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Letter

# Wittig Olefination Using Phosphonium Ion-Pair Reagents Incorporating an Endogenous Base

Anna C. Vetter, Declan G. Gilheany, and Kirill Nikitin\*



in Wittig chemistry is utterly unnecessary: we report a series of novel ion-pair phosphonium carboxylate reagents which are essentially "storable ylides". These reagents are straightforwardly prepared in excellent yields, and their fluxional nature permits clean olefination of a broad range of aldehydes and even hemiacetals.



C onstruction of a carbon–carbon double bond using the Wittig reaction has major synthetic advantages, e.g. the defined position of the new bond. Yet, the involvement of strong bases at the deprotonation stage and overall poor atom economy narrow the scope and applications of this reaction. The recent trend to modernize the Wittig reaction has prompted explorations of catalytic olefination,<sup>1</sup> including its masked-base version,<sup>2</sup> and alternative approaches to ylide generation.<sup>3</sup>

Experimental observations pointing to the possibility of ylide formation directly from salts containing quaternary phosphonium cations  $R_4P^+$  (QPC) had been reported in the past<sup>4</sup> and have recently been examined experimentally and theoretically,<sup>5</sup> notably by Holloczki and co-workers.<sup>6</sup> Their DFT results suggest that ionic QPC systems such as [Ph<sub>3</sub>PR]<sup>+</sup> PhO<sup>-</sup> are likely to generate the corresponding ylides in solution despite the lower  $pK_a$  of PhOH. Although generating an ylide in this manner is highly appealing, its broad synthetic application in Wittig reactions remains largely uncharted territory.<sup>7</sup>

We became interested in ion pairs (IP) combining QPC and mildly basic anions as sources of active ylides in connection with our earlier work<sup>8</sup> on the Wittig olefination. The chemistry of IP encompasses organic reaction mechanisms,9 enhanced molecular recognition,<sup>10</sup> and photocatalysis.<sup>11</sup> Recent general interest in IPs has arisen in conjunction with promising applications in organocatalysis<sup>12</sup> and ionic liquids,<sup>5</sup> and in both contexts, IPs containing phosphonium cations have a prominent role.<sup>13</sup> Encouraged by the enormous synthetic potential of such "storable ylides" 1 (Scheme 1) we sought a universal approach to the preparation of various Eigenbase (German: "own base") phosphonium reagents via a facile ionmetathesis route. As shown herein, the fluxional nature of these Eigenbase reagents allows clean olefination of aldehydes via the formation of semi- and nonstabilized ylides without an added base.

A key factor governing the success of the *Eigenbase* approach is the acidity of the QPC relative to the basicity of the anionic

Scheme 1. Conventional Wittig Olefination Compared to This Work: Fluxional Reagents 1 Prepared by Anion Metathesis (X = Br, Cl) Spontaneously Generate Reactive Ylides 2



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counterpart A<sup>-</sup> (Figure 1). Ideally, the desired  $pK_a$  of HA would fall within the green region of the diagram due to the



Figure 1. Side-by-side comparison of basic anions  $(pK_{a(DMSO)})$  of conjugate acids<sup>17b,18</sup>) and a benzylic QPC  $[PhCH_2PPh_3]^+$ .

following: first, if the  $pK_a$  of HA is too low (bottom red zone), the anion would be too weak a base to attain a practical overall Wittig reaction rate. Second, with too basic A<sup>-</sup> (top red zone,  $pK_a$  greatly exceeding that of the reference QPC), in situ deprotonation reaction would likely lead to isolation of reactive ylide, defying the goal of having the desired shelf-stable ionic reagent. Thus, the choice of a suitable basic anion is significantly narrowed to the green zone.

Our initial efforts were focused on salts of QPC which have sufficiently high equilibrium acidity<sup>14</sup> (e.g., the methylene group in  $[PhCH_2PPh_3]^+$  has  $pK_{a(DMSO)} = 17.4^{14a}$ ) so that fluxional acid-base interactions within the QPC-carboxylate species are likely to generate minor amounts of semistabilized ylides from, benzylic QPC as the starting point. To our minds, regarding the choice of anion, its availability and purity was equally critical. Certain bases, e.g. the imidazolate or phenoxide anion, can straightforwardly be accessed by reacting MOH (M = K or Na) with imidazole<sup>15</sup> or phenol,<sup>16</sup> respectively, but the presence of free hydroxide or moisture in the product would be a major concern due to irreversible QPC hydrolysis giving phosphine oxide. In contrast, the alkali metal carboxylates, commonly available in dry pure form, are convenient cheap sources of suitably basic endogenous anions for reagents 1. Considering that acetic acid has a  $pK_{a(DMSO)}$  of 12.3,<sup>17</sup> clearly below the  $pK_a$  of the  $[PhCH_2PPh_3]^+$  cation, acetates were chosen for the preparation of new ion-pair reagents for Wittig olefinations. When a solution of BnPPh<sub>3</sub>Br in dry ethanol was treated with an equivalent amount of KOAc and KBr was separated, the residue produced crystalline QPC acetate 1a (see Scheme 1) in 99% yield. Although the acetate 1a is a white crystalline material, its solutions in aprotic solvents, e.g. DMSO, have a characteristic pale-yellow hue. This behavior suggests the possibility of fluxional proton transfer leading to the formation of trace amounts of ylide in solution. The presence of IP in the system is consistent with the observation of long-distance through-space interactions by NOE spectroscopy as shown in the Supporting Information (SI).

The successful isolation of crystalline QPC acetate 1a was followed by other QPC carboxylates 1b-1f (Scheme 1), which were prepared in excellent yields (see SI). Analogous to 1a, all

the acetate reagents 1c-1f were formed in ethanol and precipitated using ether typically on 2–10 mmol scale. The pivalate reagent 1b, however, requires the use of MTBE and is also different in other aspects: this anion was chosen due to its slightly higher basicity ( $pK_{a(DMSO)}$  is  $12.9^{17a}$ ) and its bigger steric size. As anticipated, 1b, bearing a large *tert*-BuCOO<sup>-</sup> anion more closely matching the cation's size, is nonhygroscopic and remains shelf-stable in air while the acetates 1a, 1c, and 1f are hygroscopic and prone to slow hydrolysis by adventitious moisture. These attractive benefits have to be weighed, however, against the much higher cost of pivalatess.

Owing to good solubility in a range of solvents, the olefination of PhCHO with the pivalate **1b** works well in solvents of different polarities (Figure 2), whereby the highest



**Figure 2.** Eigenbase reagent **1b** performs olefination of benzaldehyde **3a** in various solvents (conversion to **4a**, %).

conversion to stilbene 4a is achieved in THF and its green alternative 2-MeTHF. Perhaps somewhat surprisingly, even in acetone an acceptable conversion to stilbene 4a is obtained indicating the far lower reactivity of ketones.

The scope of olefination (Table 1) illustrates the efficiency of benzylic Eigenbase reagents 1a and 1b in reactions with aromatic, heteroaromatic, and aliphatic aldehydes. Either acetate 1a (entries 1–8) or pivalate 1b (entries 9–12) produce alkenes 4a–4k in high yields. As THF affords the best result, this solvent was used for olefinations with all Eigenbase reagents (Tables 1 and 2). Overall, electron-withdrawing groups on the aldehyde facilitate the process (Table 1, entries 2, 5) compared to electron-donating groups (entries 3, 11, 12) such as ferrocenyl.<sup>19</sup> The benefits of the Eigenbase methodology are apparent with less common Wittig substrates, e.g. those containing aromatic hydroxyl groups<sup>20</sup> (entries 3, 11), and enolizable aldehydes (entries 4, 7) where very little condensation products were observed<sup>21</sup> due to the inherently mild basicity of carboxylates.

The stark difference between the ion-pair reagents and the alternative procedure using a QPC bromide and an alkali metal acetate (Scheme 2) clearly shows the benefits of the new reagents: the reaction of BnPPh<sub>3</sub>Br with *p*-anisaldehyde **3b** in the presence of potassium acetate in THF affords only traces of alkene **4h**; in contrast, using Eigenbase reagent **1a**, 81% of alkene **4h** was isolated. Thus, we conclude that the acetate anion has to be present in the form of an IP to be efficient in the olefination.

A striking example of the expanded olefination scope is of course the "unfeasible" reaction shown in Scheme 3: owing to the fluxional behavior of salt 1 and dioxane 5,<sup>22</sup> the reaction leads to cinnamic alcohols in high yields (Table 1, entry 6; Table 2, entry 3).

Other olefinations with the *o*-halogenated benzylphosphonium acetate reagent 1c (Table 2, entries 1-4) clearly show the preparative benefits of the mildly basic ion-pair reagents as

Table 1. Pre	eparative Olefinati	on of Aldehydes	with Ion-Pair
Reagents 1a	<sup>a</sup> and 1b		

1

R	2-CHO 3	THF, 40 °C, 18-72 h		Ph <i>Z/E</i> -4	R <sup>2</sup>
Entry	1	Product 4		% <sup>[b]</sup>	$Z/E^{[c]}$
1	1a	Ph	4a	95	42:58
2	<b>1</b> a	Ph	4b	97	68:32
3	1a	Ph	4c	75	5:95
4	<b>1</b> a	Ph	4d	88	8:92
5 <sup>[d]</sup>	1a	PhNO2	4e	96	43:57
6 <sup>[e]</sup>	1a	PhOH	4f	82	70:30
7	1a	PhMe	4g	88	30:70
8	1a	Phone	4h	81	39:61
9	1b		4a	90	38:62
10 <sup>[e]</sup>	1b	Ph	4i	86	37:63
11	1b	Ph HO Br	4j	95	5:95
12	1b	Ph_m_Fe	4k	75	38:62

<sup>*a*</sup>Using 2 equiv of reagent; see SI for procedures and cognate examples. <sup>*b*</sup>Yield of isolated product. <sup>*c*</sup>By <sup>1</sup>H NMR analysis. <sup>*d*</sup>rt, 20 h. <sup>*e*</sup>50 °C.

a variety of side-processes can be evoked in the presence of strong bases. Olefination of acetaldehyde, for example, furnishes *o*-brominated **4m** in very high yield. With *o*-nitrobenzaldehyde (entry 4) **1c** gives the sterically crowded Z-stilbene **4o** in accordance with our expectations for such twin *ortho*-substitution.<sup>8</sup>

Having succeeded with benzylic 1a-1c we questioned if *n*-alkyl-derived QPC carboxylates can be efficient in olefinations too. This implies the intermediacy of nonstabilized ylides and, in principle, would require an endogenous anion with significantly higher basicity. And it was true that vinylation using the acetate  $[Ph_3PMe]^+AcO^-$ , 1d, afforded only small amounts of alkene products 4p and 4q (Table 2, entries 5, 6) illustrating the necessity for a stronger base. This behavior of the acetate 1d, when compared to a known QPC methyl carbonate reagent<sup>7</sup> (at higher temperatures it offers high-yielding vinylation), suggests that irreversible breakdown of a byproduct, methylcarbonic acid, in the reaction system might be the driving force of vinylation using the methyl carbonate version.

Notwithstanding this setback, we were delighted that ethylderived **1e** gave high yields of  $\beta$ -methylstyrenes **4m**-**4t** in reactions with aromatic aldehydes (Table 2, entries 7–10).<sup>23</sup> This finding is fairly significant, as it demonstrates that the successful use of carboxylates as endogenous bases is not

Table 2. Preparative	Aldehyde	Olefination	with	Ion-Pair
Reagents 1c–1f <sup>a</sup>				

R <sup>2</sup> -	-СНО 3	<b>1</b> THF, 40 °C, 18-72 h	•	R <sup>1</sup> Z/E-4	R <sup>2</sup>
Entry	1	Product 4		% <sup>[b]</sup>	$Z/E^{[c]}$
1	1c	Br Ph	41	86	55:45
2	1c	Br	4m	88	50:50
3	1c	Br	4n	86	37:63
4 <sup>[d]</sup>	1c	Br NO <sub>2</sub>	40	98	76:24
5[e]	1d	ОМе	4p	25	-
6 <sup>[e]</sup>	1d	Fe	4q	20	-
7	1e	Me	4m	79	65:35
8[f]	1e	Me Fe	4r	66	85:15
9[f]	1e	Me	4s	72	50:50
10	1e	Me O <sub>2</sub> N	4t	88	69:31
11[g]	1f	Ph NO <sub>2</sub>	4e	90	33:67
12 <sup>[h]</sup>	1f	Ph	4u	86	80:20

<sup>*a*</sup>See SI for procedures and cognate examples. <sup>*b*</sup>Yield of isolated product. <sup>*c*</sup>By <sup>1</sup>H NMR analysis. <sup>*d*</sup>6 h. <sup>*e*</sup>50 °C, 72 h. <sup>*f*</sup>50 °C, 24 h. <sup>*g*</sup>rt, 24 h. <sup>*h*</sup>rt, 72 h.

Scheme 2. Eigenbase Reagent 1a in Direct Comparison with Attempted Use of Added Base KOAc



limited to semistabilized ylide cases; rather, carboxylates are widely applicable as efficient Eigenbase olefination reagents. Of course, in reactions of methyl-benzyl QPC acetate 1f the more acidic site wins (entries 11, 12) and a high yield of azastilbene Scheme 3. Unusual Wittig Olefination: The Fluxional Dimer 5 Generates Glycolic Aldehyde Which Reacts with Trace Equilibrium Amounts of Ylide Produced from Fluxional QPC Carboxylate (1a, R = H; 1c, R = Br)



**4u** was obtained while the vinylation product azastyrene was not observed (Scheme 4). In some *ortho*-substituted cases, and

Scheme 4. Selective Transfer of Benzyl Group Using Methyl-Benzyl QPC Acetate 1f



for 3c, predominant Z-selectivity was observed (Table 1, entries 2–4; Table 2, entries 4, 7, 10) following established Z/E selectivity trends.<sup>8b,c</sup>

In conclusion, in this report, phosphonium carboxylates containing an endogenous carboxylate base as an anion have been prepared under standard laboratory conditions in essentially quantitative yields. These Eigenbase reagents are shelf-stable crystalline materials which can spontaneously generate phosphorus ylides in solution as a result of ion-pairing interactions between the cation and the mildly basic anion. Its apparent base strengths have dramatically increased, so much as to allow for the generation of even nonstabilized phosphonium ylides—a revolution of Wittig chemistry. The Eigenbase reagents participate in a broad range of Wittig olefinations without adding any external base, metal cation, or catalyst under mild conditions (25-50 °C). While THF was chiefly the solvent in the present study, other solvents of varying polarities can be used.

The fact that the Eigenbase reactions furnish alkene products in high yields, owing to the inherently mild basicity in the reaction system, makes them attractive for challenging olefinations of aliphatic and aromatic aldehydes including condensation-prone and hydroxylated ones. Remarkably, for the first time, our approach to olefination offers an unexpected useful synthesis of allylic alcohols by a two-carbon chain elongation procedure. Work is underway on further modifications of the new proposed protocol in conjunction with the recently discovered transformation of phosphine oxide byproduct to QPC starting material<sup>24</sup> or in combination with silane-promoted hydrogenation of the alkene catalyzed by phosphine oxide.<sup>25</sup>

Considering that the olefination reaction using ion-pair Eigenbase reagents readily occurs under mild conditions points to a sequence of proton-transfer charge-controlled equilibria followed by standard Wittig olefination steps. Critically, such polarity-controlled dynamic processes have implications for the chemistry of other onium salts.  $^{26}\,$ 

# ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00133.

Procedures for the preparation of QPC carboxylates, olefination of aldehydes (PDF)

# AUTHOR INFORMATION

### **Corresponding Author**

Kirill Nikitin – School of Chemistry, University College Dublin, Dublin 4, Ireland; o orcid.org/0000-0002-1444-234X; Email: kirill.nikitin@ucd.ie

## Authors

- Anna C. Vetter School of Chemistry, University College Dublin, Dublin 4, Ireland
- **Declan G. Gilheany** School of Chemistry, University College Dublin, Dublin 4, Ireland; Octid.org/0000-0002-1272-4423

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00133

#### Notes

The authors declare no competing financial interest.

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