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Chiral lithium amides on solid support: synthesis and applications in enantioselective deprotonation of cyclic ketones

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Abstract

Several chiral amines attached to polymer support (Merrifield resin or a soluble analog) are described. Lithium amides, generated from these amines by treatment with BuLi, react with C_S-symmetrical ketones to give the corresponding enolates enantioselectively (ee up to 75%). © 1999 Elsevier Science Ltd. All rights reserved.

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Chiral amines are amongst the most versatile species in the synthesis of enantiomerically pure compounds. They are used in many guises: as resolving reagents, as ligands in chiral Lewis acid catalysts and in chiral organometallic reagents, as nucleophilic catalysts, as chiral auxiliaries connected to substrates in diastereoselective reactions, as chiral reagents or as chiral building blocks. During the last decade chiral lithium amides, derived from chiral amines, have emerged as a new powerful class of reagents allowing control of stereoselectivity in enolate chemistry and enantioselective epoxide opening.[1] Recently, combinatorial chemistry has precipitated a lot of interest in reactions and reagents on solid support. Apart from combinatorial applications, functionalized polymer reagents also offer new ways of running reactions (e.g., membrane reactors) and could allow easy recovery and multiple use of valuable reagents.[2] Developing the chemistry of chiral amines and chiral lithium amides on polymer support could lead to a new generation of improved reagents for organic synthesis. In this communication we describe several chiral amines connected to either insoluble or soluble polymer support, and preliminary results on the application of the corresponding lithium amides to directed aldol addition.

The amines were prepared from either the commercially available Merrifield resin (insoluble polymer) or from a non-crosslinked analog that we prepared by copolymerization of styrene and 4-chloromethylstyrene according to a literature procedure (soluble polymers).[3] A typical synthesis is shown in Scheme 1. Conversion of the chloromethyl group in the Merrifield polymer (**1**) to the iodomethyl group, more amenable to an S_N2 displacement, was accomplished with NaI. The linker moiety was introduced by a reaction of the iodide **2** with the appropriate monoanion derived from 1,6-hexanediol.

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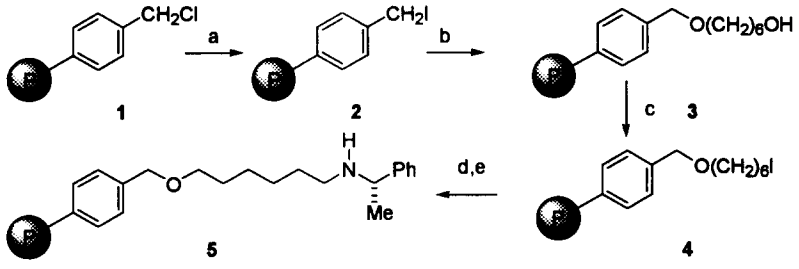
At the end of the sequence the unreacted alkyl halide groups were converted to methyls by reduction with tributyltin hydride.[4] Amine **5** was synthesized several times; the yield was typically 40% and the loading was 0.740 mmol of nitrogen per gram of polymer. The loading was independently determined by titration and by elemental analysis: both methods were in very good agreement. Structures of all polymer-supported chiral amines are shown in Fig. 1. Amines **6** and **10**, having no linker, were synthesized from the iodide **2** by treatment with the chiral amine reagent (step d) followed by removal of the unreacted halide using tributyltin hydride (step e).



Scheme 1. Reagents and conditions: (a) NaI, acetone, reflux, 2 days; (b) NaH, DMF; 1,6-hexanediol, 60°C, 48 h; (c) imidazole, Ph_3P, I_2, CH_2Cl_2, rt, 4 days; (d) *S*-(−)-α-methylbenzylamine, THF, reflux, 2 days; (e) Bu_3SnH, reflux, 2 days

Very little is known about lithium amide reagents on polymer support,[5] and we were interested if these reagents would work in deprotonation reactions at least as well (i.e., giving similar yields and regio- and diastereoselectivities) as the lithium amides well established in solution chemistry e.g., LDA or LiTMP.[6] As the model system we have chosen the well known aldol addition leading to two diastereoisomeric products[7] (Scheme 2, *anti* isomer **13** and *syn* isomer **14**). A simple model study on cyclohexanone (**15a**) and similar ketones confirmed that polymer-supported lithium amides are indeed efficient deprotonating reagents and do not influence adversely reaction diastereoselectivity (Table 1).[8]

Enantioselective deprotonation: Cyclic ketones having C_S symmetry can be deprotonated enantioselectively by chiral lithium amides to give chiral enolates in high enantiomeric purity.[1] The chirality of the enolate is then reflected in the products, leading to non-racemic derivatives (e.g., aldols). We investigated in some detail deprotonation of tropinone (**15d**) and its sulfur analog (**15c**) with chiral polymer-supported lithium amides derived from amines **5–11**.

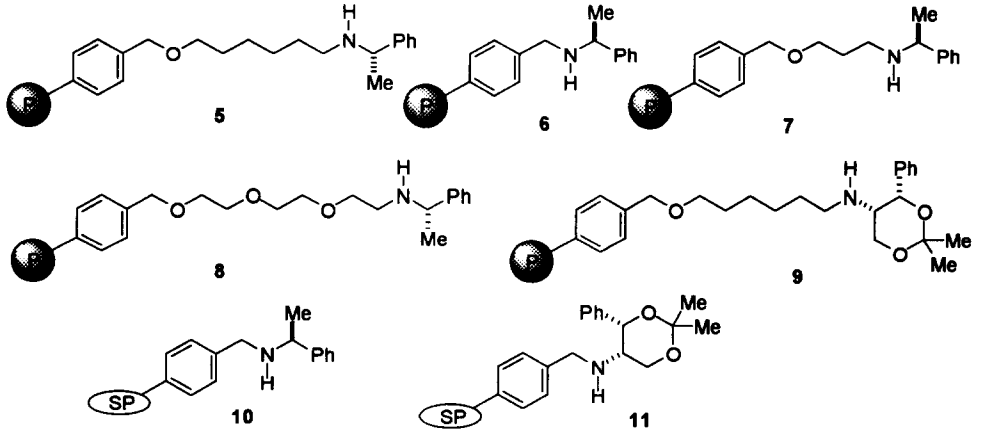
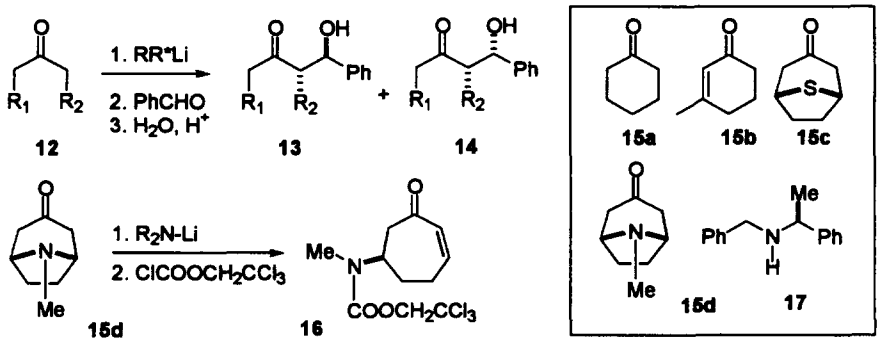


Figure 1. Structures of chiral amines on insoluble (P) and soluble (SP) polymer support



Scheme 2.

Table 1
Aldol addition of lithium enolates of cyclic ketones, generated using polymer-supported lithium amides, to benzaldehyde

Entry	Ketone	Li-amide	Ratio (13 : 14)	Yield (%)
1	**15a**	Li-5	90 : 10	57
2	**15a**	Li-8	90 : 10	58
3	**15b**	Li-8	88 : 12	60
4	**15c**	Li-9	95 : 5	63

Aldol addition reaction in these bicyclic bridged ketones is typically very diastereoselective and usually gives only one product,[1b] making it a good model reaction for studying enantioselectivity. Tropinone lithium enolate when treated with chloroformates undergoes a ring opening reaction to give **16**.[1b] This reaction is also a convenient probe of deprotonation selectivity. The results of deprotonation experiments, followed by trapping the enolate either with benzaldehyde to give *cis–anti* aldols **13c, d** or trichloroethyl chloroformate to give **16** (Scheme 2), are summarized in Table 2. Chiral lithium amides on insoluble polymer support have proven somewhat disappointing, giving often low yields and low enantioselectivities (the highest ee being 59%, Table 2, entry 7). However, soluble polymer-supported amines afforded the corresponding lithium amides which worked well, giving the aldol products in high selectivity and useful yields (cf., Table 2, entry 12).[9]

The work on optimizing the reaction conditions and the chiral amide structure is still ongoing but a few trends have already emerged. (i) Lithium chloride is a necessary additive. In fact, lithium amides could not be efficiently generated from amines **10** and **11** because of the formation of a gel which made the system heterogeneous. It is likely that the gelling is caused by non-covalent crosslinking of the polymer chains by virtue of lithium amide groups aggregating. After addition of LiCl the gel disappears, presumably the mixed LiCl–$LiNR_2$ aggregates are formed and the crosslinking is broken. Seebach has pointed out the potential for such phenomena to occur.[10] (ii) There seems to be a concentration effect in reactions involving soluble polymeric lithium amides. The concentration of the reagent must not be too high; the ee of the tropinone aldol addition was 75% at 0.026 M amide but only 30% when the concentration of the amide was raised to 0.075 M. (iii) When amines on insoluble polymer are used as precursors for lithium amides it is highly beneficial to add one additional equivalent of BuLi after deprotonation is complete but before addition of the electrophile. This operation perhaps prevents the internal proton return,[10,11] and increases the yields substantially.

In order to compare the polymer-based amide with a non-polymeric reagent we have run a tropinone aldol experiment under identical conditions but with chiral lithium amide **17** as the base. The non-

Table 2
Enantioselectivity of deprotonation of C_S-symmetrical cyclic ketones **15c, d** with chiral lithium amides on polymer support

Entry	Ketone	Li-amide	Product	Additive	ee (%)	Yield (%)
1	**15d**	Li-6	**13d**	-	14	38
2	**15d**	Li-6	**13d**	LiCl (1 eq)	24	45
3	**15d**	Li-5	**13d**	-	10	20
4	**15d**	Li-5	**13d**	LiCl (1 eq)	20	26
5	**15d**	Li-8	**13d**	-	12	71
6	**15d**	Li-6	**16**	-	10	28
7	**15d**	Li-6	**16**	LiCl (1 eq)	59	37
8	**15d**	Li-7	**16**	-	3	42
9	**15d**	Li-7	**16**	LiCl (1 eq)	6	48
10	**15d**	Li-5	**16**	-	2	22
11	**15d**	Li-5	**16**	LiCl (1 eq)	22	35
12	**15d**	Li-10	**13d**	LiCl (2 eq)	75	77
13	**15d**	Li-11	**13d**	LiCl (2 eq)	66	74
14	**15c**	Li-10	**13c, 14c**	LiCl (1 eq)	44	72
15	**15c**	Li-11	**13c, 14c**	LiCl (1 eq)	38	69

polymeric base **17** afforded identical selectivity and very similar yield: the product **13d** was isolated in 65% yield and 76% ee.[12]

This preliminary study demonstrated the potential for polymer-supported lithium amides (chiral or not) to act as useful deprotonating reagents.[13] The yields and selectivities of typical enolate reactions compare favorably with 'classical' solution chemistry.[14]

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12. All amines derived from *S*-α-methylbenzylamine gave the dextrarotatory aldol predominantly (the 1*S*,2*R*,1′*S* isomer) while amines **9** and **11** abstracted the H_R axial proton of tropinone selectively.
13. Key experimental details: The polymer-supported amines were dried by washing with THF and placing in a Soxhlet over toluene–CaH_2 for 2 days. The amine loading was established by elemental analysis. Before deprotonation, the amines were swollen in THF (rt, 30 min). Amide formation with BuLi (1 mmol per mmol of amine, 0°C, 3 h) was followed by deprotonation (0.8 mmol ketone, 78°C, overnight) and electrophile (0.8 mmol).
14. This work was supported by a grant from the National Science and Engineering Research Council of Canada.