VOLUME 70, NUMBER 10 JOC Articles MAY 13, 2005

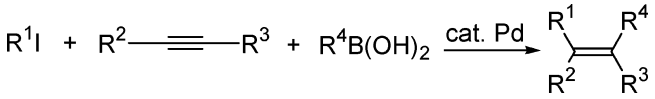
Regio- and Stereoselective Route to Tetrasubstituted Olefins by the Palladium-Catalyzed Three-Component Coupling of Aryl Iodides, Internal Alkynes, and Arylboronic Acids

Chengxiang Zhou and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

larock@iastate.edu

Received October 3, 2004



The Pd-catalyzed three-component coupling of readily available aryl iodides, internal alkynes, and arylboronic acids provides a convenient, one-step, regio- and stereoselective route to tetrasubstituted olefins in good to excellent yields, although electron-poor aryl iodides and dialkylalkynes normally afford only low yields under our standard reaction conditions. The proper combination of substrates and reaction conditions is important for high yields. The presence of water generally substantially increases the yields of the desired tetrasubstituted olefins. The reaction involves *cis*-addition of the aryl group from the aryl iodide to the less hindered or more electron-rich end of the alkyne, while the aryl group from the arylboronic acid adds to the other end. A modified, room-temperature procedure has also been successfully developed, which works very well for some substrates. Tamoxifen and its derivatives are synthesized in a concise, regio- and stereoselective manner by applying our synthetic protocol.

Introduction

The expeditious, regio- and stereoselective synthesis of tetrasubstituted olefins has provided a challenge for synthetic organic chemists for years.[1] Tetrasubstituted olefins can be obtained by carbonyl olefination reactions[2−5] (including McMurry,[3] Wittig,[4] and Horner−Wadsworth−Emmons[5] reactions), olefin metathesis,[6] and various other methods (including cycloaddition,[7] dehydration,[8] ynolate anions,[9] vinylic radical chemistry,[10] etc.). Reac-

(1) (a) Denmark, S. E.; Amburgey, J. *J. Am. Chem. Soc.* **1993**, *115*, 10386. (b) Creton, I.; Marek, I.; Normant, J. F. *Synthesis* **1996**, 1499. (c) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331. (d) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959.

(2) (a) Maciagiewicz, I.; Dybowski, P.; Skowronska, A. *Tetrahedron* **2003**, *59*, 6057. (b) Perez, E. P.; Ortiz, F. L. *Chem. Commun.* **2000**, 2029. (c) Aguero, A.; Kress, J.; Osborn, J. A. *J. Chem. Soc., Chem. Commun*. **1986**, 531. (d) Hernandez, D.; Larson, G. L. *J. Org. Chem.* **1984**, *49*, 4285.

(3) For the McMurry reaction, see: (a) Villiers, C.; Ephritikhine, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2380. (b) Ephritikhine, M. *Chem. Commun.* **1998**, 2549. (c) Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608. (d) Sabelle, S.; Hydrio, J.; Leclerc, E.; Mioslowshi, C.; Renard, P. Y. *Tetrahedron Lett.* **2002**, *43*, 3645 and references therein.

(4) For Wittig olefination, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Mulzer, J.; List, B. *Tetrahedron Lett.* **1994**, *35*, 9021. (c) Tong, X.; Kallmerten, J. *Synlett* **1992**, 845.

(5) For the Horner−Wadsworth−Emmons reaction, see: (a) Sano, S.; Takehisa, T.; Ogawa, S.; Yokoyama, K.; Nagao, Y. *Chem. Pharm. Bull.* **2002**, *50*, 1300. (b) Gallagher, G., Jr.; Webb, R. L. *Synthesis* **1974**, 122.

(6) (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210. (b) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74. (c) Anastasia, L.; Dumond, Y. R.; Negishi, E. *Eur. J. Org. Chem.* **2001**, *16*, 3039. (d) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (e) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. (f) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

(7) Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283.

(8) (a) Nakatani, K.; Izawa, T.; Isoe, S. *J. Org. Chem.* **1994**, *59*, 5961. (b) Nakatani, K.; Izawa, T.; Odagaki, Y.; Isoe, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1365.

(9) (a) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912. (b) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840. (c) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2000**, *65*, 5443. (d) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857.

10.1021/jo048265+ CCC: $30.25
Published on Web 01/13/2005

tions involving trisubstituted vinylic metal substrates (metal = B,[11] Si,[12] S,[13] Zr,[14] Sn,[15] Te,[16] etc.) or intermediates (metal = Li,[17] Mg,[18] Ni,[19] Cu,[20] Zn,[21] Pd,[22] etc.) have also been widely used in the synthesis of tetrasubstituted olefins. However, these approaches are still fairly limited in scope due to one or more of the following problems: limited generality; poor regio- and/or stereoselectivity; limited availability of starting materials; tedious multistep syntheses. Thus, developing an efficient, regio- and stereoselective route to tetrasubstituted olefins is highly desirable and a considerable challenge for the organic chemist.

Palladium-catalyzed reactions are versatile methods for carbon−carbon bond formation due to their generality and ability to tolerate a wide range of important organic functional groups.[23] The carbopalladation of alkynes has provided a versatile approach to various olefins and heterocycles.[24] The intermolecular Rh-,[25] Ni-,[26] and Pd-catalyzed[27] addition of arylboronic acids to alkynes has been reported to produce di- and trisubstituted alkenes. Some specific tetrasubstituted olefins have also been prepared in a highly efficient manner by the *intramolecular* addition of arylpalladium intermediates to internal alkynes followed by cross-coupling with boron, tin, and zinc organometallics.[28] Multicomponent reactions have attracted much attention from chemists, because they are highly atom-economical.[29] For example, palladium-catalyzed tandem reactions involving organic halides, unsaturated compounds (allene and norbornene), and organometallics (organoboron and -tin reagents) have been reported to furnish relatively complex products in a one-pot reaction.[30] The palladium-catalyzed sequential haloallylation/Suzuki cross-coupling of alkynes has been reported as a convenient synthetic route to highly functionalized 1,4-dienes.[31]

Recently, we communicated a highly efficient palladium-catalyzed synthesis of tetrasubstituted olefins involving the intermolecular coupling of an aryl iodide, an internal alkyne, and an arylboronic acid (eq 1).[32,33] Herein, we provide a full account of the scope and limitations of this chemistry. Modified, mild, room-

(10) Gansauer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3206.

(11) (a) Liu, X.; Shimizu, M.; Hiyama, T. *Angew. Chem.*, *Int. Ed.* **2004**, *43*, 879. (b) Gerard, J.; Hevesi, L. *Tetrahedron* **2004**, *60*, 367. (c) Shimizu, M.; Fujimoto, T.; Liu, X.; Minezaki, H.; Hata, T.; Hiyama, T. *Tetrahedron* **2003**, *59*, 9811. (d) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358. (e) Shimizu, M.; Fujimoto, T.; Minezaki, H.; Hata, T.; Hiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 6947. (f) Yang, F.; Cheng, C. *J. Am. Chem. Soc.* **2001**, *123*, 761. (g) Suginome, M.; Matsuda, T.; Nakamura, H.; Ito, Y. *Tetrahedron* **1999**, *55*, 8787. (h) Gerard, J.; Bietlot, E.; Hevesi, L. *Tetrahedron Lett.* **1998**, *39*, 8735.

(12) (a) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (b) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577. (c) Al-Hassan, M. I.; Miller, R. B. *J. Saudi Chem. Soc.* **2001**, *5*, 67.

(13) (a) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778. (b) Gerard, J.; Hevesi, L. *Tetrahedron* **2004**, *60*, 367. (c) Nickon, A.; Rodriguez, A. D.; Shirhatti, V.; Ganguly, R. *J. Org. Chem.* **1985**, *50*, 4218.

(14) Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228.

(15) (a) Konno, T.; Takehana, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2004**, *69*, 2188. (b) Beletskaya, I. P.; Kazankova, M. A. *Polyhedron* **2000**, *19*, 597. (c) Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221. (d) Piers, E. *Pure Appl. Chem.* **1988**, *60*, 107. (e) Piers, E.; Skerlj, R. T. *J. Chem. Soc., Chem. Commun.* **1987**, 1025. (f) Piers, E.; Skerlj, R. T. *J. Org. Chem.* **1987**, *52*, 4421. (g) Chu, K. H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 767.

(16) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6291.

(17) (a) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621 and references therein. (b) Begue, J.; Bonnet-Delpon, D.; Bouvet, D.; Rock, M. H. *J. Org. Chem.* **1996**, *61*, 9111. (c) Maercker, A.; Girreser, U. *Tetrahedron* **1994**, *50*, 8019. (d) Gurudutt, K. N.; Ravindranath, B. *Tetrahedron Lett.* **1980**, *21*, 1173.

(18) (a) Snider, B. B.; Karras, M.; Conn, R. S. E. *J. Am. Chem. Soc.* **1978**, *100*, 4624. (b) Conn, R. S. E.; Karras, M.; Snider, B. B. *Isr. J. Chem.* **1984**, *24*, 108. (c) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989.

(19) (a) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364. (b) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (c) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099.

(20) (a) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003**, *68*, 6066. (b) Wipf, P.; Smitrovich, J. H.; Moon, C. W. *J. Org. Chem.* **1992**, *57*, 3178. (c) Rao, S. A.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 5735. (d) Germanas, J.; Vollhardt, K. P. C. *Synlett* **1990**, 505. (e) Corey, E. J.; Chen, R. H. K. *Tetrahedron Lett.* **1973**, *14*, 1611. (f) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.

(21) (a) Stuedemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93. (b) Studemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299.

(22) (a) Ma, S.; Jiao, N.; Ye, L. *Chem.—Eur. J.* **2003**, *9*, 6049. (b) Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832. (c) Anastasia, L.; Dumond, Y.; Negishi, E. *Eur. J. Org. Chem.* **2001**, *16*, 3039. (d) Bauer, A.; Miller, M. W.; Vice, S. F.; McCombie, S. W. *Synlett* **2001**, 254. (e) Wang, Z.; Lu, X. *Chem. Commun.* **1996**, 535. (f) Ma, S.; Lu, X. *J. Chem. Soc*., *Chem. Commun.* **1990**, 733. (g) Takahashi, A.; Kirio, Y.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 643. (h) Al-Hassan, M. I. *Synth. Commun.* **1989**, *19*, 1619. (i) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 607. (j) Al-Hassan, M. I. *Synthesis* **1987**, *9*, 816. (k) Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121. (l) Tsuji, J.; Nogi, T. *J. Am. Chem. Soc.* **1966**, *88*, 1289.

(23) (a) Trost, B. *Science* **1991**, *234*, 1471. (b) Tsuji, J. *Palladium Reagents and Catalysis: New Perspectives for the 21st Century*; John Wiley & Sons: New York, 2004. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.

(24) For reviews, see ref 23c. For other representative examples, see: (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Sugihara, T.; Coperet, C.; Owczarczyk, Z.; Harring, L.; Negishi, E. *J. Am. Chem. Soc*. **1994**, *116*, 7923. (c) Gevorgyan, V.; Quan, L.; Yamamoto, Y. *Tetrahedron Lett*. **1999**, *40*, 4089. (d) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173. (e) Larock, R. C.; Reddy, C. K. *J. Org. Chem.* **2002**, *67*, 2027.

(25) (a) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464. (b) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358. (c) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918. (d) Lautens, M.; Yoshida, M. *Org. Lett*. **2002**, *4*, 123.

(26) Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun*. **2001**, 2688.

(27) (a) Oh, C.; Jung, H.; Kim, K.; Kim, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 805. (b) Oh, C.; Ryu, J. *Bull. Korean Chem. Soc.* **2003**, *24*, 1563. (c) For highly substituted 1,3-dienes, see: Satoh, T.; Ogino, S.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5063.

(28) (a) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett*. **1989**, *30*, 1135. (b) Grigg, R.; Sandano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton, P. M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803. (c) Grigg, R.; Sridharan, V. *Pure Appl. Chem.* **1998**, *70*, 1047. (d) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65. (e) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (f) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525.

(29) (a) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, *21*, 4101. (b) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085.

(30) (a) Yang, F. Y.; Wu, M. Y.; Cheng, C. H. *J. Am. Chem. Soc.* **2000**, *122*, 7122. (b) Huang, T. H.; Chang, H. M.; Wu, M. Y.; Cheng, C. H. *J. Org. Chem.* **2002**, *67*, 99. (c) Shaulis, K. M.; Hoskin, B. L.; Townsend, J. R.; Goodson, F. E.; Incarvito, C. D.; Rheingold, A. L. *J. Org. Chem.* **2002**, *67*, 5860. (d) Jeganmohan, M.; Shanmugasundaram, M.; Cheng, C. H. *Org. Lett.* **2003**, *5*, 881. (e) Jeganmohan, M.; Shanmugasundaram, M.; Cheng, C. H. *Chem. Commun.* **2003**, 1746. (f) Yang, F. Y.; Shanmugasundaram, M.; Chuang, S. Y.; Ku, P. J.; Wu, M. Y.; Cheng, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 12576.

(31) Thadani, A. N.; Rawal, V. H. *Org. Lett*. **2002**, *4*, 4317.

(32) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579.

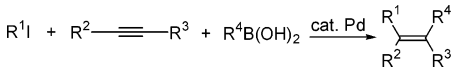
(33) For another report involving the reaction of vinylic halides, internal alkynes, and boronic acids, see: Zhang, X.; Larock, R. C. *Org. Lett.* **2003**, *5*, 2993.

TABLE 1. Optimization Studies (Eq 2)[a]

entry	ratio[b]	Pd catalyst	base	DMF/H_2O	% yield[c,d]	Ar−Ph (mmol)
1	1:2:2	5% $PdCl_2(PhCN)_2$	1 K_2CO_3	100:0	39 (35)	0.03
2	1:2:2	5% $PdCl_2$	1 K_2CO_3	100:0	36	0.03
3	1:2:2	5% $Pd(OAc)_2$	1 K_2CO_3	100:0	35	0.03
4	1:2:2	5% $Pd(dba)_2$	1 K_2CO_3	100:0	38	0.02
5[e]	1:2:2	5% $Pd(PPh_3)_4$	1 K_2CO_3	100:0	15	0.03
6[e]	1:2:2	5% $PdCl_2(PPh_3)_2$	1 K_2CO_3	100:0	31	0.04
7[e]	1:2:2	5% $Pd(OAc)_2$/10% PPh_3	1 K_2CO_3	100:0	29	0.04
8[e,f]	1:2:2	5% $Pd(OAc)_2$/10% PPh_3	1 K_2CO_3	100:0	20	0.03
9[e]	1:2:2	5% $Pd(OAc)_2$/10% $[2,4,6\text{-}(MeO)_3C_6H_4]_3P$	1 K_2CO_3	100:0	20	0.02
10[e]	1:2:2	5% $Pd(OAc)_2$/10% TMEDA	1 K_2CO_3	100:0	15	0.02
11	1:2:2	5% $PdCl_2(PhCN)_2$	1 K_2CO_3	90:10	50	0.06
12	1:2:2	5% $PdCl_2(PhCN)_2$	1 K_2CO_3	80:20	63	0.05
13	1:2:2	5% $PdCl_2(PhCN)_2$	1 $KHCO_3$	80:20	57	0.04
14	1:2:2	5% $PdCl_2(PhCN)_2$	2 $KHCO_3$	80:20	66	0.05
15	2:1:2	5% $PdCl_2(PhCN)_2$	2 $KHCO_3$	80:20	72	0.26
16	2:1:2	2% $PdCl_2(PhCN)_2$	2 $KHCO_3$	80:20	78 (75)	0.26
17	2:1:2	1% $PdCl_2(PhCN)_2$	2 $KHCO_3$	80:20	85	0.25
18	2:1:3	1% $PdCl_2(PhCN)_2$	3 $KHCO_3$	80:20	88 (86)	0.25
19	3:1:3	1% $PdCl_2(PhCN)_2$	3 $KHCO_3$	80:20	88	0.49
20	1:1:1	1% $PdCl_2(PhCN)_2$	1 $KHCO_3$	80:20	55	0.08

[a] All reactions were run on a 0.25 mmol scale (limiting reagent) employing the Pd catalyst in 10 mL of DMF/H_2O at 100 °C for 3 h unless otherwise indicated. [b] Ratio of aryl iodide/alkyne/arylboronic acid. [c] GC yields of **1a** plus **1b** based on the limiting reagent; yields of products obtained by column chromatography are reported in parentheses. [d] Regioisomers **1a** and **1b** are inseparable by GC; they are actually obtained in approximately a 1:6.5 ratio, based on ^{1}H NMR spectroscopic analysis of the products after column chromatography. [e] The reaction was run for 24 h. [f] LiCl (1 equiv) was added.

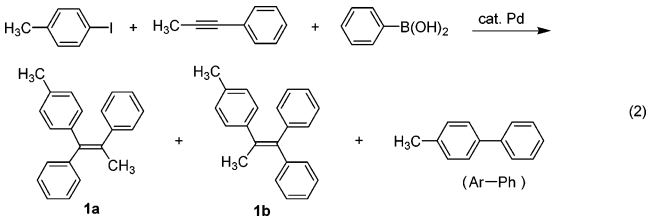
temperature reaction conditions have also been successfully developed.



(1)

Results and Discussion

(a) Optimization of the Reaction Conditions. For optimization of the reaction conditions used in our tetrasubstituted olefin synthesis, we investigated a simple, representative model system consisting of 4-iodotoluene, 1-phenyl-1-propyne, and phenylboronic acid (eq 2). In



(2)

early experiments, we found that a 35% isolated yield of a 1:6.5 mixture of regioisomeric **1a** and **1b** (as determined by ^{1}H NMR spectroscopy after column chromatography) could be obtained by the reaction of 1 equiv of 4-iodotoluene, 2 equiv of 1-phenyl-1-propyne, and 2 equiv of phenylboronic acid in the presence of 5 mol % $PdCl_2(PhCN)_2$ and 1 equiv of K_2CO_3 in DMF (Table 1, entry 1). Changing the Pd catalyst to either $PdCl_2$, $Pd(OAc)_2$, or $Pd(dba)_2$ had little effect on the yield (entries 2−4). Employing phosphine or amine ligands slows the reaction and has a detrimental effect on the yields (entries 5−10). Employing LiCl as an additive also lowers the yield of the reaction (entry 8).[34] A small amount of 4-methylbiphenyl side-product was also formed along with the desired product. We were pleased to find that the yield could be significantly improved to 50% by simply running the reaction in 90:10 DMF/H_2O (entry 11). The yield could be further increased to 63% in 80:20 DMF/H_2O (entry 12). The presence of water obviously greatly accelerates the desired reaction, perhaps because water is needed to dissolve the inorganic base that combines with the arylboronic acid to form the "ate complex", which is crucial in Suzuki-type coupling reactions.[35] The yield was slightly increased when 2 equiv of $KHCO_3$ was used as the base, instead of 1 equiv of K_2CO_3 (compare entries 12 and 14).[36] Since biaryl side-product was evident in all reactions, the alkyne was chosen as the limiting reagent in order to increase the yield. When 2 equiv of aryl iodide, 1 equiv of alkyne, and 2 equiv of arylboronic acid were employed, the yield increased to 72% (entry 15). Simply reducing the loading of the palladium catalyst further increased the yield (entries 15−17). An 85% yield of the desired tetrasubstituted olefin was obtained by employing only 1% of the palladium catalyst (entry 17). The yield could be further increased to 88% by using 3 equiv of arylboronic acid and $KHCO_3$ as the base (entry 18). The same yield was obtained when 3 equiv of aryl iodide was employed (entry 19). A moderate 55% yield of the desired product could be obtained employing a 1:1:1 ratio of the aryl iodide, alkyne, and arylboronic acid (entry 20). The "optimal" procedures from entries 18 and 19 have thus been employed for the synthesis of a wide variety of tetrasubstituted olefins.[37]

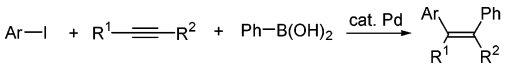
(34) For a review discussing the halide effect in Pd catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

(35) For reviews of the Suzuki reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(36) The yield is lower if 2 equiv of KF is used as the base; none of the desired product is observed if 2 equiv of KOAc is used as the base.

(37) Entries 18 and 19 were chosen as optimal conditions to extend this chemistry, for the convenience of product purification. However, the 2:1:3 (in entry 18) and the 3:1:3 (in entry 19) stoichiometries are not necessarily the best stoichiometries for an atom-economical reaction. One can certainly run the reaction using other stoichiometries for better use of all reagents.

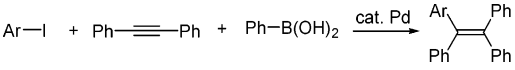
(b) Scope and Limitations. (1) Scope of the Reaction Using Various Internal Alkynes. Under our optimal conditions, a wide variety of internal alkynes have been successfully employed in this tetrasubstituted olefin synthesis (eq 3, Table 2). When iodobenzene and



(3)

phenylboronic acid are employed, the reaction works very well with 1-phenyl-1-propyne and 1-phenyl-1-hexyne and provides the desired tetrasubstituted olefins in excellent yields (entries 1 and 2). Relatively electron-poor and more sterically hindered diphenylacetylene also provides the desired tetraphenylethene in an excellent yield, although the reaction is slower and a longer reaction time (24 h) is needed (entry 3). The reaction tolerates ketone, ester, and alcohol functional groups and provides the desired tetrasubstituted olefins in good to excellent yields (entries 4−7). Although an acetal has been successfully employed in this chemistry, the product hydrolyzed on silica gel during column chromatography, providing the corresponding aldehyde in a good yield (entry 8). Electron-poor diethyl acetylenedicarboxylate and (4-nitrophenyl)-phenylacetylene have also been efficiently coupled with iodobenzene and phenylboronic acid (entries 9 and 13). Relatively electron-rich 4-octyne, however, provides the desired tetrasubstituted olefin in only a 32% yield, and the product from di-insertion of the alkyne is also isolated in a 48% yield (entry 10). None of the desired product is obtained when relatively electron-rich and sterically hindered 4,4-dimethyl-2-butyne is employed (entry 11). This may in part be due to the fact that the 4,4-dimethyl-2-butyne is relatively volatile (bp 80 °C) under our standard reaction conditions (100 °C). The terminal alkyne phenylacetylene is not a good substrate for this chemistry, since a substantial amount of tetraphenylethene is also obtained along with the desired triphenylethene product (entry 12). Presumably diphenylacetylene is first being formed by a Sonogashira-type[38] reaction of iodobenzene and phenylacetylene and then reacts with iodobenzene and phenylboronic acid in the usual fashion to generate the tetraphenylethene side-product.

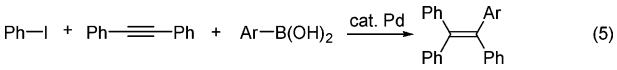
(2) Scope of the Reaction Using Various Aryl Iodides. Employing diphenylacetylene and phenylboronic acid as substrates, we then investigated the scope of the reaction using various aryl iodides (eq 4, Table 3).



(4)

Iodobenzene affords the desired tetraphenylethene in an excellent 92% yield. Electron-rich aryl iodides, such as 4-iodoanisole, 4-iodotoluene, and 3-iodotoluene, efficiently cross-couple with diphenylacetylene and phenylboronic acid to provide the corresponding tetrasubstituted olefins in good yields (entries 2−4). However, only a 48% yield of the desired product is obtained when 2-iodotoluene is used, presumably due to the steric hindrance of the *ortho* methyl group, which inhibits the addition of the *o*-tolyl group to the alkyne (entry 5). It is noteworthy that the unprotected 4-iodophenol also works well in this chemistry and provides the corresponding phenol in a good yield (entry 6). Electron-poor aryl iodides work poorly in this chemistry. For example, the relatively electron-poor 4-chloroiodobenzene provides only a 65% yield of the desired tetrasubstituted olefin (entry 7). The more electron-poor 4-iodoacetophenone provides a very poor 10% yield of the corresponding olefinic ketone (entry 8). 4-Iodonitrobenzene provides none of the desired product (entry 9). Almost quantitative conversion of this aryl iodide and phenylboronic acid to 4-nitrobiphenyl is observed instead. Presumably in this case the Suzuki-type reaction is much faster than carbopalladation of the alkyne; thus, the formation of the biaryl side-product is more favorable.

(3) Scope of the Reaction Using Various Arylboronic Acids. We next investigated the scope of the reaction using various arylboronic acids plus iodobenzene and diphenylacetylene (eq 5, Table 4). Both electron-



(5)

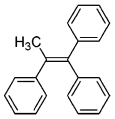
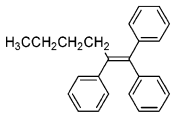
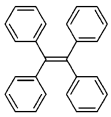
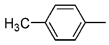
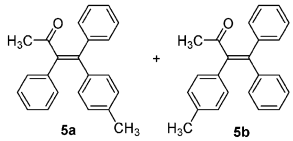
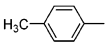
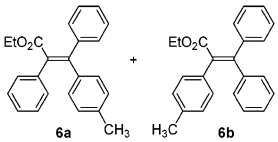
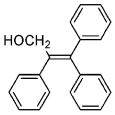
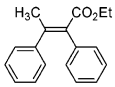
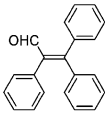
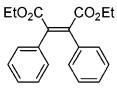
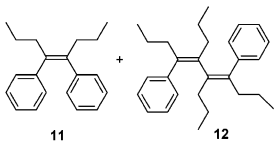
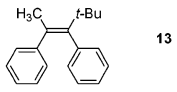
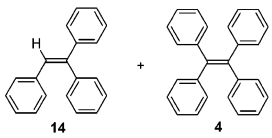
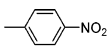
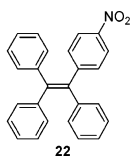
neutral and electron-rich arylboronic acids work very well in this chemistry (entries 1−4, Table 4). We were pleased to find that the scope of the reaction using various arylboronic acids is pretty general compared to that of the aryl iodides. *o*-Tolylboronic acid affords a good yield of the desired olefin (entry 5, Table 4), as opposed to the relatively poor yield obtained when using *o*-iodotoluene (entry 5, Table 3). Furthermore, electron-poor arylboronic acids, such as 4-chlorophenylboronic acid and 4-acetylphenylboronic acid, also afford the desired tetrasubstituted olefins in good yields (entries 6 and 7, Table 4). The same products could be obtained only in low yields when employing the corresponding aryl iodides and phenylboronic acid (entries 7 and 8, Table 3). On the other hand, the more electron-poor 4-nitrophenylboronic acid provides only a trace amount of the desired product (compare entry 8 in Table 4 with entry 9 in Table 3). It is noteworthy that product **22** could be obtained by employing iodobenzene, (4-nitrophenyl)phenylacetylene, and phenylboronic acid as substrates (entry 13, Table 2). Other organoboron reagents, such as sodium tetraphenylborate and potassium phenyltrifluoroborate, also work well and provide the desired tetrasubstituted olefins in good yields (entries 9 and 10). It is noteworthy that the base is still necessary in the potassium phenyltrifluoroborate reaction, since only a trace amount of the product is obtained without the $KHCO_3$ base (entry 11).[39]

(c) Regioselectivity and Stereoselectivity. This approach to tetrasubstituted olefins is often both regio- and stereoselective. The three-component reaction involves clean *cis*-addition to the alkyne in all cases studied so far. Two regioisomers have usually been obtained when unsymmetrical alkynes are employed as starting materials. The structures of the major isomers have been

(38) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Takahashi, K.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. (c) For a general review, see: Sonogashira, K. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

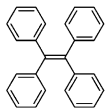
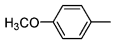
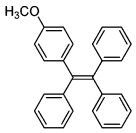
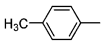
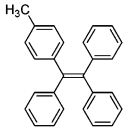
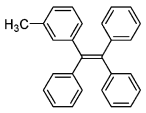
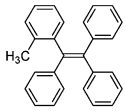
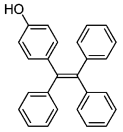
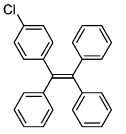
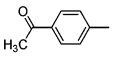
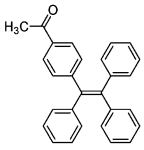
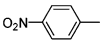
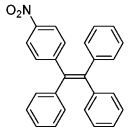
(39) For similar observations about the importance of the base when using $ArBF_3K$ in the Suzuki reaction, see: Littke A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

TABLE 2. Scope of the Internal Alkynes (Eq 3)[a]

entry	Ar	R^1	R^2	product(s)	% yield[b]
1		CH_3		 **2**	90
2		*n*-Bu		 **3**	86
3[c]				 **4**	92
4		$COCH_3$		 **5a** **5b**	80 (1:2)
5		CO_2Et		 **6a** **6b**	78 (1:2)
6		CH_2OH		 **7**	77
7		CH_3	CO_2Et	 **8**	82
8		$CH(OEt)_2$		 **9**	85
9		CO_2Et	CO_2Et	 **10**	78
10		*n*-Pr	*n*-Pr	 **11** **12**	32 + 48
11		CH_3	*t*-Bu	 **13**	0
12[c]		H		 **14** **4**	33 + 45
13				 **22**	88

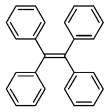
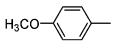
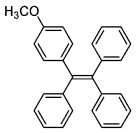
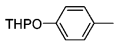
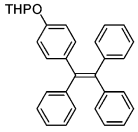
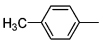
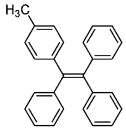
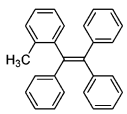
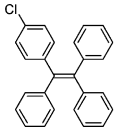
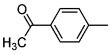
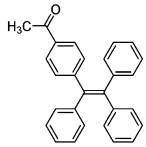
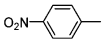
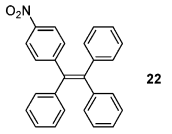
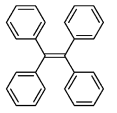
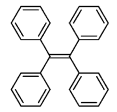
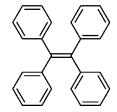
[a] All reactions were run using 0.50 mmol of aryl iodide, 0.25 mmol of alkyne, 0.75 mmol of arylboronic acid, 0.75 mmol of $KHCO_3$, and 0.0025 mmol of $PdCl_2(PhCN)_2$ in 10 mL of 4:1 DMF/H_2O at 100 °C for 12 h unless otherwise indicated. [b] The yields are based on products isolated by column chromatography; the ratio of regioisomers is given in parentheses as determined by ^1H NMR spectroscopic analysis. [c] Aryl iodide (3 equiv) was used in this entry and the reactions were run for 24 h.

TABLE 3. Scope of the Aryl Halides (Eq 4)[a]

entry	Ar	product	% yield[b]
1		 **4**	92
2		 **15**	90
3		 **16**	92
4		 **17**	89
5		 **18**	48
6		 **19**	73[c]
7		 **20**	65
8		 **21**	10
9		 **22**	0

[a] All reactions were run using 0.75 mmol of aryl iodide, 0.25 mmol of alkyne, 0.75 mmol of arylboronic acid, 0.75 mmol of $KHCO_3$, and 0.0025 mmol of $PdCl_2(PhCN)_2$ in 10 mL of 4:1 DMF/H_2O at 100 °C for 24 h. [b] The yields are based on products isolated by column chromatography. [c] The yield is based on ^1H NMR spectroscopic analysis of the crude product, which contains the desired olefin product and the 4-phenylphenol side-product.

TABLE 4. Scope of the Reaction Using Various Arylboronic Acids (Eq 5)[a]

entry	Ar	product	% yield[b]
1		 **4**	92
2		 **15**	89
3		 **23**	86
4		 **16**	92
5		 **18**	79
6		 **20**	85
7		 **21**	76
8		 **22**	trace
9	$NaBPh_4$	 **4**	90
10	$PhBF_3K$	 **4**	83
11[c]	$PhBF_3K$	 **4**	trace

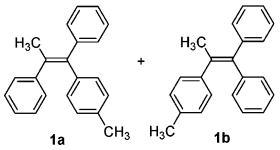
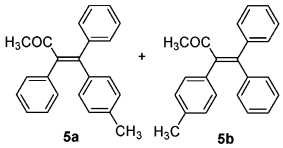
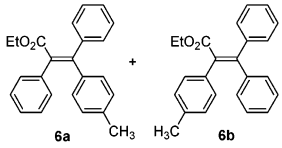
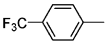
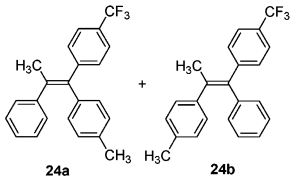
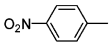
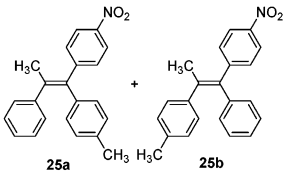
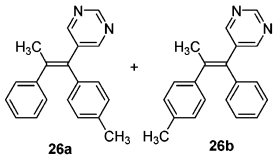
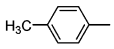
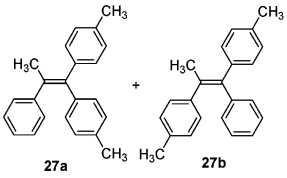
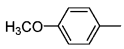
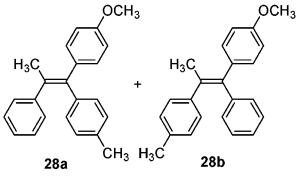
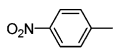
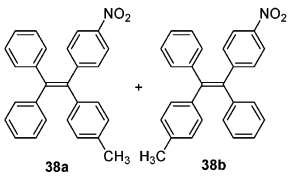
[a] All reactions were run using 0.75 mmol of aryl iodide, 0.25 mmol of alkyne, 0.75 mmol of arylboronic acid, 0.75 mmol of $KHCO_3$, and 0.0025 mmol of $PdCl_2(PhCN)_2$ in 10 mL of 4:1 DMF/H_2O at 100 °C for 24 h. [b] The yields are based on products isolated by column chromatography. [c] No $KHCO_3$ was added.

determined by examining their NOESY H−H interactions.[32] The regiochemistry is primarily controlled by steric effects, which is consistent with our previous work[40] on palladium-catalyzed additions to alkynes and analogous work of Cacchi.[41] Thus, the aryl group from the aryl iodide generally favors the less hindered end of the alkyne, while the aryl group from the arylboronic acid adds to the other end of the alkyne (entry 1, Table 5; eq 6). Electronic effects also play an important role in the regiochemistry. The aryl group from the arylboronic acid prefers to add to the more electron-poor end of the alkyne, assuming steric effects are comparable. Only a 2:1

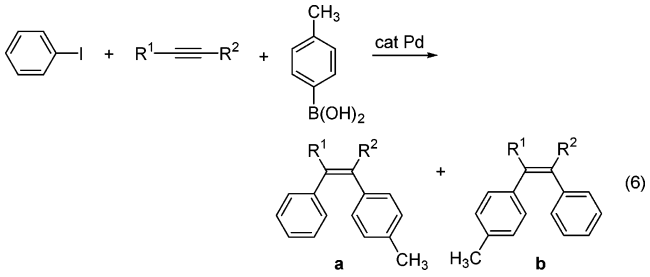
(40) (a) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, 63, 7652. (b) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1453. (c) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (d) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.

(41) (a) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Eur. J. Org. Chem.* **1999**, *3305*, 5. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Eur. J. Org. Chem.* **2000**, 4099.

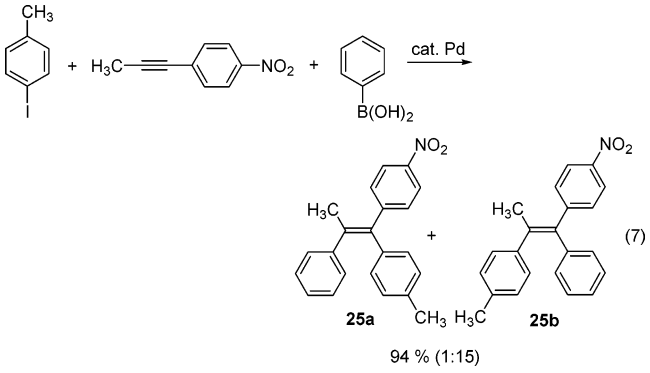
TABLE 5. Regioselectivity Studies (Eq 6)[a]

entry	R^1	R^2	products	% yield[b]
1	CH_3		 **1a** **1b**	81 (6:1)
2	$COCH_3$		 **5a** **5b**	79 (2:1)
3	CO_2Et		 **6a** **6b**	77 (2:1)
4	CH_3		 **24a** **24b**	90 (10:1)
5	CH_3		 **25a** **25b**	93 (15:1)
6	CH_3		 **26a** **26b**	91 (12:1)
7	CH_3		 **27a** **27b**	75 (3:1)
8	CH_3		 **28a** **28b**	45 (2:1)
9			 **38a** **38b**	82 (2:1)

[a] All reactions were run using 0.50 mmol of aryl iodide, 0.25 mmol of alkyne, 0.75 mmol of arylboronic acid, 0.75 mmol of $KHCO_3$, and 0.0025 mmol of $PdCl_2(PhCN)_2$ in 10 mL of 4:1 DMF/H_2O at 100 °C for 12 h unless otherwise indicated. [b] The yields are based on products isolated by column chromatography; the ratio of regioisomers is given in parentheses as determined by ^1H NMR spectroscopic analysis of the products obtained by column chromatography.

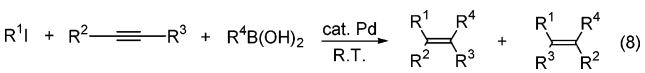


regioselectivity is observed when a ketone or ester-containing internal alkyne is employed, probably due to the opposite steric and electronic effects of the ketone or ester groups versus the phenyl group (entries 2 and 3).[42] It is interesting to note that better regioselectivity is observed if an electron-withdrawing group is introduced into the aromatic ring of the 1-phenylpropyne (compare entries 4 and 5 with entry 1). Excellent 15:1 regioselectivity is observed when 1-(4-nitrophenyl)propyne is used as the alkyne (entry 5). Introduction of an electron-poor pyrimidine group has a similar effect (compare entries 6 and 1). Poor regioselectivity along with a lower yield is observed when an electron-donating group is introduced into the aromatic ring of the 1-phenylpropyne (entries 7 and 8). It is noteworthy that the regiochemistry can be readily reversed by interconverting functionality on the aryl iodide and the arylboronic acid [compare entry 1 in Table 5 with entry 19 in Table 1 (see footnote d), and entry 5 in Table 5 with the results reported in eq 7]. For

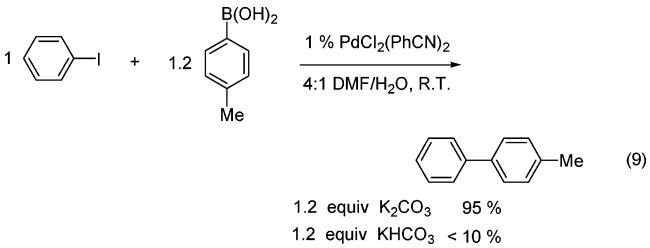


example, the minor regioisomer **25b** in the process reported in Table 5, entry 5, can be easily prepared, again with excellent 15:1 regioselectivity, simply by reversing the position of the substituents in the aryl iodide and the arylboronic acid (eq 7). The electronic effect of an electron-withdrawing nitro group has also been studied using (4-nitrophenyl)phenylacetylene as a substrate; moderate 2:1 regioselectivity is observed (entry 9).

(d) Modified Room-Temperature Reaction. Although our process normally involves clean *cis*-addition to the internal alkyne, the regioselectivity is sometimes only fair under our optimal reaction conditions (Table 5). We envisioned that better regioselectivity might possibly be accomplished under milder reaction conditions. Although only a small amount of the desired olefin product was obtained, the regioselectivity of the reaction of iodobenzene, 1-phenylpropyne, and *p*-tolylboronic acid was improved to 18:1 when we carried out the reaction at room temperature (entry 1, Table 6; eq 8). This is



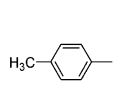
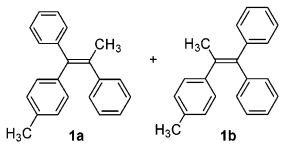
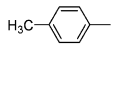
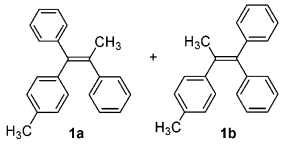
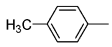
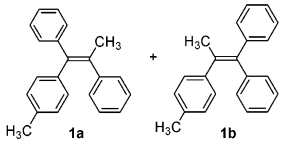
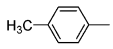
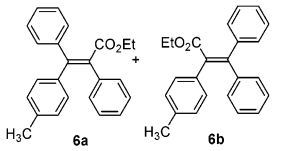
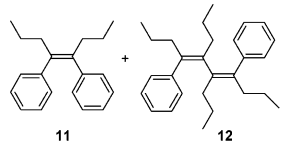
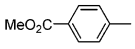
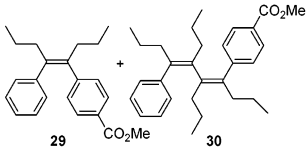
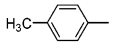
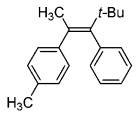
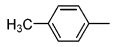
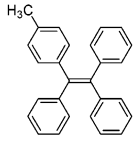
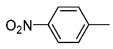
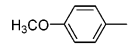
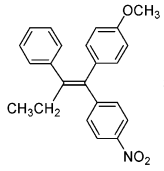
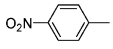
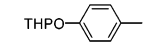
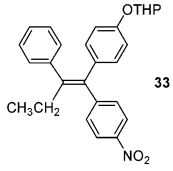
opposed to the 6:1 mixture of regioisomers obtained at 100 °C (entry 1, Table 5). With the proper choice of base, we were pleased to find that the reaction could be efficiently carried out at room temperature. For example, with K_2CO_3 as the base, the three-component reaction of iodobenzene, 1-phenylpropyne, and *p*-tolylboronic acid at room temperature after 24 h provided the desired products in an excellent 82% overall yield with excellent 18:1 regioselectivity (entry 2). The choice of the base is essential to the efficiency of the chemistry. It is important to note that the Suzuki-coupling between iodobenzene and *p*-tolylboronic acid can be accomplished using K_2CO_3 as the base at room temperature in 95% yield (eq 9).



However, the same reaction only leads to a low yield of biaryl product when $KHCO_3$ is used as the base. It is noteworthy that the minor isomer in Table 6, entry 1, could be obtained as the major product again with excellent 18:1 regioselectivity by simply using 4-iodotoluene, 1-phenyl-1-propyne, and phenylboronic acid as the starting materials (entry 3, Table 6). The regioselectivity is poor, however, when ethyl phenylpropynoate is used as the alkyne. Although an excellent 87% yield is obtained using the room-temperature conditions, the two regioisomers are obtained in a 3:2 ratio (entry 4, Table 6) as compared to the 78% yield and 2:1 regioselectivity observed earlier (entry 5, Table 2). Employing 4-octyne as the starting material is known to lead to a low yield of tetrasubstituted alkene when the process is run at 100 °C (entry 10, Table 2). A similar low yield is obtained under our room-temperature reaction conditions, since a substantial amount of double insertion product is also obtained (entries 5 and 6, Table 6). The milder reaction conditions make it possible to employ 4,4-dimethyl-2-butyne as the alkyne, and the reaction now affords the desired product regioselectively in a 42% yield (entry 7, Table 6), while none of this product is observed when the same alkyne is employed at 100 °C (entry 11, Table 2). The room-temperature reaction turns out to be sluggish and only a 20% yield of the desired product is obtained after 24 h when diphenylacetylene is used as the starting material (entry 8, Table 6). Presumably diphenylacetylene is too sterically hindered, and thus carbopalladation of this alkyne is not efficiently achieved at room temperature. The room-temperature process works well for 1-(4-nitrophenyl)-1-butyne, affording the desired products in good yields with almost complete control of the regiochemistry (entries 9 and 10, Table 6). It is noteworthy that the products obtained in these reactions are possible precursors to tamoxifen deriva-

(42) Presumably the phenyl group is more sterically hindered than the ketone or ester groups, and the ketone and ester groups are more electron-poor than the phenyl group.

TABLE 6. Synthesis of Tetrasubstituted Olefins at Room Temperature (Eq 8)[a]

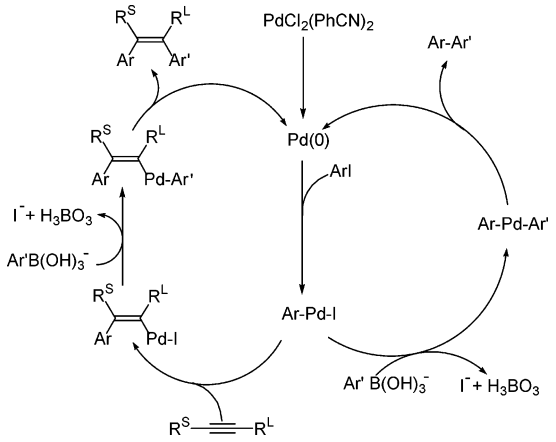
entry	R^1	R^2	R^3	R^4	product(s)	% yield[b]
1[c]		CH_3			 **1a** + **1b**	10 (18:1)
2		CH_3			 **1a** + **1b**	82 (18:1)
3		CH_3			 **1a** + **1b**	85 (1:18)
4		CO_2Et			 **6a** + **6b**	87 (2:3)
5		*n*-Pr	*n*-Pr		 **11** + **12**	28 + 61
6		*n*-Pr	*n*-Pr		 **29** + **30**	48 + 42
7		CH_3	*t*-Bu		 **31**	43 (>100:1)
8					 **16**	20
9[d]		C_2H_5			 **32**	81 (>100:1)
10[d]		C_2H_5			 **33**	68 (>100:1)

[a] All reactions were run using 0.75 mmol of aryl iodide, 0.25 mmol of alkyne, 0.75 mmol of arylboronic acid, 0.75 mmol of K_2CO_3, and 0.005 mmol of $PdCl_2(PhCN)_2$ in 10 mL of 4:1 DMF/H_2O at room temperature for 24 h unless otherwise indicated. [b] The yields are based on products isolated by column chromatography; the ratio of regioisomers is given in parentheses as determined by ^1H NMR spectroscopic analysis. [c] 0.75 mmol of $KHCO_3$ was employed instead of K_2CO_3. [d] The reaction was run under N_2. A slightly lower yield was obtained if the reaction was run under air.

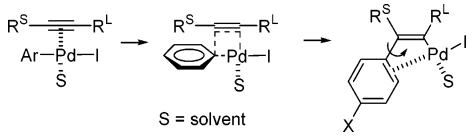
tives,[43] since demethylation of the methyl ether, followed by alkylation, is a known process to synthesize tamoxifen derivatives.[11a,22k,44,45]

(e) Reaction Mechanism. We propose the mechanism illustrated in Scheme 1 for this process, which consists of the following key steps: (1) reduction of Pd(II)

SCHEME 1



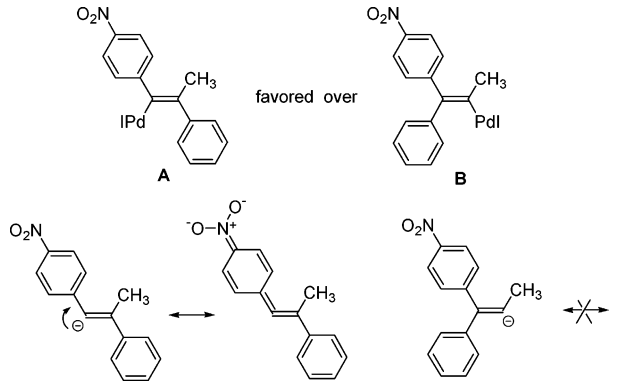
SCHEME 2. Carbopalladation of Internal Alkynes



to Pd(0), the actual catalyst, presumably by the arylboronic acid;[48] (2) oxidative addition of the aryl iodide to Pd(0); (3) *cis*-carbopalladation of the internal alkyne by the resulting arylpalladium species to generate a vinylic palladium intermediate; (4) subsequent Suzuki-type transmetalation with the "ate complex" $ArB(OH)_3^-$; (5) reductive elimination producing the tetrasubstituted olefin with simultaneous regeneration of the Pd(0) catalyst. Alternatively, transmetalation can occur directly between the initial arylpalladium intermediate and the arylboronic acid ate complex producing the biaryl side-product.

Carbopalladation of the internal alkyne by the arylpalladium intermediate (Ar-Pd-I in Scheme 1) is believed to be the key step in the catalytic cycle. This presumably proceeds through a four-member ring transition state in which the aromatic ring and Pd in Ar-Pd-I are positioned on the same side of the internal alkyne (Scheme 2).[40,41a] Thus, carbopalladation generates a vinylic palladium species by a *cis*-addition. It is reasonable to assume that the relatively large aromatic group of the Ar-Pd-I intermediate should approach the internal alkyne from the less hindered end of the internal alkyne due to steric hindrance. While *p*-iodotoluene affords a high yield of tetrasubstituted olefin in this chemistry, *o*-iodotoluene only affords a fair yield of the desired product (entries 3 and 5 in Table 3, respectively), probably because the

SCHEME 3



o-tolyl group is more sterically hindered and thus the carbopalladation is less favorable. We also believe that the aromatic ring adjacent to the Pd moiety of the vinylpalladium intermediate may coordinate with the Pd by η^1 or η^2 coordination[46a] and thus stabilize the vinylpalladium intermediate in the catalytic cycle (Scheme 2). Similar adjacent coordination has been reported in the literature.[46] This stabilization may also inhibit further insertion of another molecule of alkyne. No such stabilization of the Pd intermediate exists after insertion of a second alkyne. The facile 1,4-palladium migration from similar vinylic (and aryl) palladium species[47] to the neighboring arene provides further support for such an interaction. Electron-deficient aryl iodides generally lead to low yields in this chemistry (entries 7−9, Table 3), possibly because the electron-deficient aromatic ring is less likely to coordinate with the vinylic Pd intermediate. The addition of phosphine ligands may also interfere with coordination of the neighboring arene in these vinylic palladium intermediates and thus be responsible for the lower yields of tetrasubstituted olefin (see Table 1, entries 5−10). On the other hand, the carbopalladation process is apparently still facile when using iodobenzene and either electron-rich or electron-deficient arylboronic acids.

Another feature of this chemistry is the fact that the Pd favors the more electron-deficient end of the alkyne during carbopalladation. For example, excellent regioselectivity (15:1) is observed when 1-(4-nitrophenyl)-propyne is employed, as opposed to only 6:1 regioselectivity when using 1-phenylpropyne (compare entries 1 and 5 in Table 5). Thus, the reaction is further favored via vinylpalladium intermediate **A** over **B** by the presence of the nitro group (Scheme 3). Presumably, delocalization of the vinylic anion by the nitro group in **A** leads to a

(43) For representative reviews on tamoxifen and derivatives, see: (a) Jordan, V. C. *Nat. Rev. Drug Discovery* **2003**, *2*, 205. (b) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 883. (c) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 1081. (d) Salih, A. K.; Fentiman, I. S. *Cancer Treat. Rev.* **2001**, *27*, 261. (e) Harper, M. J. K.; Walpole, A. L. *Nature* **1966**, *212*, 87.

(44) For some representative tamoxifen syntheses, see: (a) Potter, G. A.; McCague, R. *J. Org. Chem.* **1990**, *55*, 6184. (b) Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7076. (c) Yus, M.; Ramon, D. J.; Gomez, I. *Tetrahedron* **2003**, *59*, 3219.

(45) For some representative syntheses of tamoxifen derivatives, see: (a) Yu, D. D.; Forman, B. M. *J. Org. Chem.* **2003**, *68*, 9489. (b) Valliant, J. F.; Schaffer, P.; Stephenson, K. A.; Britten, J. F. *J. Org. Chem.* **2002**, *67*, 383. (c) Foster, A. B.; Jarman, M.; Leung, O. T.; McCague, R.; Leclercq, G.; Devleeschouwer, N. *J. Med. Chem.* **1985**, *28*, 1491. (d) Watts, C. K. W.; Murphy, L. C.; Sutherland, R. L. *J. Biol. Chem.* **1984**, *259*, 4223.

(46) (a) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336. (b) Campora, J.; Gutierrez-Puebla, E.; Lopez, J. A.; Monge, A.; Palma, P.; Del Rio, D.; Carmona, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3641. (c) Campora, J.; Lopez, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147. (d) Falvello, L. R.; Fornies, J.; Navarro, R.; Sicilia, V.; Tomas, M. *J. Chem. Soc., Dalton Trans.* **1994**, 3143. (e) Fornies, J.; Menjon, B.; Gomez, N.; Tomas, M. *Organometallics* **1992**, *11*, 1187. (f) Li, C. S.; Cheng, C. H.; Wang, S. L. *J. Chem. Soc., Chem. Commun.* **1991**, 710. (g) Wehman, E.; van Koten, G.; Jastrzbeski, T. B. H.; Ossor, H.; Pfeffer, M. *J. Chem. Soc., Dalton Trans.* **1988**, 2975.

(47) (a) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (b) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 4326. (c) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. (d) Larock, R. C.; Tian, Q. *J. Org. Chem.* **2001**, *66*, 7372. (e) Tian, Q.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3329.

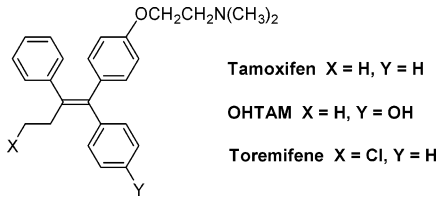
more stable anionic-like transition state and thus improves the regioselectivity of carbopalladation. It is also possible that the more stable vinylic anion in **A** is a weaker donor for Pd and leads to a more reactive vinylic palladium intermediate and therefore improves the regioselectivity of the reaction.

The proposed reaction mechanism also indicates that the arylpalladium intermediate Ar-Pd-I can undergo either the desired carbopalladation of the internal alkyne or an undesired Suzuki-type transmetalation directly with the boronic acid "ate complex". That competition limits the efficiency of our tetrasubstituted olefin synthesis. An efficient reaction requires that the rate of carbopalladation of the alkyne by Ar-Pd-I be faster than that of transmetalation of $ArB(OH)_3^-$ by Ar-Pd-I. When transmetalation is much faster than carbopalladation, the reaction favors formation of the biaryl side-product as seen when 4-iodonitrobenzene is employed (entry 9 in Table 3). The desired reaction is also less favorable when carbopalladation is much faster than transmetalation. In this case, multiple insertion of the alkyne is likely to occur, despite the fact that stabilization of the vinylic palladium intermediate by the adjacent aromatic ring should favor formation of the desired "mono-alkyne-insertion" product, as stated earlier. Such an imbalance may be responsible for the substantial amount of the di-insertion product formed when less hindered, electron-rich 4-octyne is employed (entry 10 in Table 2).

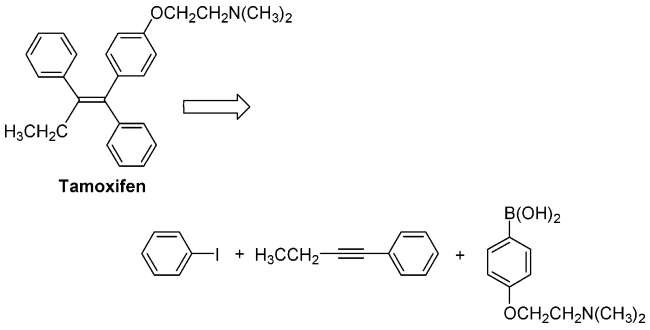
This aryl iodide−alkyne−organoboron reaction system is quite complicated, since each of the three components is highly reactive toward Pd catalysis. Depending on the reaction conditions employed, the following side-reactions would appear to be possible in our reaction system: the direct Suzuki reaction of aryl iodide and arylboronic acid;[35] homocoupling of the arylboronic acid;[48] insertion of the alkyne, followed by possible reduction;[41,49] insertion of the alkyne, followed by migration and ring closure;[47d,e] double-insertion of the alkyne, followed by ring closure to a naphthalene;[50] and multiple insertion of the alkyne.[51] Fortunately, most of the above side-reactions, except for the Suzuki reaction, are apparently suppressed under our optimal reaction conditions. Due to the many competing reactions possible in this multicomponent reaction system, the choice of reaction conditions, stoichiometry, and sometimes the proper combination of substrates are essential for the success of this chemistry.

(f) Synthesis of Tamoxifen and Derivatives. The triaryl alkene moiety is a key structure in many non-steroidal antiestrogens, and the antiestrogenic activity is highly dependent on the olefin geometry.[43] In particular, tamoxifen has been widely used for the treatment of breast cancer at all stages and is believed to be responsible for the survival of hundreds of thousands of breast cancer patients (Chart 1).[43] The regio- and stereoselective synthesis of tamoxifen and its derivatives has been of major interest to organic and pharmaceutical chemists for years, and yet it remains today a considerable challenge for the synthetic chemist. Recently, some elegant syntheses of tamoxifen and its derivatives have been reported.[3c,11a,12a,18c,21a,22k,44,45] However, either they are not regio- and stereoselective or they involve multistep procedures employing starting materials that are not readily available. Thus, a simple, regio- and stereoselective synthetic approach to tamoxifen and its derivatives is highly desirable and should pave the way for rapid development of these highly potent nonsteroidal antiestrogens.

CHART 1



SCHEME 4



By employing our new approach to tetrasubstituted olefins, we anticipated that it should be possible to prepare tamoxifen and analogues in a very concise manner. Our route to tamoxifen involves a three-component reaction of readily available iodobenzene, 1-phenyl-1-butyne, and 4-[2-(dimethylamino)ethoxy]-phenylboronic acid (Scheme 4).

The dimethylamino-containing boronic acid has been successfully synthesized in two steps from readily available starting materials. The requisite aryl bromide precursor has been obtained by reaction of *p*-bromophenol and 2-(dimethylamino)ethyl chloride (eq 10). The arylboronic acid has subsequently been prepared in good yield through reaction of the corresponding Grignard reagent with $B(OMe)_3$ (eq 11).[52]

In an attempt to control the regioselectivity, a three-component approach to tamoxifen has been attempted employing our modified room-temperature reaction conditions. However, the reaction was sluggish under those

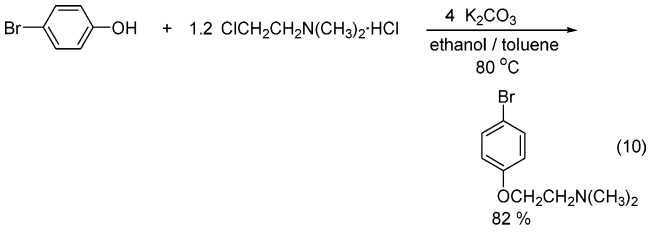
(48) (a) Miyaura, N.; Suzuki, A. *Main Group Met. Chem.* **1987**, *10*, 295. (b) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33. (c) Moreno-Manas, M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346. (d) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087. (e) Koza, D. J.; Carita, E. *Synthesis* **2002**, 2183. (f) Falck, J. R.; Mohapatra, S.; Bondlela, M.; Venkataraman, S. K. *Tetrahedron Lett.* **2002**, *43*, 8149. (g) Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525. (h) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541.

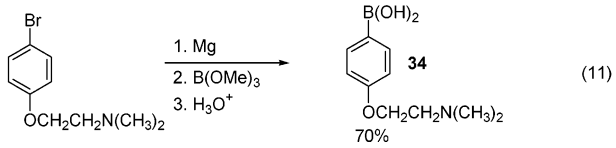
(49) We hypothesize that the reducing reagent might be formate, which could possibly be produced by the hydrolysis of DMF in the presence of base.

(50) (a) Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 6836. (b) Kotora, M.; Matsumura, H.; Gao, G.; Takahashi, T. *Org. Lett.* **2001**, *3*, 3467. (c) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770. (d) Sakakibara, T.; Tanaka, Y.; Yamasaki, T. I. *Chem. Lett.* **1986**, 797.

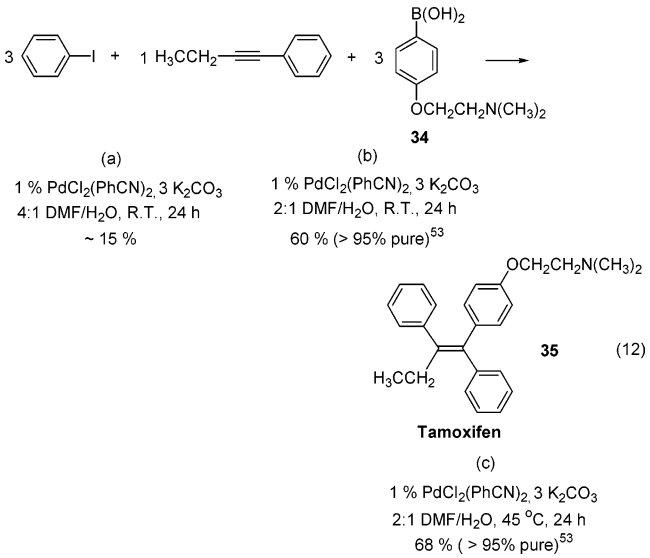
(51) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941.

(52) (a) Washburn, R. M.; Levens, E.; Albright, C. F.; Billig, F. A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 68. (b) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.





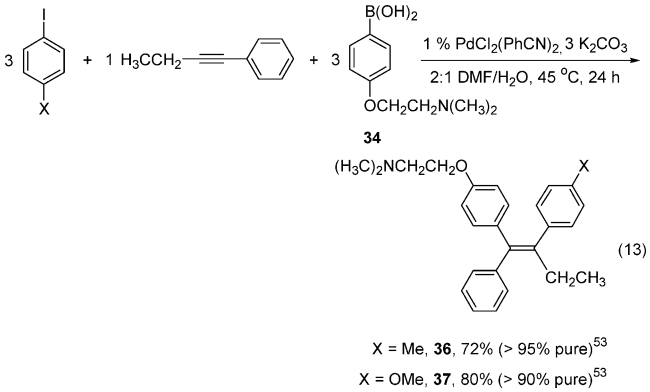
reaction conditions, and most of the starting materials remained unreacted after 24 h (eq 12). Fortunately, the



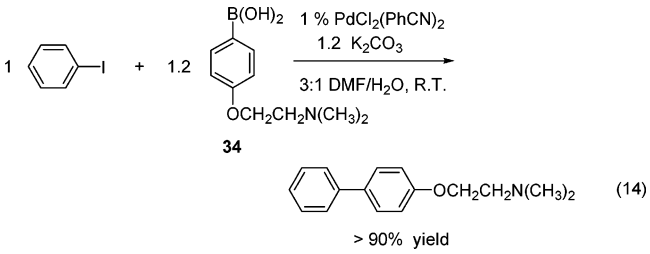
reaction could be speeded up by simply changing the amount of water. After a 48 h reaction in 2:1 DMF/H_2O, a 60% yield of the desired tamoxifen was isolated by column chromatography. It is noteworthy that the reaction seems to be highly regioselective (possibly >20:1), since the crude tamoxifen obtained is around 95% pure according to ^{1}H NMR spectral analysis.[53] By raising the reaction temperature to 45 °C, a slightly higher 68% yield of tamoxifen has been obtained in 24 h. We also observed the formation of about 2 equiv of *N*,*N*-dimethyl-2-(4-biphenyloxy)ethylamine as a side-product, which could be separated from tamoxifen by column chromatography.

The tamoxifen derivatives **36** and **37**[45d] could also be prepared using this chemistry. Thus, methyl- and methoxy-substituted tamoxifen have been obtained in good yields with good regiochemistry by simply employing 4-iodotoluene or 4-iodoanisole as the starting materials (eq 13).

This approach to tamoxifen derivatives is not very general, however, since we have found that the reaction of iodobenzene and boronic acid **34** fails to give any of



the desired product when using 1-(4-nitrophenyl)-1-butyne as the starting alkyne. No biaryl side-product is formed, and the starting materials remain essentially untouched. None of the biaryl or the tetrasubstituted olefin is observed even after heating the reaction at 100 °C for 24 h. It is interesting to note that the analogous reaction of the closely related electron-rich 4-methoxyphenylboronic acid works well for 1-(4-nitrophenyl)-1-butyne even at room temperature (entry 9, Table 6). The direct Suzuki reaction of iodobenzene and 4-[2-(dimethylamino)ethoxy]phenylboronic acid affords a high yield of biaryl at room temperature (eq 14).



It would appear that the combination of the aryl iodide, alkyne, and boronic acid might be forming a stable Pd complex, which prevents further reaction. We hypothesize such a Pd complex in which the N and O in the (dimethylamino)ethoxy group coordinate with the vinylic Pd intermediate, forming a stable chelation complex. With the strong delocalization of the vinylic anion by the nitro group, coordination of the vinylic anion to the Pd should be weakened, allowing stronger coordination of the N and O in the (dimethylamino)ethoxy group due to the *trans* effect. On the other hand, without delocalization by the nitro group, coordination of the vinylic anion to the Pd should be strong, leading to weaker coordination of the N and O in the (dimethylamino)ethoxy group. We hypothesize an equilibrium between this chelation complex and the free reactive vinylpalladium intermediate, which is free to undergo transmetalation with the boronic acid "ate complex", producing the desired product. So far, all attempts to prepare such a nitro-substituted tamoxifen by employing 1-(4-nitrophenyl)-1-butyne have failed. It is noteworthy that one can possibly obtain such tamoxifen derivatives through the triarylalkene precursor generated earlier (entries 9 and 10, Table 6), since demethylation of the methyl ether, followed by alkylation to generate tamoxifen derivatives, is well-established.[11a,22k,44,45]

(53) The purity of the product is based on ^{1}H NMR spectroscopic analysis of the crude product obtained from column chromatography. We cannot rule out the possibility that some of the minor regioisomer has been separated out during column chromatography, since the biaryl side-product and the desired tetrasubstituted olefin have very similar polarities in this case.

Conclusions

A new palladium-catalyzed route to tetrasubstituted olefins has been successfully developed. The synthesis involves a one-pot, three-component cross-coupling of readily available aryl iodides, internal alkynes, and arylboronic acids. The synthetic protocol is conceptually simple and quite practical. The reaction is quite efficient and is normally insensitive to air. In fact, the presence of water greatly facilitates formation of the desired tetrasubstituted olefins. Furthermore, the reaction can be carried out at room temperature. The mild reaction conditions accommodate a number of functional groups, such as a ketone, an ester, an alcohol, and a phenol. Thus, we envision that this chemistry should find wide application for the synthesis of tetrasubstituted olefins.

A wide variety of tetrasubstituted olefins have been prepared in good to excellent yields. The reaction involves *cis*-addition to the internal alkyne. The aryl group from the aryl iodide favors the less hindered or more electron-rich end of the alkyne, while the aryl group from the arylboronic acid adds to the other end. The proper combination of substrates, as well as reaction conditions, is important for the efficiency of the reaction. Although the reaction generates a fair amount of the biaryl side-product, it can usually be easily separated by column chromatography.

Employing this new approach to tetrasubstituted olefins, we have successfully synthesized tamoxifen and several derivatives in a very concise, regio- and stereoselective manner. We believe this synthetic protocol should allow the straightforward syntheses of various tamoxifen derivatives.

Experimental Section

(a) General Procedure for the Synthesis of Tetrasubstituted Olefins at 100 °C (Tables 2−5). DMF (8 mL), H_2O (2 mL), $KHCO_3$ (0.50 or 0.75 mmol), ArI (0.50 or 0.75 mmol), arylboronic acid (0.75 mmol), and the internal alkyne (0.25 mmol) were placed in a 6-dram vial. The contents were stirred and heated in a 100 °C oil bath for 10 min. $PdCl_2(PhCN)_2$ catalyst (0.0025 mmol, dissolved in 0.1 mL of DMF) was injected. The vial was then heated in an oil bath at 100 °C until palladium black appeared (usually 1−24 h). The reaction mixture was cooled and quenched with 30 mL of saturated NaCl solution, and the aqueous layer was extracted three times with ethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The product was isolated by chromatography on a silica gel column.

(b) General Procedure for the Synthesis of Tetrasubstituted Olefins at Room Temperature (Table 6). DMF (8 mL), H_2O (2 mL), K_2CO_3 (0.75 mmol), ArI (0.75 mmol), arylboronic acid (0.75 mmol), and the internal alkyne (0.25 mmol) were placed in a 6-dram vial. The contents were stirred at room temperature for 10 min. $PdCl_2(PhCN)_2$ catalyst (0.005 mmol in 0.1 mL of DMF) was injected. The vial was stirred at room temperature (20−30 °C) for 24 h. The reaction mixture was then quenched with 30 mL of saturated NaCl solution, and the aqueous layer was extracted three times with ethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The product was isolated by chromatography on a silica gel column.

(c) General Procedure for the Synthesis of Tamoxifen and Derivatives (Eqs 12 and 13). DMF (8 mL), H_2O (4 mL), K_2CO_3 (0.75 mmol), ArI (0.75 mmol), arylboronic acid **34** (0.75 mmol), and 1-phenyl-1-butyne (0.25 mmol) were placed in a 6-dram vial. The contents were stirred at room temperature for 10 min. $PdCl_2(PhCN)_2$ catalyst (0.0025 mmol in 0.1 mL of DMF) was injected. The vial was stirred at 45 °C for 24 h. The reaction mixture was then quenched with 30 mL of saturated NaCl solution, and the aqueous layer was extracted with ethyl ether three times. The combined organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The product was isolated by chromatography on a silica gel column.

Acknowledgment. Partial financial support from the Petroleum Research Fund administered by the American Chemical Society is gratefully acknowledged. We also acknowledge Johnson Matthey, Inc., and Kawaken Fine Chemicals Co. Ltd. for providing the palladium compounds and Frontier Scientific Co. for providing the arylboronic acids. We acknowledge the technical and creative assistance of Mr. Tanay Kesharwani, Ms. Guoxin Lu, and Mr. John Maves in the creation of the cover art.

Supporting Information Available: Experimental details and product characterization data and ^1H and ^{13}C NMR spectra for compounds **3**, **7**−**12**, **19**, **21**−**23**, **29**−**33**, **35**−**37**, **38a**, **and 38b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048265+