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Palladium/Phosphite-Catalyzed 1,4-Addition of Arylboronic Acids to Acrylic Acid Derivatives

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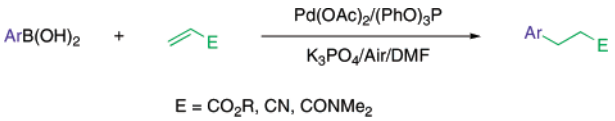
Received November 28, 2007



1,4-Addition of arylboronic acids to acrylic acid derivatives proceeds efficiently in the presence of a palladium catalyst system of $Pd(OAc)_2/(PhO)_3P$ to produce the corresponding 3-arylpropionic acid derivatives. The use of the phosphite ligand is the key to conducting the addition smoothly with suppressing the competing Mizoroki−Heck-type oxidative coupling.

The transition metal-catalyzed 1,4-conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a powerful tool for C−C bond formation. Among the various reagents, organoboron compounds are highly useful due to their commercial availability, stability, and low toxicity.[1] Since Miyaura and co-workers reported the rhodium-catalyzed 1,4-addition of arylboronic acids to enones as pioneering work,[2] the conjugate arylation has been widely developed.[3] Meanwhile, the palladium-catalyzed version has been less explored, probably due to the fact that a Mizoroki−Heck-type oxidative coupling (MH coupling)[4] takes place often competitively. Recently, several catalyst systems including $Pd^0/SbCl_3$,[5] cationic Pd^{II},[6] Pd^{II}/bipyridine,[7] $Pd^0/CHCl_3$,[8] and palladacycles,[9] which selectively promote the 1,4-addition in preference to MH coupling, have been reported. However, in most cases using such catalyst systems, substrates are limited to enones and enals, and α,β-unsaturated esters are usually converted to MH coupling products predominantly.[6a,b,d] Exceptionally, it has been reported that a Pd^{II}/bipyridine catalyst allows the 1,4-addition of some crotonates and cinnamates,[7] but there has been, to our knowledge, no selective example for the palladium-catalyzed 1,4-addition of arylboronic acids to more simple esters, β-unsubstituted acrylates, to form 3-arylpropionic acid derivatives.

3-Arylpropionic acids and their derivatives are useful building blocks in organic synthesis[10] and known to exhibit interesting biological activities.[11] During our continuous study of transition metal-catalyzed arylation of unsaturated compounds using arylboron reagents,[12] we observed a notable ligand effect in the palladium-catalyzed reaction of arylboronic acids with acrylates that the use of triphenyl phosphite can suppress MH coupling to give the corresponding 3-arylpropionates selectively. We report herein the results for the arylation of acrylate esters and related compounds.

When phenylboronic acid (**1a**) (1.2 mmol) was treated with *n*-butyl acrylate (**2a**) (1 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol) and Na_2CO_3 (2 mmol) as catalyst and base, respectively, in DMF (5 mL) at room temperature under air, the oxidative MH coupling proceeded catalytically to produce *n*-butyl cinnamate (**4a**) in 59% yield (Table 1, entry 1). A small amount of biphenyl (**5a**) was also formed as the oxidative homocoupling product of **1a**,[13] but no 1,4-adduct, *n*-butyl 3-phenylpropionate

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(11) For example, see: (a) Andersson, K.; Boije, M.; Gottfries, J.; Inghardt, T.; Li, L.; Lindstedt, A. E.-L. PCT Int. Appl. 1999, WO9962871. (b) Yan, L.; Huo, P.; Doherty, G.; Toth, L.; Hale, J. J.; Mills, S. G.; Hajdu, R.; Keohane, C. A.; Rosenbach, M. J.; Milligan, J. A.; Shei, G.-J.; Chrebet, G.; Bergstrom, J.; Card, D.; Quackenbush, E.; Wickham, A.; Mandala, S. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3679.

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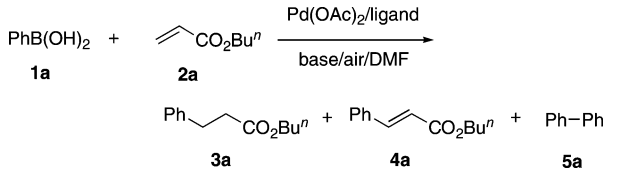
10.1021/jo702546t CCC: $40.75
Published on Web 01/15/2008

TABLE 1. Reaction of Phenylboronic Acid (1a) with *n*-Butyl Acrylate (2a)[a]



entry	ligand	base	temp (°C)	time (h)	yield (%)[b] 3a	yield (%)[b] 4a	5a (mmol)
1		Na_2CO_3	rt	48	tr	59 (58)	0.06
2		K_3PO_4	rt	48	tr	5	0.07
3		K_3PO_4	100	3	tr	26	0.24
4	$(PhO)_3P$	K_3PO_4	100	1	93 (79)	tr	0.02
5	$(PhO)_3P$	Na_2CO_3	100	6	60	14	0.04
6	$(PhO)_3P$	K_2CO_3	100	1	76	8	0.03
7	$(PhO)_3P$	Cs_2CO_3	100	1	89	tr	0.02
8	$(PhO)_3P$	KF	100	1	39	16	tr
9	$(PhO)_3P$		100	1	3	5	tr
10[c]	$(PhO)_3P$	K_3PO_4	100	1	29	tr	0.02
11	$[(2\text{-}MeC_6H_4)O]_3P$	K_3PO_4	100	1	92	tr	0.05
12	$[(4\text{-}MeC_6H_4)O]_3P$	K_3PO_4	100	1	85	tr	0.03
13	$(EtO)_3P$	K_3PO_4	100	3	tr	29	0.25
14	$(PhO)_3P$	K_3PO_4	80	1	93	tr	0.02
15	L[d]	K_3PO_4	80	1	61	9	0.08
16	$(PhO)_3P$	K_3PO_4	50	3	90	tr	0.04
17	$(PhO)_3P$	K_3PO_4	rt	36	83	4	0.08

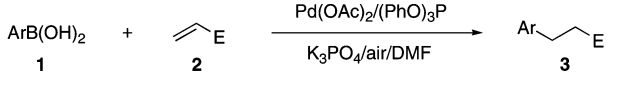
[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), ligand (0.05 mmol), base (2 mmol) in DMF (5 mL) under air. [b] GC yield based on the amount of **2a** used. The value in parentheses indicates isolated yield. [c] Under N_2. [d] L = $[(2,4\text{-}Bu_2{}^tC_6H_3)O]_3P$.

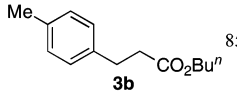
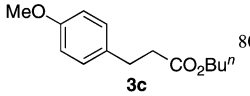
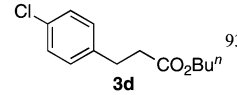
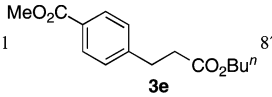
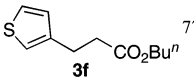
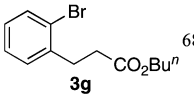
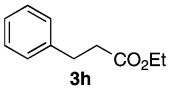
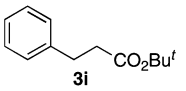
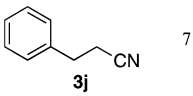
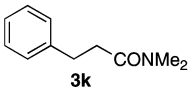
(**3a**), was detected. While K_3PO_4 was less effective as base for the MH coupling (entry 2), **4a** was formed in 26% yield at 100 °C (entry 3). Surprisingly, the addition of $(PhO)_3P$ (0.05 mmol) changed the direction of the reaction completely. Thus, with $(PhO)_3P$ and K_3PO_4, the 1,4-addition of **1a** to **2a** took place efficiently even under air to selectively afford **3a** in 93% yield within 1 h (entry 4). Among a number of bases examined (entries 4−8), K_3PO_4 gave the best result. Without any base, the reaction did not proceed catalytically (entry 9). Unlike the MH coupling, the 1,4-addition needs no oxidant in principle. However, substitution of atmosphere from air to N_2 significantly decreased the yield of **3a** (entry 10). While other triaryl phosphites such as $[(2\text{-}MeC_6H_4)O]_3P$ and $[(4\text{-}MeC_6H_4)O]_3P$ worked as well as $(PhO)_3P$, $(EtO)_3P$ did not show any positive effect (entries 11−13). At lower temperatures, the high yield production of **3a** could be attained by elongation of reaction time (entries 14 and 16−17). Thus, **3a** was obtained in 83% yield even at room temperature after 36 h, along with minor amounts of **4a** and **5a** (entry 17).

Table 2 summarizes results for the reaction using a number of arylboronic acids **1b**−**g** with acrylic acid derivatives **2a**−**e**. In the presence of the catalyst system of $Pd(OAc)_2/(PhO)_3P$ with K_3PO_4 as base, electron-rich (**1b**,**c**,**f**) and -deficient arylboronic acids (**1d**,**e**,**g**) reacted with **2a** smoothly to give the corresponding *n*-butyl 3-arylpropionates **3b**−**g** in satisfactory yields (entries 1−6). The bromo group in **1g** was tolerable under the conditions. Other alkenes such as ethyl and *tert*-butyl acrylates (**2b**,**c**), acrylonitrile (**2d**), and *N*,*N*-dimethylacrylamide (**2e**) also underwent the reaction with **1a** to form conjugate arylation products **3h**−**k** (entries 7−10).

The present reaction may be initiated by transmetalation of a divalent palladium precursor with an arylboronic acid **1** to form an arylpalladium intermediate **A** (Scheme 1). This

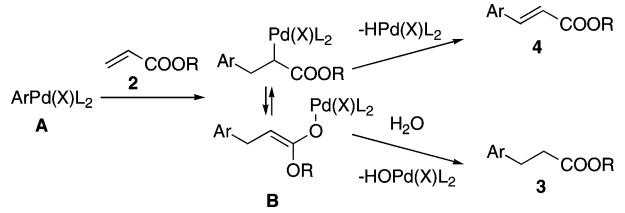
TABLE 2. Reaction of Arylboronic Acids 1 with Acrylic Acid Derivatives 2[a]



entry	1	Ar	2	E	time (h)	product	yield (%)[b]
1	**1b**	$4\text{-}MeC_6H_4$	**2a**	CO_2Bu^n	1	 **3b**	85 (84)
2	**1c**	$4\text{-}MeOC_6H_4$	**2a**	CO_2Bu^n	1	 **3c**	80 (70)
3	**1d**	$4\text{-}ClC_6H_4$	**2a**	CO_2Bu^n	1	 **3d**	93 (84)
4	**1e**	$4\text{-}(MeO_2C)C_6H_4$	**2a**	CO_2Bu^n	1	 **3e**	87 (82)
5	**1f**	3-thienyl	**2a**	CO_2Bu^n	1	 **3f**	77 (68)
6	**1g**	$2\text{-}BrC_6H_4$	**2a**	CO_2Bu^n	3	 **3g**	68 (57)
7	**1a**	Ph	**2b**	CO_2Et	1	 **3h**	(82)
8	**1a**	Ph	**2c**	CO_2Bu^t	1	 **3i**	(80)
9[c]	**1a**	Ph	**2d**	CN	1	 **3j**	71 (62)
10	**1a**	Ph	**2e**	$CONMe_2$	3	 **3k**	(68)

[a] Reaction conditions: **1** (1.2 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), $(PhO)_3P$ (0.05 mmol), K_3PO_4 (2 mmol) in DMF (5 mL) at 80 °C under air. [b] GC yield based on the amount of **2** used. The value in parentheses indicates isolated yield. [c] At 100 °C.

SCHEME 1. Reaction Pathways for the Arylation of Acrylic Acid Derivatives 2



undergoes insertion of an acrylic acid derivative **2** to yield a key palladium enolate intermediate **B**. Then, in the presence of a triaryl phosphite ligand, hydrolysis of **B** rather than β-hydrogen elimination appears to selectively take place to form **3**. In the reaction medium, water arisen from boronic acids or adventitious

one may be participated. While the exact function of the ligand is not definitive at the present stage,[14,15] one of the possibilities is to crowd on the Pd center to prevent the β-hydrogen elimination.[16] In each run performed, a minor amount of biaryl was formed. Once the oxidative homocoupling of **1** occurs, Pd^0 species may be generated. Under air, this seems to be able to be reoxidized to Pd^{II}, which circumvents catalyst deactivation.[13]

In summary, we have demonstrated that 1,4-addition of arylboronic acids to acrylic acid derivatives can be performed efficiently in the presence of a palladium catalyst system of $Pd(OAc)_2/(PhO)_3P$. The use of the phosphite ligand dramatically promotes the 1,4-addition and suppresses the competitive Mizoroki−Heck-type oxidative coupling. Thus, this protocol seems to provide a useful route to 3-arylpropionic acid derivatives.

Experimental Section

General Procedure for 1,4-Addition of Arylboronic Acids with Acrylic Acid Derivatives. To a 20-mL two-necked flask were added arylboronic acid **1** (1.2 mmol), acrylic acid derivative **2** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), $(PhO)_3P$ (0.05 mmol), K_3PO_4 (2 mmol), 1-methylnaphthalene (ca. 50 mg) as internal standard, and DMF (5 mL). The resulting mixture was stirred under air at 80 °C. GC and GC-MS analyses of the mixtures confirmed formation of **3**, **4**, and/or **5**. Then, the mixture was cooled to room temperature, and Et_2O (100 mL) and water (100 mL) were added. After the organic layer was washed by water (100 mL, three times) and dried over sodium sulfate, the solvents were evaporated under vacuum. The product was isolated by thin-layer chromatography on silica gel, using hexane−ethyl acetate (99:1, v/v) as eluant.

***n*-Butyl 3-phenylpropionate (3a) (entry 4 in Table 1):**[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.29−1.39 (m, 2H), 1.54−1.62 (m, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 4.07 (t, J = 6.6 Hz, 2H), 7.18−7.21 (m, 3H), 7.25−7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.6, 31.0, 35.9, 64.3, 126.2, 128.2, 128.4, 140.5, 173.0; HRMS *m*/*z* calcd for $C_{13}H_{18}O_2$ (M^+) 206.1307, found 206.1313.

***n*-Butyl 3-(2-bromophenyl)propionate (3g) (entry 6 in Table 2):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.30−1.39 (m, 2H), 1.55−1.63 (m, 2H), 2.64 (t, J = 8.1 Hz, 2H), 3.07 (t, J = 8.1 Hz, 2H), 4.08 (t, J = 6.6 Hz, 2H), 7.05−7.09 (m, 1H), 7.21−7.26 (m, 2H), 7.53 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.6, 31.4, 34.1, 64.4, 124.3, 127.5, 128.0, 130.4, 132.8, 139.8, 172.7; HRMS (CI) *m*/*z* (MH^+) calcd for $C_{13}H_{18}BrO_2$ 285.0490, found 285.0484.

Acknowledgment. This work was partly supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Standard experimental procedure and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702546T

(14) Triaryl phosphites have been used as ligands for Pd-catalyzed cross-coupling reactions. For recent examples, see: (a) Beller, M.; Zapf, A. *Synlett* **1998**, 792. (b) Zhang, S.; Marshall, D.; Liebeskind, L. S. *J. Org. Chem.* **1999**, *64*, 2796. (c) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830. (d) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Albisson, D. A.; Draper, S. M.; Scully, P. N.; Coles, S. J.; Hursthouse, M. B. *Chem. Eur. J.* **2003**, *9*, 3216. (e) Tsukada, N.; Sugawara, S.; Nakaoka, K.; Inoue, Y. *J. Org. Chem.* **2003**, *68*, 5961. (f) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595. (g) Kayaki, Y.; Koda, T.; Ikariya, T. *Eur. J. Org. Chem.* **2004**, 4989. (h) Ju, J.; Nam, H.; Jung, H. M.; Lee, S. *Tetrahedron Lett.* **2006**, *47*, 8673. (i) He, P.; Lu, Y.; Hu, Q.-S. *Tetrahedron Lett.* **2007**, *48*, 5283.

(15) During our investigation regarding this work, Hu's and Bedford's groups reported that phosphite-based palladacycles promote 1,4-addition of arylboronic acids to enones independently.[9c,d] In our case, a mechanism involving a similar palladacycle intermediate formed in situ cannot be excluded at the present stage. However, a ligand, tris[2,4-di(*tert*-butyl)-phenyl] phosphite, which gave the best results in their work, was found to be less effective in our system (entry 15 in Table 1).

(16) A similar effect by diphosphine ligands added in a Rh-catalyzed reaction of **1** with **2** was also observed. Zou, G.; Guo, J.; Wang, Z.; Huang, W.; Tang, J. *Dalton Trans.* **2007**, 3055.