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Asymmetric Addition of Davies's Chiral Lithium Amide to Prochiral Vinyl Phosphine Oxides

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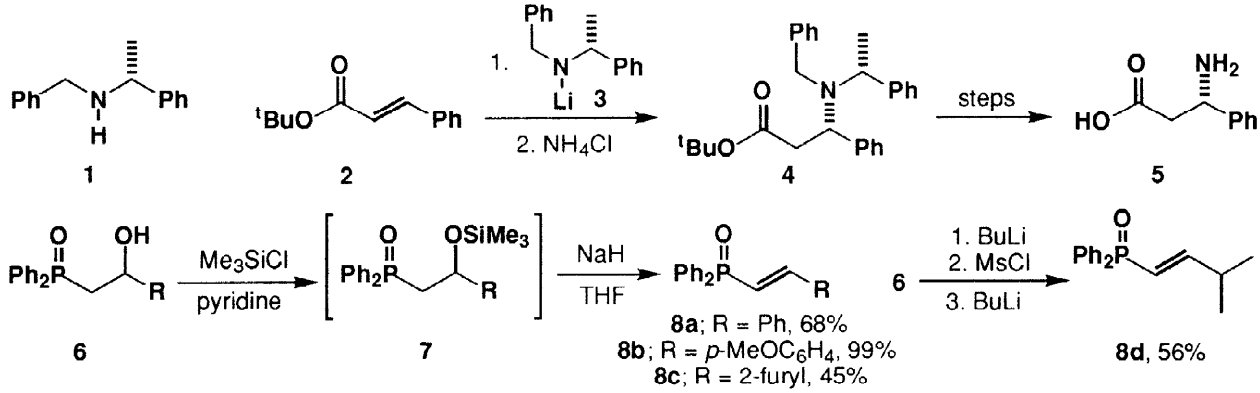
Abstract: Lithium *N*-benzyl-α-methylbenzylamide adds to prochiral vinyl phosphine oxides in the presence of trimethylsilyl chloride to provide, after protodesilylation, β-amino phosphine oxides as single diastereoisomers. A mechanism which explains the rôle of trimethylsilyl chloride is proposed.

Recently, Davies has introduced (*R*)-benzyl(α-methylbenzyl)amine **1** as a chiral ammonia equivalent for conjugate addition reactions.[1] Nucleophilic addition of the lithium amide **3** to α,β-unsaturated esters such as **2** is generally highly diastereoselective, providing high yields of β-amino esters (e.g. **4**) which are valuable intermediates in the synthesis of β-amino acids[2-4] and β-lactams.[4-5] The addition reaction is the key step in syntheses of the taxol side chain,[3] various carbapenem derivatives,[5] pumiliotoxin C[6] and the amino sugar daunosaminide.[7]

In its current form, the reaction is limited to α,β-unsaturated Weinreb amides[8] (which are easily transformed into aldehydes and ketones) and α,β-unsaturated esters.[1] For example, no addition products were isolated when the lithium amide **3** was added to even non-enolisable ketones such as chalcone.[8] Other workers have, however, added another chiral nitrogen nucleophile (the dianion of a norephedrine derivative) to vinyl sulfones[9] and a chiral enolate equivalent to vinyl phosphonates.[10] In this paper, we describe a method which allows the lithium amide **3** to be added to vinyl phosphine oxides.



β-Hydroxy phosphine oxides **6** were activated as silyl ethers[11] **7** or as mesylates[12] and eliminated under basic conditions. In each case, we obtained the vinyl phosphine oxides **8** as pure *E* isomers. We started our investigation by treating vinyl phosphine oxide **8a** with 1.2 equivalents of metallated amine[13] **1** (M = Li or MgBr) but we could recover only the starting materials in *ca.* 90% yield. At this stage of the study, we were concerned that lithiation α to phosphorus was a competing side-reaction and so we decided to protect **8a** as an α-silyl vinyl phosphine oxide. To this end, vinyl phosphine oxide **8a** was treated with LDA

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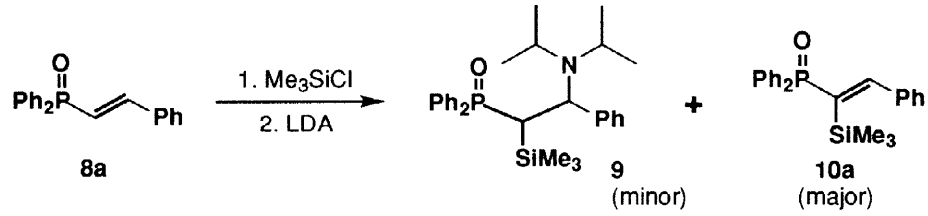
in the presence of trimethylsilyl chloride[14] providing β-amino phosphine oxide **9** as well as the required α-silyl phosphine oxide **10a**. This result was extremely encouraging because it suggested that the required nucleophilic addition might be possible if LDA was replaced by the lithium amide **3**.



Treatment of the vinyl phosphine oxides **8a-c** with the chiral lithium amide **3** in the presence of trimethylsilyl chloride provided mixtures of α-silyl phosphine oxides **11** (as single diastereoisomers) and α-silyl vinyl phosphine oxides **10**. Protodesilylation of **11** was most conveniently achieved by reacting the crude reaction mixture with TBAF in THF.[15] In this way, we were able to obtain moderate to good yields of β-amino phosphine oxides **12** as single diastereoisomers.[16] We do not know the sense of asymmetric induction: the stereochemistry is as drawn by analogy with similar reactions of α,β-unsaturated esters.[1] The reaction appears to be limited to aryl-substituted phosphine oxides (e.g. **8a-c**; entries 1-3, Table): **8d** (R = ^{i}Pr; entry 4) was recovered unchanged after being subjected to the same reaction conditions.

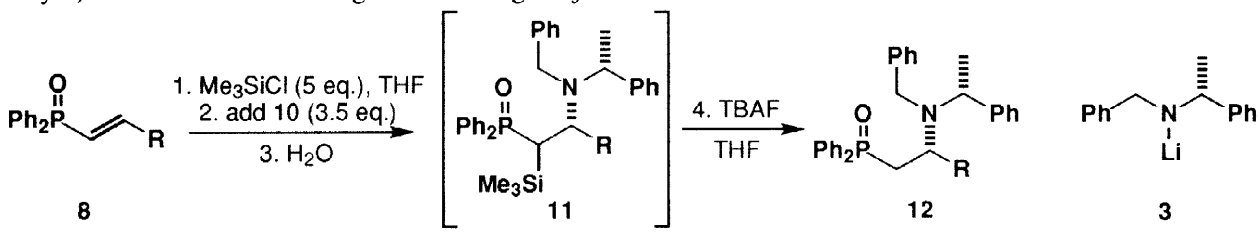


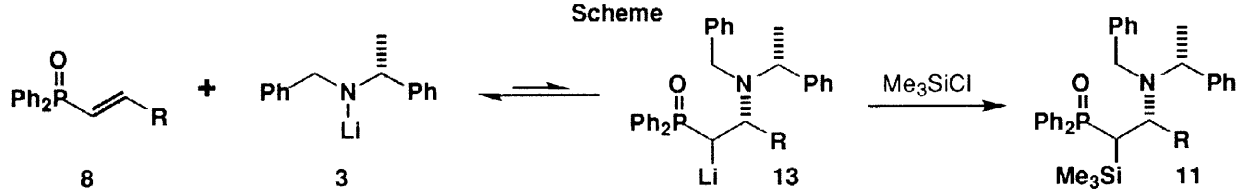
Table: Additions of lithium amide **3** to prochiral vinyl phosphine oxides **8**

Entry	starting material	R	Yield[a] (%)	diastereomeric ratio[b]
1	**8a**	Ph	65	98:2
2	**8b**	*p*-MeOC$_6$H$_4$	76	>99:1
3	**8c**	2-furyl	34	>99:1
4	**8d**	^{i}Pr	0[c]	–

[a]Yield of purified amine. [b]By ^{1}H NMR. [c]**8d** was recovered.

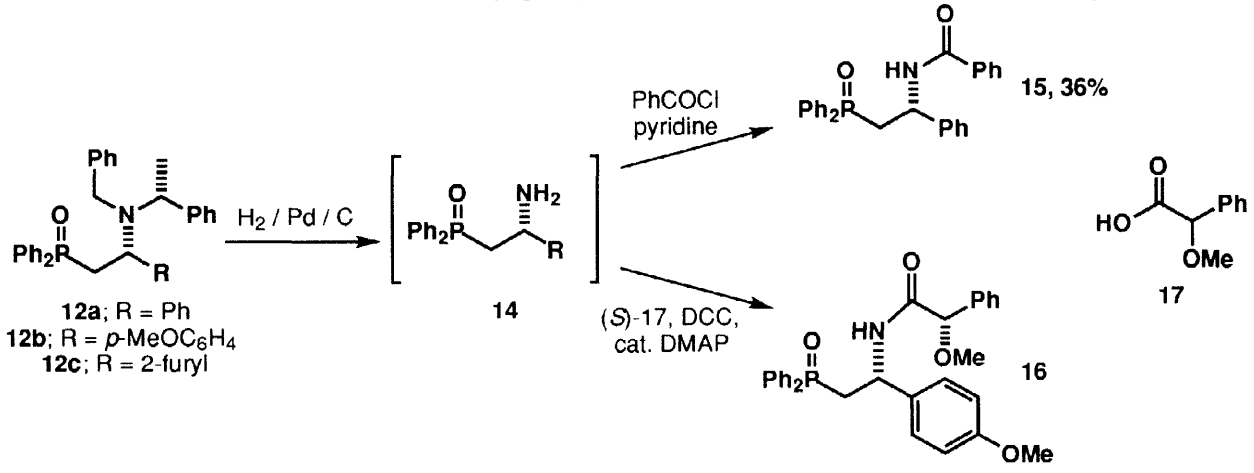
The rôle of trimethylsilyl chloride in our addition reaction (**8** → **12**) is remarkable and difficult to determine. We have suggested that trimethylsilyl chloride might simply react with α-lithiated vinyl phosphine oxides produced during the reaction to give α-silyl phosphine oxides **10**. Addition of lithium amide **3** to phosphine oxides **10** would then give the observed products, **12**. This proposal can now be dismissed because the α-silyl phosphine oxide **10a** was completely inert to our usual reaction conditions.

Scheme



Another possibility is that trimethylsilyl chloride traps out lithium derivative **13** from the equilibrium shown in the Scheme.[17] We have shown that this equilibrium lies towards the starting materials since lithiated phosphine oxide **13b** (R = *p*-MeOC$_6$H$_4$), generated by treating **12b** with butyl lithium at –10 °C,

decomposed to give the vinyl phosphine oxide **8b** and amine **1**.[18] This proposal also explains why the lithium amide **3** does not react with the vinyl phosphine oxides **8** in the absence of trimethylsilyl chloride.



The benzyl groups were removed from the β-amino phosphine oxide **12a** (R = Ph) hydrogenolytically (without cleavage of the new carbon-nitrogen bond[19]) to give the amine **14a** which was characterised as the benzamide **15**. Similar (racemic) benzamides are key intermediates in the synthesis of allylic amides.[20] The amine **14b** (R = *p*-$MeOC_6H_4$, synthesised by hydrogenolysis of **12b**) was shown to have >98% ee by comparing the 500 MHz ^1H NMR spectrum of the amide **16** with those of the diastereomeric amides obtained when amine **14b** was coupled[21] with racemic *O*-methyl mandelic acid **17**.[22]

In summary, the lithium derivative (**3**) of (*R*)-benzyl(α-methylbenzyl)amine **1** adds highly diastereoselectively to prochiral phosphine oxides provided that the reaction is performed in the presence of trimethylsilyl chloride. This solution may be useful with other electrophiles which do not react with lithium amide **3**.[8] The products of the reaction, β-amino phosphine oxides[24] **12**, are potential precursors of optically active allylic amides,[20] ligands for asymmetric catalysis[25] and chiral auxiliaries.[26]

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15. Attempted purification of the crude reaction mixture on silica gel led to desilylation of **11**, but the β-amino phosphine oxides **12** were not separable from the α-silyl phosphine oxides **10**.
16. Typical procedure: *n*-Butyllithium (2.5 cm^3 of a 1.4 $moldm^{-3}$ solution in hexanes, 3.5 mmol) was added dropwise to a stirred solution of amine **1** (738 mg, 3.5 mmol) in THF (6 cm^3) at 0 °C. The resulting red solution was stirred for 10 min, cooled to –78 °C and added dropwise by cannula to a stirred solution of the vinyl phosphine oxide **8** (1 mmol) and trimethylsilyl chloride (0.63 cm^3, 5.0 mmol) in THF (15 cm^3) at –78 °C. The reaction mixture was gradually warmed to room temperature over 17 hr, quenched with water (25 cm^3) and extracted with dichloromethane (3 × 25 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a crude product which was redissolved in THF (5 cm^3) and treated with TBAF (6.0 cm^3 of a 1.0 mol dm^{-3} solution in THF). The reaction was stirred for 1 hr, quenched with water (15 cm^3), extracted with dichloromethane (3 × 15 cm^3) and the combined organic extracts dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a crude product. Purification by flash chromatography, eluting with EtOAc–hexane (1:1) gave the β-amino phosphine oxides as colourless oils.
17. Lithium amides react slowly with trimethylsilyl chloride at –78 °C in THF: Lipschutz, B. H.; Wood, M. R.; Lindsley, C. W. *Tetrahedron Lett.*, **1995**, *36*, 4385-4388.
18. For another β-elimination of a β-amino organolithium compound, see: Barluenga, J.; Sanz, R.; Fañanás, F. J. *Tetrahedron Lett.*, **1997**, *38*, 2763-2766.
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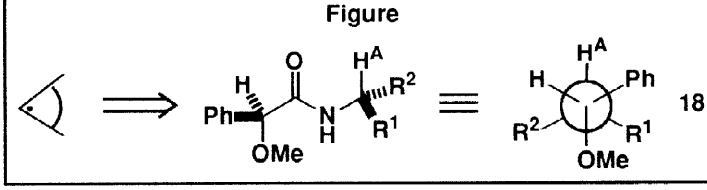
22. Trost has proposed that *O*-methyl mandelic amides generally populate the conformation in which the proton H^A more or less eclipses the carbonyl oxygen (which is omitted for clarity in the extended Newman projection in the Figure).[21] This means that the chemical shift of H^A is approximately the same for both diastereomeric amides **18** because the anisotropic effect of the phenyl ring is much the same in both compounds.[23] We had hoped to determine the sense of the asymmetric induction of our addition reaction (**8** → **12**) by comparing the ^1H NMR spectrum of amide **16** with that of its diastereoisomer but the conformations of these amides [$\delta(H^A)$ 5.02 and 5.24 ppm] are rather different to that proposed by Trost.[21] We suggest, therefore, that Trost's correlation[21] would have been unreliable with our compounds.

Figure



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23. Kreuger, C.; Trost, B. M. personal communication.
24. Satisfactory analytical data was obtained for all new compounds.
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