Horner–Wadsworth–Emmons Modification for Ramirez *gem*-Dibromoolefination of Aldehydes and Ketones Using P(O*i*-Pr)$_3$

Yuan-Qing Fang, Olga Lifchits, Mark Lautens*

Davenport Chemistry Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON, M5S 3H6, Canada
Fax +1(416)9468185; E-mail: mlautens@chem.utoronto.ca

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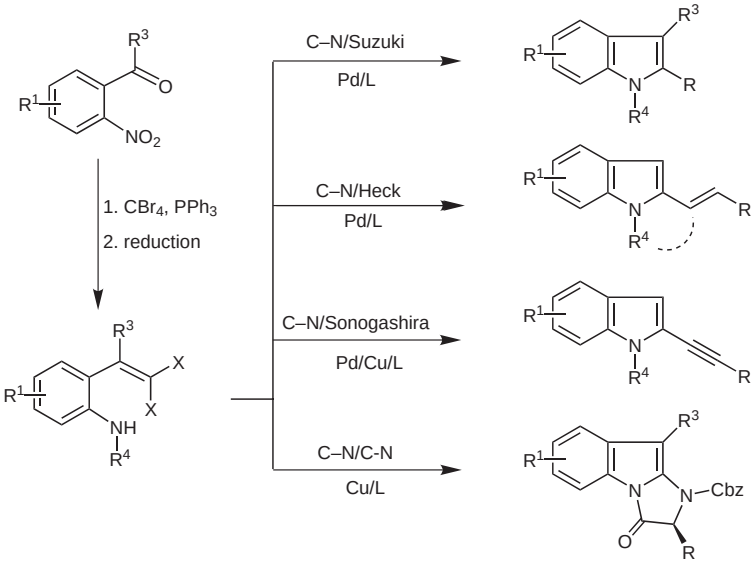
Abstract: A simple procedure for the use of triisopropylphosphite in the Ramirez olefination is described. This reagent is equally or more reactive than PPh_3 toward aldehydes and ketones in the *gem*-dibromoolefination of aldehydes and ketones. Under the reaction conditions, an α-bromoketone gave a novel tribromomethyl-substituted oxirane product in good yield. The substrate-dependent nature of this reaction suggests that this Horner–Wadsworth–Emmons equivalent of the Ramirez *gem*-dibromoolefination reaction proceeds through an ionic mechanism.

Key words: olefination, phosphite, Horner–Wadsworth–Emmons reaction, aldehydes, ketones

gem-Dibromoolefins serve as important synthetic intermediates in a variety of transformations, including Corey–Fuchs alkyne synthesis,[1] trisubstituted olefin synthesis via stereoselective cross-couplings,[2] and carbocycle or heterocycle synthesis via tandem cross-couplings.[3] Although *gem*-dihaloolefin units are rarely found in natural products, they have been used to enhance the potency and stability of biologically active compounds such as the common household insecticide deltamethrin.[4]

The most common way to prepare *gem*-dibromoolefins is by using the Ramirez olefination, a reaction involving an aldehyde (or ketone), CBr_4 and PPh_3.[5] Modified methods to cope with the reactive Lewis acidic byproduct Br_2PPh_3 using scavengers such as zinc powder or Et_3N were subsequently developed.[1,6] However, the utility of this method towards less reactive ketones remains low. Although there are alternative non-ylide approaches which use organolithium and Grignard reagents, or a copper-catalyzed redox chemistry between hydrazones and CBr_4, multiple steps are usually required.[7]

We have recently published a series of papers on the use of *gem*-dihalovinylanilines for the synthesis of indole derivatives (Scheme 1).[8] Although the one-pot, two-step procedure for preparation of the substrate gave a good yield, there are several drawbacks in large-scale preparations. The significant amount of triphenylphosphine oxide waste generated in the reaction is difficult to remove, resulting in a tedious and solvent-consuming purification process. Due to the crystalline nature of triphenylphosphine oxide, solid products cannot be purified by recrystallization and require column chromatography which is impractical on a large scale.



Scheme 1 Indole synthesis via tandem cross couplings

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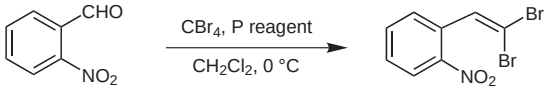
To address these issues, we examined alternative phosphorus reagents such as alkylphosphines and phosphites, since their byproducts are oils, and are therefore easier to separate. A number of reagents were screened for the *gem*-dibromoolefination of 2-nitrobenzaldehyde (**1a**) and the results are shown in Table 1.

Table 1 Ramirez Olefination with Various Phosphorus Reagents



1a **2a**

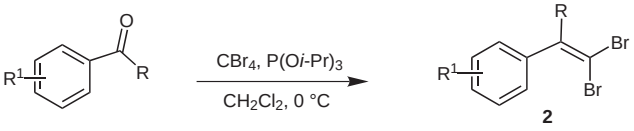
Entry	Reagent	Yield (%)[a]	Comment
1	PPh_3	95	excessive $Ph_3P(O)$ waste
2	PBu_3	<40	incomplete conversion
3	$P(OMe)_3$	48	side reaction
4	$P(OEt)_3$	57	side reaction
5	$P(Oi\text{-}Pr)_3$	92	clean, fast
6	$P(Ot\text{-}Bu)_3$	0	no reaction
7	$P(OPh)_3$	13	incomplete conversion
8	$P(OEt)_2OH$	0	no reaction
9	NaH_2PO_2	0	no reaction
10	PCl_3	0	no reaction

[a] Isolated yield using **1a** (1.0 mmol), CBr_4 (1.5 mmol), and phosphorus reagent (3 mmol).

It was found that tri-*n*-butylphosphine was less efficient than PPh_3, resulting in a moderate yield of the desired product **2a** (Table 1, entry 2). Considering the air-sensitive nature of these reagents, no further alkylphosphines were examined. We were encouraged to find that the generally inexpensive and less air sensitive trialkyl phosphites (Table 1, entries 3–7) showed greater reactivity. $P(OMe)_3$ and $P(OEt)_3$ gave the desired product in moderate yields with complete conversion of the starting material. To our delight, reaction with the bulkier $P(Oi\text{-}Pr)_3$ was very clean and rapid, giving the desired product in 92% yield. Further increasing the bulkiness of the reagent using $P(Ot\text{-}Bu)_3$, however, resulted in no reaction. Other phosphites such as triphenylphosphite and $P(OEt)_2OH$ were similarly unsuccessful, and inorganic phosphorus sources such as PCl_3 and sodium hyperphosphite were completely inactive.

With the optimal triisopropylphosphite in hand, we examined the reaction scope by comparing it to the PPh_3-mediated olefination (Table 2).[9] In general, the olefination of aldehydes gave comparable yields for both reagents (Table 2, entries 1–3). However, upon examining the scope of ketones, we found that $P(Oi\text{-}Pr)_3$ was more reactive than PPh_3, although incomplete conversion was observed in some cases (Table 2, entries 4–9). The reaction appears to be sensitive to steric hindrance in ketones, with hindered *ortho* substituents significantly slowing down the reaction as demonstrated in the case of 2′-nitroacetophenone (Table 2, entry 9). Interestingly, while the reaction of acyl cyanide **1j** under $P(Oi\text{-}Pr)_3$ gave the desired **2j** in poor yield, PPh_3-mediated reaction afforded the product in excellent yield (Table 2, entry 10).

Table 2 Scope of the $P(Oi\text{-}Pr)_3$-Mediated Ramirez Olefination of Aldehydes and Ketones



2

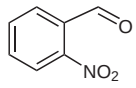
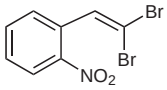
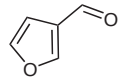
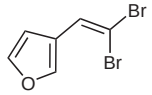
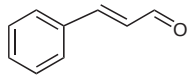
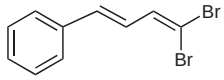
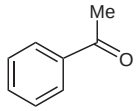
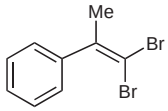
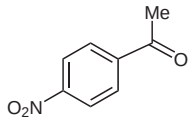
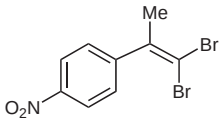
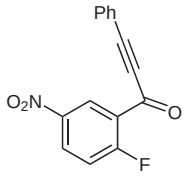
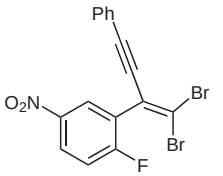
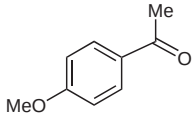
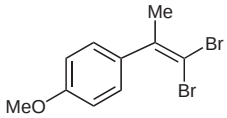
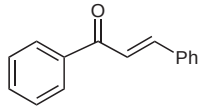
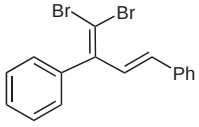
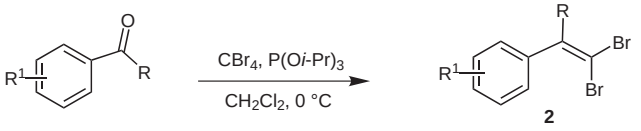
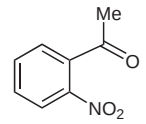
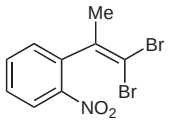
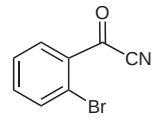
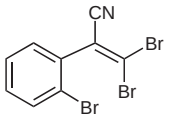
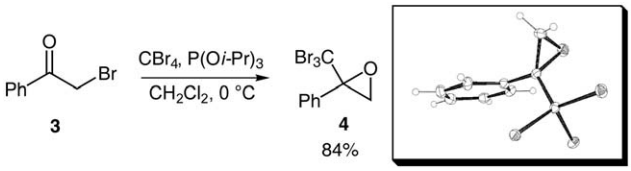
Entry	Starting material	Product	Yield (%)[a]	
			$P(Oi\text{-}Pr)_3$	PPh_3
1	 **1a**	 **2a**	92	95
2	 **1b**	 **2b**	76	88
3	 **1c**	 **2c**	94	85
4	 **1d**	 **2d**	73	<40[b]
5	 **1e**	 **2e**	73	<40[b]
6	 **1f**	 **2f**	98	69
7	 **1g**	 **2g**	62[c]	<20[b]
8	 **1h**	 **2h**	44[c]	<5[b]

Table 2 Scope of the P(O*i*-Pr)$_3$-Mediated Ramirez Olefination of Aldehydes and Ketones (continued)



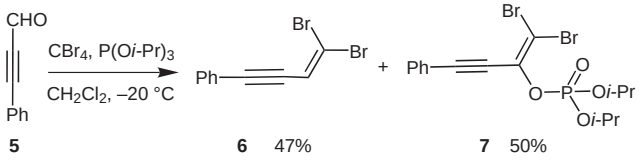
Entry	Starting material	Product	Yield (%)[a] P(O*i*-Pr)$_3$	Yield (%)[a] PPh_3
9	 **1i**	 **2i**	Trace	Trace
10	 **1j**	 **2j**	21	91

[a] Isolated yield.
[b] Conversion measured by ^{1}H NMR.
[c] Incomplete conversion



Scheme 2 P(O*i*-Pr)$_3$-mediated oxirane formation

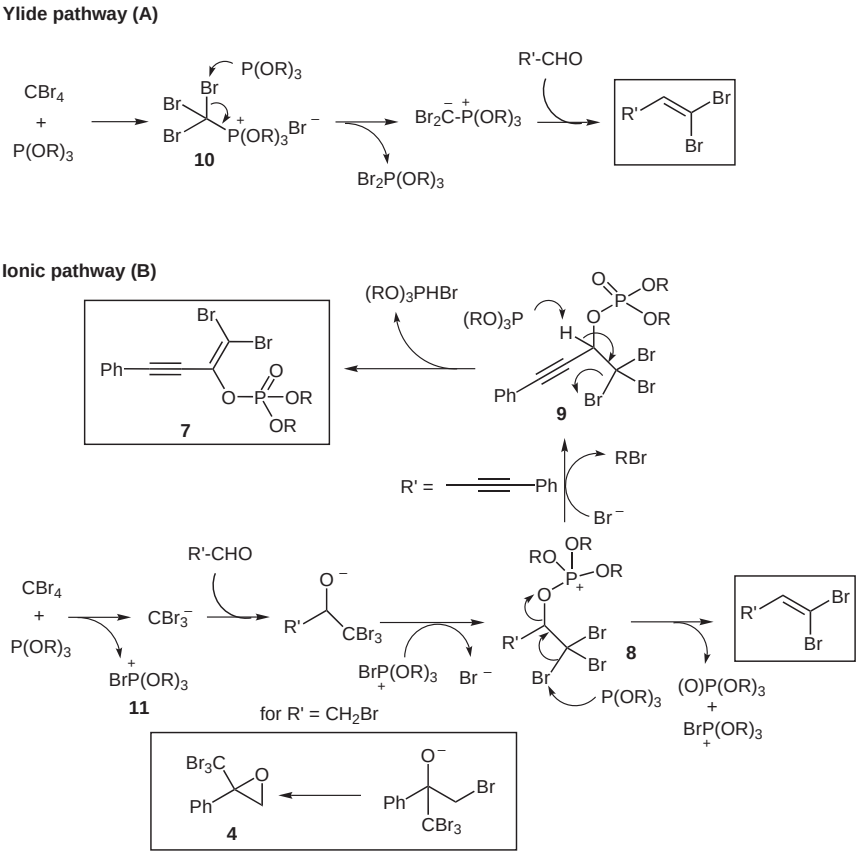
Olefination of alkynyl aldehyde **5** on the other hand resulted in a mixture of the desired *gem*-dibromoolefin **6** and a vinyl phosphate **7** (Scheme 3).[11] In contrast, a PPh_3-mediated reaction did not produce compound **7**, giving only **6** in 90% yield. The *gem*-dibromovinyl phosphate structure is known to exhibit insecticidal activity.[12]



Scheme 3 P(O*i*-Pr)$_3$-mediated Ramirez olefination of alkynyl aldehyde

An unexpected epoxide product **4** was obtained in good yield when α-bromoacetophenone (**3**) was treated with CBr_4/P(O*i*-Pr)$_3$ (Scheme 2).[10] In contrast, the reaction with CBr_4/PPh_3 gave a 1:5 mixture of the starting material and α,α-dibromoacetophenone.

Two possible mechanistic pathways for this P(O*i*-Pr)$_3$-mediated olefination are shown in Scheme 4: an ylide pathway (A) which is analogous to PPh_3-mediated reaction[5] and an ionic pathway (B). Given the substrate-



Scheme 4 Possible mechanistic pathways for phosphite-mediated Ramirez olefination

dependent behavior of this reaction, we favor the ionic pathway B, which is consistent with all the evidence.

Initial attack of phosphite to CBr_4 results in a tribromomethyl anion (CBr_3^-), which probably exists as a close ion pair with the generated phosphonium or as a pentavalent phosphorus species. Attack of the aldehyde or ketone by the CBr_3^- anion results in an alkoxide, which in the case of α-bromoacetophenone (**3**) gives epoxide **4**. This also explains why acyl cyanide afforded low yield under our conditions since cyanide is a good leaving group under CBr_3^- attack. Otherwise, the alkoxide reacts with the phosphonium to form **8**. The second molecule of phosphite attacks the bromide in **8** to give the normal olefination product. The intermediate **8** can also undergo an Arbuzov dealkylation to form a phosphate **9**. In the case of the alkynyl substrate **5**, the phosphate further undergoes an E2-elimination to afford the observed vinyl phosphate **7**, presumably due to the high acidity of the propargylic proton.

Shifting the mechanism from an ylide pathway to anionic pathways is presumably due to the change of relative stability of the phosphonium ion **10** and **11**. Due to their strong electron-withdrawing inductive while poor electron-donating effects of oxygens on the phosphorus, the positive charge of phosphonium ion **10** is localized only on phosphorus, destabilizing the intermediate. However, for the bromophosphonium **11**, its stability is improved through resonance structures (Figure 1).

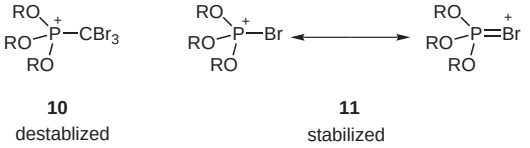
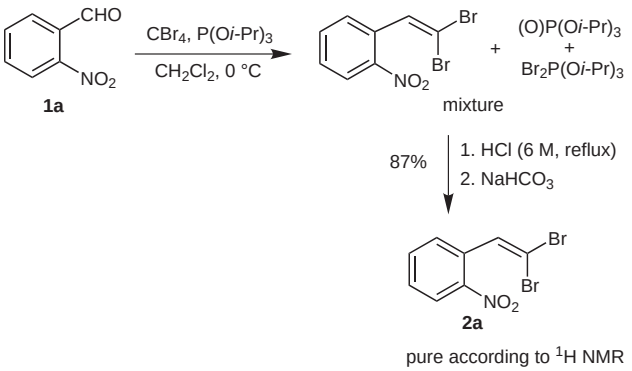


Figure 1 Comparison of possible phosphonium ion intermediates

Since the byproducts from triisopropylphosphite-mediated reaction are oils, the *gem*-dibromoolefinated products such as **2** can be purified by recrystallization. A convenient alternative protocol is a simple treatment of the crude reaction mixture with acid, which hydrolyzes triisopropylphosphate into nonhazardous phosphoric acid and isopropanol (Scheme 5), giving analytically pure product **2** in good yield after a simple acid/base workup.

In summary, we have developed a Horner–Wadsworth–Emmons equivalent of the Ramirez olefination of ketones and aldehydes using triisopropylphosphite. In general, the reactivity of triisopropylphosphite toward *gem*-dibromoolefination is comparable to PPh_3 with aldehydes and higher than PPh_3 with ketones. This phosphite-mediated reaction likely proceeds through an ionic mechanism rather than an ylide intermediate observed in PPh_3-mediated reactions.



Scheme 5 Preparation of **2a** without chromatographic separation

Acknowledgment

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(9) **General Procedure for Ramirez Olefination**
To a solution of **1a** (0.151 g, 1 mmol) and CBr_4 (0.49 g, 1.5 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of

the corresponding phosphine or phosphite (3.0 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 30 min, the reaction was warmed to r.t., quenched with $NaHCO_3$, extracted with Et_2O, and dried over $MgSO_4$. The product was isolated using column chromatography, and yields are shown in Table 2.

Preparation of 2a Using CBr_4/P(O*i*-Pr)$_3$ without Chromatographic Purification

To a solution of **1a** (2.0 g, 13.2 mmol) and CBr_4 (6.6 g, 19.9 mmol) in CH_2Cl_2 (50 mL) was added dropwise a solution of P(O*i*-Pr)$_3$ (7.2 mL, 29 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 30 min, the reaction was warmed to r.t., quenched with $NaHCO_3$, and extracted with Et_2O. After removal of solvent, the mixture was taken into concd HCl (12 M, 15 mL) and AcOH (15 mL) and heated to reflux overnight. The mixture was cooled to r.t., diluted with H_2O (50 mL), neutralized with Na_2CO_3, and extracted with Et_2O. After drying over $MgSO_4$, solvent was removed under vacuum to give an off-white solid (3.51 g, 87%). The ^{1}H NMR spectrum of the product was identical to the authentic sample.

Compound **2f**: The general procedure was followed using **1f** (0.135 g, 0.5 mmol), CBr_4 (0.250 g, 0.75 mmol), and P(O*i*-Pr)$_3$ (0.37 mL, 1.5 mol). The product was obtained as a slightly yellow solid (0.207 g, 98%). R_f = 0.41 (10% EtOAc in hexane); mp 63–65 °C. IR (neat): 3079, 2921, 1624, 1528, 1347, 1254, 1099 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.36 (2 H, m), 7.47–7.49 (2 H, m), 7.28–7.38 (4 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (J_{C-F} = 262 Hz), 144.4, 131.8, 129.7, 128.7, 126.8 (J_{C-F} = 4.6 Hz), 126.3 (J_{C-F} = 10.7 Hz), 123.5, 122.1, 117.6 (J_{C-F} = 24.5 Hz), 104.1, 98.9, 87.2. HRMS (EI): *m/z* calcd for $C_{16}H_8Br_2FNO_2$ [M]$^+$: 422.8906; found: 422.8907.

(10) Product **4**: The general procedure for Ramirez olefination was followed using α-bromoacetophenone (1.08 g, 5.4 mmol), CBr_4 (3.54 g, 10.8 mmol), and P(O*i*-Pr)$_3$ (5.3 mL, 21.6 mol). The product was obtained as a white crystalline solid (1.5 g, 80%). The single crystal suitable for X-ray determination was obtained by slow diffusion of hexanes in a solution of **4** in CH_2Cl_2. R_f = 0.70 (10% EtOAc in hexane); mp 98–100 °C. IR (neat): 3017, 1582, 1447 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.82 (2 H, m), 7.36–7.42 (3 H, m), 3.84 (1 H, d, *J* = 5.0 Hz), 3.12 (1 H, d, *J* = 5.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.3, 131.2, 129.4, 127.7, 67.8, 55.4, 45.8. HRMS (EI): *m/z* calcd for $C_9H_7Br_3O$ [M]$^+$: 367.8047; found: 367.8041.

(11) The general procedure for Ramirez olefination was followed using phenylpropynal (0.130 g, 1 mmol), CBr_4 (0.498 g, 1.5 mmol), and P(O*i*-Pr)$_3$ (0.74 mL, 3 mol) in CH_2Cl_2 at –20 °C. The crude material was separated by chromatography to give **6** (0.136 g, 47%) and **7** (0.232 g, 50%).

Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.52 (5 H, m), 6.77 (1 H, s).

Compound **7**: R_f = 0.22 (25% EtOAc in hexane). IR (neat): 2980, 2934, 2211, 1572, 1488, 1375, 1280, 1158 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.57 (2 H, m), 7.33–7.42 (3 H, m), 4.84 (2 H, septet, *J* = 6.2 Hz), 1.39 (12 H, t, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.8, 129.8, 128.6, 121.4, 99.7, 91.4 (d, J_{C-P} = 11.8 Hz), 81.3 (d, J_{C-P} = 2.4 Hz), 79.1 (d, J_{C-P} = 4.3 Hz), 74.2 (d, J_{C-P} = 6.3 Hz), 23.8 (d, J_{C-P} = 4.6 Hz), 23.7 (d, J_{C-P} = 5.4 Hz). ^{31}P NMR (300 MHz, $CDCl_3$): δ = –9.44. ESI-HRMS: *m/z* calcd for $C_{16}H_{20}O_4PBr_2$ [M + H]$^+$: 464.9460; found: 464.9458.

(12) Sledzinski, B.; Kroczynski, J.; Zwierzak, A.; Cieslak, L.; Majda, A. DE 2338847, **1974**; *Chem. Abstr*. **1974**, *83*, 54610.

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