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Enantioselective Addition of Organolithium Reagents to Imines Mediated by C_2-Symmetric Bis(aziridine) Ligands

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Abstract:

The C_2-symmetric bis(aziridine) ligands **1** - **5** have been screened in the enantioselective addition of organolithium reagents to imines. Ligand **1** (used in stoichiometric amounts) was found to be superior in terms of chemical yield and enantioselectivity, the best result being 90% yield and 89% *e.e.* in the addition of vinyllithium to imine **6a**. Use of ligand **1** in substoichiometric amounts gave poorer yield and lower enantioselectivity. The enantioselectivity of the reaction was investigated as a function of substrate, reagent, stoichiometry and temperature, but no firm mechanistic conclusions could be drawn. Preliminary results with deuterium-labelled methyllithium indicate complexation/exchange processes involving ligand, reagent and substrate.

Keywords: Aziridines; Catalysis; Enantioselection; Lithium and compounds.

Introduction. In a recent review, Denmark and Nicaise [1] summarised the current state of the art regarding asymmetric addition of simple organometallic reagents to azomethine functions (Scheme 1).

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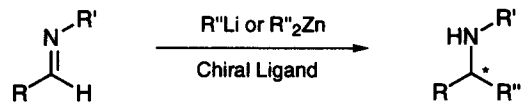
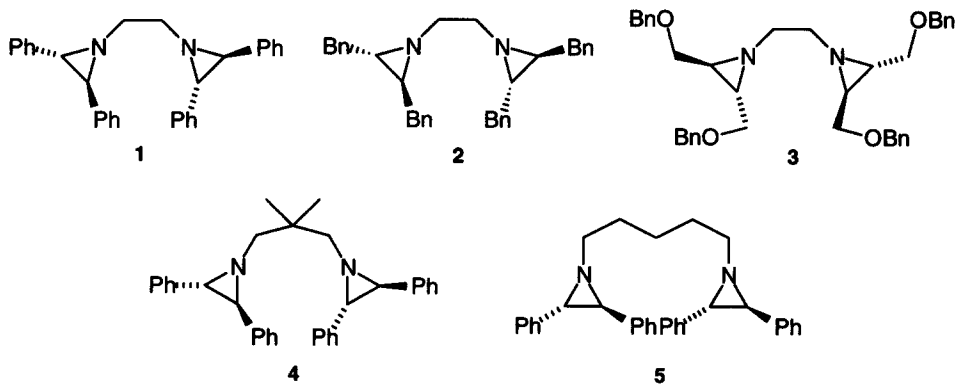


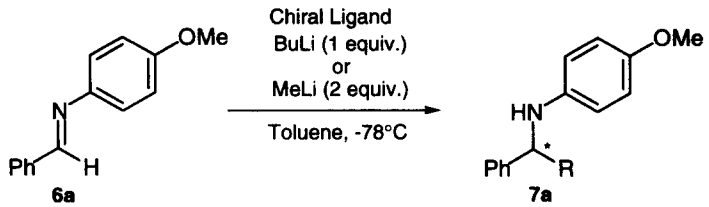
Scheme 1. Enantioselective addition of organometallics to imines.

In spite of some recent progress [2], this potentially catalytic and synthetically useful procedure for the preparation of chiral amines has received much less attention than the corresponding transformation of carbonyl compounds [3]. The development of new chiral ligands is thus desirable, particularly species which can be used in sub-stoichiometric amounts (most especially systems which display the phenomenon of ligand accelerated catalysis [4]). We have already presented some preliminary data [5c] for the addition of MeLi to imine **6a** in the presence of stoichiometric or catalytic amounts of C_2-symmetric bis(aziridine) ligands [5] (Scheme 2) and we now wish to present some new results from a broader study of this reaction type, using the ligands **1** - **5** .



Results and Discussion. The addition of butyl- or methyllithium to imine **6a** was used to screen ligands **1** - **5** and the best results from the exploratory experiments are shown in Table 1. Toluene was chosen as the solvent, in order to compare our results with the bulk of those reported in the literature [6,7]. Since ligand **1** gave a moderate but encouraging *e.e.* at the first attempt, and proved to be superior to **2** - **5** in all respects (including ease of preparation) it was chosen for closer evaluation, with further variation of alkyllithium, stoichiometry, temperature and substrate. It may be noted that in the reactions involving ligand **1**, a (ligand:organolithium) ratio of 2:1 was best for BuLi, while a ratio of 1:2 was best for MeLi. We shall return to this point later.

Table 1. Addition of methyl- or butyllithium to imine **6a** mediated by ligands **1-5**.

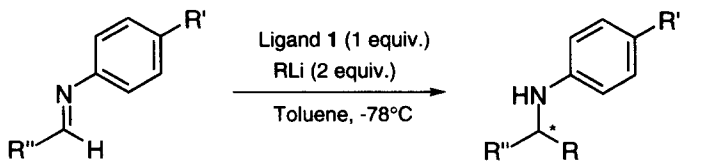


6a **7a**

Entry	Ligand (equiv)	R in RLi	Yield (%)[a]	*ee* (%)[b]	Configuration[c]
1	none	Bu	90	-	-
2	none	Me	<10	-	-
3	**1** (2)	Bu	44	68	*R*
4	**2** (2)	Bu	38	36	*R*
5	**3** (1)	Bu	41	0	-
6	**4** (1)	Bu	45	52	*R*
7	**5** (2)	Bu	50	<5	*R*
8	**1** (1)	Me	47	67	*R*

[a] Isolated yield after flash chromatography (silica gel, ethyl acetate/hexane or pentane/ether).
[b]Determined by HPLC analysis, using a chiral column (Chiralcel OD-H); racemic product synthesized by use of TMEDA as ligand. [c] See experimental part.

Table 2. Addition of various organolithiums to imine **6a** (**6b**) mediated by ligand **1**.



6a R' = OMe, R'' = Ph
6b R' = H, R'' = *p*-MeO-Ph

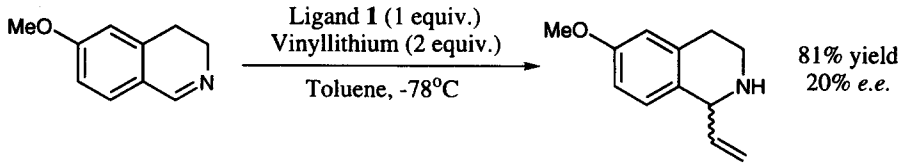
7a R' = OMe, R'' = Ph
7b R' = H, R'' = *p*-MeO-Ph

Entry	Imine	R in RLi	Yield (%)	*ee* (%)	Configuration
1	**6a**	Me	47	67	*R*
2	**6a**	*n*-Bu	56	61	*R*
3	**6b**	Ph	78	<5	-
4	**6a**	vinyl	90	89	-
5	**6a**	2-furyl	n.r.[a]	-	-
6	**6a**	2-thienyl	n.r.[a]	-	-
7	**6a**	2-picolyl	n.r.[a]	-	-

[a] Use of TMEDA as ligand gave racemic product in 50 - 60% yield.

The results of screening some readily available organolithium reagents with ligand **1** are collected in Table 2. In these experiments the (ligand:organolithium) ratio was 1:2. Use of butyllithium under these conditions gave slightly higher chemical yields as compared to methyllithium, but the *e.e.* remained around 60%. For obvious reasons, phenyllithium was not used in conjunction with **6a**, but the result with imine **6b** is included in Table 2 (entry 3)

for the sake of comparison. By far the best result in terms of both chemical yield (90%) and *e.e.* (89%) was provided by vinyllithium (entry 4). It is also interesting to note that the value of the *e.e.* is dependent on the solvent used for preparation of the vinyllithium: vinyllithium in THF was superior to vinyllithium in ether (20% *e.e.*). As shown below, however, the system is obviously substrate-dependent.



The heterocyclic organolithiums tested (Table 2, entries 5 - 7) showed a disappointing lack of reactivity, particularly since it was noted that reasonably good yields of racemic product were obtained from the addition of 2-furyl- and 2-thienyllithium to **6a** in the presence of the achiral ligand TMEDA. It was observed that the addition of butyllithium was by far the most rapid (reaction being complete in a few minutes at -78°C) and it was decided to investigate this reagent further, by variation of stoichiometry and reaction temperature.

As shown in Table 3 (entry 2) attempts to use only catalytic amounts of the ligand had a deleterious effect on both yield and *e.e.* On the other hand, using a twofold excess of ligand with respect to butyllithium had little effect (compare entries 1 and 5). Entries 4 - 6 (use of one equivalent BuLi and variation of ligand stoichiometry) are curious, with maximum *e.e.* (68%) being obtained for a ligand:BuLi ratio of 2:1 (entry 5), while changing the ligand:BuLi ratio to 4:1 actually led to a pronounced drop in enantioselectivity! For the ligand:BuLi ratio of 1:1, relatively good chemical yield and *e.e.* result (entry 6) and this can be contrasted with the corresponding reaction with MeLi, which gave no product at all under the same conditions. Overall, the results in Table 3 show that there is no obvious correlation between ligand:BuLi ratio and *e.e.*, which makes detailed interpretation of the data difficult. We would like to point out that the data presented in Table 3 were the result of multiple and reproducible experiments for each entry.

Since it was possible to use only one equivalent of BuLi, the effect of varying the reaction temperature was investigated for the ligand:BuLi ratio of 1:1, and the results are presented in Table 4. The highest *e.e.* value (65%) was obtained at the lowest temperature (-

95°C, entry 1) and the enantioselectivity was steadily eroded as the temperature was increased (entries 2- 4).

Table 3. Addition of *n*-BuLi to imine **6a** mediated by ligand **1**: variation of stoichiometry.[a]

Entry	Equiv. BuLi	Equiv. ligand **1**	Yield (%)	*ee* (%)	Configuration
1	2	1	56	61	*R*
2	2	0.1	31	44	*R*
3	2	4	50	60	*R*
4	1	4	40	50	*R*
5	1	2	44	68	*R*
6	1	1	67	60	*R*
7	4	2	51	64	*R*
8	4	1	70	50	*R*

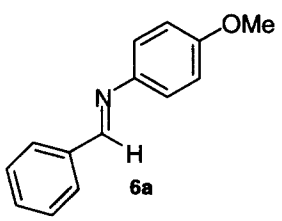
[a] Reactions run in toluene at -78°C.

Table 4. Addition of *n*-BuLi to **6a** mediated by ligand **1**(1 equiv.) at various temperatures.[a]

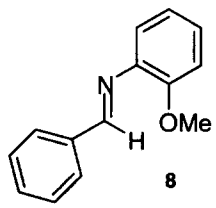
Entry	Temp. (°C)	Yield (%)	*ee* (%)
1	-95	75	65
2	-78	67	60
3	-43	69	44
4	20	45	21

[a] Reactions run in toluene.

Table 5. Addition of *n*-BuLi (1 equiv.) to **6a**, **8** and **9** mediated by ligand **1**(1 equiv.).[a]



6a



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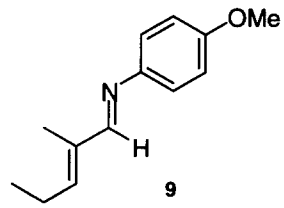

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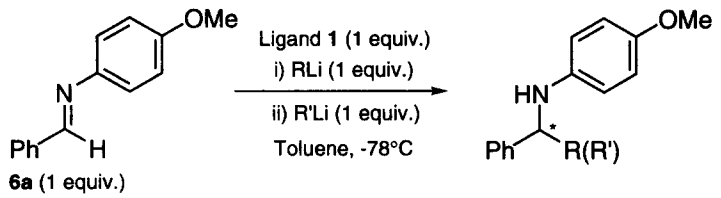
Entry	Imine	Yield (%)	*ee* (%)
1	**6a**	67	60
2	**8**	42	14
3	**9**	39	10

[a] Reactions run in toluene at -78°C.

Continuing with the ligand:organolithium ratio of 1:1, we briefly investigated the effect of changing the structure of the imine in the reactions with BuLi. The imines **8** and **9** were chosen together with the standard substrate **6a**, and the results are presented in Table 5. It was observed that the sterically more encumbered substrates **8** and **9** gave lower chemical yields and poorer enantioselectivity.

Finally, we attempted to obtain some insight on the nature of the reactive species in the addition reaction by use of deuterium-labelled methyllithium, according to Scheme 2.



Expt.	R	R'	Ratio CH_3 : CD_3 in product
1	CH_3	CD_3	30 : 70
2	CD_3	CH_3	70 : 30

Scheme 2. Deuterium-labelling studies of the addition of methyllithium to **6a** mediated by ligand **1**.

Ligand **1** (1 equiv.) and imine **6a** (1 equiv.) were dissolved in toluene under argon at -78°C. CH_3Li (1 equiv.) was added, and after 20 min. CD_3Li (1 equiv.) was added. After one hour at -78°C, quenching and workup as described in the Experimental provided a mixture of addition products, the ratio between undeuterated and deuterated product being measured by integration of the ^1H NMR spectrum. The experiment was repeated, with the inverse order of addition of the reagent, and the results are summarized in Scheme 2. In both cases, the product was enriched in the moiety transferred from the second-added nucleophile, the ratios in both experiments being identical within experimental error. This interesting result obviously warrants further investigation of complexation/exchange phenomena involving ligand, nucleophile and substrate.

In conclusion, we have screened a variety of chiral bis(aziridine) ligands for the enantioselective addition of organolithium reagents to imines. The stereoselectivity of the reaction was found to depend on many parameters, and it is difficult to draw detailed mechanistic conclusions at this point. Thus, although our best results (90% yield and 89% *e.e.*) are on a par with the best in the literature [1], we concur with the recent statement [1]

by Denmark and Nicaise: "The search for a new and practical enantioselective addition to azomethine functions will remain a challenge in synthetic chemistry for some time to come". This is particularly true for the catalytic version of the reaction [8].

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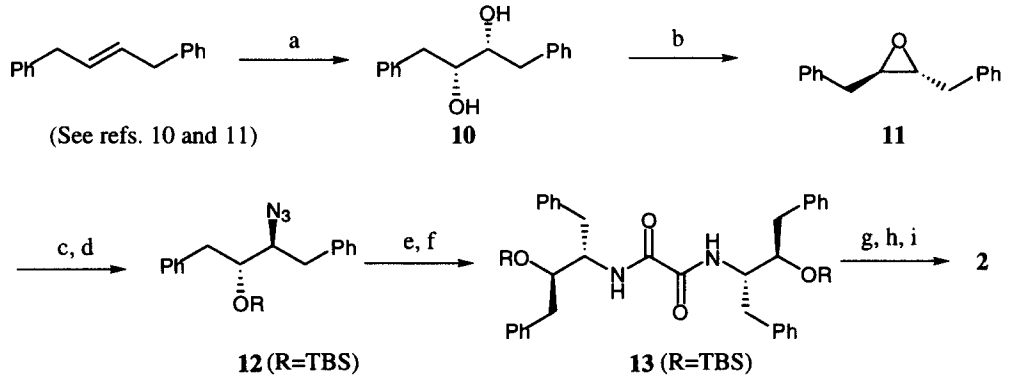
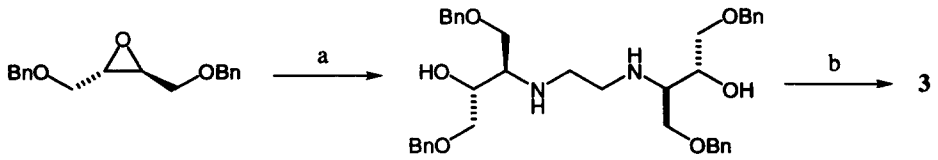
EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC-250 or a Varian XL-300 instrument ($CDCl_3$/TMS). Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument at 70 eV. IR spectra were recorded on a Perkin-Elmer 1600 FTIR instrument. Enantiomeric excess (*e.e.*) was determined by chiral HPLC using an OD-H column. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by Mikroanalytisches Laboratorium, Institut für Physikalische Chemie, University of Vienna, Austria. and Mikro Kemi AB, Uppsala, Sweden. Toluene was dried over sodium hydride and distilled under nitrogen atmosphere. All lithium reagents were titrated before use [9]. According to the supplier (Aldrich) the methyllithium solution contained 0.4% LiCl. No attempt was made to determine the halide content (if any) of the other commercially availiable organolithium reagents. The synthesis of ligands **1**, **4**, and **5** has been described previously [5c]. Ligands **2** and **3** were synthesised as shown below.



a) AD-mix-β, *t*-BuOH/H_2O, $MeSO_2NH_2$, 82%. b) (i) $MeC(OMe)_3$, *p*-TsOH, CH_2Cl_2; (ii) TMSCl, CH_2Cl_2; (iii) K_2CO_3, MeOH, 83% from **10**. c) NaN_3, NH_4Cl, 2-methoxyethanol/H_2O, 90°C, 94%. d) TBDMSCl, imidazole, DMF, rt, 94%. e) Ph_3P, THF/H_2O, reflux, 94%. f) Oxalyl chloride, toluene/pyridine, rt, 56%. g) BH_3·THF, reflux, 69%. h) Bu_4NF, THF, rt.,72 %. i) Ph_3P, DEAD, THF, rt, 67%.



(See ref. 10) **14**

a) Ethylenediamine (0.5 equiv.), reflux, 45%. b) Ph_3P. DEAD, THF, rt, 45%.

Ligand 2

(i) 1,4-butane-2*R*,3*R*-diol **10** was obtained from 1,4-diphenyl-*trans, trans,* 1,3-butadiene, via reduction [10] with sodium in ethanol followed by Sharpless dihydroxylation using AD-mix β [11a,b]. The product showed $[\alpha]_D^{24.0°C}$ -14.5 (*c* 1.1, $CHCl_3$) which can be compared to that reported for the enantiomer [11c] ($[\alpha]_D^{26.0°C}$ +4.6 (*c* 1.1, $CHCl_3$)). We have no explanation for this discrepancy, and no further attempts were made to determine the *e.e.*.

(ii) 1,4-butane-2*R*,3*R*-diol **10** (8.70 g, 36.0 mmol) was dissolved in methylene chloride (500 mL). A catalytic amount of *p*-toluenesulphonic acid was added followed by trimethyl orthoacetate (5.41 mL, 43.0 mmol). After 48 h the solvents were removed *in vacuo* and the residue was dissolved in methylene chloride (500 mL). Trimethylsilyl chloride (6.37 mL, 50.4 mmol) was added. After stirring at room temperature for 48 h the solvents were removed in vacuo to give (2*R*, 3*S*)-1,4-diphenyl-3-chloro-2-acetoxy-butane. This was directly dissolved in methanol (500 mL) and potassium carbonate (9.96 g, 72.0 mmol) was added. After 1 h the mixture was filtered and the filtercake was rinsed with ethyl acetate (20 mL). The combined solvents were removed *in vacuo* and the residue was dissolved in ethyl acetate (200 mL). The organic solution was washed with brine (50 mL) followed by saturated ammonium chloride (50 mL) and an additional amount of brine (50 mL). The organics were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The residue was purified by flash chromatography, eluting 5:95 ethyl acetate-hexane to give (2*R*,3*R*)-epoxide **11** (6.63 g, 83%) as a colourless oil. R_f (EtOAc-hexane, 1:9) 0.49. ^{1}H-NMR($CDCl_3$) 7.34-7.16 (10 H, m), 3.0 (2 H, m), 2.91 (2 H, dd, J=14.5, J=5), 2.81 (2 H, dd, J=14.5, J=5). ^{13}C-NMR($CDCl_3$): 137.2, 128.9, 128.5, 126.6, 58.7, 38.3. IR: υ_{max}(liquid film)/cm^{-1}: 3028,

2976, 2917, 1949, 1879, 1810, 1605, 1496, 1454, 1200, 1190. Anal. Calcd. for $C_{16}H_{16}O$: C,85.68; H, 7.19. Found: C, 85.77; H, 7.20. $[\alpha]_D^{22.5°C}$ +21.41 (*c* 1.06, CH_2Cl_2).

(iii) The epoxide **11** from above (6.53 g, 29.1 mmol) was dissolved in 2-methoxyethanol (116 mL) and water (14.5 mL). Ammonium chloride (2.80 g, 52.4 mmol) and sodium azide (7.95 g, 122.3 mmol) were added in that order. The reaction mixture was stirred at 95°C for 17 h, at which point TLC (10% EtOAc/hexane) indicated only a minor amount of epoxide left in the reaction mixture. The solution was cooled to room temperature and then poured into water (200 mL). The aqueous phase was extracted with ether (3 × 50 mL) and the combined organics were washed with brine (50 mL), saturated ammonium chloride (50 mL) and dried over $MgSO_4$. After filtration and removal of solvents *in vacuo,* the residue was purified by flash chromatography, eluting with 5:95 EtOAc-hexane to give azidoalcohol **12** (R=H) (7.78 g, 94 %) as an oil. R_f (EtOAc-hexane, 1:9) 0.29. ^{1}H-NMR ($CDCl_3$) 7.39-7.20 (10 H, m), 3.88 (1 H, m), 3.67 (1 H, m, J=4.5), 3.05 (2 H, m), 2.82 (2 H, m), 1.82 (1 H, dd, J=4.0, J=2.0). ^{13}C-NMR ($CDCl_3$): 137.5, 137.4, 129.3, 129.2, 128.7, 128.6, 126.8, 74.1, 67.5, 39.2, 36.3. IR: υ_{max}(liquid film)/cm^{-1}: 3426, 3028, 2920, 2108(N_3), 1603(Ph), 1495(Ph). Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 72.18; H, 6.43; N, 15.92. $[\alpha]_D^{23.0°C}$ +3.35 (*c* 1.02, CH_2Cl_2).

(iv) The azido alcohol **12** (R=H) from above (7.26 g, 27.2 mmol) and imidazole (2.78 g, 40.8 mmol) were dissolved in dry DMF (40 mL) under an argon atmosphere. 1,1-(Dimethylethyl)dimethylsilyl chloride (8.19 g , 54.3 mmol) was added neat in portions. After 42 h the reaction mixture was added to water (100 mL) and ether (200 mL). The phases were separated and the organic phase was washed with saturated ammonium chloride (2 × 50 mL), dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and the residue was purified by flash chromatography, eluting with hexane to give **12** (R=TBS) (9.73 g, 94 %) as an oil. R_f (EtOAc-hexane, 1:9) 0.71. ^{1}H-NMR ($CDCl_3$) 7.38-7.15 (10 H, m), 3.96 (1 H, m), 3.60 (1 H, m), 2.67 (2 H, m), 2.61 (2 H, m), 0.86 (9 H, s), -0.6 (3 H, s), -0.35 (3 H, s). ^{13}C-NMR (CDCl3) 138.2, 138.0, 129.8, 129.1, 128.6, 128.3, 126.7, 126.4, 76.0, 68.1, 39.2, 36.5, 25.8, 17.9, -4.8, -5.3. IR: υ_{max}(liquid film)/cm^{-1} 3414, 2953, 2856,

2100 (azide), 1649. Anal. Calcd. for $C_{22}H_{31}N_3OSi$: C, 69.25; H, 8.19; N, 11.01. Found: C, 69.53; H, 7.94; N, 11.16. $[\alpha]_D^{23.0°C}$ +5.78 (*c* 1.02, CH_2Cl_2).

(v) The silyl ether **12** (R=TBS) from above (9.79 g, 25.6 mmol) and triphenylphosphine (8.88 g, 33.9 mmol) were dissolved in THF (45 mL) under an argon atmosphere. Water (20 mL) and THF (40 mL) were added and the mixture was refluxed for 1 h. An additional amount of triphenylphospine (3.0 g, 11.4 mmol) was added and the mixture was refluxed for an additional 17 h. After cooling, THF was removed *in vacuo* and the residue was extracted with CH_2Cl_2 (3 × 60 mL). The organics were dried over $MgSO_4$, filtered, and the solvents removed *in vacuo*. The residue was purified by flash chromatography, eluting with EtOAc-hexane as a gradient from 1:20 to 1:1. This gave the primary amine corresponding to **12** (8.56 g, 94%) as an oil. R_f (EtOAc-pentane, 1:1) 0.38. ^{1}H-NMR ($CDCl_3$) 7.37-7.16 (10 H, m), 3.85 (1 H, m), 3.10 (1 H, m), 2.94-2.78 (3 H, m), 2.63 (1 H, dd, J=13.0, J=9.0), 1.36 (2 H, bs), 0.86 (9 H, s), -0.08 (3 H, s), -0.39 (3 H, s). ^{13}C-NMR ($CDCl_3$) 139.5, 139.2, 129.7, 129.1, 128.5, 128.1, 126.2, 126.0, 76.92, 57.2, 39.5, 38.0, 26.0, 25.8, 17.9, -4.9, -5.3. IR: υ_{max}(liquid film)/cm^{-1} 3376, 3064, 3028, 2928, 2856, 1943, 1802, 1664, 1496, 1456, 1252. Anal. Calcd. for $C_{22}H_{33}NOSi$: C,74.31; H, 9.35; N, 3.94. Found: C, 74.52; H, 9.41; N, 4.08. $[\alpha]_D^{25.0°C}$+26.8 (*c* 1.05, CH_2Cl_2).

(vi) The amine from above (8.54 g, 24.0 mmol) was dissolved in dry toluene (100 mL) under argon atmosphere. Pyridine (5.0 mL, 62.45 mmol) was added *via* a syringe and the temperature was lowered to 0°C. Oxaloyl chloride (1.12 mL, 12.7 mmol) was added dropwise. After 1 h, cooling was removed and the mixture was stirred at room temperature for 17 h. The mixture was added to ethyl acetate (200 mL) and washed with saturated $CuSO_4$ (50 mL) and water (50 mL). The combined aqueous phases were extracted with ethyl acetate (2 × 100 mL). The combined organics were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo* . The residue was purified by flash chromatography, eluting with 5% ethyl acetate-hexane to give **13** (5.40 g, 56%) as an oil. R_f (EtOAc-hexane, 1:9) 0.53. ^{1}H-NMR ($CDCl_3$) 7.45-7.12 (20 H, m), 4,24-4.05 (4 H, m), 3.07 (2 H, dd, J=4.5, J=13.0), 2.93 (2 H, dd, J=4.5, J=13.0), 2.88-2.76 (4 H, m), 0.94 (18 H, s), 0.06 (6 H, s), -0.30 (6 H, s). ^{13}C-NMR ($CDCl_3$) 158.8, 137.9, 137.6, 129.4, 128.9, 128.4, 128.3, 126.5, 126.3,

74.7, 55.0, 40.1, 35.0, 25.8, 17.9, -4.8, -5.2. IR: υ_{max}(liquid film)/cm^{-1} 3392, 3086, 3063, 3028, 2954, 2929, 2886, 2857, 2251, 1674. $C_{46}H_{64}N_2O_4Si_2$: C, 72.20; H, 8.43; N, 3.66. Found C, 72.35; H, 8.29; N, 3.74. $[\alpha]_D^{24.0°C}$-7.81 (*c* 1.6, CH_2Cl_2).

(vii) Compound **13** (196 mg, 0.256 mmol) was dissolved in THF (15 mL) under an argon atmosphere. BH_3·THF complex (2 mL, 2 mmol) was added dropwise and the mixture was refluxed 48 h. After cooling, ethyl acetate (100 mL) and water (50 mL) were added and the phases were separated. The aqueous phase was extracted with methylene chloride (2 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. The residue was purified by flash-chromatography, eluting with 30 % ether-pentane to give the diamine (130 mg, 69%) as an oil. R_f (EtOAc-hexane, 1:3) 0.43. ^{1}H-NMR ($CDCl_3$) 7.39-7.08 (20 H, m), 3.78 (2 H, ddd, J=7.5), 2.89 (7 H, m) 2.72 (7 H, m), 2.02 (2 H, bs), 0.80 (18 H, s), -0.20 (6 H , s), -0.55 (6 H, s). ^{13}C-NMR ($CDCl_3$) 139.9 139.5, 129.7, 129.1, 128.4, 128.1, 126.2, 125.9, 75.14, 64.8, 48.9, 38.1, 37.5, 25.9, 17.9, -4.8, -5.6. IR: υ_{max}(liquid film)/cm^{-1} 3304, 3062, 3026, 2928, 2855, 1654, 1603, 1496, 1456, 1361, 1252. $C_{46}H_{68}N_2O_2Si_2$: C, 74.94; H, 9.30; N, 3.80. Found C, 74.76; H, 9.45; N, 3.94. $[\alpha]_D^{24.0°C}$ +26.4 (*c* 1.15, CH_2Cl_2).

(viii) The diamine from above (2.77 g, 3.76 mmol) was dissolved in dry THF (10 mL) under argon atmosphere. Tetrabutylammonium fluoride (18.0 mL, 18.8 mmol, 1 M solution in THF) was added and the solution was stirred at room temperature for 36 h. The solvents were removed *in vacuo* and the residue was partitioned between methylene chloride (50 mL) and water (20 mL) The phases were separated and the aqueous phase was extracted with methylene chloride (2 × 50 mL). The combined organics were dried over $MgSO_4$, filtered and the solvents removed *in vacuo*. The residue was purified by flash chromatography, eluting with 5%-10% methanol-EtOAc to give the desired diaminodiol (1.36 g, 72%) as crystals (mp 102.0-104.0°C). R_f (MeOH-EtOAc 1:9) 0.14. ^{1}H-NMR ($CDCl_3$) 7.39-7.11 (20 H, m), 3.85 (2H, ddd, J=2.5, J=5.0), 2.98-2.56 (12 H, m), 2.42 (6 H, m). ^{13}C-NMR ($CDCl_3$)138.9, 138.7, 129.1, 129.0, 128.5, 128.4, 126.4, 126.2, 71.5, 62.3, 46.9, 38.6, 34.8. IR: υ_{max}(liquid film)/cm^{-1} 3384, 3061, 3026, 2927, 1602, 1495, 1454, 1078, 1046. $C_{34}H_{40}N_2O_2$: C, 80.28; H, 7.93; N, 5.51. Found C, 80.42; H, 8.11; N, 5.67. $[\alpha]_D^{25.0°C}$-6.64 (*c* 1.24, CH_2Cl_2).

(ix) The diaminodiol from above (1.36 g, 2.67 mmol) and triphenylphosphine (2.10 g, 8.01 mmol) were dissolved in THF (50 mL) under an argon atmosphere. DEAD (1.26 mL, 8.01 mmol) was added dropwise to the solution. The mixture was stirred at room temperature for 12 h and precipitation of triphenylphosphine oxide was observed. Solvents were removed *in vacuo* and the residue was purified by flash chromatography, first eluting 50% EtOAc-Hexane followed by 10% methanol-EtOAc. The purification was repeated in order to remove all traces of phosphine oxide to **2** (0.85 g, 67%) as crystals (mp 57.5°C-58.5°C). R_f (MeOH-EtOAc 1:9)=0.30. ^{1}H-NMR ($CDCl_3$): 7.35-7.11 (20 H, m), 2.97-2.72 (6 H, m), 2.59 (2 H, dd, J = 8, J=26), 2.53 (2 H, dd, J = 8.0, J = 26.0), 2.15 (2 H, ddd, J=4.0, J=6.0, J=9.0), 1.92 (2 H, m), 1.40 (2 H, m). ^{13}C-NMR ($CDCl_3$): 139.7, 139.4, 131.9, 128.7, 128.4, 128.3, 126.1, 52.9, 47.9, 43.8, 39.6, 32.1. IR: υ_{max}(liquid film)/cm^{-1} 3885, 3061, 3027, 2922, 2854, 1603, 1495, 1454, 1119, 1073, 1029, 910. $C_{34}H_{36}N_2$: C, 86.40; H, 7.68; N, 5.93. Found C, 86.46; H, 7.72; N, 5.82. $[\alpha]_D^{25.0°C}$+10.9 (*c* 1.27, CH_2Cl_2).

Ligand 3

(i) 1,4-benzyloxy-*2S,3S*-butyloxirane (1.42 g, 5.00 mmol) and ethylenediamine (160 μL, 2.5 mmol) were mixed and refluxed during 3 days under an argon atmosphere. The reaction mixture was partitioned between ether (50 mL) and water (50 mL). The aqueous phase was extracted with ether (2 × 50 mL) and the combined organic phases were dried over $MgSO_4$ and the solvents removed *in vacuo*. The crude product was purified by flash chromatography, eluting with 0-50% methanol-ether to give **14** (850 mg, 45%) as an oil and recovered starting material (100 mg, 7 %). R_f (methanol-methylene chloride, 1:1) 0.45. ^{1}H-NMR ($CDCl_3$): 7.40-7.23 (20 H, m), 4.49 (4 H, AB, J_{AB}=12.0), 4.491 (4 H, AB, J_{AB}=11.0), 4.00 (2 H, app. q, J=4.8), 3.69 (2 H, bs), 3.60 (4 H, d, J=5.2), 3.57 (2 H, dd, J=10.0, J=5.2), 3.52 (2 H, dd, J=10.0, J=5.2), 2.94 (2 H, app. q, J=5.2), 2.81 (4 H, AA'BB'). ^{13}C-NMR: 137.81, 137.6, 128.23, 128.19, 127.76, 127.57, 127.49, 73.15, 71.32, 69.09, 68.47, 58.94, 46.15. IR: υ_{max}(liquid film)/cm^{-1}: 3331, 3087, 3063, 3030, 2861, 1496, 1454. FABMS calcd. for $C_{38}H_{49}N_2O_6$([M+H]$^+$): 629.3591. Found: 629.3611. $[\alpha]_D^{27.5°C}$ -42.9 (*c* 1.05, CH_2Cl_2).

(ii) Compound **14** (0.81g, 1.23 mmol) was dissolved in THF (15 mL) and put under an argon atmosphere. Triphenylphosphine (0.81 g, 3.07 mmol) was added followed by diethyl azodicarboxylate (0.40 mL, 2.56 mmol). The reaction mixture was stirred for 24 h followed by evaporation *in vacuo*. The product was purified by a filtration through silica using ether followed by methanol for elution. The methanol solution was collected and the solvents were removed *in vacuo*. The residue was purified by flash chromatography eluting 20:1 EtOAc-methanol to give 1,2-*bis*-2*R*,3*R*-[(bensyloxymethyl)aziridinyl]ethane **3** (340 mg, 45%) as an oil. R_f (EtOAc-Methanol, 20:1) 0.57. ^{1}H-NMR($CDCl_3$): 7.40-7.20 (20 H, m), 4.52 (4 H, AB, J_{AB}=12.0), 4.51 (4 H, app. s), 3.75 (2 H, dd, J=11.0, J=4.0), 3.62 (2 H, dd, J=11.0, J=8.0), 3.46 (4 H, m), 3.0 (2 H, AA´of AA´BB´), 2.65 (2 H, BB´of AA´BB´), 2.20 (2 H, m), 1.74 (2 H, m). ^{13}C-NMR:166.45, 129.59, 128.32, 127.60, 72.93, 72.79, 72.23, 66.16, 51.94, 42.21, 39.54. IR: υ_{max}(liquid film)/cm^{-1}: 3029, 2856, 1718, 1654, 1496, 1453. Anal. Calcd. for $C_{38}H_{44}N_2O_2$: C, 77.00; H, 7.48; N, 4.73. Found: C, 77.12; H, 7.27; N, 4.65. $[\alpha]_D^{21.5°C}$ +7.55 (*c* 1.1, CH_2Cl_2).

Addition of lithium reagents to imines

*Typical procedure for the addition of butyllithium to imine **6a** using chiral bis(aziridine) ligands (Table 1, entries 3-7; Table 2, entry 2; Tables 3, 4 and 5.)*

To a solution of *N*-phenylmethylene-4-methoxybenzeneamine **6a** (20 mg, 0.090 mmol) and ligand (**1**) (78 mg, 0.180 mmol) in 3.5 mL toluene at -78°C under an argon atmosphere, was added butyllithium (0.06 mL, 0.090 mmol, 1.5 M solution in hexane). The reaction was quenched by addition of methanol at -78°C after 60 min. The solvents were removed *in vacuo* and the residue was purified by flash-chromatography, eluting with 0-25% ethyl acetate-hexane to give *N*-(4-methoxyphenyl)-α-butylbenzenemethaneamine. The enantiomeric excess was determined by chiral HPLC using a Chiracel OD-H column (10% isopropyl alcohol in hexane gave baseline separation, major isomer 11.4 min. and minor isomer after 10.5 min.). The absolute configuration was determined by comparing both the optical rotation and the retention times on the chiral column to literature values [6]. The physical and spectral data were in accord with those reported [7]. For yields and enantioselectivity, see Tables 1-5.

*Addition of methyl lithium to imine **6a** in the presence of chiral bis(aziridine) ligand **1** (Table 1, entry 8)*

To a solution of *N*-phenylmethylene-4-methoxybenzeneamine **6a** (80 mg, 0.383 mmol) and **1** (159 mg, 0.383 mmol) in toluene (7.0 mL) at -78°C under an argon atmosphere, was added methyllithium (0.85 mL, 0.765 mmol, 0.9 M solution in ether) over 1h. The reaction, followed by TLC (15% ether/pentane), was quenched by addition of methanol at -78°C after 12 h. After reaching room temperature the reaction mixture was added to water (5 mL) and the layers were separated. The aqueous phase was extracted with ether (3 × 5 mL) and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. The residue was purified by flash chromatography, eluting with 5-15 % ether-pentane to give *N*-(4-methoxyphenyl)-α-methylbensenemethaneamine. The enantiomeric excess was determined by chiral HPLC using a Chiracel OD-H column (2% isopropyl alcohol in hexane gave baseline separation, major isomer 27.24 min. and minor isomer after 24.01 min.). The absolute configuration was determined by comparing both the optical rotation and the retention times on the chiral column to literature values [6]. The physical and spectral data were in accord with those reported (see supplementary material in ref. 6). For yields and enantioselectivity, see Tables 1 and 2.

*Addition of Phenyllithium to **6b** (Table 2, entry 3)*

To a solution of *N*-(p-methoxyphenylmethylene)-benzeneamine **6b** (40 mg, 0.189 mmol) and **1** (0.189 mmol) in THF (3.5 mL) at -78°C under an argon atmosphere was added phenyllithium (0.12 mL, 0.19 mmol, 1.6 M solution in cyclohexane/ether 70/30) over 60 minutes. The reaction was monitored by TLC (50% ethyl acetate/hexane). After 3h the reaction was quenched by addition of methanol at -78°C. Some silica gel was added to the reaction mixture and the solvents were removed *in vacuo* . The residue was immediately purified by flash chromatography, eluting with 25-50% EtOAc-hexane to give *N*-(2-methoxyphenyl)-α-phenylbenzenemethaneamine (42.8 mg, 78%) as an oil. The enantiomeric excess was determined by chiral HPLC using Chiracel OD-H Column (10% isopropyl alcohol in hexane as eluent gave baseline separation, and the two isomers had retention times 18.5 min and 14.1 min.) R_f (EtOAc-Hexane 1:9) 0.59.^{1}H-NMR ($CDCl_3$) 7.49-7.38 (4 H , m), 7.35 (2H, AA´of AA´BB´, J_{AB}=8.5), 7.21 (2 H, m), 6.95 (2 H, BB´of

AA'BB', J_{AB} = 8.5), 6.79 (1 H, app. t, J=7.0), 6.62 (2 H, app. d, J=7.5), 5.55 (1 H , s), 4.30 (1 H, bs), 3.90 (3 H, s). ^{13}C-NMR: 129.1, 128.7, 128.6, 127.3, 127.2, 117.6, 114.1, 113.4, 110.3, 108.8, 62.4, 55.2. IR: υ_{max}(liquid film)/cm^{-1} 3413, 3051, 3027, 2933, 2836, 2360, 1888, 1602, 1502, 1463, 1427, 1313, 1249, 1178. Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found C, 83.27; H, 6.70; N, 4.69. $[\alpha]_D^{21.5°C}$ +1.67 (*c* 0.3, CH_2Cl_2). No attempt was made to determine the absolute configuration of the major enantiomer.

Addition of vinyllithium to ***6a*** (Table 2, entry 4)

To a solution of *N*-phenylmethylene-4-methoxybenzeneamine **6a** (80 mg, 0.38mmol) and ligand **1** (151 mg, 0.38 mmol) in toluene (3.5 mL) at - 78°C under an argon atmosphere was added vinyllithium (0.44 mL, 0.76 mmol, 1.74 M solution in THF, freshly prepared from butyllithium and tetravinyltin) [12]. The reaction mixture was stirred for two hours followed by addition of methanol. Some silica was added to the reaction mixture and the solvents were removed *in vacuo*. The residue was purified by flash chromatography 0-25% ethyl acetate in hexane to give *N*-(p-methoxyphenyl)-α-ethenylbenzenemethaneamine (80 mg, 89%). The enantiomeric excess was determined by chiral HPLC using a Chiracel OD-H column to be 89% (10% isopropyl alcohol in hexane gave baseline separation, major isomer 13.76 min. and minor isomer after 11.72 min.). The data obtained were in accord with those reported (see supplementary material in ref. 13). No attempt was made to determine the absolute configuration of the major enantiomer.

Addition of butyllithium to ***8*** (Table 5, entry 2)

To a solution of *N*-phenylmethylene-2-methoxybenzeneamine **8** (40 mg, 0.18 mmol) and **1** (78 mg, 0.18 mmol) in toluene (3.5 mL) at -78°C under an argon atmosphere was added butyllithium (0.11 mL, 0.18 mmol, 1.58 M solution in hexane). The reaction mixture was stirred at -78°C for two hours followed by addition of methanol at that temperature. Some silica was added to the reaction mixture and the solvents were removed *in vacuo*. The residue was purified by flash chromatography, eluting with 0-15 % EtOAc-hexane to give *N*-(o-methoxyphenyl)-α-butylbenzenemethaneamine (20 mg, 42%) as an oil. The enantiomeric excess was determined by chiral HPLC to be 14% using a Chiracel OD-H

column (10% isopropyl alcohol in hexane gave baseline separation, major isomer 9.70 min. and minor isomer after 13.83 min.). R_f (EtOAc-hexane, 1:19) 0.41. ^{1}H-NMR($CDCl_3$): 7.44-7.22 (5 H, m), 6.83 (1 H, dd, J = 7.5, J= 1.5), 6.78 (1 H, dt, J = 7.5, J = 1.5), 6.65 (1 H, dt, J=7.5, J=1.5), 6.41 (1H, dd, J=8.0, J=1.5), 4.75 (1 H, bs), 4.35 (1 H, app. t, J = 6.5), 3.96 (3H, s), 1.90 (2 H, m), 1.42 (4 H, m), 0.96 (3 H, app. t, J = 7.0). ^{13}C-NMR($CDCl_3$): 146.55, 144.55, 137.35, 128.44, 126,37, 121.11, 116.08, 110.80, 109.18, 58.07, 55.44, 38.79, 28.54, 13.99. IR: υ_{max}(liquid film)/cm^{-1} 3430, 3062, 2932, 2858, 2364, 1603, 1512, 1454, 1427, 1242, 1222, 1176, 1030. Anal. Calcd. for $C_{18}H_{23}NO$ C, 80.26; H, 8.61; N, 5.20. Found C, 80.09; H, 8.63; N, 5.21. $[\alpha]_D^{21.5°C}$ + 6.56 (*c* 0.51, CH_2Cl_2). No attempt was made to determine the absolute configuration of the major enantiomer.

Addition of butyllithium to ***9*** (Table 5, entry 3)

To a solution of **9** (50 mg, 0.24 mmol) and **1** (102 mg, 0.24 mmol) under an argon atmosphere at -78°C in toluene (3.5 mL) was added butyllithium (0.16 mL, 0.24 mmol, 1.53 M in hexane). The reaction mixture was stirred for 2 h followed by addition of methanol at -78°C. The solvents were removed *in vacuo* and the crude product was purified by flashchromatography, eluting 0-25% EtOAc-hexane to give *N*-(4-methoxyphenyl)-α-butyl-*trans*-2-(2-pentenyl)-methaneamine (18 mg, 39%) as an oil. The enantiomeric excess was determined to be 10% by chiral HPLC using a Chiracel OD-H column (5 % isopropyl alcohol in hexane gave baseline separation, major isomer 7.97 min. and minor isomer after 7.47 min.). R_f (EtOAc-hexane, 1:19) 0.28.^{1}H-NMR ($CDCl_3$): 6.74 (2 H, AA´of AA´BB´, J_{AB}=8.5), 6.55 (2 H, BB´ of AA´BB´, J_{AB}=8.5), 5.40 (1 H, bt, J=7.0), 3.74(3 H, s), 3.58(1H, t, J=7.0), 3.40 (1 H, bs), 2.04 (2 H, app. q, J=7.5), 1.55 (2 H, m), 1.51 (3 H, s), 1.34 (4 H, m), 0.94 (3 H, t, J=7.5), 0.92 (3 H, t, J=6.8). ^{13}C-NMR ($CDCl_3$): 151.56, 142.13, 134.48, 128.94, 114.57, 114.43, 62.02, 55.76, 34.23, 28.61, 22.59, 20.95, 14.18, 14.06, 11.15. IR: υ_{max}(liquid film)/cm^{-1} 3403, 2959, 2932, 2871, 1512, 1244, 1237, 1038, 819. Anal. Calcd. for $C_{17}H_{27}NO$ C, 78.11; H, 10.41; N, 5.36. Found C, 78.38; H, 10.31; N, 5.41. $[\alpha]_D^{21.5°C}$ -0.17 (*c* 0.71, CH_2Cl_2). No attempt was made to determine the absolute configuration of the major enantiomer.

*Addition of vinyllithium to 8-methoxy-3,4-dihydroisoquinoline using bis(aziridine) ligand **1** to give 1-vinyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline.*

To a solution of 8-methoxy-3,4-dihydroisoquinoline (50 mg, 0.31 mmol) and **1** (258 mg, 0.62 mmol) in toluene (3.5 mL) under an argon atmosphere at -78°C was added vinyllithium (0.78 mL, 0.62 mmol, 0.8 M in THF, freshly prepared from butyllithium and tetravinyltin) [12]. The reaction mixture was stirred for 2 h followed by addition of methanol at -78°C. The solvents were removed *in vacuo* and the crude product was purified by flash-chromatography eluting 5:95 MeOH-CH_2Cl_2 to give of 1-vinyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (47 mg, 81 %) as crystals (mp 59.5-60.5°C). The enantiomeric excess was determined to be 20 % by chiral HPLC using a Chiracel OD-H column (5 % isopropyl alcohol in hexane gave baseline separation, major isomer 16.5 min. and minor isomer after 18.3 min.). R_f(1:9 MeOH/CH_2Cl_2) 0.11. ^{1}H-NMR ($CDCl_3$): 7.00 (1H, d, 8.5), 6.71 (dd, 1H, J=8.5, J=2.5), 6.63 (1 H, d, J=2.5), 5.92 (1 H, m), 5.25 (1 H, m), 5.20 (1 H, app. d, J=0.8), 4.42 (1 H, bd, J=7.5), 3.78 (3 H, s), 3.25 (1H, AA' of AA'BB', J_{AB}=12), 3.02 (1H, m), 2.96-2.66 (2H, m), 2.16 (bs, 1 H). ^{13}C-NMR ($CDCl_3$): 158.0, 140.58, 136.1, 128.9, 128.4, 116.97, 113.6, 112.0, 59.8, 55.2, 41.5, 29.9. IR: υ_{max}(liquid film)/cm^{-1} 3413, 3051, 2836, 2360, 1602, 1502, 1313, 1249, 1032, 736. FABMS calcd. for $C_{12}H_{16}NO$([M+H]$^+$): 190.1232. Found: 190.1232. $[\alpha]_D^{22.5°C}$ -21.11 (*c* 0.94, CH_2Cl_2). No attempt was made to determine the absolute configuration of the major enantiomer.

Deuterium labeling experiments.

To a solution of **1** (156.8 mg, 0.378 mmol) and **6a** (80 mg, 0.378 mmol) in toluene (7 mL) at -78°C under an argon atmosphere was added methyllithium (0.29 mL, 0.378 mmol, 1.3M in diethyl ether). The mixture was stirred at -78°C for 20 minutes followed by addition of deuterated methyl lithium (0.76 mL, 0.378 mmol, 0.5 M in diethylether). After 1 h the reaction mixture was quenched by addition of methanol. Some silica was added to the reaction mixture and the solvents were removed *in vacuo*. The residue was purified by flash chromatography, eluting with 0-15% ether-pentane to give 19 mg (22%) as a mixture of the two products. The ratio between the undeuterated and deuterated products was determined to be (30:70), by comparison of the ^{1}H-NMR integrals for the methyl and methoxy groups. The

physical and spectral data were in accord with those reported (see supplementary material in ref. 6).

The above experiment was repeated, with inverse order of addition of the organolithium reagents. The ratio of undeuterated and deuterated products was determined to be (70:30).

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