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$P[N(i\text{-Bu})CH_2CH_2]_3N$: Nonionic Lewis Base for Promoting the Room-Temperature Synthesis of α,*β*-Unsaturated Esters, Fluorides, Ketones, and Nitriles Using Wadsworth−Emmons Phosphonates

Venkat Reddy Chintareddy,[†] Arkady Ellern,[‡] and John G. Verkade*,[†]

[†]*Department of Chemistry, Gilman Hall and* [‡]*Molecular Structure Laboratory,*
Iowa State University, Ames, Iowa 50011, United States

jverkade@iastate.edu

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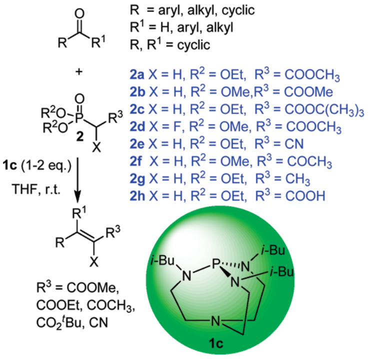

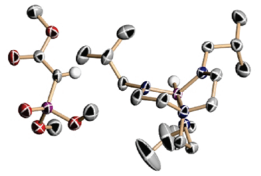

Molecular structure of reactive intermediate formed by **2b** and **1c**

The bicyclic triaminophosphine $P(RNCH_2CH_2)_3N$ (R = *i*-Bu, **1c**) serves as an effective promoter for the room-temperature stereoselective synthesis of α,*β*-unsaturated esters, fluorides, and nitriles from a wide array of aromatic, aliphatic, heterocyclic, and cyclic aldehydes and ketones, using a range of Wadsworth−Emmons (WE) phosphonates. Among the analogues of **1c** [R = Me (**1a**), *i*-Pr (**1b**), Bn (**1d**)], **1a** and **1b** performed well, although longer reaction times were involved, and **1d** led to poorer yields than **1c**. Functionalities such as cyano, chloro, bromo, methoxy, amino, ester, and nitro were well tolerated. We were able to isolate and characterize (by X-ray means; see above) the reactive WE intermediate species formed from **2b** and **1c**.

Introduction

The Wadsworth−Emmons (WE) reaction is versatile, having numerous applications in the synthesis of intermediates for fine chemicals such as perfumes, fragrances, insecticides, carotenoids, pheromones, pharmaceuticals, and prostaglandins.[1−3] WE reactions are key steps in the total synthesis of biologically active

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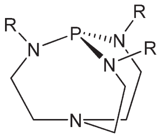
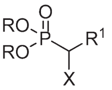
molecules such as Maytansine (anticancer),[3c] Leukotriene B4 (leukocyte function promoter),[2e] Aurodox (antibiotic),[2e] Lipoxin A4 (anti-inflammatory mediator),[2e] Amphoteronolide B (aglycone of the antibiotic amphotericin),[2e] X-14547A (antibiotic),[2e] providencin (anticancer),[2j] macrolides (antibiotics),[2k] trichostatic acid (anticancer),[2l] Brevenal (brevetoxin inhibitor),[2m] and Berkelic acid[3d] (a natural product with selective activity against ovarian cancer). The WE reaction is also a key step in the synthesis of Oseltamivir, a widely used antiviral drug for the treatment and prevention of influenza.[3e] With inherent advantages, such as the use of inexpensive triethylphosphite as a starting material for the synthesis of phosphonates, ease of product separation, and excellent reactivity of the phosphonate reagent, the WE reaction has enjoyed a broader scope of utility than the Wittig reaction.[2a,3]



1

1a : R = Me ($pK_a = 32.90$)
1b : R = *i*-Pr ($pK_a = 33.63$)
1c : R = *i*-Bu ($pK_a = 33.53$)
1d : R = Bn

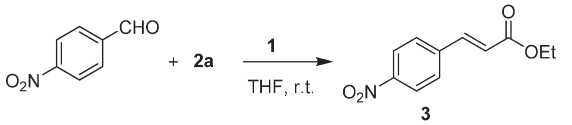
FIGURE 1. Proazaphosphatranes used in this study.



2a X = H, R = OEt, $R^1 = COOCH_2CH_3$
2b X = H, R = OMe, $R^1 = COOCH_3$
2c X = H, R = OEt, $R^1 = COOC(CH_3)_3$
2d X = F, R = OEt, $R^1 = COOCH_2CH_3$
2e X = H, R = OEt, R^1 = CN
2f X = H, R = OMe, $R^1 = COCH_3$
2g X = H, R = OEt, $R^1 = CH_3$
2h X = H, R = OEt, R^1 = COOH

FIGURE 2. Phosphonates employed in this work.

TABLE 1. Survey of Proazaphosphatranes in the Reaction of *p*-Nitrobenzaldehyde with 2a in the Presence of 1 equiv of 1[a]



1	*t* (h)	yield (%)[b] [*E*/*Z*][c]
1a	5.5	95 [99/1]
1b	4.0	94 [99/1]
1c	0.5	96 [99/1]; lit.: 89 [100/0],[15a] 74 [100/0],[5d] 95,[19b] 98 [99/1],[18] 90 [99/1][3a]
1d	6.0	60 [96/4]
none	20.0	no reaction

[a] See Experimental Section for conditions. [b] Isolated yields after column chromatography. [c] *E*/*Z* ratios were determined by ^1H NMR spectroscopic integration.

Condensation of an aldehyde or a ketone with a phosphonate to give an α,β-unsaturated ester or nitrile (see scheme in the abstract) is traditionally effected in the presence of strong stoichiometric ionic bases such as KOH,[4] $Ba(OH)_2$,[5] NaH,[6] BuLi,[6,7] benzyltrimethylammonium hydroxide (Triton B),[6,8] LiOH,[9a−d] Et_3N-LiBr,[9e,f] KHMDS/18-crown-6,[8,10a] K_2CO_3/$KHCO_3$/phase transfer conditions,[10b] and KO^tBu/18 crown-6.[11] *N*-Ethylpiperidine assisted by $Sn(OSO_2CF_3)_2$ has also been employed as a base.[12] Barrett et al. reported an application of the nonionic base 1,1,3,3-tetramethylguanidine (TMG) in combinatorial chemistry involving WE reactions,[13] and Simoni et al. described the use of 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD) as a nonionic base for WE reactions in refluxing THF.[14a] In 2002, Nagao et al. used *i*-PrMgBr as promoter for WE reactions,[14b] and in 2008, Davies et al. reported WE reactions using MeMgBr as base.[14c] Several reports of solid reagents/catalysts for WE reactions have also appeared, for example, SiO_2-supported 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU),[15] KF/alumina,[16] MgAlO-*t*-Bu

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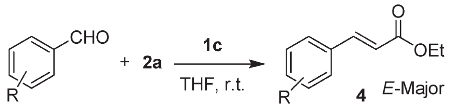
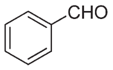
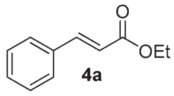
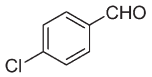
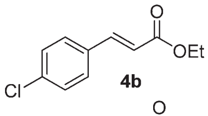
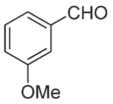
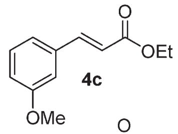
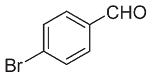
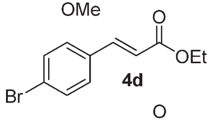
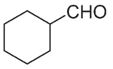
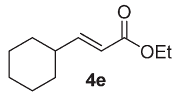
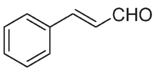
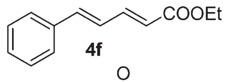
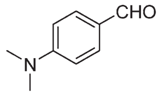
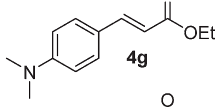
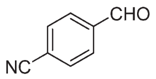
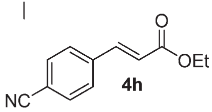
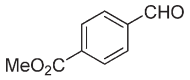
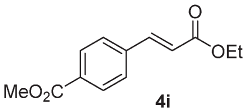
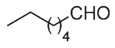
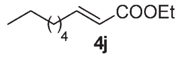
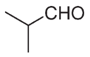
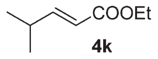
TABLE 2. WE Reactions of Various Aldehydes with 2a in the Presence of 1 equiv of 1c[a]



Aldehyde	Time (h)	Product (**4**)	Yield (%)[b] (*E*/*Z*)[c]
	3.0	 **4a**	86 (99/1) Lit.: 34.3 (95/5),[16b] 75-92 (100/0),[14a] 88 (98/2),[15a] 76 (99/1)[3a]
	5.0	 **4b**	89 (97/3) Lit.: 80 (58/42),[6g] 98 (99/1),[3a] 91(100/0),[17] 97 (99/1)[15a]
	24.0	 **4c**	69 (100/0)
	6.0	 **4d**	89 (97/3)
	4.0	 **4e**	78 (83/17) Lit.: 83 (99/1),[15a] 80 (99/1)[3a]
	2.0	 **4f**	93 (99/1) Lit.: 63 (96/4),[9c] 71 (100/0),[9a] 50 (99/1)[3a]
	4.0	 **4g**	94 (99/1)
	6.0	 **4h**	90 (95/5) Lit.: 95 (97/3)[15a]
	6.0	 **4i**	90 (95/5)
	2.5	 **4j**	91 (96/4) Lit.: 96,[6r] 76[10b]
	1.5	 **4k**	88 (96/4) Lit.: 91,[6n] 97,[6o] 60,[6p] 58,[6q] 80[9e]

[a]See Experimental Section for conditions. [b]Isolated yields after column chromatography. Only the *E* isomer was isolated. [c]*E*/*Z* ratios were determined by ^{1}H NMR spectroscopic integration.

hydrotalcite,[3a] a MgLa mixed oxide,[17] and nano MgO.[18] WE reactions are also useful in solid phase syntheses using DBU as base.[19] Problems encountered in some of the aforementioned methods include longer reaction times arising from moderate chemoselectivity (resulting in Knoevenagel adduct formation or Cannizzarro and Meerwein–Pondorf–Verley reductions[13,16]) and the lack of ketone participation.[3a,14a,15] Heterogeneous catalysts such as MgAlO-*t*-Bu hydrotalcite,[3a] MgLa mixed oxides,[17] macroreticular anion-exchange resin Amberlyst A-26 (OH$^-$ form),[3f] and nano MgO[18] require 130 °C to obtain reasonable yields of WE products, but heterogeneous metal oxide catalysts must be prepared in a process requiring 450 °C for up to 6 h,[3a,17] and activation of Ba(OH)$_2$ as a catalyst requires 200 °C.[5] An ionic liquid methodology has been described that uses up to 5 equiv of LiOH·H$_2$O as a promoter.[9a] Apart from this, to the best of our knowledge there is no report of a catalyst that operates at room temperature with wide functional group tolerance using a commercially available catalyst.

We have previously reported that the commercially available[20a] proazaphosphatranes **1a**, **1b**, and **1c** (Figure 1) are exceedingly strong nonionic bases that are useful in a wide variety of important organic transformations[20b−g] as organocatalysts,

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(17) Kantam, M. L.; Kochkar, H.; Clacens, J.-M.; Veldurthy, B.; Garcia-Ruiz, A.; Figueras, F. *Appl. Catal. B* **2005**, *55*, 177–183.

(18) Choudary, B. M.; Mahendar, K.; Ranganath, K. V. S. *J. Mol. Catal. A: Chem.* **2005**, *234*, 25–27.

(19) (a) Yamazaki, K.; Kondo, Y. *Chem. Commun.* **2002**, 210–211, and references therein. (b) Bouziane, A.; Helou, M.; Carboni, B.; Carreaux, F.; Demerseman, B.; Bruneau, C.; Renaud, J.-L. *Chem.—Eur. J.* **2008**, *14*, 5630–5637.

as ligands in metal-assisted coupling reactions, and as stoichiometric reagents.[21]

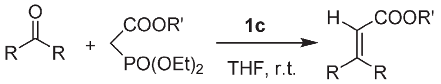
Results and Discussion

Here we report a convenient, efficient, and stereospecific synthesis of α,β-unsaturated esters, fluorides, and nitriles from a wide array of aromatic, heterocyclic, aliphatic, and cyclic aldehydes and ketones, using a range of WE phosphonates **2a**−**2f** (Figure 2) in the presence of a proazaphosphatrane of type **1** (see scheme in the abstract). In screening **1a**−**1d** in the reaction shown in Table 1, we found that **1d**[20c,d] did not perform as well as **1a**−**1c**. Among the latter compounds, **1c** gave an excellent yield of product in the shortest time. Why **1c** is the best promoter is not clear since its basicity is less than (but close to) that of **1b**, although it is perhaps less sterically encumbered than **1b**. As expected, no reaction occurred in the absence of a proazaphosphatrane given the mildness of our conditions. It may be mentioned that we observed earlier that **1a** promoted a few WE reactions, but the scope of this transformation was not investigated.[22] Pleasingly, Cannizarro and MPV reductions were not observed in the reactions in Table 1, in contrast to their frequent occurrence in the presence of ionic bases such as NaOH and LDA.[13]

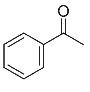
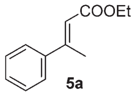
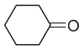
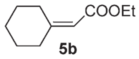
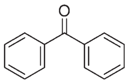
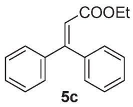
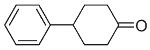
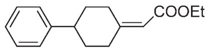
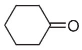
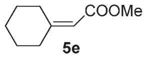
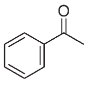
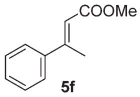
We initially tested **1c** in the reaction of *p*-nitrobenzaldehyde with **2a** using 12.5 mol % of **1c**, resulting in a 78% yield of product ($E/Z = 99/1$) in 7 h. Increasing the mol % of **1c** to 25, 50, and 100 resulted in an 86%, 90%, and 95% isolated yield of product ($E/Z = 99/1$ in each case) in 3.0, 1.0, and 0.5 h, respectively. Product yields did not appear to correlate with steric or basicity trends of the proazaphosphatranes. The effect of organic solvent polarity on this reaction was examined by allowing *p*-nitrobenzaldehyde to react with triethyl phosphonoacetate **2a** for 0.5 h in the presence of 1 equiv of **1c** at room temperature. The effect of solvent polarity was minimal as shown by the excellent isolated product yields shown for **3** in polar solvents such as tetrahydrofuran (THF) and 1,4-dioxane (96% and 94% yields, respectively) and for the nonpolar solvents toluene and benzene (94% and 95% yields, respectively).

To evaluate the scope of the transformation, we employed a range of aldehydes in their reaction with **2a** in the presence of 1 equiv of **1c** (Table 2). 4-Chlorobenzaldehyde and 4-bromobenzaldehyde provided good isolated product yields (products **4b** and **4d**, respectively), while 3-methoxybenzaldehyde (Table 2, **4c**) gave a moderate yield of product. Electron-deficient, acid-sensitive 4-cyanobenzaldehyde **4h** and the ester-functionalized aldehyde **4i** gave excellent yields of *trans*-configured esters. An enolizable aliphatic acyclic and a sterically bulky aldehyde gave an excellent and moderate product ester yield, respectively (entries **4j** and **4k**). Interestingly, the yield of the conjugated ester **4f** exceeded that previously reported in the literature. An electron-donating amino-functionalized aldehyde with phosphonate **2a** resulted in an excellent yield of α,β-ester **4g**. Good to excellent yields of *E* product were obtained in all cases. In the reaction in Table 2 that produced **4h**, promoter **1c** in protonated form was recovered in 87% yield according to our previous report,[23] thus enhancing the appeal of **1c** for possible recovery in these syntheses.

TABLE 3. WE Reactions of 2 with Various Ketones in the Presence of 1 equiv of 1c[a]



2
5 *E* Major

Ketone	Time (h)	(**2**)	Product (**5**)	Yield (%)[b] (*E/Z*)[c]
	24.0 24.0	**2a** **2a**	 **5a**	47 (99/1) 67 (99/1)[d] Lit.: no reaction[e,3a] Lit.: 35 (87/13),[4c] 36 (85/15)[16b]
	8.0	**2a**	 **5b**	89 Lit.: 90,[3a] 79[16b]
	24.0 36.0	**2a** **2a**	 **5c**	43 61[d] Lit.: 20,[15b] 77,[6k] 92[6l]
	12.0	**2a**	 **5d**	83
	10.0	**2b**	 **5e**	68 Lit.: 98,[6j] 85[9c]
	24.0	**2b**	 **5f**	73 (100/0)

[a]See Experimental Section for conditions. [b]Isolated yields after column chromatography. [c]*E/Z* ratios were determined by ^{1}H NMR spectroscopic integration. [d]2 equiv of **1c** was used. [e]No yield was obtained using MgAlO-*t*-Bu hydrotalcite catalyst.

Ketones are well-known to be difficult substrates for WE reactions.[3a,9c,14a,15,17,18] As shown in Table 3, both aromatic and aliphatic ketones reacted with phosphonate **2a** or **2b** in the presence of 1 equiv of **1c** at room temperature, affording the desired products in poor to good yields, although time requirements were longer than in the case of aldehydes. However, the *E/Z* ratio was higher for **5a** than those in literature reports[3a,15,17] for this compound. It is noteworthy that some of the literature procedures[3a,15] reported failure of such reactions, gave poor yields, or operated at higher temperatures (typically at 130 °C[3a,17,18]). The reaction of acetophenone with **2a** resulted in a 47% yield of product **5a** in the presence of 1 equiv of **1c**, but with 2 equiv, a 67% yield of product was realized after 24 h. Similarly, benzophenone with 1 equiv of

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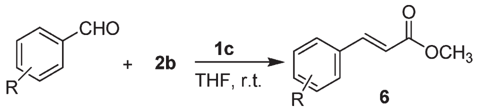
(20) (a) Proazaphosphatranes **1a**−**1c** are commercially available from Aldrich, and **1a** and **1b** can also be obtained from Strem Chemicals. (b) Venkat Reddy, Ch.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2005**, *7*, 4427–4430. (c) Chintareddy, V. R.; Wadhwa, K.; Verkade, J. G. *J. Org. Chem.* **2009**, *74*, 8118–8132. (d) Wadhwa, K.; Chintareddy, V. R.; Verkade, J. G. *J. Org. Chem.* **2009**, *74*, 6681–6690. (e) Wadhwa, K.; Verkade, J. G. *J. Org. Chem.* **2009**, *74*, 5683–5686. (f) Wadhwa, K.; Verkade, J. G. *J. Org. Chem.* **2009**, *74*, 4368–4371. (g) Venkat Reddy, Ch.; Verkade, J. G. *J. Org. Chem.* **2007**, *72*, 3093–3096. (h) Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467–475.

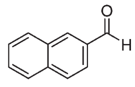
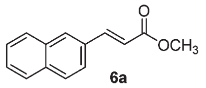
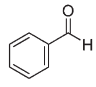
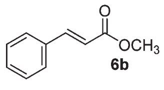
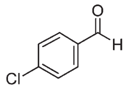
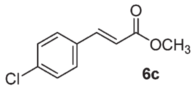
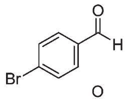
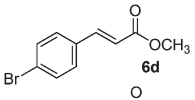
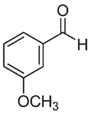
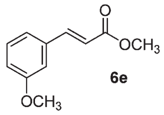
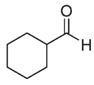
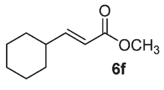
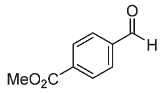
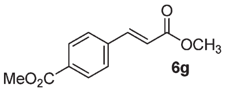
(21) For reviews of proazaphosphatrane chemistry, see: (a) Verkade, J. G. New Aspects of Phosphorus Chemistry II. *Top. Curr. Chem.* Majoral, J. P., Ed., **2002**, *233*, 1−44. (b) Verkade, J. G.; Kisanga, P. B. *Tetrahedron* **2003**, *59*, 7819–7858. (c) Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37*, 3–14. (d) Urgaonkar, S.; Verkade, J. G. *Spec. Chem.* **2006**, *26*, 36–39.

(22) Wang, Z.; Verkade., J. G. *Heteroatom Chem.* **1998**, *9*, 697–689.

(23) Kisanga, P.; D'Sa, B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 8047–8052. Also see the Supporting Information for experimental details.

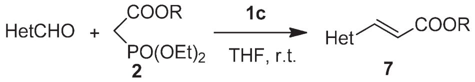
TABLE 4. WE Reactions of Aldehydes with 2b in the Presence of 1 equiv of 1c[a]

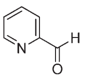
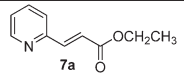
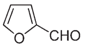
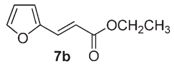
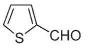
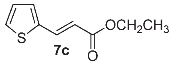
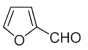
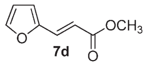
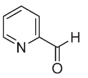
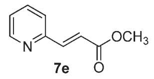


Aldehyde	Time (h)	Product (**6**)	Yield (%)[b] (*E*/*Z*)[c]
	5.5	 **6a**	89 (99/1) Lit.: 79[6m]
	1.0	 **6b**	91 (99/1) Lit.: 80 (*E*/*Z* = 31/69)[10]
	4.0	 **6c**	94 (99/1) Lit.: 98,[18] 97,[3f] 94[6m]
	6.0	 **6d**	91 (94/6)
	24.0	 **6e**	91 (94/6)
	4.5	 **6f**	76 (83/17) Lit.: 62,[14c] 83,[18] 41[6m],80[8b]
	9.0	 **6g**	90 (93/7)

[a]See Experimental Section for conditions. [b]Isolated yields after column chromatography. Only the *E* isomer was isolated. [c]*E*/*Z* ratios were determined by ^{1}H NMR spectroscopic integration.

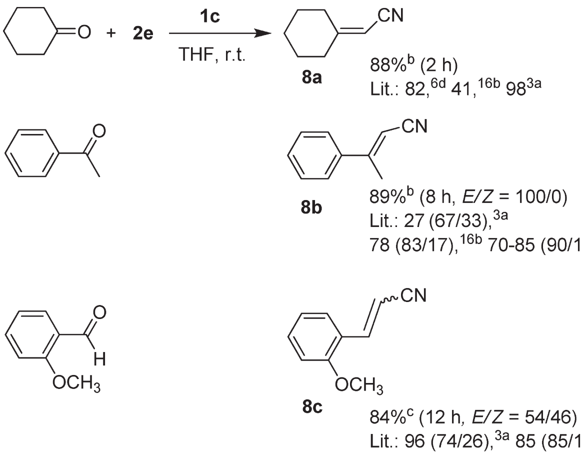
TABLE 5. WE Reactions with Various Heterocyclic Aldehydes in the Presence of 1 equiv of 1c[a]



HetCHO	Time (h)	(**2**)	Product (**7**)	Yield (%)[b] (*E*/*Z*)[c]
	8.0	**2a**	 **7a**	82 (90/10) Lit.: 86 (95/5),[9f] 74[9a]
	2.0	**2a**	 **7b**	90 (99/1) Lit.: 86(99/1),[3a] 86 (100/0)[9c]
	12.0	**2a**	 **7c**	91 (99/1) Lit.: 75 (100/0)[6i]
	2.20	**2b**	 **7d**	84 (99/1) Lit.: 100,[6s] 73 (99/1),[18] 71 (100/0)[6m]
	12.0	**2b**	 **7e**	80 (87/13)

[a]See Experimental Section for conditions. [b]Isolated yields after column chromatography. Only the *E* isomer was isolated. [c]*E*/*Z* ratios were determined by ^{1}H NMR spectroscopic integration.

SCHEME 1. Synthesis of α,β-Unsaturated Nitriles in the Presence of 1 equiv of 1c[a]



8a: 88%[b] (2 h)
Lit.: 82,[6d] 41,[16b] 98[3a]

8b: 89%[b] (8 h, *E*/*Z* = 100/0)
Lit.: 27 (67/33),[3a]
78 (83/17),[16b] 70-85 (90/10)[9b]

8c: 84%[c] (12 h, *E*/*Z* = 54/46)
Lit.: 96 (74/26),[3a] 85 (85/15),[17]
96 (74/26)[3a]

[a]See Experimental Section for conditions. [b]Isolated yields after column chromatography. Reaction times appear in parentheses. [c]Isolated yield of *E*/*Z* mixture.

2a gave a 43% yield of product **5c** in 24 h, whereas in 36 h using 2 equiv of **1c**, a 61% product yield was obtained. Interestingly, the reaction of acetophenone with **2b** gave exclusively the *E* isomeric product (**5f**) in 73% isolated yield.

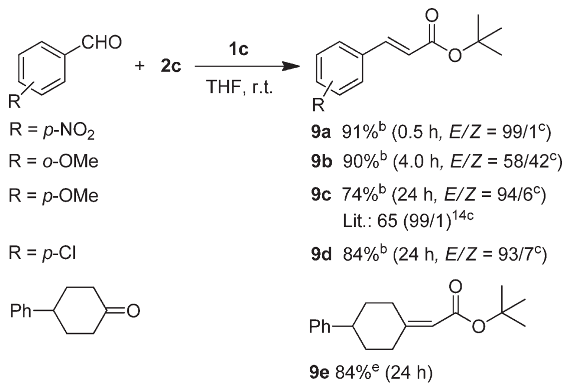
We then investigated reactions of phosphonate **2b** with a variety of aldehydes (Table 4). Except for cyclohexyl aldehyde, the yields and *E*/*Z* ratios are good to excellent. For the reaction involving 3-methoxybenzaldehyde, an extended reaction time was required. Electron-neutral aldehydes such as benzaldehyde and 2-napthaldehyde with phosphonate **2b** gave a good and excellent yield of the unsaturated esters **6a** and **6b**, respectively. 4-Chlorobenzaldehyde and 4-bromobenzaldehyde provided excellent isolated product yields (**6c** and **6d**, respectively), while cyclohexanecarboxaldehyde (**6f**) gave a moderate product yield. The electron-deficient, acid-sensitive, ester-functionalized aldehyde gave an excellent yield of *trans*-ester **6g**.

Results for the use of heterocyclic aldehydes containing oxygen, nitrogen, and sulfur as heteroatom in the WE reaction with **2a** or **2b** in the presence of 1 equiv of **1c** are presented in Table 5. Good to excellent product yields were obtained with good to excellent stereoselectivity. The two five-membered heterocyclic aldehydes in Table 5 gave excellent isolated yields of the corresponding products (entries **7b** and **7c**), whereas **7a** was isolated in good yield. The versatility of our protocol was extended with phosphonate **2b** with the heterocyclic aldehydes furan-2-carboxaldehyde and pyridine-2-carboxaldehyde, providing an 84% and 80% yield of α,β-unsaturated product, respectively.

In Scheme 1 is illustrated the ability of **1c** to promote the synthesis of α,β-unsaturated nitriles via WE reactions employing phosphonate **2e** in its reaction with two different ketones and an aldehyde. In the cases of cyclohexyl ketone and benzaldehyde, our protocol is superior.

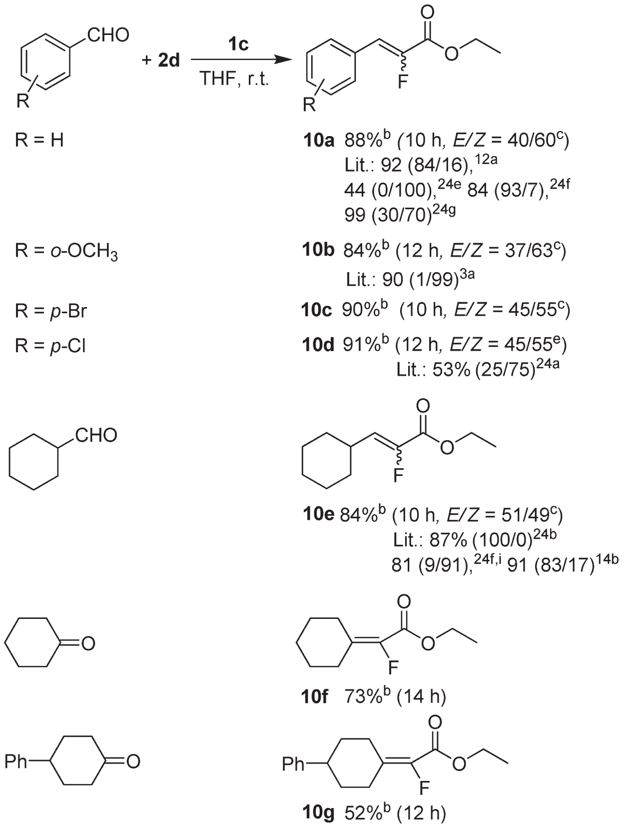
The reaction of the bulky phosphonate **2c** with various aldehydes and a ketone also proceeded efficiently (Scheme 2) in moderate to excellent yields. The formation of α-fluoro esters shown in Scheme 3 is especially attractive for the synthesis of biologically important molecules.[24,12a] As seen in Scheme 3, Z isomer formation is enhanced using an α-fluoro ester substrate. Electron-neutral and electron-rich aldehydes participated with equal ease. The ketones shown

SCHEME 2. Synthesis of Bulky Esters Using 1 equiv of 1c[a]



[a]See Experimental Section for conditions. [b]Isolated yields after column chromatography. Reaction times appear in parentheses. Only the *E* isomer was isolated. [c]*E*/*Z* ratio was determined by ^{1}H NMR spectroscopy.

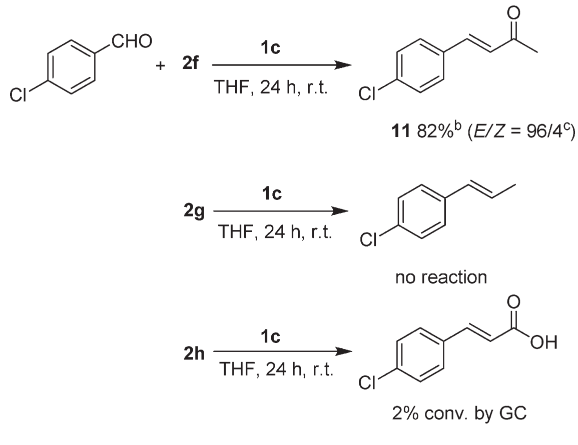
SCHEME 3. Synthesis of α-Fluoro Esters Using 1 equiv of 1c[a]



[a]See Experimental Section for conditions. [b]Isolated yield of *E*/*Z* mixture. Reaction times appear in parentheses. [c]*E*/*Z* ratio was determined by ^{19}F NMR spectroscopy.

in Scheme 3 also reacted with phosphonate **2d**, providing a good yield of product at room temperature. It is worth noting here that the products **9a**−**d** in Scheme 3 are prepared by our method for the first time except **9c**, although such bulky esters have been synthesized previously via the Mizoroki−Heck reaction.[25]

SCHEME 4. Some Test Examples with Different Phosphonates Using 1 equiv of 1c[a]



[a]See Experimental Section for conditions. [b]Isolated yield after column chromatography, isolated yield of *E* isomer. [c]*E*/*Z* ratio was determined by ^{1}H NMR spectroscopy.

Synthesis of an α,β-unsaturated ketone using acetyl phosphonate **2f** proceeded in good yield (Scheme 4), whereas no reaction occurred for alkyl phosphonate **2g** with 4-chlorobenzaldehyde using 1 equiv of **1c**. Not surprisingly, the acid-containing phosphonate **2h** (which could be expected to protonate **1c**) gave only a 2% conversion by GC−MS analysis under the same reaction conditions.

The pathway of the WE reaction has been extensively discussed in the literature.[1,2,3a,26] Seyden-Penne[26f] et al. reported the presence of carbanions in lithium or potassium

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(24) See for example: (a) Suzuki, Y.; Sato., M. *Tetrahedron Lett.* **2004**, *45*, 1679–1681. (b) Bargiggia, F.; Santos, S. D.; Piva, O. *Synthesis* **2002**, 427–437. (c) Ziemer, F.; Willms, L.; Bauer, K.; Bieringer, H.; Rosinger, C.; Demassey, J. U.S. Patent 5,972,839 (Hoechst Schering AgrEvo GmbH); *Chem. Abstr.* **1999**, *129*, 105502. (d) Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1990**, *55*, 4639–4642. (e) Kitazume, T.; Tanaka, G. *J. Fluorine Chem.* **2000**, *106*, 211–215. (f) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536–4537. (g) Sano, S.; Kuroda, Y.; Saito, K.; Ose, Y.; Nagao, Y. *Tetrahedron* **2006**, *62*, 11881–11890. (h) Miyake, N.; Kitazume, T. *J. Fluorine Chem.* **2003**, *122*, 243–246. (I) Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **2004**, *45*, 1679–1681. (j) Sano, S.; Saito, K.; Nagao, Y. *Tetrahedron Lett.* **2003**, *44*, 3987–3990.

(25) For selected references on Mizoroki−Heck reactions see: (a) Nadri, S.; Joshaghani, M.; Rafiee, E. *Appl. Catal. A* **2009**, *362*, 163–168. (b) Mohanty, S.; Suresh, D.; Balakrishna, M. S.; Mague, J. T. *Tetrahedron* **2007**, *64*, 240–247. (c) Dawood, K. M. *Tetrahedron* **2007**, *63*, 9642–9651. (d) Mino, T.; Shirae, Y.; Sasai, Y.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2006**, *71*, 6834–6839. (e) Han, Y.; Lee, L. J.; Huynh, H. V. *Organometallics* **2009**, *28*, 2778–2786. (f) Kantchev, E. A. B.; Peh, G-R; Zhang, C.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 3949–3952. (g) Han, Y.; Huynh, H. V.; Koh, L. L. *J. Organomet. Chem.* **2007**, *692*, 3606–3613. (h) Huynh, H. V.; Neo, T. C.; Tan, G. K. *Organometallics* **2006**, *25*, 1298–1302. (i) Martinez, R.; Voica, F.; Genet, J.-P.; Darses, S. *Org. Lett.* **2007**, *9*, 3213–3216.

(26) For mechanistic studies, see: (a) Izod, K. *Coord. Chem. Rev.* **2002**, *227*, 53–173. (b) Abdou, W. M.; Khidre, M. D.; Khidre, R. E. *Eur. J. Med. Chem.* **2009**, *44*, 526–532. (c) Strzalko, T.; Seyden-Penne, J.; Froment, F.; Corset, J.; Simonnin, M. P. *Can. J. Chem.* **1988**, *66*, 391–396. (d) Strzalko, T.; Seyden-Penne, J.; Froment, F.; Corset, J.; Simonnin, M. P. *J. Chem. Soc., Perkin Trans 2* **1987**, *6*, 783–789. (e) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Org. Chem.* **1984**, *49*, 3517–3527. (f) Bottin-Strzalko, T.; Corset, J.; Froment, F.; Pouet, M. J.; Seyden-Penne, J.; Simonnin, M. P. *J. Org. Chem.* **1980**, *45*, 1270–1276. (g) Bottin-Strzalko, T.; Seyden-Penne, J.; Pouet, M-J; Simonnin, M. P. *J. Org. Chem.* **1978**, *43*, 4346–4351. (h) Motoyoshiya, J.; Kusaura, T.; Kokin, K.; Yokoya, S.-I.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* **2001**, *57*, 1715–1721. (i) Webb, G. A.; Simonnin, M. P.; Seyden-Penne, J.; Bottin-Strzalko, T. *Mag. Reson. Chem.* **1985**, *23*, 48–51. (j) Bonfanti, J.-F.; Craig, D. *Tetrahedron Lett.* **2005**, *46*, 3719–3723. (k) Arnett, E. M.; Wernett, P. C. *J. Org. Chem.* **1993**, *58*, 301–303. (l) Brandt, P.; Norrby, P.-O.; Martin, I.; Rein, T. *J. Org. Chem.* **1998**, *63*, 1280–1289. (m) Ando, K. *J. Org. Chem.* **1999**, *64*, 6815–6821.

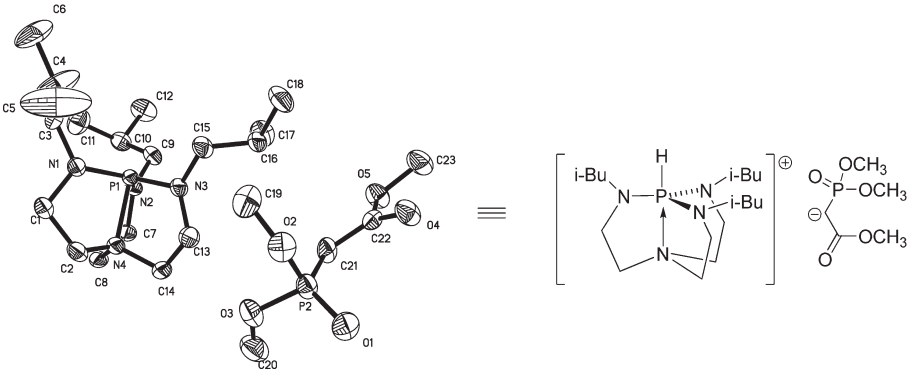


FIGURE 3. Molecular structure of **12** (H atoms are omitted for clarity).

salts of M[$(C_2H_5O)_2P(O)CHCOOCH_3$], which were characterized using proton, carbon, and phosphorus NMR, and IR spectroscopies. Brandt,[26l] Motoyoshiya,[26h] and Ando[26m] et al. reported computational studies on the WE reaction pathway.

In the present work we found that the active methylene group of trimethyl phosphonoacetate (pK_a ~18−19 in DMSO,[1g] ~12 in H_2O[27]) is deprotonated by **1c** (pK_a 33.53 in CH_3CN[28]). By cooling an acetonitrile/hexanes solution of a 1:1 mixture of these two components at freezer temperature for 1−3 h, it became possible to grow colorless crystalline needles of **12** that melted at room temperature (see Supporting Information for conditions). The molecular structure shown by X-ray means (Figure 3) was determined at −70 °C (see Supporting Information for details). It should be noted, however, that water is stoichiometrically formed in the WE reaction. Thus water in the presence of **1c** is likely to be in equilibrium with [H**1c**]$^+$[OH^-] wherein the hydroxide ion is a potentially catalytically active species that can also deprotonate the phosphonate substrate as **1c** is converted to its protonated analogue.

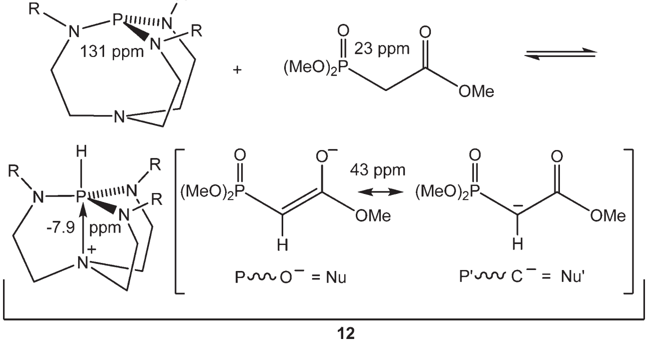
TABLE 6. Pertinent Bond Lengths in 12

bond	av length (pm)[a]	calcd length (pm)[b]	X-ray determined length (pm)	bond character
C−C	154	140.5	138.6(4)	partial double bond
C═C	134			
C−O	143	124.5	122.9(3)	double bond
C═O	120			
P−O	163	149.9	146.8(2)	double bond
P═O	ca. 150			
P−C	180[b]	173.6	170.7(3)	partial double bond
P═C	1.66[c]			

[a] From Huheey, J. E.; Keiter, E. A.; Keiter, R. L. *Inorganic Chemistry*, 4th ed.; Harper Collins College Publishers: New York, 1993, except where indicated otherwise. [b] P−C mean length from *Interatomic Distances and Configurations in Molecules and Ions*; Sutton, L. E., Ed.; Chemical Society: London, Special Publication No. 11, 1958, and No. 18, 1965. [c] P═C length in a simple ylide: (a) Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960; p 224. (b) Bart, J. C. *J. Chem. Soc. B* **1969**, 350−365.

From Table 6 it is seen that our experimental values for pertinent bond lengths of the anion of **12** match well those calculated by others for the gas phase global minimum of this anion at the B3LYP/6-31+G* level.[26l] The large P−C−C angle noted by these authors (128°) is significantly larger than the 122.7(2)° we observed by X-ray means; the former value being well outside of 3× the standard deviation of the latter. It is not presently clear why this discrepancy exists, although crystal packing effects could be responsible. It is interesting to note that the apparent partial double bond nature of the carbon−carbon and phosphorus−carbon linkages in the WE intermediate anion is reflected in both the calculated and the X-ray-determined bond length values. However, a similar departure from the expected nature of the P═O and C═O bonds does not seem to affect these linkages as measured by both the calculation and the X-ray determination of their lengths.

SCHEME 5. Equilibrium Formed by 1c and 1 equiv of Trimethyl Phosphonoacetate with ^{31}P NMR Chemical Shifts Measured in C_6D_6



In the solid state, **12** is composed of the transannulated protonated proazaphosphatrane H**1c**$^+$ cation and the free intermediate [$(MeO)_2P(O)CHC(O)OMe$]$^-$ anion, suggesting that the equilibrium between equimolar trimethyl phosphonoacetate and **1c** involves the formation of the ionic salt **12** (Scheme 5 and Figure 3). The room-temperature ^{31}P NMR spectrum consists of four major peaks at 131 (sharp), 43 (broad), 23 (broad), and −8.0 (sharp) ppm, which we assign to **1c**, the anion of **12**, the trimethyl phosphonoacetate molecule, and the cation of **12**, respectively. The assignments of the broad peaks accord well with those made earlier for equilibria reached in DME with trimethyl phosphonoacetate in the presence of LiOt-Bu or LiOCH$(CF_3)_2$.[1g,29] The assignment for the fourth peak is consonant with the ^{31}P chemical shift we observed

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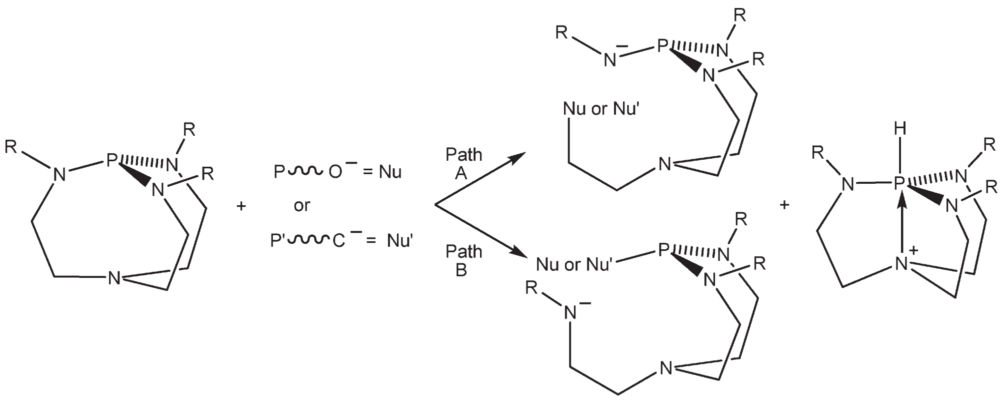
(27) The reported pK_a of triethyl phosphonoacetate in water is 11.9: Sokolov, M. P.; Gazizov, I. G.; Mavrin, G. V. *Zh. Obshch. Khim.* **1989**, *59*, 1043–1047.

(28) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 5431–5432.

(29) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

SCHEME 6. Possible Pathways for the Destruction of 1c in the Presence of 12



separately for this cation as the chloride salt in $CDCl_3$,[20h] and we assign the first peak to **1c** on the basis of the spectrum of this compound in C_6D_6 measured separately. The breadth of the 43 and 23 ppm peaks is consistent with an equilibrium between the neutral and anionic forms of the phosphonoacetate. After warming the NMR tube to 50 °C for 30 min, major sharp peaks at 26.5, 14, and 9.2 ppm arose at the expense of the peaks at 131, 43, and 23 ppm resonances. The prominent upfield peak for the cation of **12** persisted in all of the ^{31}P spectra discussed here. The intensity changes suggested that **1c** was being consumed by a reaction with the anion of **12**. After 1 h at 50 °C, the NMR spectrum had not changed appreciably, but after 2 h, the peak for **1c** had almost disappeared and the broad peaks at 43 and 23 had grown quite small, leaving prominent sharp peaks at 26.5, 14, and 9.5 ppm, in addition to a large sharp peak at 7.9 pm for the cation of **12**. After 16 h at 50 °C, the only prominent peaks remaining were the ones at 26, 14, and 10 ppm in addition to the cation peak at 7.7 ppm, and the peak at 23 ppm had grown considerably smaller.

The three prominent peaks for the final products could be accounted for by the reactions depicted in Scheme 6 wherein the proazaphosphatrane (**1c** in the present instance) is nucleophilically attacked at an N−C carbon in Path A by Nu or Nu′ (see Scheme 5 for definitions of these symbols) or at the phosphorus by these nucleophiles (Path B). Here the anionic charges are balanced by the cation of **12**. The two anionic products of Path A could well have coincident ^{31}P NMR chemical shifts in view of the large separation between the Nu and Nu′ moieties and the phosphorus. The much smaller separation between these fragments and the phosphorus in the two products of Path B could give rise to two ^{31}P NMR chemical shifts.

Conclusions

In summary, as shown in Tables 1−5 and Schemes 1−4, our methodology is eminently suitable for synthesizing WE products via the reaction of a variety of phosphonates with aromatic, aliphatic, cyclic, and heterocyclic aldehydes in the presence of **1c** as a promoter. Good to excellent yields were obtained in the vast majority of cases. In the 69 instances for which literature yields are available for these reactions involving aldehyde or ketone substrates (see corresponding parenthesized data in Tables 1−5 and Schemes 1−3), our yields were comparable in 24 cases, higher in 31, and lower in 14 cases. It is worthy to note here that our protocol gave better or comparable yields even at room temperature over MgAlO-*t*-Bu hydrotalcite,[3a] MgLa mixed oxides,[17] and nano MgO[18] catalysts that operate at 130 °C. The reaction conditions for our protocol are compatible with aryl substrates bearing a variety of functional groups on the phenyl ring such as, cyano, chloro, bromo, methoxy, amino, ester, and nitro. Several desirable features of **1c** as a promoter in addition to its commercial availability, are its optimum steric properties provided by the *iso*-butyl groups, the electron-richness of the phosphorus arising from the donating capability of all three virtually planar nitrogens adjacent to the phosphorus, and the possibility for augmented phosphorus basicity arising from transannular bonding between the bridgehead nitrogen and the phosphorus atom[30] during its catalytic cycle. Under room-temperature reaction conditions, the generally excellent chemo- and stereoselectivity, wide scope, and good to excellent product yields encountered with promoter **1c** make our methodology particularly attractive compared with other catalyst systems usually employed in WE reactions. The molecular structure of **12** determined by X-ray means strongly supports the intermediacy of such a species in the WE reaction. To the best of our knowledge, **12** represents the first structurally characterized example of a WE intermediate by noncalculational means.

Experimental Section

General Procedure for the Synthesis of α,*β*-Unsaturated Esters, Ketones, Fluorides, and Nitriles. An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with aldehyde (1 mmol) and phosphonate (1.2 mmol). The flask was capped with a rubber septum, degassed under reduced pressure, and refilled with argon. Then THF (2 mL) was introduced through a cannula. Proazaphosphatrane **1** (1−2 mmol, as indicated in the footnotes of the tables and schemes) was then added to the flask under argon atmosphere. Proazaphosphatranes **1a**, **1b**, and **1d** were dissolved in 2 mL of THF before addition to the Schlenk flask containing the aldehyde and phosphonate. Finally, the Schlenk flask was again degassed under reduced pressure and refilled with argon. The reaction mixture was stirred at room temperature until the starting aldehyde had been completely consumed as judged by TLC. After completion of the reaction, the crude reaction mixture was loaded onto a small silica gel column and filtered with ethyl acetate/hexanes (1:1), and the crude product was subjected to ^1H NMR spectroscopy to determine the *E*/*Z* ratio. The crude product was then purified by silica gel column chromatography using an eluent

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(30) Karpati, T.; Veszpremi, T.; Thirupathi, N.; Liu, X.; Wang, Z.; Ellern, A.; Nyulaszi, L.; Verkade, J. G. *J. Am. Chem. Soc.* **2006**, *128*, 1500–1512.

mixture of hexanes and ethyl acetate. The yields reported are isolated yields of *E* isomers unless otherwise stated.

Acknowledgment. The National Science Foundation is gratefully acknowledged for financial support of this research in the form of a grant (0750463). We also thank Dr. Weiping Su for kindly providing a sample of **1d**.

Supporting Information Available: General considerations; procedure for recovery of **1c**; ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectroscopic data and copies of corresponding spectra; details of the X-ray data collection, structure solution, and structure refinement; tables of crystal data, atomic coordinates, bond distances, and bond angles for **12** and its CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.