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Palladium(II)-Catalyzed Annulation of Alkynes with *ortho*-Ester-Containing Phenylboronic Acids

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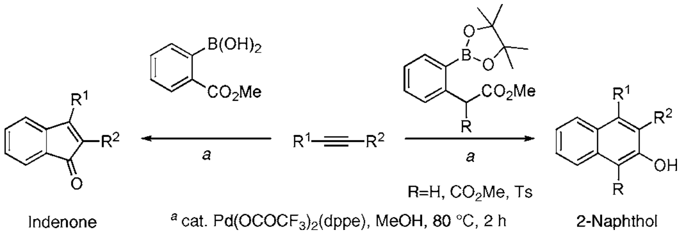
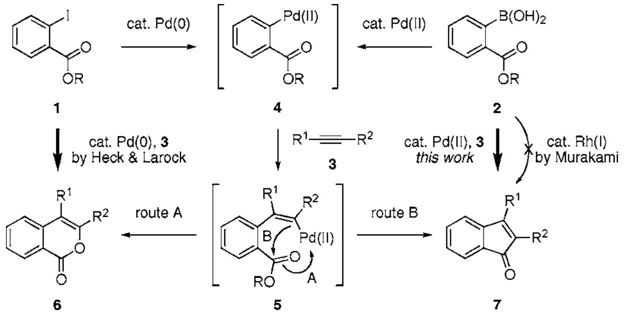
ABSTRACT



^{a} cat. Pd(OCOCF$_3$)$_2$(dppe), MeOH, 80 °C, 2 h

Palladium(II) catalyzes annulation of internal alkynes with methyl 2-boronobenzoate and (2-boronophenyl)acetate to provide 2,3-disubstituted indenones and 3,4-disubstituted 2-naphthols, respectively. The annulation reaction would proceed through transmetalation of Pd(II) with the boron reagents and insertion of the alkynes, followed by unprecedented 1,2-addition of the generated alkenylpalladium(II) species to the intramolecular ester group.

Scheme 1. Annulation of Internal Alkynes **3** with *o*-(Alkoxycarbonyl)phenyl Iodide **1** and Boronic Acid **2**



Palladium(0)-catalyzed annulation of unsaturated carbon−carbon bonds with aryl halides bearing a functional group at their ortho position is one of the most efficient methods for syntheses of carbo- and heterocycles.[1] While electrophilic functional groups such as aldehyde,[2] ketone,[3] and nitrile[4] are used for the preparation of indenols and indenones, the ester group[5] does not function as an electrophile and produces isocoumarin **6** instead of indenone **7** via nucleophilic addition of the oxygen atom of the adjacent ester carbonyl to the generated alkenylpalladium(II) intermediate **5** (Scheme 1, route A). The arylpalladium(II) intermediates **4** in these annulations are usually generated by oxidative addition of aryl halide **1** to a Pd(0) catalyst, but an alternative method, i.e., transmetalation of an arylmetallic species, such as

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[1] (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111−124. (b) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435−1442. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644−4680.

[2] (a) Tao, W.; Silverberg, L. J.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1989**, *8*, 2550−2559. (b) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *J. Organomet. Chem.* **1992**, *436*, C9−C12. (c) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *Organometallics* **1996**, *15*, 3509−3519. (d) Vicente, J.; Abad, J.-A.; López-Peláez, B.; Martínez-Viviente, E. *Organometallics* **2002**, *21*, 58−67. (e) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579−4583. (f) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089−4092.

[3] Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545−3546.

[4] (a) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *121*, 3238−3239. (b) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276−9287. (c) Tian, Q.; Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 339−347.

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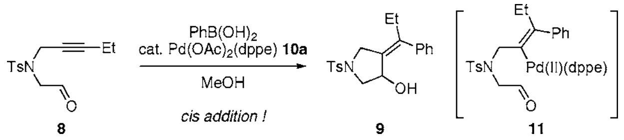
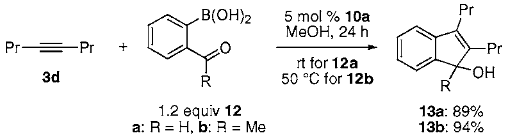
arylboronic acid **2** with Pd(II) catalyst, has hardly been employed for the annulation processes.[2c,6] On the other hand, Rh(I)-catalyzed annulation of unsaturated carbon−carbon bonds with *o*-formyl-, acetyl-, and cyanophenylboronic acid[7,8] via well-known transmetalation with the boronic acids[9] was recently reported. However, the alkenylrhodium(I) intermediate generated by coordination and subsequent insertion of alkynes into the arylrhodium(I) species also turned out to be unsuitable for 1,2-addition to the intramolecular ester group.[8,10] Herein, we describe a newly discovered Pd(II)-catalyzed annulation of internal alkynes with phenylboronic acids bearing ester groups at their ortho position leading not only to 2,3-disubstituted indenones (Scheme 1, route B) but also to 3,4-disubstituted 2-naphthols.

Recently, we discovered the *palladium(0)/monophosphine*-catalyzed trans-selective arylative cyclization of 5-alkynals with arylboronic acids via an “anti-Wacker”-type oxidative addition and concomitant transmetalation.[11] During the ligand screening of the cyclization of alkynal **8**, *palladium(II)/diphosphine*, i.e., [1,2-bis(diphenylphosphino)ethane (dppe)]-palladium(II) diacetate (**10a**),[12] proved to catalyze cis-selective arylative cyclization (Scheme 2).[13] The latter selectivity is in striking contrast to the former and would result from transmetalation of the Pd(II) catalyst with the arylboronic acid and insertion of the C−C triple bond into the arylpalladium(II) bond followed by 1,2-addition to the adjacent carbonyl group of intermediate **11**. The carbopalladation pathway would also be supported by the fact that this catalyst promoted annulation of 4-octyne (**3d**) with *o*-formyl and *o*-acetyl-phenylboronic acids (**12a**,**b**) (Scheme 3). Next, we examined whether this catalyst was also effective for the annulation with *o*-(methoxycarbonyl)phenylboronic acid (**2a**).

Scheme 2. $Pd(OAc)_2(dppe)$-Catalyzed Cis-Selective Arylative Cyclization of Alkynal **8**



Scheme 3. $Pd(OAc)_2(dppe)$-Catalyzed Annulation of **3d** with Boronic Acids **12a**,**b**



To our surprise, the reaction of diphenylacetylene (**3a**) with a slight excess of **2a** and 5 mol % of $Pd(OAc)_2$(dppe) **10a** in methanol on heating at 80 °C led to formation of not isocoumarin but 2,3-diphenylinden-1-one (**7a**) in high yield (Table 1, entry 1). Methanol was an essential solvent for the annulation, and aprotic nonpolar solvents were less effective (entries 1 vs 2−7). Although in situ catalyst preparation from $Pd(OAc)_2$ and dppe was also effective (entry 8), $Pd(OAc)_2$ itself or ligated with a monophosphine did not promote the cyclization (entries 9 and 10). Reaction with dppe-ligated Pd(0) catalyst was very slow and gave **7a** in low yield (entry 11).[14] The counteranion of the Pd(II) catalyst also plays an important role in the annulation, and trifluoroacetate turned out to be most effective (entries 1 and 12−14).

Boronic ester **2b** as well as boronic acid **2a** worked as transmetalating reagents and provided **7a** in quantitative yield (entry 15). As with electrophiles, ethyl and isopropyl esters were as reactive as a methyl ester (entries 15 vs 16, 17), but

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(5) (a) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713−5716. (b) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770−8779. (c) Beletskaya, I. P.; Kashin, A. N.; Litvinov, A. E.; Tyurin, V. S.; Valetsky, P. M.; van Koten, G. *Organometallics* **2006**, *25*, 154−158. See also ref 2a.

(6) Pd(II)-catalyzed organic transformations using arylboron reagents are as follows but are fewer than Rh(I)-catalyzed ones. 1,4-Addition to α,β-unsaturated carbonyls: (a) Ohe, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1423−1431. (b) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768−2770. (c) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317−4324. (d) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Lett.* **2005**, *34*, 720−721. (e) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2005**, *24*, 5025−5032. (f) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Tetrahedron Lett.* **2007**, *48*, 4007−4010. (g) Gini, F.; Hessen, B.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 5309−5312. (h) Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651−9653. (i) Lin, S.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 7167−7170. (j) Yamamoto, T.; Iizuka, M.; Ohta, T.; Ito, Y. *Chem. Lett.* **2006**, *35*, 198−199. (k) He, P.; Lu, Y.; Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2007**, *9*, 343−346. 1,2-Addition to aldehydes and ketones: (l) Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, *128*, 16504−16505. (m) Yamamoto, T.; Ohta, T.; Ito, Y. *Org. Lett.* **2005**, *7*, 4153−4155. (n) Suzuki, K.; Arao, T.; Ishii, S.; Maeda, Y.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47*, 5789−5792. (o) Qin, C.; Wu, H.; Cheng, J.; Chen, X.; Liu, M.; Zhang, W.; Su, W.; Ding, J. *J. Org. Chem.* **2007**, *72*, 4102−4107. See also ref 6k. 1,2-Addition to nitriles: (p) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302−2303. (q) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3551−3558. (r) Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 6765−6768. (s) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987−5990.

(7) (a) Shintani, R.; Okamoto, K.; Hayashi, T. *Chem. Lett.* **2005**, *34*, 1294−1295. (b) Matsuda, T.; Makino, M.; Murakami, M. *Chem. Lett.* **2005**, *34*, 1416−1417.

(8) (a) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339−3341. (b) Miura, T.; Nakazawa, H.; Murakami, M. *Chem. Commun.* **2005**, 2855−2856.

(9) (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (b) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13−21. (c) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217−224.

(10) In situ generated alkenylrhodium(I) intermediates were reported to be unsuitable for intramolecular nucleophilic addition to the ester group.[8] However, there are a few reports on 1,2-addition of alkyl- or arylrhodium(I) intermediates to the intramolecular ester group. (a) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54−55. (b) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1390−1391.

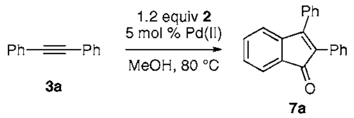
(11) Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406−1407.

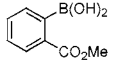
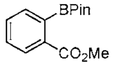
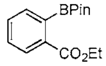
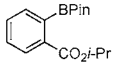
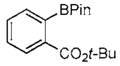
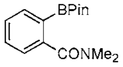
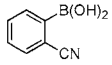
(12) (a) Marson, A.; van Oort, A. B.; Mul, W. P. *Eur. J. Inorg. Chem.* **2002**, 3028−3031. (b) Bianchini, C.; Meli, A.; Oberhauser, W. *Organometallics* **2003**, *22*, 4281−4285.

(13) Unpublished result. The details will be published as a full paper. During our manuscript preparation, a related reaction was reported by Lu. Song, J.; Shen, Q.; Xu, F.; Lu, X. *Org. Lett.* **2007**, *9*, 2947−2950.

(14) The initial step would involve oxidative addition of **2a** to Pd(0) to generate arylpalladium(II) species. (a) Ohe, T.; Ohe, K.; Uemura, S.; Sugita, N. *J. Organomet. Chem.* **1988**, *344*, C5−C7. (b) Cho, C. S.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **1995**, *496*, 221−226. (c) Cho, C. S.; Motofusa, S.; Uemura, S. *Tetrahedron Lett.* **1994**, *35*, 1739−1742. (d) Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 883−888.

Table 1. Optimizations for Pd(II)-Catalyzed Synthesis of Indenone **7a**



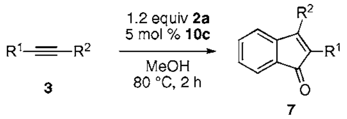
entry[a]	2[b]	catalyst	time (h)	yield (%)
1	 **2a**	Pd(OAc)$_2$(dppe) **10a**	2	93
2	**2a**	**10a**	8	57
3	**2a**	**10a**	8	31
4	**2a**	**10a**	8	24
5	**2a**	**10a**	8	12
6	**2a**	**10a**	8	8
7	**2a**	**10a**	8	1
8	**2a**	Pd(OAc)$_2$ + dppe	4	87
9	**2a**	Pd(OAc)$_2$	8	0
10	**2a**	Pd(OAc)$_2$(PPh$_3$)$_2$	8	0
11	**2a**	Pd(dppe)$_2$	8	23
12	**2a**	PdCl$_2$(dppe) **10b**	8	10
13	**2a**	Pd(O$_2$CCF$_3$)$_2$(dppe) **10c**	2	95
14	**2a**	[Pd(PhCN)$_2$(dppe)](SbF$_6$)$_2$ **10d**	2	67
15	 **2b**	**10c**	2	100
16	 **2c**	**10c**	2	99
17	 **2d**	**10c**	2	91
18	 **2e**	**10c**	8	20
19	 **2f**	**10c**	16	15
20	 **2g**	**10c**	48	20

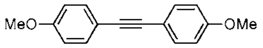
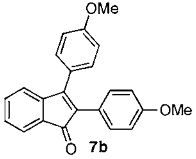
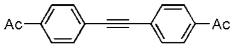
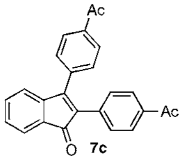
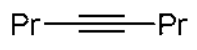
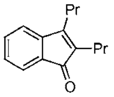
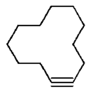
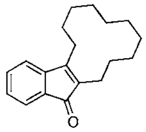
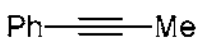
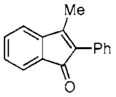
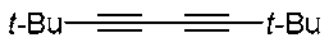
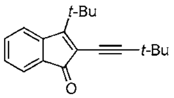
[a] Reactions in MeOH (entries 1 and 8−20), DMF (entry 2), acetonitrile (entry 3), THF (entry 4), 1,4-dioxane (entry 5), 1,2-dichloroethane (entry 6), and toluene (entry 7). [b] Pin = pinacolato.

a *tert*-butyl ester, amide, and nitrile were less reactive (entries 18−20). It is worth noting that the reactivity order of the esters and nitrile groups observed in the annulation is similar to that with organolithium[15] and organomagnesium[16] reagents but opposite to that with Rh(I) catalyst.[17]

Next, annulation reactions using other alkynes **3b**−**g** were examined (Table 2). Diarylacetylenes **3b** and **3c** bearing electron-donating or electron-withdrawing substituents at the para positions provided 2,3-diarylindenones **7b** and **7c** in high yields (entries 1 and 2). In the annulation of dialkylacetylene **3d** and cycloalkyne **3e**, 2,3-dialkylindenones **7d** and **7e** along with a small amount of isocoumarins **6d** and **6e** were formed. Remarkably, use of unsymmetrical alkynes **3f** and **3g** led to the formation of unsymmetrical indenones **7f** and **7g** with regiochemistry different from the Pd(0)-catalyzed preparation of indenones from *o*-halo-benzaldehydes[2e] or benzonitrile.[4b] Unfortunately, the annulation reactions of alkynyl esters, alkynylsilanes, and terminal alkynes were unsuccessful.

Table 2. Pd(II)-Catalyzed Synthesis of Indenones **7**



entry	substrate **3**	product **7**	yield (%)
1	 **3b**	 **7b**	98
2[a]	 **3c**	 **7c**	84
3[b]	 **3d**	 **7d**	83
4[c]	 **3e**	 **7e**	58
5	 **3f**	 **7f**	83 (5:1)
6	 **3g**	 **7g**	31

[a] Reaction in DMF−MeOH (1:1). [b] A trace of isocoumarin **6d** was also observed. [c] Isocoumarin **6e** was also obtained in 15% yield.

The annulations with both *o*-cyano- and *o*-(methoxycarbonyl)-phenyl derivatives afford the same indenones, whereas those with their homologues, i.e., *o*-(cyanomethyl)- and *o*-[(methoxycarbonyl)methyl]-phenyl derivatives, would provide different products, i.e., 2-naphthylamine[4a,4c] and 2-naphthols, respectively. In fact, annulation of **3b** with boronates **14a**−**c** containing aliphatic ester groups provided 3,4-disubstituted 2-naphthols **15a**−**c** in high yields (Scheme 4). The 1-unsubstituted 2-naphthol **15a** obtained here can be readily converted to a 2,2′-binaphthol, a substrate proving increasingly useful as a chiral ligand in organic chemistry.[18] Base-free conditions for the cyclization allow transformation of active methyne compounds **14b**,**c** into 1-substituted 2-naphthols **15b**,**c** and not indenes.[19]

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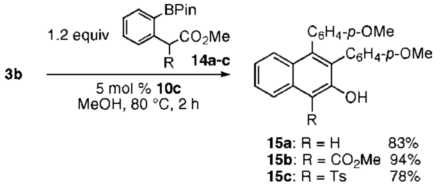
(15) Holm, T. *Acta Chem. Scand.* **1969**, *23*, 1829−1831.

(16) Entemann, C. E., Jr.; Johnson, J. R. *J. Am. Chem. Soc.* **1933**, *55*, 2900−2903.

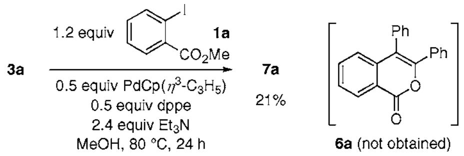
(17) [Rh(OH)(COD)]$_2$-catalyzed annulation of **3d** with **2a** in MeOH gave **7d** in 18% yield, which is better than the yield reported in ref 8a.

Scheme 4. Pd(II)-Catalyzed Synthesis of 2-Naphthols **15**



Finally, the Pd(0)-catalyzed annulation of **3a** with methyl *o*-iodobenzoate (**1a**) was revisited to gather evidence for the addition of the alkenylpalladium intermediate **5** in Scheme 1 to the intramolecular ester group. The reaction conditions for the Pd(II)-catalyzed annulation [Pd-dppe (1:1), MeOH solvent] were applied to the Pd(0)-catalyzed one (Scheme 5).[20] In contrast to Larock and Heck's reports,[5] indenone **7a** was exclusively formed but in poor yield even when a stoichiometric amount of base to regenerate Pd(0) and 0.5 equiv of catalysts were employed. The complete product change and low conversion would result from the diphosphine ligand[21] and inefficiency in reduction of in situ generated Pd(II) to Pd(0),[22] respectively.

Scheme 5. Pd(0)-Catalyzed Annulation of **3a** with *o*-Iodobenzoate **1a**



In summary, we have developed a new preparative method for 2,3-disubstituted indenones and 3,4-disubstituted 2-naphthols based on the Pd(II)-catalyzed annulation of internal alkynes with *ortho*-ester-containing phenylboronic acids. To the best of our knowledge, these annulations represent the first example of intramolecular nucleophilic addition of an organopalladium(II) species to an alkoxycarbonyl group. Our indenone synthesis has advantages of using a much smaller amount of boronic acid, lower reaction temperature, shorter reaction time, and cheaper catalyst over the Rh(I)-catalyzed one with *o*-cyanophenylboronic acid.[8a] The synthesis of 2-naphthols makes good use of the electrophilic character of the ester. Furthermore, our Pd(II)/Pd(0) redox-free system with no base additive would promote the catalytic cycle more smoothly than the Pd(0)-catalyzed annulation with *o*-halobenzoate, where the Pd(0) catalyst must be oxidized to Pd(II) by the aryl halide and regenerated by reduction of (alkoxo)Pd(II) formed by 1,2-addition of an alkenylpalladium(II) intermediate to the proximal carbonyl group. The application of annulations with functionalized phenylboronic acids leading to other carbo- and heterocycles and its asymmetric process are underway in this laboratory.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) PdCp(η^3-C_3H_5) was employed for the Pd(0) precatalyst, which should generate phosphine-ligated Pd(0) and CpC_3H_5 in the presence of an excess of phosphines. Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850−5858.

(21) Reaction in DMF also provided **7a** exclusively but in low yield. The ratio of the ligand to Pd proved to be important because use of $Pd(dppe)_2$ as a Pd(0) catalyst resulted in the formation of a mixture of **6a** and **7a**.

(22) Use of inorganic bases such as KOAc, Na_2CO_3, AgOAc, and Ag_2CO_3 or a reductant such as Zn resulted in similar or lower conversion of **3a**. Furthermore, Pd(II) catalysts **10a−d** turned out to be less effective than the Pd(0) catalyst and must not be reduced under the reaction conditions.