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Solid-phase supported chiral lithium amides used in deprotonation reactions

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Abstract—The lithium salt of polymer supported phenylethyl amine showed surprisingly high enantioselectivity in the asymmetric deprotonation reaction of cyclohexene oxide. The polymer supported chiral lithium amide base also proved to be more reactive compared to the free chiral lithium amide base. This is a new insight in the development and mechanism of chiral lithium amide bases used in asymmetric reactions. © 2003 Published by Elsevier Science Ltd.

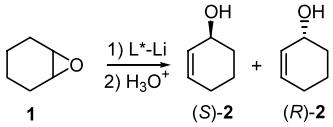
1. Introduction

Over the last few decades methods for using chiral lithium amides in organic transformations such as deprotonation reactions of conformationally locked prochiral cyclic ketones,[1] asymmetric deprotonation reactions of epoxides to allylic alcohols,[2] aromatic and benzylic functionalization of tricarbonyl(η^6-arene)-chromium complexes[3] has been developed. The development of new chiral bases to be used as ligands in deprotonation reactions has been intense. Deprotonation reactions can also be performed by using sub-stoichiometric amounts of chiral bases together with bulk bases.[4] One disadvantage with several of these chiral bases is that they are expensive, due to long and complicated synthetic routes.

The stereoselectivity and especially the conversion in the deprotonation reactions are highly dependent on the aggregation of the lithium amides. It has been shown that smaller aggregates react faster than larger ones.[5]

To avoid complications from formation of several diverse aggregates, and to promote small aggregates one approach could be the utilization of solid supported chiral lithium amide bases. A polymer solid supported chiral amide base also has the advantage that it can be utilized in combinatorial chemistry and parallel synthesis where normal extraction procedures are not possible. In solid supported case only a filtration and wash is necessary which gives higher flexibility if the asymmetric deprotonation is a part of a multistep synthesis performed on for instance a Bohadan miniblock. Furthermore, the possibility of recycling the chiral amine base could be a large benefit when using amines that are not commercially available and have been synthesized. Two earlier reports have shown that chiral lithium and magnesium amide bases attached to a solid support can be used in enantioselective deprotonation reactions.[6] To the best of our knowledge there exists only one paper describing the use of solid supported chiral lithium amide bases.[6a] Recently, a method using bulk bases on solid support and a catalytic amount of chiral lithium amide was developed for deprotonation of epoxides.[7] This encouraged us to start a study on the asymmetric deprotonation of prochiral epoxides.

In this paper we will present the use of solid supported chiral lithium amides used in asymmetric deprotonation reaction of cyclohexene oxide **1** to give the allylic alcohol 2-cyclohexene-1-ol **2** (Scheme 1).



Scheme 1.

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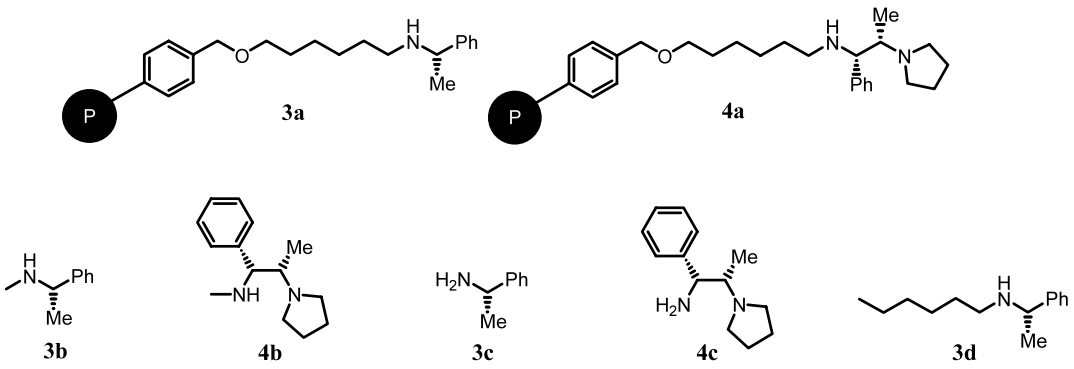


Scheme 2.

We have chosen two ligands on the polymer support, phenylethylamine **3c** and 1-phenyl-2-pyrrolidin-1-yl-propylamine **4c**, the latter is a derivate of methyl-(1-phenyl-2-pyrrolidin-1-yl-propyl)-amine **4b** a ligand with well known reaction properties.[8,13] The ligand **4b** exhibits one additional property to form internal coordination with a lithium cation, an ability that the polymer supported phenylethyl amine lacks (Scheme 2).

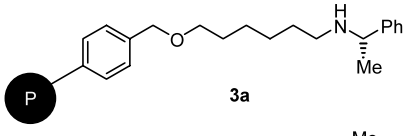
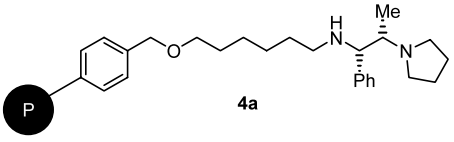
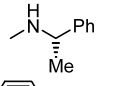
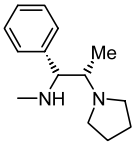
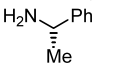
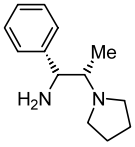
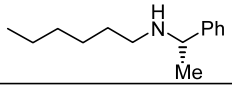
The reason for using a spacer of six carbons is to increase the distance between the amine proton and the polymer support to facilitate both the lithiation of the amine and the deprotonation reaction: The site of reaction and coordination will be more accessible for coordinating solvent and substrate.

We report herein that a surprisingly high enantiomeric excess and an increase in reactivity in the deprotonation reaction when using polymer supported phenylethyl amine as ligand was obtained.

2. Results and discussion

By using equal amounts of the polymer supported phenylethyl amine **3a** and *n*-BuLi in the deprotonation

Table 1. The results from deprotonation of **1** in THF at 20°C

Entry	Ligand	Time (h)	Conv. (%)	*ee*[a] (%) (*S*)-**2**
1	 **3a**	12	67	91
2	 **4a**	72	12	70
3	 **3b**	22	47	19
4	 **4b**	25	95	93
5	 **3c**	5	37	5.3
6	 **4c**	6.5	15	0
7	 **3d**	22	43	21

[a] Determined by chiral GC.

reaction we observed an astonishing high increase of the stereoselectivity (91% *ee* instead of 5.3% from the lithium salt of phenylethyl amine **3c** itself) (entries 1 and 5, Table 1).

Polymer supported phenylethyl amine **3a** is built from a secondary amine while phenylethyl amine **3c** itself is a primary amine. To be able to compare **3a** with a secondary amine, phenylethyl amine was methylated to **3b** and used together with *n*-BuLi in the deprotonation reaction. An expected increase of the enantiomeric outcome was observed, but still the results are far from the results of the polymer supported ligand. Even when comparing **3a** with **3d**, a secondary amine with a *n*-hexyl chain which in a comparison can correspond to the spacer in **3a**, the increase in the stereoselectivity was striking.

However, the polymer supported lithium salt of 1-phenyl-2-pyrrolidin-1-yl-propylamine **4a** did not show the same stereoselectivity (70% *ee*) in the deprotonation reaction as the free secondary amide **4b** (93% *ee*). It seems that the bidentate amide does not reach the high *ee* observed for the non-polymer supported one. Another interesting observation is that the yield doesn't seem to be affected using **3a** compared to **3b**. The non-polymer supported bidentate ligand, **4b**, resulted in a higher yield compared to the polymer supported **4a**. The explanations for this might be found in the dynamics of these species.

Previous studies have shown that the bidentate chiral lithium amide form, in coordinating solvents, a dimer in solution in which the lithiums exhibit different degrees of coordination.[9] One of the lithiums is tetra-coordinated and the other one is tri-coordinated. Coordination of substrate is supposed to take place at the tri-coordinated site.[9] This tri-coordinated lithium lacks the coordination from internal coordinating groups since it is only coordinated by two amide nitrogens and one solvent molecule. In the solid supported case the lithium has to have an internal coordination from the pyrrolidine amine nitrogen and this might have a negative effect upon reactivity and selectivity. The amide has to be a monomer in the solid supported case. Thus, the conclusion to be drawn could be that reactions in solution demand internal coordinating groups, limits the number of different aggregates formed, and the reactivity and the selectivity will be enhanced. In the solid supported case this internal coordination might be deleterious for the reaction. Previously we have shown that chiral lithium amide bases possessing several internal coordination group result in inactive non selective and sluggish reagents, due to lack of accessibility of the substrate for the reagent.[10] Furthermore, chiral lithium amide bases with internal coordination potential generated from primary amines are well documented to have low selectivity.[11]

The chiral lithium amide bases lacking internal coordinating groups show a very different behavior. In solution, these bases form several different types of aggregates such as ladders, dimers, trimers, etc. resulting in a reagent exhibiting low selectivity and reactivity. However, in the polymer supported case we define only one type of aggregate, the monomer, with only coordinating solvent molecules. This is a reagent with high accessibility for substrate, which will result in a high selectivity and reactivity in the asymmetric deprotonation reaction. These observations clearly support a mechanistic pathway involving a monomeric activated complex.

3. Conclusions

In summary, we have shown that a well studied and commercial available chiral amine can be used as a chiral lithium amide base, giving high enantiomeric excess (91%) of the 2-cyclohexene-1-ol in the deprotonation reaction of cyclohexeneoxide, provided that it is attached to a solid support. However, a chiral amine designed to be used in solution with internal coordinating groups resulted, when attached to a solid support, in a decrease of the enantiomeric excess from 93 to 70% of the 2-cyclohexene-1-ol. This difference we attribute to reduction of aggregation diversity and inhibition of availability to substrate, respectively. Simple commercial solid supported chiral amine bases show a potential to be used in combinatorial chemistry and parallel synthesis where extraction procedures of the free base is not possible.

The loading of the polymer supported ligands was measured by FMOC quantitation to 0.34 mmol/g for **3a** and 0.27 mmol/g for **4a**. This gives a total reaction yield of 47 and 40%, respectively of the synthesis of **3a** and **4a**, respectively.

4. Experimental

4.1. General

Glassware and syringes were dried at 50°C in a vacuum oven before transfer into a glove box (Mecaplex GB 80 equipped with a gas purification system removing oxygen and moisture) containing a nitrogen atmosphere. All dry solvents was distilled from sodium/benzophenone and stored under N_2. Chromatographic analyses were carried out on a Varian Star 3400 CX gas chromatograph. All GC analyses were run on a chiral stationary phase column (CP-Chirasil-DEX CB, 25 m, 0.32 mm) from Chrompack. All analyses were performed at 135°C (injector: 225°C; detector: 250°C) with He as carrier gas. All UV-analysis were performed on a Varian Cary 100 Bio UV–vis spectrophotometer with a Varian Cary Win UV Scan application at 301 nm. NMR spectra were recorded using a Varian Unity 400 MHz spectrometer. IR spectra were recorded using a Perkin–Elmer 1600 series FTIR.

4.2. HRMS analysis

The samples were weighed, 0.5 mg of each compound, dissolved and diluted to 1 ml with methanol. From

each solution an aliquot of 5 μl was injected on an analytical column, Ace C18 3 μm, 150×3.0 mm. Separated through a gradient (5–95% acetonitrile in 0.2% formic acid, flow rate 0.5 ml/min, column oven temperature 50°C) and detected by a diode-array detector (190–350 nm) and a quadrupole time-of-flight mass spectrometer (QTof micro, Micromass UK) operated in electrospray ionization positive ion mode (capillary voltage 3.0 kV, cone voltage 40 V, ion energy 10 eV, mass range 80–1000 m/z, scan rate 1 s and inter scan delay 0.1 s). The detector signals were monitored, evaluated and reported. To compensate for drifts in the mass scale a reference solution with a known compound was infused continuously, i.e. a lock mass. In this case the lock mass was leucine enkephaline (m/z 556.2771 in positive ionization mode). The purity of each sample was defined as the relative purity of the total absorbance chromatogram between 190 and 350 nm. The accurate mass was calculated and compared to the suggested elemental composition. The error was reported in mDa. The instrument specification for calculations of accurate mass is 5 ppm.

4.3. Synthesis

4.3.1. Synthesis of polymer with a spacer. *Transhalogenation*: To a round-bottom flask Merrifield® resin (0.84 mmol/g, 5 g, 4.2 mmol) was added. To the polymer acetone (75 ml) and NaI (8.4 mmol, 1.25 g). The reaction mixture was refluxed for 48 h. The solvent was filtered off and the polymer was washed with DMF (3×30 ml).

Homologation: DMF (75 ml) was added to the polymer and NaH (washed with hexane, 0.5 equiv., 2.1 mmol, 0.05 g) and 1,6-hexanediol (1.5 equiv., 0.75 g, 6.3 mmol) was added. The reaction mixture was heated at 60°C for 48 h. The solvent was filtered off and the polymer was washed with DMF (3×30 ml) and dichloromethane (3×30 ml).

Transhalogenation: In a round-bottom flask, dichloromethane (75 ml) was added. Triphenylphosphine (1.2 equiv., 5 mmol, 1.31 g) imidazole (1.2 equiv., 5 mmol, 0.34 g), and iodine (1.2 equiv., 5 mmol, 1.3 g) and then finally the polymer was added and the reaction was stirred at rt for 4 days according to published procedures.[12] The solvent was filtered off and the polymer was washed with dichloromethane (3×30 ml).

Amination: The polymer was washed with THF (3×30 ml) before THF (75 ml) was added. The chiral amine (4 equiv., 16.8 mmol) was added and the reaction was allowed to reflux for 48 h. To the reaction mixture was added Bu_3SnH (4.2 mmol, 1.22 g, 1.11 ml) and the mixture was then allowed to reflux for 48 h. The final product was washed with THF, DMF, dichloromethane and DEE and was stored under N_2.

4.3.2. Synthesis of 3b. To a round-bottom flask were added NaH (0.782 g, 19.5 mmol, prewashed with dry hexane) and dry THF (45 ml). To the round-bottom flask was added (*R*)-phenylethyl amine (18.2 mmol, 2.20 g, 2.35 ml) in dry THF (37 ml). The solution was stirred over night. Methyl iodide (18.2 mmol, 2.63 g, 1.16 ml) in dry THF (23 ml) was added dropwise over 2 h. The solution was stirred for 8 h. The reaction was quenched with ice cold brine (100 ml) and extracted with diethyl ether (4×25 ml). The combined organic phases were dried over Na_2SO_4. Evaporation in vacuo gave a light yellow oil which was distilled (bp 86°C/20 mmHg) at reduced pressure using a vigreux to yield **3b** (2.14 g, 87%) as a colorless oil (>99% NMR). $[\alpha]_D^{25} = -69$ (c 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 293 K): δ 7.33 (2H, d, $J_{H-H} = 5.6$, Ph), δ 7.30 (2H, d, $J_{H-H} = 5.6$, Ph), δ 7.23 (1H, t, $J_{H-H} = 7.38$, Ph), 4.08 ppm (1H, q, $J_{H-H} = 5.22$, PhC<u>H</u>), 2.47 ppm (3H, dd, $J_{H-H} = 6.6$, C<u>H</u>$_3$NH), 1.38 ppm (3H, s, C<u>H</u>$_3$CH); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K): δ 147.73 (Ph), δ 128.38 (Ph), δ 128.11 (Ph), 126.82 (Ph), δ 126.70 (Ph), δ 125.59 (Ph), δ 76.95 (<u>C</u>H), δ 43.21 (<u>C</u>H$_3$), δ 25.65 (<u>C</u>H$_3$); IR: 3330, 2977–2771, 1599, 1491, 1448, 1371, 1312, 1143, 1073, 1030, 948, 835, 759, 699 cm^{-1}; HRMS: calcd for $C_9H_{13}N$ 135.10408 found [M+H$^+$] 136.1126, error −0.3.

4.3.3. Synthesis of 3d. Phenylethyl amine (7.27 g, 60 mmol) was dissolved in chloroform (50 ml) and 1-hexanal (120 mmol, 12.01 g) was added. The solution was allowed to reflux with a heavier-than water trap over night. The solvent was removed by evaporation in vacuo and the imine was dissolved in ethanol (50 ml). $NaBH_4$ (3.4 g, 90 mmol) was added and reaction mixture was allowed to stand for 6 h at rt. The solvent was removed evaporation in vacuo and water (20 ml) was added. The aqueous phase was extracted three times with dichloromethane and the collected organic phases were washed with brine, dried over Na_2SO_4. Evaporation in vacuo gave a yellow oil which was distilled (110°C/7×10^{-3} mbar) at reduced pressure using a vigreux to yield the amine **3d** (9.85 g, 80%) as a colorless oil (>99% NMR) $[\alpha]_D^{25} = -58$ (c 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 293 K): δ 7.21 (2H, d, $J_{H-H} = 5.0$, Ph), δ 7.12 (2H, d, $J_{H-H} = 5.3$, Ph), δ 7.08 (1H, t, $J_{H-H} = 7.9$, Ph), 4.05 ppm (1H, q, $J_{H-H} = 6.47$, PhC<u>H</u>), 3.65 ppm (2H, t, $J_{H-H} = 6.47$, C<u>H</u>$_2$NH), 2.21 ppm (2H, m, C<u>H</u>$_2$CH$_2$), 1.31 ppm (3H, dd, $J_{H-H} = 6.69$, C<u>H</u>$_3$), 1.18–1.33 ppm (6H, m, C<u>H</u>$_2$CH$_2$), 0.83 ppm (3H, t, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K): δ 147.73 (Ph), δ 128.40 (Ph), δ 128.30 (Ph), 126.70 (Ph), δ 126.67 (Ph), δ 125.59 (Ph), δ 77.25 (<u>C</u>H), δ 51.27 (<u>C</u>H$_3$), δ 46.6 (<u>C</u>H$_2$), δ 32.5 (<u>C</u>H$_2$), δ 32.2 (<u>C</u>H$_2$), δ 27.4 (<u>C</u>H$_2$), δ 23.1 (<u>C</u>H$_2$), δ 14.0 (<u>C</u>H$_3$); IR: 3370, 3020–2858, 1729, 1599, 1485, 1448, 1366, 1241, 1106, 1019, 910, 856, 758, 699 cm^{-1}; HRMS: calcd for $C_{14}H_{23}N$ 205.1830 found [M+H$^+$] 206.1909, error 1.1.

4.3.4. Synthesis of 4c. The synthesis was prepared as in published procedures of (1*R*,2*S*)-*N*-methyl-1-phenyl-2-pyrrolidinyl-propaneamine but instead of using methylamine (30 ml, 240 mmol, 33% in ethanol), ammonia (240 mmol, 25% in water, 18 ml) and no additional water was added.[13] The product was distilled (bp 140°C/15 mmHg) at reduced pressure using a vigreux to yield **4c** (60%) as a colorless oil (>99% NMR). $[\alpha]_D^{25} = -30$ (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 293 K): δ 7.30 (2H, d, $J_{H-H} = 5.7$, Ph), δ 7.20 (2H, d,

$J_{H-H}=5.7$, Ph), δ 7.12 (1H, t, $J_{H-H}=7.0$, Ph), δ 4.10 ppm (1H, d, $J_{H-H}=5.4$, PhC$\underline{H}$N), 2.50–2.57 ppm (4H, m, NC$\underline{H}_2$), δ 2.28 ppm (1H, m, C$\underline{H}$N), 1.90 ppm (2H, br s, N$\underline{H}_2$), 1.75–1.83 ppm (4H, m, C$\underline{H}_2$), 0.80 ppm (3H, d, $J_{H-H}=6.0$ C$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K): δ 148.82 (Ph), δ 132.51 (Ph), δ 132.27 (Ph), 130.30 (Ph), δ 130.12 (Ph), δ 125.54 (Ph), δ 77.62 (C$\underline{H}$CH$_3$), δ 72.25 (C$\underline{H}$Ph), δ 51.39 (C$\underline{H}_2$), δ 51.37 (C$\underline{H}_2$); δ 45.12 (C$\underline{H}_2$), δ 45.0 (C$\underline{H}_2$) δ 25.73 (C$\underline{H}_3$); IR: 3380, 2969, 1659, 1620, 1464, 1381, 1322, 1215, 1142, 1103, 1020, 912, 732 cm^{-1}; HRMS: calcd for $C_{14}H_{22}N_2$ 218.1783 found [M+H$^+$] 219.1861, error 0.2.

4.3.5. Synthesis of 4b. The amine was prepared as previously described.[13]

4.4. FMOC quantitation

The quantitation was following published procedures.[14]

Protection: To an ice cold slurry of the polystyrene amino resin (0.5 g) and Na_2CO_3 (10%, 10 ml), was added a solution of FMOC–Cl (1 g, 3.9 mmol) in dioxane (10 ml). The slurry was allowed to react for 2 h at rt. To the slurry water (200 ml) was added. The water phase was washed with DEE (2×50 ml) and then the water phase was acidified to pH 3 with conc. HCl. The acidic phase was filtered of and the resin was washed with water and ethyl acetate and allowed to dry under reduced pressure. The protection of the amine was repeated twice.

Deprotection: The FMOC amino resin (5 mg) was weighed into a 10 ml volumetric flask. To the flask were added piperidine (0.4 ml) and dichloromethane (0.4 ml). The mixture was allowed to cleave for 30 min. Then MeOH (1.6 ml) and dichloromethane (7.6 ml) were added to bring the total volume up to 10 ml. The spectrophotometer was zeroed with a blank solution containing piperidine (0.4 ml), MeOH (1.6 ml) and dichloromethane to make a total volume of 10 ml. The absorbance was measured at 301 nm and the loading level was given by following equation.

$$\text{Loading (mmol/g)} = A_{301} \times 10 \text{ ml}/7800 \times \text{wt} \quad (1)$$

Where A_{301} is the absorbance at 301 nm, 7800 is the extinction coefficient of the piperidine–fluorenone adducts, and wt is the weight of resin used in mg.

4.5. Typical example of deprotonation reaction of 1 with lithiated polystyrene amine resin

The polystyrene amine resin (1 g) was weighed into a Schlenk-filter and dry THF (3 ml) was added. To the filter *n*-BuLi (2.4 M, 3 ml) was added and allowed to lithiate the amine. The solution was filtered off and the resin was washed with dry THF (5×5 ml) to remove unreacted *n*-BuLi. To the Schlenk-filter dry THF (3 ml) and freshly distilled cyclohexene oxide (**1**) (10 μl, 0.1 mmol) was added. The conversion of **1** to **2** and the enantiomeric outcome of the deprotonation reaction were measured by chiral GC. (t_R(**1**) = 4.10 min, t_R((*S*)-**2**) = 7.81 min, t_R((*R*)-**2**) = 8.15 min.

4.6. Typical deprotonation reaction of 1 with lithium amides

These experiments were performed according to earlier published procedures.[9]

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References

1. (a) Simpkins, N. S. *Chem. Commun*. **1986**, 88; (b) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523; (c) Koga, K. *Pure Appl. Chem*. **1994**, *66*, 1487; (d) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc*. **1986**, *108*, 543; (e) Shirai, R.; Sato, D.; Aoki, K.; Tanaka, M.; Kawasaki, H.; Koga, K. *Tetrahedron* **1997**, *53*, 5963; (f) Yamashita, T.; Sato, D.; Kiyoto, T.; Kumar, A.; Koga, K. *Tetrahedron Lett*. **1996**, *37*, 8195; (g) Yamashita, T.; Sato, D.; Kiyoto, T.; Kumar, A.; Koga, K. *Tetrahedron* **1997**, *53*, 16987.
2. (a) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439; (b) Hodgson, D. M.; Witherington, J.; Moloney, B. A. *Tetrahedron: Asymmetry* **1994**, *5*, 337; (c) Hodgson, D. M.; Witherington, J.; Moloney, B. A. *Tetrahedron: Asymmetry* **1994**, *4*, 1649; (d) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361; (e) O'Brien, P.; Poumellec, P. *Tetrahedron Lett*. **1996**, *37*, 8057; (f) Bigi, A.; Mordini, A.; Thurner, A.; Faigl, F.; Poli, G.; Toke, L. *Tetrahedron: Asymmetry* **1998**, *9*, 2293; (g) Whitesell, J. K.; Felman, S. W. *J. Org. Chem*. **1980**, *45*, 755; (h) Bhuniya, D.; DattaGupta, A.; Singh, V. K. *J. Org. Chem*. **1996**, *61*, 6108; (i) Hodgson, D. M.; Gibbs, A. R. *Tetrahedron Lett*. **1997**, *38*, 8907; (j) Tierny, J. P.; Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1019; (k) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc*. **1998**, *120*, 10760; (l) Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc*. **2000**, *122*, 6610; (m) Milne, D.; Murphy, P. J. *Chem. Commun*. **1994**, 675; (n) Asami, M. *J. Synth. Org. Chem. (Jpn)* **1996**, *54*, 188; (o) Asami, M.; Inoue, S. *Tetrahedron* **1995**, *51*, 11725; (p) Asami, M.; Suga, T.; Honda, K.; Inoue, S. *Tetrahedron Lett*. **1997**, *38*, 6425; (q) Cox, J. P.; Simpkins, S. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1; (r) Asami, M. *Chem. Lett*. **1984**, 829–832; (s) Pettersen, D.; Amedjkouh, M.; Nilsson, L.; Sten, O.; Ahlberg, P. *J. Chem. Soc., Perkin 2* **2002**, 1307.
3. (a) Price, D. A.; Simpkins, N. S.; McLeod, A. M.; Watt, A. P. *J. Org. Chem*. **1994**, *59*, 1961; (b) Ewin, R. A.; Simpkins, N. S. *Synlett* **1996**, 317; (c) Gibson, S. E.; Potter, P. C. V.; Smith, M. H. *Chem. Commun*. **1996**, 2757; (d) Gibson, S. E.; Ham, P.; Jefferson, G. R.; Smith, M. H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2161; (e) Cowton, E. L. M.; Gibson, S. E.; Schneider, M. J.; Smith, M. H. *Chem. Commun*. **1996**, 839.

4. (a) Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *Tetrahedron* **2002**, *58*, 4669; (b) Bertilsson, S. K.; Södergren, M. J.; Andersson, P. G. *J. Org. Chem.* **2002**, *67*, 1567.
5. Schlosser, M. In *Organometallics in Synthesis*; Schlosser, M., Ed. Organoalkali Reagents; John Wiley & Sons: Chichester, 1994; p. 17.
6. (a) Majewski, M.; Ulaczyk, A.; Wang, F. *Tetrahedron Lett* **1999**, *40*, 8755–8758; (b) Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Chem. Commun.* **2001**, 1722.
7. Seki, A.; Asami, M. *Tetrahedron* **2002**, *58*, 4655.
8. Colman, B.; deSousa, S. E.; O′Brien, P.; Towers, D. T.; Watson, W. *Tetrahedron: Asymmetry* **1999**, *10*, 4175.
9. Amedjkouh, M.; Pettersen, D.; Nilsson Lill, S. O.; Davidsson, O.; Ahlberg, P. *Chem. Eur. J.* **2001**, *7*, 4368–4377.
10. See Ref. 2h; deSousa, S. E.; O'Brien, P.; Pilgram, C. D. *Tetrahedron* **2002**, *58*, 4643–4654.
11. Johansson, A.; Pettersson, A.; Davidsson, Ö. *J. Organomet. Chem.* **2000**, *608*, 153–163.
12. Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473–1479.
13. Pettersen, D.; Amedjkouh, M.; Nilsson Lill, S. O.; Dahlén, K.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1654–1661.
14. For FMOC-protection, see: Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404–3409. For FMOC-deprotection and quantitation, see: Bunin, B. *Combinatorial Index*; Cloth. Academic Press: London, 1997; pp. 219–220.