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A General Cyclocarbonylation of Aryl Bromides and Triflates with Acetylenes: Palladium-Catalyzed Synthesis of 3-Alkylidenefuran-2-ones

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Furanones represent an important family of organic compounds that are present in several natural products and bioactive derivatives.[1] More specifically, this structural motif is found in a wide variety of therapeutically interesting drug candidates that have anti-inflammatory,[2] cardiotonic,[3] analgesic,[4] anticancer,[5] anticonvulsant,[6] antimicrobial,[7] and antiviral activities[8] (Figure 1). Selected examples of currently marketed drugs with the furanone scaffold are Basidalin, Ascorbic acid, Narthogenin, Butalactin, and Rofecoxib.

Although several strategies are known for the preparation of a variety of furanone derivatives,[1] the synthesis of 3-alkylidenefuran-2-ones is less well studied. Aside from the traditional cyclodehydration of γ-keto acids and subsequent aldol condensation with aromatic aldehydes, few routes have been reported by means of the transition-metal-catalyzed cyclization of appropriately functionalized acetylenic substrates (Scheme 1).[9]

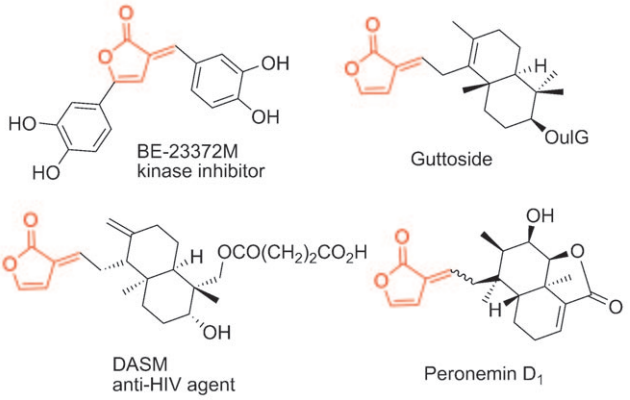
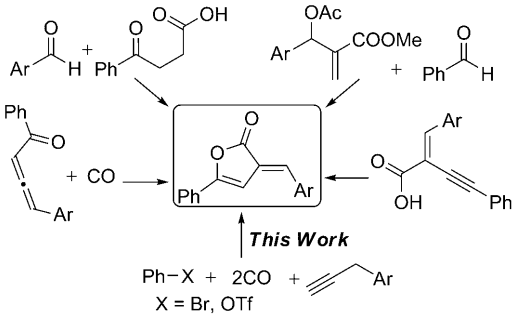


Figure 1. Selected examples of bio-active furanones.



Scheme 1. Synthetic strategies towards the formation of 3-alkylidenfuranones.

On the other hand, palladium-catalyzed carbonylative coupling reactions have been demonstrated to be powerful tools for the synthesis of substituted aromatic carboxylic acid derivatives by using CO as a cheap and readily available C1 source.[10] During the last few years, we have disclosed a number of novel or improved palladium-catalyzed carbonylations.[11] Examples include the aminocarbonylation of aryl halides to form primary amides,[11b,c] the carbonylative Heck reactions of aryl/vinyl triflates to give chalcones,[11d] and the reductive carbonylation of aryl bromides to form aldehydes, which is also applied on an industrial scale,[11f] among others. During the course of our studies on palladium-catalyzed carbonylative Sonogashira coupling reactions,[11g] we observed the formation of (*E*)-3-benzylidene-5-phenylfuran-2(3*H*)-one as a minor product in the reaction of bromobenzene with benzyl acetylene. This unusual double carbonylation process interested us because there is limited precedent for this type of carbonylation, with only one publication to date. Therein, Alper and Huang describe the reaction of aryl iodides with 1-aryl-3-propynes to give furanones.[12a] More specifically, they used $Pd(OAc)_2$ (5 mol%) as the catalyst system at relatively high pressures of carbon monoxide (20–80 bar). Unfortunately, only limited functional group tolerance was demonstrated and no examples of the use of heterocycles were included. Therefore, the need to develop a general procedure for the carbonylation of available aryl-X derivatives to give furanones under mild conditions still exists.

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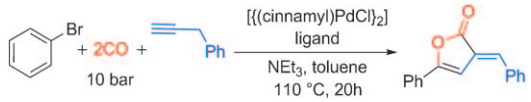
Herein, we report the first general catalytic double carbonylation process of aryl bromides and alkynes that also allows for the carbonylation of aryl triflates. These processes proceed at 80–110 °C and 5–10 bar of carbon monoxide. In exploratory experiments on the carbonylation of bromobenzene with benzylacetylene, it turned out that a catalyst system consisting of [{(cinnamyl)PdCl}$_2$] with Xantphos[13] as the ligand in toluene worked well (88% yield of (*E*)-3-benzylidene-5-phenylfuran-2(3*H*)-one; Table 1, entry 7). Other commonly used bidentate ligands, such as 1,2-bis(diphenylphosphino)ethane (DPPE) and 1,4-(diphenylphosphino)butane (DPPB), resulted in low conversion and yield (15 and 19%, respectively; Table 1, entries 4 and 5). However, the use of BuPAd$_2$ (cata*CX*ium A; Ad = adamantyl), a versatile ligand in palladium-catalyzed coupling reactions,[14] also gave 85% of the desired furanone. Lowering the pressure (5 bar) or temperature (80 °C) in the presence of Xantphos also resulted in good yields of the furanone (60 and 76% yield, respectively; Table 1, entries 8 and 9).

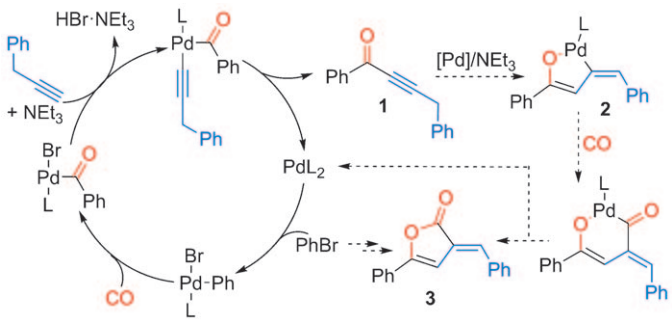
Table 1. Palladium-catalyzed cyclocarbonylation of bromobenzene.[a]



Entry	Ligand ([mol%])	Conversion [%][b]	Yield [%][b]
1	PCy_3 (4)	35	28
2	PPh_3 (4)	80	62
3	$BuPAd_2$ (4)	93	85
4	DPPE (2)	29	15
5	DPPB (2)	35	19
6	DPPF (2)	100	82
7	Xantphos (2)	100	88
8[c]	Xantphos (2)	77	60
9[d]	Xantphos (2)	100	76

[a] Bromobenzene (1.0 mmol), benzyl acetylene (1.0 mmol), CO (10 bar), [{(cinnamyl)PdCl}$_2$] (1 mol%), ligand, toluene (2 mL), NEt_3 (2.0 mmol), 110 °C, 20 h. [b] Conversion and yield were determined by GC by using hexadecane as the internal standard. [c] 80 °C. [d] CO (5 bar).

The possible reaction mechanism for the formation of (*E*)-3-benzylidene-5-phenylfuran-2(3*H*)-one is shown in Scheme 2. Initially, a carbonylative Sonogashira reaction takes place between bromobenzene and benzyl acetylene to afford alkynone **1**.[11g] Next, reaction of **1** with hydridopalladiumbromide, which is generated within the first cycle (see Scheme 2), should result in the formation of isomerized complex **2**. A subsequent second carbonylation reaction leads to furanone **3**.

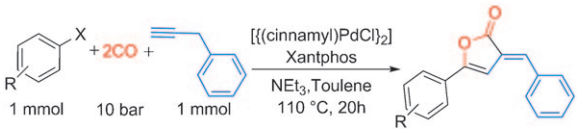


Scheme 2. Proposed reaction mechanism.

After having found suitable conditions for the double carbonylation of bromobenzene (Table 1, entry 7), we explored the scope and limitations of this methodology. As shown in Table 2 and Scheme 3, the generality and versatility of the current methodology is proved by synthesizing more than 20 different furanone derivatives in good to excellent yields.

In addition to aryl bromides, aryl triflates were examined in this type of reaction.[15] To our delight, this catalytic system worked well in the cyclocarbonylation of several aryl

Table 2. Palladium-catalyzed cyclocarbonylation of aryl bromides/triflates.[a]



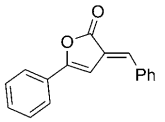
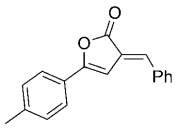
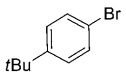
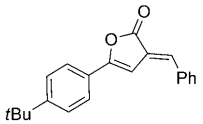
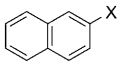
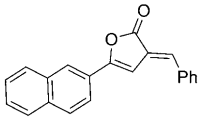
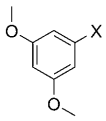
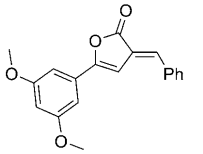
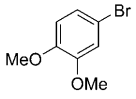
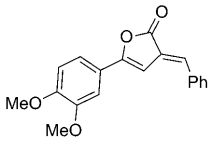
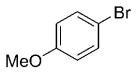
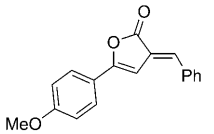
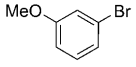
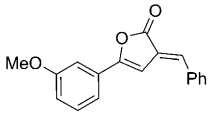
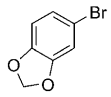
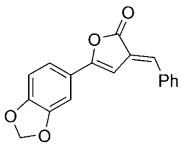
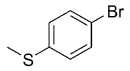
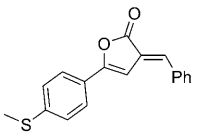
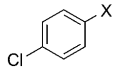
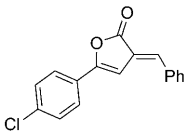
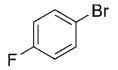
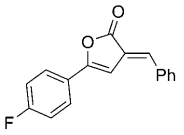
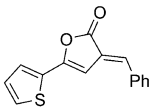
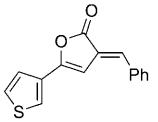
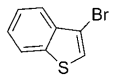
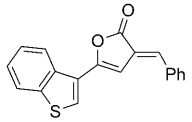
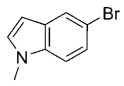
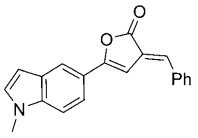
Entry	ArX		Furanone	Yield [%][b]
1		X = OTf		68
2		X = Br		83
3		X = OTf		78
4		X = Br		75
5				85
6		X = OTf		50
7		X = Br		73
8		X = OTf		78
9		X = Br		85
10				60
11				85
12				81

Table 2. (Continued)

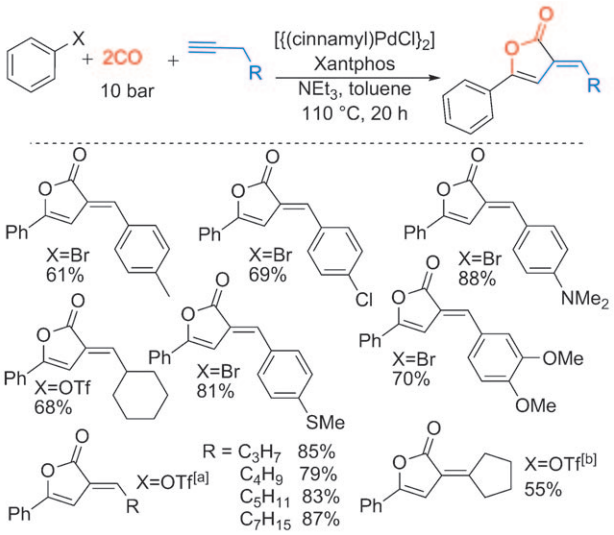
Entry	ArX		Furanone	Yield [%][b]
13				88
14				85
15		X = OTf		67
16		X = Br		85
17				91
18				54
19				79
20				56
21				66

[a] ArX (1.0 mmol), benzyl acetylene (1.0 mmol), CO (10 bar), [{(cinnamyl)PdCl}$_2$] (1 mol%), Xantphos (2 mol%), toluene (2 mL), NEt_3 (2 mmol), 110°C, 20 h. [b] Isolated yield.

triflates to give the corresponding furanones in good to excellent yield (Table 2, entries 1, 3, 6, 8, and 15).

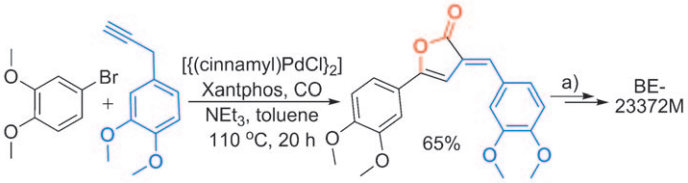
Next, different 1-aryl-3-propynes were synthesized[16] and subjected to the cyclocarbonylation reaction with bromobenzene. As shown in Scheme 3, five different furanones were obtained in good isolated yields (61–88%) irrespective of the electronic nature of the substrate. More interestingly, aliphatic 3-propynes also worked well in this system. Six furanones resulting from the reaction of aliphatic alkynes are shown in Scheme 3, and yields of 55–87% were achieved. However, NO_2-, CHO-, and CH_3CO-substituted aryl bromides and aromatic acetylenes failed to give the corresponding products under these conditions.

Finally, the usefulness of the presented methodology is illustrated in the straightforward synthesis of the permethylated kinase inhibitor BE-23372M. Treatment of 3,4-dimethoxybromobenzene with 3-(3′,4′-dimethoxyphenyl)-prop-1-yne in the presence of [{(cinnamyl)PdCl}$_2$] (1 mol%) and Xantphos (2 mol%) under carbon monoxide (10 bar) afforded the desired product in 65% yield (Scheme 4).



Scheme 3. Palladium-catalyzed cyclocarbonylation of 3-aryl-1-propynes with PhX (reaction conditions: PhX (1.0 mmol), 3-aryl-1-propyne (1.0 mmol), CO (10 bar), [{(cinnamyl)PdCl}$_2$] (1 mol%), Xantphos (2 mol%), toluene (2 mL), NEt_3 (2.0 mmol), 110°C, 20 h, isolated yield). [a] Yield determined by NMR spectroscopy. [b] Yield determined by GC.

In conclusion, a general and efficient method for the synthesis of 5-aryl-3-alkylidenfuranones has been developed. For the first time it has been demonstrated that readily available (hetero)aryl bromides and aryl triflates can be doubly carbonylated with benzyl acetylenes and also aliphatic alkynes. The generality of this methodology is proven by more than 30 examples that proceed in good yields. Notably, the straightforward synthesis of permethylated BE-23372M, a kinase inhibitor, is achieved. Further developments of the present catalytic system, as well as for propargylic derivatives, are currently underway.



Scheme 4. Synthesis of permethylated BE-23372M. a) see reference [1d].

Experimental Section

Typical procedure for the cyclocarbonylation of bromobenzene and benzyl acetylene to form a furanone: [{(Cinnamyl)PdCl}$_2$] (1 mol%) and Xantphos (2 mol%) were transferred into a vial (4 mL reaction volume) equipped with a septum, a small cannula, and a stirring bar. After the vial was purged with argon, bromobenzene (1 mmol), benzyl acetylene

(1.2 mmol), toulene (2 mL), and NEt_3 (2 mmol) were injected into the vial by syringe. The vial was then placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments under an argon atmosphere. After flushing the autoclave three times with CO, a pressure of 10 bar was established and the reaction was performed for 20 h at 110 °C. After the reaction, the autoclave was cooled to room temperature and the pressure was carefully released. Water (6 mL) was added to the reaction mixture and the solution was extracted with ethyl acetate (3–5 × 2–3 mL). The extracts were adsorped onto silica gel and the crude product was purified by column chromatography by using *n*-heptane and *n*-heptane/AcOEt (10:1) as the eluent. The product was obtained in 206 mg (83 % yields) as yellow solid.

Acknowledgements

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Keywords: alkynes · aryl triflates · carbonylation · furanones · homogeneous catalysis · palladium

[1] a) Y. S. Rao, *Chem. Rev.* **1976**, *76*, 625–694; b) Y. S. Rao, *Chem. Rev.* **1964**, *64*, 353–388; c) B. El Ali, H. Alper, *Synlett* **2000**, 161–171; d) S. Tanaka, T. Okabe, S. Nakajima, E. Yoshida, H. Morishima, *J. Antibiotics* **1994**, *47*, 297–300.

[2] a) M. S. Y. Khan, A. Husain, *Pharmazie* **2002**, *57*, 448–452; b) M. M. Alam, A. Husain, S. M. Hasan, Suruchi, T. Anwer, *Eur. J. Med. Chem.* **2009**, *44*, 2636–2642.

[3] L. Leite, D. Jansone, M. Veveris, H. Cirule, Y. Popelis, G. Melikyan, A. Avetisyan, E. Lukevics, *Eur. J. Med. Chem.* **1999**, *34*, 859–865.

[4] K. Gottesdiener, D. R. Mehlisch, M. Huntington, W. Yuan, P. Brown, B. Gertz, S. Mills, *Clin. Ther.* **1999**, *21*, 1301–1312.

[5] A. A. Moosavi-Movahedi, S. Hakimelahi, J. Chamani, G. A. Khodarahmi, F. Hassanzadeh, F. Luo, T. W. Ly, K. Shia, C. Yen, M. L. Jain, R. Kulatheeswaran, C. Xue, M. Pasdarb, G. H. Hakimelahi, *Bioorg. Med. Chem.* **2003**, *11*, 4303–4313.

[6] W. E. Klunk, D. F. Covey, J. A. Ferrendelli, *Mol. Pharmacol.* **1982**, *22*, 438–443.

[7] H. Wu, Z. Song, M. Hentzer, J. B. Andersen, S. Molin, M. Givskov, N. Hoiby, *J. Antimicrob. Chemother.* **2004**, *53*, 1054–1061.

[8] A. I. Hashem, A. S. Youssef, K. A. Kandeel, W. S. Abou-Elmagd, *Eur. J. Med. Chem.* **2007**, *42*, 934–939.

[9] a) R. Rossi, F. Bekkina, C. Bechini, L. Mannina, P. Vergamini, *Tetrahedron* **1998**, *54*, 135–156; b) J. Boukouvalas, O. Marion, *Synlett* **2006**, 1511–1514; c) S.-G. Lim, B.-I. Kwon, M.-G. Choi, C.-H. Jun, *Synlett* **2005**, 1113–1116; d) V. Nair, S. Bindu, V. Sreekumar, N. P. Path, *Org. Lett.* **2003**, *5*, 665–667; for furanones formed from allenones, see: e) M. S. Sigman, C. E. Kerr, B. E. Eaton, *J. Am. Chem. Soc.* **1993**, *115*, 7545–7546; f) L. S. Trifonov, A. S. Orahovats, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1992**, *75*, 1872–1879; g) C. G. Lee, K. Y. Lee, S. J. Kim, J. N. Kim, *Bull. Korean Chem. Soc.* **2007**, *28*, 719–720.

[10] For reviews on palladium-catalyzed carbonylations, see: a) R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515–5548; b) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176–4196; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133; c) A. Brennführer, H. Neumann, M. Beller, *ChemCatChem* **2009**, *1*, 28–41; d) R. Skoda-Földes, L. Kollár, *Curr. Org. Chem.* **2002**, *6*, 1097–1119; e) M. Beller, B. Cornils, C. D. Frohning, C. W. Kohlpaintner, *J. Mol. Catal. A: Chem.* **1995**, *104*, 17–85.

[11] a) X.-F. Wu, H. Neumann, M. Beller, *ChemCatChem* **2010**, *2*, 509–513; b) X.-F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 9750–9753; c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2010**, *5*, 2168–2172; d) X.-F. Wu, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 5412–5416; *Angew. Chem. Int. Ed.* **2010**, *49*, 5284–5288; e) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 7474–7477; *Angew. Chem. Int. Ed.* **2010**, *49*, 7316–7319; f) S. Klaus, H. Neumann, A. Zapf, D. Strübing, S. Hübner, J. Almena, T. Riermeier, P. Groß, M. Sarich, W. R. Krähnert, K. Rossen, M. Beller, *Angew. Chem.* **2006**, *118*, 161–165; *Angew. Chem. Int. Ed.* **2006**, *45*, 154–158; g) X.-F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 12104–12107; h) X.-F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 14596–14602; i) X.-F. Wu, H. Neumann, M. Beller, *Tetrahedron Lett.* **2010**, *51*, 6146–6149; j) X. F. Wu, B. Sundararaju, H. Neumann, P. H. Dixneuf, M. Beller, *Chem. Eur. J.* **2011**, *17*, 106–110; k) X. F. Wu, H. Jiao, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 726–733; l) X. F. Wu, H. Neumann, M. Beller, *Adv. Synth. Catal.* **2011**, *353*, 788–792.

[12] a) Y. Huang, H. Alper, *J. Org. Chem.* **1991**, *56*, 4534–4536; b) J. Kiji, T. Okano, H. Kimura, K. Saiki, *J. Mol. Catal. A: Chem.* **1998**, *130*, 95–100.

[13] a) E. Zuidema, L. Escorihuela, T. Eichelsheim, J. J. Carbo, C. Bo, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2008**, *14*, 1843–1853; b) M. Schreuder Goedheijt, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Mol. Catal. A: Chem.* **1998**, *134*, 243–249; c) A. J. Sandee, R. S. Ubale, M. Makkee, J. N. H. Reek, P. C. J. Kamer, J. A. Moulijn, P. W. N. M. van Leeuwen, *Adv. Synth. Catal.* **2001**, *343*, 201–206; d) A. Buhling, P. C. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1997**, *16*, 3027–3037; e) A. J. Sandee, L. A. van der Veen, J. N. H. Reek, P. C. J. Kamer, M. Lutz, A. L. Spek, P. W. N. M. van Leeuwen, *Angew. Chem.* **1999**, *111*, 3428–3432; *Angew. Chem. Int. Ed.* **1999**, *38*, 3231–3235.

[14] For some other applications of this catalyst system, see: a) H. Neumann, A. Brennführer, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2437–2442; b) A. Brennführer, H. Neumann, S. Klaus, T. Riermeier, J. Almena, M. Beller, *Tetrahedron* **2007**, *63*, 6252–6258; c) A. G. Sergeev, A. Zapf, A. Spannenberg, M. Beller, *Organometallics* **2008**, *27*, 297–300; d) H. Neumann, A. Brennführer, P. Groß, T. Riermeier, J. Almena, M. Beller, *Adv. Synth. Catal.* **2006**, *348*, 1255–1261; e) H. Neumann, A. Brennführer, M. Beller, *Chem. Eur. J.* **2008**, *14*, 3645–3652; f) A. Tewari, M. Hein, A. Zapf, M. Beller, *Tetrahedron* **2005**, *61*, 9705–9709; g) A. Ehrentraut, A. Zapf, M. Beller, *Synlett* **2000**, 1589–1592; h) A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem.* **2000**, *112*, 4315–4317; *Angew. Chem. Int. Ed.* **2000**, *39*, 4153–4155; i) A. Tewari, M. Hein, A. Zapf, M. Beller, *Synthesis* **2004**, 935–941; j) A. Köllhofer, T. Pullmann, H. Plenio, *Angew. Chem.* **2003**, *115*, 1086–1088; *Angew. Chem. Int. Ed.* **2003**, *42*, 1056–1058; k) A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 209–217; l) A. G. Sergeev, A. Spannenberg, M. Beller, *J. Am. Chem. Soc.* **2008**, *130*, 15549–15563.

[15] For selected recent examples of Pd-catalyzed coupling reactions of aryl triflates, see: a) B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 12898–12899; b) L. J. Goossen, C. Linder, N. Rodríguez, P. P. Lange, *Chem. Eur. J.* **2009**, *15*, 9336–9349; c) B. Tréguier, A. Hamze, O. Provot, J.-D. Brion, M. Alami, *Tetrahedron Lett.* **2009**, *50*, 6549–6552; d) D. J. Schipper, M. El-Salfiti, C. Whipp, K. Fagnou, *Tetrahedron* **2009**, *65*, 4977–4983; e) L. J. Goossen, N. Rodriguez, C. Linder, *J. Am. Chem. Soc.* **2008**, *130*, 15248–15249; f) L. R. Odell, J. Saevmarker, M. Larhed, *Tetrahedron Lett.* **2008**, *49*, 6115–6118; g) X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195–200; h) M. L. N. Rao, D. Banerjee, D. N. Jadhav, *Tetrahedron Lett.* **2007**, *48*, 6644–6647; i) G. A. Molander, D. E. Petrillo, N. R. Landzberg, J. C. Rohanna, B. Biolatto, *Synlett* **2005**, 1763–1766; j) G. Xu, Y.-G. Wang, *Org. Lett.* **2004**, *6*, 985–987.

[16] Z. Zhang, D. C. Leitch, M. Lu, B. O. Patrick, L. L. Schafer, *Chem. Eur. J.* **2007**, *13*, 2012–2022.

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