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Synthesis of polymer-supported chiral lithium amide bases and application in asymmetric deprotonation of prochiral cyclic ketones

Lili Ma and Paul G. Williard*

Department of Chemistry, Brown University, Providence, RI 02912, USA

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Abstract—Polymer-supported chiral amines were effectively prepared from amino acid derivatives and Merrifield resin. Treatment of polymer-supported amines with *n*-butyllithium gave the corresponding polymer-suppported chiral lithium amide bases, which were tested in the asymmetric deprotonation reactions of prochiral ketones. Trimethylsilyl enol ethers were obtained in up to 82% ee at room temperature. The polymer-supported chiral lithium amides can be readily recycled and reused without any significant loss of reactivity or selectivity.

1. Introduction

More recently, chiral lithium amide bases (CLAB's) have been successfully used in asymmetric reactions[1] such as the aldol reaction,[2,3] alkylation,[4,5] rearrangement of expoxides,[6,7] and deprotonation of prochiral ketones.[8,9] Due to the potential application of the chiral enolates in total synthesis, asymmetric deprotonation reactions have attracted special attention. For example, Simpkins et al. reported the deprotonation of prochiral ketones by *C*2 symmetric amides.[10,11] Koga et al. synthesized diamines with different *N*-alkyl groups and subsequently applied the corresponding lithium amides in the asymmetric deprotonation reactions.[12,13] Henderson systematically studied magnesium amide base-mediated enantioselective deprotonation processes.[14,15]

Despite the increasing use of polymeric chiral reagents in organic synthesis, the number of papers dealing with asymmetric deprotonation using polymer-supported CLAB's is still limited.[16–18] The polymer-supported CLAB's share several common advantages as other supported reagents utilized in solid phase organic synthesis (SPOS), such as easy separation of the products, and simple recycling of supported CLAB's by filtration, which is important for precious demanding ligands.[19] More importantly, there are three additional beneficial polymeric effects we are pursuing with these supported CLAB's. Firstly, the supported CLAB's are less likely to participate in aggregation equilibria. Secondly, the asymmetric deprotonation reactions mediated by supported CLAB's are possible over a large temperature range. Hence, it will be a great improvement to achieve enantioselectivity with the supported CLAB's at room temperature instead of the commonly used low temperature.[20] Finally, in contrast to the aggregation of reactive species in solution, supported CLAB's will favor the separation of reactive species and potentially enhance the reactivity and enantioselectivity. Taking advantage of this 'pseudodilution effect',[21] the supported CLAB's will be significantly less dependent on additives in asymmetric reactions.

Herein, we report the synthesis and characterization of polymer-supported CLAB's, as well as their application in asymmetric deprotonation reactions of prochiral cyclic ketones. We also report on an optimized procedure for the synthesis of polymer-supported CLAB's with a six carbon spacer between the functional groups and polymer backbone.

2. Results and discussion

Merrifield resin was chosen as the polymer backbone for CLAB's in our study because of its readily availability and the fact that the substitution of the chloromethyl group requires no harsh reaction conditions. Considering the total effect of the swelling ability, physical stability,

* Corresponding author. E-mail: pgw@brown.edu

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and number of reactive sites on a single bead, the commonly used chloromethylated polystyrene beads have a cross-linking degree between 1% and 2%, a particle size between 100 and 200 mesh, and a loading in the range of 1–1.5 mmol/g. The functional groups in our amide bases are readily prepared from amino acids via the corresponding amino alcohols obtained according to Shioiri's method.[22] These amino alcohols were converted into sodium alkoxides and then substituted for chloride[23] on the resins to form polymer-supported aminoethers **1a**–**c**, as shown in Scheme 1.

Although these reactions are straightforward and give good to excellent yields, it was hard to attach prolinol to Merrifield resin using this method. The steric hindrance around nitrogen is small, and hence nitrogen alkylation occurred much more readily than oxygen alkylation. This could not be avoided under any reaction conditions we examined. Two other functional groups we incorporated into our polymer-supported CLAB's were diamines synthesized via a modification of Koga's procedure.[24,25] They were attached to the polymer through the nitrogen atom. The resulting polymer-supported diamines **2a** and **2b** are also shown in Scheme 1. Polymer-supported (*R*)-α-methylbenzylamine **3**, previously reported by Henderson,[16] was also examined in our study. FTIR and ^{13}C gel phase NMR were used to characterize the structure of the functionalized resins, and elemental analysis exhibited the expected values for nitrogen with yields in the range of 89–96%.

The reactivity of bound species sometimes differs significantly from their unbound analogues. In general, the yields decreased as a result of constrained mobility and the steric effect of the bulky polymer matrix. The constrained mobility makes it harder to achieve the transition state geometry and the polymeric backbones slow down the diffusion of reactants. This inherent limitation derived from the heterogeneous nature of polymers can be addressed by adding a spacer between the functional group and the polymer backbone, which allows enough mobility and separates further the functional groups from the polymer backbones.[26,27]

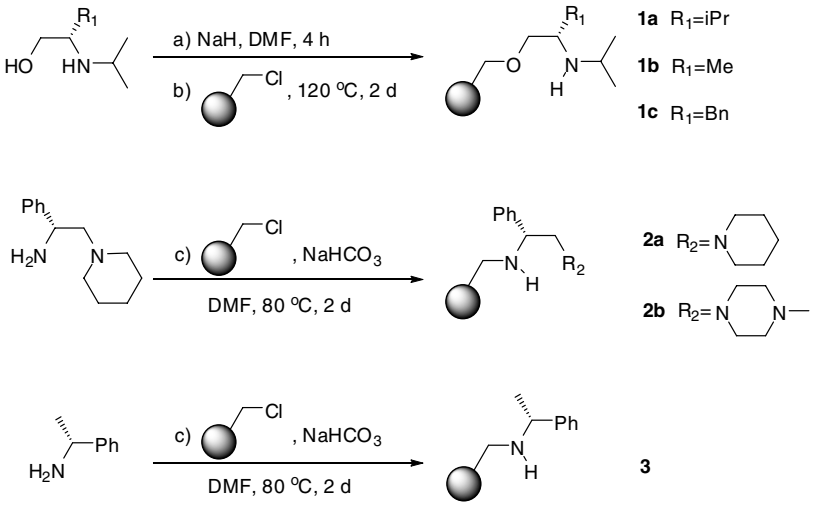
We synthesized **4** with a six carbon spacer using a carbon–carbon linkage,[28,29] as shown in Scheme 2.

This all carbon-linker, bearing a robust carbon–carbon bond attached to the polymer backbone, requires more synthetic steps than the alternatives discussed below. Hence, after five steps, the final loading amount of amine is only 0.16 mmol/g. Additionally, the use of a Grignard reagent in the first synthetic step caused difficulties in filtration and washing procedures. These limitations led us to choose a carbon–oxygen linkage for the direct attachment of our CLAB's to the Merrifield resin backbone. Hence, for practical reasons, we settled on a six carbon spacer with a carbon oxygen attachment to the resin backbone,[30,31] as shown in Scheme 3.

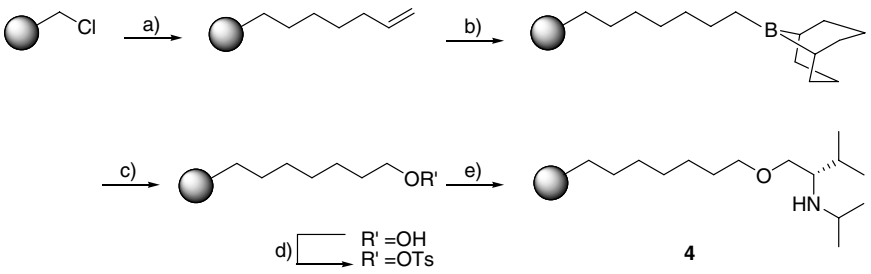
The procedure utilized to synthesize polymeric amines **5a** and **5b** was modified from that reported by Johansson[17] and Majewski.[18] The synthetic steps utilized include transhalogenation, etherification, transhalogenation again and finally amination. We found that in the presence of tetrabutylammonium iodide (TBAI), the first transhalogenation from Cl to I is not necessary, and the etherification of Merrifield resin takes place at room temperature with almost quantitative transformation.

Figure 1 lists the structure as well as the loading amount of polymeric amines used in our study. The maximum loading amount (f_{max}) was calculated from the initial chloride loading of Merrifield resin. The conditions used to prepare polymeric lithium amides utilized excess *n*-BuLi at room temperature for 20 min. It is important to wash off excess *n*-BuLi with a fresh solvent, otherwise butylation by-product is observed. The amount of lithium amide on the polymer was also determined by acid–base titration of the methanol washings,[23] and these titration values were in agreement with elemental analysis.

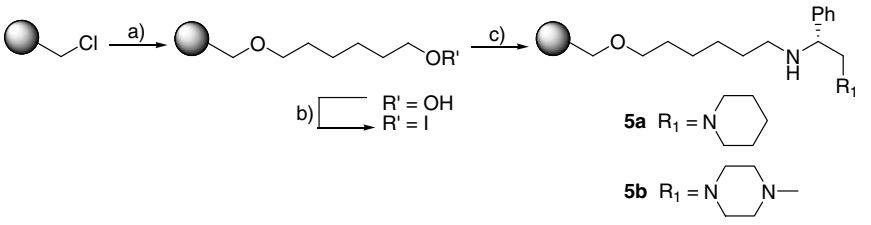
While numerous polymer-supported reagents have been utilized in organic synthesis, the use of polymer-supported chiral lithium amide bases is not widespread. We chose to study asymmetric enolization reactions assisted by poly-



Scheme 1. Synthesis of polymer-supported chiral amines without spacers.



Scheme 2. Synthesis of polymer-supported chiral amine with an all carbon spacer. Reagents and conditions: (a) $ClMg(CH_2)_4CH{=}CH_2$, Li_2CuCl_4, THF, 65 °C, 2 d; (b) 9-BBN, THF, rt, 1 d; (c) $Bu_4NOH/MeOH$, H_2O_2, 19 h; (d) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 48 h; (e) sodium (*S*)-2-isopropylamino-3-methylbutoxide, THF, rt, 2 d.



Scheme 3. Synthesis of polymer-supported chiral amines with ether spacers. Reagents and conditions: (a) $HO(CH_2)_6OH$, TBAI, NaH, DMF, rt, 2 d; (b) PPh_3, imidazole, I_2, THF, rt, 4 d; (c) $H_2NCHPhCH_2R_1$, $NaHCO_3$, DMF, microwave, 160 °C, 2 h.

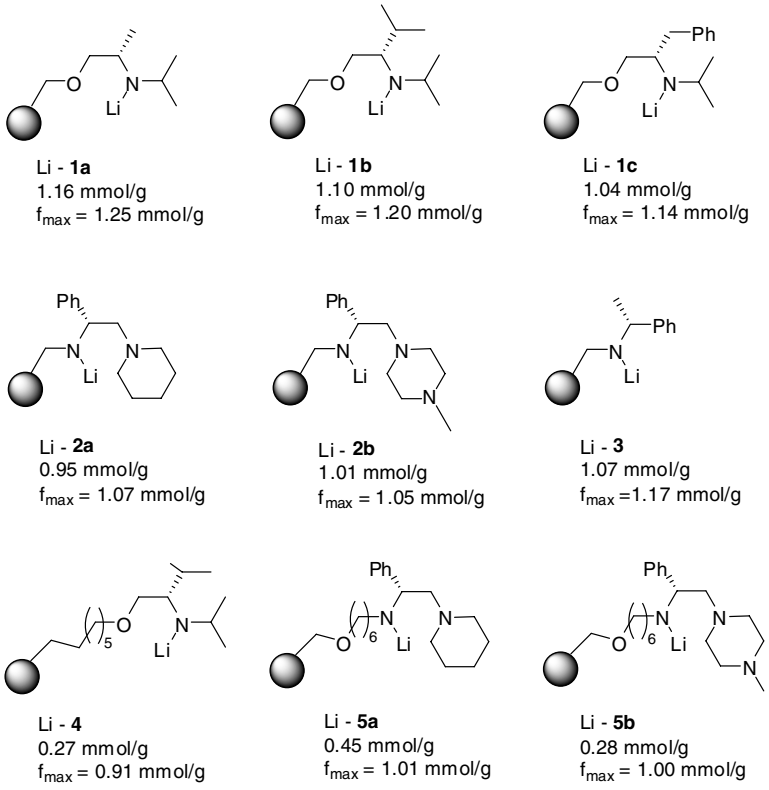


Figure 1. Actual loading amount and maximum loading amount of polymer-supported chiral lithium amide bases.

mer-supported CLAB's considering the importance of enantioselective reactions in synthetic organic chemistry.

Various prochiral ketones can be used in the deprotonation reaction, such as 4-substituted or 2,6-disubstituted cyclohexanones, or bridged tropinones. In our initial trials, we chose 4-methylcyclohexaone to establish the optimal reaction conditions. The steric interaction between the polymeric backbones and the chiral groups can disrupt the stereochemistry of the reactions, and sometimes, even re-

verse the direction for enatioselectivity.[32] As shown in Table 1, the major enatiomers were (*R*), the same as the similar non-polymeric homogenous reactions reported by Koga et al.[33]

For entries 1–4, when we reduced the equivalents of 4-methylcyclohexanone, both yield and enantiomeric excess increased considerably. For polymeric reagents derived from resin beads, only a small amount of the reactive sites are located on the bead's surface. Some functional groups are buried inside the polymer beads and thus not accessible. Reducing the amount of ketone amount reduces the reliance upon these unaccessible functional groups.

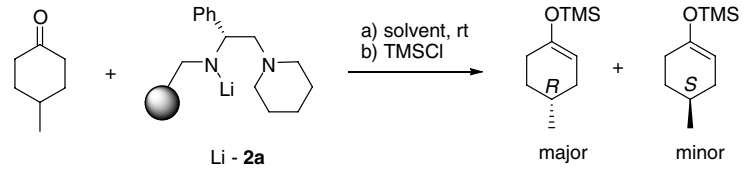
The deprotonation reactions reported by non-polymeric amides were usually performed at −78 °C for more than 30 min. We were pleased to observe that the deprotonation reaction by polymeric amide took only 5 min to be completed at room temperature (Table 1, entry 6). The reactivity was not affected in a range of time from 10 min to 30 min. Time was not a key variable for these polymeric lithium amide deprotonation reactions.

The overall reactivity in THF was much better than that in diethyl ether or toluene, as indicated in Table 1. We ascribe this to the better swelling ability of THF than Et_2O or toluene for the Merrifield resin.[34]

The reactivity of lithium amide bases in the homogeneous solution is often affected by their aggregation state. A common observation is that the reactivity decreases in the order of monomer, dimer, trimer.[35] Even though the monomer is the most reactive species, it is not the dominant species in the solution. This has led to the utilization of different additives to break the less reactive aggregates into more reactive monomers. For example, LiX is widely used by others including Corey,[36] Collum,[37] Seebach.[38] Hexamethylphosphoramide (HMPA) was used by Koga[39] both as a co-solvent and as an additive. It is noteworthy that 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) is preferred by Henderson,[40] because it is less toxic than HMPA. Based on the reasoning that the lithium aggregates would be separated into the more reactive monomers upon immobilization on a solid support, we investigated the additive effect for polymer-supported CLAB's, and confirmed that these supported lithium amides were indeed less dependent on additives. More specifically, we found that when THF was used, no matter, which additives were utilized, the reactivity remained the same (Table 1, entries 7–9). By comparing entry 6 with entries 7–9, we can see that without any additive, the reactivity did not change much. Hence we were able to conclude that the asymmetric deprotonation reaction by polymer-supported chiral lithium amide bases exhibited no obvious dependence upon additives in THF.

Having the optimal reaction conditions in hand, we moved on to investigate the deprotonation of other sterically hindered cyclic ketones. These results are summarized in Table 2. The bulkiness of the substrate decreases in the order of *tert*-butyl, isopropyl, phenyl, and methyl. As we can see in Table 2, the ee is not in the same order. The least hindered 4-methylcyclohexaone gave the highest ee (Table 2, entry 1). In a series of studies mainly by Koga, and also by Henderson, it has been reported that 4-isopropyl or 4-*tert*-butyl cyclohexanone gave the highest ee in most

Table 1. Effect of reaction conditions on the asymmetric deprotonation of 4-methylcyclohexanone by Li-**2a**

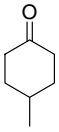
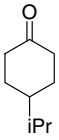
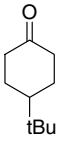
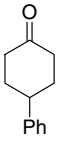
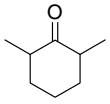
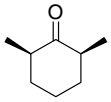


Li - **2a** major minor

Entry	*t* (min)	*T* (°C)	Solvent	Additive	Yield[a] (%)	ee[b] (%)
1[c]	30	22	THF	No	72	28
2[d]	30	22	THF	No	77	31
3	30	22	THF	No	91	33
4[e]	30	22	THF	No	96	39
5	10	22	THF	No	77	33
6	5	22	THF	No	81	36
7	5	22	THF	LiCl	92	36
8	5	22	THF	DMPU[f]	78	34
9	5	22	THF	HMPA[g]	93	37
10	5	22	Et_2O	LiCl	57	33
11	5	22	Et_2O	DMPU	76	14
12	5	22	Et_2O	HMPA	62	20
13	5	22	Toluene	LiCl	51	37
14	5	22	Toluene	DMPU	58	13
15	5	22	Toluene	HMPA	42	12

[a] Yields determined by GC using dodecane as an internal standard.
[b] ee determined by GC using a Chiralsil-DEX CB capillary column.
[c,d,e] 4-Methylcyclohexanone was 0.8 equiv, 0.6 equiv, 0.2 equiv, respectively, compared with the polymeric amide. All other entries used 0.4 equiv ketone.
[f] DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.
[g] HMPA = hexamethylphosphoramide.

Table 2. Asymmetric deprotonation of different prochiral ketones with Li-**2a**

Entry	Ketone[a]	Major enantiomer	Yield[b] (%)	ee[c] (%)
1		(*R*)	94	41
2		(*R*)	91	34
3		(*R*)	93	31
4		(*R*)	86	33
5[d]		(*S*)	92	57
6		(*S*)	90	71

[a] 0.2 equiv ketone was also used and gave similar results.
[b] Yields determined by GC using dodecane as an internal standard.
[c] ee determined by GC using a Chiralsil-DEX CB capillary column.
[d] Starting material is a mixture of diastereomeric ketone. *cis*:*trans* = 80:20.

cases.[14,41] Comparison of these two sets of results strongly suggested that the polymer matrix did play a role in the deprotonation transition state, and favored the substituents usually considered less enantioselective in the homogeneous reactions.

We also studied the asymmetric enolization of 2,6-dimethyl cyclohexanone. The 80:20 diastereomeric mixtures of 2,6-dimethylcyclohexaone gave improved results compared to 4-substituted cyclic ketones. When pure *cis*-2,6-dimethylcyclohexanone was used, the enantiomeric excess went as high as 71%. Since the axial α-protons are lost in preference to equatorial hydrogens, due to a stereoelectronic effect, the closer position of 2,6-dimethyl groups seemed to exert more influence than 4-methyls on the transition state and helped to increase the ee.

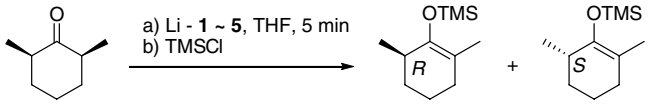
Most often the heterogeneous reactions tend to be slow and less selective as a result of the presence of the polymer backbone. As we mentioned before, the polymer backbone slows done the diffusion and decreases the reaction rate under otherwise identical conditions. Also, the presence of a bulky polymer causes difficulties for the reactive species to achieve the transition state. The asymmetric deprotonation of 2,6-dimethylcyclohexanone by different polymeric lithium amides is listed in Table 3.

For lithium amides derived from polymer-supported aminoethers, the ee's are below 20% (Table 3, entries 1–3). For those derived from diamines, the ee's are higher than 50% (Table 3, entries 4–7), so diamines are much better than aminoethers. The difference between these two types of functional groups is ascribed to the different internal ligation in the bidentate lithium amide by nitrogen and by oxygen. Some factors, which could affect the ligation status are as follows: firstly, all supported aminoethers carry the group needed for internal coordination closer to the polymer backbone, while supported diamines have their coordinating group closer to the reactive site. Secondly, oxygen is a better ligand for lithium than nitrogen because of steric considerations, that is, it is divalent whereas nitrogen is trivalent.

For non-polymeric deprotonation reactions, a low temperature such as −78 or −106 °C is a requirement for high enantiomeric excess due to kinetic control. Comparing the asymmetric deprotonation by polymeric lithium amides at −78 °C and at room temperature (Table 3, entries 4 and 5), we can see that the ee change in polymeric reactions was considerably smaller than that in non-polymeric reactions. *It is significant that the reaction with polymeric reagents do not require sub-ambient temperature and can be carried out at room temperature.* One main reason is that the supported CLAB's are less likely to participate in the aggregation equilibria as their non-bound counterparts in solution, and the reactive species remains the same throughout the temperature range. The hydrophobic matrix of the polystyrene backbone also contributes to the increased stability of water sensitive trimethylsilyl enol ethers.

Encouraged by these results, we next examined **2b** with a reduced loading amount from 1.0 mmol/g to 0.5 mmol/g

Table 3. Asymmetric deprotonation of *cis*-2,6-dimethylcyclohexanone by different polymer-supported chiral lithium amide bases



Entry	Li-amide	*T* (°C)	Major enantiomer	Yield[a] (%)	ee[b] (%)
1	Li-**1a**	22	(*R*)	75	18
2	Li-**1b**	22	—	68	<2
3	Li-**1c**	22	(*R*)	61	17
4	Li-**2a**	22	(*S*)	92	71
5	Li-**2a**	−78	(*S*)	82	77
6	Li-**2b**	22	(*S*)	90	81
7[c]	Li-**2b**	22	(*S*)	94	82
8	Li-**3**	22	—	59	<2
9	Li-**4**	22	(*R*)	53	15
10	Li-**5a**	22	(*S*)	82	54
11	Li-**5b**	22	(*S*)	79	62

[a] Yields determined by GC using dodecane as an internal standard.
[b] ee determined by GC using a Chiralsil-DEX CB capillary column.
[c] Loading amount was reduced to 0.5 mmol/g.

Table 4. Reusability of polymer-supported chiral lithium amide Li-**2b** in asymmetric deprotonation of *cis*-2,6-dimethylcyclohexanone

Cycle	1	2	3	4	5	6
Yield (%)	90	92	90	86	87	85
ee (%)	81	80	79	79	80	80

(entry 7). It afforded 82% ee in 94% yield after 5 min at room temperature. We did not explore the 0.1 mmol/g functionalized polymers, but we would expect that with 10 times difference in functionality, there would be a significant change in ee. Improvements in ee obtained by lowering the loading amount of amines indicated not only the existence of non-accessible reactive sites but also the site–site interactions of bounded lithium amides.

Unexpected results were obtained when we put a spacer between the amines and the polymer matrix (Table 3, entries 9 and 10). Even though we chose the reaction conditions for attaching spacers carefully and the final loading amount of **2a** is comparable to the results of Johanson[17] and Majewski,[18] the amine functionalization was still not quantitative, as indicated by elemental analysis. The polymer supported by-products still existed in the polymers and had adverse effect on the asymmetric deprotonation reactions.

Koga studied the same reaction at −78 °C with HMPA as an additive, reported up to 96% ee. Although our highest observable ee is 82%, we did prove that the polymeric amide assisted reaction can be performed at room temperature without an additive with a good ee. We cannot overemphasize the practical advantage of conducting these reactions with CLAB's at room temperature.

Having established the asymmetric deprotonation strategy, we moved on to develop an efficient recycling method. For this purpose, the deprotonation of *cis*-2,6-dimethylcyclohexanone was repeated with the same polymer-supported Li-**2b**, and various washing sequences were examined. The polymeric amines were readily regenerated by consecutive washing with THF, acetone, methanol, CH_2Cl_2, H_2O, and methanol. We conclude that the recycled polymeric amides can be used up to six times with only a slight drop of yield and with an unchanged enantiomeric excess. ^{13}C gel phase NMR as well as titration of polymeric CLAB's were also recorded, proving that no changes occur in the polymer with respect to its structure and basicity (Table 4).

3. Conclusions

After synthesizing several different polymer-supported CLAB's and investigating their reactivity and stereoselectivity, we drew the following conclusions. The polymeric reagents are definitely reusable up to five or six times without an observable decrease in reactivity or stereoselectivity. Although we did not determine the maximum number of times that our polymeric reagents could be reused, we suggest that the limiting factor for reusability is the actual physical destruction of the reagent itself due to mechanical manipulation. This is visible by the eye and can also be determined by a decreasing recovery of the polymeric base in sequential reactions.

We also concluded that the influence of temperature on both the enantioselectivity and the reaction yield was not always predictable. In other words decreasing temperature did not necessarily lead to an increase in enantioselectivity as is commonly observed with non-polymeric reagents. This suggests to us that the reactive species in solution and the reaction mechanisms through which the CLAB's operate do not change significantly spanning a temperature range of room temperature down to −78 °C. In retrospect, this might have been anticipated because the polymeric reagents are unlikely to participate in the complex aggregation equilibria that are known to take place with non-polymeric lithium amide bases. We view this as an advantage of the use of polymeric CLAB's, because reactions do not require significant cooling to obtain a maximum enantioselectivity.

In addition, we suggest the polymeric CLAB's also modify the enantioselectivity in asymmetric reactions depending upon the bulkiness of the substrate with which they react and also upon the structure of the polymeric reagent. The polymer steric effect we observed here was not large enough to reverse the direction for the enantioselective reaction, but it did exhibit selectivity that differs from their non-polymeric counterparts. It is noteworthy that the non-polymeric CLAB's reported by others exhibit the best enantioselectivity when larger substrates are used, while our polymeric CLAB's favored the smaller substrates such as 4-methylcyclohexaone.

Finally, we can conclude that polymeric CLAB's offer some special advantages over non-polymeric reagents not only because they can be recycled and can be utilized at room temperature, but also because they can provide some beneficial polymeric effects in terms of the separation of reactive species. Efforts to improve the ee's in reactions utilizing polymeric CLAB's are currently ongoing in our lab.

4. Experimental

4.1. General

All reactions were conducted under a N_2 atmosphere in an oven-dried glassware equipped with magnetic stirring bars. The synthesis was performed on Merrifield resin (1% crosslinked, 1.0–1.5 mmol Cl/g, 100–200 mesh) purchased from Aldrich. Cyclic ketones were purified by distillation (4-methylcyclohexanone, 4-isopropylcyclohexanone) or by recrytallization (4-*tert*-butylcyclohexanone, 4-phenylcyclohexaone) from pentane before use. *cis*-2,6-Dimethylcyclohexanone was obtained by passing the diastereomeric mixture from silica gel (Whatman silica gel 60, particle size 230–400 mesh, hexanes/ether = 10:1). DMPU was purified by distillation over CaH_2 (75 °C/0.5 mmHg). HMPA was purified by distillation over CaH_2 (88 °C/0.5 mmHg). All solvents were purified by solvent-dispensing system. For thin-layer chromatography

(TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating.

Elemental analysis was performed by Quantitative Technology, INC in order to determine the percentage of nitrogen or other significant elements. NMR spectra were recorded on a Bruker 400 MHz spectrometer. For ^{13}C gel phase NMR, pulse width was 18 μs, delay between pulses was 0.2 s, line broadening was 2 Hz. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR from 50 mg dry pellets with 1–2 mg of polymer. Gas chromatographic analyses were carried out on a Hewlett Packard HP 6890 gas chromatograph equipped with a FID detector. All GC analyses were run on a chiral stationary-phase column (CP-Chirasil-DEX CB, 25 m, 0.32 mm) from Varian (Cat. No. CP 7503). The column was held at a constant temperature (injector 250 °C, detector 275 °C) with helium (2 mL/min) as a carrier gas.

4.2. General procedure for the synthesis of polymer-supported aminoethers

A solution of (*S*)-2-isopropylaminoalcohol (6 mmol, 2.2 equiv) in DMF (8 mL) was added via syringe to a suspension of sodium hydride (0.25 g, 9 mmol, 3.2 equiv) in DMF (25 mL) at 0 °C under N_2. The mixture was stirred at 0 °C for 2–4 h, then quickly poured into a suspension of Merrifield resin (2 g, 1.39 mmol Cl/g, DF = 0.16) in DMF (16 mL) at 0 °C. The reaction was flushed with N_2, and smoothly stirred for 48 h at 120 °C. The functionalized polymer resin was then isolated by filtration, thoroughly washed with DMF (10 mL × 3), acetone (10 mL × 3), methanol (10 mL × 3), CH_2Cl_2 (10 mL × 3), methanol/water (1:1, 10 mL × 3), and methanol (10 mL × 3) until no detectable Cl^- (by $AgNO_3$). The polymer was then dried in vacuo for 16 h at 40–50 °C to afford the title compound.

4.2.1. Compound 1a. Elemental analysis $[(C_{10}H_{10})_{0.01}(C_8H_8)_{0.83}(C_{15}H_{23}NO)_{0.16}]$: N, 1.79. Found: N, 1.63, corresponding to 1.16 mmol amine/g. ^{13}C NMR (gel, 100 MHz, $CDCl_3$): δ 127.8, 74.7, 73.0, 49.5, 45.3, 40.3, 24.0, 22.9, 18.0. IR (KBr) ν 3451, 3319, 3019, 2920, 1945, 1745, 1601, 1491, 1446, 1363, 1169, 1086, 748, 693, 532 cm^{-1}.

4.2.2. Compound 1b. Elemental analysis $[(C_{10}H_{10})_{0.01}(C_8H_8)_{0.83}(C_{17}H_{27}NO)_{0.16}]$: N, 1.73. Found: N, 1.54, corresponding to 1.10 mmol amine/g. ^{13}C NMR (gel, 100 MHz, $CDCl_3$): δ 126.9, 73.0, 70.7, 59.6, 46.5, 40.3, 29.5, 23.7, 23.5, 18.7, 18.6. IR (KBr) ν_{max} 3452, 3026, 2926, 1934, 1801, 1602, 1485, 1450, 1366, 1175, 1094, 756, 698, 538 cm^{-1}.

4.2.3. Compound 1c. Elemental analysis $[(C_{10}H_{10})_{0.01}(C_8H_8)_{0.83}(C_{21}H_{27}NO)_{0.16}]$: N, 1.63. Found: N, 1.46, corresponding to 1.04 mmol amine/g. ^{13}C NMR (gel, 100 MHz, $CDCl_3$): δ 139.2, 128.3, 73.1, 71.6, 55.9, 45.6, 40.3, 38.4, 23.3. IR (KBr) ν_{max} 3440, 3319, 3032, 2918, 1939, 1745, 1601, 1490, 1448, 1363, 1169, 1081, 1020, 904, 753, 698, 537 cm^{-1}.

4.3. General procedure for the synthesis of polymer-supported amines

Merrifield resin (10 g, 1.30 mmol Cl/g, DF = 0.14) was fully swelled in DMF (100 mL) for 30 min, and then, to this solution was added $NaHCO_3$ (6.72 g, 80 mmol, 6.2 equiv), and (*R*)-1-phenyl-2-piperidinoethylamine or (*R*)-1-phenyl-2-(4-methylpiperazinyl)ethylamine (40 mmol, 3.1 equiv). The reaction mixture was stirred under N_2 at 80 °C for 2 days. The functionalized polymer resin was then isolated by filtration, thoroughly washed with DMF (50 mL × 2), acetone (50 mL × 3), methanol (50 mL × 3), CH_2Cl_2 (50 mL × 3), methanol/water (1:1, 50 mL × 3), and methanol (50 mL × 3). The polymer was then dried in vacuo for 16 h at 40–50 °C to afford the title compound.

4.3.1. Compound 2a. Elemental analysis $[(C_{10}H_{10})_{0.01}(C_8H_8)_{0.85}(C_{22}H_{28}N_2)_{0.14}]$: N, 2.97. Found: N, 2.67, corresponding to 0.95 mmol amine/g. ^{13}C NMR (gel, 100 MHz, $CDCl_3$): δ 145.1, 128.4, 66.5, 58.3, 55.1, 51.8, 40.4, 26.2, 24.6. IR (KBr) ν_{max} 3304, 3023, 2903, 1943, 1751, 1601, 1490, 1447, 1354, 1116, 1066, 1025, 904, 746, 700, 532 cm^{-1}.

4.3.2. Compound 2b. Elemental analysis $[(C_{10}H_{10})_{0.01}(C_8H_8)_{0.85}(C_{22}H_{29}N_3)_{0.14}]$: N, 4.30. Found: N, 4.25, corresponding to 1.01 mmol amine/g. ^{13}C NMR (gel, 100 MHz, $CDCl_3$): δ 142.5, 127.6, 65.6, 58.1, 55.2, 53.1, 51.1, 46.1, 40.5, 29.7. IR (KBr) ν_{max} 3309, 3025, 2919, 1944, 1721, 1601, 1491, 1454, 1369, 1163, 1010, 906, 748, 700, 532 cm^{-1}.

4.4. General procedure for the synthesis of polymer-supported chiral amines with spacers

4.4.1. Etherification. To a round-bottomed flask were added 1,6-hexanediol (2.32 g, 19.7 mmol, 3.5 equiv) and TBAI (0.72 g, 1.92 mmol, 0.4 equiv). The flask was put under vacuum and back filled with N_2 several times before DMF (40 mL) was added. At 0 °C, a NaH (0.44 g, 18 mmol, 3.2 equiv) suspension in DMF (8 mL) was added and then stirred at 0 °C for 1 h. The resulting sodium alkoxide was added to a fully swelled Merrifield resin (4 g, 1.39 mmol Cl/g, DF = 0.16) in DMF (32 mL). The reaction mixture was kept shaking at room temperature for 2 days. The solvent was filtered off and the polymer was washed with DMF (50 mL × 3), acetone (50 mL × 3), methanol (50 mL × 3), CH_2Cl_2 (50 mL × 3), methanol/water (1:1, 50 mL × 3), and methanol (50 mL × 3). The polymer was then dried in vacuo for 16 h at 40–50 °C to yield 4.3 g of white beads. Elemental analysis $[(C_{10}H_{10})_{0.01}(C_8H_8)_{0.83}(C_{15}H_{22}O_2)_{0.16}]$: O, 4.09. Found: O, 3.84, corresponding to 1.20 mmol alcohol/g. ^{13}C NMR (gel, 100 MHz, $CDCl_3$): δ 128.3, 72.7, 70.1, 62.5, 40.3, 32.6, 29.6, 26.0, 25.5. IR (KBr) ν_{max} 3595, 3472, 3023, 2933, 1943, 1741, 1601, 1491, 1448, 1360, 1176, 1091, 1016, 906, 749, 699, 532 cm^{-1}.

4.4.2. Transhalogenation. In a round-bottomed flask, the polymer (3.87 g, 1.20 mmol/g, 4.64 mmol alcohol) and THF (76 mL) were added. After 30 min swelling, triphenylphosphine (5.42 g, 20.1 mmol, 4.4 equiv), imidazole (3.0 g,

44 mol, 9.6 equiv) were added. At 0 °C, iodine (4.43 g, 17.4 mmol, 3.8 equiv) was added. The reaction was kept shaking for 4 days at room temperature. The solvent was filtered off and the polymer was washed with THF (50 mL × 3), acetone (50 mL × 3), methanol (50 mL × 3), saturated Na_2SO_3 (50 mL × 1), H_2O (50 mL × 2), methanol (50 mL × 3), CH_2Cl_2 (50 mL × 3), methanol/water (1:1, 50 mL × 3), and methanol (50 mL × 3). The polymer was then dried in vacuo for 16 h at 40–50 °C to yield 4.12 g of yellow beads. Elemental analysis $[(C_{10}H_{10})_{0.01}$-$(C_8H_8)_{0.83}(C_{15}H_{21}OI)_{0.16}]$: I, 14.24. Found: I, 6.88, corresponding to 0.54 mmol iodide/g. ^{13}C NMR (gel, 100 MHz, $CDCl_3$): δ 128.1, 72.6, 69.8, 40.3, 33.3, 30.2, 29.5, 25.1, 7.1. IR (KBr) ν_{max} 3030, 2928, 1944, 1741, 1601, 1491, 1447, 1360, 1094, 1022, 900, 753, 700, 531 cm^{-1}.

4.4.3. Amination. The polymer (0.25 g, 0.54 mmol I/g, 0.14 mmol I) was fully swelled in DMF (2 mL) in a microwave reactor vial for 30 min. To this solution was added $NaHCO_3$ (0.035 g, 0.41 mmol, 3 equiv), and (*R*)-1-phenyl-2-piperidinoethylamine or (*R*)-1-phenyl-2-(4-methylpiperazinyl)ethylamine (1.12 mmol, 8 equiv). The reaction was then performed under microwave irradiation at 160 °C for 2 h. The functionalized polymer resin was then isolated by filtration, thoroughly washed with DMF (10 mL × 3), acetone (10 mL × 3), methanol (10 mL × 3), CH_2Cl_2 (10 mL × 3), ethanol/water (1:1, 10 mL × 3), and methanol (10 mL × 3). The polymer was then dried in vacuo for 16 h at 40–50 °C to afford the title compound.

4.4.4. Compound 5a. Elemental analysis $[(C_{10}H_{10})_{0.01}$-$(C_8H_8)_{0.83}(C_{28}H_{40}N_2O)_{0.16}]$: N, 2.89. Found: N, 1.26, corresponding to 0.45 mmol amine/g. ^{13}C NMR (gel, 100 MHz, $CDCl_3$): δ 128.0, 72.6, 70.2, 66.6, 62.6, 60.0, 54.6, 47.9, 45.5, 40.4, 32.6, 30.0, 27.2, 26.2, 24.5. IR (KBr) ν_{max} 3436, 3026, 2925, 1943, 1680, 1602, 1492, 1450, 1368, 1251, 1079, 1025, 839, 753, 698, 535 cm^{-1}.

4.4.5. Compound 5b. Elemental analysis $[(C_{10}H_{10})_{0.01}$-$(C_8H_8)_{0.83}(C_{28}H_{41}N_3O)_{0.16}]$: N, 4.27. Found: N, 1.17, corresponding to 0.28 mmol amine/g. ^{13}C NMR (gel, 100 MHz, $CDCl_3$): δ 128.2, 72.5, 70.4, 65.6, 59.8, 55.2, 53.3, 46.0, 40.4, 29.9, 27.1, 26.2. IR (KBr) ν_{max} 3435, 3025, 2923, 1943, 1681, 1601, 1491, 1450, 1360, 1094, 1023, 753, 699, 534 cm^{-1}.

4.5. General procedure for the formation and titration of lithium amide bases

An oven-dried Schlenk tube was charged with polymer-supported amine (0.5 mg, ~0.5 mmol polymeric amine), dry THF (5 mL) and a stirring bar. After swelling for 30 min at rt, *n*-butyllithium (2.42 M hexanes solution, 6 equiv) was added and the reaction mixture was stirred at room temperature for an additional 20 min. The excess *n*-BuLi was washed off with fresh dry THF (20 mL × 5) and swelled again in THF at − 78 °C. The polymeric amides were then quenched with 5 mL methanol and stirred for an additional 30 min. The resulting polymer beads were then washed with fresh THF (20 mL × 5). The lithium methoxide bases in the combined THF washings were then titrated to a phenolphthalein end point.

4.6. General procedure for the deprotonation of cyclic ketones

An oven-dried vial was charged with polymer-supported amine (0.22 g, 0.2 mmol polymeric amine), dry THF (2 mL) and a stirring bar. After swelling for 30 min at rt, *n*-butyllithium (2.42 M hexanes solution, 6.3 equiv) was added and the reaction mixture was stirred at room temperature for an additional 20 min. The excess *n*-BuLi was washed off with fresh dry THF (10 mL × 5) and swelled again in THF. Dodecane (GC internal standard) was added, followed by cyclic ketone (0.08 mmol, 0.4 equiv). The reaction was kept at room temperature for 5 min before 1 mL Et_3N and 0.1 mL TMSCl (0.8 mmol, 4.0 equiv) were added. A portion of the reaction mixture (0.2 mL) was withdrawn and diluted with 1 mL dry ether. The top clear solution was passed through a short pad of silica gel and analyzed by GC.[40]

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