Reactivity series for *s*-BuLi/diamine-mediated lithiation of *N*-Boc pyrrolidine: applications in catalysis and lithiation of *N*-Boc piperidine†

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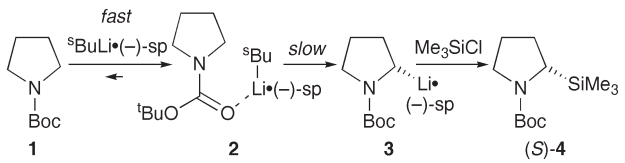
Using competition experiments between a range of ligands and (−)-sparteine, a reactivity series for *N*-Boc pyrrolidine lithiation using *s*-BuLi/diamines has been constructed; the results indicate that the *s*-BuLi/(+)-sparteine surrogate complex is more reactive than *s*-BuLi/(−)-sparteine and this has been exploited in the selection of ligand pairs for ligand exchange catalytic asymmetric lithiation of *N*-Boc pyrrolidine and lithiation of *N*-Boc piperidine.

There is considerable evidence to indicate that diamines such as (−)-sparteine ((−)-sp) and TMEDA influence the reactivity of organolithium reagents.[1] The effects imparted on organolithiums complexed by (−)-sparteine have led to the development of high yielding and highly enantioselective deprotonation reactions α to nitrogen,[2] oxygen[3] and phosphorus.[4] A typical example is the *s*-BuLi/(−)-sparteine-promoted lithiation–Me_3SiCl trapping of *N*-Boc pyrrolidine **1**[5] (**1** → **4**) which is believed to proceed by a three-step process.[6,7] In the first step, reversible precomplexation of the *s*-BuLi/(−)-sparteine complex to *N*-Boc pyrrolidine **1** generates complex **2**. Rate limiting lithiation then occurs to give α-amino organolithium **3** which is usually configurationally stable and is subsequently trapped by a reaction with Me_3SiCl to give adduct **4** (Scheme 1).[8,9]

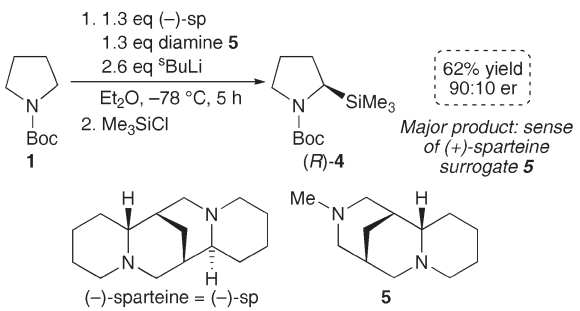
Although ~25 different chiral diamines have been examined for the conversion of **1** → **4**, these studies have, not surprisingly, focused on the enantioselectivity that arises.[10–16] As a result, information that allows effective comparison of *reactivity* of *s*-BuLi/diamine complexes is sparse. Indeed, to the best of our knowledge, only one quantitative rate comparison of RLi/diamine complexes has been described: Collum *et al.* investigated nucleophilic addition to an imine and imine α-deprotonation for a range of *n*-BuLi/diamine and PhLi/diamine complexes.[17] Thus, we set out to determine an empirical order of reactivity of different *s*-BuLi/diamine complexes for the lithiation of *N*-Boc pyrrolidine **1**. For this, an operationally simple approach was devised in which competition experiments between two different ligands would be used to assay relative reactivity. We proposed to investigate the lithiation-Me_3SiCl trapping of *N*-Boc pyrrolidine **1** using (−)-sparteine as a reference diamine in competition with either chiral diamines that give the opposite sense of asymmetric induction to (−)-sparteine or achiral diamines. In this way, the enantiomer ratio (er) of adduct **4** would be used as a measure of the relative reactivity of *s*-BuLi/diamine compared to *s*-BuLi/(−)-sparteine and this would ultimately enable us to compile a reactivity series.



Scheme 1

Mixtures of two chiral ligands have previously been used to investigate relative reactivities by Corey[18] and Kagan[19] (asymmetric dihydroxylations), by Bolm,[20] Noyori[21] and Soai[22] (additions of Et_2Zn to benzaldehyde) and by Blackmond (asymmetric hydrogenation).[23,24] However, a competition experiment approach using different chiral ligands for asymmetric deprotonation has not previously been described. Herein, we present a reactivity series for *N*-Boc pyrrolidine lithiation using *s*-BuLi and a range of chiral and achiral ligands. This series is compiled from a set of competition experiments. Furthermore, we demonstrate how this reactivity order can be used to identify suitable ligand pairs for our recently disclosed ligand exchange catalytic asymmetric deprotonation[25] and to develop a higher yielding enantioselective lithiation of *N*-Boc piperidine.

Initially, we chose to evaluate the relative reactivity of the *s*-BuLi complexes of (−)-sparteine and *N*-Me diamine **5**. The *s*-BuLi/*N*-Me diamine **5** complex reacts with *N*-Boc pyrrolidine **1** to give, after trapping with Me_3SiCl, adduct (*R*)-**4** of 95 : 5 er (84% yield) making it an effective (+)-sparteine surrogate.[12] To our surprise, when 2.6 equiv of *s*-BuLi was combined with 1.3 equiv of each of (−)-sparteine and *N*-Me diamine **5** for the deprotonation-trapping of *N*-Boc pyrrolidine **1**, adduct (*R*)-**4** of 90 : 10 er (*i.e.* the same sense as (+)-sparteine surrogate deprotonation) was formed in 62% yield (Scheme 2). *This result shows that s-BuLi/diamine **5** is more*



Scheme 2

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† Electronic supplementary information (ESI) available: Representative experimental procedures for results in Tables 1/2 and Scheme 3, and information on ligand synthesis. See DOI: 10.1039/b603804m

Table 1 Lithiation-trapping of *N*-Boc pyrrolidine **1** to give **4** using *s*-BuLi/(−)-sparteine/diamine (competition experiment) and *s*-BuLi/diamine (normal experiment)

		Competition experiment[a]		Normal experiment[b]	
Entry	Ligand	Yield (%)[c]	Er, *S* : *R*[d]	Yield (%)[c]	Er, *S* : *R*[d]
1	(−)-sp	—	—	87[e]	95 : 5
2	TMEDA	63	52 : 48	86	*rac*
3	*rac*-TMCDA	57	51 : 49	89[f]	∼*rac*
4	**5**	62	10 : 90	84[e]	5 : 95
5	**6**	67	69 : 31	29	*rac*
6	**7**	78	68 : 32	73[g]	10 : 90
7	**8**	64	68 : 32	27[g]	11 : 89
8	PMDETA	81	84 : 16	37	*rac*
9	**9**	42	90 : 10	35[g]	∼rac
10	**10**	77	95 : 5	5	*rac*

[a] Competition experiment: (i) 2.6 eq *s*-BuLi, 1.3 eq (−)-sp, 1.3 eq ligand, −78 °C, 5 h; (ii) Me_3SiCl. [b] Normal experiment: (i) 1.3 eq *s*-BuLi, 1.3 eq ligand, −78 °C, 5 h; (ii) Me_3SiCl. [c] Isolated yield after chromatography. [d] Er determined by chiral GC. [e] Ref. 12. [f] Beak reported that use of (*R*,*R*)-TMCDA gave 89% GC yield of ∼*rac*-**4** (ref. 10). [g] Ref. 16.

reactive than s-BuLi/(−)-sparteine even though the two diamines are similarly sterically hindered. Our interpretation of this competition result assumes that we are measuring the relative rate of deprotonation (**2** → **3**) from a complex **2** composed of one of each of *N*-Boc pyrrolidine, *s*-BuLi and diamine (which is consistent with the rate law[9] and a computational investigation of the reaction[26]) rather than the relative rate of irreversible complexation[27] of *s*-BuLi/diamines. We also assume that (−)-sparteine and diamine **5** are each fully complexed to *s*-BuLi. Further support for the enhanced reactivity of *s*-BuLi/diamine **5** was obtained by carrying the deprotonation of *N*-Boc pyrrolidine **1** using 1.3 equiv of *s*-BuLi, 0.4 equiv of diamine **5** and 0.7 equiv of (−)-sparteine as this gave an 83% yield of essentially racemic product **4** (51 : 49 er).[28]

To complete the full ligand reactivity order, we performed analogous competition experiments between (−)-sparteine and a range of diamines (TMEDA and **6–10**) and one triamine (PMDETA) (Table 1). Full details on the synthesis of the diamines are given in the electronic supplementary information.† The results of the competition experiments should be compared with those obtained with *s*-BuLi/(−)-sparteine alone (entry 1) and with each of the individual *s*-BuLi/diamine results (normal experiment).

When TMEDA and (−)-sparteine were competed with each other, adduct (*S*)-**4** of 52 : 48 er was obtained (63% yield) (Entry 2), clearly showing that the *s*-BuLi/TMEDA complex is more reactive than *s*-BuLi/(−)-sparteine (equal reactivity of the *s*-BuLi/diamine complexes would have given **4** in ∼75 : 25 er). This conclusion, together with the higher reactivity of *s*-BuLi/*N*-Me diamine **5** over *s*-BuLi/(−)-sparteine is not obvious from the isolated yields of the normal experiments which are in the range 84–87% (entries 1, 2 and 4) and indicates the usefulness of the competition approach. In a similar fashion, we used competition experiments to establish the reactivity order of *s*-BuLi/diamine complexes of (+)-sparteine surrogates **5** (*N*-Me), **7** (*N*-Et) and **9** (*N*-$CH_2{}^tBu$). The two least reactive *s*-BuLi/diamine complexes (from **9** and **10**) had the most sterically hindered *N*-alkyl groups. In these cases, adduct (*S*)-**4** was generated in 90 : 10 er (for **9**, Entry 9) and 95 : 5 er (for **10**, entry 10) indicating that reactivity was dominated by the *s*-BuLi/(−)-sparteine complex. Reassuringly, diamines **9** and **10** also gave low yields when combined with *s*-BuLi for the normal experiments (entries 9–10). On the basis of the competition experiments shown in Table 1, a ligand order for ten ligands in the *s*-BuLi/diamine-mediated lithiation of *N*-Boc pyrrolidine **1** was established (Fig. 1).[29]

To illustrate the usefulness of ligand reactivity orders such as that depicted in Fig. 1, we used it to identify effective chiral catalyst/bulk ligand combinations for ligand exchange catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1**.[25] When *s*-BuLi and sub-stoichiometric amounts of (−)-sparteine are used to deprotonate **1**, low yield and moderate enantioselectivity result. This is presumably because the (−)-sparteine is "trapped" in complex **3** (Scheme 1) and is not recycled to regenerate the reactive *s*-BuLi/(−)-sparteine complex. Thus, to solve this problem, we included an "unreactive" *s*-BuLi/bulk diamine complex in the reaction mixture so that the bulk diamine could exchange with the chiral catalyst (*e.g.* (−)-sparteine) to allow efficient catalysis. The key design feature is that the *s*-BuLi/chiral diamine catalyst complex should be considerably more reactive than the *s*-BuLi/bulk diamine complex. Thus, we selected the three diamines (PMDETA, **9** and **10**) that give the least reactive *s*-BuLi/diamine complexes (Fig. 1) and studied ligand exchange catalysis with *s*-BuLi and 0.3 equiv of each of (−)-sparteine and the (+)-sparteine surrogate, *N*-Me diamine **5** (Table 2).

Initially, we used PMDETA as the bulk ligand and found that *s*-BuLi/(−)-sparteine gave lower enantioselectivity (60 : 40 er, entry 1) than *s*-BuLi/diamine **5** (79 : 21 er, entry 2). From this, we conclude that even less reactive *s*-BuLi/bulk diamine complexes are needed for efficient catalytic asymmetric deprotonation and the larger the difference in reactivity between the *s*-BuLi/diamine complexes, the more efficient the catalysis. Indeed, using the least reactive *s*-BuLi/diamine complexes (from **9** and **10**), improved catalytic results were observed and crucially, in all cases, *s*-BuLi/*N*-Me diamine **5** complex gave higher yield and er than *s*-BuLi/(−)-sparteine. Under optimum conditions (1.3 equiv *s*-BuLi, 0.3 equiv. diamine **5** and 1.0 equiv. bulk diamine **10**), adduct

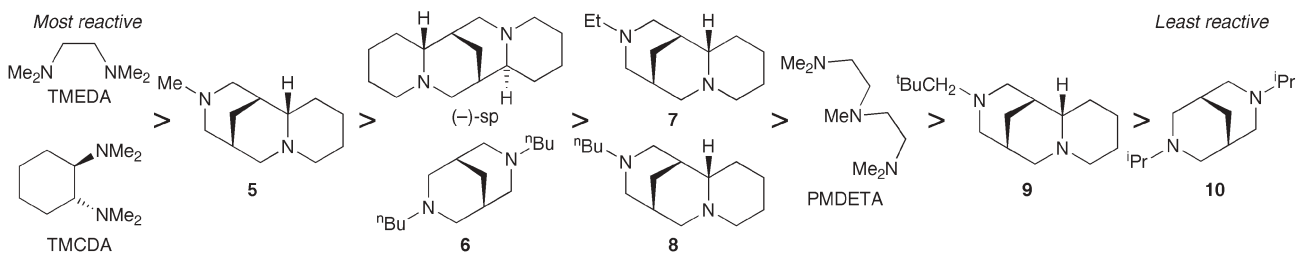
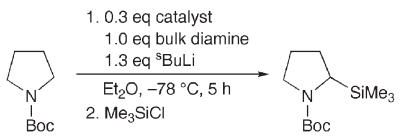


Fig. 1 Reactivity order for *s*-BuLi/diamine complexes in the lithiation-trapping of *N*-Boc pyrrolidine **1**.

Table 2 Catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1**



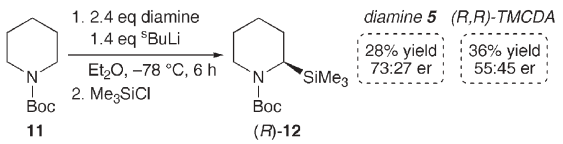
1 **4**

Entry	Catalyst	Bulk ligand	Yield (%)[a]	Er, *S*:*R*[b]
1	(−)-sp	PMDETA	64	60:40
2	**5**	PMDETA	70	21:79
3	(−)-sp	**9**	69	83:17
4	**5**	**9**	84	11:89
5	(−)-sp	**10**	69	88:12
6	**5**	**10**	78	6:94

[a] Isolated yield after chromatography. [b] Er determined by chiral GC.

(*R*)-**4** of 94 : 6 er was generated in 78% yield (entry 6) which is nearly the same as the stoichiometric result (84% yield, 95 : 5 er;[12] Table 1, entry 4).

Finally, we reasoned that it should be possible to use the most reactive *s*-BuLi/diamine complexes (TMCDA and *N*-Me diamine **5**) to carry out asymmetric lithiation-trapping reactions that proceed in low yield using *s*-BuLi/(−)-sparteine. Previously, Beak reported that deprotonation of *N*-Boc piperidine **11** using *s*-BuLi/(−)-sparteine gave only an 8% isolated yield of adduct (*S*)-**12** of 87 : 13 er[30] (use of *s*-BuLi/TMEDA gave *rac*-**12** in 94% yield[31]).[32] Under slightly modified conditions (excess of diamines), we obtained a 28% yield of (*R*)-**12** of 73 : 27 er with diamine **5** and a 36% yield of (*R*)-**12** of 55 : 45 er with (*R*,*R*)-TMCDA (Scheme 3).[33] Under these conditions with (−)-sparteine, none of adduct **12** was formed. This shows the lower reactivity of *s*-BuLi/(−)-sparteine compared to *s*-BuLi/*N*-Me diamine **5** or TMCDA and is in line with our competition experiment-derived reactivity order (Fig. 1).



11 (*R*)-**12**

Scheme 3

In conclusion, a reactivity series for *N*-Boc pyrrolidine lithiation using *s*-BuLi/diamines has been constructed. Of particular note, the results indicate that the *s*-BuLi/*N*-Me diamine **5** ((+)-sparteine surrogate) complex is more reactive than *s*-BuLi/(−)-sparteine. Consequently, ligand exchange catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **1** *and* lithiation of *N*-Boc piperidine **11** are more efficient using *s*-BuLi/diamine **5** than with *s*-BuLi/(−)-sparteine. This therefore opens up new synthetic opportunities for *s*-BuLi/diamine **5**-mediated asymmetric deprotonation reactions.

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28 This result also suggests that ligand exchange catalysis (see ref. 25) is occurring to some extent, with the less reactive *s*-BuLi/(−)-sparteine as the regenerating system.
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