$Ph_2P(O)$ Group for Protection of Terminal Acetylenes

Xin Yang,[a] Daisuke Matsuo,[a] Yoshinori Suzuma,[a] Jing-Kun Fang,[a] Feng Xu,[a] Akihiro Orita,*[a] Junzo Otera,*[a] Shingo Kajiyama,[b] Nagatoshi Koumura,[b,c] Kohjiro Hara[c]

[a] Department of Applied Chemistry, Okayama University of Science, 1-1 Ridai-cho, Kita-ku, Okayama 700-0005, Japan
Fax +81(86)2569533; E-mail: orita@high.ous.ac.jp

[b] Graduated School of Pure and Applied Science, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba 305-8571, Japan

[c] National Institute of Advanced Industrial Science and Technology, Research Center for Photovoltaics, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan

Received 30 May 2011

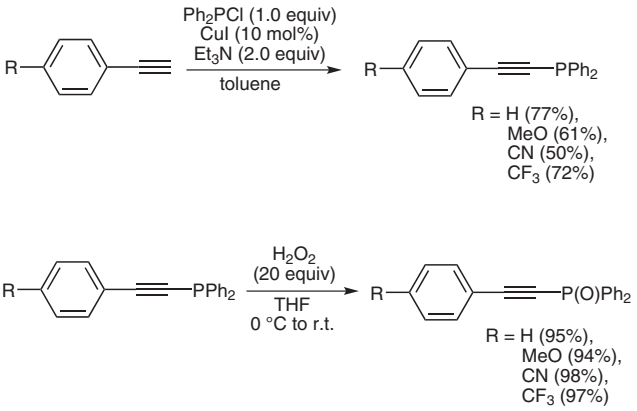
Abstract: A protecting group $Ph_2P(O)$ for terminal ethyne was newly developed. This protecting group can be introduced readily to terminal ethyne by CuI-catalyzed phosphination and subsequent oxidation with H_2O_2. $Ph_2P(O)$-protected ethynes remained intact in Sonogashira coupling, and their high polarity enabled easy separation of the desired coupling product from by-products. By treatment with *t*-BuOK, $Ph_2P(O)$-protected ethynes were transformed to the corresponding terminal ethynes.

Key words: alkynes, phosphorylation, protecting groups, coupling

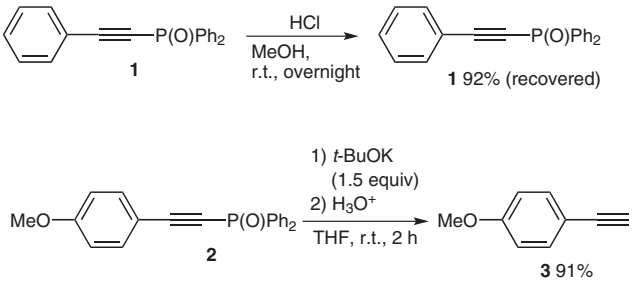
The protection/deprotection of functional group is one of the fundamental technologies in organic synthesis.[1] An ideal protecting group needs to satisfy the following issues: (i) facile introduction to the target functional group, (ii) stability during the desired transformation such as C–C bond formation and (iii) facile deprotection under mild reaction conditions. Terminal acetylenes are usually protected by silyl and dimethyl(hydroxyl)methyl groups.[2] We have been involved in the syntheses of acetylene derivatives[3] and their applications to organic materials such as organic field-effect transistors (OFET)[4] and organic light-emitting diodes (OLED).[5] Although we take advantage of Sonogashira coupling,[6] we frequently experienced troublesome separation of the desired compound from the remaining starting materials and by-products because of their similar polarities. We have established double elimination protocols of β-substituted sulfones for access to acetylenes[3] and demonstrated the usefulness of the vinylsulfone intermediates as arylethyne precursors, which enabled facile isolation because of their high polarity.[3a–3c] We therefore envisioned that a polar protecting group for terminal ethynes would give rise to a new technology which effects facile isolation. We have now found out that the diphenylphosphoryl group, $Ph_2P(O)$, serves as a protecting group for terminal ethynes to realize facile isolation.

The $Ph_2P(O)$ group was introduced to terminal ethynes by treatment with Ph_2PCl in the presence of a catalytic amount of CuI followed by oxidation with H_2O_2 (Scheme 1).[7] All phosphorylethynes could be purified by column chromatography on silica gel.

In order to investigate stability of the $Ph_2P(O)$ protecting group, phosphorylethynes are subjected to acid or base treatment. Phosphorylethyne **1** remained unchanged in MeOH–HCl aqueous solution, and 92% of **1** was recovered (Scheme 2). In sharp contrast to this, treatment of **2** with *t*-BuOK followed by aqueous workup gave the terminal ethyne **3** in 91% yield.



Scheme 1 Synthesis of ethynylphosphines

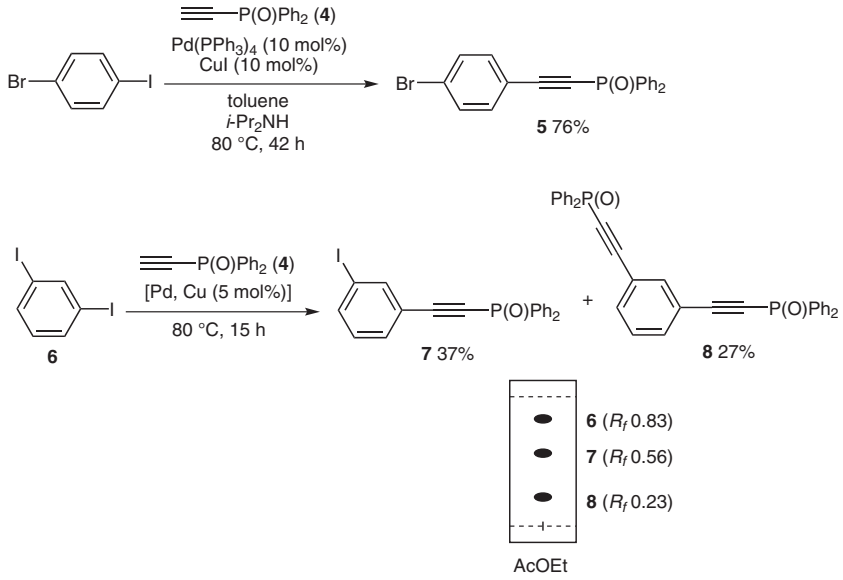


Scheme 2 Evaluation of stability of ethynylphosphines

The diphenylphosphoryl–ethyne bond remained intact in Sonogashira coupling, and a coupling reaction of 1-bromo-4-iodobenzene with phosphorylethyne **4** gave the desired 4-bromophenylethynylphosphine oxide (**5**) in 76% yield (Scheme 3). In Sonogashira coupling between 1,3-diiodobenzene (**6**) and phosphorylethyne **4**, a thin layer chromatography (TLC) analysis indicated formation of mono- and diadducts **7** and **8**. As we expected, high polar-

SYNLETT 2011, No. 16, pp 2402–2406
Advanced online publication: 08.09.2011
DOI: 10.1055/s-0030-1261223; Art ID: U04611ST
© Georg Thieme Verlag Stuttgart · New York

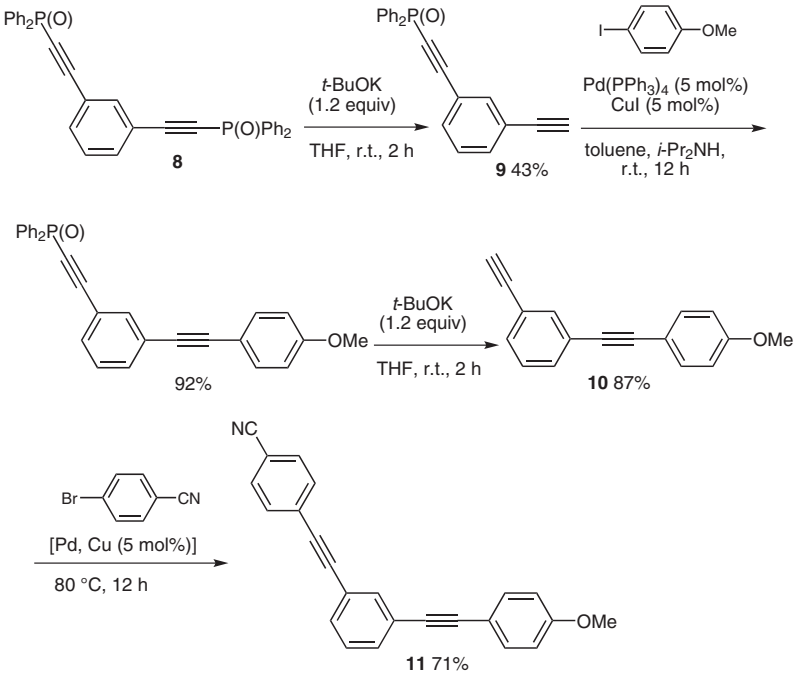
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



Scheme 3 Sonogashira coupling with phosphorylethyne **4**

ity of phosphine oxide enables easy separation of **7** and **8** by a column chromatography on silica gel: R_f 0.56 for monoadduct **7** and R_f 0.23 for diadduct **8** in EtOAc. For instance, in 10-mmol scale of coupling reaction, 140 g of silica gel, 30 times weight of the crude product, enabled isolation of **7** in a pure form, while the same scale of coupling reaction between **6** and trimethylsilylethyne required 260 g of silica gel, 70 times weight of the crude product, for separation of mono- and di(silylethynyl)-adducts which showed R_f 0.59 and R_f 0.41 in hexane, respectively.

The polarity-assisted separation technology by using Ph$_2$P(O) group realized a straightforward synthesis of unsymmetrically substituted phenyleneethynylenes which we had prepared previously by taking advantage of highly polar building blocks such as halo-[3a] or formyl-substituted vinylsulfones.[3a] Treatment of **8** with 1.2 equivalents of *t*-BuOK followed by column chromatography provided **9** in 43% yield, which served as a building block for unsymmetrically substituted phenyleneethynylenes (Scheme 4). When Sonogashira coupling of **9** with 1-iodo-4-methoxybenzene followed by *t*-BuOK-catalyzed dephosphorylation was carried out, 1-ethynyl-3-(4-methoxyphenylethynyl)benzene **10** was obtained in high yield (92% and 87% in each step). Subjection of **10** to coupling with 1-bromo-4-cyanobenzene afforded unsymmetrically substituted phenyleneethynylene **11** in 71% yield.



Scheme 4 Synthesis of unsymmetrically substituted phenyleneethynylene **11**

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

We established previously the syntheses of amino-/cyano-substituted phenyleneethynylenes[8] and succeeded in their applications to sensitizers for dye-sensitized solar cells (DSSCs).[9] For access to a branched acetylenic dye having two diphenylamino donor groups, we designed $Ph_2P(O)$-protected building block **12**. When 1,3,5-triethynylbenzene was subjected to the phosphoryl protection protocol, monophosphorylethyne **12** was obtained in 57% yield (two steps). In this reaction, **12** could be readily separated from di- and triphosphorylated derivatives. Monophosphorylethyne **12** was transformed successfully to **13** by Sonogashira coupling with 1-iodo-4-diphenylaminobenzene and subsequent *t*-BuOK-catalyzed dephosphorylation. Coupling of **13** with 4-bromophenylethynylbenzene gave the desired branched phenyleneethynylene having diphenylamino groups **14** in 53% yield (Scheme 5). Introducing carboxylic group to the branched acetylenic dye is in progress in order to anchor the dye to TiO_2 film.

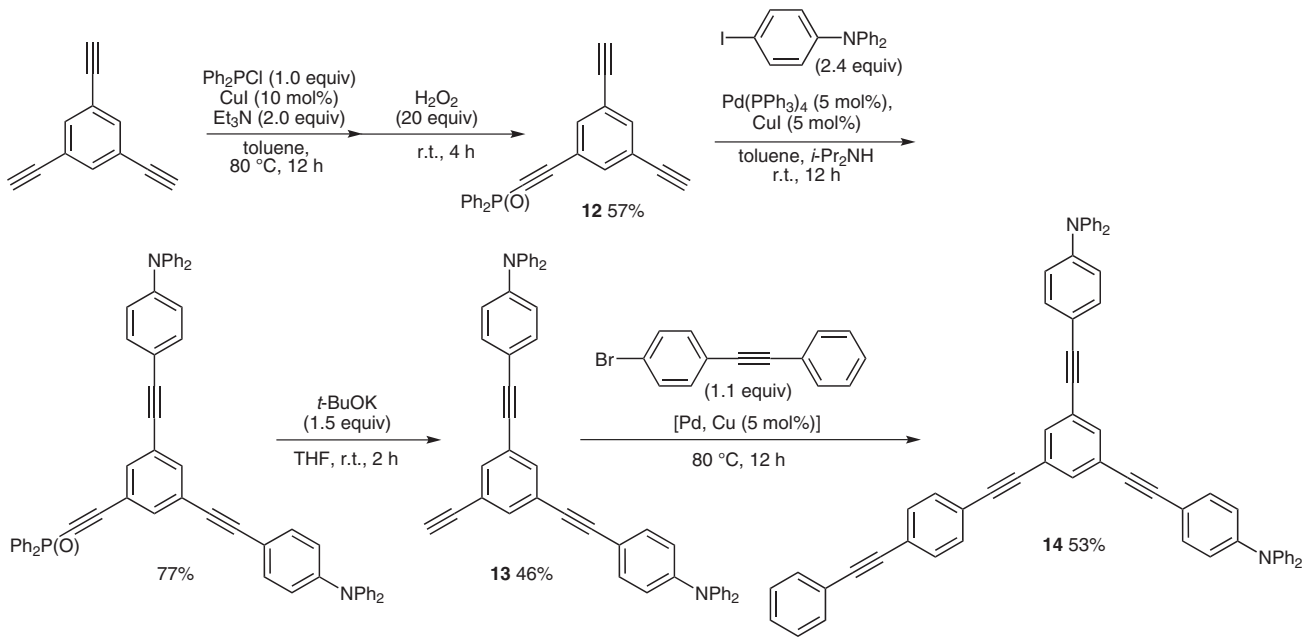
Encouraged by usefulness of the $Ph_2P(O)$-protection as mentioned above, we investigated a new synthetic route for enantiopure double-helical phenyleneethynylene **15** which had been prepared by utilizing monosilyl-protected 2,2′-diethynyl-1,1′-binaphthyl **16** as a key building block (Scheme 6).[10] Enantiopure organic molecules having highly expanded π-systems have attracted great attention as new type of optical materials because they exhibit chiral information in electronic circular dichroism (ECD) and circularly polarized luminescence (CPL).[11] Preparation of **16** was not so easy because separation of **16** from bissilylated product **17** was tedious due to their similar R_f values. In sharp contrast, mono-$Ph_2P(O)$-protected 2,2′-diethynyl-1,1′-binaphthyl **19** could be easily isolated from a mixture of crude products: R_f in EtOAc, 0.60 (**19**), 0.17 (by-product **20**) and 0.97 (starting compound **18**).[12] Intermolecular Sonogashira coupling of **19** with 1,3-diiodobenzene proceeded smoothly to give **21** in 98% yield, and $Ph_2P(O)$ groups of **21** were removed by treatment with *t*-BuOK (76% yield). When **22** was subjected to Sonogashira coupling with 1,3-diiodobenzene, intermolecular coupling and the subsequent cyclization proceeded successfully to afford **15** in 22% yield.

In summary, we have established a new methodology for protection of terminal ethynes by utilizing the $Ph_2P(O)$ group. This protection group can be installed by treatment of phenylethynes with Ph_2PCl in the presence of CuI followed by H_2O_2-oxidation. While $Ph_2P(O)$-protected ethynes remain intact in Sonogashira coupling, treatment of them with strong base such as *t*-BuOK enables facile deprotection to provide the corresponding ethynes. Highly polar features of $Ph_2P(O)$-protected ethynes allow their facile separation from by-products which are inseparable or difficult-to-separate when the trimethylsilyl group is used instead of $Ph_2P(O)$. By taking advantage of this highly polar protecting group, phenyleneethynylenes **14** having expanded π-system and enantiopure double-helical phenyleneethynylene **15** have been synthesized successfully. Further applications of $Ph_2P(O)$-protected ethynes to other C–C bond-forming reaction are under investigation to explore new aryleneethynylene materials.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

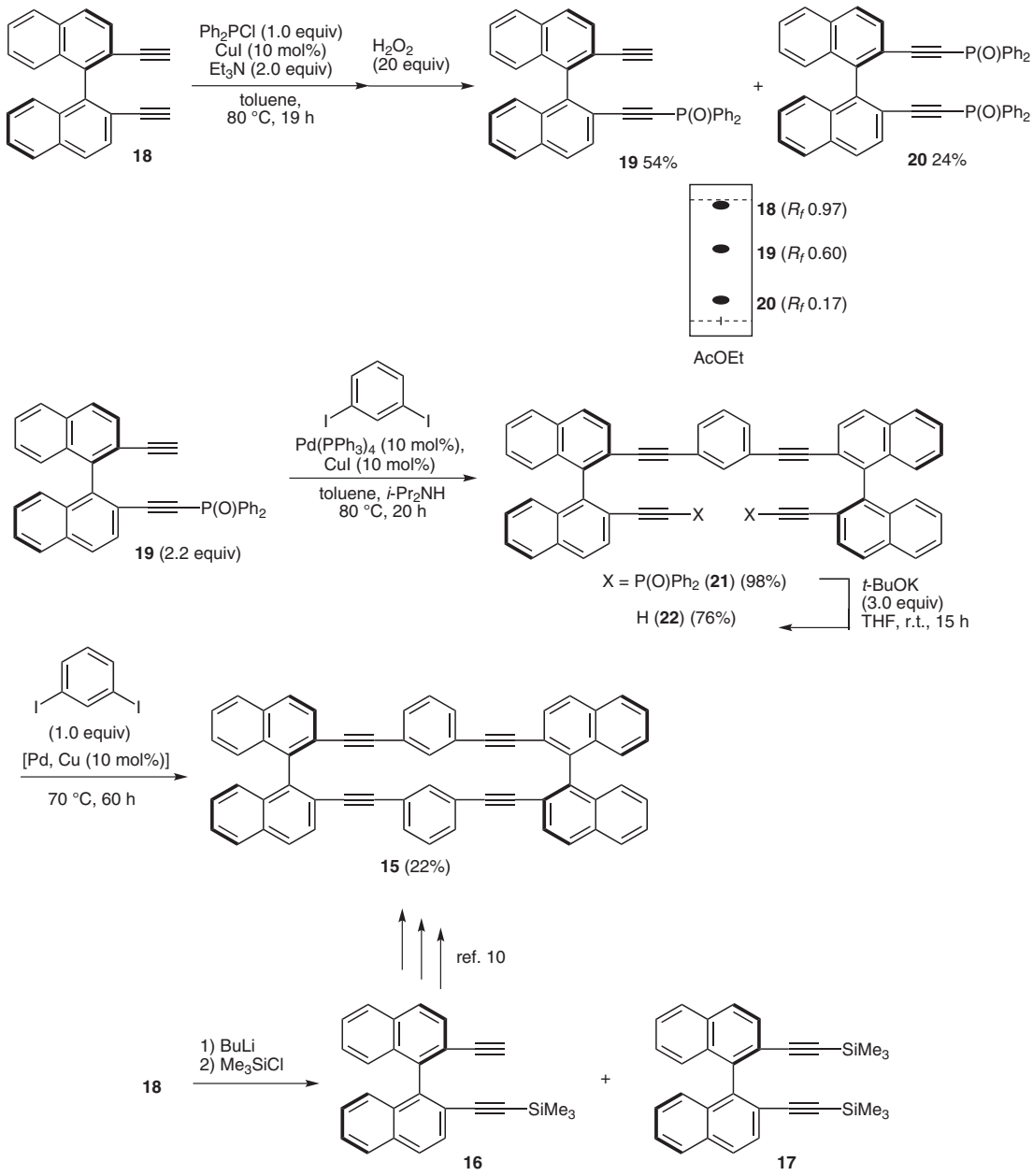
Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas and matching fund subsidy for private universities from the Ministry of Education, Culture, Sports, Science and Technology, Japan, the Japan Society for the Promotion of Science (JSPS) through the 'Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program),' initiated



Scheme 5 Synthesis of branched phenyleneethynylene **14**

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



Scheme 6 Synthesis of enantiopure acetylenic cyclophane **15**

by the Council for Science and Technology Policy (CSTP) and Okayama Prefecture Industrial Promotion Foundation.

References and Notes

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3th ed.; John Wiley & Sons, Inc.: New York, **1999**.

(2) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3th ed.; John Wiley & Sons, Inc.: New York, **1999**, 654–659.

(3) (a) Doi, T.; Orita, A.; Matsuo, D.; Saijo, R.; Otera, J. *Synlett* **2008**, 55. (b) Ye, F.; Orita, A.; Doumoto, A.; Otera, J. *Tetrahedron* **2003**, *59*, 5635. (c) Orita, A.; Ye, F.; Doumoto, A.; Otera, J. *Chem. Lett.* **2003**, *32*, 104. (d) Orita, A.; Taniguchi, H.; Otera, J. *Chem. Asian J.* **2006**, *1*, 430. (e) Orita, A.; Nakano, T.; Yokoyama, T.; Babu, G.; Otera, J. *Chem. Lett.* **2004**, *33*, 1298. (f) Orita, A.; Miyamoto, K.; Nakashima, M.; Ye, F.; Otera, J. *Adv. Synth. Catal.* **2004**, *346*, 767. (g) Ye, F.; Orita, A.; Yaruva, J.; Hamada, T.; Otera, J. *Chem. Lett.* **2004**, *33*, 528.

(4) (a) Matsuo, D.; Yang, X.; Hamada, A.; Morimoto, K.; Kato, T.; Yahiro, M.; Adachi, C.; Orita, A.; Otera, J. *Chem. Lett.* **2010**, *39*, 1300. (b) Oyamada, T.; Shao, G.; Uchiuzou, H.; Nakanotani, H.; Orita, A.; Otera, J.; Yahiro, M.; Adachi, C. *Jpn. J. Appl. Phys.* **2006**, *45*, L1331.

(5) (a) Mao, G.; Orita, A.; Fenenko, L.; Yahiro, M.; Adachi, C.; Otera, J. *Mater. Chem. Phys.* **2009**, *115*, 378. (b) Fenenko, L.; Shao, G.; Orita, A.; Yahiro, M.; Otera, J.; Svechnikov, S.; Adachi, C. *Chem. Commun.* **2007**, 2278.

(6) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777. (c) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. For a most recent review, see: (d) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(7) In phosphination step, polar by-products were observed at the bottom on TLC, and so we are trying to avoid the by-product formation: van Assema, S. G. A.; Tazelaar, C. G. J.; Bas de Jong, G.; van Maarseveen, J. H.; Schakel, M.; Lutz, M.; Spek, A. L.; Slootweg, J. C.; Lammertsma, K. *Organometallics* **2008**, *27*, 3210.
(8) (a) Fang, J.-K.; An, D.-L.; Wakamatsu, K.; Ishikawa, T.; Iwanaga, T.; Toyota, S.; Akita, S.-I.; Matsuo, D.; Orita, A.; Otera, J. *Tetrahedron* **2010**, *66*, 5479. (b) Fang, J.-K.; An, D.-L.; Wakamatsu, K.; Ishikawa, T.; Iwanaga, T.; Toyota, S.; Matsuo, D.; Orita, A.; Otera, J. *Tetrahedron Lett.* **2010**, *51*, 917.
(9) Yang, X.; Fang, J.-K.; Suzuma, Y.; Xu, F.; Orita, A.; Otera, J.; Kajiyama, S.; Koumura, N.; Hara, K. *Chem. Lett.* **2011**, *40*, 620.
(10) An, D.-L.; Nakano, T.; Orita, A.; Otera, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 171.
(11) (a) Tsumatori, H.; Nakashima, T.; Kawai, T. *Org. Lett.* **2010**, *12*, 2362. (b) Kawai, T.; Kawamura, K.; Tsumatori, H.; Ishikawa, M.; Naito, M.; Fujiki, M.; Nakashima, T. *ChemPhysChem.* **2007**, *8*, 1465.
(12) **Synthesis of 15**:
(i) **Synthesis of 19**: To a flask were added **18** (1.51 g, 5.0 mmol), Ph_2PCl (0.92 mL, 5.0 mmol), CuI (95.2 mg, 0.5 mmol), toluene (20 mL) and Et_3N (1.4 mL), and the mixture was stirred under nitrogen at 80 °C for 19 h. After EtOAc had been added, the mixture was filtered, and the filtrate was washed with 10% NH_3 (aq) and brine, and dried over Na_2SO_4. After filtration, the solvents were evaporated, and the crude product was subjected to the next reaction. To a flask were added the crude products, 30% aq H_2O_2 (5.0 mL) and THF (25 mL) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h and then at r.t. for 3 h. After workup with CH_2Cl_2–H_2O, the organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solvents were evaporated and the crude product was subjected to column chromatography on silica gel (Daisogel IR-60-63/210, EtOAc) to give **19** (1.35 g, 54% yield) and **20** (0.83 g, 24% yield). **Compound 19**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.81 (s, 1 H), 7.02–7.22 (m, 6 H), 7.31–7.39 (m, 6 H), 7.42–7.46 (m, 2 H), 7.52–7.57 (m, 2 H), 7.70 (d, *J* = 8.6 Hz, 1 H), 7.79 (d, *J* = 8.6 Hz, 1 H), 7.95 (q, *J* = 8.3 Hz, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.55, 82.11, 85.48 (d, *J* = 169.7 Hz), 104.20 (d, *J* = 30.5 Hz), 118.30 (d, *J* = 4.8 Hz), 120.64, 126.21, 126.34, 126.96, 127.23, 127.69, 127.98, 128.13, 128.24 (d, *J* = 13.6, 13.6 Hz), 128.48, 128.78, 130.21, 130.51 (d, *J* = 11.5, 11.5 Hz), 131.50, 131.70 (d, *J* = 2.8, 2.8 Hz), 132.02, 132.22, 132.72, 133.05 (d, *J* = 121.0, 121.0 Hz), 133.00, 133.82, 139.54, 141.88. HRMS: *m*/*z* [M + H$^+$] calcd for $C_{36}H_{24}OP$: 503.1565; found: 503.1555. **Compound 20**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93–7.01 (m, 4 H), 7.07–7.13 (m, 4 H), 7.19–7.41 (m, 16 H), 7.61 (t, *J* = 8.2 Hz, 2 H), 7.74 (d, *J* = 8.6 Hz, 2 H), 7.96 (t, *J* = 8.9 Hz, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 86.37 (d, *J* = 166.8 Hz), 103.25 (d, *J* = 29.3 Hz), 118.35 (d, *J* = 4.0 Hz), 126.23, 127.69, 127.99, 128.12, 128.30 (d, *J* = 13.0, 13.6 Hz), 128.80, 130.03, 130.21 (d, *J* = 11.7, 11.5 Hz), 131.59, 131.83, 131.87, 132.16, 132.38 (d, *J* = 120.9, 120.9 Hz), 133.68, 141.04 (d, *J* = 2.2 Hz). HRMS: *m*/*z* [M + H$^+$] calcd for $C_{48}H_{33}O_2P_2$: 703.1956; found: 703.1962.
(ii) **Synthesis of 21**: To a flask were added **19** (1.01 g, 2.0 mmol), 1,3-dibromobenzene (300 mg, 0.91 mmol), $Pd(PPh_3)_4$ (104 mg, 0.09 mmol), CuI (17.1 mg, 0.09 mmol), diisopropylamine (5 mL) and toluene (25 mL), and the mixture was stirred under nitrogen at 80 °C for 20 h. After workup with EtOAc–H_2O, the organic layer was washed with aq NH_4Cl and brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (EtOAc) to give **21** (0.96 g, 98% yield) in a pure form. **Compound 21**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.48 (s, 1 H), 6.53 (d, *J* = 7.9 Hz, 2 H), 6.84 (t, *J* = 7.9 Hz, 1 H), 7.03–7.09 (m, 4 H), 7.11–7.15 (m, 4 H), 7.17–7.26 (m, 8 H), 7.31–7.39 (m, 12 H), 7.45–7.56 (m, 4 H), 7.70 (d, *J* = 8.3 Hz, 2 H), 7.80 (d, *J* = 8.6 Hz, 2 H), 7.90 (d, *J* = 8.3 Hz, 2 H), 7.94–7.97 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 84.23, 86.49, 91.00 (d, *J* = 306.0 Hz), 104.29 (d, *J* = 29.6 Hz), 118.25 (d, *J* = 4.0 Hz), 121.43, 122.59, 126.15, 126.40, 126.81, 127.17, 127.64, 127.83, 128.11, 128.17 (d, *J* = 13.3, 13.6 Hz), 128.39, 128.47, 130.17, 130.32 (d, *J* = 11.8, 11.4 Hz), 130.84, 131.48, 131.65 (d, *J* = 2.5, 2.5 Hz), 131.77, 132.24, 132.77, 132.82, 132.91 (d, *J* = 125.9, 125.9 Hz), 133.38, 138.90, 142.08. HRMS: *m*/*z* [M + H$^+$] calcd for $C_{78}H_{49}O_2P_2$: 1079.3208; found: 1079.3196.
(iii) **Synthesis of 22**: To a flask were added **21** (534 mg, 0.50 mmol), *t*-BuOK (167 mg, 1.5 mmol) and THF (10 mL), and the mixture was stirred under nitrogen at r.t. for 15 h. After workup with CH_2Cl_2–H_2O, the organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solvents were evaporated, and the crude product was subjected to column chromatography on silica gel (hexane–CH_2Cl_2, 1:1) to give **22** (246 mg, 73% yield) in a pure form. **Compound 22**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.79 (s, 2 H), 6.44 (s, 1 H), 6.50 (dd, *J* = 1.6, 7.8 Hz, 2 H), 6.84 (t, *J* = 7.5 Hz, 1 H), 7.18–7.33 (m, 8 H), 7.44–7.53 (m, 4 H), 7.74 (d, *J* = 9.3 Hz, 4 H), 7.94 (q, *J* = 7.9 Hz, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 80.79, 82.80, 89.51, 92.67, 120.44, 121.26, 122.99, 126.26, 126.39, 126.55, 126.70, 126.81, 127.70, 128.01, 128.03, 128.05, 128.12, 128.86, 130.73, 132.34, 132.39, 132.90, 133.03, 133.62, 139.90, 140.60.
(iv) **Synthesis of 15**: To a flask were added **22** (68 mg, 0.1 mmol), 1,3-diiodobenzene (33 mg, 0.1 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), CuI (2 mg, 0.01 mmol), diisopropylamine (5 mL) and toluene (45 mL), and the mixture was stirred under nitrogen at 70 °C for 60 h. After workup with CH_2Cl_2–H_2O, the organic layer was washed with aq NH_4Cl and brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane–CH_2Cl_2, 4:1) to give **15** (16 mg, 22% yield) in a pure form as a white powder. **Compound 15**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.89–6.95 (m, 6 H), 7.05 (d, *J* = 8.5 Hz, 4 H), 7.22 (t, *J* = 7.0 Hz, 4 H), 7.42 (t, *J* = 7.0 Hz, 4 H), 7.76 (d, *J* = 8.5 Hz, 4 H), 7.86 (d, *J* = 8.5 Hz, 4 H), 7.87 (d, *J* = 8.5 Hz, 4 H), 7.92 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 90.4, 92.1, 121.8, 123.6, 126.4, 126.7, 126.8, 128.1, 128.2, 129.2, 129.6, 132.7, 133.0, 136.9, 138.6.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.