Kinetic Probes

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# Chiral Bases as Useful Probes of Lithium Amide Reactivity**

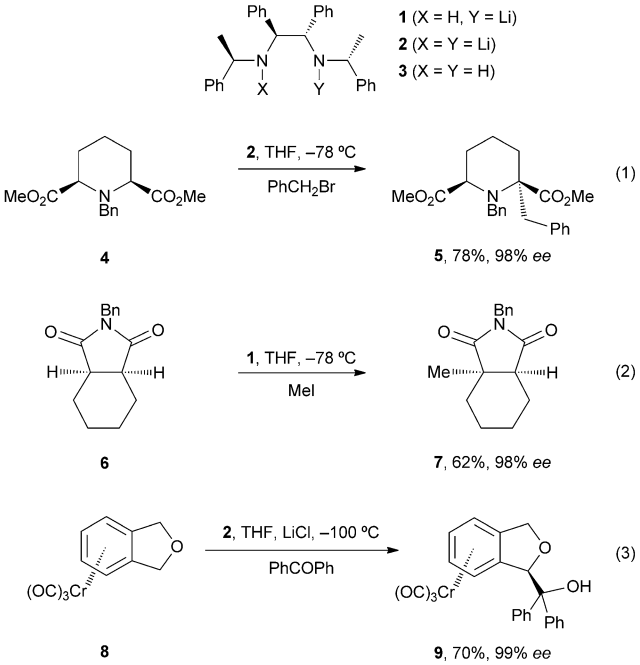
*Mark R. Prestly and Nigel S. Simpkins**

Lithium amides are indispensable as strong bases in organic synthesis, particularly for the generation of metal enolates from compounds that possess C=O functions of all types.[1] These reagents exhibit complex structural behavior, particularly in solution, in which the formation of aggregates and mixed aggregates is commonplace, leading to a mechanistically rich repertoire of enolization and metalation chemistry.[2]

Our own interest in this area has focused on the use of chiral lithium amides in asymmetric lithiation processes.[3] One key finding in this regard is the exceptional levels of enantioselectivity that are frequently provided by lithium amide **1** and bislithium amide **2** (both derived from diamine **3**), in diverse asymmetric metalation reactions (Scheme 1, Eq. (1)–(3)).[4]

In the asymmetric alkylation of piperidine diester **4**, the use of lithium bisamide **2** proved essential for attaining both optimal yield and asymmetric induction.[5] The explanation for the much cleaner reactions observed using this base compared to LDA and simpler chiral lithium amides was not clear. In the case of systems that are prone to overreaction, such as ring-fused imide **6**, we found the use of the diamine motif as a monolithium amide preferable.[6] In reactions of certain chromium arenes, for example, **8**, the diamine motif again provided excellent results.[7] In their studies in this area, Gibson and co-workers found identical *ee* values with **1** and **2** using a benzyl methyl ether complex, and speculated that the bislithium amide could be the more reactive base. Thus, reactions involving diamine **3** with one equivalent or less of BuLi might still involve the more reactive bislithiated base **2**, formed by lithium exchange of **1**.[8]

It occurred to us that experiments involving in situ competition between a chiral and an achiral base would directly provide the relative reaction rates for the two bases through the *ee* values of the formed products. This concept appeared attractive to us, because, despite extensive mechanistic and structural research on lithium amides, it is difficult to extract meaningful comparisons of rates of (typical substrate) deprotonation by different bases under the usual types of conditions used for synthesis.[9]




***Scheme 1.*** Enantioselective deprotonation reactions using diamine-derived bases **1** and **2**.

Previously, O'Brien and co-workers used competition experiments to assess the relative reactivity of *s*BuLi/diamine complexes, enabling them to identify ligand combinations suitable for catalytic deprotonation of *N*-Boc pyrrolidine.[10]

Herein we describe our own preliminary competition results in this area, which provide some new insights into lithium amide reactivity, and enable some clarification of the apparent superior reactivity of diamine-derived bases. The competition results can also be extended to provide data on lithium exchange between different amines (see below).

Bearing in mind the ubiquitous nature of ketone enolizations, we chose 4-*tert*-butyl-cyclohexanone (**10**) as our test system to use with both chiral and achiral lithium amides.[11] A selection of lithium amide bases was tested for the formation of enol silane **11** (Table 1).

All enolizations were carried out in the presence of LiCl, which has been demonstrated to improve the level of asymmetric induction in enolizations with chiral bases.[12] Base **13** (Table 1, entry 2) was included as an achiral analogue of **1** (entry 3), and gave reproducibly modest chemical yields, even if reaction times were extended.[13] The simple chiral bases **14**, which was used by us in many applications, and **16**, one of a range of fluorinated bases developed by Koga and co-workers,[14] gave very similar results, the sense of induction

[*] M. R. Prestly, Prof. N. S. Simpkins
School of Chemistry, University of Birmingham
Edgbaston, Birmingham, B15 2TT (UK)
E-mail: N.simpkins@bham.ac.uk

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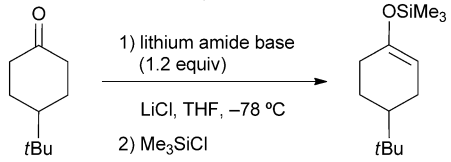
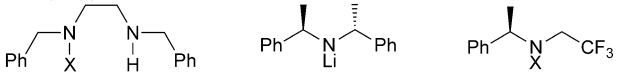
***Table 1:*** Benchmark enol silane synthesis.




**10** **11**

| Entry[a] | Base | Conv. [%] | *ee* [%] | Configuration |
|---|---|---|---|---|
| 1 | LDA | 99 | – | – |
| 2 | **13** | 39 | – | – |
| 3 | **1** | 99 | 58 | (*R*) |
| 4 | **14** | 99 | 81 | (*S*) |
| 5 | **16** | 99 | 78 | (*S*) |

[a] Both the conversion and the *ee* value of the product were determined by GC analysis of the crude product, using a Chiralsil DEX-CB capillary column. All values are averages from duplicate runs. LDA = lithium diisopropylamide.




**12** (X = H)
**13** (X = Li)

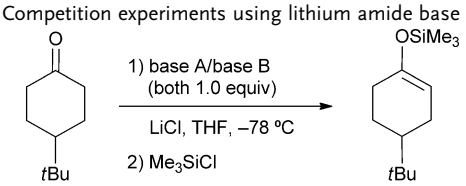
**14**

**15** (X = H)
**16** (X = Li)

being opposite to that observed with base **1** (Table 1, entries 4 and 5).

Competition experiments, in which ketone **10** was reacted with a 1:1 mixture of two bases, were then run, again in the presence of LiCl (Table 2).

***Table 2:*** Competition experiments using lithium amide base mixtures.




**10** **11**

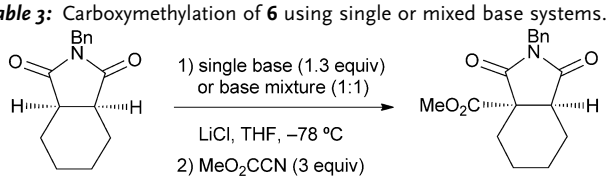
| Entry | Base A | Base B | Conv. [%] | *ee* [%]/Configuration |
|---|---|---|---|---|
| 1 | LDA | **1** | 98 | 57 (*R*) |
| 2 | LDA | **14** | 99 | 36 (*S*) |
| 3 | LDA | **16** | 99 | 50 (*S*) |
| 4 | **14** | **1** | 99 | 35 (*R*) |
| 5 | **14** | **13** | 56 | 11 (*S*) |

The most striking result for this substrate is that reaction of **10** with a 1:1 mixture of base **1** and LDA gives exactly the same product outcome as reaction with base **1** alone (Table 1, entry 1). Whatever the myriad possibilities for base aggregates and mixed aggregates, it is clear that the presence of an equimolar amount of LDA does nothing to diminish the (albeit moderate) selectivity afforded by the diamine motif.

It can be estimated that both (monolithium) bases react with the ketone at similar rates (Table 2, entry 2), with LDA decreasing the *ee* value that was obtained with **14** alone from 81% (Table 1, entry 4) to only 36%. The same situation prevails for base **16** (Table 2, entry 3). When two chiral bases are in competition with each other, it is the diamine-derived system that "wins out" (Table 2, entry 4). Thus, despite the fact that the simple base **14** leads to a significantly higher enantioselectivity (81% (*S*)) than base **1** (58% (*R*)), the overall selectivity emerging from the competition is 35% (*R*). Finally, when chiral base **14** (81% *ee*) competes with the achiral diamine-derived lithium amide **13**, the asymmetric induction is almost completely eroded (Table 2, entry 5). Although the diamine-derived base dominates the outcome of the reaction, the involvement of **13** again leads to modest overall conversion.

Confirmation of the trends observed in enolization and enol silane formation were sought in a dissimilar system. We chose to conduct asymmetric carboxymethylation of imide **6** using Mander's reagent (Table 3).

***Table 3:*** Carboxymethylation of **6** using single or mixed base systems.




**6** **17**

| Entry | Base A | Base B | Yield[a] [%] | *ee*[b] [%] |
|---|---|---|---|---|
| 1 | LDA | – | 43 | – |
| 2 | **1** | – | 93 | 97 |
| 3 | LDA | **1** | 89 | 99 |

[a] Yield of isolated product. [b] Determined by HPLC analysis using a Chiralpak OD column.

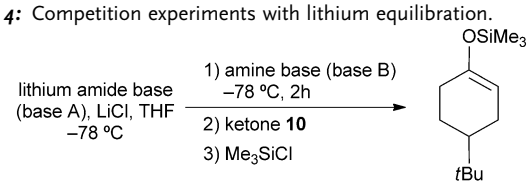
For this system, we achieved low levels of conversion using LDA as base (43%), and the yields obtained in the absence of LiCl were even worse (around 10–20%). As expected from our previous work,[3,4c,6a] including that summarized in Eq. (2), base **1** provided excellent results, with substituted imide (−)-**17** being generated in high yield and with exemplary levels of selectivity. As observed for the ketone system, the enantioselectivity that was achieved in the synthesis of (−)-**17** using base **1** was not affected by the presence of LDA.

The results that show diamine base **1** effectively competing with LDA for enolizable substrates provide impetus for probing the possible use of base **1** (or analogues) as a catalytic chiral base, in the presence of LDA or a similar lithium amide as bulk recycling base. Although the chemistry of such catalytic chiral lithium amide bases is reasonably well-established for epoxide rearrangement to allylic alcohols,[15] the corresponding systems for enolization, explored by Koga and co-workers, are not very effective.[16]

In order for a base such as **1** to act as a catalyst, it must be more reactive toward a substrate than the bulk recycling base, and there must be an effective lithium transfer between the two types of base. To probe this aspect, we devised experiments in which the enolization event is preceded by competition between the secondary amines for lithium, that is, a secondary amine and a lithium amide (derived from a different amine) are premixed and allowed to "equilibrate" before the addition of ketone **10** (Table 4).[17]

***Table 4:*** Competition experiments with lithium equilibration.




**11**

| Entry | Base A | Base B | Conv. [%] | *ee* [%]/Configuration[a] |
|---|---|---|---|---|
| 1 | LDA | **3** | 77 | 6 (*R*) |
| 2 | **16** | $iPr_2NH$ | 81 | 69 (*S*) |
| 3 | LDA | **15** | 98 | 83 (*S*) |
| 4 | **13** | **15** | 86 | 56 (*S*) |
| 5 | **16** | **12** | 37 | 61 (*S*) |
| 6 | **1** | **12** | 46 | rac. |
| 7 | **13** | **3** | 25 | rac. |

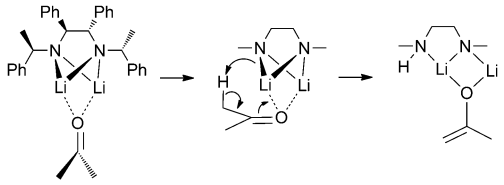
[a] rac. signifies less than 2% *ee*.

Having established that base **1** outpaces LDA in the enolization of **10** (Table 2), it can be seen that very little of active **1** is being generated during the low-temperature pre-equilibration of **3** and LDA (Table 4, entry 1). In other words, LDA does not deprotonate **3**. In contrast, lithium exchange occurs in the reactions summarized in entries 2 and 3 (Table 4), with highly effective transfer of lithium from LDA to fluorinated amine **15**, generating lithium amide **16** (entry 3). In both cases, the level of asymmetric induction approximates that achieved with **16** alone. Analogous lithium transfer is also observed from achiral diamine-derived lithium amide **13** to fluorinated base **15**, although the level of induction appears somewhat decreased (Table 4, entry 4). The reciprocal base pair **12** and **16** shows a similar level of induction (Table 4, entry 5).

As previously established by Koga and co-workers,[16] the acidifying influence of a β-trifluoroethyl substituent is highly effective in promoting lithium transfer. While the diamine-derived lithium amide **1** appears exceptional in some cases in terms of reactivity and enantioselectivity, there is little lithium transfer to diamine **3** using LDA as bulk base. Therefore, in order to design an exceptional base with the potential as a catalytic lithium amide, we probably need to incorporate $CF_3$ groups into a diamine motif such as **3**.

At present, we can only speculate as to the reasons for the high kinetic reactivity of diamine-derived base **1**. In epoxide rearrangements, lithium amides with an internally coordinated tertiary amine appear more reactive than LDA.[15] Amines and chelating ligands can also accelerate enolizations under certain conditions.[2a,c] For our vicinal secondary amine systems, we support the suggestion of Gibson et al. that reactions involving **1** or **2** proceed via a reactive bislithium amide structure.[8] The doubly bridged $N_2Li_2$ arrangement has been observed for this type of structure,[18] which we would expect to be highly activating toward a coordinated carbonyl moiety (Scheme 2).[19,20]

This proposal, like Gibson's observations, mentioned above, requires "a ready exchange of lithium cations between all the nitrogen sites in the system". However, this appears contrary to the lack of lithium exchange seen when diamine **3** is mixed with LDA (Table 4 entry 1). Could lithium exchange




***Scheme 2.*** Possible mode of enolization by bislithium amide **2** (substituents omitted from second and third structures for clarity).

be facilitated between two diamine molecules? The results summarized in entries 6 and 7 of Table 4 suggest that this is indeed the case, that is, in a mixed system of chiral and achiral diamine components, lithium equilibration favors achiral lithium amide **13**, thus leading to racemic enol silane **11**. This intriguing result, although unexpected, opens up new possibilities for catalysis and requires further study in other systems.

In conclusion, we have demonstrated that competition experiments involving mixtures of achiral and chiral (non-racemic) lithium amides can provide insights into the kinetic competency of these bases with two different types of substrates (Tables 2 and 3). With knowledge of the relative reaction rates of these experiments, pre-equilibration studies can also provide information about lithium transfer between different types of amines (Table 4). Our results show exceptional reactivity of lithium bases derived from 1,2-diamines (especially **3**), possibly because of the intermediacy of a bislithium amide base. Further studies are underway, with the aim of establishing "league tables" of lithium amide reactivity with key types of substrates, and new and efficient catalytic systems for reactions with chiral bases.

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