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The Remarkable Effect of $ZnCl_2$ on Asymmetric Enolisation Reactions of Chiral Bases

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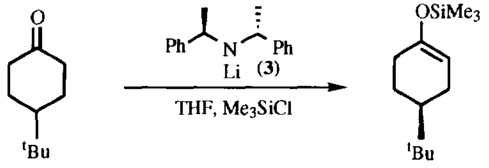
Abstract: The addition of $ZnCl_2$ to the chiral lithium amide base **3** dramatically affects the level of asymmetric induction observed in asymmetric enolisation reactions of certain cyclic ketones, the enantiomeric excess of aldol products obtained increasing on addition of *ca.* 0.4 equivalents of $ZnCl_2$, but then decreasing again if more $ZnCl_2$ is employed.

As part of our studies of asymmetric enolisation reactions mediated by chiral lithium amide bases we recently described the dramatic improvements in enantiomeric excess which can be achieved in these reactions by the inclusion of LiCl in the reaction mixture, e.g. in the conversion of 4-*tert*-butylcyclohexanone **1** into enol silane **2** by amide base **3**, Scheme 1.[1]



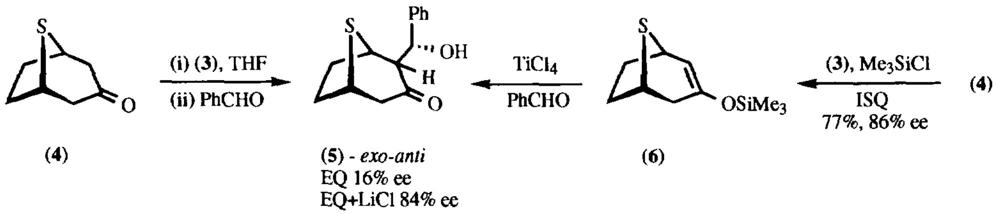
(1) **(2)**

conditions	**ee of (2) (%)**
ISQ	69
EQ	23
EQ+LiCl	83

Scheme 1

This finding is particularly significant in that enolisation by lithium amides under external quench conditions (EQ) in the presence of LiCl (EQ+LiCl procedure) allows high levels of asymmetric induction which were previously only attainable by use of the Me_3SiCl *in situ* quench (Me_3SiCl-ISQ) procedure. The EQ+LiCl conditions therefore allow asymmetric enolisation followed by electrophilic quench, for example direct aldol reaction, without the requirement to proceed via an enol silane derivative. In our search for other salt additives which would further improve the performance of the chiral lithium amide bases we have found a remarkable effect of $ZnCl_2$, which we describe herein.

Enolisation of the sulphur bridged ketone **4** by base **3**,[2] carried out at -78°C according to the usual EQ protocol, followed by addition of PhCHO gives the aldol product **5** in 80% yield but with an enantiomeric excess of only 16%, Scheme 2.[3]



Scheme 2

The same aldol product can be prepared using our previously described EQ+LiCl procedure, which gives **5** in 71% yield and in a greatly improved enantiomeric excess of 84%, as anticipated. Comparison with the Me_3SiCl-ISQ method was also possible by forming the enol silane **6**, followed by subsequent reaction with PhCHO mediated by $TiCl_4$, giving **5** in 43% yield and 86% enantiomeric excess.

After probing the utility of a range of salts as potential additives for chiral base reactions, we obtained a promising preliminary result with $ZnCl_2$, and then proceeded to check the enantiomeric excess of **5** produced under EQ-type conditions (i.e. EQ+$ZnCl_2$), with varying amounts of $ZnCl_2$ added to the chiral base prior to enolisation, Table 1.[4]

Table 1. ee of 5 by reaction of 4 with 3 in the presence of $ZnCl_2$

$ZnCl_2$ (equiv)[a]	0.00	0.05	0.10	0.20	0.40	0.60	0.70	0.80	0.90	1.00
ee of **5** (%)[b]	15	73	76	86	86	74	63	(68)	45	21

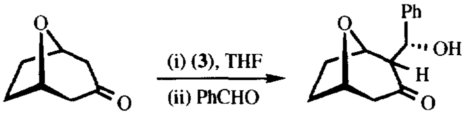
(a) Reactions carried out at -78°C with 1.2 equiv of lithium amide to 1 equiv of ketone; figure shown is equiv. of $ZnCl_2$ relative to lithium amide.

(b) Established by HPLC of purified samples except figure in brackets determined by NMR.[5]

In reactions employing up to about 0.4 equiv. of $ZnCl_2$ a marked improvement in enantioselectivity is observed, allowing **5** to be prepared in up to 86% ee. Remarkably however, if more than about 0.4 equiv. of $ZnCl_2$ is employed then the ee of the aldol product **5** is reduced, eventually approaching a very low level similar to that observed in the absence of added salt.[6] This behaviour is quite different to that observed when LiCl is employed as additive, in which case a sharp rise in the ee of aldol products is observed on adding about 0.1 equiv. of LiCl but little or no subsequent decrease in ee is observed with higher proportions of salt.[7]

The type of behaviour seen with the sulphur bridged ketone **4** was also seen in analogous aldol reactions of the corresponding oxabicyclic ketone **7** to give **8**, Table 2.[8]

Table 2. ee of 8 by reaction of 7 with 3 in the presence of $ZnCl_2$



(7) (8)

$ZnCl_2$ (equiv)	0.00	0.10	0.20	0.40	0.50	0.60	0.70	0.80	0.90	1.00
ee of **8** (% by HPLC)[5]	34	74	72	70	74	68	62	52	51	47

Again, a maximum is observed in the enantiomeric excess of **8** achieved at 0.1–0.6 equiv. of $ZnCl_2$, with the use of more salt giving poorer asymmetric induction, although in this case the plot of ee *vs* equiv of salt has much more of a plateau, and the overall changes in ee are less marked, than in the reactions of **4**.

Whilst we previously ascribed the LiCl effect to the conversion of a poorly stereoselective lithium amide dimer into a more selective mixed lithium amide–lithium chloride aggregate,[9] the origins of the $ZnCl_2$ effect are more obscure. Clearly, the lithium amide could react with the $ZnCl_2$ to generate zinc amide species and LiCl, eq. 1–3.

$$R_2NLi + ZnCl_2 \rightleftharpoons R_2NZnCl + LiCl \qquad \text{(eq. 1)}$$

$$R_2NZnCl + R_2NLi \rightleftharpoons (R_2N)_2Zn + LiCl \qquad \text{(eq. 2)}$$

$$2 \times R_2NZnCl \rightleftharpoons (R_2N)_2Zn + ZnCl_2 \qquad \text{(eq. 3)}$$

Initially, our reaction was to regard the $ZnCl_2$ effect as a disguised LiCl effect, since addition of $ZnCl_2$ to the lithium amide could clearly liberate LiCl, which would be expected to enhance enantioselectivity in asymmetric enolisation. However, the markedly different profiles of the graphs of ee versus equivalents of $ZnCl_2$, plotted using the data in Tables 1 and 2, compared to the data for EQ+LiCl reactions, suggests that the situation is more complex.[10]

Despite our incomplete understanding of salt effects in chiral base reactions, the effectiveness of LiCl and $ZnCl_2$ in enhancing the levels of asymmetric induction in many of these reactions is a very useful supplement to this chemistry. Judging from the few examples where the salt effects have been compared, it seems that very similar improvement in ee is possible with both LiCl and $ZnCl_2$. Efforts to prepare and fully characterise the chiral zinc diamide species $(R_2N)_2Zn$, in order to test this compound (and mixtures with $ZnCl_2$) in asymmetric enolisations are underway.[11]

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References and Footnotes

1. (a) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533; (b) Bunn, B. J.; Simpkins, N. S.; Spavold, Z.; Crimmin, M. J.; *J. Chem. Soc., Perkin Trans. 1*, **1993**, 3113. These results have been verified by other groups, see (c) Majewski, M.; Lazny, R. *Tetrahedron Lett.* **1994**, *35*, 3653; (d) Wild, H. *J. Org. Chem.* **1994**, *59*, 2748
2. Sasaki, S.; Eguchi, S.; Hioki, T. *Heterocycles* **1979**, *13*, 293.
3. The diastereoselectivity and absolute sense of asymmetric induction are assumed to be the same as in the corresponding reactions of the azabicyclic analogue tropinone, see Majewski, M.; Zheng, G-Z. *Can. J. Chem.* **1992**, *70*, 2618.
4. Typical experimental conditions for asymmetric enolisation in the presence of added salts can be found in reference 1b; solutions of freshly fused $ZnCl_2$ in THF were used in place of LiCl. Aldol product 5 found be of 86% ee had $[\alpha]_D^{24}$ -88 (*c* 2 in CH_2Cl_2).
5. HPLC analysis of **5** and **8** was carried out on a cyclobond 1 2000SP column using an eluent of 70% aqueous triethylamine (0.1%, pH 5):30% MeCN at a flow rate of 1ml/min, using detection at 210nm. ^1H NMR analysis of **5** was also possible by recording spectra in C_6D_6 in the presence of 4 equiv of (*R*)-TFAE.
6. Similar remarkable salt effects have been observed by Collum and coworkers in their studies of the *E/Z*-selectivity of enolate formation, see Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.
7. One explanation for the results shown in Tables 1 and 2 would involve racemisation, perhaps via a retroaldol mechanism, induced by high concentrations of $ZnCl_2$. At present we cannot rule out such a possibility, although we have evidence against such an explanation. Firstly, the drop in ee at high levels of $ZnCl_2$ additive seen for ketones **4** and **7** is not observed for the coresponding azabicyclic ketone tropinone, in which case high ee values approaching 80% are maintained, even with 1.0 equiv. of $ZnCl_2$. Secondly, conducting a typical enolisation reaction of **4** with 0.4 equiv. of $ZnCl_2$ and then adding an extra 0.6 equiv. of $ZnCl_2$ gives the same ee as normally observed with 0.4 equiv $ZnCl_2$.
8. Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, *49*, 207.
9. Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227.
10. For comparison, some ee values for **5**, obtained under EQ+LiCl conditions are: 73% (0.1 equiv. LiCl), 86% (0.6 equiv.) and 76% (1.0 equiv.).
11. Alkylzinc amides are reported to effect enolisation of ketones, see (a) Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069; (b) van der Steen, F. H.; Boersma, J.; Spek, A. L.; van Koten, G. *Organometallics* **1991**, *10*, 2467.

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