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We have been able to bind the barely water-soluble condensing agent EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) to POPC liposomes. When these liposomes were exposed to a library of tryptophan-containing dipeptides such as H-Asp-Trp-OH, H-Trp-Trp-OH, H-Glu-Trp-OH, H-Gly-Trp-OH, only H-Trp-Trp-OH was bound to the liposomes and therefore oligomerized with significant yields (*i.e.* out of the theoretically possible 16 tetrapeptides, H-Trp-Trp-Trp-Trp-OH makes about 70% of all tetrapeptides formed) [8]. The other peptides are too hydrophilic and were not selected. With this type of selection, tryptophan oligomers can be formed. The products of such an oligomerization become more hydrophobic with increasing length and remain attached to the liposomal matrix. We have therefore two selection steps, one arising from the choice of the monomer, and one from the possibility of polymerizing water-insoluble compounds on the liposome membrane.

As an alternative to the use of a hydrophobic condensing agent, we have carried out direct polymerization of N-carboxy anhydride (NCA) amino acids, such as NCA-Trp. Also in this case, we could obtain long oligomers (up to a polymerization degree of 29), which cannot be obtained by aqueous polymerization methods in the absence of liposomes [8].

The selectivity and specificity of the liposome membrane can be changed and regulated by the type of lipidic surfactants (*i.e.* addition of ionic co-surfactants). For example, the positively charged DDAB (didodecyldimethylammonium bromide) forms stable mixed liposomes with POPC. This lipidic bilayer can now also attract negatively charged amino acid derivatives – for example NCA-glutamic acid – and induce polymerization. The possibility of obtaining co-oligopeptides made out of hydrophobic and ionic amino acids in the same molecule is the next challenge. As a matter of fact, we have been able to condense the dipeptide H-His-Trp-OH to the corresponding hexapeptide. Recognizing the catalytic character of the imidazole group, this may open up ways to construct simple, catalytically active polypeptides.

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## Enantioselective Proton Transfer Chemistry: Asymmetric Synthesis with Chiral Lithium Amide Bases

Nigel S. Simpkins\*

**Keywords:** Asymmetric synthesis · COST · Lithium amide bases · Proton transfer

Enantioselective proton transfer chemistry has been relatively underdeveloped, considering the potential power and broad applicability of this approach [1]. Notable early contributions in this area include the enantioselective protonation of enolates by Duhamel and Plaquevent [2], and the asymmetric rearrangement of cyclohexene oxide by reaction with a chiral lithium amide, described by Whitesell and Feldman [3].

We have devoted a substantial part of our research effort to the development of desymmetrisation reactions using chiral lithium amide bases, including **1** and **2**, and have helped to establish this approach as a tool for asymmetric synthesis. Much of this

chemistry involves the reaction of a cyclic (or polycyclic) prochiral ketone with a chiral lithium amide base in a process that involves the base selecting between enantiotopic hydrogens. For example, the use of base **1** allows the conversion of ketone **3** into the enol silane **4**, and the azabicyclic ketone **5** into the aldol product **6**, both in high enantiomeric excess (Scheme 1).

This type of transformation has obvious applications in target synthesis. For example we have prepared the unique alkaloid toxin anatoxin-a **7** (the unnatural enantiomer) by this method [4], as well as a protected form of thymine polyoxin C **8** [5]. Current activities in this area involve the development of a strategy for the synthesis of functionalised intermediates possessing the [5-8-5] framework found in natural products such as the ophiobolins and fusicoccins, *e.g.* conversion of ketone **9** into the complex intermediate **10**, as shown in Scheme 2 [6].

In addition to applications in the area of enolate chemistry, chiral lithium amides have also been used to generate reactive anions, in non-racemic form, from a considerable range of non-ketonic substrates. Examples include the enantioselective synthesis of

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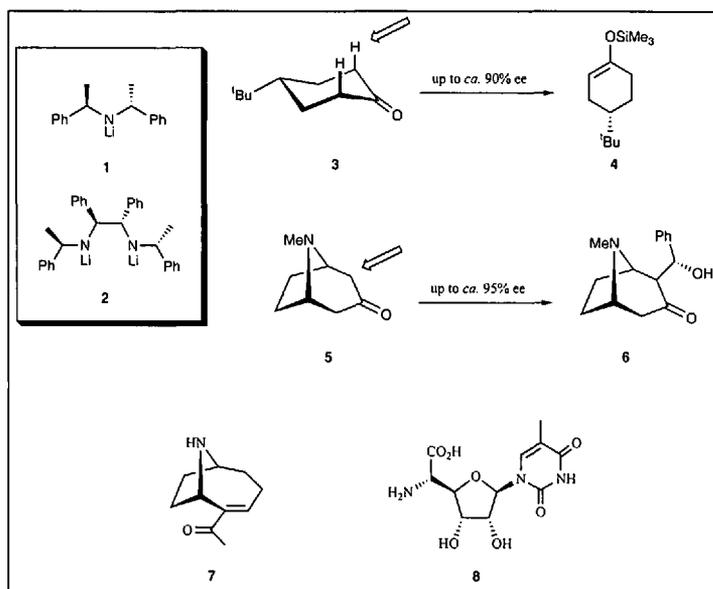
chemistry involves the reaction of a cyclic (or polycyclic) prochiral ketone with a chiral lithium amide base in a process that involves the base selecting between enantiotopic hydrogens. For example, the use of base **1** allows the conversion of ketone **3** into the enol silane **4**, and the azabicyclic ketone **5** into the aldol product **6**, both in high enantiomeric excess (Scheme 1).

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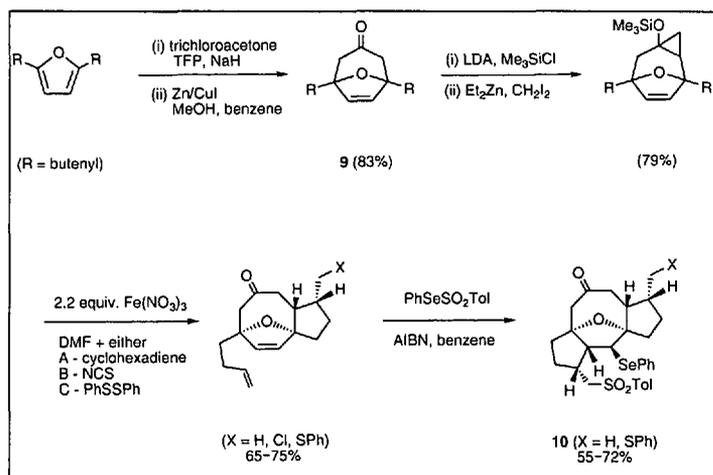
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Scheme 1



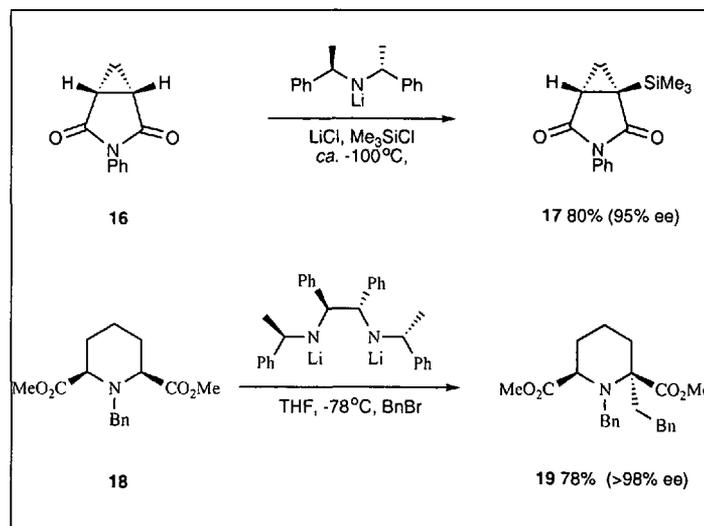
Scheme 2



sulfoxides [7], tricarbonyl( $\eta^6$ -arene)chromium complexes [8] and phosphine oxides [9,10], as represented by the chiral products **11–15**. In each case the product originates from a chiral base reaction of a symmetrical substrate which serves to introduce the highlighted substituent.

Our present activities, aimed at further extending the applications of chiral lithium amides, are focussed on developing desymmetrisation reactions of polyfunctional substrates. Examples include the conversion of imide **16** into the silylated deriv-

Scheme 3



ative **17** [11], and the alkylation reactions of piperidine diester **18** to give products of general structure **19** [12] (Scheme 3). This last example is notable for the extremely good levels of both diastereo- and enantiocontrol observed, and opens up an interesting new avenue for the synthesis of enantiomerically pure piperidines and cyclic amino acids.

In summary, chiral lithium amide base chemistry continues to develop apace, and we expect to see many more applications of these reagents in organic synthesis over the years to come.

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