Available online at www.sciencedirect.com

Tetrahedron Letters

Tetrahedron Letters 48 (2007) 51–54

P–C Bond formation via direct and three-component conjugate addition catalyzed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)

Zhiyong Jiang, Yan Zhang, Weiping Ye and Choon-Hong Tan*

Department of Chemistry, 3 Science Drive 3, National University of Singapore, Singapore 117543, Singapore

Received 25 September 2006; revised 25 October 2006; accepted 2 November 2006

Abstract—The direct addition of P(O)–H bonds (dialkyl phosphites and diphenyl phosphonite) across various activated alkenes was catalyzed effectively by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). This is a mild, rapid and efficient protocol to generate P–C bonds. This simple procedure allows a series of dialkyl alkylphosphonates and trisubstituted phosphine oxides to be prepared in high yields. Further investigation resulted in a convenient one-pot, three-component reaction containing diphenyl phosphonite, malononitrile and an aldehyde.

1. Introduction

The versatile nature of phosphorus allows it to play a major role in modern synthetic chemistry.[1] Phosphonates and phosphorus ylides are important synthetic intermediates used in Wittig and related reactions.[2] Chiral phosphines have also found significant synthetic utility as ligands in metal catalyzed reactions.[3] Aminophosphonates and aminophosphinates, as isoteric analogues of aminoacids, have been intensively studied as stable transition state analogues and enzyme inhibitors.[4] Natural products containing P–C bonds also show interesting biological activities.[5]

Amongst various methods to generate P–C bonds, the addition of P(O)–H bonds across alkenes[6] is one of the most utilized. There are three general approaches: (a) the phospha-Michael reaction of activated alkenes, most commonly promoted by alkaline metal alkoxides,[6,7] or the use of tetramethylguanidine (TMG),[8] Lewis acids[9] or microwaves;[10] (b) addition to unactivated olefins promoted by radical initiators such as AIBN;[11] (c) hydrophosphorylation of unactivated alkenes catalyzed by transition metals.[12]

Bicyclic guanidine bases such as 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD) are known as superbases due to their high pKa values.[13] They have been reported to promote various reactions including the Wittig reaction,[14] the addition of azoles to α,β-unsaturated nitriles[15] and Knoevenagel reactions.[16] We reported that TBD can catalyze efficiently the Michael reaction between 1,3-dicarbonyl donors and a range of alkenes.[17] It has also been shown recently that TBD can catalyze ring-opening polymerization of cyclic esters.[18] Herein, we describe mild and efficient protocols to construct P–C bonds via the conjugate addition to activated alkenes.

We found that 20 mol % of TBD catalyzed the reaction between diphenyl phosphite and phenylmaleimide **1a** (Fig. 1). The reaction was complete within 5 min and a

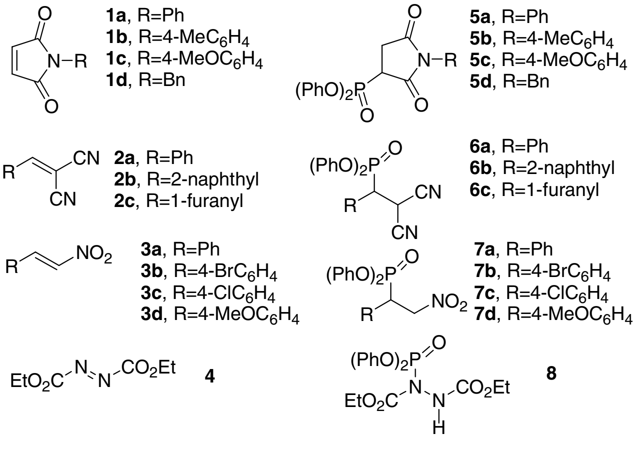


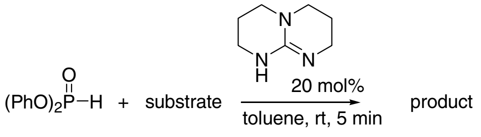
Figure 1. Reactants of diphenylphosphite addition across alkenes.

---

* Corresponding author. Tel.: +65 6874 2845; fax: +65 6779 1691; e-mail: chmtanch@nus.edu.sg

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.019

Table 1. Reactions between diphenyl phosphite and various alkenes

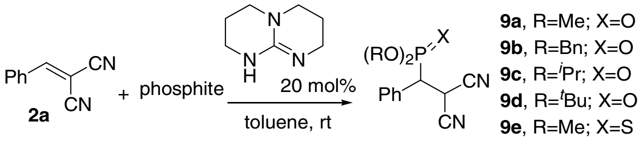


Entry	Substrate	Product	Yield[a] (%)
1	**1a**	**5a**	85
2	**1b**	**5b**	88
3	**1c**	**5c**	70
4	**1d**	**5d**	99
5	**2a**	**6a**	88
6	**2b**	**6b**	94
7	**2c**	**6c**	78
8	**3a**	**7a**	90[b]
9	**3b**	**7b**	87[b]
10	**3c**	**7c**	81[b]
11	**3d**	**7d**	80
12	**4**	**8**	86

[a] Isolated yield.

[b] THF as the solvent.

Table 2. Reactions between various phosphites and 2-benzylidenemalononitrile **2a**

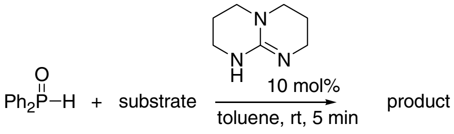


Entry	Phosphite	Product	Time (h)	Yield[a] (%)
1	$(\mathrm{MeO})_2\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{-H}$	**9a**	2	82
2	$(\mathrm{BnO})_2\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{-H}$	**9b**	0.5	99
3	$({}^i\mathrm{PrO})_2\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{-H}$	**9c**	2	71
4	$({}^t\mathrm{BuO})_2\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{-H}$	**9d**	2	65[b]
5	$(\mathrm{MeO})_2\overset{\mathrm{S}}{\overset{\|}{\mathrm{P}}}\mathrm{-H}$	**9e**	1	99

[a] Isolated yield.

[b] 40 mol % TBD.

Table 3. Reactions between diphenylphosphine oxide and various alkenes



Entry	Substrate	Product	Yield[a] (%)
1	**1a**	**12a**	99
2	**1d**	**12b**	73
3	**1e**	**12c**	97
4	**1f**	**12d**	86
5	**10a**	**13a**	80
6	**10b**	**13b**	98
7	**10c**	**13c**	99
8	**10d**	**13d**	97
9	**10e**	**13e**	80
10	**11**	**14**	84

[a] Isolated yield.

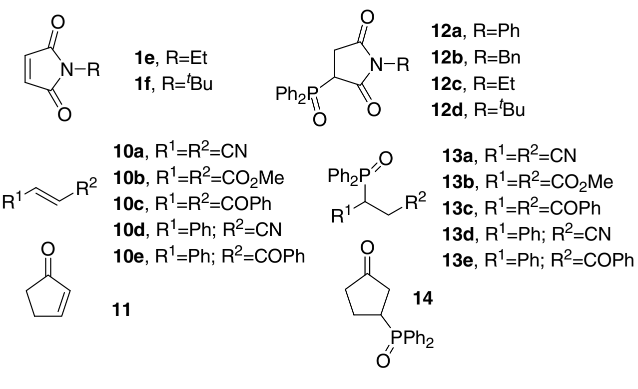


Figure 2. Diphenylphosphine oxide addition across alkenes.

high yield of the addition product **5a** (Table 1, entry 1) was obtained. Toluene, THF and dichloromethane were found to be suitable solvents. Various arylmaleimides **1a–c** and benzylmaleimide **1d** (entries 1–4) were suitable substrates, although alkylmaleimides gave lower yields. 2-Arylidene malononitriles **2a–c** (entries 5–7) including heteroaromatic types were also suitable substrates. α-Nitrostyrenes **3a–d** (entries 8–11), containing either electron withdrawing or electron donating substituents, were also useful substrates. Interestingly, P–N bonds can also be effectively constructed using diethyl azodicarboxylate **4** as a substrate (entry 12). Adduct **8** is similar to the betaine intermediate of the Mitsunobu reaction.[19] A range of P(III) compounds containing oxygen and nitrogen substituents was shown to add to dialkyl azodicarboxylate, giving various penta- and hexa-coordinated products.[20]

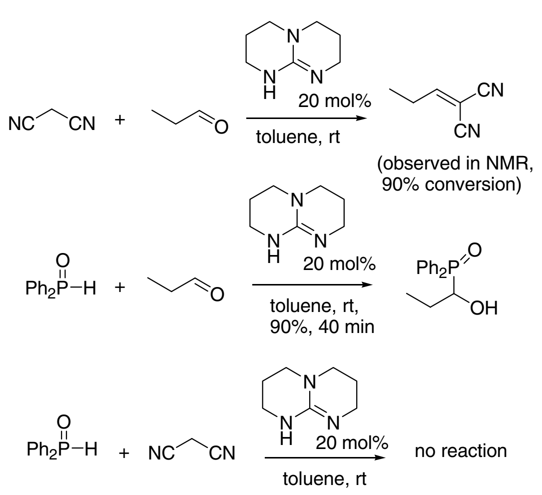
With 2-benzylidenemalononitrile **2a** as the acceptor, different phosphites were investigated (Table 2). Various phosphites including dimethyl phosphite (entry 1), dibenzyl phosphite (entry 2) and diisopropyl phosphite (entry 3) added smoothly and the reactions were completed between 30 and 120 min. However, di-*tert*-butyl phosphite (entry 4) was particularly slow and gave a poor yield even when the amount of catalyst was increased. Dimethyl thiophosphite (entry 5) was more active than the corresponding dimethyl phosphite (entry 1); resulting in a faster reaction and gave a better yield.

The P(O)–H protons are more acidic in alkylphosphine oxides than in phosphites. This is reflected in the nucleophilicity of the corresponding anions and therefore the rate of reaction. With 10 mol % of TBD, in toluene, diphenylphosphine oxide was added smoothly to various maleimides, including aliphatic ones, with high yields (Table 3, entries 1–4). The reactions were completed within 5 min. Linear alkenes such as fumaronitrile **10a** (Fig. 2), dimethyl fumarate **10b**, *trans*-1,2-dibenzoylethylene **10c**, cinnamonitrile **10d**, *trans*-chalcone **10e** and 2-cyclopenten-1-one **11** (entries 5–9) were useful substrates for this reaction. For all substrates, parallel experiments were conducted in the absence of a catalyst. In the time frame of the catalyzed reaction, no product was observed for the control reactions.

In multicomponent reactions (MCRs), a product is assembled from three or more starting materials through a series of bimolecular reactions.[21] The ability to form two or more C–C and/or C-heteroatom bonds in a single operation is the main attraction of MCRs. In most cases, almost all of the atoms in the starting materials contribute to the newly formed product resulting in a high atom economy. A typical challenge for MCRs is to carry out the reaction in a manner in which only the desired product is formed and the side products are minimized.

We were interested in using 2-alkylidene malononitriles and 2-arylidenemalononitriles as acceptors for the addition reaction with diphenylphosphine oxide. 2-Arylidene malononitriles such as **2a**–**c** were easily obtained through the Knoevenagel reaction between malononitrile and aromatic aldehydes.[22] However, we were unable to obtain 2-alkylidenemalononitriles using such protocols. While we were able to observe the 2-alkylidenemalononitriles in the reaction mixture using NMR (90% conversion after 40 min), we were not able to purify them cleanly (Scheme 1). These products were also not stable on storage.

It is also well known that phosphonates can undergo aldol-type reactions with aldehydes.[23] We were able to obtain a high yield of α-hydroxyphosphine oxides when 20 mol % of TBD was used to catalyze the addition of diphenylphosphine oxide to propanal (Scheme 1). This reaction is as fast as the Knoevenagel reaction used to generate the 2-alkylidenemalononitriles. After 40 min, 100% conversion was observed and an isolated yield of 90% was obtained.



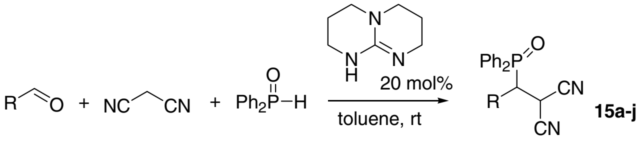
Scheme 1. Parallel reactions using malononitriles, propanal and diphenylphosphine oxide.

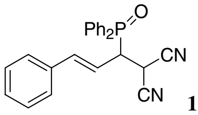
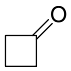
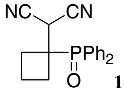
We then attempted a one-pot, three-component reaction consisting of malononitrile, diphenylphosphine oxide and propanal. The only product observed was adduct **15a** (Table 4, entry 1). The reaction was completed within 15 min, giving a high yield of **15a**. It is interesting to note that the possible side reaction leading to the aldol product was not observed in this reaction. A range of aliphatic and aromatic aldehydes were reacted which gave the corresponding adducts **15b**–**i** in high yields within 1 h (entries 2–9). A high regioselectivity was observed for α,β-unsaturated aldehydes such as *trans*-cinnamaldehyde (entry 10). Another possible side reaction, the Michael-type reaction between diphenylphosphine oxide and *trans*-cinnamaldehyde was not detected. Under the same reaction conditions, cyclic ketones such as cyclopentanone and cyclohexanone gave only Knoevenagel products. However, cyclobutanone (entry 11) reacted smoothly to give adduct **16**.

The experiments have shown that this reaction is not only suitable for malononitrile, but also for other Knoevenagel donors such as ethyl 2-cyanoacetate and benzoylacetonitrile. This approach should allow a range of useful P–C bond-containing compounds to be generated. Using our one-pot three-component protocol, however, we were not successful preparing **6a**–**c** by adding diphenyl phosphite, malononitrile and aldehydes; only the Knoevenagel products were observed.

In conclusion, we have developed a mild, rapid and efficient protocol to generate P–C bonds. This simple procedure allows a series of dialkyl alkylphosphonates and trisubstituted phosphine oxides to be prepared in

Table 4. Three-component reactions of diphenylphosphine oxide, malononitrile and aldehydes or ketones



Entry	Aldehyde/ketone	Product	Time (h)	Yield[a] (%)
1	R = Et	**15a**	0.25	96
2	R = ^{n}Pr	**15b**	1.0	82
3	R = ^{i}Pr	**15c**	1.5	87
4	R = *tert*-Pentyl	**15d**	1.0	95
5	R = *c*-Hexyl	**15e**	0.25	86
6	R = ^{t}Bu	**15f**	48	76
7	R = Ph	**15g**	0.25	97
8	R = 4-MeOC$_6$H$_4$	**15h**	1.0	80
9	R = 2-Naphthyl	**15i**	1.5	97
10	R = Cinnamyl	 **15j**	1.0	70
11		 **16**	48	93

[a] Isolated yield.

high yields. A convenient one pot, three-component reaction, containing diphenyl phosphonite, malononitrile and an aldehyde was catalyzed effectively by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). Possible side reactions leading to aldol products were not observed. A high regioselectivity for α,β-unsaturated aldehydes was observed.

2. Experimental

A typical experimental procedure of the three-component addition is described. Propionaldehyde (0.05 mmol, 1.0 equiv 4 μl) and malononitrile (0.05 mmol, 1.0 equiv, 3.3 mg) were added into a glass vial containing 90 μl of toluene. This is followed by TBD (0.01 mmol, 0.2 equiv, 1.4 mg in 10 μl tol). After 1 min, diphenylphosphine oxide (0.06 mmol, 1.2 equiv, 12 mg in 100 μl tol) was added dropwise into the stirring reaction mixture. The reaction was completed in 15 min. 2-[1-(Diphenylphosphoryl)propyl]malononitrile **15a** was obtained as a white solid (15.6 mg, 96%) after flash chromatographic purification.

Acknowledgements

This work was supported by a grant from the National University of Singapore (R-143-000-222-112). We thank the Medicinal Chemistry Program for their financial support. We also thank Dr. Martin J. Lear for helpful discussions.

Supplementary data

Experimental procedures and spectral data of the products are presented. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.019.

References and notes

1. (a) *New Aspects in Phosphorus Chemistry I*; Majoral, J.-P., Ed.; Springer: Berlin Heidelberg, 2002; (b) *New Aspects in Phosphorus Chemistry II*; Majoral, J.-P., Ed.; Springer: Berlin Heidelberg, 2002.
2. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
3. Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
4. (a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur and Silicon* **1991**, *63*, 193; (b) Palocios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899.
5. (a) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237; (b) Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589.
6. For reviews, see: (a) Pudovik, A. N.; Konovalova, I. V. *Synthesis* **1979**, 81; (b) Enders, D.; Saint-Dizier, A.; Lannou, M. I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29.
7. (a) Miller, R. C.; Bradley, J. S.; Hamilton, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 5299; (b) Bodalski, R.; Pietrusiewicz, K. *Tetrahedron Lett.* **1972**, *13*, 4209.
8. Simoni, D.; Invidiata, F. P.; Manferdini, M.; Lampronti, I.; Rondanin, R.; Roberti, M.; Pollini, G. P. *Tetrahedron Lett.* **1998**, *39*, 7615.
9. Green, K. *Tetrahedron Lett.* **1989**, *30*, 4807.
10. Stockland, R. A., Jr.; Taylor, R. I.; Thompson, L. E.; Patel, P. B. *Org. Lett.* **2005**, *7*, 851.
11. (a) Semenzin, D.; Etemad-Moghadam, G.; Albouy, D.; Diallo, O.; Koenig, M. *J. Org. Chem.* **1997**, *62*, 2414; (b) Han, L.-B.; Zhao, C.-Q. *J. Org. Chem.* **2005**, *70*, 10121.
12. (a) Shulyupin, M. O.; Kazankova, M. A.; Beletskaya, I. P. *Org. Lett.* **2002**, *4*, 761; (b) Xu, Q.; Han, L.-B. *Org. Lett.* **2006**, *10*, 2099.
13. (a) Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2001**, *3*, 1523; (b) Kaljurand, I.; Rodima, T.; Pihl, A.; Mäemets, V.; Leito, I.; Koppel, I. A.; Mishima, M. *J. Org. Chem.* **2003**, *68*, 9988.
14. Simoni, D.; Rossi, M.; Rondanin, R.; Mazzali, A.; Baruchello, R.; Malagutti, C.; Roberti, M.; Invidiata, F. P. *Org. Lett.* **2000**, *2*, 3765.
15. Horváth, A. *Tetrahedron Lett.* **1996**, *37*, 4423.
16. Subba Rao, Y. V.; De Vos, D. E.; Jacobs, P. A. *Angew. Chem., Int. Ed* **1997**, *361*, 2661.
17. Ye, W. P.; Xu, J. Y.; Tan, C.-T.; Tan, C.-H. *Tetrahedron Lett.* **2005**, *46*, 6875.
18. Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 4556.
19. Mitsunobu, O. *Synthesis* **1981**, 1.
20. Kumar, N. S.; Kumar, K. P.; Kumar, K. V. P. P.; Kommana, P.; Vittal, J. J.; Swamy, K. C. K. *J. Org. Chem.* **2004**, *69*, 1880.
21. Yus, M.; Ramón, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.
22. (a) Textier-Boullet, F.; Foucaud, A. *Tetrahedron Lett.* **1982**, *23*, 4927; (b) Zhang, M.; Zhang, A.-Q. *Synth. Commun.* **2004**, *34*, 4531.
23. (a) Wynberg, H.; Smaardijk, A. A. *Tetrahedron Lett.* **1983**, *24*, 5899; (b) Smaardijk, A. A.; Noorda, S.; van Bolhuis, F.; Wynberg, H. *Tetrahedron Lett.* **1985**, *26*, 493.