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A New Condensation Synthesis of Allenes and Dienes

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Summary: A phosphorus methylide, Ti(IV) halide alkoxide, and hindered silylamide base comprise a convenient "carbon atom" synthon for the condensation of aromatic and aliphatic aldehydes to allenes and dienes, respectively.

The allene functionality possesses intriguing properties of structure and reactivity that make it important in organic synthesis.[1] Allenes and higher cumulenes are found in a growing number of biologically active compounds; a timely example is found in the mechanism of action of the antitumor antibiotic neocarzinostatin.[2] We report here a new method for the selective synthesis of allenes by condensation of aromatic aldehydes with a "carbon atom" synthon derived from a phosphorus methylide.

Symmetric 1,3-disubstituted allenes 1 are conveniently obtained by the methodology outlined in eq 1 and Table I, involving the one-pot, anaerobic treatment of a titanium trichloride alkoxide with 1 equiv of tris(dimethylamino)phosphorus methylide, 4 equiv of hindered amide base, and 4 equiv of aldehyde at room temperature in dry THF or toluene solvent, followed by aqueous workup.[3] Aldehydes may be employed in stoichiometric amounts (2 equiv per ylide) if 2 equiv of a different aldehyde are introduced first (vide infra). Use of $(Me_2N)_3P{=}^{13}CH_2$ establishes the ylide as the source of the central allene carbon. This condensation process is an improvement on the reactions of silyl-substituted phosphorus ylides with ketones, which give equimolar amounts of allenes and alkenes.[4] A related process involves the production of allenes from $Ph_3P{=}CH_2$ and imines at high temperature.[5] The method reported here is distinct from other olefination syntheses of allenes[6] in that 2 equiv of carbonyl compound are incorporated into the product.

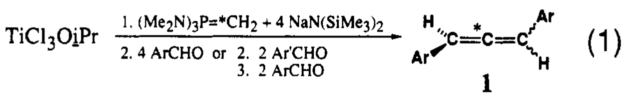
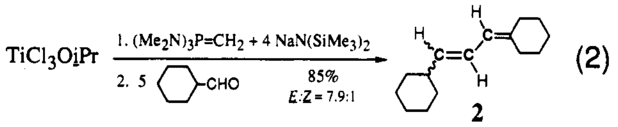


Table I. Isolated Yields (%, with Respect to Ylide) of 1,3-Diarylallenes from Aromatic Aldehydes

entry	substrate	yield
a	$4\text{-}CH_3C_6H_4CHO$	56
b	$3\text{-}CH_3C_6H_4CHO$	57
c	$2\text{-}CH_3C_6H_4CHO$	69
d	$4\text{-}OCH_3C_6H_4CHO$	52
e	$3\text{-}OCH_3C_6H_4CHO$	45
f	$2\text{-}OCH_3C_6H_4CHO$	46
g	$3,4,5\text{-}(OMe)_3C_6H_2CHO$	61
h	$4\text{-}NMe_2C_6H_4CHO$	32
i	$3\text{-}F\text{-}4\text{-}OCH_3C_6H_3CHO$	17
j	ferrocene carboxaldehyde	60
k	2-naphthaldehyde	40

Aldehydes bearing an α-proton afford 1,3-dienes rather than allenes. For example, cyclohexanecarboxaldehyde gives diene 2 (*E*/*Z* ratio of 7.9:1) in 85% yield (eq 2).



Ketones are significantly less reactive than aldehydes due to steric factors. Thus, benzophenone undergoes a slow reaction to afford not an allene but rather the corresponding alkene, 1,1-diphenylethylene, in 56% yield. Acetophenone undergoes base-mediated aldol reactions, but 1,1,1-trifluoroacetophenone provides the corresponding allene in 14% yield.

Benzaldehydes bearing electron-withdrawing groups (p-NO_2, p-Br, p-CHO, m-CHO) are not tolerated in the procedure of eq 1, since these substrates undergo base-induced oligomerization.[7] This effect can be partially countered by the presence of a resonance electron-donating

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(1) (a) Schuster, H. F.; Coppola, G. M. Allenes in Organic Synthesis; John Wiley & Sons: New York, 1984. (b) Landor, S. R., Ed. The Chemistry of the Allenes; Academic Press: San Diego, 1982; Vols. 1–3. (c) Patai, S., Ed. The Chemistry of Ketenes, Allenes, and Related Compounds; John Wiley & Sons: New York, 1980; Vols. 1–2.

(2) (a) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493–4496. (b) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057–8059. (c) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387–1416.

(3) A typical procedure is as follows; all manipulations except workup and chromatography are conducted under inert atmosphere. A THF solution of $TiCl_3(O\text{-}i\text{-}Pr)$ (freshly prepared from $TiCl_4$ and $Ti(O\text{-}iPr)_4$) is treated with a THF solution containing 4 equiv of $NaN(SiMe_3)_2$ (Aldrich, 95%, used as received) and 1 equiv of $(Me_2N)_3P{=}CH_2$[17] to produce a cloudy dark red-brown solution, which may be stored for at least 2 weeks at −20 °C. This mixture is treated with a solution of the aldehyde (4–6 equiv in THF) with vigorous mixing, whereupon a rapid color change usually occurs, signaling completion of the reaction. Alternatively, 2 equiv of an aldehyde may be added (either 4-methylbenzaldehyde or 3,4,5-trimethoxybenzaldehyde is typically chosen to facilitate chromatographic separation from the product), followed after 5 min by ≥2 equiv of a second aldehyde; only the latter substrate is incorporated. Partitioning between ether and aqueous tartaric acid (to remove titanium byproducts) and column chromatography provide the desired allenes. All allenes prepared here display the characteristic ^{13}C NMR resonance in the 204–210 ppm range for the central carbon atom. The reaction may also be performed in lower yield by generation of the phosphorus methylide in situ from $P(NMe_2)_3$, MeI, and $NaN(SiMe_3)_2$, followed by addition of titanium reagent and aldehyde.

(4) (a) Gilman, H.; Tomasi, R. A. *J. Org. Chem.* **1962**, *27*, 3647–3650. (b) Schmidbaur, H.; Stühler, H. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 321–322. (c) Bestmann, H. J. *Pure Appl Chem.* **1980**, *52*, 771–788.

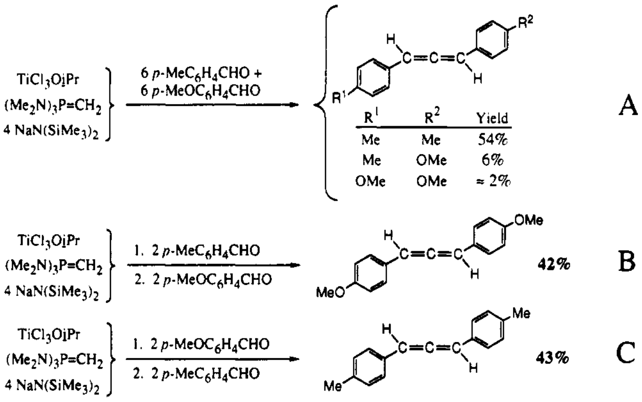
(5) Bestmann, H. J.; Seng, F. *Tetrahedron* **1965**, *21*, 1373–1381.

(6) (a) Hamlet, Z.; Barker, W. D. *Synthesis* **1970**, 543–544. (b) Bestmann, H. J.; Denzel, T.; Salbaum, H. *Tetrahedron Lett.* **1974**, 1275–1276. (c) Bestmann, H. J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198–1207. (d) Yoshida, T.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 1276–1277. (e) Dennehy, R. D.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1992**, 35–36. (f) Tucker, C. E.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 9888–9890. (g) Pelter, A.; Smith, K.; Jones, K. D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 747–748. (h) Buchwald, S. L.; Grubbs, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 5490–5491.

(7) $NaN(SiMe_3)_2$ reacts with benzaldehydes to form α-aminoalkoxides, $ArC(H)[N(SiMe_3)_2](O^-)$, which can be readily detected by ^{13}C NMR. For related monomeric species involving dialkylamide bases, see: Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979–3982. Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078–1083. We have observed that electron-deficient aldehydes also undergo rapid attack by the α-aminoalkoxides to give α-amino-ω-alkoxy polyacetals, making these aldehydes unavailable for conversion to allenes in the presence of excess amide base.

0022-3263/93/1958-1298$04.00/0

Scheme I



functionality. Thus, no allene is obtained from 3-fluorobenzaldehyde, but 4-methoxy-3-fluorobenzaldehyde is a somewhat better substrate (Table I, entry i).

Maximum yields are achieved with 4 equiv of NaN(SiMe$_3$)$_2$, which are required for the clean generation[8] of a species having ^{31}P and ^{13}C NMR resonances characteristic of a titanium-substituted ylide.[9] We suggest that the active reagent prior to the addition of aldehyde is (Me$_2$N)$_3$P═C[H][Ti(Cl)(O*i*Pr)(N(SiMe$_3$)$_2$)] or a functional equivalent,[10] leaving 2 equiv of base active in the reaction mixture. The reactions summarized in Scheme I demonstrate that these extra base equivalents can be complexed by added aldehyde[7] and that a second type of aldehyde may be converted into allene. Thus, direct competition shows 4-methylbenzaldehyde to be more reactive than 4-methoxybenzaldehyde (Scheme I, reaction A), yet each symmetrical allene may be *exclusively* obtained by the appropriate stepwise addition of aldehydes (reactions B and C). Although yields are somewhat diminished, this protocol makes it possible to employ expensive aldehydes in stoichiometric amounts.

A preliminary exploration of the reaction mechanism has been accomplished by addition of reagents in a stepwise fashion [TiCl$_3$O-*i*-Pr + NaN(SiMe$_3$)$_2$ + (Me$_2$N)$_3$P═CH$_2$ + NaN(SiMe$_3$)$_2$ + ArCHO + NaN(SiMe$_3$)$_2$ + Ar′CHO].[11] Formation of (*E*)-vinylphosphonium salts [(Me$_2$N)$_3$PCH═CHAr]Cl[12] is observed after the addition of 1 equiv of aldehyde via elimination of titanium oxide.[13] The reaction mechanism is therefore presumed to involve the allenic phosphorane[14] (Me$_2$N)$_3$P═C═CHAr derived from deprotonation[15] of a vinylphosphonium salt intermediate, as previously suggested for a reaction of silyl-substituted ylides.[4a,16] Preliminary experiments demonstrate that mixed allenes may be selectively generated in low yield (10–30% overall) by treatment of the vinylphosphonium salt with base and a second aldehyde. Furthermore, allenes may be prepared from electron-deficient substrates by this procedure, since little or no free amide base is present when aldehyde is introduced.

The condensation route to allenes outlined here allows for the practical application of a new retrosynthetic strategy for allene synthesis, since a large majority of existing synthetic methods involve isomerization of a preassembled three-carbon unit, as in the base-mediated rearrangement of propargylic derivatives.[1] Further studies of the reaction scope and mechanism, as well as applications to the synthesis of cyclic allenes, allenic oligomers, and functional 1,2,4-trien-6-yne neocarzinostatin analogues,[2] will be reported in due course.

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Supplementary Material Available: Experimental details and characterization of allene and diene products (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[8] A mixture of TiCl$_3$O-*i*-Pr, (Me$_2$N)$_3$PCH$_2$, and 3 equiv of NaN(SIMe$_3$)$_2$ is comprized of two species in roughly equimolar amounts, as indicated by ^{31}P NMR resonances at 55 and 52 ppm.[9,10] Both are apparently competent for allene formation: in many cases, 3 equiv of base and aldehyde are sufficient, but 4 equiv are routinely employed to maximize yields.

[9] For a mixture of TiCl$_3$O-*i*-Pr, (Me$_2$N)$_3$P═^{13}CH$_2$, and 4 NaN(SiMe$_3$)$_2$ in THF: ^{31}P, 55.2 ppm; ^{13}C, 115.1 ppm [CH in DEPT, correlates to ^{1}H resonance at 5.56 ppm in ^{1}H,^{13}C-correlated NMR]; $^1J_{P,C} = 89$ Hz. These values closely resemble those of (Me$_2$N)$_3$P═C(H)(ZrCp$_2$Cl): ^{31}P, 60.9 ppm; ^{13}C, 115.1 ppm; $^1J_{P,C} = 88.9$ Hz. For characterization of the latter complex and related metal-substituted phosphorus ylides, see: (a) Schmidbaur, H.; Pichl, R.; Müller, G. *Chem. Ber.* 1987, *120*, 39–44. (b) Schmidbaur, H.; Pichl, R.; Müller, G. *Chem. Ber.* 1987, *120*, 789–794. (c) Schmidbaur, H.; Pichl, R. *Z. Naturforsch.* 1985, *B40*, 352–356.

[10] Extra equivalents of silyl amide base may engage in reversible coordination to titanium.[8,9]

[11] TiCl$_3$O-*i*-Pr in THF is treated sequentially at room temperature with THF solutions containing 1 equiv each of base (forming TiCl$_2$(O-*i*-Pr){N(SiMe$_3$)$_2$]), methylide, base (forming the deep red/brown titanium-substituted ylide species discussed above), and aldehyde. The resulting vinylphosphonium salt precipitates in some cases and may be isolated or treated in situ with another equiv of base, followed rapidly by 1 equiv of a second aldehyde.

[12] (a) For [(Me$_2$N)$_3$PCH═CH(*p*-C$_6$H$_4$CH$_3$]Cl: ^{1}H NMR (D$_2$O) δ 7.54 (d, $J = 7.8$ Hz, 2 H), 7.29 (m, 3 H, aromatic and vinyl CH), 6.52 (dd, $^3J_{HH} = 17.7$, $^3J_{PH} = 21.6$ Hz, 1 H), 2.73 (d, $J_{PH} = 9.9$ Hz, 18 H), 2.34 (s, 3 H); ^{13}C{^{1}H decoupled} NMR (D$_2$O) δ 151.7 (d, $^2J_{PC} = 6.0$ Hz), 143.0, 131.8, 130.4, 128.9, 106.3 (d, $^1J_{PC} = 160.7$ Hz), 36.5 (d, $J_{PC} = 2.8$ Hz), 21.3; ^{31}P{^{1}H decoupled} NMR (D$_2$O) δ 48.3. (b) For [(Me$_2$N)$_3$PCH═CH(*p*-C$_6$H$_4$CH$_3$]BPh$_4$ precipitated from H$_2$O: similar ^{1}H, ^{13}C, and ^{31}P NMR to above with the addition of BPh$_4$ resonances; IR (KBr, cm^{-1}) 3220 (m), 2982 (m), 1602 (w), 1480 (m), 1300 (m), 1181 (m), 993 (s), 741 (s), 707 (s). Anal. Calcd for $C_{39}H_{47}N_2BP\cdot{}^1/_2(H_2O)$: C, 76.97; H, 7.95; N, 6.90. Found: C, 76.84; H, 7.92; N, 6.92. (c) For [(Me$_2$N)$_3$PC$_a$H═C$_b$HC$_6$H$_5$]Cl derived from (Me$_2$N)$_3$P═^{13}CH$_2$ and Ph^{13}CHO without isolation: similar ^{1}H, ^{13}C, and ^{31}P NMR to above, plus $^1J_{PC(a)} = 154.8$ Hz, $^1J_{C(a)C(b)} = 67.5$ Hz, $^1J_{HC(a)} = 162.3$ Hz, $^1J_{HC(b)} = 158.6$ Hz. (d) For analogous phosphonium salts derived from PPh$_3$, see: Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* 1990, *55*, 5033–5036.

[13] For similar eliminations involving silicon and tin, see: (a) Bestmann, H. J.; Bomhard, A.; Dostalek, R.; Pichl, R.; Riemer, R.; Zimmermann, R. *Synthesis* 1992, 787–792. (b) Plénat, F. *Tetrahedron Lett.* 1981, *22*, 4705–4708. (c) Grützmacher, H.; Pritzkow, H. *Organometallics* 1991, *10*, 938–946. (d) Bestmann, H. J. *Pure Appl. Chem.* 1980, *52*, 771–788.

[14] For electron-deficient allenic phosphoranes, see ref 13d and: (a) Bestmann, H. J. *Angew. Chem., Int. Ed. Engl.* 1977, *16*, 349–364. (b) Saalfrank, R. W. *Tetrahedron Lett.* 1975, 4405–4408. (c) Bestmann, H. J.; Saalfrank, R. W. *Angew. Chem., Int. Ed. Engl.* 1970, *9*, 367–368.

[15] For a related process, see: Stang, P. J.; Arif, A. M.; Zhdankin, V. V. *Tetrahedron* 1991, *47*, 4539–4546.

[16] We have observed that ylide-bridged metallacycles [(Cl)(X)Ti-C═P(NMe$_2$)$_3$]$_2$ (X = Cl, NMe$_2$) give allenes in moderate yield upon treatment with aldehydes (Hughes, K. A.; Dopico, P. G.; Sabat, M.; Finn, M. G. *Angew. Chem.*, in press). No such metallacycles are formed in the titanium–alkoxide system described above, but both processes may proceed through allenic phosphorane intermediates.

[17] Issleib, V. K.; Lischewski, M. *J. Prakt. Chem.* 1970, *312*, 135–144.