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An Efficient, Regio- and Stereoselective Palladium-Catalyzed Route to Tetrasubstituted Olefins

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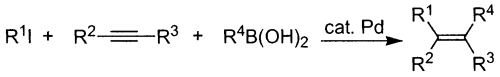
ABSTRACT



An efficient, regio- and stereoselective palladium-catalyzed route to tetrasubstituted olefins has been developed, which involves the intermolecular coupling of an aryl iodide, an internal alkyne, and an arylboronic acid. The reaction involves *cis*-addition of the aryl group from the aryl halide to the less hindered or less electron-poor end of the alkyne, while the aryl group from the arylboronic acid adds to the other end.

The expeditious, regio- and stereoselective synthesis of tetrasubstituted olefins has provided a challenge for synthetic organic chemists for years.[1] Although tetrasubstituted olefins can be obtained by the McMurry reaction[2] or Wittig olefination,[3] the generality, as well as the regio- and stereoselectivity, of these procedures are major problems. Recent approaches to tetrasubstituted olefins involve alkyne carbolithiation[4] and reactions employing CF_3-containing oxiranes,[5] organosilanes,[6] electrotelluration,[7] and ynolate anions.[8] However, these approaches do not generally employ readily available starting materials, sometimes lack regio- and stereoselectivity, and are fairly limited in scope.

Palladium-catalyzed reactions are versatile methods for carbon−carbon bond formation as a result of their generality and ability to tolerate a wide range of important organic functional groups.[9] For example, palladium has provided useful synthetic approaches to specific tetrasubstituted olefins by the *intramolecular* addition of arylpalladium intermediates to internal alkynes, followed by cross-coupling with boron, tin, and zinc organometallics.[10] The *intermolecular* carbopalladation of alkynes has interested organic chemists for years.[11] Recently, the *intermolecular* Rh-,[12] Ni-,[13] and Pd-catalyzed[14] addition of arylboronic acids to alkynes has been reported to produce di- and trisubstituted alkenes. Rawal et

(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) Ephritikhine, M. *Chem. Commun.* **1998**, 2549. (b) Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608. (c) Sabelle, S.; Hydrio, J.; Leclerc, E.; Mioslowshi, C.; Renard, P. Y. *Tetrahedron Lett.* **2002**, *43*, 3645 and references therein.

(3) For a representative review for Wittig olefination, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(4) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621 and references therein.

(5) Shimizu, M.; Fujimoto, T.; Minezaki, H.; Hata, T.; Hiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 6947.

(6) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577.

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

(8) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840.

(9) (a) Trost, B. *Science* **1991**, *234*, 1471. (b) Tsuji J. *Palladium Reagents and Catalysis: Innovations in Organic Synthesis*; Wiley: New York, 1995. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.

(10) (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.

(11) For representative examples, see: (a) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L.; Negishi, E. *J. Am. Chem. Soc.* **1994**, *116*, 7923. (b) Gevorgyan, V.; Quan, L.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089. (c) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173. (d) Larock, R. C.; Reddy, C. *J. Org. Chem.* **2002**, *67*, 2027.

(12) (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.

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

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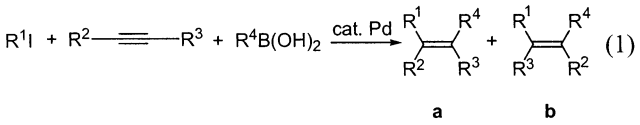
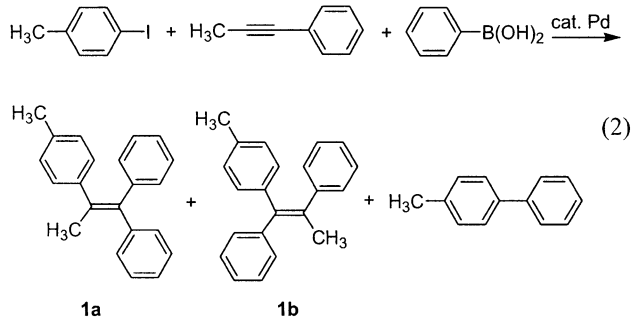
al. have also reported the palladium-catalyzed sequential haloallylation/Suzuki cross-coupling of alkynes as a convenient synthetic route to 1,3-dienes.[15] Herein we present a new, highly efficient, palladium-catalyzed synthesis of tetrasubstituted olefins involving the *intermolecular* cross-coupling of an aryl iodide, an internal alkyne, and an arylboronic acid (eq 1).



(1)

To develop this methodology, we chose a simple, representative model system consisting of 4-iodotoluene, 1-phenylpropyne, and phenylboronic acid on which to optimize the reaction conditions (eq 2).



(2)

In early experiments, we found that a 36% yield of the desired tetrasubstituted olefins (**1a** and **1b** in a 6.5:1 ratio) could be obtained by reaction of 1 equiv of 4-iodotoluene, 1 equiv of 1-phenylpropyne, 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). A small amount of 4-methylbiphenyl side product was also formed. Since no aryl iodide was left after the reaction, there must be some unknown side reaction, such as multiple alkyne insertion leading to oligomerization. Doubling the amount of alkyne had little effect on the yield (entry 2). We were pleased to find that the side reactions could be significantly suppressed by simply running the reaction in DMF/H_2O (entry 3). The yield could be increased to 63% in 80:20 DMF/H_2O (entry 4). Water is obviously very important in these reactions, 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.[16] The yield can be slightly increased if 2 equiv of $KHCO_3$ is used as the base, instead of 1 equiv of K_2CO_3 (entry 6).[17] 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 and 1 equiv of alkyne were employed, the yield increased to 72% (entry 7). The yield could be further increased by simply reducing the amount of palladium catalyst (entries 7−9). An 85% yield of the desired tetrasubstituted olefin was obtained by employing only 1% of the palladium catalyst (entry 9). The yield could be further increased to 88% by using 3 equiv of boronic acid and $KHCO_3$ (entry 10). The same yield was obtained when 3 equiv of aryl iodide was employed (entry 11).[18] The "optimal" procedures from entries 10 and 11 have thus been employed for the synthesis of a wide variety of tetrasubstituted olefins.

Table 1. Optimization Studies (eq 2)[a]

entry	ratio[b]	Pd (%)	base	DMF/H_2O	% yield[c,d]	Ar-Ph (mmol)
1	1:1:2	5	1 K_2CO_3	100/0	36	0.03
2	1:2:2	5	1 K_2CO_3	100/0	39 (35)	0.03
3	1:2:2	5	1 K_2CO_3	90/10	50	0.06
4	1:2:2	5	1 K_2CO_3	80/20	63	0.05
5	1:2:2	5	1 $KHCO_3$	80/20	57	0.04
6	1:2:2	5	2 $KHCO_3$	80/20	66	0.05
7	2:1:2	5	2 $KHCO_3$	80/20	72	0.26
8	2:1:2	2	2 $KHCO_3$	80/20	78 (75)	0.26
9	2:1:2	1	2 $KHCO_3$	80/20	85	0.25
10	2:1:3	1	3 $KHCO_3$	80/20	88 (86)	0.25
11	3:1:3	1	3 $KHCO_3$	80/20	88	0.49

[a] All reactions were run on a 0.25-mmol scale (limiting reagent) employing $PdCl_2(PhCN)_2$ as the catalyst in 10 mL of DMF/H_2O at 100 °C for 3 h. [b] Ratio of aryl iodide:alkyne:boronic acid. [c] GC yields 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 6.5:1 ratio, based on ^1H NMR spectroscopic analysis.

As indicated in Table 2, this approach to tetrasubstituted olefins is quite versatile. Using diphenyl-acetylene as the alkyne, electron-rich aryl iodides work quite well (entries 1−3), whereas the electron-poor aryl iodide *p*-ClC_6H_4I gave a significantly lower yield of tetrasubstituted olefin (entry 4). In the latter case, the starting alkyne was partially recovered. Both electron-rich and electron-poor arylboronic acids afford decent yields (entries 5 and 6). A variety of unsymmetrical internal alkynes, including ketone- and ester-containing alkynes, have been successfully employed in this process (entries 7−10). Unfortunately, electron-rich dialkylacetylenes, such as 4-octyne, have thus far only led to low yields using our present reaction conditions. The mild reaction conditions tolerate many functional groups, including ether, ester, ketone, nitro, and CF_3 groups.

This approach to tetrasubstituted olefins is usually highly stereoselective and often quite regioselective. This three-component reaction involves clean *cis*-addition to the alkyne. Two regioisomers have usually been obtained when unsymmetrical alkynes are employed as starting materials. The regiochemistry can be readily reversed by interconverting functionality on the aryl iodide and arylboronic acid (compare

(14) Oh, C.; Jung, H.; Kim, K.; Kim, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 805.
(15) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317.
(16) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147 and references therein.
(17) The yield is slightly 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.
(18) When employing diphenylacetylene as the alkyne, a slightly higher yield is obtained if 3 equiv of aryl iodide is used instead of 2 equiv.

Table 2. Synthesis of Tetrasubstituted Olefins (eq 1)[a]

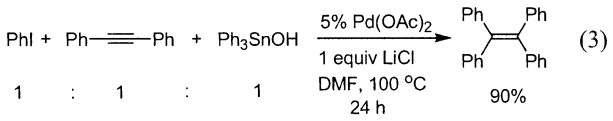
entry	R^1	R^2	R^3	R^4	product(s)	% yield[b]
1[c]	C_6H_5	C_6H_5	C_6H_5	C_6H_5	**2**	92
2[c]	p-$CH_3C_6H_4$	C_6H_5	C_6H_5	C_6H_5	**3**	92
3[c]	p-$CH_3OC_6H_4$	C_6H_5	C_6H_5	C_6H_5	**4**	90
4[c]	p-ClC_6H_4	C_6H_5	C_6H_5	C_6H_5	**5**	65
5[c]	C_6H_5	C_6H_5	C_6H_5	p-$CH_3OC_6H_4$	**4**	88
6[c]	p-$CH_3OC_6H_4$	C_6H_5	C_6H_5	3,5-$F_2C_6H_3$	**6**	80
7	p-$CH_3C_6H_4$	CH_3	C_6H_5	C_6H_5	**1a**, **1b**	86 (6.5:1)
8	p-$CH_3C_6H_4$	C_2H_5	C_6H_5	C_6H_5	**7a**, **7b**	80 (6:1)
9	p-$CH_3C_6H_4$	$COCH_3$	C_6H_5	C_6H_5	**8a**, **8b**	80 (2:1)
10	p-$CH_3C_6H_4$	$CO_2C_2H_5$	C_6H_5	C_6H_5	**9a**, **9b**	78 (2:1)
11	C_6H_5	CH_3	C_6H_5	p-$CH_3C_6H_4$	**1b**, **1a**	81 (6:1)
12	C_6H_5	CH_3	p-$CF_3C_6H_4$	p-$CH_3C_6H_4$	**10a**, **10b**	90 (10:1)
13	C_6H_5	CH_3	3,5-pyrimidinyl	p-$CH_3C_6H_4$	**11a**, **11b**	91 (12:1)
14	C_6H_5	CH_3	p-$O_2NC_6H_4$	p-$CH_3C_6H_4$	**12a**, **12b**	93 (15:1)
15	p-$CH_3C_6H_4$	CH_3	p-$O_2NC_6H_4$	C_6H_5	**12b**, **12a**	94 (15:1)
16	C_6H_5	C_2H_5	C_6H_5	p-$CH_3OC_6H_4$	**13a**, **13b**	85 (5:1)

[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 3 h unless otherwise indicated. [b] The yields are based on products isolated by column chromatography; the ratio of regioisomers as determined by ^1H NMR spectroscopic analysis is given in parentheses. [c] Three equivalents of aryl iodide was used in these entries, and the reactions were run for 24 h.

entries 7 and 11; 14 and 15). The structures of the major isomers have been determined by investigating their NOESY H−H interactions (see Supporting Information). The regiochemistry is primarily controlled by steric effects, which is consistent with our previous work on palladium-catalyzed additions to alkynes[19] and analogous work of Cacchi.[20] 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 favors the more hindered end of the alkyne. Electronic effects also play an important role in the regiochemistry. The aryl group from the arylboronic acid is more likely to add to the more electron-poor end of the alkyne. For example, better regioselectivity is observed if an electron-withdrawing group is introduced into the aromatic ring of 1-phenylpropyne (entries 11−15). Excellent 15:1 regioselectivity is obtained when 1-(4-nitrophenyl)propyne is used as the alkyne (entry 14). It is noteworthy that the minor regioisomer in this process can be prepared, again with excellent 15:1 regioselectivity, simply by reversing the position of the substituents in the aryl iodide and arylboronic acid (entry 15).

This methodology allows us to synthesize in one step from readily available starting materials a convenient precursor to tamoxifen, a widely used drug for breast cancer (entry 16).[21] The desired regioisomer **13a**[22] was obtained as a 5:1 regioisomeric mixture in 85% yield. Recrystallization afforded pure **13a** in 48% isolated yield. This process should afford a convenient synthesis of a wide variety of tamoxifen analogues.[2b,23]

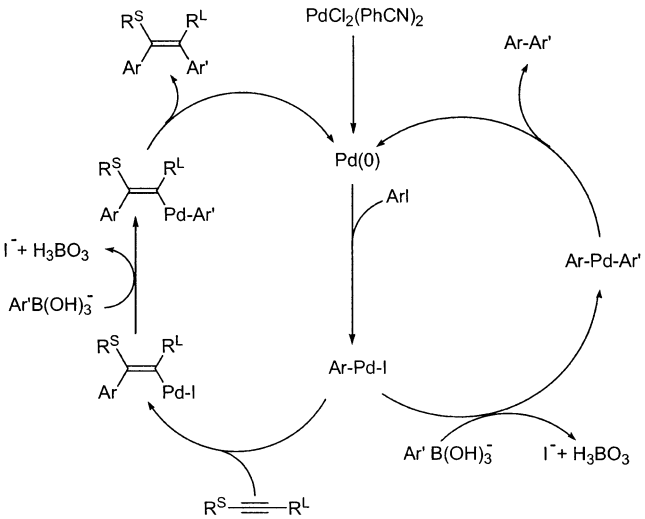
This methodology is not limited to organoboron reagents. We have also obtained excellent preliminary results using arylstannanes (eq 3). The desired tetraphenylethylene have been obtained in 90% GC yield by the reaction of 1 equiv of iodobenzene, 1 equiv of diphenylacetylene, and 1 equiv of triphenyltin hydroxide in the presence of 5 mol % $Pd(OAc)_2$ and 1 equiv of LiCl in DMF at 100 °C for 24 h.



(3)

We propose the mechanism in Scheme 1 for this process: (1) reduction of Pd(II) to Pd(0), the actual catalyst; (2) oxidative addition of the aryl iodide to Pd(0); (3) *cis*-carbopalladation of the internal alkyne to generate a vinylic palladium intermediate, where Pd favors the larger or more

Scheme 1



electron-deficient end of the alkyne; (4) subsequent Suzuki-type transmetalation with the "ate complex" $ArB(OH)_3^-$ or the arylstannane; and (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 arylboron or -tin species producing the biaryl side product.

In summary, by the proper choice of reaction conditions, reagents, and stoichiometry, we have developed a new, very convenient, conceptually simple one-step Pd-catalyzed route to tetrasubstituted olefins. A variety of tetrasubstituted olefins can be obtained by this simple, direct approach. We are currently exploring the scope and limitations of this useful process.

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Supporting Information Available: The preparation of the tetrasubstituted olefins, product characterization data, ^1H and ^{13}C NMR spectra, and H−H COESY/NOESY spectra for compounds **1b**, **10a**, **11a**, **12a**, and **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034435D

(19) (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) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.

(20) (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. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Eur. J. Org. Chem.* **2000**, 4099.

(21) For a representative review, see: Salih, A. K.; Fentiman, I. S. *Cancer Treat. Rev.* **2001**, *27*, 261.

(22) Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121.

(23) (a) Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. *Chem. Rev.* **1999**, *99*, 723. (b) Churruca, F.; San, M. R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2002**, *4*, 1591. (c) Valliant, J. F.; Schaffer, P.; Stephenson, K. A.; Britten, J. F. *J. Org. Chem.* **2002**, *67*, 383.