

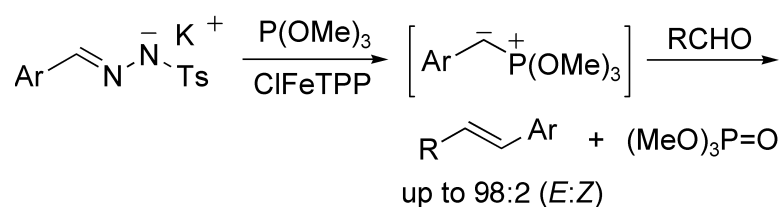
Communication

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 A New Class of Phosphorus Ylides Leading to High *E*  
 Selectivity with Semi-stabilizing Groups in Wittig Olefinations**

Varinder K. Aggarwal, J. Robin Fulton, Chris G. Sheldon, and Javier de Vicente

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## Generation of Phosphoranes Derived from Phosphites. A New Class of Phosphorus Ylides Leading to High *E* Selectivity with Semi-stabilizing Groups in Wittig Olefinations

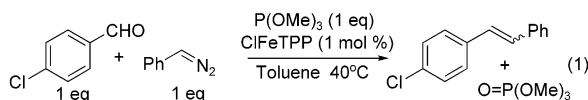
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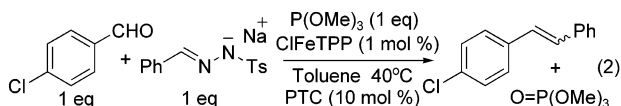
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The Wittig reaction occupies a position of central importance in the assembly of organic molecules as it generates a double bond with generally high levels of geometrical control.<sup>1</sup> Despite an enormous number of theoretical and experimental studies over its long history, it is surprising that the only variation of the groups on phosphorus ylides are carbon and nitrogen substituents.<sup>2</sup> Phosphorus ylides bearing oxygen substituents have never been reported as they cannot be prepared by the standard method of phosphite alkylation (due to the Arbuzov reaction).<sup>3</sup> If such ylides could be prepared, substantial differences in both reactivity and selectivity could be expected due to the considerable difference in electronic and steric properties of oxygen substituents relative to carbon substituents. To study this new class of potential Wittig reagents, we considered the possibility of generating the phosphorus ylides by carbene transfer (Scheme 1). In this Communication, we report our success in achieving this goal and the discovery that this new class of ylides led to high levels of *E* selectivity with semi-stabilized ylides.<sup>4</sup>

Slow addition of phenyldiazomethane to a toluene solution of (MeO)<sub>3</sub>P, *p*-chlorobenzaldehyde, and catalytic amounts of *meso*-tetraphenylporphyrin iron chloride (ClFeTPP) resulted in the formation of the corresponding alkenes with an *E/Z* selectivity of 86:14 (eq 1). The air stable Fe(III) complex was presumably reduced by phenyldiazomethane to the catalytically active Fe(II)–porphyrin complex,<sup>5</sup> which has recently been employed in related Wittig olefination of aldehydes with ethyl diazoacetate (EDA) in the presence of Ph<sub>3</sub>P.<sup>6</sup> We reasoned that the Fe(III) complex should be as equally effective as the highly air- and moisture-sensitive Fe(II) complex, and indeed it was.



As the yields in our olefination with phenyldiazomethane were low (30%), partially due to diazo dimerization and azine formation, we decided to generate phenyldiazomethane in situ from the corresponding sodium tosylhydrazone salt (eq 2). This procedure has proven to be a highly effective and safe alternative to handling phenyldiazomethane and has been employed in the sulfur ylide mediated epoxidation of carbonyl compounds,<sup>7</sup> cyclopropanation of alkenes,<sup>8</sup> and homologation of aldehydes.<sup>9</sup> Indeed, under these new conditions, the olefin yield increased to 74%; however, a slightly lower *E/Z* selectivity (82:18) was observed (eq 2).



Further optimization revealed that high *E* selectivity and high yield could be achieved using the potassium salt of the hydrazone

### Scheme 1. Proposed Route via Carbene Transfer

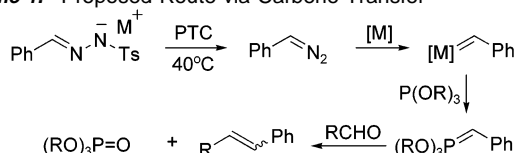


Table 1. Olefinations with a Range of Aldehydes and Hydrazones

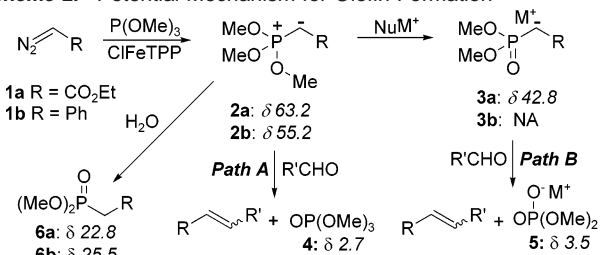
entry	R	R'	yield (%) <sup>a</sup>	<i>E/Z</i> <sup>b</sup>
1	4-(Cl)C <sub>6</sub> H <sub>4</sub>	Ph	92	97:3
2	4-(MeO)C <sub>6</sub> H <sub>4</sub>	Ph	95	97:3
3	2,6-(Me) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Ph	86	97:3
4	( <i>E</i> )-PhCH=CH	Ph	88	86:14
5	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	Ph	91	93:7
6	Ph	4-(Cl)C <sub>6</sub> H <sub>4</sub>	88	96:4
7	Ph	4-(MeO)C <sub>6</sub> H <sub>4</sub>	84	98:2
8	Ph	4-(CN)C <sub>6</sub> H <sub>4</sub>	79	84:16

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by GC-MS.

and the process could be applied to a range of carbonyl compounds (Table 1, entries 1–5). Furthermore, the methodology could be extended to include more functionalized tosylhydrazone precursors (Table 1, entries 6–8). While electron-donating groups on the aromatic ring increased *E* selectivity, electron-withdrawing groups resulted in lower *E/Z* selectivity. The new process is exceptionally clean and practical: following aqueous workup, the only component in the organic phase was the olefin. Compared to standard Wittig reactions, this process provides a step change in ease of preparing pure alkenes and could therefore find applications in industry.

Interestingly, under the optimized conditions, Ph<sub>3</sub>P only gave a 62:38 *E/Z* ratio of alkenes with *p*-ClArCHO. This demonstrates the superiority of the new class of phosphorus ylides and the substantial difference in selectivity observed in changing from carbon to oxygen substituents on phosphorus.

Ethyl diazoacetate (EDA) could also be employed with (MeO)<sub>3</sub>P to give  $\alpha,\beta$ -unsaturated esters. In contrast to the use of phosphines where high *E* selectivity is observed, we were surprised to find that when using (MeO)<sub>3</sub>P the *E* selectivity was very much reduced (69:31, *E/Z*). Clearly, this new class of ylides shows very different selectivity to ylides bearing carbon substituents on phosphorus. We reasoned that the high *E* selectivity could potentially be restored if the ylide **2a** could be intercepted by a nucleophile in an Arbuzov-type process to furnish the phosphonate anion **3a**, which is known to give high *E* selectivity (Scheme 2).<sup>10</sup> Thus, the same reactions were conducted in the presence of LiBr. Under optimized conditions, this combination of reagents did indeed provide high yields and high selectivities with a broad range of aldehydes (Table 2).

**Scheme 2.** Potential Mechanism for Olefin Formation<sup>a</sup><sup>a</sup> <sup>31</sup>P NMR chemical shifts are listed in italics.**Table 2.** Olefinations Using EDA with a Range of Aldehydes

entry	R	yield (%) <sup>a</sup>	<i>E:Z</i> <sup>b</sup>
1	Ph	86	96:4
2	4-(MeO)C <sub>6</sub> H <sub>4</sub>	59	98:2
3	2,6-(Me) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	45	94:6
4	( <i>E</i> )-PhCH=CH	90	89:11
5	4-(CH <sub>3</sub> CO)C <sub>6</sub> H <sub>4</sub>	75	95:5
6	4-(Cl)C <sub>6</sub> H <sub>4</sub>	90	96:4
7	PhCH <sub>2</sub>	92	90:10
8	c-C <sub>6</sub> H <sub>11</sub>	82	94:6

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by GC-MS.

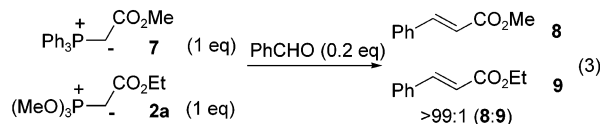
Interestingly, addition of LiBr to our tosylhydrazone system did not result in an increase of the *E/Z* selectivity.

These reactions are presumed to proceed via iron-catalyzed carbene transfer to the phosphite to form a phosphorus ylide. However, two different pathways could be envisioned for olefin formation (Scheme 2): (i) Wittig reaction (path A) leading to trimethyl phosphate **4** or (ii) Horner–Wadsworth–Emmons (HWE) reaction (path B) via phosphonate anion **3** which would generate phosphonate anion byproduct **5**. Phosphonate anion **3** could be formed in an Arbuzov reaction from ylide **2**.

To determine which pathway was operative, reactions were followed by <sup>31</sup>P NMR (Scheme 2). In the absence of halide ions, both diazo compounds **1a/b** led to new intermediates which, upon treatment with H<sub>2</sub>O, gave the known phosphonates **6a/b** and, upon treatment with PhCHO, led to the olefins and trimethyl phosphate **4** and none of the phosphonate anion **5**. These observations are consistent with ylide **2a/b** as the new intermediate and reactions occurring through a Wittig process. Interestingly, olefination reactions that used hydrazone salts as the diazo precursor gave exclusively trimethyl phosphate **4** as the phosphorus-containing byproduct, indicating that these are also Wittig-type reactions.

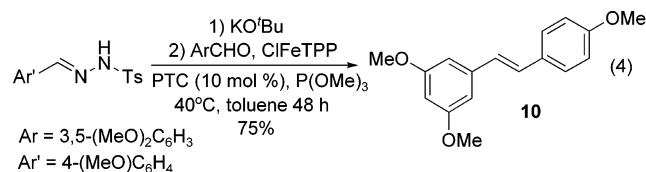
In contrast, in reactions involving EDA and LiBr, the phosphorus byproduct formed was found to be **5** and the known anion **3a** was observed as a transient intermediate. Thus, in the presence of LiBr, an Arbuzov-type reaction has indeed intervened, leading to a new base-free method for conducting a HWE reaction. This could clearly find application with especially base sensitive substrates. It is well-known that lithium ions can influence selectivity in Wittig reactions<sup>11</sup> but in our case it is the bromide ion which is responsible for improvements in selectivity with EDA as LiBPh<sub>4</sub> returned a similar ratio of olefins as under salt-free conditions (63:38, *E:Z*).

Ylide **2a** is substantially less hindered than ylide **7** and, on the basis of steric effects, would be expected to be the more reactive. To test the differences in reactivity, we conducted a competition experiment between the stabilized ylides **2a** and **7** (eq 3). This experiment only gave olefin **8**, indicating that the more hindered ylide **7** is substantially more reactive than the alkoxy-substituted ylide **2a**. In other words, there is a very significant electronic effect



resulting in stabilization of the alkoxy-substituted ylide. Presumably, the origin of this stability is through improved overlap of the negative charge on carbon with the lower-lying P–O antibonding ( $\sigma^*$ ) orbitals.<sup>12</sup> The increased *E* selectivity observed with ylide **2b** can perhaps be rationalized based on these observations of relative ylide stability. This ylide is perhaps best regarded not as a semi-stabilized ylide, which traditionally gives low selectivity, but as a stabilized ylide which, according to the Vedejs model,<sup>13</sup> is known to give high *E* selectivity. The low selectivity with ester-stabilized ylides is more difficult to rationalize and is currently being analyzed computationally.

Finally, the efficiency of this new process is demonstrated in the synthesis of the recently reported anticancer compound **10**.<sup>14</sup> The Wittig reaction leading to stilbene derivatives usually gives low selectivity, and therefore alternative routes or an additional *E* → *Z* equilibration step is required.<sup>15</sup> The use of our new protocol gave the desired substituted stilbene with 97:3 *E/Z* selectivity (eq 4), providing a clean and efficient route to this compound.



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**Supporting Information Available:** The use of alternative phosphites, experimental procedures, compound characterization data, and mechanistic <sup>31</sup>P NMR data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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