Lithium Amide Bases--A Primer

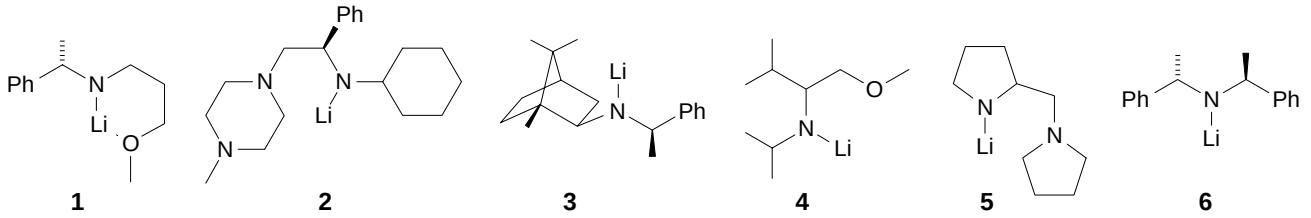
Lithium Diisopropylamide (LiN(i-Pr)$_2$, LDA, pK$_a$ ≈ 36). This is the cheapest and most convenient base for deprotonations of compounds whose pKa is less than 36. Hindered and certain heterosubstituted ketones are sometimes reduced.[1] In this case use LiTMP or LiHMDS. The amine is volatile and can be removed even from enolate solutions by distillation. LDA can be prepared from Li°.[1b]

Lithium Diethylamide (LiNEt$_2$). Used for isomerization of epoxides to allyl alcohols. Can be used for deprotonations of C-H acids, but is more prone to give addition products than more hindered amides like LDA. May be superior to LDA in sterically hindered situations.

Lithium 2,2,6,6-Tetramethylpiperidide (LiTMP, pK$_a$ ≈ 37).[4, 8, 9] This is the most potent and least nucleophilic of the amide bases. It is kinetically faster than LDA, and will smoothly do many deprotonations not possible with LDA. Interference by the amine (e.g. in acylations) is minimal because of high steric hindrance. Disadvantage: the amine precursor is expensive. CAUTION: The reaction between *n*-BuLi and the amine is slow at -78°C and is best done at 0°C.[5]

Lithium Bis(trimethylsilyl)amide (aka Hexamethyldisilazide) (LiN(SiMe$_3$)$_2$, LiHMDS).[2] A considerably weaker (pKa ≈ 30) base than the dialkylamides above. Used where a delicate touch is needed (e.g. for enolate alkylation when halide is part of the molecule[3]) and where hydride reduction occurs with LDA. LiHMDS will give the thermodynamic enolate under appropriate conditions.

Chiral Amide Bases.[6a, 7] Progress is slow, but a number of interesting systems have been tested (**1**[6g], **2**[6b], **3**[6c], **4**[6d],**5**[6e], **6**[6f]).



1 **2** **3** **4** **5** **6**

Structure and Mechanisms. The importance of lithium amides in synthesis has prompted many studies of their solution [2b, 6h, i, 8] and solid state[9] structures, and mechanisms of action.[6j, 6k, 10]

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