The Effect of Added Salts on Enantioselective Transformations of Cyclic Ketones by Chiral Lithium Amide Bases

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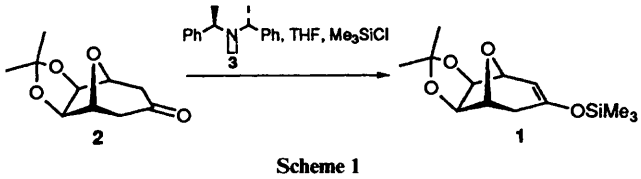
The asymmetric transformation of certain cyclic ketones, using enantiomerically pure chiral lithium amide bases, has been carried out using several reaction protocols. In general, the enantioselectivity observed in the conversion of ketones into non-racemic enol silanes is optimal under *in situ* quench (ISQ) conditions, with products of lower enantiomeric excess being obtained using the external quench (EQ) protocol. However, substantial improvements in the enantiomeric excess of products obtained from EQ reactions can be achieved if either LiCl or $ZnCl_2$ is included in the reaction mixture.

The asymmetric transformation of a prochiral cyclic ketone into a chiral non-racemic derivative, *via* asymmetric enolisation by an enantiomerically pure chiral lithium amide base, has become a useful synthetic method.[1] Most of the reactions of this type conducted have involved conversion of the ketone into an enantiomerically enriched enol silane derivative using the *in situ* quench (ISQ) procedure.[2] This method involves premixing of the lithium amide base and Me_3SiCl at low temperature, prior to addition of the ketone, thereby providing a powerful electrophile to react with the enolate as it is formed. Although the Me_3SiCl–ISQ method has become widely accepted to give optimal enantioselectivity in chiral base-mediated transformations, we felt that a closer comparison of the ISQ reactions with the alternative, more traditional, external quench (EQ) approach was warranted. We recently described our initial studies in this area, which showed that the ISQ conditions do indeed give superior results to the EQ variants, in a range of reactions, but that the enantiomeric excess (ee) of products available by the EQ protocol can be dramatically enhanced by the addition of LiCl.[3-5] Here we describe this novel type of 'salt effect' in detail, including new results obtained with a range of salts other than LiCl, especially $ZnCl_2$.[6]

Results and Discussion

We first became interested in the contrasting results obtained under ISQ and EQ reaction conditions in the preparation of the enol silane **1** from the oxabicyclic ketone **2** (Scheme 1).[3,4] Using



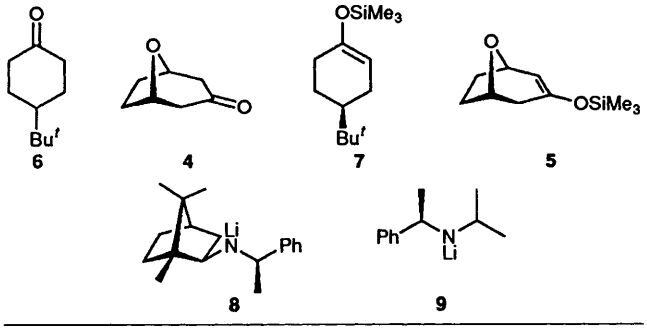
2 1

Scheme 1

the chiral base **3** at −78 °C we obtained the enol silane **1** of 70% ee using ISQ conditions, but material of only 27% ee under EQ conditions. This behaviour appears to be quite general for a number of ketone–chiral base combinations, with the ISQ reactions giving substantially higher levels of selectivity than the EQ versions, as shown in Table 1.

That these contrasting results could be due to enolate equilibration under EQ conditions can be discounted, since the rate of such equilibration is far too slow at such low temperatures.† Further evidence that the effectiveness of the

Table 1 Enantiomeric excess of products from ISQ, EQ and EQ + LiCl type reactions



6 4 7 5 8 9

Ketone	Product and yields (%)	Base	Enantiomeric excess (%) ISQ	EQ	EQ + LiCl (0.5 equiv.)
6	**7** (73–85)	**3**	69	23	83
6	**7** (68–81)	**8**	21	13	27
6	**7** (62–89)	**9**	46	23	86
2	**1** (83–98)	**3**	70	27	58

ISQ conditions is not simply due to the presence of an immediate electrophilic trap is that ISQ reactions with Me_3SiBr did not give the improved level of selectivity seen with Me_3SiCl (*e.g.* enol silane **7** of only 20% ee was obtained from the enolisation of ketone **6** using base **3**).

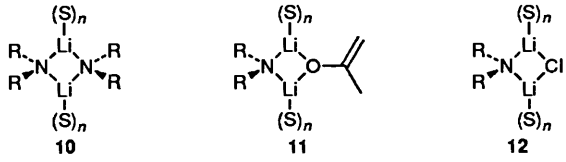
In order to try and explain these results it is necessary to consider the key differences between the two types of reaction conditions. Under EQ conditions, the reaction is accompanied by a build-up of the chiral enolate and the generation of chiral amine. Only when reaction is complete is the Me_3SiCl added in order to convert the enolate into the desired enol silane. Under the ISQ conditions, quenching of the enolate by Me_3SiCl can presumably occur whilst the deprotonation is proceeding. In this type of reaction we would, therefore, expect no build-up of enolate, but instead a release of LiCl. The accumulation of ionic products, either lithium enolate or LiCl, may have important effects in modifying the nature of the lithium amide species in solution, for example by converting a lithium amide dimer **10** into a mixed aggregate **11** or **12**.[8] Clearly, each of these species

† 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.[7]

Table 2 Enantiomeric excess for conversion of **4** into **5** using base **3**

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

may exhibit quite different selectivities in asymmetric reactions with prochiral ketones.



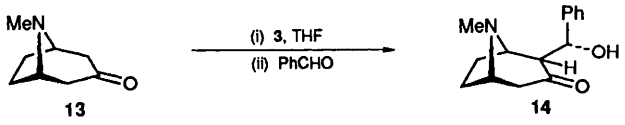
10 **11** **12**

e.g. S = THF, HMPA, amine, etc., n = 1 or 2

Recent results from Collum's group demonstrating that certain added salts, such as LiCl, can have a remarkable effect on the *E*/*Z* selectivities in certain ketone enolisations, prompted us to focus on the presence of LiCl as a key factor in the effectiveness of the ISQ reactions.[9] We initiated our study of the salt effect on the asymmetric deprotonations of oxabicyclic ketone **4**, using base **3**, by comparing the results obtained under ISQ and EQ conditions with those obtained under EQ conditions in the presence of various amounts of LiCl (*i.e.* EQ + LiCl conditions; Table 2).

The results for the formation of enol silane **5** show that the selectivity seen in the EQ reaction is dramatically enhanced (up to 84% ee) by the addition of only 0.1 equiv. of LiCl, and no subsequent drop in selectivity is seen when 1 equiv. or more of LiCl is used. As can be seen in Table 1 (final column), the EQ + LiCl conditions also give much improved results, compared with the corresponding EQ reaction, for enolisations involving the conversion of 4-*tert*-butylcyclohexanone **6** and the oxabicyclic ketone **2** into the enol silanes **7** and **1**, respectively. Most remarkably, the EQ + LiCl reaction involving 4-*tert*-butylcyclohexanone **6** and lithium amide **9** gives almost twice the level of asymmetric induction seen in the corresponding ISQ reaction. This suggested that, in this case, the addition of LiCl to the ISQ reaction might be expected to improve the ee of the enol silance produced. This proved to be the case, with the Me_3SiCl–ISQ reaction, carried out in the presence of 0.5 equiv. of LiCl (ISQ + LiCl) giving the enol silane product **7** in 69% ee.

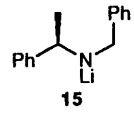
The EQ + LiCl experiments in Table 1 were each conducted using 0.5 equiv. of LiCl (compared to the amount of lithium amide employed), which appeared to give optimal results in the case of ketone **4**. In order to examine the effect of very small amounts of LiCl on the EQ reactions, we next carried out further experiments involving the aldol reaction of tropinone **13** to give **14** (Scheme 2, Table 3).*



13 **14**

Scheme 2

As seen with the enol silane **5**, the ee of the aldol product **14** increases sharply on adding small amounts of LiCl to the base solution used for enolisation. 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. Analogous results were also obtained in the aldol reaction of **13** when lithium amide **9** was employed (EQ—24% ee and EQ + LiCl—66% ee), and when **15** was used as the chiral base (EQ—30% ee and EQ + LiCl—72% ee).



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The finding that the addition of LiCl to EQ deprotonations significantly improves the ee of resulting chiral products prompted us to survey briefly other salts for similar effects (all using the base **3**). Examples of salts tried include LiBr, LiF, KCl, NaCl, NaBr and $MgBr_2$ (all at 0.5 equiv.), none of which gave any improvement in the normal EQ aldol reaction of tropinone. Of the more powerful Lewis acid additives that were tried, $SnCl_4$ and $TiCl_4$ did not appear to be compatible with the lithium amide, and gave none of the desired product **14**, whereas $ZnCl_2$ gave a very good (85% ee) enhancement of selectivity. To date, $ZnCl_2$ appears to be the most effective additive in the EQ type of chiral base reaction, with the use of *ca.* 0.5 equiv. giving optimal results.

At present, the improved selectivities seen in asymmetric enolisations under ISQ or EQ + salt conditions, compared to EQ conditions, are difficult to rationalise. The observation that the Me_3SiCl–ISQ and EQ + LiCl procedures give good results, but that the Me_3SiBr–ISQ and EQ + LiBr do not, is good evidence that the success of the ISQ reactions derives from the presence of LiCl, and not merely the presence of a reactive silicon electrophile. Since the presence of LiCl has been shown to change dramatically the solution structure of certain types of lithium amide[11] (and to allow the isolation of mixed aggregates of lithium amide and LiCl in some cases),[12] the improved selectivity seen in the EQ + LiCl examples given is almost certainly due to modification of the lithium amide reagent. 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, such as **12**.† The source of the Me_3SiCl–ISQ effect could also be LiCl, released on mixing the lithium amide and the Me_3SiCl, or formed as the enol silane formation proceeds.

The fact that salts other than LiCl, such as LiBr, do not give the same effect on enantioselectivity should not be altogether surprising, given that Collum and co-workers have previously demonstrated different behaviour of lithium amides on addition of LiBr, rather than LiCl, both spectroscopically,[11] and in the results of *E*/*Z* enolisation studies already mentioned.[9] The improved results that we obtained using $ZnCl_2$ could also, in part, be due to released LiCl, although other effects involving Lewis acid complexation with the ketone function might also be important. Further work is underway to determine the reactive species responsible for the observed selectivity in the ISQ and EQ + salt reactions.

Previously, the Me_3SiCl–ISQ conditions have been considered to be crucial for optimal selectivity, thus effectively limiting the chiral base ketone enolisations to the formation of enol silanes. The discovery that comparable or even higher enantioselectivities can be achieved simply by including LiCl or $ZnCl_2$ in the reaction medium should significantly broaden the

* A single aldol product **14**, assigned the *exo-anti* configuration, is obtained from these reactions.[10]

† 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.[13]

Table 3 Enantiomeric excess for conversion of **13** into **14** using base **3**

	EQ	EQ + LiCl								
LiCl (equiv.)	0.00	0.01	0.03	0.05	0.07	0.09	0.20	0.30	0.50	0.80
ee (%)	24	35	42	59	62	66	79	77	78	80

scope of this type of reaction and stimulate further synthetic applications.

Experimental

The general experimental procedures utilised in this work have been described previously.[4] Full data for the compounds described in this paper, along with details of ee determinations can also be found in previous papers.[1,3,4,14]

3-*Trimethylsiloxy*-8-*oxabicyclo*[3.2.1]*oct*-2-*ene* **5**.—*By the* in situ *quench* (*ISQ*) *procedure.* A solution of the chiral lithium amide **3** was prepared by treatment of a solution of the corresponding secondary amine (581 mg, 2.58 mmol), in THF (20 cm^3) at −78 °C under N_2, with BuLi (1.6 mol dm^{-3} solution in hexanes; 1.61 cm^3, 2.58 mmol). After 5 min the solution was allowed to warm to room temperature and then recooled to −78 °C when Me_3SiCl (1.09 cm^3, 8.56 mmol) was added to it. After 2 min the ketone **4** (217 mg, 1.72 mmol) in THF (2 cm^3) was also added to the mixture, the temperature being kept at −78 °C. After 45 min at −78 °C the reaction was quenched with saturated aqueous $NaHCO_3$ (50 cm^3) and the two phases separated. The aqueous layer was then extracted with light petroleum (3 × 50 cm^3). The combined extracts were washed with saturated aqueous $CuSO_4$ (5 × 50 cm^3), dried ($MgSO_4$) and evaporated to give the title compound **5** as a colourless oil (270 mg, 79%); ν_{max}(film)/cm^{-1} 2955, 1656 and 891; δ_H(250 MHz; $CDCl_3$) 0.19 (9 H, s), 1.60–1.75 (2 H, m), 1.80–2.20 (3 H, m), 2.67 (1 H, dd, *J* 4 and 17), 4.47–4.58 (2 H, m) and 5.04 (1 H, dt, *J* 0.7 and 5); δ_C(67.5 MHz; $CDCl_3$) 0.27 (CH_3), 29.03 (CH_2), 35.77 (CH_2), 39.58 (CH_2), 72.23 (CH), 73.04 (CH), 108.26 (CH) and 147.36 (C); *m*/*z* 105 (M^+ − $OSiMe_3$, 17%). The above procedure gives optically active **5** of 82% ee, as determined by chiral HPLC methods,[4] with $[\alpha]_D^{24}$ −13.1 (*c* 1.6, EtOAc).

By the external quench (*EQ*) *or* (*EQ* + *LiCl*) *procedure.* A solution of the chiral lithium amide **3** was prepared by treatment of a solution of the corresponding secondary amine (645 mg, 2.86 mmol) in THF (20 cm^3), at −78 °C under N_2, with BuLi (1.6 mol dm^{-3} solution in hexanes; 1.79 cm^3, 2.86 mmol). After 5 min the solution was allowed to warm to room temperature and then recooled to −78 °C [at this point the amount of LiCl (as a solution in THF) indicated in the Schemes was added if required; in this case LiCl (8.1 mg, 0.1 equiv.) was added to it in THF (2 cm^3)]. After this the ketone **4** (241 mg, 1.91 mmol) in THF (2 cm^3) was added to the mixture which was then stirred for 15 min before the addition of Me_3SiCl (1.21 cm^3, 9.5 mmol). The reaction mixture was stirred at −78 °C for a further 30 min and then worked up as above to give **5** (283 mg, 75%) in 84% ee spectroscopically identical with that obtained previously.

2-(α-*Hydroxybenzyl*)-1αH,5αH-*tropan*-3-*one* **14** *by External Quench* (*EQ*) *or* (*EQ* + *Salt*) *Procedure.*—A solution of the chiral lithium amide **3** was prepared by treatment of a solution of the corresponding secondary amine (371 mg, 1.64 mmol) in THF (20 cm^3), at −78 °C under N_2, with BuLi (1.6 mol dm^{-3} solution in hexanes; 1.03 cm^3, 1.64 mmol). After 5 min the solution was allowed to warm to room temperature and then recooled to −78 °C before addition of a solution of tropinone **13** (153 mg, 1.10 mmol) in THF (2 cm^3). After 1 h benzaldehyde (0.13 cm^3, 1.3 mmol) was added to the reaction mixture which was then stirred and maintained at −78 °C for a further 15 min; saturated aqueous NH_4Cl (25 cm^3) was then added to the mixture. The product was extracted into $CHCl_3$ (3 × 50 cm^3), and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an oil. Examination of the ^1H NMR spectrum ($CDCl_3$) of this crude sample in the presence of (*R*)-TFAE * indicated an ee of 24%.

Similar runs carried out by adding the appropriate amount of LiCl or $ZnCl_2$ (made from freshly fused salt as a *ca.* 0.25 mol dm^{-3} solution in THF) to the solution of lithium amide **3** prior to the addition of tropinone gave the ee results for **14** shown in Table 3.

Purification of the crude samples by crystallisation (**14** is unstable to column chromatography on silica gel) from Et_2O gave pure **14** in 69–75% yield. A purified sample of 41% ee had $[\alpha]_D^{24}$ −9.4 (*c* 0.49 in $CHCl_3$), {lit.,[1g] $[\alpha]_D^{20}$ +23 (*c* 0.0173 in $CHCl_3$) for optically pure material}.

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* (*R*)-TFAE = (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

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