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Improved enantioselectivity by using novel bulk bases in chiral lithium amide catalysed deprotonations: mixed dimers as reagents and catalysts

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Abstract—Novel bulk bases have been developed yielding improved enantioselectivity of chiral lithium amide catalysed deprotonations as compared to using the bulk base lithium diisopropylamide (LDA). The new bulk bases are 2-lithio-1-methylimidazole, 2-(lithiomethyl)-1-methylimidazole, 2-lithio-furan and 1,8-diazabicyclo-6-lithio[5.4.0]undec-7-ene which have been used together with chiral lithium amides in deprotonations of cyclohexene oxide. Using the chiral lithium amides enhanced stereoselectivities (96% ee) have been reached. The reactivity change has been traced to the formation of novel reagents—mixed dimers—formed from a bulk base molecule and a molecule of a chiral lithium amide. The results also show that DBU, which has commonly been used as an additive to alter reactivity and enantioselectivity in deprotonations, has another important role. DBU is lithiated under the conditions used and becomes a bulk base, which forms catalytic mixed dimers with the chiral lithium amides. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Chiral lithium amides are being developed for enantioselective deprotonation reactions of, for example, epoxides and ketones.[1] Such reactions are synthetically important since the chiral products are useful intermediates in organic synthesis.[2] The chiral lithium amides are often used in stoichiometric amounts or in excess. Alternatively, there have also been a number of attempts to run the enantioselective deprotonation reactions under catalytic conditions.[3] The chiral lithium amide has been used in substoichiometric amounts (typically 5–20 mol%) and the less reactive lithium diisopropylamide (LDA) has been used as a bulk base, i.e. as a catalyst-regenerating base, to obtain a catalytic cycle.[4] However, non-enantioselective deprotonation by LDA yielding racemic product competes with that of the chiral base, resulting in lower enantioselectivity than in the stoichiometric reaction.

Thus, in order to improve the degree of enantioselectivity in catalytic deprotonations access to bulk bases with lower kinetic basicity than LDA, but comparable thermodynamic basicity, are required. In our search for such bases we have used 1-methylimidazole and 1,2-dimethylimidazole as precursors.[5] These azoles undergo carbon deprotonation at the C2-position and the C2-methyl by *n*-BuLi to yield the

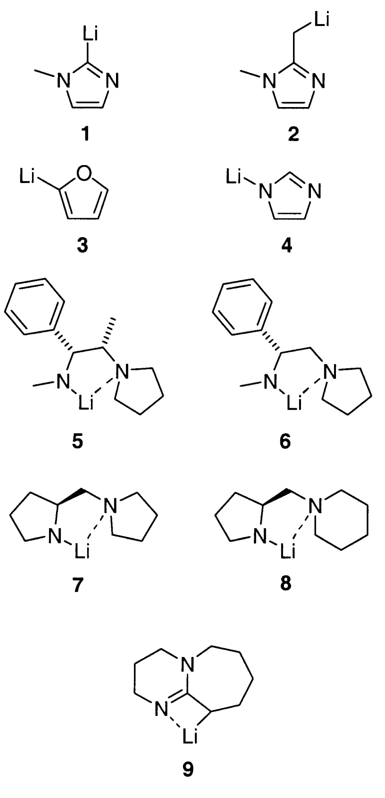

Figure 1.

Keywords: allylic alcohols; asymmetric catalysis; epoxides; mixed dimers; rearrangement.

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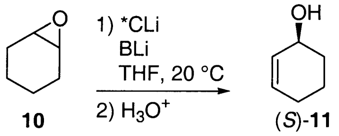


Scheme 1. Enantioselective chiral lithium amide (*CLi) catalysed deprotonation in presence of bulk base (BLi) of cyclohexene oxide **10**.

carbenoid compound 2-lithio-1-methylimidazole **1** and 2-(lithiomethyl)-1-methylimidazole **2**, respectively (Fig. 1).[5,6]

In THF, we have shown by NMR spectroscopy that **1** and **2** have basicities comparable to LDA. The deprotonating ability of bases **1** and **2** has been studied using cyclohexene oxide **10** as a substrate. In contrast to LDA, compounds **1** and **2** did not measurably yield any deprotonation of the epoxide. This is presumably due to the fact that proton transfers to carbon are usually slower than that to a more electronegative atom like nitrogen. These properties indicated that **1** and **2** should be useful as bulk bases in catalytic asymmetric deprotonations.

In this paper we present the results obtained using the two new bulk bases 2-lithio-furan **3** and *N*-lithio-imidazole **4** together with **1** and **2** and 1,8-diazabicyclo-6-lithio[5.4.0]undec-7-ene **9** and the chiral lithium amide catalysts lithium (1*R*,2*S*)-*N*-methyl-1-phenyl-2-pyrrolidinylpropanamide **5** (independently developed by O'Brien et al.[8] and ourselves[7]), lithium (*S*)-*N*-methyl-1-phenyl-2-pyrrolidinoethylamide **6**,[2] lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide **7**[4a,b,9]and lithium (*S*)-2-(piperidin-1-ylmethyl)pyrrolidide **8**[4a,b,9] (Fig. 1) in enantioselective deprotonations of cyclohexene oxide **10** (Scheme 1).

2. Results and discussion

2.1. Epoxide rearrangement

All the bulk bases except *N*-lithio-imidazole **4** were found to be strong enough bases to generate the chiral lithium amide. The results with the regenerating bulk bases are collected in Table 1. In the absence of any lithium amide catalyst, the bulk bases **1–3** were found to be non-reactive towards the

Table 1. Stoichiometric and catalytic enantioselective deprotonation of cyclohexene oxide (0.1 M) in THF at 20.0°C using the chiral lithium amides **5–8**

Entry	[Catalyst][a] (M)	Bulk base/conc.[a] (M^{-1})	[DBU][a] (M)	Reaction time[b] (h)	Yield[c] (%)	ee[d] (%)
1		**1**/0.2		252	0	–
2		**2**/0.2		149	0	–
3		**3**/0.2		209	0	–
4		**9**/0.2		220	4	0
5		**9**/0.2	0.5	232	2.5	0
6	**5**/0.1			25	95	93
7	**5**/0.2			25	96	93
8	**5**/0.02	LDA/0.2		32	90	22
9	**5**/0.02	**1**/0.2		198	96	93
10	**5**/0.02	**2**/0.2		13	96	93
11	**5**/0.02	**3**/0.2		14	91	93
12	**5**/0.02	**9**/0.2	0.5	56	93	69
13	**5**/0.1	**9**/0.2		240	57	89
14	**5**/0.1	**9**/0.2	0.5	60	88	94
15	**5**/0.1	**2**/0.1		28	96	96
16	**5**/0.1	**2**/0.1		23	96	96
17	**6**/0.1			16	70	77
18	**6**/0.02	LDA/0.2		32	86	19
19	**6**/0.02	**1**/0.2		69	58	73
20	**6**/0.02	**2**/0.2		42	65	73
21	**6**/0.1	**1**/0.1		36	63	72
22	**6**/0.1	**2**/0.1		22	46	13
23	**7**/0.1			8	78	80
24	**7**/0.02	LDA/0.2		12	63	68
25	**7**/0.02	**1**/0.2		28	84	76
26[e]	**7**/0.1	**1**/0.6		1	81	76
27	**7**/0.02	**2**/0.2		8	78	80
28	**7**/0.02	LDA/0.2	0.5	7	89	74
29	**7**/0.02	**9**/0.2	0.5	7	81	79
30	**7**/0.1	**1**/0.1		6	82	76
31	**7**/0.1	**2**/0.1		6	73	78
32	**8**/0.1			8	76	72
33	**8**/0.02	LDA/0.2		12	66	59
34	**8**/0.02	**1**/0.2		12	80	75
35[e]	**8**/0.1	**1**/0.6		5	88	75
36	**8**/0.02	**2**/0.2		12	71	75
37[e]	**8**/0.1	**2**/0.6		5	80	74
38	**8**/0.1	**1**/0.1		4	86	75
39	**8**/0.1	**2**/0.1		4	88	75

[a] Total initial concentration.
[b] The reaction was quenched at the time stated.
[c] The yield was determined by GC-analysis.
[d] The ee of (*S*)-**11** was determined by chiral GC.
[e] The initial epoxide concentration was 0.5 M.

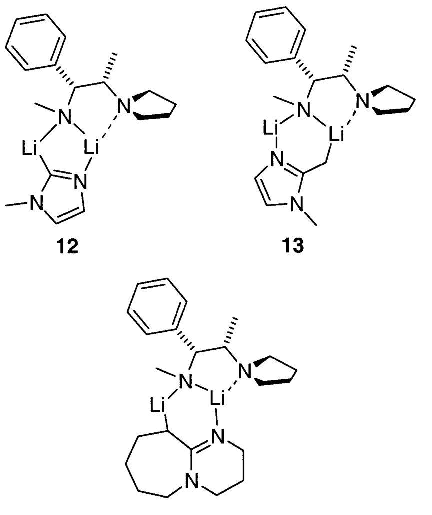
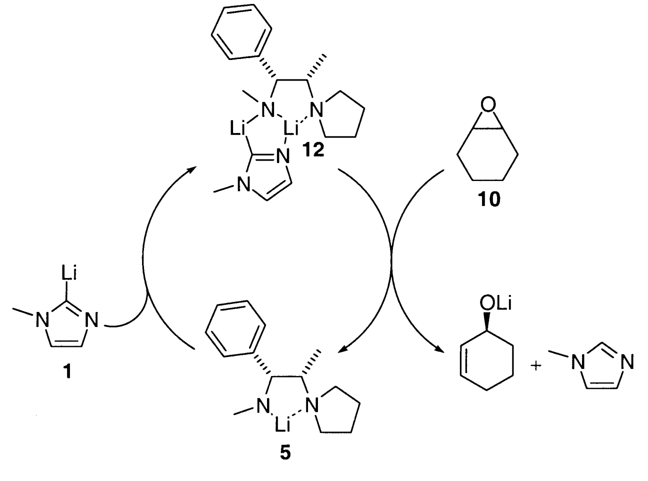


Figure 2. Mixed dimers built from monomers of **5** and monomers of **1**, **2** and **9**, respectively, have been shown by multinuclear NMR investigations to be the major species present in THF.

epoxide (entries 1–3). Bulk base **9** did yield only a very slow deprotonation of the epoxide (entries 4 and 5).

Using chiral base **5** in stoichiometric amount or in excess of epoxide **10** (entries 6 and 7) (*S*)-2-cyclohexen-1-ol (*S*)-**11** is formed in 93% ee. In contrast, using a sub-stoichiometric amount of chiral base **5** and LDA as a bulk base gave (*S*)-**11** in only 22% ee (entry 8). When employing either **1**, **2** or **3** as bulk base the reactions gave 93% ee of (*S*)-**11** (entries 9–11). However, the catalytic reaction was much slower using **1** than the reaction with **2**. Furthermore, the reaction using the bulk base **2** is faster than that with LDA. Thus, a 96% yield was achieved within 13 h without a change of the enantioselectivity (entry 10). Surprisingly, chiral base **5** together with stoichiometric amounts of either **1** or **2** increased the enantioselectivity to 96% ee (entries 15 and 16). This is further discussed below as are the results obtained in the presence of the bulk base **9**.

The stoichiometric reaction of Singh's chiral base **6** with epoxide **10** in THF gave (*S*)-**11** in 77% ee (entry 17). In contrast, using LDA as a bulk base the ee decreased to 19% (entry 18). The catalytic reaction of chiral base **6** in the presence of either **1** or **2** on the other hand gave improved enantioselectivity up to 73% ee of (*S*)-**11** (entries 19 and 20). Using stoichiometric amounts of epoxide **10**, chiral base **6** and **1** or **2** resulted in ees of 72 and 13%, respectively (entries 21 and 22).



Scheme 2. Catalytic cycle using the mixed dimer catalyst **12** in presence of the bulk base **1** producing (*S*)-**11** and the precursor of **1**, 1-methylimidazole.

Using Asami's chiral base **7** in stoichiometric amounts produced (*S*)-**11** in 80% ee (entry 23), but using sub-stoichiometric amounts of **7** and LDA as a bulk base lowered the ee to 68% (entry 24). The ee increased to 76% when **1** was used as a bulk base (entries 25 and 26). The enantioselectivity increased further when **2** was used in place of **1** (entry 27). In the case of chiral base **7**, improved selectivity was obtained when using **1** or **2** (entries 25–27) as a bulk base. Interestingly, sub-stoichiometric amounts of chiral base **7** in the presence of both LDA and DBU as an additive gave 74% ee of (*S*)-**11** (entry 28), but when employing chiral base **7** with bulk base **9**, (*S*)-**11** was formed in 79% ee (entry 29). Rearrangement of epoxide **10** in a solution with equimolar amounts of **7** and **1** or **2** resulted in ees of 76 and 78%, respectively (entries 30 and 31).

Reaction of epoxide **10** with chiral base **8** gave (*S*)-**11** in 72% ee (entry 32). Similarly, reaction with sub-stoichiometric amounts of chiral base **8** in presence of the bulk base LDA resulted in a lower ee of 59% (entry 33). In contrast when **1** or **2** were used as bulk bases (entries 34–36) a slight increase of the ee to 75% compared with the stoichiometric reaction with **8** was noticed. Similarly rearrangement of epoxide **10** with equimolar amounts of chiral base **8** and **1** or **2** resulted in a 75% ee of (*S*)-**11** (entries 38 and 39).

2.2. Mixed dimers as reagents or catalysts

The sometimes increased enantioselectivity obtained with the novel bulk bases over the corresponding reactions using only the chiral lithium amides suggested to us that new reagents were present in the former cases. Interestingly, we found by NMR spectroscopy using the [^{15}N, ^{6}Li]-isotopologue of chiral base **5** and bulk bases **1** and **2**, that mixed dimers **12** and **13**, respectively, were formed in THF (Fig. 2).[5] These species were found to be more stable than the homodimer of chiral base **5**, which has been shown to be the reagent in some ether solutions in absence of bulk bases **1** and **2**.[5] Therefore the new reagents in the enantioselective deprotonations when using bulk bases **1** and **2** with chiral lithium amide **5** are the mixed dimers.

Scheme 2 shows a catalytic cycle involving the chiral amide **5**, the mixed dimer **12** and the bulk base **1**.

The above findings have led us to explore the potential of mixed dimers in both catalytic and stoichiometric enantioselective deprotonations.

We have previously reported that the rate limiting transition state in the deprotonation of epoxide **10** by chiral base **5** is built from one dimer of the lithium amide and one epoxide molecule.[7] It is possible that deprotonation by the mixed dimers is making use of a rate-limiting transition state built from a mixed dimer and an epoxide.

2.3. On the role of DBU as an additive

It has been reported that addition of amidines like DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) alters the reactivity and the enantioselectivity in epoxide rearrangements.[3a,4] In light of our findings, together with earlier reports, we envisioned that DBU under the conditions used, may be lithiated and working as a bulk base besides being a strongly solvating agent.[10] Indeed, NMR studies have shown that DBU is deprotonated by either *n*-BuLi or LDA to give lithiated DBU **9** (Fig. 1).[10] LDA appears not to be strong enough to completely deprotonate DBU. An equilibrium mixture composed of **9**, DBU, LDA and diisopropylamine is obtained. These findings led us to investigate the usefulness of **9** as a bulk base. Using multinuclear NMR and isotopically labelled **5** together with **9** it has been shown that a mixed dimer **14** is formed (Scheme 2) similar to those obtained with **1** and **2** and chiral lithium amide in THF.[10]

In Table 1, entry 13 the result of the reaction of the epoxide **10** with equimolar amounts of **5** and twice the equimolar amount of **9** is shown. Under these conditions the rearrangement was much slower and the ee of (*S*)-**11** was lowered to 89% compared to 93% (entry 6). Using a reaction mixture with the same composition as in entry 13 but with the addition of DBU (entry 14) resulted in shorter reaction times and an increase of the ee to 94%. This demonstrates that DBU also plays an important solvation role in which it influences both the enantioselectivity and rates. In entry 12 the amide **5** is used in sub-stoichiometric amounts and the initial concentration of bulk base **9** is ten times that of **5** and the concentration of DBU is the same as in entry 14. Under these conditions the reaction time was short but the ee was lowered to 69%. The latter result is possibly due to a competing racemic reaction of **9** with **10** and or racemisation of **11** by **9**.

3. Conclusion

Novel bulk bases have been developed yielding improved enantioselectivity of chiral lithium amide catalysed deprotonation as compared to using the bulk base LDA. The reactivity change has been traced to the formation of novel reagens—mixed dimers—formed from a bulk base molecule and molecule of a chiral lithium amide.

4. Experimental

4.1. General

All syringes and glass vessels used were dried overnight in a vacuum oven (50°C) before being transferred into a glove box (Mecaplex GB 80 equipped with a gas purification system that removes oxygen and moisture) containing a nitrogen atmosphere. Typical moisture content was less than 0.5 ppm. All handling of the compounds was carried out with gas-tight syringes. The solvent THF used was distilled from sodium and benzophenone. The concentration of the commercially available *n*-BuLi (ca. 2.5 M in hexanes, Acros) was determined by titration.[7] Cyclohexene oxide, 1-methylimidazole, DBU, and furan (Sigma-Aldrich) were distilled from CaH_2. 1,2-Dimethylimidazole and imidazole (Aldrich) were purified by distillation. All precursors were by NMR spectroscopy and GC found to be not less than 99.3% chemically pure. The diamine precursor of **5** was prepared in 99.2% ee as found by chiral GC.[7] The diamine precursor of **6** was prepared as described earlier by Bhuniya et al.[2f] They reported an enantiomeric excess of at least 97% based on optical rotation. The diamine precursors of **7** and **8** were synthesised using a method recently developed in our laboratory.[9] The enantiomeric purity was determined by optical rotation, $[\alpha]_D^{20}=+8.87$ (*c* 2.24, EtOH) and $[\alpha]_D^{20}=+15$ (*c* 7.75, EtOH), respectively, comparing with literature data.[11] For all chiral base reactions the reported ees for the deprotonation of epoxide **10** in the literature has been reproduced.[4a,b,8] All GC analyses were run on a chiral stationary phase column (CP-Chirasil-DEX CB, 25 m, 0.32 μm) from Chrompack. The column was held at 90°C (injector 225°C, detector 250°C) using helium (2 mL min^{-1}) as a carrier gas. t_R(**10**)=3.25 min, t_R((*S*)-**11**)=7.45 min, t_R((*R*)-**11**)=7.90 min.

4.2. Catalytic deprotonation of cyclohexene oxide 10

The bulk bases were prepared from *n*-BuLi and the appropriate precursor, i.e. 1-methylimidazole (**1**), 1,2-dimethylimidazole (**2**), furan (**3**), imidazole (**4**) or diisopropylamine (LDA). In the case of the crystalline precursors 1,2-dimethylimidazole and imidazole, 2.0 M stock solutions in THF were prepared.

Amine **5** (4.4 μL, 0.02 mmol) and 1-methylimidazole (16 μL, 0.20 mmol) were added to THF (881 μL) in a reaction vessel in the glove box. After transfer out of the glove box *n*-BuLi (89 μL, 2.47 M in hexanes, 0.22 mmol) was added to the reaction vessel in a nitrogen atmosphere. The yellow reaction solution was allowed to equilibrate at 20.0°C for 10 min in a thermostat. The reaction was started by addition of cyclohexene oxide **3** (10 μL, 0.10 mmol) to the reaction mixture. To follow the reaction, samples (50 μL) were withdrawn at different times and diluted with diethyl ether (500 μL). The solutions were quenched in saturated NH_4Cl (250 μL) and washed with brine (250 μL). The samples were analysed by chiral GC and the reaction yield of **11** was determined using a standard added after the quenching as previously described.[7]

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