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

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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-supported 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.

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1. Introduction

More recently, chiral lithium amide bases (CLAB's) have been successfully used in asymmetric reactions such as the aldol reaction,\(^2,^3\) alkylation,\(^4,^5\) rearrangement of epoxides,\(^6,^7\) 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,
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 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 13C 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 backbone30,31 as shown in Scheme 3.

The procedure utilized to synthesize polymeric amines 5a and 5b was modified from that reported by Johansson17 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 (fmax) 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-
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-

Scheme 2. Synthesis of polymer-supported chiral amine with an all carbon spacer. Reagents and conditions: (a) ClMg(CH$_2$)$_4$CH=CH$_2$, Li$_2$CuCl$_4$, THF, 65 °C, 2 d; (b) 9-BBN, THF, rt, 1 d; (c) Bu$_4$NOH/MeOH, H$_2$O$_2$, 19 h; (d) TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 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$_2$)$_6$OH, TBAI, NaH, DMF, rt, 2 d; (b) PPh$_3$, imidazole, I$_2$, THF, rt, 4 d; (c) H$_2$NCHPhCH$_2$R$_1$, NaHCO$_3$, DMF, microwave, 160 °C, 2 h.

Figure 1. Actual loading amount and maximum loading amount of polymer-supported chiral lithium amide bases.
verse the direction for enatioselectivity. As shown in Table 1, the major enantiomers were \((R)\), the same as the similar non-polymeric homogenous reactions reported by Koga et al.

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 \(-78\, ^\circ\text{C}\) 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 Et₂O or toluene for the Merrifield resin.

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. 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, \(\text{LiX}\) is widely used by others including Corey, Collum, Seebach. Hexamethylphosphoramide (HMPA) was used by Koga 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, 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-methylcyclohexanone 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 cases.

### Table 1. Effect of reaction conditions on the asymmetric deprotonation of 4-methylcyclohexanone by \(\text{Li-2a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(t) (min)</th>
<th>(T) (°C)</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield(^a) (%)</th>
<th>ee(^b) (%)</th>
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<tr>
<td>1(^c)</td>
<td>30</td>
<td>22</td>
<td>THF</td>
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<td>72</td>
<td>28</td>
</tr>
<tr>
<td>2(^d)</td>
<td>30</td>
<td>22</td>
<td>THF</td>
<td>No</td>
<td>77</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>22</td>
<td>THF</td>
<td>No</td>
<td>91</td>
<td>33</td>
</tr>
<tr>
<td>4(^e)</td>
<td>30</td>
<td>22</td>
<td>THF</td>
<td>No</td>
<td>96</td>
<td>39</td>
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<td>10</td>
<td>22</td>
<td>THF</td>
<td>No</td>
<td>77</td>
<td>33</td>
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<tr>
<td>6</td>
<td>5</td>
<td>22</td>
<td>THF</td>
<td>No</td>
<td>81</td>
<td>36</td>
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<tr>
<td>7</td>
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<td>22</td>
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<td>LiCl</td>
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<td>36</td>
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<td>8</td>
<td>5</td>
<td>22</td>
<td>THF</td>
<td>DMPU(^f)</td>
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<td>34</td>
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<tr>
<td>9</td>
<td>5</td>
<td>22</td>
<td>THF</td>
<td>HMPA(^g)</td>
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<td>37</td>
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<td>22</td>
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<td>LiCl</td>
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<td>5</td>
<td>22</td>
<td>Et₂O</td>
<td>HMPA</td>
<td>62</td>
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<td>13</td>
<td>5</td>
<td>22</td>
<td>Toluene</td>
<td>LiCl</td>
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<td>37</td>
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<td>22</td>
<td>Toluene</td>
<td>DMPU</td>
<td>58</td>
<td>13</td>
</tr>
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<td>15</td>
<td>5</td>
<td>22</td>
<td>Toluene</td>
<td>HMPA</td>
<td>42</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^a\) 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.
Asymmetric deprotonation of different prochiral ketones with Li-2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Major enantiomer</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tr>
<td>1</td>
<td></td>
<td>(R)</td>
<td>94</td>
<td>41</td>
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<tr>
<td>2</td>
<td></td>
<td>(R)</td>
<td>91</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>(R)</td>
<td>93</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>(R)</td>
<td>86</td>
<td>33</td>
</tr>
<tr>
<td>5d</td>
<td></td>
<td>(S)</td>
<td>92</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>(S)</td>
<td>90</td>
<td>71</td>
</tr>
</tbody>
</table>

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.

For lithium amides derived from polymer-supported amineethers, 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 amineethers. 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 amineethers carry the group needed for internal coordination closer to the polymer backbone, while supported diamines have their coordinating group closer to the reactive site. Second, 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 °C 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>
<thead>
<tr>
<th>Entry</th>
<th>Li-amide</th>
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<th>Major enantiomer</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tr>
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<td>(R)</td>
<td>75</td>
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<td>2</td>
<td>Li-1b</td>
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<td>—</td>
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<td>(R)</td>
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<td>4</td>
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<td>(S)</td>
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</tr>
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<td>(S)</td>
<td>82</td>
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</tr>
<tr>
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<td>(S)</td>
<td>90</td>
<td>81</td>
</tr>
<tr>
<td>7a</td>
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<td>(S)</td>
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<td>Li-5b</td>
<td>22</td>
<td>(S)</td>
<td>79</td>
<td>62</td>
</tr>
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</table>

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.
Li-hexanone was repeated with the same polymer-supported this purpose, the deprotonation of we moved on to develop an efficient recycling method. For reactions with CLAB's at room temperature.

Unlimited observable ee is 82%, we did prove that the polymeric amides can be used up to six times with only a slight drop in yield and with an unchanged enantioselectivity. 13C 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).

Having established the asymmetric deprotonation strategy, we moved on to develop an efficient recycling method. For this purpose, the deprotonation of cis-2,6-dimethycyclohexanone was repeated with the same polymer-supported Li-2b, and various washing sequences were examined. The polymeric amides were readily regenerated by consecutive washing with THF, acetone, methanol, CH2Cl2, H2O, 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 enantioselective excess. 13C 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).

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

<table>
<thead>
<tr>
<th>Cycle</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
<td>Yield (%)</td>
<td>90</td>
<td>92</td>
<td>90</td>
<td>86</td>
<td>87</td>
<td>85</td>
</tr>
<tr>
<td>ee (%)</td>
<td>81</td>
<td>80</td>
<td>79</td>
<td>79</td>
<td>80</td>
<td>80</td>
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</tbody>
</table>

(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 and Majewski, 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 over-emphasize 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-dimethycyclohexanone was repeated with the same polymer-supported Li-2b, and various washing sequences were examined. The polymeric amides were readily regenerated by consecutive washing with THF, acetone, methanol, CH2Cl2, H2O, 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 enantioselective excess. 13C 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).

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 N2 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 C1/g, 100–200 mesh) purchased from Aldrich. Cyclic ketones were purified by distillation (4-methylcyclohexanone, 4-isopropylcyclohexane) or by recrystallization (4-tert-butylcyclohexane, 4-phenylcyclohexane) 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). DMF was purified by distillation over CaH2 (75 °C/0.5 mmHg). HMPA was purified by distillation over CaH2 (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 phosphomolybdate 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 1H 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-ssilasilDEX 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 aminooethers

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, 9.9 mmol, 3.2 equiv) in DMF (25 mL) at 0 °C under N2. 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 C1/g, DF = 0.16) in DMF (16 mL) at 0 °C. The reaction was flushed with N2, 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) and acetone (10 mL × 3), methanol (10 mL × 3), CH2Cl2 (10 mL × 3), methanol/water (1:1, 10 mL × 3), and methanol (10 mL × 3) until no detectable Cl– (by AgNO3). 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 [(C10H10)0.01-(C8H8)0.83(C15H22O2)0.16]: N, 1.79. Found: N, 1.63, corresponding to 1.16 mmol amine/g. 13C NMR (gel, 100 MHz, CDCl3): 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 [(C10H10)0.01-(C8H8)0.83(C17H27NO)0.16]: N, 1.73. Found: N, 1.54, corresponding to 1.10 mmol amine/g. 13C NMR (gel, 100 MHz, CDCl3): 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) νmax 3452, 3026, 2926, 1934, 1801, 1602, 1485, 1450, 1366, 1175, 1094, 756, 698, 538 cm–1.

4.2.3. Compound 1c. Elemental analysis [(C10H10)0.01-(C8H8)0.83(C15H22O2)0.16]: N, 1.63. Found: N, 1.46, corresponding to 1.04 mmol amine/g. 13C NMR (gel, 100 MHz, CDCl3): δ 139.2, 128.3, 73.1, 71.6, 55.9, 45.6, 40.3, 38.4, 23.3. IR (KBr) νmax 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 NaHCO3 (6.72 g, 80 mmol, 6.2 equiv), and (R)-1-phenyl-2-piperidinoethanamine or (R)-1-phenyl-2-(4-methylpipernazinyl)ethanamine (40 mmol, 3.1 equiv). The reaction mixture was stirred under N2 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), CH2Cl2 (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 [(C10H10)0.01-(C8H8)0.83(C22H26N2)0.14]: N, 2.97. Found: N, 2.67, corresponding to 0.95 mmol amine/g. 13C NMR (gel, 100 MHz, CDCl3): δ 145.1, 128.4, 66.5, 58.3, 55.1, 51.8, 40.4, 26.2, 24.6. IR (KBr) νmax 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 [(C10H10)0.01-(C8H8)0.83(C22H26N3)0.14]: N, 4.30. Found: N, 4.25, corresponding to 1.01 mmol amine/g. 13C NMR (gel, 100 MHz, CDCl3): δ 142.5, 127.6, 65.6, 58.1, 55.2, 53.1, 51.1, 46.1, 40.5, 29.7. IR (KBr) νmax 3309, 3025, 2919, 2944, 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. Ethenylation. 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 N2 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), CH2Cl2 (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 [(C10H10)0.01-(C8H8)0.83(C15H22O2)0.16]: O, 4.09. Found: O, 3.84, corresponding to 1.20 mmol alcohol/g. 13C NMR (gel, 100 MHz, CDCl3): δ 128.3, 72.7, 70.1, 62.5, 40.3, 32.6, 29.6, 26.0, 25.5. IR (KBr) νmax 3595, 3472, 3023, 2933, 1943, 1741, 1601, 1491, 1448, 1346, 1176, 1091, 1016, 906, 749, 699, 552 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 then filtered off and the polymer was washed with THF (50 mL × 3), acetone (50 mL × 3), methanol (50 mL × 3), saturated Na2SO3 (50 mL × 1), H2O (50 mL × 2), methanol (50 mL × 3), CH2Cl2 (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. The solvent was then washed with fresh dry THF (10 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 (0.2 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

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 NaHCO3 (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), CH2Cl2 (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 [(C10H10)0.01-(C6H6)0.83(C28H41N3O)0.16]: N, 4.27. Found: N, 1.17, corresponding to 0.28 mmol amine/g. 13C NMR (gel, 100 MHz, CDCl3): 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) νmax 3436, 3026, 2925, 1943, 1680, 1602, 1492, 1450, 1368, 1251, 1079, 1025, 839, 753, 699, 535 cm−1.

4.4.5. Compound 5b. Elemental analysis [(C10H10)0.01-(C6H6)0.83(C28H40N2O)0.16]: N, 2.89. Found: N, 1.26, corresponding to 0.45 mmol amine/g. 13C NMR (gel, 100 MHz, CDCl3): δ 128.0, 72.6, 70.4, 65.6, 59.8, 55.2, 53.3, 46.0, 40.4, 29.9, 27.1, 26.2. IR (KBr) νmax 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 Et3N 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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References