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Enantioselective deprotonation of ketones using a novel heterodimer chiral amide base

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Abstract—A novel heterodimer chiral base system has been prepared and reacted with a series of prochiral ketones in the presence of TMSCl to give efficient formation of the corresponding enol ethers in an enantiomeric excess up to 85%.

Chiral lithium amides are being developed as useful reagents for the preparation of nonracemic compounds.[1] They have been exploited for enantioselective deprotonation reactions such as epoxides and ketones. These reactions are synthetically important since the chiral products are useful intermediates in organic synthesis.[2] Because enolates are interesting carbon nucleophiles, their generation enantioselectively is becoming widely used in order to prepare enantiomerically enriched building blocks for synthesis.

Koga has devised an approach to the catalytic asymmetric deprotonation of 4-substituted cyclohexanones based on the regeneration of the catalytic chiral lithium base by an achiral lithium amide. However the use of additives in excess such DABCO and HMPA was necessary to achieve the optimum enantioselectivity.[3] A very desirable situation would be a way of regenerating the chiral lithium amide base from the amine without a competitive racemic reaction and need of excess additives especially cancerogenic HMPA.

In our search for such bases we have used 1-methylimidazole **1** and DBU **2** as precursors.[4] The latter undergo carbon deprotonation by *n*-BuLi to yield the carbenoid compound 2-lithio-1-methylimidazole **1** and 3-lithio-DBU **4**, respectively (Fig. 1).[4,5]

Studies within our laboratories have shown how heterodimers built from chiral lithium amides and such bulk bases can be employed as alternatives to their more widely used lithium homodimers or monomer counterparts in catalytic deprotonation of *meso*-epoxides.[6] It has been previously reported that addition of organolithiums to enolizable ketones is often problematic and adduct yields tend to be low.[7] This drawback could be used advantageously in deprotonation reactions promoted by heterodimers.

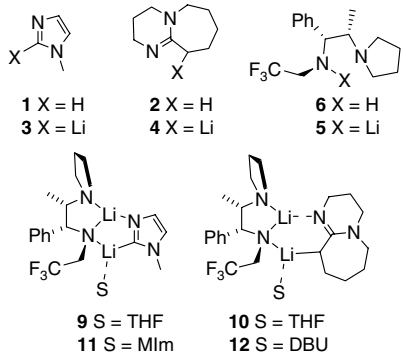

Figure 1.

Thus, we envisioned that an enantioselective deprotonating reagent could be built from chiral lithium amide **5** and bulky bases **3** or **4**. Based on these considerations, herein, we report the first use of such heterodimeric complexes as reagents in the enantioselective deprotonation of conformationally locked ketones.

In THF, we have shown by NMR spectroscopy that **3** and **4** have basicities comparable to LDA.[4] The deprotonating ability of bases **3** and **4** has been studied using cyclohexene oxide as a substrate. In contrast to

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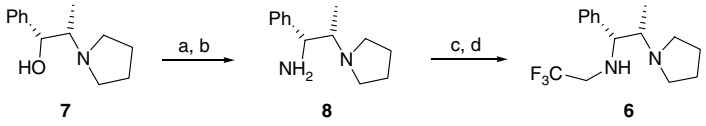


Scheme 1. Reagents and conditions: (a) 3 equiv Et_3N, 1.5 equiv MsCl, THF, 0 °C, 60 min; (b) 2 equiv Et_3N, 20 equiv NH_3/H_2O, rt, 16 h; (c) 1.5 equiv CF_3CO_2Et, EtOH, rt, 16 h; (d) $LiAlH_4$, THF, 0 °C and then reflux, 4 h.

LDA, compounds **3** and **4** 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 those to a more electronegative atom like nitrogen. These properties indicated that **3** and **4** would be useful as bulk bases in catalytic asymmetric deprotonations.

Chiral diamine (1*R*,2*S*)-*N*-(2,2,2)-trifluoroethyl-1-phenyl-2-pyrrolidinylpropanamine **6** was prepared as outlined in Scheme 1. The design of **6** was based on its similarity with Koga's diamine and would be more effective as chiral base. Thus (1*R*,2*S*)-**7**, generated from (1*R*,2*S*)-norephedrine,[8] was subjected to mesylation in THF followed by reaction with aqueous ammonia to give (1*R*,2*S*)-1-phenyl-2-pyrrolidinylpropanamine **8**. The latter underwent trifluoroacetylation followed by reduction with LAH to give the corresponding diamine **6**.

By analogy with previously reported work,[4] lithium amide **5** was supposed to build heterobimers of type **9**–**12** in the presence of bases **3** or **4** in solution in THF. Multinuclear NMR analysis of THF solutions of chiral base **5** revealed the existence of the chiral amide **5** as a homodimer with a single ^6Li resonance at δ 1.05. Furthermore, when **6** was titrated with up to 0.5 equiv of **3** in solution in THF a new set of two ^6Li signals in a 1:1 ratio appeared at δ 2.15 and δ 2.40. These results indicate the presence of a new complex with two different lithiums. Similarly ^1H and ^{13}C show that **6** had been deprotonated to provide **5**. The new species was identified as the heterodimer **11**, in which one lithium was solvated by **1** that resulted from protonation of **3**.

However, only a small amount of heterodimer was observed when a THF solution of chiral amide **5** was titrated with **1**. Indeed, upon addition of 1 equiv of **1** to a solution of **5**, the ^6Li spectrum showed only a downfield shift of the ^6Li resonance from δ 1.05 to δ 1.49, presumably as a consequence of Li-solvation by **1**, along with signals from the heterodimer in a 9:1 ratio, respectively. Further addition of **1** up to 2 equiv resulted in a shift of the largest peak at δ 1.85. These observations suggest that **5** is not a strong enough base to deprotonate **1**.

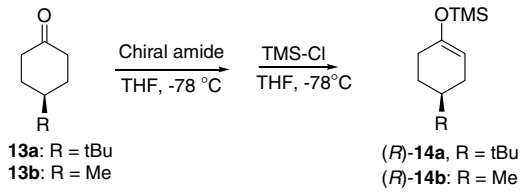
The stereoselectivities of the new chiral base **5** in deprotonation were studied using 4-*t*-Bu-cyclohexanone **13a** as a substrate. The results are summarized in Table 1.[9] In the first place we evaluated the chiral lithium amide **5** using the 'in situ quench protocol'.[10] Using chiral base **5** in a stoichiometric amount, the silylenol ether (*R*)-**14a** was obtained in 79% yield and 85% enantiomeric excess. Similarly but under the 'external quench protocol' conditions the silylenol ether could be obtained in 98% conversion and 75% ee (Scheme 2).

We then turned our attention to the heterodimer **9** and we were delighted to find that the stoichiometric reaction resulted in 89% conversion with 63% ee, under external quench conditions. Under these conditions, the reaction also yielded a substantial amount of alkylation product, by competing addition of **3** to the ketone. We

Table 1. Enantioselective deprotonation of ketone to give silylenol under different conditions

Entry	R	Bulk base (equiv)	Quench	Time	Conversion (%)[a]	Ee (%)[a]
1	*t*-Bu	None	IQ	70 min	79	85
2	*t*-Bu	None	EQ	70 min	98	75
3	*t*-Bu	**3** (1.0)	EQ	70 min	98	63
4	*t*-Bu	**3** (1.0)	EQ[b]	70 min	98	63
5	*t*-Bu	**3** (1.0)	EQ[c]	90 min	93	66
6	*t*-Bu	**4** (1.0)	EQ[d]	60 min	91	46
7	*t*-Bu	BuLi (1.0)	EQ	70 min	78	48
8	Me	None	EQ	3 h min	98	34
9	Me	**4** (1.0)	EQ[c]	3 h min	97	33
10	Me	**4** (1.0)	EQ[d]	2 h min	73	8
11	*t*-Bu	**3** (0.2)	EQ[c]	60 min	79	47
12	*t*-Bu	**3** (0.2)	EQ	2 h	82	35

[a] The yield and ee were determined by chiral GC-analysis: Chirasil-DEX CB column. Configuration assignment based on comparison with literature data.
[b] TMSCl was added 3 min after addition of ketone.
[c] 1 equiv Methylimidazole was added in excess.
[d] 1 equiv DBU was added in excess.



Scheme 2.

wondered whether an early external quench would influence the reaction outcome. This was not the case since addition of TMSCl 3 min after that of the ketone resulted in a similar 63% ee despite a conversion of 97% (entry 4), and less alkylation adduct was produced. In contrast using one equivalent excess of **1** gave improved enantioselectivity up to 66% ee (entry 5) and no alkylation product formation.

The ee decreased to 46% when **4** is used as achiral base (entry 6). Furthermore, and more interestingly, the reaction in the presence of 1 equiv excess of BuLi the reaction resulted in an enantioselectivity of 48% ee with 78% conversion and no alkylated byproduct. It is reasonable to suggest a heterodimer built from **5** and BuLi to be the reactive species. This constitutes the first example of such use of BuLi in a mixed aggregate for deprotonation reactions.

The above-mentioned slow proton transfer to carbon rather than to nitrogen, prompted us to explore the potential of the mixed dimer in catalytic enantioselective reaction. Thus, control reactions were run to evaluate competitive reactivity of **3** towards ketone in absence of chiral lithium amide. It was found that the alkylation was the main reaction resulting in addition of **3** to ketone as shown with both NMR and mass spectroscopy. The reaction proceeded with 82% conversion and with only 8% deprotonation occurred after 70 min. Similarly, reaction with only **4** gave deprotonation product in only 3% after 2 h.

In entry 11, the lithium amide is used in sub-stoichiometric amounts and the initial concentration of **3** is five times that of **5** and no excess of **1**. This resulted in a lower ee of 35% (entry 12). In the presence of 1 equiv excess of **1** the ee increased up to 47% (entry 11). The low enantioselectivity under catalytic conditions is possibly due to a competing non-enantioselective reaction of **3** with the ketone. This demonstrates the important solvation effect and its influence on the enantioselectivity and reactivity.

In conclusion, having prepared a new chiral base derived from norephedrine, synthetically useful silylenol ethers were prepared in up to 85% ee. We have demonstrated for the first time the use of heterodimer built from a chiral base and a bulk base for such a reaction, including BuLi. Although a lower ee was obtained, attempts to run the reaction under catalytic and external quench conditions show the potential for this methodology.

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9. Typical procedure for the enantioselective deprotonation (entry 1, internal quench): A round bottomed flask was charged with a solution of **6** (29 μL, 0.1 mmol) in dry THF (2 mL) under nitrogen atmosphere. The solution was cooled to −78 °C and *n*-BuLi (2.26 M in hexane, 45 μL, 0.1 mmol) was added dropwise. The reaction mixture was left for 15 min at room temperature. The reaction mixture was rapidly cooled to −78 °C and chlorotrimethylsilane (0.5 mL, 0.5 mmol) was added dropwise (in the case of external quench, TMSCl was added 3 min prior to addition of triethylamine). After the reaction mixture had been stirred for 2 min at this temperature a solution of 4-*tert*-butylcyclohexanone (1 M in THF, 100 μL, 0.1 mmol) was added dropwise over 5 min. After 70 min triethylamine (2 mL) was added, followed by a saturated solution of NH_4CL (2.5 mL). The reaction mixture was warmed to room temperature, extracted with diethyl ether and the organic phase washed with water. The combined aqueous phase was extracted with diethyl ether (10 mL), and the organic phase was dried over Na_2SO_4. The reaction conversion and the enantiomeric ratio was determined by GC analysis Chirasil-DEX CB capillary column, carrier gas He (2 mL/min), 80 °C (1 min)–130 °C; temperature gradient: 1.5 °C/min, $t_R = 25.8$ min (*S*)-**14a**, $t_R = 26.1$ min (*R*)-**14a**.
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