REGIO- AND STEREOSPECIFIC SYNTHESIS OF ALLYLIC TERTIARY AMINES

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E and Z allylic amines have been synthesised by stereospecific elimination of  $Ph_2PO_2^-$  from pure diastereoisomers (3) and (4).

A good synthesis of allyl amines should control both the position and the geometry of the double bond. In the displacement of allylic halides by amines,<sup>1</sup> the position of the double bond may change by allylic rearrangement<sup>2</sup> before,<sup>3</sup> during,<sup>4</sup> or even in some cases after<sup>5</sup> the reaction. Regiochemical control has been effected in a number of ways, e.g. by [3,3] sigmatropic rearrangements of thiocyanates<sup>6</sup> or trichloroimidates,<sup>7</sup> by vinyl cuprate addition to Mannich equivalents,<sup>8</sup> or by Wittig reactions.<sup>9</sup> Stereochemical control is more difficult. Both the cuprate<sup>8</sup> and Wittig<sup>9</sup> routes give *cis* double bonds and both have been modified (by the use of vinyl alanates<sup>8</sup> or by varying the conditions of the Wittig reaction<sup>10</sup>) to favour the *trans* isomer. The Wittig route always gives some of the unwanted isomer and separation is often difficult.

We have used the Horner modification of the Wittig reaction to synthesise single isomers of alkenes,<sup>11</sup> dienes,<sup>12</sup> and vinyl ethers<sup>13</sup> without separation from the other geometrical isomer. Using diphenylphosphinoyl ( $Ph_2PO$ ) as the anion-stabilising group and lithium as the counter-ion allows the isolation of alcohols (1). Separation of the diastereoisomers followed by stereospecific

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syn elimination of  $Ph_2PO_2^-$  gives, separately, both the <u>Z</u> and the <u>E</u> alkene.



The successful application of this method to the synthesis of alkyl amines demanded that the anion from (2) did not eliminate amide ion. In fact the starting materials (2) can be made by the formal reverse of this reaction - the Michael addition<sup>14</sup> of a secondary amine to vinyldiphenylphosphine oxide.<sup>15</sup> The anion of (2) could be made at  $0^{\circ}$ C with BuLi in THF without loss of amine (even weakly basic morpholine) and added cleanly to aldehydes and ketones. The adducts (3) and (4) were separated from starting materials by flash<sup>16</sup> or column chromatography and the combined yields were good even with enolisable ketones (entries 1, 6, 7 and 9, table).





In the cases where  $R^1 \neq R^2$ , the diastereoisomers (3) and (4) were separated by chromatography or fractional crystallisation, or in one case by t-butyldimethylsilyl ether<sup>17</sup> formation, chromatography, and desilylation. Recrystallisation gave pure<sup>18</sup> (3) or (4) with no detectable trace of the other isomer. Completion of the Horner-Wittig reaction (NaH, DMF, 30°C) gave allyl amines (5) and (6) in high yield. These were isolated as their crystalline HCl salts and shown to be single geometrical isomers by IR and NMR.

## Table

Entry	$R_2$	$R^1$	$R^2$	Yield	Ratio (3) · (4)	Separation Method*	Yield (5) (6)	
							(-)	(-)
1	(CH <sub>2</sub> ) <sub>5</sub>	CH <sub>3</sub>	CH3	75	-	-	72	
2	20	CH3	н	69	51 : 49	А	74	81
3		Ph	н	$80^{a}$	52 : 48	В	72	86
4		i-Pr	CH3	36 <sup>a,b</sup>	20 : 80	С	86	91
5	$-(CH_2)_5^2$			77	-	-	71	
6	(CH <sub>2</sub> ) <sub>4</sub>	CH3	CH3	70	-	-	76	
7	23 -1	n-Pr	CH3	63 <sup>a</sup>	28 : 72	С	88	87
8	-(CH <sub>2</sub> ) <sub>5</sub> -			70	-	-	80, <sup>C</sup> 85	
9	(CH <sub>2</sub> ) <sub>2</sub> 0	CH3	CH3	65	-	-	9	0
10	4 4	CH3	н	$75^{a}$	50 : 50	В	71	78
11		Ph	Н	$77^{a}$	66 : 34	D	68	71
12	-( <sup>CH</sup> 2) <sub>5</sub> -			68			81	

a. Reaction in THF with LiBr; rest in  $\text{Et}_2\text{O}$  with LiBr.

- b. When the reaction was performed at  $-30^{\circ}$ C in THF, a yield of 46% and a 25:75 ratio of (3) : (4) was observed.
- c. Elimination with DBN ( $CH_2Cl_2$  under reflux)
- <u>Separation Methods</u>: A, HPLC (EtOAc, 85%; Et<sub>3</sub>N, 3%; light petroleum, b.p.
   60 80<sup>o</sup>C, 12%), B, Fractional Crystallisation (EtOAc), C, Column
   Chromatography (SiO<sub>2</sub>, EtOAc, 85%; Et<sub>3</sub>N, 3%; light petroleum, b.p. 60 80<sup>o</sup>C, 12%), D, 1. t-BuMe<sub>2</sub>SiCl, 2. preparative TLC, 3. n-Bu<sub>4</sub>NF, THF; see ref. 17.

The aldehyde adducts (3) and (4) are formed in rougly equal amounts (entries 2, 3, 10 and 11, table) in contrast to the alkene synthesis<sup>11</sup> where erythro selectivity is usually high. Stereoselectivity is higher for the ketone adducts (entries 4 and 7) and favours the threo isomer. The reaction is always regio-specific even when the double bond is exocyclic to a six-membered ring (entries 5, 7, and 11).

The table gives a range<sup>18</sup> of amines all containing piperidine, pyrrolidine, or morpholine. Electrophiles include aliphatic and aromatic aldehydes, cyclic and acyclic ketones. Yields of products from symmetrical ketones are high (entries 1, 6, 9 and 5, 8, 12) and even with the separation needed in other cases, yields are nearly as high, normally allowing the conversion of (1) into 30 - 40% of both isolated amines. We are now extending the scope of this reaction to primary and secondary amines and to other substitution patterns.

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- 17. All new compounds gave satisfactory spectra and analytical data. Disubstituted <u>E</u> and <u>Z</u> isomers (5) and (6) were identified by I.R. and  $\overline{I}_{H}$ 18. NMR coupling constants. Trisubstituted isomers were identified by n.O.e in the <sup>1</sup>H NMR.

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