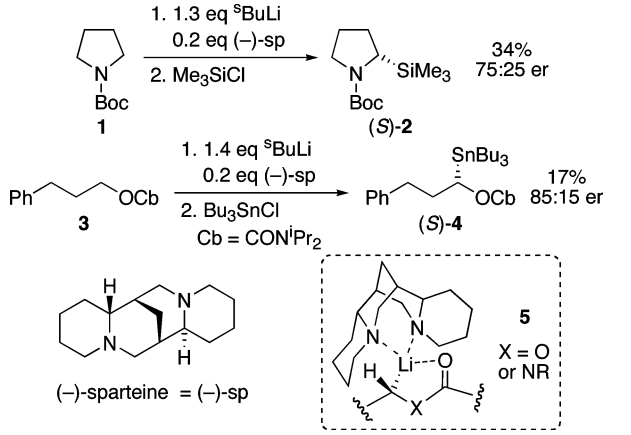
(−)-Sparteine is a widely utilized chiral diamine for *stoichiometric* asymmetric synthesis,[1,2] but reports of catalytic applications are rare. Notable exceptions, which proceed with high enantioselectivity using *substoichiometric* amounts of (−)-sparteine, include additions to imines,[3] carbolithiations,[4] conjugate addition to enoates,[5] and Pd-mediated oxidation.[6] In the area of asymmetric deprotonation reactions,[7] use of substoichiometric (−)-sparteine has had mixed success. Whereas the α-lithiation rearrangement of an epoxide gave similar yield and enantioselectivity under both stoichiometric and catalytic conditions,[8] lithiation trapping of *N*-Boc pyrrolidine **1** or *O*-alkyl carbamate **3** was far less successful (Scheme 1). For example, in our hands, use of 1.3 equiv of *s*-BuLi and 0.2 equiv of (−)-sparteine on **1** gave (*S*)-**2** of 75:25 er in 34% yield[9] (stoichiometric: 87% yield, 95:5 er[10]), and use of 1.4 equiv of *s*-BuLi and 0.2 equiv of (−)-sparteine on **3** gave (*S*)-**4** of 85:15 er in 17% yield (stoichiometric: 73% yield, 99:1 er). In these substoichiometric examples, the yield *and* enantioselectivity obtained from **1** and **3** suggest that the diamine does not readily dissociate from the lithiated complexes **5** so that the reactive *s*-BuLi/(−)-sparteine complex is not regenerated.

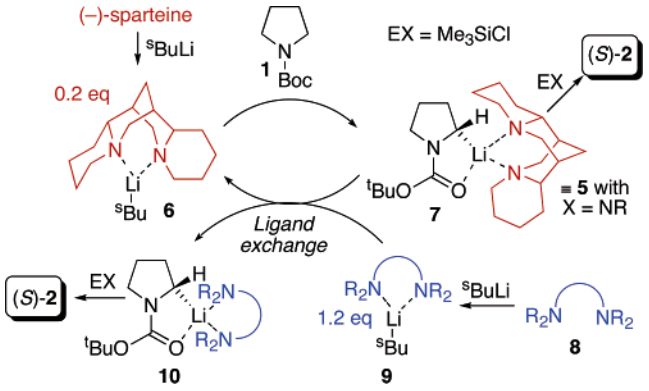
Thus, we set out to devise a conceptually different catalytic approach in which a ligand exchange process would enable the chiral ligand to be recycled from the lithiated complexes **5** such that high yield *and* enantioselectivity should be possible. An outline of our proposed approach is shown in Scheme 2 for *N*-Boc pyrrolidine **1**. We envisaged that a stoichiometric achiral diamine **8** would displace (−)-sparteine from **7** (≡ **5**, X = NR) thus producing a new organolithium/diamine complex **10** and regenerating the active *s*-BuLi/(−)-sparteine complex **6**, which could reenter the catalytic cycle. Subsequent electrophilic trapping of either **7** or **10** (or both) with Me_3SiCl after the usual lithiation time would then produce (*S*)-**2**. For such an approach to work, several criteria must be met: (i) ligand exchange must occur;[11] (ii) organolithiums **7** and **10** must be configurationally stable[12] during the ligand exchange; and (iii) deprotonation of **1** using *s*-BuLi/(−)-sparteine complex **6** must be faster than that using the achiral *s*-BuLi/diamine complex **9**.[13] Wu and Chong have recently reported a related ligand exchange concept for conjugate addition to enones using organoboron reagents.[14] We now report the application of a ligand exchange strategy to *s*-BuLi/diamine-mediated catalytic asymmetric deprotonation.

To implement the projected ligand exchange approach, a suitable achiral diamine **8** needed to be designed. For this, our ligand variation study on the lithiation trapping of *N*-Boc pyrrolidine **1**[15] was a useful guide. Thus, whereas *N*-Me diamine **11** behaved as a (+)-sparteine surrogate, the sterically hindered *N*-*i*-Pr diamine **12** failed to deprotonate **1** (even though *s*-BuLi/diamine **12** has been used in other reactions[16]). This suggested that *s*-BuLi complexes of structurally similar achiral diamines, such as bispidine **13**,[17] might be slow lithiators and thus suitable for catalysis. Consistent with this idea, lithiation trapping of **1** and **3** using excess *s*-BuLi/diamine **13** furnished adducts *rac*-**2** and *rac*-**4** in 5 and 15% isolated yields,

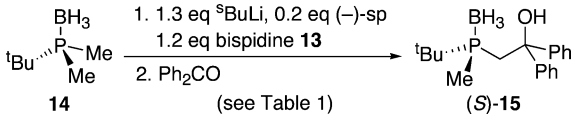
Scheme 1



Scheme 2



Scheme 3



respectively. Hence, *s*-BuLi/bispidine **13** was investigated with either (−)-sparteine or (+)-**11** in three catalytic reactions: **1** → **2**, **3** → **4**, and **14** → **15** (Scheme 3).

To our delight, when the lithiation−Me_3SiCl trapping of *N*-Boc pyrrolidine **1** was attempted using 1.3 equiv of *s*-BuLi, 0.2 equiv of (−)-sparteine, and 1.2 equiv of bispidine **13**, adduct (*S*)-**2** of 90:10 er was obtained in 76% yield (entry 1) (stoichiometric: 87%, 95:5 er). Even better enantioselectivity was obtained using 0.2 equiv of (+)-sparteine surrogate **11** in combination with 1.2 equiv of

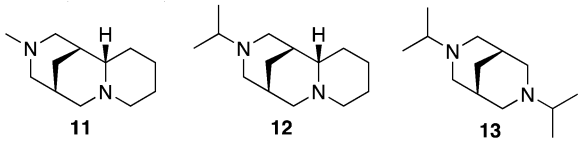


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Table 1. Catalytic Asymmetric Deprotonation−Electrophilic Trapping

entry	SM	diamine	equiv	product[a]	yield (%)	er[b]
1	**1**	(−)-sp	0.2	(*S*)-**2**	76	90:10
2	**1**	(+)-**11**	0.2	(*R*)-**2**	66	6:94
3	**3**	(−)-sp	0.2	(*S*)-**4**	77	92:8
4	**3**	(+)-**11**	0.2	(*R*)-**4**	72	6:94
5	**3**	(−)-sp	0.1	(*S*)-**4**	54	81:19
6	**3**	(+)-**11**	0.06	(*R*)-**4**	63	15:85
7	**14**	(−)-sp	0.2	(*S*)-**15**	67	83:17
8	**14**	(+)-**11**	0.2	(*R*)-**15**	68	11:89

[a] Reaction conditions: 1.3 equiv of *s*-BuLi, 1.2 equiv of bispidine **13**, 0.06−0.2 equiv of (−)-sparteine ((−)-sp) or (+)-**11**, Et_2O, −78 °C, 5 h for **1** and **3** or 3 h for **14** then add electrophile (Me_3SiCl for **1**, Bu_3SnCl for **3**, Ph_2CO for **14**). [b] Enantiomeric ratio determined by chiral GC (Betadex 120) for **2** and by chiral HPLC (Chiracel OD) for **4** and **15**.

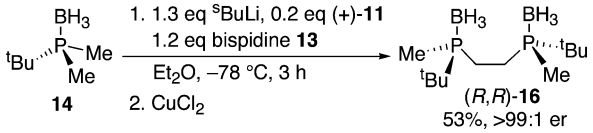
bispidine **13**; the antipode (*R*)-**2** of 94:6 er was formed in 66% yield (entry 2), approaching the stoichiometric result (84% yield, 95:5 er[10]). Deprotonation of *O*-alkyl carbamate **3** with 1.3 equiv of *s*-BuLi, 0.2 equiv of (−)-sparteine, and 1.2 equiv of bispidine **13** and trapping gave stannane (*S*)-**4** of 92:8 er in 77% yield (entry 3) (stoichiometric: 73% yield, 99:1 er). Similarly, use of Me_3SiCl in place of Bu_3SnCl gave the (*S*)-trimethylsilyl adduct[18] of 89:11 er in 69% yield (stoichiometric: 64% yield, 98:2 er). As with **1**, (+)-**11** performed better than (−)-sparteine in the deprotonation of **3** under otherwise identical conditions; (*R*)-**4** of 94:6 er was generated in 72% yield (entry 4), which is almost identical to the stoichiometric result (84%, 96:4 er[10]).

An investigation into lower chiral diamine loadings was carried out using *O*-alkyl carbamate **3** (entries 5 and 6). Use of 0.1 equiv of (−)-sparteine and 1.2 equiv of bispidine **13** with **3** gave (*S*)-**4** of 81:19 er (54% yield), whereas use of just 0.06 equiv of (+)-**11** under the same conditions gave (*R*)-**4** of 85:15 er (63% yield). The reduced enantioselectivity with <0.2 equiv of chiral diamine suggests that background deprotonation by free *s*-BuLi or *s*-BuLi/bispidine **13** is significant. Indeed, reaction of *O*-alkyl carbamate **3** with *s*-BuLi alone or *s*-BuLi/bispidine **13** gave adduct *rac*-**4** in 17 and 15% yields, respectively.

Similar success was obtained in the catalytic asymmetric lithiation trapping of phosphine borane **14**.[16,19] Lithiation of **14** with 1.3 equiv of *s*-BuLi, 0.2 equiv of (−)-sparteine, and 1.2 equiv of bispidine **13** followed by benzophenone quench gave (*S*)-**15** of 83:17 er in 67% yield (entry 7). This compares well with 83% yield of (*S*)-**15** of 88:12 er under stoichiometric conditions.[16] The antipode (*R*)-**15** was prepared in 68% yield and 89:11 er using 0.2 equiv of (+)-**11** and 1.2 equiv of bispidine **13** (entry 8) (stoichiometric result: 78% yield, 96:4 er[16]).

Finally, to showcase our catalytic asymmetric deprotonation methodology, we applied it to the synthesis of bis-phosphine boranes (*R*,*R*)- and (*S*,*S*)-**16**, precursors of useful chiral bis-phosphines for asymmetric hydrogenation.[19b] Thus, lithiation of phosphine borane **14** using 1.3 equiv of *s*-BuLi, 0.2 equiv of (+)-**11**, and 1.2 equiv of bispidine **13** followed by Cu(II)-promoted dimerization of the intermediate organolithium gave (*R*,*R*)-**16** (53% yield, >99:1 er by chiral HPLC) and *meso*-**16** (15% yield) (Scheme 4). This catalytic asymmetric synthesis of (*R*,*R*)-**16** is the shortest and most direct approach to date.[20] The analogous reaction with (−)-sparteine gave (*S*,*S*)-**16** of >99:1 er in 46% yield (with 12% *meso*-**16**).

Scheme 4



In summary, a novel ligand exchange approach to catalytic asymmetric deprotonation−electrophilic trapping has been developed. Using (−)-sparteine and our previously reported (+)-sparteine surrogate **11**, this methodology allows access to either enantiomer of useful products in good yields using substoichiometric amounts of chiral diamines.

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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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