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Communications

An Enhancement of Enantioselectivity in Chiral Lithium Amide Deprotonations Due to Lithium Chloride

Barry J. Bunn and Nigel S. Simpkins*

Department of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, U.K.

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Summary: Substantial improvements in the enantiomeric excess of products obtained from chiral base-mediated reactions of prochiral ketones under external quench (EQ) conditions are observed if the deprotonation is carried out in the presence of added LiCl.

Recently, Collum's group has shown that certain added salts, such as LiCl, can have a remarkable effect on the *E*/*Z* selectivities in ketone enolizations.[1] Thus, in the enolization of 3-pentanone by lithium 2,2,6,6-tetramethylpiperidide the kinetic *E*/*Z* selectivity normally obtained in THF at low temperature is only about 5:1, whereas in the presence of 0.3–0.4 equiv of LiCl this ratio increases to 50–60:1. Surprisingly, if larger quantities of LiCl are employed, e.g., 1 equiv or more, the *E*/*Z* selectivity returns to only about 10:1. We were intrigued by these remarkable results, and in particular we spectulated that a similar improvement in lithium amide enolization stereoselectivity due to added lithium salts might also be observed in enantioselective enolizations mediated by enantiomerically pure chiral lithium amide bases.[2] Here we show that substantial improvements in the enantiomeric excess (ee) of products obtained from chiral base-mediated reactions are indeed observed if the deprotonation is carried out in the presence of added LiCl (an example of an LiX effect).[3]

It has been shown previously that a number of cyclic ketones can be converted directly into nonracemic products by treatment with a chiral base, by a reaction involving breaking the symmetry of the starting ketone through kinetic selection between two enantiotopic α-hydrogens—so-called "enantioselective deprotonation".[4] In a typical experiment a ketone is converted into a nonracemic enol silane by one of two procedures; the base and Me_3SiCl are premixed prior to the addition of the ketone, the in situ quench (ISQ) technique,[5] or the base is allowed to react with the ketone *before* Me_3SiCl is introduced, the external quench (EQ) mode. We initiated our study of the LiX effect on the asymmetric deprotonations of oxabicyclic ketone **1**, using base **2**, by comparing the results obtained under ISQ and EQ conditions with those obtained under EQ conditions in the presence of various amounts of LiCl (EQ + LiCl), Scheme I.[6]

The results for the formation of enol silane **3** show that the ISQ technique gives much higher enantioselectivity (82%) than the EQ quench protocol (33%)[7] but that the selectivity seen in the EQ reaction is dramatically enhanced

(1) (a) Galiano-Roth, A. S.; Kim, Y-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053. (b) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.

(2) (a) For a review of chiral lithium amide chemistry, see: Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1. (b) While our work was in progress a paper concerning asymmetric deprotonations of *cis*-3,5-dimethylcyclohexanone appeared, which included one enolization reaction in the presence of added LiBr which gave a modest improvement in enantiomeric excess; see: Majewski, M.; Gleave, D. M. *J. Org. Chem.* **1992**, *57*, 599.

(3) (a) For an excellent review, including discussion of LiX effects, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) For previous examples of LiX effects involving reactions of lithium amides, see: DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. (c) For an LiX effect on the *C*/*O* regiochemistry of enolate alkylation, see: Jackman, L. M.; Dunne, T. S. *J. Am Chem. Soc.* **1985**, *107*, 2805. (d) For a LiBr-dependent enantioselective alkylation see: Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657.

(4) Cox, P. J.; Simpkins, N. S. *Synlett* **1991**, 321.

(5) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(6) The enantiomeric excess of enol silane **3** was estimated by subjecting a derived α-[(3,5-dinitrobenzoyl)oxy]ketone to chiral HPLC analysis, as described for an analogous system; see ref 4.

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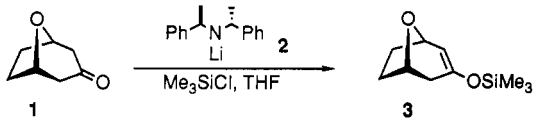
Scheme I

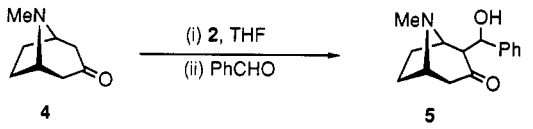


1 3

ee for conversion of **1** to **3** using base **2**

	ISQ	EQ	EQ+LiCl				
ee (%)	82	33	63	84	82	83	84
LiCl (eq.)	0.00	0.00	0.05	0.10	0.40	0.70	1.50

Scheme II



4 5

ee for conversion of **4** into **5** using base **2**

	EQ			EQ+LiCl			
ee (%)	24	35	42	59	62	66	78
LiCl (eq.)	0.00	0.01	0.03	0.05	0.07	0.09	0.5

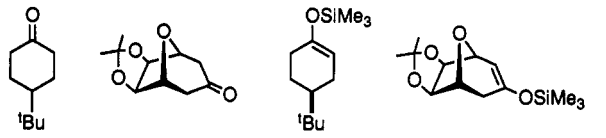
(up to 84%) by the addition of only 0.1 equiv of LiCl. Unlike the *E*/*Z* ratios mentioned above, no subsequent drop in selectivity is seen when 1 equiv or more of LiCl is used.

In order to verify this type of ee enhancement with another system, and to examine the effect of very small amounts of LiCl on the EQ reactions, we carried out further experiments involving the aldol reaction of tropinone **4** to give **5**, Scheme II.[8]

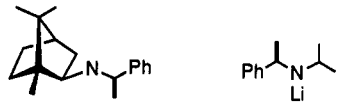
As seen with enol silane **3**, the ee of the aldol product **5** increases sharply on adding small amounts of LiCl to the base solution used for enolization.[9] Since the ISQ technique is not widely applicable, this example is particularly significant in demonstrating that good levels of enantioselectivity can be achieved in EQ reactions involving electrophiles other than Me_3SiCl. The generality of the EQ + LiCl effect was then further demonstrated by conducting additional experiments involving converting 4-*tert*-butylcyclohexanone **6** and oxabicyclic ketone **7** into enol silanes **8** and **9** respectively, Table I.[10]

From the results shown it can be seen that the LiCl effect on EQ-type enolizations appears to be quite general for several different ketones using a number of different bases. Particularly dramatic is the improvement in the ee of the enol silane **8** obtained using base **11** when LiCl is included. In this case the EQ + LiCl conditions give far superior results, even in comparison to the ISQ conditions.

Table I. Enantiomeric Excess of Products from ISQ, EQ, and EQ + LiCl Type Reactions[a]



6 7 8 9



10 11

ketone	product and yields (%)	base	enantiomeric excess[b] (%) ISQ	EQ	EQ + LiCl
6	8 (73–85)	2	69	23	83
6	8 (68–81)	10	21	13	27
6	8 (72–89)	11	46	23	86
7	9 (83–98)	2	70	27	58

[a] All reactions involving LiCl utilized 0.5 equiv based on the amount of lithium amide employed (1.2 or 1.5 equiv based on the ketone). [b] The ee figures are estimated by comparison with our previous rotation data for enol silane **8** and by chiral HPLC for **9**.

At present, the improved selectivities seen in asymmetric enolizations under ISQ or EQ + LiCl conditions, compared to EQ conditions, are difficult to rationalize. It is possible that the LiCl effect involves conversion of a poorly selective lithium amide dimer/monomer mixture into a much more selective mixed aggregate, for example, $R_2NLi{\cdot}LiCl{\cdot}(solvent)_n$.[11] The source of the ISQ effect could also be LiCl, released on mixing the lithium amide and the Me_3SiCl, or formed as the enol silane formation proceeds. Further work is underway to determine the reactive species responsible for the observed selectivity in the ISQ and EQ + LiCl reactions.

Previously, the Me_3SiCl–ISQ conditions have been considered to be crucial for optimal selectivity, thus effectively limiting the chiral base ketone enolizations to the formation of enol silanes. The discovery that comparable, or even higher enantioselectivities, can be achieved simply by including LiCl in the reaction medium should significantly broaden the scope of this type of reaction and stimulate further synthetic applications.

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Supplementary Material Available: Experimental procedures, compound characterization data, NMR spectra, and HPLC results (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) (a) Under the kinetic conditions used, the rate of enolate equilibration is far too low to account for the different results from EQ and ISQ experiments; see: ref 1b and ref 7b–d. (b) Xie, L.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 3123. (c) Fataftah, Z. A.; Kopka, I. E.; Rathke, J. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. (d) Pratt, N. E.; Albizati, K. F. *J. Org. Chem.* **1990**, *55*, 770.

(8) A single aldol product **5**, assigned the *exo-anti* configuration, is obtained from these reactions; see: Majewski, M.; Zheng, G-H. *Synlett* **1991**, 173.

(9) The ee of aldol product **5** was estimated by examination of its ^1H NMR spectrum in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol.

(10) The ee of enol silane **9** was determined by chiral HPLC as described in ref 4. The ee of enol silane **8** was estimated by polarimetry, by comparison with our previous results; see: Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron*, **1990**, *46*, 523.

(11) (a) For a detailed account of lithium amide mixed aggregates, see: Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575. (b) In a previous study of the reactions of certain types of chiral bases it was possible to make some correlation between the aggregation state of the base and the optimal conditions for asymmetric deprotonations; see: Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761.