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Are there concentration effects in enantioselective deprotonation of cyclic ketones?

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Abstract—Deprotonation of tropinone and its sulfur analog (8-thiabicyclo[3.2.1]octan-3-one, TBON) with chiral lithium amides (e.g. lithium *N*-benzyl-α-methylbenzylamide), followed by addition of the resulting enolates to benzaldehyde, affords non-racemic products, the enantiomeric excess of which depends on the concentration of the lithium amide.

Enantioselective deprotonation of cyclic ketones having C_S symmetry have introduced a new dimension into enolate chemistry.[1] Reactions involving chiral lithium amides have advanced the understanding of a number of features of reactions involving enolates, and several synthetic applications of the enantioselective deprotonation strategy have been reported.[1,2] The search for more selective reagents and conditions led to the development of effective chiral lithium amide bases[3] and to elaboration of better conditions for deprotonation chemistry including the rational use of additives (most notably LiCl, but also TMEDA and HMPA),[4] the use of the amide precursors (amines) as the corresponding hydrochloride salts,[5] and some insight into reaction kinetics.[6]

Although a large number of cyclic ketones have been investigated, bicyclic, bridged ketones are especially good substrates for enantioselective deprotonation.[1] Tropinone (**1a**), and similar heterocyclic ketones provide good scaffolds for the synthesis of natural products and also proved useful for studying the reaction from the methodology development standpoint.[5,7] A simplified picture of the enantioselective deprotonation of tropinone, and similar ketones, is shown in Scheme 1. The lithium amide base (**2**) discriminates between the two axial enantiotopic protons.[8] The important features of this process include complexation of the lithium amide to the carbonyl oxygen to form the complex **3** prior to proton transfer,[9] and complexation of the amine originating from the lithium amide reagent to the lithium enolate produced in the reaction.[10] The latter complex is shown as **4**, with enolate aggregation ignored. It is well known that lithium amides are usually aggregated and also form mixed oligomers with additives (e.g. lithium halides) and that enolates are likewise aggregated and also form mixed oligomers with lithium amides and other species.[11] These general aspects of deprotonation are reasonably well established and supported by experimental evidence, although some of them are somewhat surprising. It was, for example, pointed out recently by Collum that complexation of the amine to the lithium enolate in a THF solution seems contrary to the observation that the ability of secondary amines to interact with lithium is similar to the complexing ability of THF.[12] The reaction description in Scheme 1 is thus greatly simplified and it should be recognized that the formation of the enolate (in reality an oligomer of **4**) from the ketone **1** (the latter is, presumably, monomeric) involves significant reorganization. Nevertheless, even such a simplistic picture has some uses.

Due to the complexity of the reacting system it should not be surprising that a number of variables such as solvent, temperature, structure of the base, additives and work-up conditions (the latter are especially important when reversible reactions with electrophiles are involved) can have a pronounced effect on the enantioselectivity which is normally measured on the final product—after the reaction with the appropriate electrophile. Indeed some experimental protocols for reactions involving chiral lithium amides involved complicated temperature regimens.[13] In a number of studies on ketone deprotonation, alkylation of carbonyl compounds and epoxide opening substantial solvent effects have been noted. With some substrate–base combinations selectivity of the epoxide opening was solvent dependent and differences were observed between reactions in THF, ether or benzene.[14a,b] Alkylation reactions were more efficient and selective in toluene than in ether or THF,[14c–e] and deprotonation with the bidentate bases developed by Koga was more selective in THF than in ether.[1d] In our earlier work involving chiral lithium amides we noted the importance of some experimental conditions, such as slow addition of the carbonyl compound to the lithium amide solution

Keywords: enantioselective deprotonation; chiral lithium amides; tropinone; concentration effects; enolates.

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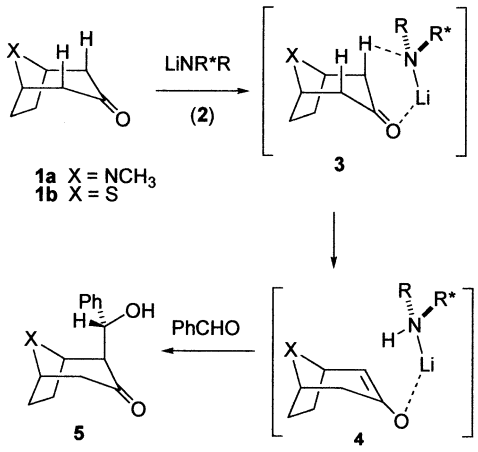
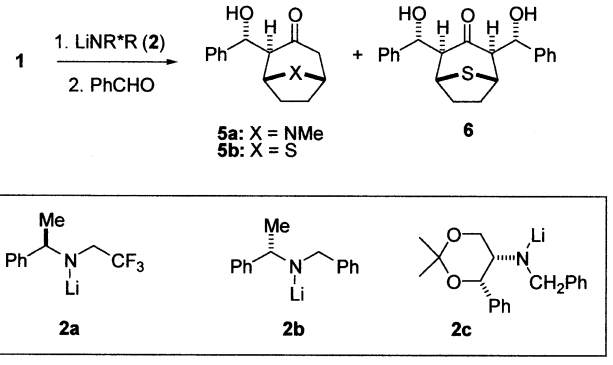


Scheme 1.

or generation of the lithium amide—LiCl complex in situ, standardization of which was essential for reproducibility and high enantioselectivity.[15]

Reagent concentration is a variable that is often not fully appreciated by synthetic chemists. This was pointed out eloquently by Curran in a discussion of free radical reactions, an area where synthetic applications benefited greatly from the solid physical chemistry foundations constructed earlier and the importance of reagent concentrations was recognized from the onset.[16] Several authors have reported pronounced concentration effects in polar reactions, including reactions of enolates.[17] Of special note here is a recent study by Streitwieser and coworkers, who determined that the dimer–monomer equilibrium of lithium enolates controls the efficiency of monoalkylation (as opposed to polyalkylation) and pointed out that the aggregation equilibrium makes ketones effectively more acidic at higher concentrations.[18]

Below, we describe preliminary observations on the effect of lithium amide concentration on enantioselectivity, made recently in our group during work on enantioselective deprotonation of tropinone (**1a**) and its sulfur analog (**1b**). Both compounds had been deprotonated with chiral lithium amides before,[1] but, initially, the experiments involving 8-thiabicyclo[3.2.1]octan-3-one (TBON, **1b**) proved difficult to reproduce.[19] In a typical aldol reaction TBON had a tendency to yield two products: aldol **5b** as the major product (one diastereoisomer only) and the bis-aldol **6**,



Scheme 2.

Table 1. Enantiomeric excess of aldol **5b** generated at different concentrations of chiral base **2a**

Entry	Conc. of **2a** [M]	**5b/6**	ee (%)	Yield (%)
1	0.12	86:14	46	55
2	0.10	88:12	53	61
3	0.050	80:20	64	65
4	0.035	84:16	71	72

that typically accounted for 10–15% of the crude product (Scheme 2).[19] This behavior is quite unprecedented and was not observed with other ketones. During efforts to optimize the reaction conditions we noticed differences in ee of the product **5b** after changing the concentration of the base (lithium amide **2a**). The results are summarized in Table 1.

All reactions were run in the presence of one molar equivalent of LiCl (per amine) and 1.2 equiv. of the lithium amide per mole of the ketone was used in all cases. Under these conditions significant amounts of the bis-aldol **6** were formed. The detailed procedure is described in Section 1, but it should be noted that the work-up conditions proved to be an important variable: the reaction was quenched at −78°C and the extractive work-up followed immediately. Leaving the reaction mixture for a period of time after quenching resulted in lower yields and enantiomeric excess (ee) of the product and poor reproducibility. The ee of the major aldol **5b** was measured on the crude product by NMR spectroscopy in the presence of a chiral shift reagent. Use of a more concentrated lithium amide solution (0.1 M or above) resulted in a significant lowering of the ee of the product. The ee of compound **5b** was ca. 25% higher when the experiments were carried out in a dilute solution (cf. Table 1 entries 1 and 4). Further dilution (beyond 0.03 M) had no effect. Each experiment was repeated several times and reproducibility of the results for ee and yields was generally within 5%, but it should be noted that, on average, one in ten experiments failed for no obvious reasons (the yield was very low and starting material was recovered). Such experiments were rejected. The origin of the bis-aldol **6** lies most likely in the procedure: the reactions were run with ca. 10–15% excess of the lithium amide to minimize the chance of equilibration via proton transfer from the unreacted ketone to the enolate. This is a common procedure in preparative enolate chemistry. Thus, the formation of the bis-aldol could be attributed to the excess base. However, we have noticed that running the reaction with 1 equiv. of the base, but letting the mixture to warm up to 0°C after quenching but prior to the extractive work-up, resulted in low yields and formation of significant amounts of **6** (up to 17% of the product). Clearly, equilibration via the retro-aldol mechanism and proton transfer between the ketone and the enolate cannot be ruled out.

In principle, changing the concentration of a reagent could affect the reaction in a variety of ways by influencing the rate, causing a change in the reaction mechanism, or even by changing the dynamics of heat deposition. If the differences in ee were due to the latter phenomenon the results would likely be not very reproducible. In order to gain some insight into heat deposition issues we monitored carefully the temperature of the mixture during the addition of the ketone to the solution of the lithium amide. Typically, the lithium

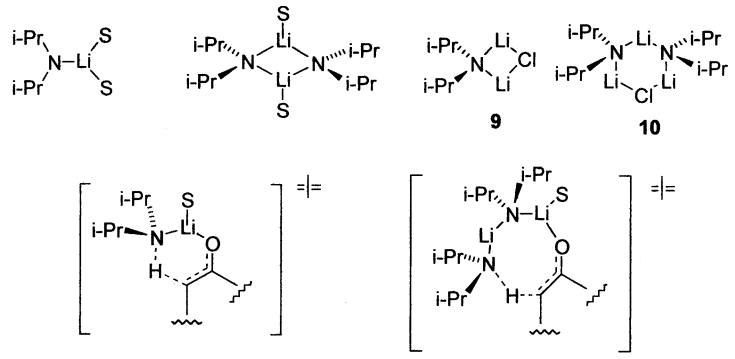


Figure 1. Different forms of LDA (disolvated monomer, dimer, mixed dimers with LiCl) and examples of different transition states for lithiation (cf. Ref: 20,21).

amide was generated in THF at 0°C, and then the solution was cooled to −78°C. The ketone, dissolved in THF was then added over 5–15 min via a syringe. Changing the time of ketone addition from 5 to 15 min did not make any difference. A small increase in temperature was observed in all cases. The magnitude of this increase was 1.5–1.9°C for the more concentrated lithium amide solution (0.10 M) and 0.8–0.9°C in cases involving the dilute solution (0.035 M). In all cases the temperature quickly returned to −78°C and remained stable. Pre-cooling the ketone solution to −78°C, followed by a quick transfer of this solution to the flask containing the lithium amide solution via a syringe wire, resulted in unchanged yield and enantioselectivity, even though a brief increase of the temperature (ca. 8°C) was observed. We concluded that the heat deposition, resulting from the exothermicity of the reaction, was not the cause of the observed differences in enantiomeric excess.

Similar experiments using other lithium amide bases (**2b** and **c**) and different ketone substrates (tropinone and *cis*-2,6-dimethylcyclohexanone) are summarized in Table 2. Aldol **5a**, derived from tropinone, showed small variations in ee when the concentration of the lithium amide base (**2a**, **b**, or **c**) was changed. Dimethylcyclohexanone was deprotonated by amide **2b** and the reaction has shown poor enantioselectivity that was essentially unaffected by the concentration of the base (Scheme 3).

It would be reasonable to expect that concentration of the lithium amide might affect the deprotonation process. Lithium diisopropylamide (LDA), the most extensively studied of the lithium amide bases, is known to exist primarily as a dimer in THF.[12] Initially, kinetic studies suggested that it is the monomeric form of LDA which is the reacting species.[6] In a recent paper, however, Collum described a more detailed study of ester deprotonation which revealed a complex scenario. Depending on the solvent different oligomers of LDA participate in the lithiation step; disolvated monomer in THF, monosolvated dimer in *t*-BuOMe, both monosolvated monomer and tetrasolvated dimer in THF/HMPA.[20] A transition state for deprotonation involving a dimer was proposed (Fig. 1).[20] In the presence of lithium halides, LDA forms mixed dimers such as **9** and **10**.[21] Structures of species potentially relevant are shown in Fig. 1 to illustrate the wealth of species that might be involved. The ratio of lithium chloride to lithium amide, which presumably affects the distribution of the reagents (i.e. the lithium amide monomer, dimer, and mixed dimers), is an important parameter, and it was demonstrated that there is a monotonic relationship between this ratio and deprotonation enantioselectivity.[22] Concentration could also affect the distribution of the reacting species and thus influence enantioselectivity. We would like to stress, however, that the preliminary data reported above should be treated with caution. It has been pointed out that yields and relative rate constants (and also, implicitly, selectivities) cannot be used to probe organolithium reaction mechanisms—hard kinetic data are needed.[20] In some systems, most notably with TBON, concentration makes a difference and the potential for concentration effects should not be forgotten, especially when scaling up a reaction. Is there some unusual feature in TBON chemistry? Formation of the bis-aldol **6** seems to indicate that there is. Is the bis-aldol formation responsible for differences in ee, due for example to kinetic resolution? We are pursuing this line of enquiry. Since the concentration influences aggregation and reactivity of lithium enolates,[14e,18] it could also have a secondary effect on the enantiomeric excess of the product. The enantioselectivity of deprotonation is only reflected in the optical purity of the product if there is no kinetic resolution in the reactions of the two diastereoisomeric complexes, involving the chiral amine and the two enantiomers of the enolate, with the electrophiles. Reactions giving mediocre yields should be carefully evaluated.

Table 2. Enantiomeric excess of products from reactions of chiral enolates generated at different reagent concentration

Entry	Ketone	Base	Conc. [M]	Product	ee (%)	Yield (%)
1	**1a**	**2a**	0.10	**5a**	80	76
2	**1a**	**2a**	0.035	**5a**	88	88
3	**1a**	**2b**	0.10	**5a**	72	77
4	**1a**	**2b**	0.080	**5a**	73	67
5	**1a**	**2b**	0.042	**5a**	75	61
6	**1a**	**2b**	0.026	**5a**	76	70
7	**1a**	**2c**	0.15	**5a**	51	68
8	**1a**	**2c**	0.10	**5a**	57	74
9	**1a**	**2c**	0.026	**5a**	65	64
10	**1b**	**2b**	0.10	**5b**	35	72
11	**1b**	**2b**	0.035	**5b**	45	78
12	**7**	**2b**	0.15	**8**	47	58
13	**7**	**2b**	0.10	**8**	53	62
14	**7**	**2b**	0.035	**8**	55	64

Scheme 3.

1. Experimental

1.1. General

All air-sensitive reactions were carried out under nitrogen. Tetrahydrofuran (THF) was distilled from sodium and benzophenone immediately before each experiment. The chiral amines, precursors to the lithium amides **2a** and **b** were prepared by using known procedures,[23] and were dried over calcium hydride and distilled under reduced pressure before use. Commercially available solution of *n*-BuLi in hexanes (Aldrich) was used to generate lithium amides, the solution was periodically titrated using 2,5-dimethoxybenzyl alcohol as the indicator. Lithium chloride was dried at 130–150°C under vacuum overnight. The spectral data of all the products (**5**, **6**, **8**) were identical to those reported in the literature.[7b,19,24]

During our previous studies on enantioselective deprotonation of tropinone we have established that ee could be measured accurately by NMR spectroscopy using the chiral shift reagent method, even when the enantiomer ratio was high, in which case there is potentially a large error of measurement of the minor enantiomer. Thus, 10 measurements on the same sample of **2b** having ee of 97% resulted in the mean value of 96.8 and standard deviation of 1.2 at the 95% confidence level.[26] Reproducibility of data from different reactions is, potentially, a cause for greater concern, since, as pointed out in the discussion, the complexity of the reacting system leads to a large number of variables that must be standardized. In our experience with tropinone,[5,7b,15a,22,26] the reproducibility of ee data was within 3%. Experiments with other ketones were repeated three times and the results were averaged. The ee values were typically within 4%.

The lithiation procedure was identical in all cases (except the concentration of the starting amine solution) and is illustrated below.

1.1.1. Exo-2-(hydroxybenzyl)-8-thiabicyclo[3.2.1]octan-3-one (5b). The 0.035 M solution of the lithium amide was generated by adding a solution of *n*-BuLi in hexanes (0.28 mL of 2.2 M solution, 0.62 mmol), dropwise, to a solution of (*S*)-*N*-benzyl-α-methylbenzylamine (0.130 g, 0.62 mmol) in THF (15 mL) at 0°C, and, after stirring for 45 min adding LiCl (0.026 g, 0.62 mmol) in THF (2.5 mL). The resulting solution was stirred for 20 min at 0°C, cooled to −78°C, and TBON (**1b**, 0.072 g, 0.51 mmol) in THF (1 mL) was added dropwise over 5 min. The resulting solution was stirred at −78°C for 3 h to ensure complete enolate formation. Benzaldehyde (0.072 mL, 0.70 mmol) in THF (1 mL) was then added and the solution was stirred at −78°C for 30 min, followed by quenching with saturated aqueous NH_4Cl (2 mL) and immediate extraction with diethyl ether (4×15 mL). The combined extracts were dried ($MgSO_4$) and the solvents were removed. The ratio of the aldol to **5b** to bis-aldol **6** and the ee of the major product **5b** were determined by NMR at this stage as described before.[19] Pure compound **5b** was obtained after dry flash chromatography (CH_2Cl_2→CH_2Cl_2/AcOEt, 1:1). Yields and ee values are listed in Tables 1 and 2.

The relative and absolute configuration of **5a** were determined before by chemical and crystallographic methods.[25] The stereochemistry of **5b** was assigned by analogy and is believed to be as shown in Scheme 2, when bases **2a** or **c** were used (the product was laevorotatory). Base **2b** gave the enantiomer of the structure **5a** (or **5b**) as the major product (dextrarotatory).

1.1.2. 1-Acetyloxy-2,6-dimethylcyclohex-1-ene (8). Compound **8** (and its enantiomer) have been synthesized before during studies on enantioselective deprotonation.[24] The procedure described above was followed. The product was purified by column chromatography (hexane/AcOEt, 10:1). The ee of the product was determined by NMR in the presence of $Eu(hfc)_3$ as described by Simpkins.[24] Base **4b** gave the laevorotatory isomer as the major product (structure **8**, as drawn).

1.1.3. (4*S*,5*S*)-*N*-Benzylamino-2,2-dimethyl-4-phenyl-1,3-dioxane. Benzaldehyde (0.64 mL, 6.00 mmol) and glacial acetic acid (0.8 mL) were added to a solution of (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (1.06 g, 5.00 mmol) in MeOH (20 mL) at 0°C. Solid $NaBH_3CN$ (0.32 g, 5.0 mmol) was then added, the mixture was allowed to warm up to room temperature and NaOH aq. (20%, 10 mL) was added. The resulting solution was concentrated on a rotary evaporator till most of MeOH was removed and then was extracted with Et_2O (3 × 50 mL); the combined extracts were dried ($MgSO_4$) and the solvents were removed. The crude product was purified by column chromatography (SiO_2, increasing concentration of AcOEt in hexane, 1:9→1:3) which yielded the pure product as an oil (1.25 g, 84%). $[\alpha]_D^{25}$=87.3 (*c*, 1.02, CH_2Cl_2). IR (neat): ν=3358 cm^{-1}. ^1H NMR (300 MHz): δ, 6.8–7.4 (m, 10H), 5.15 (d, J=2 Hz, 1H), 4.11 (dd, J_1=2 Hz, J_2=12 Hz, 1H), 4.03 (dd, J_1=1.8 Hz, J_2=10 Hz, 1H), 3.65 (d, J=14 Hz, 1H), 3.50 (d, J=14 Hz, 1H), 2.60 (m, 1H), 2.05 (br, 1H), 2.56 (s, 6H). ^{13}C NMR (75 MHz): δ, 140.7, 140.2, 128.7, 128.4, 128.3, 128.2, 127.5, 127.2, 126.9, 126.3, 99.5, 74.0, 63.4, 54.0, 51.0, 30.1, 19.1. Anal. calcd for $C_{19}H_{23}NO_2$: C, 76.72; H, 7.80; N, 4.71. Found: C, 76.64; H, 7.76; N, 4.82.

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