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# Highly Regiocontrolled Pd-Catalyzed Cross-Coupling Reaction of Terminal Alkynes and Allenylphosphine Oxides

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The cross-coupling of a variety of terminal alkynes **1** with allenylphosphine oxides **2** catalyzed by a $Pd(OAc)_2$-TDMPP system provided conjugated endo-enynes **3** solely, while the TCPC-catalyzed reaction of the same regents led to the exclusive formation of exo-isomers **4**. The mechanistic rationale for these selective transformations was proposed. Synthetic usefulness of the prepared exo-enyne **4** was demonstrated in the synthesis of multisubstituted diarylbenzylphosphine oxides **5** via the Pd-catalyzed [4+2]-benzannulation reaction.

The development of straightforward and atom-economic approaches toward conjugated enynes, important synthetic blocks and essential units found in a variety of biologically active compounds,[1] has been a subject of considerable interest during the past decade. Various transition[2,3] and rear-earth[4] metals have been successfully employed in addition reactions of terminal alkynes to alkynes and allenes to provide a multitude of different enynes. Although a number of efficient protocols were developed, achieving high degrees of regio- and stereoselectivity, especially in reactions involving allenes, often presents a problem.[5] During our investigation of the scope of the Pd-catalyzed [4+2] benzannulation reaction,[6] we searched for efficient and selective ways of assembling phosphorus-containing enynes as it will allow for direct approach to phosphorus-containing aryls and biaryls. This type of enyne with an *exo*-methylene moiety (***i***, EWG = $Ph_2PO$, Scheme 1) is available via hydroiodination of allenylphosphine oxides followed by Sonogashira coupling, as reported by Ma and co-workers.[7] Furthermore, these ***i*** and endo-enynes ***ii*** are both accessible via Trost Pd-catalyzed addition of alkynes to allenes (EWG = COOR, Scheme 1).[3c] It was shown that either exo-enyne ***i*** or its endo-isomer ***ii*** can be obtained as major products depending on the type of Pd-catalyst used. Although this protocol had never provided perfect regiocontrol, we chose this method as a potential approach toward both exo (***i***, EWG = $R_2PO$) and endo (***ii***, EWG = $R_2PO$) phosphorus-containing enynes. We hoped that careful optimization of the reaction conditions would allow for the selective synthesis of these useful synthons which were planned to be tested in the subsequent Pd-catalyzed benzannulation reaction with conjugated diynes. The present paper documents the results on these studies.

## Results and Discussion

**Pd-Catalyzed Addition of Terminal Alkynes to Allenylphosphine Oxides.** First, we tested the reaction of alkynes and allenylphosphine oxides catalyzed by a $Pd(OAc)_2$−tris-(2,6-dimethoxyphenyl)phosphine (TDMPP) combination (conditions **A**), which was reported to provide the highest endo-selectivity on the allenyl ester substrates.[3c] To our delight, the reaction of 1,1-disubstituted allene **2a** with phenylacetylene (**1a**) proceeded smoothly to give endo-product **3aa**[8] *as a single isomer* in

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(2) For recent reviews on reductive coupling of two alkynes, see: (a) Bruneau, C.; Dixneuf, P. *Acc. Chem. Res.* **1999**, *32*, 311. (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. For Pd-catalyzed reactions, see: (d) Gevorgyan, V. Alkynyl substitution via alkynylpalladation-reductive elimination. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 1, pp 1463−1469. (e) Trost, B. M.; McIntosh, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 7255. (f) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Ruhter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698. (g) Trost, B. M.; Frontier, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 11727. (h) Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 11107. (i) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835.

(3) For Rh-catalyzed reductive coupling of alkyne and allene, see: (a) Yamaguchi, M.; Omata, K.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 5689. (b) For Ru-catalyzed reactions, see: Yamaguchi, M.; Kido, Y.; Omata, K.; Hirama, M. *Synlett* **1995**, 1181. For Pd-catalyzed reactions, see: (c) Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816.

(4) See, for example: (a) Nishiura, M.; Hou, Z.; Wakatsuki, Y.; Yamaki, T.; Miyamoto, T. *J. Am. Chem. Soc.* **2003**, *125*, 1184. (b) Haskel, A.; Straub, T.; Dash, A. K.; Eisen, M. S. *J. Am. Chem. Soc.* **1999**, *121*, 3014.

(5) Mixtures of regio- and stereoisomers are normally obtained in transition metal-catalyzed reductive couplings of acetylenes and allenes. See refs 2d and 3.

(6) (a) Gevorgyan, V.; Takeda, A.; Homma, M.; Sadayori, N.; Radhakrishnan, U.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 6391. (b) Gevorgyan, V.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, *576*, 232.

(7) Ma, S.; Xie, H.; Wang, G.; Zhang, J.; Shi, Z. *Synthesis* **2001**, 713.

(8) The structure and configuration of compound **3aa** were confirmed by single-crystal X-ray crystallography. See Supporting Information for details.

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**SCHEME 1**

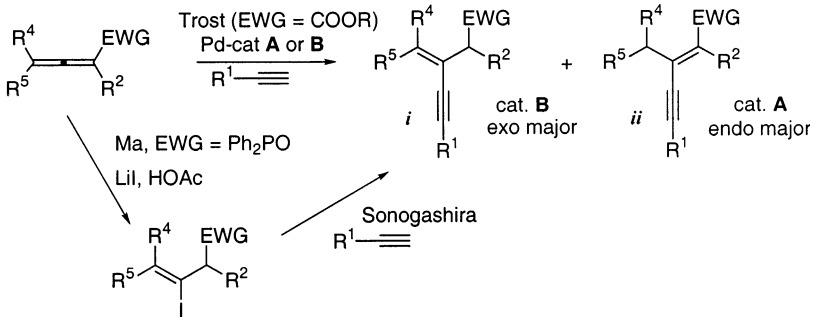
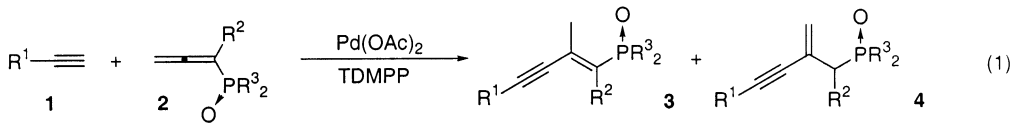
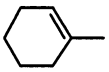



**TABLE 1. Pd-Catalyzed Reductive Cross-Coupling of Acetylenes and Allenylphosphine Oxides**



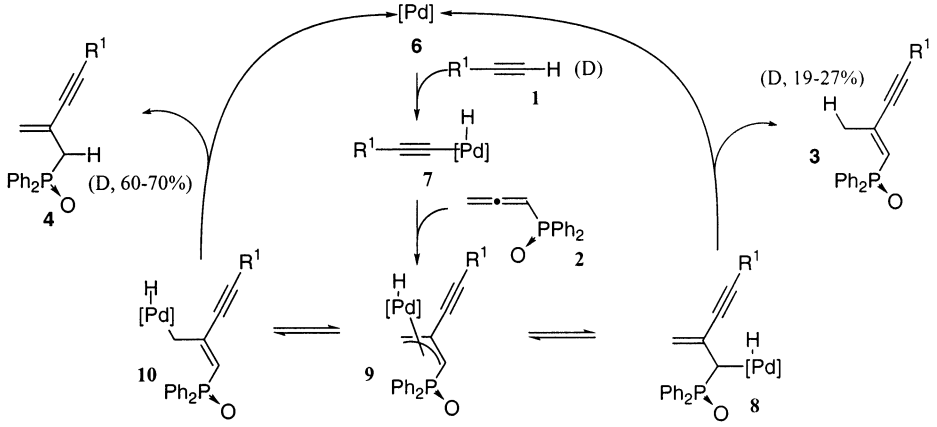

(1)

| # | $R^1$ | | $R^2$ | $R^3$ | | Conditions[a] | Product 3 | Product 4 | Yield,[b] % |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Ph | **1a** | Me | Ph | **2a** | **A** | **3aa** | - | 77 |
| 2 | | **1a** | H | Ph | **2b** | **A** | **3ab** | - | 90 |
| 3 | Bu | **1b** | | | **2a** | **A**[c] | **3ba** | - | 90 |
| 4 | | **1b** | | | **2b** | **A**[c] | **3bb** | | 73 |
| 5 |  | **1c** | | | **2a** | **A** | **3ca** | - | 85 |
| 6 | | **1c** | | | **2b** | **A** | **3cb** | - | 88 |
| 7 |  | **1d** | | | **2a** | **A** | **3da** | - | 90 |
| 8 | $MeOCH_2$ | **1e** | | | **2a** | **A** | **3ea** | - | 84 |
| 9 | | **1b** | H | $N(i\text{-}Pr)_2$ | **2c** | **A**[c] | **3bc** | - | 73 |
| 10 | TMS | **1f** | | | **2a** | **A** | **3fa** | - | 75 |
| 11 | p-$FC_6H_4$ | **1g** | | | **2b** | **A** | **3gb** | - | 80 |
| 12 | | **1a** | | | **2b** | **B** | - | **4ab** | 76 |
| 13 | | **1b** | | | **2b** | **B** | - | **4bb** | 86 |
| 14 | | **1d** | | | **2b** | **B** | - | **4db** | 60 |
| 15 | | **1f** | | | **2b** | **B** | - | **4fb** | 59 |
| 16 | | **1g** | | | **2b** | **B** | - | **4gb** | 54 |
| 17 | p-$MeC_6H_4$ | **1h** | | | **2b** | **B** | - | **4hb** | 57 |
| 18 | p-$MeOC_6H_4$ | **1i** | | | **2b** | **B** | - | **4ib** | 50 |
| 19 | p-$MeSC_6H_4$ | **1j** | | | **2b** | **B** | - | **4jb** | 66 |
| 20 | p-$NO_2C_6H_4$ | **1k** | | | **2b** | **B** | - | **4kb** | 35 |
| 21 | p-$CF_3C_6H_4$ | **1l** | | | **2b** | **B** | - | **4lb** | 46 |
| 22 | p-$MeOOCC_6H_4$ | **1m** | | | **2b** | **B** | **3mb** | **4mb** | 45[d] |

[a] Reagents and conditions: (**A**) $Pd(OAc)_2$ (10 mol %), TDMPP (20 mol %), 1 M THF, rt; (**B**) TCPC (5 mol %), 1 M $CH_2Cl_2$, rt. [b] Isolated yield. [c] $Pd(OAc)_2$ (5 mol %) and TDMPP (10 mol %) were employed. [d] Isolated yield of a major component. **3mb** was detected by GC/MS as a minor component in an 18:82 mixture.

good yield (eq 1, Table 1, entry 1). Monosubstituted allene **2b**, under the same conditions, provided the corresponding endo-enyne **3ab** in very high yield (Table 1, entry 2). Variation of the nature of terminal acetylenes employed showed that the reaction with alkyl- (entries 3 and 4), alkenyl- (entries 5−7), aryl- (entries 1, 2, and 11), silylacetylenes (entry 10) and propargyl ether (entry 8) remained high yielding and perfectly regioselective regardless of the substitution pattern of the allene. The reaction of allenyl phosphonamide **2c** under the same conditions also proceeded uneventfully, providing the corresponding product **3bc** in good yield (entry 9). In most

**SCHEME 2**




cases 10 mol % of palladium acetate and 20 mol % of TDMPP (condition **A**) were necessary to drive the reaction to completion. However, in certain cases we were able to reduce the amount of palladium and phosphine ligand twice with neither yield nor selectivity being affected (entries 3, 4, and 9). Remarkably, all allenylphosphine oxides, in contrast to allenyl esters,[3c] under catalytic system **A** reacted with a variety of alkynes in a perfectly regioselective manner providing the endo-enynes **3** as sole products, with no traces of exo-isomers **4** being detected. It deserves noting that the reactions did not proceed smoothly under strictly anhydrous conditions; the addition of small amounts of water (0.2−2.0 equiv) appeared to be necessary for successful addition reactions.[9]

Next, we attempted the synthesis of disubstituted exo-enynes **4**, which are potentially the most attractive phosphorus-containing substrates for the subsequent benzannulation reaction.[10] Initial experiments were performed by using a TCPC-TTMPP[11] combination, which was reported to provide the best exo-selectivity in the coupling of acetylenes with allenyl esters.[3c] In our hands, this catalytic system provided moderate selectivity (**4ab**:**3ab** 80:20), while a TCPC-TDMPP combination gave somewhat better results (**4ab**:**3ab** 90:10). Optimization revealed that the phosphine-free conditions (conditions **B**, 5 mol % of TCPC in $CH_2Cl_2$) allowed for the exclusive formation of exo-enyne **4**. The coupling of alkynes bearing alkyl (Table 1, entry 13), alkenyl (entry 14), and silyl (entry 15) substituents was also perfectly regiocontrolled. The electronic properties of the substituent at the para-position of arylacetylenes did not affect selectivity in the reaction; reactions of both electron-rich (entries 17−19) and electron-poor (entries 16, 20, and 21) substrates furnished the corresponding exo-enyne **4** as a single isomer. Acetylene **1m** provided the only example without perfect regiocontrol; small amounts of regioisomeric **3mb** were detected by GC/MS analysis of the crude reaction mixtures (Table 1, entry 22). In all other cases, employment of catalytic system **B** led to exclusive formation of the exo-enynes **4**.

We propose the following mechanistic rationale for the observed highly regiocontrolled condensation of terminal alkynes with allenylphoshine oxides. The catalytic cycle starts from the oxidative addition of Pd-species **6** to terminal acetylene **1** providing complex **7**, which after carbopalladation of allene **2** produces $\eta^3$-complex **9** (Scheme 2). $\eta^3 \leftrightarrow \eta^1$ equilibrium with the less bulky (phosphine free) and more electrophilic Pd(IV) complex derived from TCPC produces $\eta^1$-complex **8**, in which electrophilic Pd resides at the most electron-rich carbon atom. The same equilibrium drives the less electrophilic and more bulky Pd(II) complex derived from $Pd(OAc)_2$ or $Pd_2dba_3$[12] toward $\eta^1$-species **10.** Reductive elimination of **8** and **10** produces **4** and **3**, respectively. Experiments with phenylacetylene-$d_1$ revealed selective deuterium incorporation into the methyl group of **3** under conditions **A** and into the methylene group of **4** under conditions **B**.[13] The equilibrium **10** ↔ **9** ↔ **8** is additionally supported by the fact that thermodynamically more stable **3** was obtained as a single reaction product under catalytic system **B** at elevated temperatures. When product **4** was subjected to the latter reaction conditions, no formation of **3** was observed, thus ruling out a possible equilibrium between products **3** and **4**.

**(b) Pd-Catalyzed [4+2] Benzannulation of Phosphine Oxide Containing Enynes.** First we attempted [4+2] benzannulation of enynes **3**, which poses a substantial challenge, since as was shown before the cycloaddition of trisubstituted E-enynes proceeds sluggishly

(9) Although the role of water is not completely understood, strictly anhydrous conditions render somewhat less selective and less reproducible results. For some examples of use of $H_2O$ or ROH additives in the Pd-catalyzed reactions, see: (a) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545. (b) Wellace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A. J.; Cowden, C, J.; Ashwood, M. S.; Cotrell, I. F.; Dolling, U.-H.; Reider, P. J. *Org. Lett.* **2001**, *3*, 671.

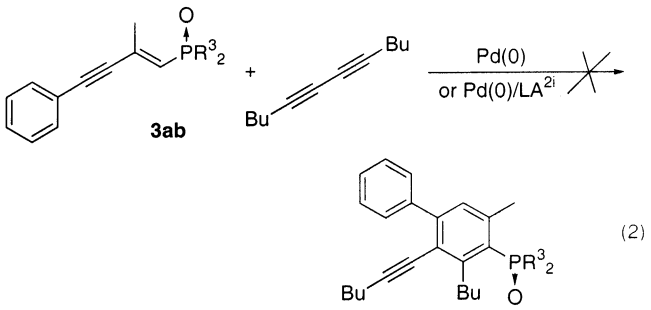
(10) It was found that 2,4-disubstituted enynes undergo the Pd-catalyzed benzannulation reaction much easier than 1,2,4-trisubstituted enynes. See ref 6a.

(11) TCPC = [1,2,3,4-tetrakis(methoxycarbonyl)-1,3-butadiene-1,4-diyl]palladium; TTMPP = tris(2,4,6-trimethoxyphenyl)phosphine.

(12) In early works[2f] Trost proposed that the catalytic system Pd(OAc)$_2$-TDMPP works in Pd(II)-Pd(IV) manifold. We believe that it is unlikely that Pd(II) species can survive in the presence of several reducing agents, such as terminal alkynes and phosphines present in the reaction mixture. The tendency for Pd(II) to be easily reduced into Pd(0) species under variety of reaction conditions is well-known. See: *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: Hoboken, NJ, 2002. In addition, our test experiments indicated that the $Pd_2dba_3$/*o*-$Tol_3P$ combination works as selective a the s Pd(OAc)$_2$-TDMPP system, albeit a bit slower, to provide endo-enynes **3**. Furthermore, it also was shown by Trost[2g] and by us[2i] that Pd(0) complexes enable head-to-tail homo- and cross-coupling of acetylenes to be catalyzed.

(13) Significant deuterium scrambling between deuterated terminal acetylenes and eventual proton sources in the presence of transition metals is well documented. See refs 2h and 3a,b.

if at all.[6a] The fact that electron-withdrawing substituents facilitate the cycloaddition reaction[6a] brought some hope that **3** can potentially be employed in the aforementioned annulation reaction (eq 2). However, all attempts to




(2)

synthesize arylphosphine oxides via benzannulation of **3** under a variety of reaction conditions[14] failed; starting materials were recovered virtually intact (eq 2).

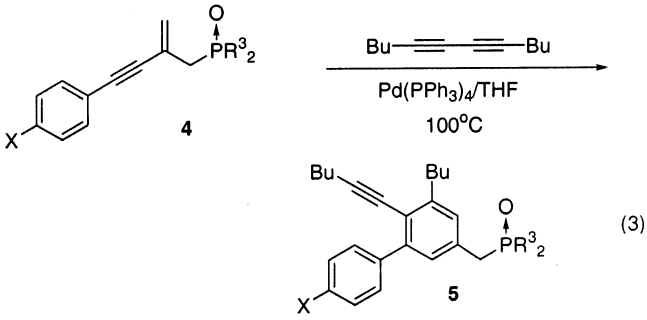
Next, we attempted the synthesis of multisubstituted benzylphosphine oxides **5** via the Pd-catalyzed benzannulation of exo-enynes **4**. As expected, the less substituted exo-enynes **4** underwent smooth cycloaddition with 5,7-dodecadiyne (eq 3, Table 2). A series of aryl-substituted enynes were tested under the standard reaction conditions reported previously for benzannulation of disubstituted enynes.[6a] The reaction showed excellent functional group compatibility, neither phosphine oxide moiety nor various functional groups at the aryl ring compromised the benzannulation. All of the enynes tested, both with electron-releasing (Table 2, enties 3−5) and electron-withdrawing (entries 2, 6−8) substituents, smoothly underwent the reaction producing the corresponding benzylphosphine oxides **5a**,**g**−**m**[15] in good to high yields (Table 2, entiries 1−8).

In conclusion, we described the first examples of perfectly regiocontrolled transition metal-catalyzed addition of terminal alkynes to allenes. This method allowed for the efficient synthesis of endo- (**3**) and exo-conjugated enynes (**4**) as single regioisomers. The plausible mechanism for the formation of endo- (**3**) or exo-product (**4**) based on the different Pd sources was proposed. Efficient synthesis of diarylbenzylphosphine oxides from exo-enynes **4** via the Pd-catalyzed benzannulation reaction was demonstrated. Synthetic studies toward bis(benzylphosphines) via different modes of double benzannulation of phosphorus-containing enynes are currently underway in our laboratories.

## Experimental Section

Acetylene **1m** was prepared according to the known procedure[16] and its spectral properties were identical with ones reported in the literature.[17] Procedures for the preparation of

**TABLE 2. Palladium-Catalyzed Cross-Benzannulation of Exo-Enynes 4 with 5,7-Dodecadiyne**




(3)

| no. | enyne **4** | X | product **5** | yield, % |
|---|---|---|---|---|
| 1 | **4ab** | H | **5a** | 75 |
| 2 | **4gb** | F | **5** | 84 |
| 3 | **4hb** | Me | **5h** | 60 |
| 4 | **4ib** | MeO | **5i** | 76 |
| 5 | **4jb** | MeS | **5j** | 86 |
| 6 | **4kb** | $NO_2$ | **5k** | 68 |
| 7 | **4lb** | $CF_3$ | **5l** | 75 |
| 8 | **4mb** | COOMe | **5m** | 85 |

alkyne **1j**, allenylphosphine oxides **2a**−**c**, and selected products **3**−**5** and their analytical data are provided below. For analytical and spectral data of other compounds, see the Supporting Information. All other reagents and solvents used were commercially available.

**1j:** A solution of t-BuOK (13.49 g, 120 mmol) in anhydrous THF (130 mL) was added dropwise to a stirred suspension of $[Ph_3PCH_2Br]Br$ (25 g, 57 mmol) in anhydrous THF (150 mL) under argon atmosphere at −78 °C. 4-(Methylthio)benzaldehyde (8.68 g, 57 mmol) was added dropwise to the formed yellow suspension. The mixture was stirred for 10 min at −78 °C, then warmed to room temperature and quenched with saturated aq $NH_4Cl$ (100 mL). The organic phase was separated and the aqueous layer was extracted with ether (2 × 50 mL). Combined organic phases were dried ($MgSO_4$), filtered, and concentrated to a volume of approximately 100 mL. Then, 500 mL of hexane was added and the precipitated phosphine oxide was filtered off. The clear hexane filtrate was evaporated and the residue was distilled in a vacuum, bp 74−76 °C (1 mmHg), yield 2.7 g (18.2 mmol, 32%). Spectral properties of obtained compound **1j** were identical with those reported in the literature.[18]

**2a:**[19] Diphenylchlorophosphine (1 mL, 5.5 mmol) was added dropwise to a stirred mixture of 2-butyn-1-ol (375 μL, 5 mmol) and dry triethylamine (765 μL, 5.5 mmol) in anhydrous DMF (10 mL) under argon atmosphere. The mixture was stirred for 2 h at −15 °C, then warmed to room temperature, and the stirring was continued for another 2 h. The mixture was quenched with 5% aqueous NaCl solution and extracted with a 1:1 pentane−ether mixture. The organic phase was evaporated and the residue was purified by preparative column chromatography on silica gel (eluent: EtOAc) to obtain **2a** as a colorless solid. Yield 976 mg (3.61 mmol, 72%). $^1$H NMR (500.13 MHz, $CDCl_3$) δ 7.74−7.69 (m, 4H), 7.52−7.48 (m, 2H), 7.45−7.41 (m, 4H), 4.62 (dq, $^4J_{PH}$ = 11.2 Hz, $^5J_{HH}$ = 3.1 Hz, 2H), 1.92 (dt, $^3J_{PH}$ = 11.9 Hz, $^5J_{HH}$ = 3.1 Hz, 3H); $^{13}$C NMR (125.76 MHz, $CDCl_3$) δ 212.1 (d, $^2J_{PC}$ = 7.3 Hz), 132.3 (+), 132.1 (+, 4C, d, $^3J_{PC}$ = 9.4 Hz), 131.3 (2C, d, $^1J_{PC}$ = 94.8 Hz), 128.7 (+, 4C, d, $^2J_{PC}$ = 12.2 Hz), 92.7 (d, $^1J_{PC}$ = 101.5 Hz), 76.3

(14) All conditions normally used for the benzannulation reaction (see ref 2i) had been tried: (A) $Pd(PPh_3)_4$ (5−10 mol %) in THF or toluene (1 M) at 100−120 °C; (B) $Pd_2dba_3$-$CHCl_3$ (5 mol %), *o*-$Tol_3P$ (20 mol %) in THF or toluene (1 M) at 60−80 °C; (C) $Pd(PPh_3)_4$ (5 mol %), $Pd(OAc)_2$ (5 mol %), and TDMPP (15 mol %) in toluene (1 M) at 60−100 °C with and without the addition of Lewis acid activator ($Et_2$-AlCl, 25 mol %). No formation of benzannulation products was detected under the listed conditions.

(15) Pd-catalyzed enyne−diyne benzannulation is a regiospecific process. The regiochemistry of this reaction was established previously (see ref 6a). Nonetheless, the regiochemistry of the selected benzannulation product **5h** was again confirmed by 2D NMR experiments; see Supporting Information for details.

(16) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280.

(17) Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* **1997**, *62*, 8957.

(18) Fuerstner, A.; Nikolakis, K. *Liebigs Ann. Org. Bioorg. Chem.* **1996**, 2107.

(19) Berlan, J.; Battioni, J. P.; Koosha, K. *Bull. Soc. Chim. Fr.* **1977**, 183.

(−, d, $^3J_{PC}$ = 12.8 Hz), 14.6 (+, d, $^2J_{PC}$ = 5.8 Hz); $^{31}$P NMR (202.46 MHz, $CDCl_3$) $\delta$ 28.3.

**2b:**[20] A solution of diphenylchlorophosphine (17.9 mL, 100 mmol) in anhydrous dichloromethane (150 mL) was added dropwise to a mixture of propargyl alcohol (11.6 mL) and dry triethylamine (22.2 mL) in anhydrous dichloromethane (200 mL) under argon atmosphere at −78 °C. The mixture was allowed to warm to 10 °C and was poured into a cold solution of HCl (concentrated, 5 mL) in water (200 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed (water, brine), dried ($MgSO_4$), filtered, and evaporated. The solid residue was recrystallized from a hexane−dichloromethane mixture to obtain the title compound as colorless crystals, mp 99−100 °C. Yield 18.636 g (77.57 mmol, 78%).

**2c:** 2-Butyn-1-ol (1 mmol, 75 $\mu$L) was added to a stirred mixture of bis(diisopropylamino)chlorophosphine (1.1 mmol, 29.9 mg) and triethylamine (153 $\mu$L) in dry DMF (2 mL). The mixture was stirred at 0 °C for 2 h before being warmed up to room temperature. DMF was evaporated in a vacuum and the residue was purified by preparative column chromatography on silica gel (eluent: hexanes−EtOAc, 1:1) to afford **2c** as colorless crystals. Yield 264.4 mg (0.88 mmol, 88%). $^1$H NMR (500.13 MHz, $CDCl_3$) $\delta$ 4.65−4.62 (m, 2H), 3.55−3.49 (m, 4H), 1.91−1.87 (m, 3H), 1.25 (dd, $J$ = 6.8, 1.1 Hz, 12H), 1.18 (dd, $J$ = 6.8, 1.1 Hz, 12H); $^{31}$P NMR (202.46 MHz, $CDCl_3$) $\delta$ 23.1; GC/MS $m/z$ 300 ($M^+$, 10), 247 ((i-$Pr_2N)_2PO^+$, 100).

**Preparation of Endo-Enynes 3: Typical Procedure.** A 3-mL Wheaton microreactor was loaded with $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), TDMPP (88.5 mg, 0.2 mmol), allenylphosphine oxide (**2b**) (240 mg, 1 mmol), and toluene (2 mL). Phenylacetylene (**1a**) (1.2 mmol, 125 $\mu$L) was added and the reaction mixture was stirred at room temperature for 1 h. Then the mixture was filtered through a short column of silica gel (eluent: EtOAc) and concentrated. Preparative column chromatography of the residue on silica gel (eluent: $CH_2Cl_2$−EtOAc, 2:1) gave **3ab** as a colorless solid. Yield 308 mg (0.9 mmol, 90%).

**3ab:** $^1$H NMR (400.13 MHz, $CDCl_3$) $\delta$ 7.78−7.73 (m, 4H), 7.49−7.44 (m, 8H), 7.34−7.31 (m, 3H), 6.48 (d, $^2J_{PH}$ = 23.4 Hz, 1H), 2.33 (m, 3H); $^{13}$C NMR (100.61 MHz, $CDCl_3$) $\delta$ 141.8 (d, $^2J_{PC}$ = 12.5 Hz), 134.6 (d, $^1J_{PC}$ = 106.3 Hz), 132.3 (d, $^2J_{PC}$ = 11.1 Hz), 131.5 (d, $^3J_{PC}$ = 9.9 Hz), 129.6, 129.2, 129.1, 129.0, 127.1 (d, $^1J_{PC}$ = 101.0 Hz), 122.7, 93.3, 91.5 (d, $^3J_{PC}$ = 25.6 Hz), 21.5 (d, $^3J_{PC}$ = 5.8 Hz); $^{31}$P NMR (161.98 MHz, $CDCl_3$) $\delta$ 19.4; IR (KBr) 3028, 2851, 2334, 2185, 1591, 1430, 1192, 1117, 992, 836 cm$^{-1}$; GC/MS $m/z$ 342 ($M^+$, 100); HRMS calcd for $C_{23}H_{19}OP$ 342.1174, found 342.1183.

**3ea:** $^1$H NMR (500.13 MHz, $CDCl_3$) $\delta$ 7.70−7.65 (m, 4H), 7.55−7.51 (m, 2H), 7.50−7.46 (m, 4H), 4.31 (s, 2H), 3.41 (s, 3H), 2.19 (m, 3H), 1.88 (d, $^3J_{PH}$ = 13.4 Hz, 3H); $^{13}$C NMR (125.76 MHz, $CDCl_3$) $\delta$ 134.9 (d, $^2J_{PC}$ = 13.1 Hz), 133.9 (d, $^1J_{PC}$ = 96.3 Hz), 133.3 (d, $^1J_{PC}$ = 103.5 Hz), 132.2, 131.9 (d, $^3J_{PC}$ = 9.8 Hz), 129.0 (d, $^2J_{PC}$ = 11.9 Hz), 94.0, 87.3 (d, $^3J_{PC}$ = 22.6 Hz), 60.8, 58.1, 22.5 (d, $^3J_{PC}$ = 6.4 Hz), 22.4 (d, $^2J_{PC}$ = 12.9 Hz); $^{31}$P NMR (202.46 MHz, $CDCl_3$) $\delta$ 29.1; IR (KBr) 2975, 2947, 2818, 2360, 1979, 1578, 1432, 1367, 1259, 1181, 1083, 893, 748, 696, 539 cm$^{-1}$; GC/MS $m/z$ 324 ($M^+$, 100); HRMS calcd for $C_{20}H_{21}O_2P$ 324.1279, found 324.1290.

**3fa:** $^1$H NMR (400.13 MHz, $CDCl_3$) $\delta$ 7.66−7.63 (m, 4H), 7.49−7.47 (m, 2H), 7.45−7.43 (m, 4H), 2.14 (m, 3H), 1.86 (d, $^3J_{PH}$ = 13.4 Hz, 3H), 0.18 (s, 9H); $^{13}$C NMR (100.61 MHz, $CDCl_3$) $\delta$ 134.8 (d, $^2J_{PC}$ = 12.7 Hz), 134.1 (d, $^1J_{PC}$ = 96.0 Hz), 133.0 (d, $^1J_{PC}$ = 103.1 Hz), 131.7, 131.5 (d, $^3J_{PC}$ = 9.7 Hz), 128.6 (d, $^2J_{PC}$ = 12.0 Hz), 105.1 (d, $^3J_{PC}$ = 21.3 Hz), 103.2, 22.0 (d, $^2J_{PC}$ = 12.9 Hz), 21.9 (d, $^3J_{PC}$ = 6.5 Hz), −0.1; $^{31}$P NMR (161.98 MHz, $CDCl_3$) $\delta$ 29.2; IR (KBr) 2096, 1575, 1190 cm$^{-1}$; GC/MS $m/z$ 352 ($M^+$, 100); HRMS calcd for $C_{21}H_{25}OPSi$ 352.1412, found 352.1408.

(20) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: New York, 1981.

**Preparation of Exo-Enynes 4: Typical Procedure.** A 5-mL Wheaton microreactor was loaded with TCPC (40.3 mg, 0.1 mmol), allenylphosphine oxide (**2b**) (480 mg, 2 mmol), and $CH_2Cl_2$ (4 mL). Phenylacetylene (**1a**) (219 $\mu$L, 2.1 mmol) was added and the reaction mixture was stirred at room temperature for 12−18 h, until GC/MS analysis showed the reaction complete. Then, the reaction was directly loaded on a column of silica gel and elution with $CH_2Cl_2$−EtOAc (1:1) gave compound **4ab** as a colorless solid. Yield 520 mg (1.52 mmol, 76%). An analytical sample was obtained by recrystallization from hexane−$CH_2Cl_2$.

**4ab:**[7] mp 126 °C; $^1$H NMR (500.13 MHz, $CDCl_3$) $\delta$ 7.83 (m, 4H), 7.50−7.42 (m, 6H), 7.23 (m, 3H), 7.14 (m, 2H), 5.61 (dd, $^4J_{PH}$ = 4.1 Hz, $^2J_{HH}$ = 0.8 Hz, 1H), 5.56 (dd, $^4J_{PH}$ = 4.4 Hz, $^2J_{HH}$ = 0.8 Hz, 1H), 3.35 (d, $^2J_{PH}$ = 13.9 Hz, 2H); $^{13}$C NMR (125.76 MHz, $CDCl_3$) $\delta$ 132.8 (d, $^1J_{PC}$ = 100.0 Hz, 2C), 132.3 (+, 2C), 131.9 (+, 2C), 131.7 (+, d, $^3J_{PC}$ = 9.3 Hz, 4C), 128.9 (+, d, $^2J_{PC}$ = 11.8 Hz, 4C), 128.7 (+), 128.5 (+, 2C), 127.4 (−, d, $^3J_{PC}$ = 8.7 Hz), 123.0, 121.3 (d, $^2J_{PC}$ = 9.1 Hz), 90.4, 90.0 (d, $^3J_{PC}$ = 4.5 Hz), 39.0 (−, d, $^1J_{PC}$ = 66.9 Hz); $^{31}$P NMR (161.98 MHz, $CDCl_3$) $\delta$ 26.8; $^1$H−$^{13}$C HMQC ($CDCl_3$, 500.13 MHz, 125.76 MHz) $\delta_H/\delta_C$ 7.83/131.7, 7.52/132.3, 7.45/128.9, 7.23/128.7, 7.23/128.5, 7.14/131.9 (5.61/127.4 and 5.56/127.4), 3.35/39.0; GC/MS $m/z$ 342 ($M^+$, 30), 341 (M − H, 40), 201 ($Ph_2PO^+$, 100).

**4jb:** mp 107 °C dec; $^1$H NMR (500.13 MHz, $CDCl_3$) $\delta$ 7.83−7.79 (m, 4H), 7.48−7.40 (m, 6H), 7.07 (d, $J$ = 8.4 Hz. 2H), 7.03 (d, $J$ = 8.4 Hz, 2H), 5.58 (d, $^4J_{PH}$ = 3.7 Hz, 1H), 5.52 (d, $^4J_{PH}$ = 3.8 Hz, 1H), 3.33 (d, $^2J_{PH}$ = 13.8 Hz, 1H), 2.43 (s, 3H); $^{13}$C NMR (125.76 MHz, $CDCl_3$) $\delta$ 139.9, 132.8 (d, $^1J_{PC}$ = 100.0 Hz, 2C), 132.3 (+, 2C), 132.2 (+, 2C), 131.6 (+, d, $^3J_{PC}$ = 9.3 Hz, 4C), 128.9 (+, d, $^2J_{PC}$ = 11.7 Hz, 4C), 127.2 (−, $^3J_{PC}$ = 8.6 Hz), 125.9 (+, 2C), 121.3 (d, $^3J_{PC}$ = 8.9 Hz), 119.3, 90.3, 90.1 (d, $^3J_{PC}$ = 4.2 Hz), 39.1 (−, d, $^1J_{PC}$ = 66.9 Hz), 15.7 (+); $^{31}$P NMR (202.46 MHz, $CDCl_3$) $\delta$ 26.7; GC/MS $m/z$ 388 ($M^+$, 40), 387 (M − H, 40), 201 ($Ph_2PO^+$, 100).

**Pd-Catalyzed Benzannulation with 5,7-Dodecadiyne: Typical Procedure.** An oven-dried 1-mL Wheaton microreactor was loaded with $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), 5,7-dodecadiyne (100 $\mu$L, 0.55 mmol), and dry THF (500 $\mu$L). The mixture was stirred for 15 min until homogenized, then transferred into a 3-mL microreactor preloaded with enyne **4ab** (171 mg, 0.5 mmol) and dry THF (500 $\mu$L). The mixture was stirred at 100 °C for 12 h, and the reaction progress was monitored by GC/MS. When the reaction was complete, the solvent was removed in a vacuum and the residue was purified by preparative column chromatography on silica gel (eluent: hexanes−EtOAc, 2:1) to obtain **5a** an as oil. Yield 189 mg (0.38 mmol, 75%). An analytical sample was obtained by recrystallization from hexane−$CH_2Cl_2$.

**5a:** mp 121−122 °C; $^1$H NMR (500.13 MHz, $CDCl_3$) $\delta$ 7.73−7.68 (m, 4H), 7.54−7.51 (m, 2H), 7.46−7.43 (m, 4H), 7.36−7.26 (m, 5H), 6.92 (s, 1H), 6.81 (s, 1H), 3.63 (d, $^2J_{PH}$ = 14.1 Hz, 2H), 2.71 (t, $J$ = 7.8 Hz, 2H), 2.28 (t, $J$ = 6.9 Hz, 2H), 1.25−1.46 (m, 2H), 1.45−1.39 (m, 2H), 1.34−1.26 (m, 4H), 0.91 (t, $J$ = 7.3 Hz, 3H), 0.85 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (125.76 MHz, $CDCl_3$) $\delta$ 146.0, 144.4, 141.4, 132.6 (d, $^1J_{PC}$ = 99.1 Hz, 2C), 132.2 (+, 2C), 131.7 (+, d, $^3J_{PC}$ = 8.9 Hz, 4C), 130.4 (d, $^2J_{PC}$ = 8.3 Hz), 129.8 (+, 3C), 129.2 (+, d, $^3J_{PC}$ = 5.5 Hz), 128.9 (+, d, $^2J_{PC}$ = 11.6 Hz, 4C), 127.9 (+, 2C), 127.3 (+), 120.7, 38.7 (−, d, $^1J_{PC}$ = 66.0 Hz), 35.1 (−), 33.1 (−), 31.0 (−), 23.0 (−), 22.3 (−), 19.7 (−), 14.5 (+), 14.0 (+); $^{31}$P NMR (202.46 MHz, $CDCl_3$) $\delta$ 27.8; GC/MS $m/z$ 504 ($M^+$, 30), 303 (M − $Ph_2PO$, 70), 201 ($Ph_2PO^+$, 100). Anal. Calcd for $C_{35}H_{37}OP$: C 83.30, H 7.39, Found: C 83.30, H 7.50.

**5g:** mp 100−101 °C; $^1$H NMR (500.13 MHz, $CDCl_3$) $\delta$ 7.72−7.68 (m, 4H), 7.54−7.51 (m, 2H), 7.46−7.44 (m, 4H), 7.32 (dd, $J_{HH}$ = 8.4 Hz, $J_{HF}$ = 5.6 Hz, 2H), 7.00 (ps-t, $J_{HH} \approx J_{HF}$ = 8.4 Hz, 2H), 6.89 (s, 1H), 6.80 (s, 1H), 3.63 (d, $^2J_{PH}$ = 13.9 Hz, 2H), 2.69 (t, $J$ = 7.7 Hz, 2H), 2.29 (t, $J$ = 6.9 Hz, 2H), 1.51−1.46 (m, 2H), 1.46−1.40 (m, 2H), 1.33−1.25 (m, 4H), 0.91 (t, $J$ = 7.3 Hz, 3H), 0.86 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (125.76

MHz, $CDCl_3$) $\delta$ 161.5 (d, $^1J_{FC}$ = 245.1 Hz), 146.1, 143.4, 137.4, 132.6 (d, $^1J_{PC}$ = 94.6 Hz, 2C), 132.2 (2C), 131.7 (+, d, $^3J_{PC}$ = 9.3 Hz, 4C), 131.4 (+, d, $^3J_{FC}$ = 7.4 Hz, 2C), 130.4 (d, $^2J_{PC}$ = 9.3 Hz), 129.9 (+, d, $^3J_{PC}$ = 4.6 Hz), 129.1 (+, d, $^3J_{PC}$ = 4.6 Hz), 128.9 (+, d, $^2J_{PC}$ = 12.0 Hz, 4C), 120.8, 114.7 (d, $^2J_{FC}$ = 21.3 Hz, 2C), 98.1, 78.4, 38.6 (−, d, $^1J_{PC}$ = 65.7 Hz), 35.1 (−), 33.1 (−), 31.0 (−), 23.0 (−), 22.3 (−), 19.7 (−), 14.4 (+), 14.0 (+); $^{19}$F NMR (470.59 MHz, $CDCl_3$) $\delta$ −117.5; $^{31}$P NMR (202.46 MHz, $CDCl_3$) $\delta$ 27.7.

**5h:** mp 96−98 °C; $^1$H NMR (500.13 MHz, $CDCl_3$) $\delta$ 7.72−7.68 (m, 4H), 7.54−7.51 (m, 2H), 7.47−7.43 (m, 4H), 7.25 (d, $J$ = 8.2 Hz, 2H), 7.12 (d, $J$ = 8.2 Hz, 2H), 6.90 (s, 1H), 6.79 (s, 1H), 3.63 (d, $^2J_{PH}$ = 14.1 Hz, 2H), 2.70 (t, $J$ = 7.8 Hz, 2H), 2.36 (s, 3H), 2.29 (t, $J$ = 6.9 Hz, 2H), 1.52−1.47 (m, 2H), 1.47−1.41 (m, 2H), 1.34−1.27 (m, 4H), 0.91 (t, $J$ = 7.3 Hz, 3H), 0.86 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (125.76 MHz, $CDCl_3$) $\delta$ 146.0, 144.3, 138.5, 137.0, 132.6 (d, $^1J_{PC}$ = 97.1 Hz, 2C), 132.2 (+, 2C), 131.7 (+, d, $^3J_{PC}$ = 8.9 Hz, 4C), 130.3 (d, $^2J_{PC}$ = 7.9 Hz), 129.7 (+, 2C), 129.6 (+, d, $^3J_{PC}$ = 4.6 Hz), 129.2 (+, d, $^3J_{PC}$ = 4.6 Hz), 128.9 (+, d, $^2J_{PC}$ = 11.7 Hz, 4C), 128.6 (+, 2C), 120.7, 97.8, 78.7, 38.7 (−, d, $^1J_{PC}$ = 66.1 Hz), 35.1 (−), 33.1 (−), 31.0 (−), 23.0 (−), 22.3 (−), 21.6 (+), 19.8 (−), 14.5 (+), 14.0 (+); $^{31}$P NMR (202.46 MHz, $CDCl_3$) $\delta$ 27.9; GC/MS $m/z$ 518 ($M^+$, 15), 461 (M − Bu, 7), 317 (M − $Ph_2PO$, 70), 201 ($Ph_2PO^+$, 100). Anal. Calcd for $C_{36}H_{39}OP$: C 83.36, H 7.58. Found: C 83.26, H 7.50.

**5j:** mp 118 °C; $^1$H NMR (500.13 MHz, $CDCl_3$) $\delta$ 7.72−7.68 (m, 4H), 7.53−7.51 (m, 2H), 7.46−7.43 (m, 4H), 7.29 (d, $J$ = 8.3 Hz, 2H), 7.20 (d, $J$ = 8.3 Hz, 1H), 6.90 (s, 1H), 6.79 (s, 1H), 3.62 (d, $^2J_{PH}$ = 14.0 Hz, 2H), 2.69 (t, $J$ = 7.7 Hz, 2H), 2.50 (s, 3H), 2.30 (t, $J$ = 6.9 Hz, 2H), 1.51−1.46 (m, 2H), 1.46−1.41 (m, 2H), 0.91 (t, $J$ = 7.3 Hz, 3H), 0.87 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (125.76 MHz, $CDCl_3$) $\delta$ 146.1, 143.7, 138.3, 137.4, 132.6 (d, $^1J_{PC}$ = 98.0 Hz, 2C), 132.2 (+, 2C), 131.7 (+, d, $^3J_{PC}$ = 9.3 Hz, 4C), 130.4 (d, $^2J_{PC}$ = 8.3 Hz), 130.2 (+, 2C), 129.8 (+, d, $^3J_{PC}$ = 4.6 Hz), 129.1 (+, d, $^3J_{PC}$ = 4.6 Hz), 128.9 (+, d, $^2J_{PC}$ = 12.0 Hz, 4C), 120.6, 98.1, 78.5, 38.7 (−, $^1J_{PC}$ = 65.7 Hz), 35.1 (−), 33.1 (−), 31.0 (−), 23.0 (−), 22.3 (−), 19.7 (−), 16.3 (+), 14.5 (+), 14.0 (+); $^{31}$P NMR (202.46 MHz, $CDCl_3$) $\delta$ 27.7.

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**Supporting Information Available:** Analytical and spectral data for compounds **3**−**5**, 2D NMR data for compound **5h**, and $^1$H and $^{13}$C NMR charts for all unknown compounds; X-ray data for compound **3aa**. This material is available free of charge via the Internet at http://pubs.acs.org..

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