JOC Article

Tetrasubstituted Olefin Synthesis via Pd-Catalyzed Addition of Arylboronic Acids to Internal Alkynes Using O_2 as an Oxidant

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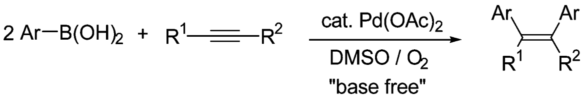
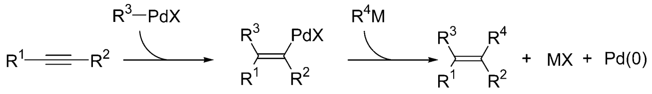


The Pd(II)-catalyzed reaction of arylboronic acids and internal alkynes provides a convenient route to a wide variety of tetrasubstituted olefins. The reaction is conducted in DMSO using molecular O_2 as an oxidant in the absence of any base. The reaction involves the cis addition of two aryl groups from the arylboronic acid to opposite ends of the triple bond of the internal alkyne. The synthesis tolerates a wide variety of functional groups, including alcohol, aldehyde, ester, TMS, and acetal groups. Electron-rich dialkylacetylenes, such as 4-octyne, provide highly substituted 1,3-dienes in moderate yields. The very mild O_2/DMSO conditions also afford good to excellent yields of biaryls by the homocoupling of arylboronic acids.

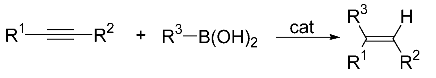
Introduction

The regio- and stereoselective synthesis of tetrasubstituted olefins has provided a challenge to synthetic organic chemists for years.[1] 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. For example, the carbopalladation of alkynes has provided a versatile approach to various heterocycles, carbocycles, and highly substituted olefins.[2] The vinylic palladium intermediate generated by the carbopalladation of an alkyne can be trapped by various reagents leading to highly substituted olefins (Scheme 1). 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] We have also 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.[1f,4]

SCHEME 1



The late transition-metal-catalyzed addition of arylboronic acids to unsaturated substrates has emerged as an effective method for the synthesis of highly substituted olefins. For example, Rh-,[5] Ni-,[6] or Pd-catalyzed[7] additions of arylboronic acids to alkynes have been reported to produce di- or trisubstituted olefins (eq 1).



(1)

Using a stoichiometric amount of Ag_2CO_3 as an oxidant, an efficient synthesis of highly substituted 1,3-butadienes has been

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[1] For recent representative examples, see: (a) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840. (b) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (c) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003**, *68*, 6066. (d) Liu, X.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 879. (e) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778. (f) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765 and references therein. (g) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506.

[2] (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.

[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.

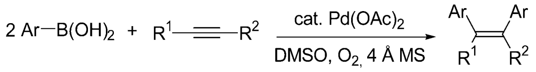
10.1021/jo060104d CCC: $33.50

TABLE 1. Optimization Studies (Eq 3)[a]

entry	DMSO/THF/H_2O	catalyst	oxidant	4-Å MS	time (h)	yield of **1**[b] (%)	biphenyl[c] (mmol)
1	0/100/0	5% $Pd(OAc)_2$	air	No	48	trace	trace
2	20/80/0	5% $Pd(OAc)_2$	air	No	48	36	0.12
3	50/50/0	5% $Pd(OAc)_2$	air	No	48	51	0.15
4	80/20/0	5% $Pd(OAc)_2$	air	No	48	55	0.22
5	100/0/0	5% $Pd(OAc)_2$	air	No	48	60 (55)	0.25
6	100/0/0	5% $Pd(OAc)_2$	O_2	No	24	65 (59)	0.32
7	**100/0/0**	**5% $Pd(OAc)_2$**	**O_2**	**Yes**	**24**	**80 (73)**	**0.33**
8	80/0/20	5% $Pd(OAc)_2$	O_2	No	24	73	0.31
9	66/0/34	5% $Pd(OAc)_2$	O_2	No	24	75 (70)	0.32
10	50/0/50	5% $Pd(OAc)_2$	O_2	No	24	52	0.26
11	20/0/80	5% $Pd(OAc)_2$	O_2	No	24	20	0.08
12[d]	100/0/0	5% $Pd(OAc)_2$	O_2	Yes	24	42	0.35
13[e]	100/0/0	5% $Pd(OAc)_2$	O_2	Yes	24	35	0.33
14[f]	100/0/0	5% $Pd(OAc)_2$	O_2	Yes	24	trace	0.07
15	100/0/0	5% $Pd(OAc)_2$	No[g]	Yes	24	25	0.10
16	100/0/0	5% $Pd_2(dba)_3$	O_2	Yes	24	30	0.12
17	100/0/0	5% $Pd(PPh_3)_4$	O_2	Yes	24	< 10	0.06
18	100/0/0	5% $PdCl_2(PPh_3)_2$	O_2	Yes	24	trace	trace
19	100/0/0	5% $PdCl_2$	O_2	Yes	24	trace	trace
20[h]	100/0/0	5% $Pd(OAc)_2$	O_2	Yes	24	50	0.13

[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] KOAc in the amount of 1 equiv was added. [e] K_2CO_3 in the amount of 1 equiv was added. [f] 4,4,5,5-Tetramethyl-2-phenyl-1,3,2-dioxaborolane in the amount of 1.25 mmol was employed instead of phenylboronic acid. [g] The reaction was run under N_2. [h] Phenylboronic acid in the amount of 0.5 mmol was employed.

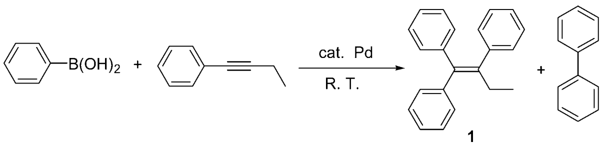
developed by Miura et al. by the Pd-catalyzed reaction of arylboronic acids and internal alkynes.[8] The economic and environmental advantages of molecular oxygen as a chemical oxidant are apparent, and the selective Pd-mediated aerobic oxidation of organic molecules has provided many significant advances in recent years.[9] Recently, we communicated preliminary results on the synthesis of tetrasubstituted olefins by the Pd-catalyzed addition of two aryl groups from an arylboronic acid to internal alkynes using O_2 as the oxidant (eq 2).[10] Herein, we wish to provide a full account of the scope and limitations of this chemistry. Noteworthy is the observation that highly substituted 1,3-dienes can be obtained as the product when an electron-rich alkyne, like 4-octyne, is employed. The very mild O_2/DMSO conditions also afford various biaryls in good to excellent yields by the homocoupling of arylboronic acids.



(2)

Results and Discussion

Optimization of the Tetrasubstituted Olefin Synthesis. We first examined the reaction of phenylboronic acid and 1-phenyl-1-butyne in THF in the presence of 5 mol % of $Pd(OAc)_2$, using air as the oxidant (eq 3). However, only a trace of the desired tetrasubstituted olefin was obtained (Table 1, entry 1).



(3)

To our delight, using DMSO as a co-solvent greatly increased the yield. The desired tetrasubstituted olefin was obtained in a 36% yield when 5 equiv of phenylboronic acid and 1 equiv of 1-phenyl-1-butyne were employed in 20:80 DMSO/THF, using air as an oxidant at room temperature for 48 h (entry 2). The tetrasubstituted olefin was obtained in higher yields when more DMSO was employed as the solvent (entries 2−5). A 60% yield was obtained using only DMSO as the solvent (entry 5). This $Pd(OAc)_2$/DMSO system has proven to be quite useful in aerobic oxidation reactions.[9] The unique coordinating ability of DMSO could play an important role in facilitating the aerobic oxidation of Pd(0) to Pd(II), thus completing the catalytic cycle (see the later mechanistic discussion). The reaction proceeds faster using O_2 as the oxidant, and a 65% yield is obtained in 24 h (entry 6). Adding 4-Å molecular sieves (MS, 4 Å, 0.2 g for a 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 7). The role of the MS is not clear. We first speculated that MS absorb the water in the system, which facilitates the catalytic cycle. If so, adding water to the reaction system should affect the catalytic cycle and a lower conversion of the alkyne to product would be expected. However, the reaction proceeds well when some water is added. In fact, a slightly higher yield was obtained using an 80:20 or 66:34 DMSO/H_2O co-solvent than was obtained in pure DMSO

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

(7) (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. For an example involving the formation of a highly substituted cyclopentadiene, see: (c) Du, X.; Suguro, M.; Hirabayashi, K.; Mori A. *Org. Lett.* **2001**, *3*, 3313.

(8) Satoh, T.; Ogino, S.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5063.

(9) (a) Stahl, S. S. *Science* **2005**, *309*, 1824. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400 and references therein. (c) Steinhoff, B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 11268. (d) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 353. (e) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724. (f) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, 218. (g) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (h) Brink, G.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636. (i) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (j) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298.

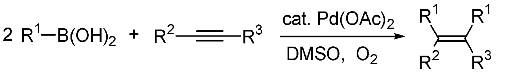
(10) Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, *7*, 259.

(compare entries 8, 9, and 6). Only when a 1:1 mixture of DMSO and H_2O was employed did the yield actually drop below the yield observed when using pure DMSO (entry 10). A solvent consisting of 1:4 DMSO/H_2O provided only a 20% yield (entry 11). The lower yields possibly arise from solubility problems with the organic substrates in such aqueous solvent systems. The presence of a base is known to facilitate the homocoupling of vinylic and arylboronic acids.[11,12] However, adding a base suppresses formation of the tetrasubstituted olefin (entries 12 and 13). Only a 42% yield was obtained when 1 equiv of KOAc was employed as the base (entry 12), and the addition of K_2CO_3 afforded an even lower yield (entry 13). Only a trace of the desired tetrasubstituted olefin was obtained when an arylboronic ester, 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane, was used instead of phenylboronic acid (entry 14). Without the molecular O_2 oxidant, the reaction is sluggish (entry 15).

Like other Pd(II)-catalyzed aerobic oxidation reactions,[9] the Pd source is critical for the success of this chemistry. $Pd(OAc)_2$ is superior to any other Pd catalyst so far tested. Much lower yields of the desired product were obtained using $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ (entries 16 and 17). The presence of chloride ion greatly suppresses the reaction, and only a trace of the desired product was obtained when $PdCl_2(PPh_3)_2$ or $PdCl_2$ was used as the catalyst (entries 18 and 19). Similar observations have been made in other Pd(II)-catalyzed aerobic oxidation reactions run in DMSO.[9]

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] additions of arylboronic acids to internal alkynes. A 50% yield of the desired tetrasubstituted olefin was obtained when only 2 equiv of phenylboronic acid was employed (entry 20). Thus, the optimal, very simple, “base free” procedure described in entry 7 of Table 1 has been chosen as our “optimal” procedure and employed for the synthesis of a wide variety of tetrasubstituted olefins.[13]

Scope and Limitations. As indicated in Table 2, this approach to tetrasubstituted olefins is quite versatile (eq 4). The reaction proceeds well using 1-phenyl-1-propyne or 1-phenyl-1-hexyne (entries 2 and 3).



(4)

The reaction of *p*-tolylboronic acid and 1-phenyl-1-butyne provides a slightly higher yield than that of phenylboronic acid (compare entries 1 and 4). When *p*-tolylboronic acid is used, a wide variety of internal alkynes have been screened (entries 5−17). 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 6−12). When the acetal-containing phenylpropynal diethyl acetal was employed, the desired tetrasubstituted acetal-containing olefin was initially formed as observed by GC-MS. However, the acetal-containing olefin was not stable on silica gel, and the corresponding aldehyde **7** was obtained in an 80% yield after column chromatography (entry 8). The electron-rich and sterically bulky alkynes 1-trimethylsilyl-1-propyne and 4,4-dimethyl-2-pentyne failed to produce any of the desired tetrasubstituted olefins (entries 13 and 14). The terminal alkyne, phenylacetylene, fails to provide the desired trisubstituted product, possibly as a result of multiple insertions of the alkyne leading to oligomerization (entry 15). The relatively electron-poor diethyl acetylenedicarboxylate has been successfully employed, producing the desired olefin in a 55% yield (entry 16). The relatively electron-poor and sterically hindered alkyne 3-phenyl-1-(2,4,5-trimethoxyphenyl)propynone produced the desired olefin **13** in a 66% yield (entry 17). 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 (compare entries 18 and 1). Thus, an excellent 90% yield is obtained when 1-(4-nitrophenyl)-1-butyne is allowed to react with *p*-tolylboronic acid (entry 18). This reaction involves the clean cis addition of the two aryl groups from the arylboronic acid to the alkyne. The structure of product **14** has been determined by examining its NOESY H−H interactions.[14]

When 1-(4-nitrophenyl)-1-butyne is used as the alkyne, a wide variety of arylboronic acids have been successfully employed in this process. Electron-rich and electron−neutral arylboronic acids work quite well in this chemistry and afford the desired tetrasubstituted olefins in good yields (entries 18−24). It is noteworthy that acetal-containing arylboronic acids work quite well, and the desired acetal-containing tetrasubstituted olefins have been obtained in good yields (entries 20 and 21). However, electron-poor arylboronic acids afford significantly lower yields of the tetrasubstituted olefins. Only a 53% yield of the desired tetrasubstituted olefin was obtained when 3,5-difluorophenylboronic acid was employed (entry 25). None of the desired tetrasubstituted olefin was observed when 4-nitrophenylboronic acid was utilized (entry 26). Relatively low yields were obtained when the sterically hindered arylboronic acids 2-methylphenylboronic acid and 2-methoxyphenylboronic acid were employed (entries 27 and 28). When *E*-2-phenylvinylboronic acid was utilized, only a complex mixture was obtained after column chromatography, possibly because the triene product is not stable and decomposes (entry 29). None of the desired product was observed when 2-thienylboronic acid was employed (entry 30). It is interesting that no 2,2′-bithiophene side product was observed either. It is quite possible that the stable S-chelating vinylpalladium intermediate forms, tying up the palladium catalyst and killing the reaction.

Only a trace of the desired tetrasubstituted olefin is observed from the GC-MS analysis of the crude products when electron-rich dialkylacetylenes, like 4-octyne, are employed. A highly substituted 1,3-diene formed from 2 equiv of boronic acid and 2 equiv of alkyne was obtained instead. Both electron-rich and electron-poor arylboronic acids afford analogous 1,3-dienes in

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[11] For the homocoupling of boronic acids or esters in the presence of a base, see: (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. (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.

[12] For the homocoupling of boronic acids or esters in the absence of a base, see: (a) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346. (b) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541.

[13] Entry 7 was chosen as the “optimal” conditions for exploring the scope of this chemistry because of the convenience of product purification. However, the stoichiometry is not necessarily the best stoichiometry from an atom-economical view. Considering the availability of the starting alkynes and boronic acids, one can certainly run the reaction using other stoichiometries for better use of all reagents.

[14] See Supporting Information in ref 10 for detailed information.

TABLE 2. Synthesis of Tetrasubstituted Olefins (Eq 4)[a]

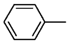
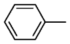
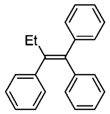
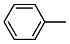
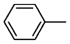
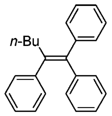
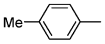
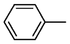
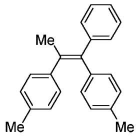
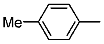
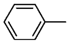
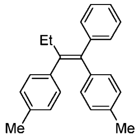
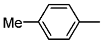
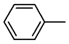
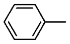
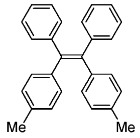
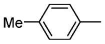
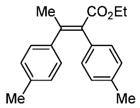
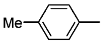
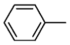
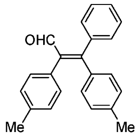
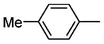
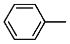
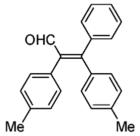
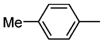
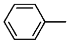
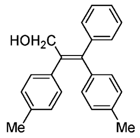
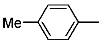
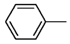
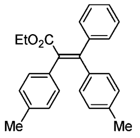
entry	R^1	R^2	R^3	temp. (°C)	product		yield[b] (%)
1		Et		r.t.		**1**	73
2		*n*-Bu		r.t.		**2**	71
3		Me		r.t.		**3**	81
4		Et		r.t.		**4**	80
5				50		**5**	76
6	Me	Me	CO_2Et	50		**6**	66
7		CHO		50		**7**	78
8		$(EtO)_2CH$		50		**7**	80
9		$HOCH_2$		50		**8**	72
10		EtO_2C		50		**9**	77

Table 2. (Continued)[a]

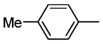
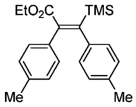
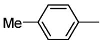
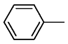
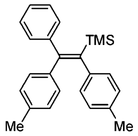
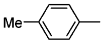
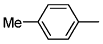
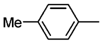
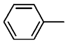
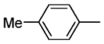
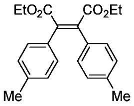
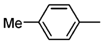
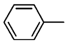
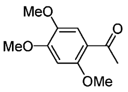
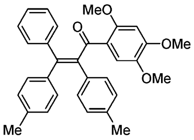
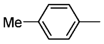
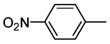
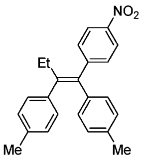
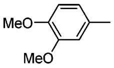
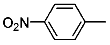
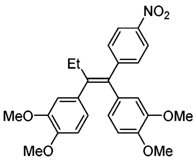
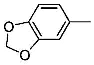
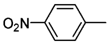
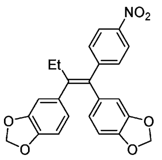
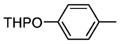
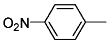
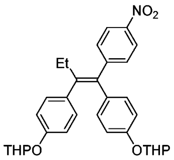
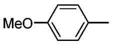
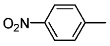
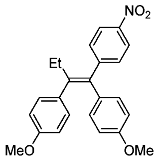
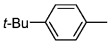
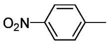
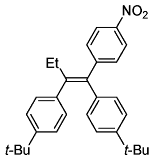
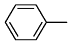
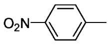
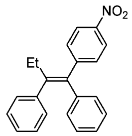
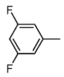
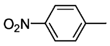
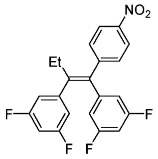
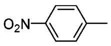
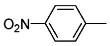
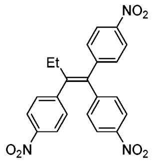
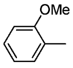
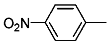
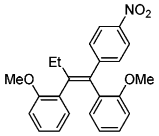
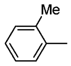
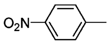
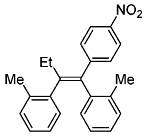
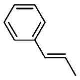
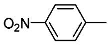
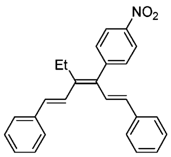
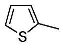
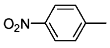
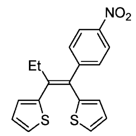
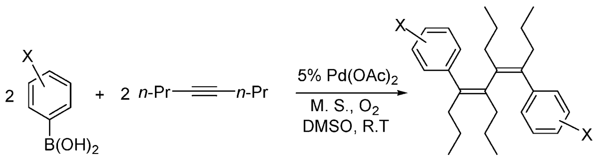
entry	R^1	R^2	R^3	temp. (°C)	product	yield[b] (%)
11		EtO_2C	TMS	50	 **10**	72
12			TMS	50	 **11**	70
13		CH_3	TMS	50	——	0
14		CH_3	*t*-Bu	r.t.	——	0
15		H		r.t.	——	–[c]
16		CO_2Et	CO_2Et	50	 **12**	55
17				50	 **13**	66
18		Et		r.t.	 **14**	90
19		Et		r.t.	 **15**	80
20		Et		r.t.	 **16**	73
21		Et		r.t.	 **17**	82

Table 2. (Continued)

entry	R^1	R^2	R^3	temp. (°C)	product	yield[b] (%)
22		Et		r.t.	 **18**	88
23		Et		r.t.	 **19**	82
24		Et		r.t.	 **20**	86
25		Et		50	 **21**	53
26		Et		r.t.	 **22**	0
27		Et		50	 **23**	61
28		Et		50	 **24**	50
29		Et		50	 **25**	–[c]
30		Et		50	 **26**	0

[a] All reactions were run employing 0.0125 mmol of $Pd(OAc)_2$, 1.25 mmol of boronic acid, 0.25 mmol of the 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. [c] A complex mixture is obtained after column chromatography.

moderate yields (eq 5). In fact, the electron-poor 3-nitrophenylboronic acid affords a slightly higher yield than the electron-rich 4-methoxyphenylboronic acid (compare entries a and e in eq 5). The reason for the formation of such 2:2 adducts is not clear. It is possible that the carbopalladation of 4-octyne is more facile due to its electron-rich nature and steric accessibility (see the later mechanistic discussion).

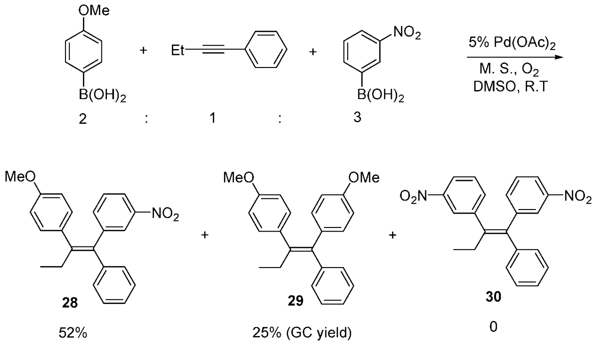


(5)

27a-e

	X	% yield
(**a**)	4-OMe	48
(**b**)	4-Me	50
(**c**)	H	52
(**d**)	4-CO$_2$Me	58
(**e**)	3-NO$_2$	63

To prepare an unsymmetrical tetrasubstituted olefin through the addition of two different groups to an internal alkyne, we have examined a three-component reaction employing electron-rich *p*-methoxyphenylboronic acid, 1-phenyl-1-butyne, and electron-poor *m*-nitrophenylboronic acid (eq 6). We were pleased to obtain the desired unsymmetrical tetrasubstituted olefin **28** in a 52% yield. The symmetrical tetrasubstituted olefin (*Z*)-1,2-di-(4-methoxyphenyl)-1-phenyl-1-butene (**29**) was also obtained in a 25% yield, but none of the dinitrophenyl-containing olefin **30** was observed. These results suggest that the three-component reaction proceeds through the methoxyphenyl-containing vinylpalladium intermediate **31** and not the nitrophenyl-containing vinylpalladium intermediate **32** (Figure 1). It is possible that the vinylpalladium intermediate **31** is more stable than **32**, because the neighboring electron-rich methoxyphenyl group can coordinate with the Pd moiety in the vinylic intermediate **31** more readily and, therefore, stabilizes the vinylic Pd intermediate more than the electron-poor nitrophenyl group stabilizes intermediate **32**. A similar observation has been made in our previous tetrasubstituted olefin synthesis.[1f]

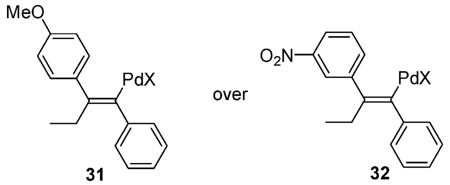


(6)

Homocoupling of Boronic Acids.

$$2\ \mathrm{R{-}B(OH)_2} \xrightarrow[\mathrm{DMSO,\ O_2}]{5\%\ \mathrm{Pd(OAc)_2}} \mathrm{R{-}R} \tag{7}$$

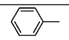
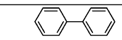
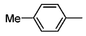
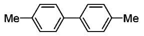
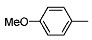
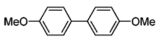
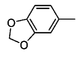
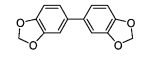
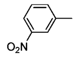
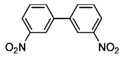
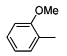
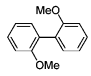
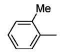
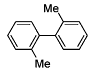
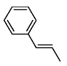
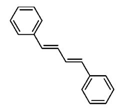
During our tetrasubstituted olefin syntheses, a fair amount of biaryl side product is usually obtained. The aerobic oxidative homocoupling of arylboronic acids, using DMSO as the solvent in the absence of either a base or a phosphine ligand, is unprecedented.[11,12] We were pleased to find that this homocoupling reaction is quite general under our very mild reaction conditions (eq 7, Table 3). Electron-neutral (entry 1), electron-rich (entries 2−4), electron-poor (entry 5), and sterically hindered (entries 6 and 7) arylboronic acids, as well as a vinylboronic acid (entry 8), all afford the desired biaryl or diene products in good to excellent yields. We believe that these mild reaction conditions provide a useful route to some base-sensitive symmetrical biaryls, which might not be easily prepared using previous procedures.



31 **32**

FIGURE 1. Possible intermediates.

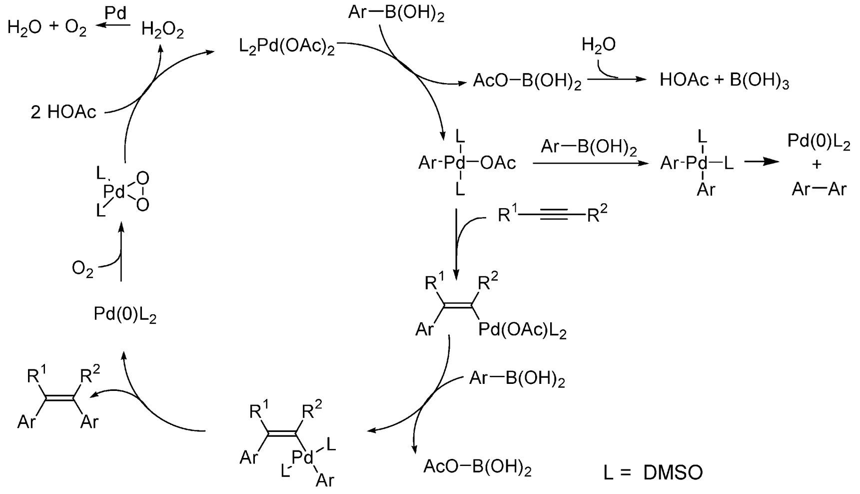
TABLE 3. Homocoupling of Boronic Acids Using Pd(OAc)$_2$/DMSO/O$_2$[a]

entry	temp. (°C)	R	product	% yield[b]
1	r.t.			88
2	r.t.			90
3	r.t.			86
4	r.t.			80
5	r.t.			81
6	50			76
7	50			72
8	50			79

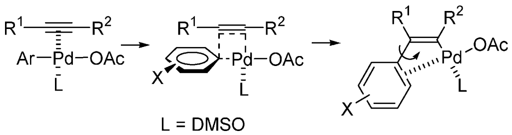
[a] All reactions were run employing 0.05 mmol of Pd(OAc)$_2$, 1.0 mmol of boronic acid, and 0.2 g of 4-Å MS under an O$_2$ balloon in 2 mL of DMSO at the indicated temperature for 24 h. [b] The yields are based on products isolated by column chromatography.

Reaction Mechanism. We propose the mechanism illustrated in Scheme 2 for our tetrasubstituted olefin synthesis. This process appears to involve 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 the simultaneous generation of Pd(0); (5) DMSO-promoted formation of a peroxopalladium(II) species;[9f] and (6) regeneration of the Pd(OAc)$_2$ catalyst by protonation of the peroxo species.[9] Alternatively, the Pd-promoted homocoupling of two molecules of boronic acid could occur, as shown in Scheme 2, which would produce the biaryl side product often observed.

SCHEME 2. Proposed Mechanism



SCHEME 3. Carbopalladation of Alkyne



Carbopalladation of the internal alkyne by the arylpalladium intermediate, $ArPd(OAc)L_2$ in Scheme 2, is the key step in the catalytic cycle. This step presumably proceeds through a four-membered ring transition state in which the aromatic ring and the Pd in $ArPd(OAc)L_2$ are positioned on the same side of the internal alkyne (Scheme 3).[15] Thus, carbopalladation generates a vinylic palladium species by a cis addition to the alkyne. When the electron-poor 4-nitrophenylboronic acid is utilized, the carbopalladation process is less favorable compared with the transmetalation process, which leads to the homocoupling of the boronic acid. As a result, none of the desired tetrasubstituted olefin is obtained (Table 2, entry 26).

The regeneration of the Pd(II) catalyst by aerobic oxidation of Pd(0) is critical for the 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).[9] Thus, the presence of DMSO and molecular O_2 greatly facilitates the reaction.

When the electron-rich dialkylacetylene 4-octyne was employed, a 2:2 adduct, a 1,3-diene, was obtained, and only a trace of the normal tetrasubstituted olefin 1:2 adduct was observed. Analogous products resulted from the di-insertion of the alkyne, which has also been obtained in our previous tetrasubstituted olefin synthesis employing the same alkyne.[1f] Due to the electron-rich nature and steric accessibility of 4-octyne, the carbopalladation of two alkynes may be facile, leading to a relatively stable vinylpalladium intermediate after the insertion of 2 molecules of alkyne. Although less likely, it is also possible that the initial arylpalladium intermediate is coordinated to two molecules of 4-octyne and, thus, carbopalladation involves a cascade addition of the arylpalladium to the two alkynes, leading to the 2:2 adducts.

Conclusions

A novel Pd-catalyzed addition of arylboronic acids to internal alkynes is described, which provides a wide variety of tetrasubstituted olefins. The reaction is conducted in DMSO using molecular O_2 as an oxidant in the absence of any added base. The reaction involves the cis addition of two aryl groups from the arylboronic acid to opposite ends of the triple bond of the internal alkyne. The synthesis tolerates a wide variety of functional groups, including alcohol, aldehyde, ester, TMS, and acetal groups. The synthesis of an unsymmetrical tetrasubstituted olefin is demonstrated through the addition of two electronically differentiated arylboronic acids to an internal alkyne. The reaction of electron-rich and electron-poor arylboronic acids and an electron-rich dialkylacetylene, 4-octyne, provides highly substituted 1,3-dienes in moderate yield. The very mild O_2/DMSO reaction conditions also afford biaryls and 1,3-dienes in good to excellent yields by the homocoupling of aryl and vinylboronic acids.

Experimental Section

General Procedure for the Synthesis of Tetrasubstituted Olefins (Table 2 and Eq 5). $Pd(OAc)_2$ (0.0125 mmol), the internal alkyne (0.25 mmol), the arylboronic acid (1.25 mmol), MS (Fisher Chemicals, type 4 Å, grade 514, 8−12 mesh, beads, 0.2 g), and DMSO (2 mL) were placed in a 6-dram vial. The vial was sealed with a septum, degassed, and equipped with an O_2 balloon. The contents were stirred at room temperature or at 50 °C for 24 h. The reaction mixture was quenched with 20 mL of saturated NaCl solution. The resulting mixture was extracted three times with ethyl ether (30 mL each time). 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.

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Supporting Information Available: Experimental details and product characterization data, ^1H and ^{13}C NMR spectra for compounds **6**, **11**, **12**, **13**, **15**, **19**, **20**, **23**, **24**, **27a**, **27d**, **27e**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] The cis addition of arylpalladium intermediates to internal alkynes is generally observed in carbopalladation processes. For representative reviews of carbopalladation, see ref 2b,c and: (a) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1453. (b) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (c) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42.