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# $PhCH{=}P(MeNCH_2CH_2)_3N$: A Novel Ylide in the Wittig Reaction

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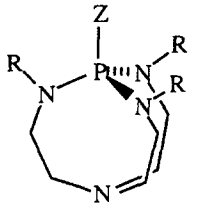
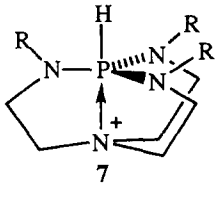
**Abstract:** The title semi-stabilized ylide prepared from the commercially available non-ionic superbase $P(MeNCH_2CH_2)_3N$ reacts with aldehydes to give alkenes in high yield with surprisingly quantitative E selectivity.



The Wittig reaction is an important approach to the synthesis of alkenes, and it has attracted much attention from the mechanistic as well as synthetic points of view.[1,2] The stereochemistry of the product alkene is governed primarily by the nature of the phosphorus ylide precursor. Non-stabilized ylides, bearing an α-alkyl group, tend to give Z alkenes whereas stabilized ylides, bearing a π acceptor group at the α carbon generally react with high selectivity for the E configuration. Semi-stabilized ylides, such as methinyl phenyl and methinyl vinyl generally yield a mixture of Z and E isomers in absence of metal ions. Factors that can affect the product stereochemistry, such as the structure of the phosphonium salt,[3] the presence of a metal cation[4] and the reaction conditions,[5] have been extensively investigated. Herein we report that the novel semi-stabilized polycyclic ylide **1** (formed from **2** via **3**(Br)) reacts with aldehydes to give alkenes in high yield and with unexpectedly high E stereoselectivity.



| | Z | R |
|---|---|---|
| **1** | =CHPh | Me |
| **2** | lone pr | Me |
| **3** | $^{+}CH_2Ph$ | Me |
| **4** | =O | Me |
| **5** | lone pr | *i*-Pr |
| **6** | $^{+}CH_3$ | Me |



**7**

Earlier we reported that the commercially available nonionic superbase **2**[6] reacts with alkyl halides to give phosphonium salts.[7] Following a similar procedure, the benzyl phosphonium salt **3**(Br) was synthesized in 74% yield.[8] Intermediate **3**(Br) was then converted to ylide **1** in situ followed by aldehyde addition giving exclusively E alkenes in high yield[9] Table 1) plus **4**.

The deprotonation of **3** to form **1** when monitored by $^{31}P$ NMR spectroscopy revealed that 2 h after adding NaHMDS, the peak for starting material **3**(Br) at δ 47.47 was accompanied by a new peak at δ 21.41. After 7 h only the δ 21.41 signal remained and it was assigned to the ylide **1.** The pale yellow color developed by the reaction mixture is consistent with ylide formation. The reaction mixture was filtered followed by removal of the solvent under vacuum to give crude ylide **1**. Attempts to purify **1** by sublimation or column chromatography were unsuccessful.

Normally, Wittig reactions of semi-stabilized ylides give rise to E isomers of the major product when sodium or potassium ions are present.[4] Although the presence of sodium ions in our reaction system may be responsible for increasing the E/Z ratio, complete E selectivity is not achievable by adding these ions.[4] By contrast, $[PhCH_2PPh_3]Cl$ gave E and Z-stilbene in a 63:37 ratio (96% conversion) under the same conditions. Thus the stereoelectronic properties of polycyclic ylide **1** appear to be responsible for quantitatively converting both aromatic and alphatic aldehydes to exclusively E-alkenes (Table 1). Although the salt **3**(Br) can also be dehydrohalogenated with LDA within 2 h at room temperature, the alkene produced upon adding aldehyde contained a small amount of Z isomer according to TLC, whereas this was not the case when NaHMDS was used. Whether or not the change in alkali metal is responsible for this observation is not clear. When $[PhCH_2P(i\text{-}PrNCH_2CH_2)_3N]Br$ (a more sterically congested

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analogue of **1**) was dehydrohalogenated by NaHMDS and treated with benzaldehyde under identical conditions, again only E-stilbene was obtained, although the conversion (35%) was low. Comparison of the results in Table 2 obtained with $[PhCH_2P(NMe_2)_3]Br$, an acyclic analogue of **3**(Br), revealed that the E selectivity of the corresponding ylide formed in situ was substantially less in most cases than with **1**, although E isomers did predominate.

**Table 1. Wittig reactions with ylide 1.**[a]

| | PhCH=CR$^1$R$^2$ | | yield[b] | E:Z[c] |
|---|---|---|---|---|
| carbonyl compound | R$^1$ | R$^2$ | % | ratio |
| PhCHO | Ph | H | 91 | E only[d] |
| *p*-$MeOC_6H_4CHO$ | Ph | H | 93 | E only[4a] |
| *p*-$ClC_6H_4CHO$ | Ph | H | 93 | E only[4a] |
| *trans*-PhCH=CHCHO | *trans*-$PhCH=CH_2$ | H | 94 | E only[e] |
| *c*-$C_6H_{11}CHO$ | *c*-$C_6H_{11}$ | H | 90 | E only[f] |
| $CH_3(CH_2)_5CHO$ | $CH_3(CH_2)_5$ | H | 93 | E only[g] |
| $C_2H_5CH(CH_3)CHO$ | $C_2H_5CH(CH_3)$ | H | 86 | E only[f] |
| PhCOMe[i] | Ph | Me | 35 | 56:44[h] |
| $(CH_2)_4C=O$ | $(CH_2)_4$ | | trace | |

[a]All reactions were carried out under argon with the mmolar ratios of **3**:NaHMDS:aldehyde = 0.6:0.6:0.5 for 15 min at room temperature except where indicated. [b]Isolated yields are based on the aldehyde. [c]The isomer ratio was determined by comparison of $^1$H NMR spectra of the crude product **4** with literature data. [d]*Aldrich Library of $^{13}$C and $^1$H FT-NMR spectra*, **1993**, *2*, 36A. [e]Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723; Kang, S-K; Namkoong, E-Y; Yamaguchi, T. *Synth. Commun.* **1997**, *27*, 641. [f]Underwood, G. M.; Chan, A. K.; Green, T.; Watts, C. T.; Kingsbury, C. A. *J. Org. Chem.* **1973**, *38*, 2735. [g]Negishi, E.-I.; Takahashi, T.; Akiyoshi, K. *J. Organomet. Chem.* **1987**, *334*, 181. Yamane, T.; Kikukawa, K.; Takagi, M.; Matsuda, T. *Tetrahedron* **1973**, *29*, 955. [h]*Aldrich Library of $^{13}$C and $^1$H FT-NMR spectra*, **1993**, *2*, 36B. [i]Reaction carried out at 60 °C for 12 h.

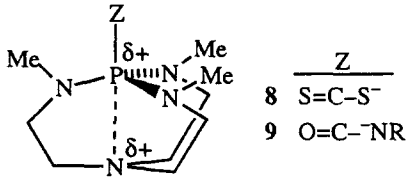
**Table 2. Wittig reactions with the ylide generated from $PhCH_2P(NMe_2)_3Br$.**[a]

| | PhCH=CR$^1$R$^2$ | | conversion[b] | E:Z[c] |
|---|---|---|---|---|
| carbonyl compound | R$^1$ | R$^2$ | % | ratio |
| Ph | Ph | H | 98 | 76:24 |
| $C_6H_4$ | Ph | H | 99 | 74:26 |
| $C_6H_4$ | Ph | H | 100 | 79:21 |
| *trans*-PhCH=CHCHO | *trans*-PhCHCHMe | H | 93 | E |
| *c*-$C_6H_{11}$ | $C_6H_{11}$ | H | 100 | E |
| $CH_3(CH_2)_5CHO$ | $CH_3(CH_2)_5$ | H | 100 | 83:17 |
| $C_2H_5CH(CH_3)CHO$ | $C_2H_5CH(CH_3)$ | H | 100 | E |
| PhCOMe | Ph | Me | 41 | 77:23 |
| $(CH_2)_4C=O$ | $(CH_2)_4$ | | trace | |

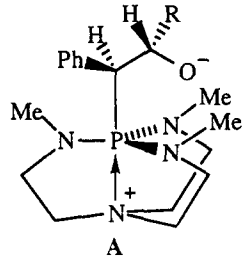
[a]Reaction conditions were identical to those listed in Table 1, and with the mmolar ratios $PhCH_2P(NMe_2)_3Br$:NaHMDS:aldehyde = 0.6:0.6:0.5. [b]Determined by $^1$H NMR spectra of the crude alkene. [c]Determined with the same method given in Table 1.

The quantitative stereoselectivity exhibited by ylide **1** with aldehydes must be associated with its bicyclic structure. From the untransannulated structure of **5**[10] and by analogy **2**, it can be seen that the electron density on phosphorus may potentially be enhanced by transannulation of the bridgehead nitrogen. However, the available evidence suggests that like **6**(I),[7] **3**(Br) is also untransannulated, unlike cation **7**[11] for example, wherein the P-$N_{ax}$ distance is 1.967 Å compared with 3.293 Å in **5**. This

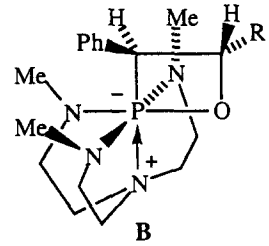
conclusion is substantiated by the $\delta^{31}P$ value of **3**(Br) (47.47 ppm) which is close to that of its methyl analogue **6**(I) (48.28 ppm[7]). However, $\delta^{31}P$ for **1** (21.41 ppm) lies considerably upfield from the corresponding values for $(Me_2N)_3P{=}CH_2$ (70.8 ppm) and $(Et_2N)_3P{=}CH_2$ (67.2 ppm)[12] suggesting the presence of at least some transannulation in **1**. Moreover the three "equatoral" nitrogens in both **5** and **7** have substantially planar geometies, thereby forcing their exocyclic alkyl substituents to remain fixed above the equatoral nitrogens and thus providing at least partial steric shielding of the phosphorus which is likely to be more effective in ylide **1** than in its acyclic analogue $PhCH{=}P(NMe_2)_3$ wherein P-N bond rotation can occur. Since an electron rich phosphorus increases the E:Z ratio in Wittig products, while increased steric hindrance of phosphorus substituents decreases this ratio, it is tentatively concluded from our results that the partial transannulation of the bridgehead nitrogen in ylide **1** (and in the corresponding ylide of **5**) may become augmented during the reaction with an aldehyde to account for the quantitative E selectivity in the alkene product. Partial transannulation has been observed by us in the partially




| | Z |
|---|---|
| **8** | S=C–S$^-$ |
| **9** | O=C–$^-$NR |




**A**




**B**

transannulated carbon-bound zwitterion **8** which is sufficiently stable to be isolated and structured ($P{-}N_{ax}$ = 3.008 Å[13]) whereas its acyclic analog $S_2CP(NMe_2)_3$[13] is not. Moreover, **2** catalyzes the trimerization of isocyanates to isocyanurates presumably via the carbon-bound zwitterionic intermediate **9**, whereas $P(NMe_2)_3$ does not catalyze this reaction.[14] Partial transannulation is thus likely to increase the electron density on phosphorus during Wittig reactions involving **1** or the corresponding semistabilized ylide of **5**. Whether such transannulation occurs in either or both intermediate **A** (arising by initial nucleophilic attack of phosphorus on carbon) and intermediate **B** (subsequently formed from **A** or in cycloaddition of the reactants) is not yet resolved.[15]

Steric effects of the rigid cage ylide **1** become important in its reaction with ketones (Table 1). The reactions are quite sluggish and the Wittig product of acetophenone was isolated in only 35% yield even though vigorous reaction conditions were employed (refluxing over 12 h). The smaller fraction of E product (56:44) compared with that obtained via $PhCH{=}P(NMe_2)_3$ (77:23, Table 1) is also consistent with the greater effective steric hindrance of **1** and/or steric inhibition of transannulation in intermediate **A** in its reaction with ketones. Cyclopentanone gave no Wittig product under our conditions with **1** or with $PhCH{=}P(NMe_2)_3$.

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[8] To a stirred solution of **2** (0.216 g, 1.00 mmol) made by our literature preparation (Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75) in $CH_3CN$ (3 mL) in an ice bath was added benzyl bromide (0.171 g, 1.00 mmol). A white solid precipitated after a few minutes. After stirring for 24 h, ether (3 mL) was added, and the mixture was filtered to give a solid which was washed with 2 × 1 mL portions of THF and dried under vacuum to give **3** (0.29 g, 75% ): $^1$H NMR ($CDCl_3$): 2.76 (d, 9H, $J$ = 12 Hz), 2.87-3.00 (m, 12H), 3.71 (d, 2H, $J$ = 15 Hz), 7.31-7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$): 130.97 (d, $J$ = 6.75 Hz), 130.17 (d, $J$ = 6 Hz), 129.38 (d, $J$ = 3 Hz), 127.96 (d, 3.75 Hz), 51.27, 49.34 (d, $J$ = 2.25 Hz), 36.40 (d, $J$ = 2.25 Hz), 33.23 (d, $J$ = 121 Hz); $^{31}$P NMR ($CDCl_3$): 47.47. Anal. Calcd. for $C_{16}H_{28}N_4PBr$: C, 49.62, H, 7.29, N, 14.47. Found C, 49.53, H, 7.50, N, 14.32.

[9] In a typical procedure a solution of sodium bis(trimethylsilyl)amide (NaHMDS) (0.6 mmol) in THF (1.5 mL) at 0 °C was added to a suspension of **3** (0.6 mmol) in THF (1.5 mL). After the solution was stirred at room temperature for 8 h, an aldehyde (0.5 mmol) was added by syringe. The reaction mixture was then stirred under the reaction conditions stated in Table 1 followed by quenching with saturated aqueous $NaHCO_3$ (5 mL). The phases were separated and the water layer was washed with ether (3 × 10 mL). The organic layers were combined and dried with $MgSO_4$. The solvent was removed with a rotary evaporator and then under vacuum to give the crude product which was purified by flash chromatography (hexane:ethyl acetate = 80:1) to give the alkene. The aqueous layer was extracted with toluene (3 × 10 mL) to give **4** whose $^{31}$P and $^1$H NMR spectra are consistent with those in the literature (Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. Z. *Anorg. Allg. Chem.* **1989**, *578*, 75).

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