An Intriguing Effect of Polymer-Bound Lithium Amides in Catalytic Enantioselective Rearrangement of *meso*-Epoxides Mediated by Chiral Lithium Amides

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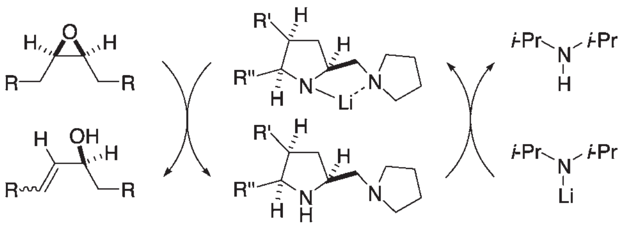
Polymer-bound lithium dialkylamides were prepared from the corresponding polymer-bound amines and butyllithium. The reagent was successfully employed as an *in situ* regenerating agent of a chiral lithium amide in a catalytic enantioselective rearrangement of *meso*-epoxides, and chiral allylic alcohols were obtained in up to 95% ee.

Asymmetric transformations mediated by chiral lithium amides have attracted much interest in recent years.[1] We have been studying enantioselective rearrangement of epoxides to chiral allylic alcohols using chiral lithium pyrrolidides.[2] The reaction using a catalytic amount of the chiral lithium amides proceeded similarly in the presence of excess achiral lithium amides such as lithium diisopropylamide (LDA).[3] The results indicated that the reaction of the chiral lithium amides with epoxide was faster than that of LDA and the chiral lithium amides were regenerated *in situ* by lithium-hydrogen exchange between LDA and the resulting chiral amines (Scheme 1).

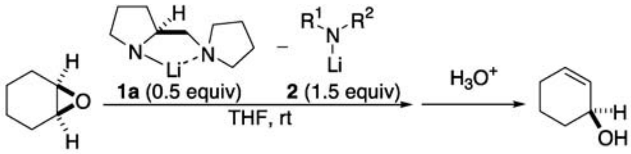


Scheme 1.

A great deal of research on polymer-bound reagents is currently in progress.[4] Although these reagents have the advantages that they are easily removed from reaction mixtures and may be recycled, less reactivity in comparison with the corresponding monomeric reagents is often a drawback. We anticipated that this drawback would become an advantage provided polymer-bound lithium amide[5] is employed as a regenerating agent of a chiral lithium amide in the above mentioned catalytic reaction, because the non-enantionselective reaction with achiral lithium amide is diminished. In this communication, we wish to report a catalytic enantioselective rearrangement of *meso*-epoxides by the combined use of a chiral lithium amide and excess polymer-bound lithium amide.

Firstly, we examined enantioselective rearrangement of cyclohexene oxide using 0.5 equiv of lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide (**1a**) and 1.5 equiv of lithium *N*-isopropylbenzylamide (**2a**) or lithium *N*-cyclohexylbenzylamide (**2b**) in THF at rt for 24 h. As the lithium amides **2a**,**b** gave better selectivities (Table 1, Entries 1, 2) than LDA (63%, 48% ee),[3a] the corresponding polymer-bound amines were

Table 1. Effect of achiral lithium amides

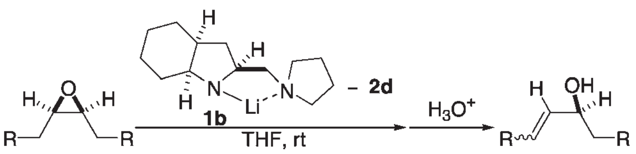


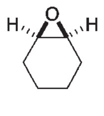
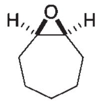
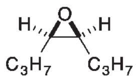
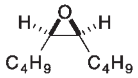
Entry	2	Achiral Lithium Amide R¹	R²	Time / h	Yield / %[a]	ee / %[b]
1	**a**	*i*-Pr	$PhCH_2$	24	86	64
2	**b**	*c*-C_6H_{11}	$PhCH_2$	24	87	65
3	**c**	*i*-Pr	●–C_6H_4–CH_2	24	84	73
4	**d**	*c*-C_6H_{11}	●–C_6H_4–CH_2	24	89	73
5[c]	**d**	*c*-C_6H_{11}	●–C_6H_4–CH_2	40	87	64
6[d]	**d**	*c*-C_6H_{11}	●–C_6H_4–CH_2	96	88	51

[a]Isolated yield after benzoylation. [b]Determined by HPLC analysis (Opti-pak TA, Waters, Ltd.) of the benzoate ester. [c]The reaction was carried out using 0.2 equiv of **1a** and 1.8 equiv of **2d**. [d]The reaction was carried out using 0.1 equiv of **1a** and 1.9 equiv of **2d**.

prepared from *N*-isopropyl-*p*-vinylbenzylamine (20 mol%) or *N*-cyclohexyl-*p*-vinylbenzylamine (20 mol%), styrene (78 mol%), and divinylbenzene (2 mol%) in the presence of a catalytic amount of AIBN by copolymerization.[6] Then we examined the time-conversion relationship of the reaction of the polymer-bound lithium amide, prepared from the corresponding polymer-bound amine and butyllithium, and cyclohexene oxide by GC. A considerable amount of cyclohexene oxide remained unreacted (84%) and only a little 2-cyclohexenol (7%) was detected even after 24 h at 0 °C in the presence of 1.5 equiv of **2d** in THF, while LDA gave 17% of 2-cyclohexenol with unreacted cyclohexene oxide (75%) under the same reaction conditions. Encouraged by this observation, we examined the catalytic enantioselective deprotonation of cyclohexene oxide using 0.5 equiv of **1a** and 1.5 equiv of insoluble polymer-bound lithium amide **2c** or **2d** in THF at rt for 24 h. In both cases, (*S*)-2-cyclohexenol was obtained in good yield with higher ee (73% ee, Table 1, Entries 3, 4) than those obtained using LDA, **2a**, or **2b**, as expected. We next tried to reduce the amount of **1a**. The ee of the resulting 2-cyclohexenol was gradually decreased to 64% ee (87% yield) and 51% ee (88% yield), respectively, as the amount of **1a** was reduced to 0.2 equiv (with 1.8 equiv of **2d**) and 0.1 equiv (with 1.9 equiv of **2d**) (Table 1, Entries 5, 6). However, it is notable that the effectiveness of polymer-bound lithium amide as an *in situ* regenerator of a chiral lithium amide was realized.

Table 2. Catalytic enantioselective rearrangement of epoxides[a]



Entry	Epoxide	1b / Equiv	2d / Equiv	Time / h	Yield / %[b]	ee / %
1		0.2	1.8	12	89	94[c]
2		0.1	1.9	24	91	91[c]
3		0.05	1.95	36	89	89[c]
4		0.05	1.45	36	91	92[c]
5		0.05	1.3	72	76	91[c]
6		0.05	1.45	72	54	94[c]
7		0.05	1.45	48	90	93[d]
8		0.05	1.45	72	93	95[d]

[a]Reaction was carried out according to the typical procedure.[7] [b]Isolated yield after benzoylation. [c]Determined by HPLC analysis (Opti-pak TA, Waters, Ltd.) of the benzoate ester. [d]Determined by ^{1}H-NMR of the corresponding acetate in the presence of Eu(hfc)$_3$.

Then, we applied the new system to a chiral lithium amide **1b**, prepared from (2*S*,3a*S*,7a*S*)-2-(pyrrolidin-1-ylmethyl)octahydroindole, which showed much higher selectivity than **1a** in the reaction.[3b] (*S*)-2-Cyclohexenol was obtained in good yield with very high ee (94% ee) by using 0.2 equiv of **1b** and 1.8 equiv of **2d** (Table 2, Entry 1). Although the ee of the product was decreased slightly as the amount of **1b** was reduced (Table 2, Entries 2, 3), the alcohol as high as 92% ee was obtained in high yield by decreasing the amount of **2d** to 1.45 equiv (Table 2, Entry 4). It is of interest that the selectivity of the reaction was enhanced using 0.05 equiv of **1b** and 1.45 equiv of **2d** (92% ee) as compared with that using stoichiometric amount (1.5 equiv) of **1b** (89% ee) by the reaction at rt.[3b] As the good result was obtained for cyclohexene oxide, the reaction was applied to cycloheptene oxide, *cis*-4-octene oxide, and *cis*-5-decene oxide using 0.05 equiv of **1b** and 1.45 equiv of **2d**. High selectivity was achieved in every case and the corresponding (*S*)-alcohols were obtained in high enantioselectivities (>92% ee) (Table 2, Entries 6–8). It should be noted that the selectivity of the reaction with *cis*-4-octene oxide (Table 2, Entry 7) was significantly improved compared with that obtained using 0.2 equiv of **1b** with 1.8 equiv of LDA (85%, 83% ee).[3b]

In conclusion, we have prepared polymer-bound lithium amide **2c**,**d** and shown the intriguing effect of **2c**,**d** as a superior reagent to regenerate chiral lithium amide *in situ* in the catalytic enantioselective deprotonation of *meso*-epoxides, and chiral allylic alcohols were obtained in up to 95% ee using 0.05 equiv of chiral lithium amide **1b**.

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Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

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7 Typical experimental procedure (Table 2, Entry 1) is as follows; To the mixture of polymer-bound *N*-cyclohexyl-*p*-vinylbenzylamine (1.17 g) and (2*S*,3a*S*,7a*S*)-2-(pyrrolidin-1-ylmethyl)octahydroindole (42 mg, 0.20 mmol) in THF (9 mL) was added a hexane solution of butyllithium (1.24 mL, 2.0 mmol) at rt and stirred for 0.5 h. Cyclohexene oxide (98 mg, 1.0 mmol) in THF (1 mL) was added to the mixture and stirring was continued for 12 h at rt. After quenching with saturated aqueous NH_4Cl, the resin was removed by filtration and washed well with CH_2Cl_2. The organic layer was washed with 1 M HCl and brine, successively, and dried over anhyd Na_2SO_4. After removal of the solvent at atmospheric pressure, the resulting crude product was benzoylated with benzoyl chloride, pyridine, and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine. After the addition of excess *N*,*N*-dimethyl-1,3-propandiamine, water was added to the mixture. The organic layer was washed with 1 M HCl and brine, successively, and dried over anhyd Na_2SO_4. The organic layer was concentrated *in vacuo* and the crude product was purified by preparative TLC, followed by bulb-to-bulb distillation (120 °C/0.65 mmHg) to give (*S*)-2-cyclohexenyl benzoate (180 mg, 89%, $[\alpha]_D^{20}$ −210.2° (*c* 1.00, $CHCl_3$)). The ee was determined to be 94% by HPLC analysis using Opti-pak TA.