

## Enantioselective Alkylation of *N*-(Trimethylsilyl)benzaldehyde Imine

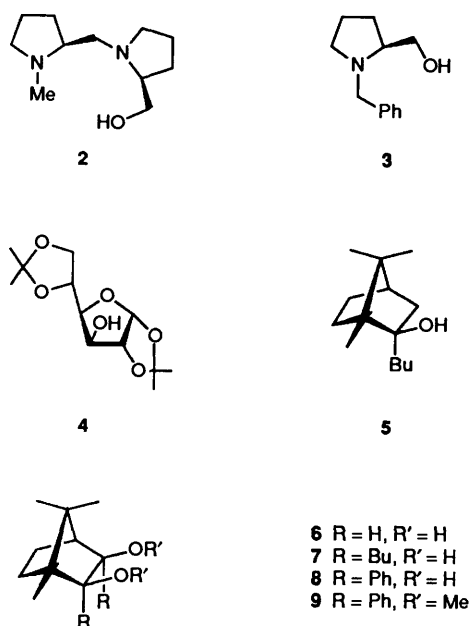
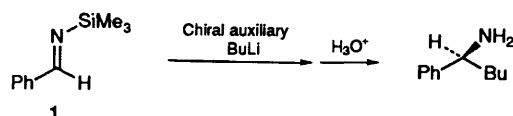
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*N*-(Trimethylsilyl)benzaldehyde imine was alkylated with chirally modified organometallic reagents to give optically active primary amines in moderate to good yields with an enantiomeric excess (e.e.) of up to 62%.

Although there is a wealth of literature on stereoselective addition of organometallic reagents to aldehydes or ketones,<sup>1</sup> no example of enantioselective addition to C=N double bonds has been reported. Further, a few examples of diastereoselective addition of organometallic reagents to chiral imine derivatives have been reported<sup>2</sup> although silylimines have been shown to afford primary amines in such reactions;<sup>3</sup> the stereochemical consequences of the latter were not, however, investigated. As part of a synthetic programme we have studied the addition of organometallic reagents such as butyllithium and a Grignard reagent to *N*-(trimethylsilyl)benzaldehyde imine in the presence of chiral modifiers such as chiral alcohols, diols and amino alcohols.

*N*-(Trimethylsilyl)benzaldehyde imine **1**, prepared according to the method of Hart,<sup>3</sup> and the organometallic reagent reacted in the presence of a chiral auxiliary to afford the enantiomerically pure primary amine after aqueous work-up (see Scheme 1); Table 1 shows the enantioselectivities of the amines



Scheme 1

obtained in these reactions. These results show that *N*-(trimethylsilyl)benzaldehyde imine **1** is alkylated asymmetrically in the presence of a chiral modifier to afford an enantiomerically pure primary amine, to our knowledge, the first time that

**Table 1** Enantioselective alkylation of *N*-(trimethylsilyl)benzaldehyde imine with butyllithium in the presence of chiral modifier

Run	Chiral modifier	Solvent	Amine obtained		
			Yield <sup>a</sup> (%)	E.e. <sup>b</sup> (%)	Config'n.
1 <sup>c</sup>	<b>2</b>	THF	27	4.0	<i>R</i>
2 <sup>c</sup>	<b>3</b>	THF	35	14	<i>S</i>
3 <sup>c</sup>	<b>4</b>	Hexane	41	11	<i>R</i>
4 <sup>c</sup>	<b>5</b>	Hexane	62	4.9	<i>R</i>
5 <sup>d</sup>	<b>6</b>	Hexane	74	2.9	<i>R</i>
6 <sup>d</sup>	<b>7</b>	Hexane	75	25	<i>R</i>
7 <sup>d</sup>	<b>7</b>	Ether	74	12	<i>S</i>
8 <sup>d</sup>	<b>8</b>	Hexane	63	9.1	<i>R</i>
9 <sup>d</sup>	<b>8</b>	Ether	76	62	<i>S</i>
10 <sup>e</sup>	<b>8</b>	Ether	78	44	<i>S</i>
11 <sup>d,g</sup>	<b>8</b>	Ether	32	11	<i>S</i>
12 <sup>d</sup>	<b>8</b>	Toluene	64	7.2	<i>S</i>
13 <sup>d</sup>	<b>8</b>	Diisopropyl ether	90	8.0	<i>S</i>
14 <sup>f</sup>	<b>9</b>	Ether	64	0.6	<i>R</i>

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by comparison of maximum rotation reported in the literature.<sup>10</sup> <sup>c</sup> [chiral modifier]:[BuLi]:[silyl imine] = 1:2:0.5. <sup>d</sup> [chiral modifier]:[BuLi]:[silyl imine] = 2:5:0.5. <sup>e</sup> [chiral modifier]:[BuLi]:[silyl imine] = 1:3:0.5. <sup>f</sup> [chiral modifier]:[BuLi]:[silyl imine] = 2:1:0.5. <sup>g</sup> BuMgBr was used as alkylating agent.

enantioselective alkylation of an imine has been reported to give an enantiomerically pure primary amine.

Although optically active amino alcohols such as **2**<sup>4</sup> or **3**<sup>5</sup> have been reported as effective chiral auxiliaries for asymmetric alkylation of aldehydes, they gave only poor enantioselectivities in the asymmetric alkylation of the silyl imine, isolation of the enantiomerically pure product from the reaction mixture proving difficult. The chiral alcohols **4**<sup>6</sup> and **5**<sup>7</sup> and the diols **6**,<sup>8</sup> **7**<sup>7</sup> and **8**<sup>7</sup> proved to be superior chiral modifiers for the enantioselective alkylations since the ease of their separation from the reaction mixture allowed their re-use and resulted in a higher isolated yield of amine. The chiral auxiliaries used were easily prepared according to literature procedures,<sup>4-8</sup> and of them the chiral diol **8** gave the best result (62% e.e.). Butyllithium afforded both a higher yield and greater selectivity compared with the corresponding Grignard reagent (run 11). Although diethylzinc has proved effective as an alkylating agent for aldehydes,<sup>9</sup> the silyl imine failed to react in its presence with amino alcohols or diols. A remarkable solvent effect was also observed when **8** was used for the addition of butyllithium to **1**. It should be noted that the absolute configuration of the amine obtained in the addition of butyllithium depends on the solvent employed. Since the result obtained using dimethyl ether **9** gave racemic amine (run 14), it is apparent that the hydroxy group of chiral diols plays an important role in this reaction. Chiral lithium alkoxide prepared from the diol **8** and butyllithium could act as a chiral modifier of butyllithium during enantioselective addition (see Fig. 1), two equivalents of the chiral alkoxides interacting with the Li cation of butyllithium.

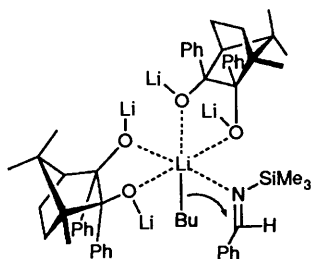


Fig. 1 Proposed transition state of alkylation of the silyl imine

An equimolar amount of the chiral alkoxide lowered the enantioselectivity of the amine produced (run 10).

Further extension of this methodology to the synthesis of other primary amines in optically active form is under way.

### Experimental

**Typical Procedure for the Enantioselective Alkylation of the Silyl Imine 1.**—To a mixture of the diol **8** (3.22 g, 10 mmol) in dry ether (30 ml) at 0 °C under dry nitrogen was added a hexane solution of butyllithium (1.5 mol dm<sup>-3</sup>; 20 ml). After the mixture had been stirred for 1 h at the same temperature, it was evaporated to dryness and the resulting white powder was suspended in dry ether (40 ml). An ethereal solution of *N*-(trimethylsilyl)benzaldehyde imine (0.89 g, 5 mmol) was added dropwise to the above suspension of chiral alkylating agent at -78 °C and stirred for 5 h at the same temperature; it was then quenched by dropwise addition of water and 1 mol dm<sup>-3</sup> HCl. The aqueous layer was separated, neutralized with NH<sub>4</sub>OH and extracted with ether. Work-up of the latter gave an oily residue which upon bulb-to-bulb distillation afforded 1-phenylpentylamine {(0.62 g), 76%; [ $\alpha$ ]<sub>D</sub> -10.4

(neat)} of 62% e.e. based on comparison with the maximum rotation.<sup>10</sup>

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