ORGANIC
LETTERS

2005
Vol. 7, No. 2
259−262

# Synthesis of Tetrasubstituted Olefins by Pd-Catalyzed Addition of Arylboronic Acids to Internal Alkynes

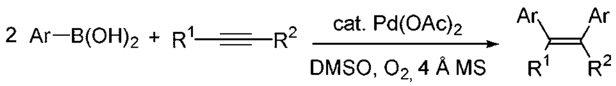
**Chengxiang Zhou and Richard C. Larock***

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

*larock@iastate.edu*

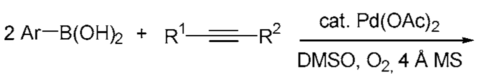
**Received November 2, 2004**

## ABSTRACT



**Tetrasubstituted olefins are readily prepared by the Pd-catalyzed *cis* addition of two aryl groups from an arylboronic acid to opposite ends of the triple bond of internal alkynes. The synthesis proceeds under very mild reaction conditions and tolerates a wide variety of functional groups, including alcohol, aldehyde, ester, TMS, and acetal groups.**

The expeditious regio- and stereoselective synthesis of tetrasubstituted olefins has been of interest to organic chemists for years.[1] The carbopalladation of alkynes has been widely applied in the synthesis of highly substituted olefins.[2] For example, some specific tetrasubstituted olefins have been prepared by the intramolecular carbopalladation of internal alkynes, followed by cross-coupling with organoboron or organostannane reagents.[3] Recently, we reported an efficient regio- and stereoselective synthesis of tetrasubstituted olefins by the Pd-catalyzed intermolecular three-component coupling of an aryl (or vinylic) iodide, an internal alkyne, and an arylboronic acid.[4] The Rh-,[5] Ni-,[6] or Pd-catalyzed[7] additions of arylboronic acids to alkynes have been reported to produce highly substituted olefins. Herein, we wish to report the synthesis of tetrasubstituted olefins by the Pd-catalyzed addition of two aryl groups from an arylboronic acid to internal alkynes under very mild reaction conditions (eq 1).



(1)

We first examined the reaction of phenylboronic acid and 1-phenyl-1-butyne in THF in the presence of 5% of $Pd(OAc)_2$ (eq 2). However, only a trace of the desired tetrasubstituted olefin was obtained (entry 1, Table 1). To our delight, using DMSO as a cosolvent greatly increased the yield. For example, in the presence of 5% $Pd(OAc)_2$, the tetrasubstituted olefin was obtained in a 51% yield when 5 equiv of phenylboronic acid and 1 equiv of 1-phenyl-1-butyne were employed in 50:50 DMSO/THF using air as an oxidant at room temperature for 48 h (entry 2). The yield was increased to 60 % using only DMSO as the solvent (entry 3). This

---

(1) For recent representative examples, see: (a) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778. (b) Liu, X.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 879. (c) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003**, *68*, 6066. (d) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (e) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840.

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

(3) (a) Grigg, R.; Sridharan, V. *Pure Appl. Chem.* **1998**, *70*, 1047. (b) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65. (c) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (d) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525.

(4) (a) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579. (b) Zhang, X.; Larock, R. C. *Org. Lett.* **2003**, *5*, 2993.

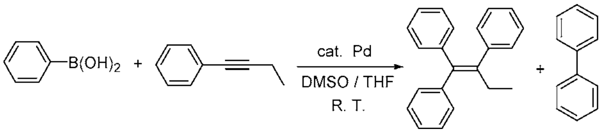
(5) (a) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464. (b) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358. (c) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*,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

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

(7) (a) Satoh, T.; Ogino, S.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5063. (b) Oh, C.; Jung H.; Kim, K.; Kim, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 805. (c) Oh, C.; Ryu, J. *Bull. Korean Chem. Soc.* **2003**, *24*, 1563. For an example involving the formation of a highly substituted cyclopentadiene, see: (d) Du, X.; Suguro, M.; Hirabayashi, K.; Mori A. *Org. Lett.* **2001**, *3*, 3313.

10.1021/ol047759q CCC: $30.25

**Table 1.** Optimization Studies[a]

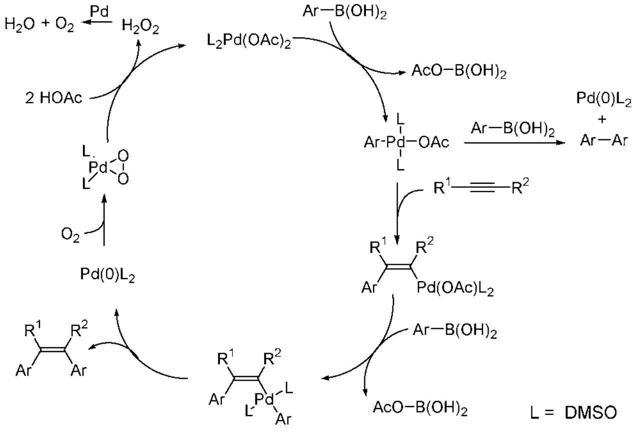


(2)

| entry | DMSO/THF | oxidant | 4 Å MS | time (h) | yield (%)[b] | biphenyl (mmol)[c] |
|---|---|---|---|---|---|---|
| 1 | 0/100 | air | no | 48 | trace | trace |
| 2 | 50/50 | air | no | 48 | 51 | 0.15 |
| 3 | 100/0 | air | no | 48 | 60 (55) | 0.25 |
| 4 | 100/0 | $O_2$ | no | 24 | 65 (59) | 0.32 |
| 5 | 100/0 | $O_2$ | yes | 24 | 80 (73) | 0.33 |
| 6[d] | 100/0 | $O_2$ | yes | 24 | 42 | 0.35 |
| 7 | 100/0 | no[e] | yes | 24 | 25 | 0.10 |
| 8[f] | 100/0 | $O_2$ | yes | 24 | 30 | 0.12 |
| 9[g] | 100/0 | $O_2$ | yes | 24 | trace | trace |

[a] Unless otherwise indicated, the reaction was run employing 1.25 mmol of phenylboronic acid and 0.25 mmol of 1-phenyl-1-butyne in the presence of 5 mol % of $Pd(OAc)_2$ in 2 mL of solvent. [b] GC yields based on the limiting reagent (alkyne); yields of products obtained by column chromatography are reported in parentheses. [c] GC yield. [d] 1 equiv of KOAc was employed. [e] The reaction was run under $N_2$. [f] 5 mol % of $Pd(dba)_2$ was used. [g] 5 mol % of $PdCl_2$ was used.

**Scheme 1**



$Pd(OAc)_2$/DMSO system has proven to be quite useful in aerobic oxidation reactions.[8] Presumably the presence of DMSO facilitates the reoxidation of Pd(0) to Pd(II) by air, thus completing the catalytic cycle (see the latter mechanistic discussion). The reaction proceeds faster using $O_2$ as the oxidant, and a 65% yield is obtained in 24 h (entry 4). Adding 4 Å molecular sieves (4 Å MS, 0.2 g for the 0.25 mmol reaction scale) to the reaction system further increases the yield. Thus, an 80% yield of tetrasubstituted olefin has been obtained in DMSO in the presence of 4 Å MS at room temperature (entry 5). The role of the molecular sieves is not clear. Possibly the presence of molecular sieves facilitates heterogeneous Pd catalysis on the molecular sieve surface,[9] or the molecular sieves absorb the water in the system, which facilitates the catalytic cycle (see Scheme 1). The presence of base suppresses the formation of the tetrasubstituted olefin. Only a 42% yield was obtained when 1 equiv of KOAc was employed as a base (entry 6). Without the oxidant, the reaction is sluggish. Only a 25% yield of the tetrasubstituted olefin is obtained when the reaction is run under $N_2$ (entry 7). It is noteworthy that trisubstituted olefins are not observed in our process, despite the fact that trisubstituted olefins have been reported as the major products in the Rh-,[5] Ni-,[6] or Pd-catalyzed[7] addition of arylboronic acids to internal alkynes. Interestingly, the Pd source is critical for the success of this chemistry. $Pd(OAc)_2$ is superior to any other Pd catalyst so far tested. Only a 30% yield of the desired product was obtained using $Pd_2(dba)_3$ instead of $Pd(OAc)_2$ (entry 8), and only a trace of the desired product is obtained when $PdCl_2$ is used as the catalyst (entry 9). Similar observations have been made in other Pd(II)-catalyzed aerobic oxidation reactions run in DMSO.[8] Thus, the optimal, very simple, "baseless" procedure described in entry 5 has been employed for the synthesis of a wide variety of tetrasubstituted olefins.

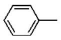
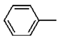
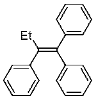
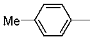
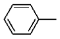
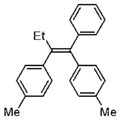
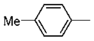
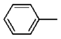
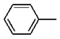
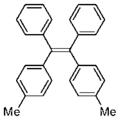
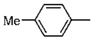
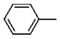
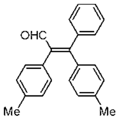
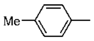
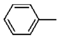
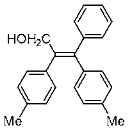
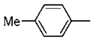
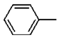
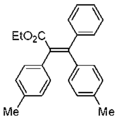
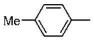
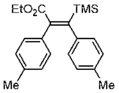
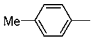
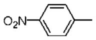
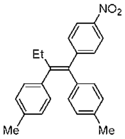
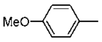
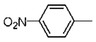
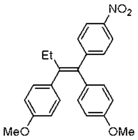
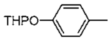
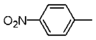
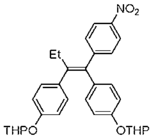
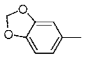
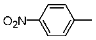
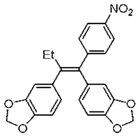
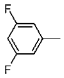
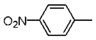
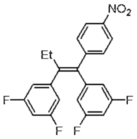
As indicated in Table 2, this approach to tetrasubstituted olefins is quite versatile. The reaction of *p*-tolylboronic acid and 1-phenyl-1-butyne provides a yield slightly higher than that of phenylboronic acid (compare entries 1 and 2). Using *p*-tolylboronic acid, a wide variety of internal alkynes has been screened (entries 3−8). Diphenylacetylene works quite well, although the reaction needs to be run at 50 °C (entry 3). Aldehyde-, alcohol-, ester-, and TMS-containing alkynes have also been successfully employed without protection, and the chemistry provides the desired tetrasubstituted olefins in good yields (entries 4−7). Unfortunately, electron-rich dialkylacetylenes, such as 4-octyne, have been unsuccessful in producing the desired tetrasubstituted olefins in good yield. A higher yield of the desired product is obtained with the introduction of an electron-withdrawing nitro group into the aromatic ring of 1-phenyl-1-butyne, which is consistent with our previous work on the synthesis of tetrasubstituted olefins.[4] Thus, an excellent 90% yield is obtained when 1-(4-nitrophenyl)-1-butyne is allowed to react with *p*-tolylboronic acid (entry 8). The reaction involves *cis*-addition to the alkyne of two aryl groups from the arylboronic acid. The structure of product **8** has been determined by investigating its NOESY H−H interactions (see Supporting Information). Using 1-(4-nitrophenyl)-1-butyne as the alkyne, a wide variety of arylboronic acids have been successfully employed in this process in good yields (entries 9−12). For example, an 88% yield of the desired product is obtained when *p*-methoxyphenylboronic acid is used (entry 9). Electron-rich acetal-containing arylboronic acids work quite well in this chemistry (entries 10 and 11). However, electron-poor 3,5-difluorophenylboronic acid gave a significantly lower yield of tetrasubstituted olefin (entry 12). Because the mild "baseless" reaction conditions tolerate many functional groups, including aldehyde, ketone, alcohol, ester, acetal, and

---

(8) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400 and references therein. (b) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, *2*, 218. (c) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (d) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (e) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298.

(9) For a review covering the use of molecular sieves in organic synthesis, see: De Vos, D. E.; Dams, M.; Sels, B. F.; Jacobs, P. A. *Chem. Rev.* **2002**, *102*, 3615.

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

| entry | Ar | $R^1$ | $R^2$ | temp (°C) | product | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  | Et |  | r.t. |  1 | 73 |
| 2 |  | Et |  | r.t. |  2 | 80 |
| 3 |  |  |  | 50 |  3 | 76 |
| 4 |  | CHO |  | 50 |  4 | 78 |
| 5 |  | $HOCH_2$ |  | 50 |  5 | 72 |
| 6 |  | $EtO_2C$ |  | 50 |  6 | 77 |
| 7 |  | $EtO_2C$ | TMS | 50 |  7 | 72 |
| 8 |  | Et |  | r.t. |  8 | 90 |
| 9 |  | Et |  | r.t. |  9 | 88 |
| 10 |  | Et |  | r.t. |  10 | 82 |
| 11 |  | Et |  | r.t. |  11 | 73 |
| 12 |  | Et |  | 50 |  12 | 53 |

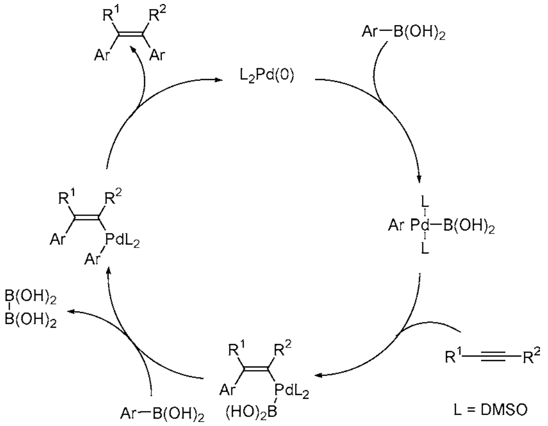
[a] The reaction employs 0.0125 mmol of $Pd(OAc)_2$, 1.25 mmol of arylboronic acid, 0.25 mmol of alkyne, and 0.2 g of 4 Å MS under an $O_2$ balloon in 2 mL of DMSO at the indicated temperature for 24 h. [b] The yields are based on products isolated by column chromatography.

TMS groups, this chemistry should be quite useful in the synthesis of highly functionalized tetrasubstituted olefins.

A possible mechanism for this process is illustrated in Scheme 1. It involves the following key steps: (1) transmetalation of the arylboronic acid by the $Pd(OAc)_2$ catalyst; (2) *cis*-carbopalladation of the internal alkyne by the resulting arylpalladium intermediate to generate a vinylic palladium intermediate; (3) transmetalation with another molecule of arylboronic acid; (4) reductive elimination producing the tetrasubstituted olefin with simultaneous generation of Pd(0); (5) DMSO-promoted formation of a peroxopalladium(II) species;[8c] and (6) regeneration of the $Pd(OAc)_2$ catalyst by protonation of the peroxo species.[8c] Regeneration of the Pd(II) catalyst by aerobic oxidation of Pd(0) is critical for completion of the catalytic cycle. The unique coordinating ability of DMSO could play an important role in facilitating the aerobic oxidation of Pd(0) to Pd(II).[8a,c] Thus, the presence of DMSO and molecular $O_2$ facilitates the reaction. Alternatively, the Pd-promoted homocoupling[10] of two molecules of boronic acid could occur, which would produce the biaryl side product observed.

Alternatively, a Pd(0)-catalyzed mechanism is also possible, as shown in Scheme 2. The key steps here would be (1) oxidative addition of the arylboronic acid to Pd(0), which generates an arylpalladium(II) species;[10e,11] (2) carbopalladation; (3) transmetalation to produce a B−B or perhaps a B−O bond; and (4) reductive elimination that might then occur in a fashion similar to that shown previously in Scheme 1. This would produce the tetrasubstituted olefin and regenerate the Pd(0) catalyst. The mechanism shown in Scheme 1 would appear to be more favorable since there appears to be no precedent for the formation of such B−B or B−O bonds and the fact that the presence of DMSO and $O_2$ greatly facilitates the reaction. However, we cannot completely rule out the mechanism shown in Scheme 2, especially when a fair amount of the desired product is observed even under an $N_2$ atmosphere (entry 7, Table 1). It is possible that both mechanisms operate in this reaction system.

**Scheme 2**



In summary, a novel Pd-catalyzed reaction between an arylboronic acid and an internal alkyne has been successfully developed. A wide variety of tetrasubstituted olefins have been obtained in good to excellent yields by this simple process. The mild, “baseless” reaction conditions tolerate many functional groups, including aldehyde, ketone, alcohol, ester, TMS, and acetal groups. We believe this chemistry should be quite useful in the synthesis of highly functionalized tetrasubstituted olefins.

**Acknowledgment.** Partial financial support from the National Science Foundation and the Petroleum Research Fund administered by American Chemical Society are gratefully acknowledged. We also acknowledge Johnson Matthey, Inc. and Kawaken Fine Chemicals Co. Ltd. for providing the palladium compounds and Frontier Scientific Co. for the arylboronic acids.

**Supporting Information Available:** Reaction procedures, product characterization data, $^1H$ and $^{13}C$ NMR spectra for compounds **1**−**12**, and COSEY and NOESY spectra for compound **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047759Q

---

(10) (a) Miyaura, N.; Suzuki, A. *Main Group Met. Chem.* **1987**, *10*, 295. (b) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2393. (c) Gillmann, T.; Weeber, T. *Synlett* **1994**, 649. (d) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33. (e) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346. (f) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087. (g) Koza, D. J.; Carita, E. *Synthesis* **2002**, 2183. (h) Falck, J. R.; Mohapatra, S.; Bondlela, M.; Venkataraman, S. K. *Tetrahedron Lett.* **2002**, *43*, 8149. (i) Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525. (j) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541.

(11) Cho, C.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85.