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Development of a General Palladium-Catalyzed Carbonylative Heck Reaction of Aryl Halides

Xiao-Feng Wu, Helfried Neumann, Anke Spannenberg, Thomas Schulz, Haijun Jiao,
and Matthias Beller*

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a,
18059 Rostock, Germany

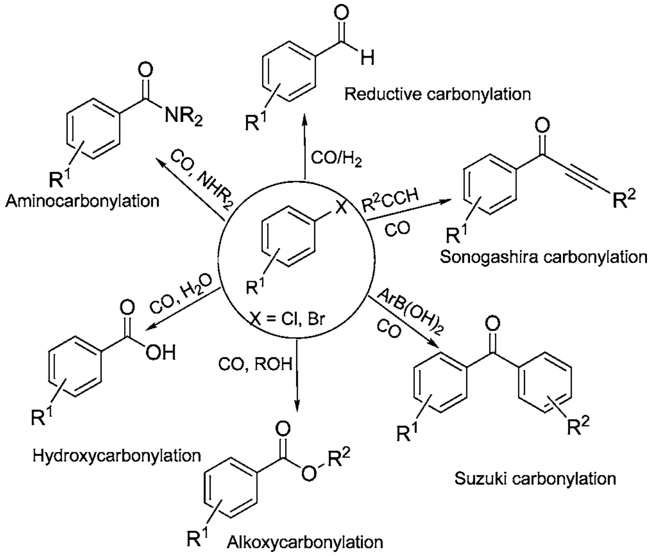
Received July 7, 2010; E-mail: matthias.beller@catalysis.de

Abstract: The first general palladium-catalyzed carbonylative vinylation of aryl halides with olefins in the presence of CO has been developed. Applying a catalyst system consisting of [(cinnamyl)PdCl]$_2$ and bulky imidazolylphosphine ligand **L1** allows for the efficient and selective synthesis of α,β-unsaturated ketones under mild reaction conditions. Starting from easily available aryl halides and olefins, versatile building blocks can be prepared in a straightforward manner. The generality and functional group tolerance of this novel protocol is demonstrated.

Introduction

Palladium-catalyzed coupling reactions of aryl halides and related compounds have become a powerful toolbox for synthetic organic chemistry. Within the last two decades these methods gained increasing importance both in large scale industrial processes as well as for the development of new materials and biologically active compounds owing to their broad functional group tolerance and wide substrate scope.[1] Among the different palladium-catalyzed C−C and C−X (X = N, O, S) coupling reactions, carbonylation reactions allow for the straightforward access to (hetero)aromatic carboxylic acid derivatives.[2] Starting from easily available aryl halides the synthesis of esters, amides, acids, ketones, and aldehydes has been well established (Scheme 1).[3]

Scheme 1. Palladium-Catalyzed Carbonylation Reactions of Aryl Halides



On the other hand, the seemingly simple carbonylative coupling of an aryl halide with CO and olefins is merely described in the literature. Larock and co-workers[4] reported the first *intramolecular* carbonylative cyclization of aryl iodides to indanones. Later on, the group of Larhed extended this protocol to aryl bromides and chlorides applying microwave conditions.[5] Miura and co-workers presented the cross-carbonylation of aryl iodides with five-membered cyclic olefins using the PdCl$_2$/PPh$_3$. However, only two single examples of this type of reaction were disclosed.[6] On the basis of our interest in palladium-catalyzed carbonylations, we recently reported a novel methodology for the synthesis of chalcones[7] via coupling of aryl/vinyl triflates with styrenes in the presence of carbon monoxide. Unfortunately, applying more easily available aryl halides as substrates failed under these conditions. Therefore, the need to develop a general procedure for carbonylative vinylations of aryl halides still exists. Herein, we report a novel catalytic process for the carbonylation of aryl halides that allows carbonylation of aryl halides with various important classes of olefins such styrenes, acrylates, and enol ethers for the first time. This process proceeds under mild conditions and leads to interesting building blocks for heterocycles and biologically active compounds.

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(1) Selected books and reviews: (a) Negishi, E.-I. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002. (b) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH: Weinheim, 2004. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (d) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (e) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 2337. (f) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, 2283. (g) Chen, G.; Chan, A. S. C.; Kwong, F. Y. *Tetrahedron Lett.* **2007**, *48*, 473.

(2) For reviews on palladium-catalyzed carbonylations see: (a) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (b) Brennführer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, *1*, 28. (c) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402. (d) Beller, M. Carbonylation of Benzyl- and Aryl-X Compounds. In *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2002; pp 145−156. (e) Skoda-Földes, R.; Kollár, L. *Curr. Org. Chem.* **2002**, *6*, 1097. (f) Tsuji, J. *Palladium Reagents and Catalysts*: *Innovations in Organic Synthesis*; Wiley: Chichester, 1995. (g) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A: Chem.* **1995**, *104*, 17. (h) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation, Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991.

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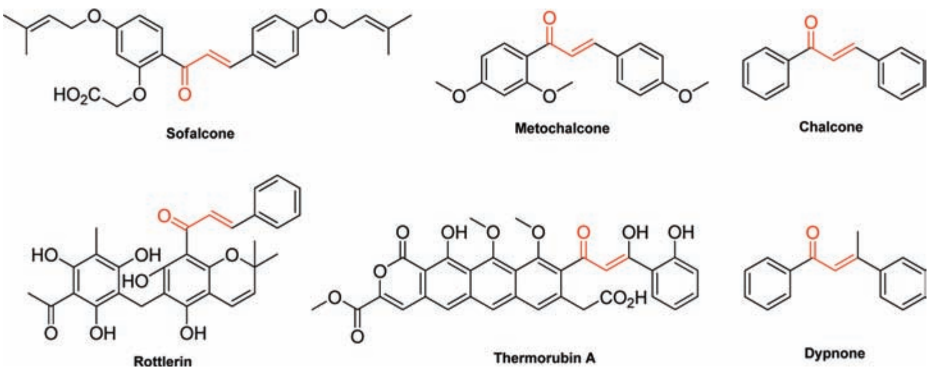
Scheme 2. Selected Examples of Bioactive Chalcones



Due to the importance of chalcones (1,3-diarylpropen-1-ones) as part of the flavonoid family, we studied the reaction of iodobenzene with styrene in the presence of carbon monoxide as a model system in more detail. Notably, various naturally occurring chalcones display interesting biological activities, including anticancer, anti-inflammatory, antioxidant, cytotoxic, antimicrobial, analgesic, antipyretic, antianginal, antihepatotoxic, antimalarial, and antiallergic properties (Scheme 2).[8] Moreover, they have been used as key intermediates in the preparation of novel bioactive compounds.[9] In the past chalcones have been mainly synthesized by aldol condensations between aromatic aldehydes and ketones (Claisen−Schmidt condensation).[10] Unfortunately, in this procedure relatively strong bases are usually required. Obviously, a general palladium-catalyzed carbonylative vinylation would represent a valuable complement for their synthesis.[11]

Results and Discussion

The initial approach to the carbonylation of iodobenzene with styrene was based on our previous work applying phenyl triflate. However, applying the previously optimized catalyst system with 1,3-bisdiphenylphosphinopropane (dppp) as ligand led to less than 5% yield of the desired product. On the other hand the combination of [(cinnamyl)PdCl]$_2$ and **L1**[12] in the presence of NEt$_3$ in dioxane at 5 bar of CO resulted in 15% of chalcone (Table 1, entry 1). Applying structurally similar ligands or other commercially available mono- and bidentate ligands showed disappointingly low reactivity (Table 1, entries 2−10). 1,2-Bis[{di(adamantan-1-yl)phosphino}methyl]benzene,[13] which

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(3) For selected examples of palladium-catalyzed carbonylations of aryl halides see: (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327. (c) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761. (d) Neumann, H.; Brennführer, A.; Gross, P.; Riermeier, T.; Almena, J.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 1255. (e) Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Gross, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 154. (f) Brennführer, A.; Neumann, H.; Klaus, S.; Riermeier, T.; Almena, J.; Beller, M. *Tetrahedron* **2007**, *63*, 6252. (g) McNulty, J.; Nair, J. J.; Robertson, A. *Org. Lett.* **2007**, *22*, 4575. (h) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460. (i) Liu, J.; Peng, X.; Sun, W.; Zhao, Y.; Xia, C. *Org. Lett.* **2008**, *18*, 3933. (j) Sergeev, A. G.; Zapf, A.; Spannenberg, A.; Beller, M. *Organometallics.* **2008**, *27*, 297. (k) Neumann, H.; Brennführer, A.; Beller, M. *Chem.—Eur. J.* **2008**, *14*, 3645. (l) Zhang, Z.; Liu, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1139. (m) Ambrosini, L. M.; Cernak, T. A.; Lambert, T. H. *Synthesis* **2010**, *5*, 870–881.

(4) Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804.

(5) Wu, X.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 346.

(6) Satoh, T.; Itaya, T.; Okuro, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 7267.

(7) Wu, X.-F.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5284.

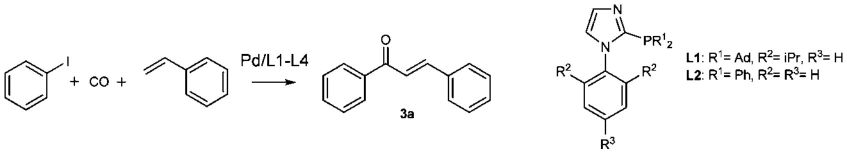
(8) Dhar, D. N. *The Chemistry of Chalcones and Related Compounds*; Wiley: New York, 1981; p 213. (b) Anto, R. J.; Sukumaran, K.; Kuttan, G.; Rao, M. N. A.; Subbaraju, V.; Kuttan, R. *Cancer Lett.* **1995**, *97*, 33. (c) Weber, W. M.; Hunsaker, L. A.; Abcouwer, S. F.; Deck, L. M.; Jagt, D. L. V. *Bioorg. Med. Chem.* **2005**, *13*, 3811. (d) Weber, W. M.; Hunsaker, L. A.; Roybal, C. N.; Bobrovnikova-Marjon, E. V.; Abcouwer, S. F.; Royer, R. E.; Deck, L. M.; Jagt, D. L. V. *Bioorg. Med. Chem.* **2006**, *14*, 2450. (e) Modzelewska, A.; Pettit, C.; Achanta, G.; Davidson, N. E.; Huang, P.; Khan, S. R. *Bioorg. Med. Chem.* **2006**, *14*, 3491. (f) Nowakowska, Z. *Eur. J. Med. Chem.* **2007**, *42*, 125. (g) Bandgar, B. P.; Gawande, S. S.; Bodade, R. G.; Totre, J. V.; Khobragade, C. N. *Bioorg. Med. Chem.* **2010**, *18*, 1364. (h) Bonesi, M.; Loizzo, M. R.; Statti, G. A.; Michel, S.; Tillequin, F.; Menichini, F. *Bioorg. Med. Chem.* **2010**, *18*, 1990. (i) Damazio, R. G.; Zanatta, A. P.; Cazarolli, L. H.; Chiaradia, L. D.; Mascarello, A.; Nunes, R. J.; Yunes, R. A.; Silva, F. R. M. B. *Eur. J. Med. Chem.* **2010**, *45*, 1332. (j) Reddy, M. V. R.; Pallela, V. R.; Cosenza, S. C.; Mallireddigari, M. R.; Patti, R.; Bonagura, M.; Truongcao, M.; Akula, B.; Jatiani, S. S.; Reddy, E. P. *Bioorg. Med. Chem.* **2010**, *18*, 2317. (k) Das, U.; Doroudi, A.; Gul, H. I.; Pati, H. N.; Kawase, M.; Sakagami, H.; Chu, Q.; Stables, J. P.; Dimmock, J. R. *Bioorg. Med. Chem.* **2010**, *18*, 2219. (l) Tu, H.-Y.; Huang, A.; Hour, T.; Yang, S.; Pu, Y.; Lin, C. *Bioorg. Med. Chem.* **2010**, *18*, 2089–2098.

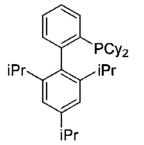
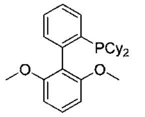
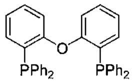
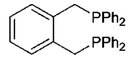
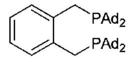
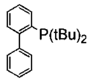
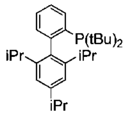
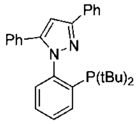
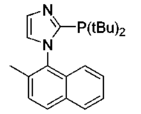
(9) For selected examples of application see: (a) Xu, L.; Xia, C.; Hu, X. *Chem. Commun* **2003**, 2570. (b) Koltunov, K. Y.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* **2005**, *46*, 8391. (c) Liang, Y.; Dong, D.; Lu, Y.; Wang, Y.; Pan, W.; Chai, Y.; Liu, Q. *Synthesis.* **2006**, *19*, 3301. (d) Mueller, A.; Stuermer, R.; Hauer, B.; Rosche, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 3316. (e) Wang, Y.; Ye, J.; Liang, X. *Adv. Synth. Catal.* **2007**, *349*, 1033. (f) Sido, A. S. S.; Chassaing, S.; Kumarraja, M.; Pale, P.; Sommer, J. *Tetrahedron Lett.* **2007**, *48*, 5911. (g) Saito, A.; Umakoshi, M.; Yagyu, N.; Hanzawa, Y. *Org. Lett.* **2008**, *10*, 1783. (h) Murugan, K.; Srimurugan, S.; Chen, C. *Chem. Commun.* **2010**, *46*, 1127. (i) Sugiura, M.; Sato, N.; Sonoda, Y.; Kotani, S.; Nakajima, M. *Chem. Asian. J.* **2010**, *5*, 478. (j) Wang, J.; Wang, X.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, *46*, 1751. (k) Wang, J.; Qi, C.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, *46*, 2124. (l) Guo, S.; Xie, Y.; Hu, X.; Xia, C.; Huang, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 2728. (m) Tang, S.; He, J.; Sun, Y.; He, L.; She, X. *J. Org. Chem.* **2010**, *75*, 1961.

(10) For selected methodologies to chalcones see: (a) Trost, B. M.; Jonasson, C.; Wuchrer, M. *J. Am. Chem. Soc.* **2001**, *123*, 12736. (b) Yadav, J. S.; Reddy, B. V. S.; Vishnumurthy, P. *Tetrahedron Lett.* **2005**, *46*, 1311. (c) Mueller, T. J. J. *Eur. J. Org. Chem.* **2005**, 1834. (d) Miranda, P. O.; Ramirez, M. A.; Padron, J. I.; Martin, V. S. *Tetrahedron Lett.* **2006**, *47*, 283. (e) Schramm, O. G.; Mueller, T. J. J. *Adv. Synth. Catal.* **2006**, *348*, 2565. (f) Marion, N.; Carlqvist, P.; Gealageas, R.; de Fremont, P.; Maseras, F.; Nolan, S. P. *Chem.—Eur. J.* **2007**, *13*, 6437. (g) Yu, M.; Li, G.; Wang, S.; Zhang, L. *Adv. Synth. Catal.* **2007**, *349*, 871. (h) Bustelo, E.; Dixneuf, P. H. *Adv. Synth. Catal.* **2007**, *349*, 933. (i) Yadav, J. S.; Reddy, B. V. S.; Vishnumurthy, R. *Tetrahedron Lett.* **2008**, *49*, 4498. (j) Liu, D. N.; Tian, S. K. *Chem.—Eur. J.* **2009**, *15*, 4538. (k) Artok, L.; Kus, M.; Aksin-Artok, O.; Dege, F. N.; Ozkihnc, F. Y. *Tetrahedron* **2009**, *65*, 9125. (l) Dhakshinamoorthy, A.; Alvaro, M.; Garcia, H. *Adv. Synth. Catal.* **2010**, *351*, 2271.

(11) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4257.

Table 1. Optimization of the Model System[a]

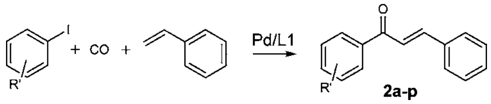


Entry	Ligand	mol [%]	Yield of **3a** [%][b]
1	**L1**	6	15
2	**L2**	6	0
3	PCy_3	6	2
4	PPh_3	6	5
5		6	3
6		6	2
7	DPPF	3	0
8	DPPE	3	0
9		3	6
10		3	0
11		3	2
12	$P(^tBu)_3 \cdot HBF_4$	6	10
13		6	10
14		6	12
15		6	13
16		6	12
17	**L1**	4	42
18	**L1**	2	29
19	**L1**	4	38[c]
20	**L1**	4	55[d]
21	**L1**	4	70[e]
22	**L1**	4	66[f]

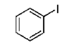
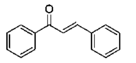
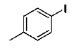
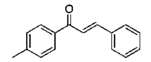
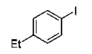
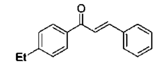
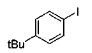
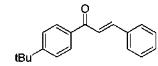
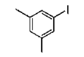
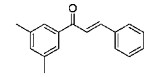
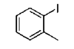
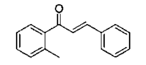
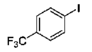
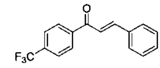
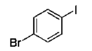
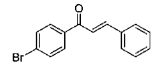
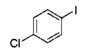
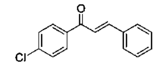
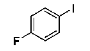
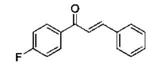
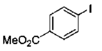
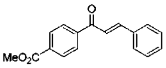
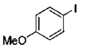
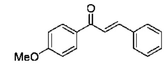
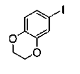
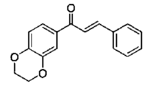
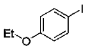
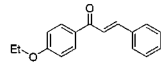
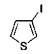
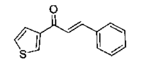
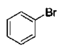
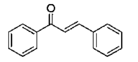
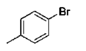
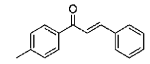
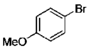
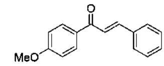
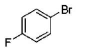
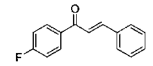
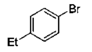
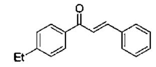
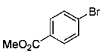
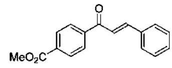
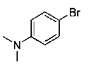
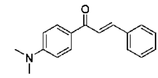
[a] Iodobenzene (1 mmol), styrene (2 mmol), $[(cinnamyl)PdCl]_2$ (1 mol %), ligand (6 mol %), NEt_3 (2 mmol), dioxane (2 mL), CO (5 bar), 100 °C, 20 h. [b] Determined by GC; hexadecane as internal standard. [c] 4 equiv of styrene. [d] Dioxane (0.5 mL), 4 equiv of styrene. [e] Dioxane (0.5 mL), 6 equiv of styrene. [f] Dioxane (0.5 mL), 8 equiv of styrene, PCy_3 (tricyclohexylphosphine), DPPE (1,2-bis(diphenylphosphino)ethane), DPPF (1,1′-bis(diphenylphosphino)ferrocene).

showed high reactivity in the reductive carbonylation of vinyl triflates, led to complete conversion but gave only 2% of the target product (Table 1, entry 11). Instead, significant amounts of benzoic anhydride and *N*,*N*-diethylbenzamide are formed. Tri-*tert*-butylphosphine and other di-*tert*-butyl-substituted phosphines also gave only low yields (10−13%) of the carbonylative product (Table 1, entries 12−16). However, to our delight, the yield of the target product was improved to 42% by decreasing

Table 2. Variation of Aryl Halides[a]



2a-p

Entry	Aryl halides	Product	Yield [%][b]
1		 **2a**	68
2		 **2b**	75
3		 **2c**	78
4		 **2d**	90
5		 **2e**	85
6		 **2f**	41[c]
7		 **2g**	59[c] 70[d]
8		 **2h**	74[d]
9		 **2i**	81
10		 **2j**	89
11		 **2k**	57[d]
12		 **2l**	84
13		 **2m**	87
14		 **2n**	79
15		 **2o**	75
16		 **2a**	55[c]
17		 **2b**	60[e]
18		 **2l**	85[e]
19		 **2j**	80[e]
20		 **2c**	66[e]
21		 **2k**	60[e]
22		 **2p**	72[e]

[a] Aryl iodide (1 mmol), styrene (6 mmol), [(cinnamyl)PdCl]$_2$ (1 mol %), **L1** (4 mol %), NEt$_3$ (2 mmol), dioxane (0.5 mL), CO (5 bar), 100 °C, 20 h. [b] Isolated yield. [c] 30−40% of the "normal" Heck product was formed. [d] 80 °C, CO (10 bar), 40 h. [e] [(Cinnamyl)PdCl]$_2$ (2 mol %), 2-(di-*tert*-butylphosphino)-1-(naphthalene-1-yl)-1*H*-pyrrole (8 mol %), 120 °C, CO (10 bar).

the amount of ligand **L1** (Table 1, entries 1, 17 and 18). Even better yields (70%) were obtained by optimizing the concentration of solvent and styrene (Table 1, entry 21).

With suitable conditions in our hand (Table 1, entry 14), the scope of the carbonylation process with regard to the aryl halides and olefins was next examined (Tables 2 and 3). The generality of the protocol is proven by the reaction of 32 different substrates, which all gave the desired products in moderate to excellent yields. Electron-rich and electron-deficient aryl iodides and bromides gave good yields (57−89%) of the corresponding α,β-unsaturated ketones (Table 2, entries 7−14).

Most substrates shown gave clean conversion with no competing formation of Heck products.[14] Heteroaryl substrates, e.g., 3-iodothiophene (Table 2, entry 15), were also efficiently transformed, and the reaction showed good functional group tolerance. In general, both meta- and para-substituted benzenes were successfully transformed into the corresponding products with good yields and excellent chemoselectivity (75−90%; Table 2, entries 2−5). However, ortho-substituted iodobenzene gave a lower yield of the corresponding ketone together with a certain amount of 1-methyl-2-styrylbenzene (Table 2, entry 6). Notably, applying 2-(di-*tert*-butylphosphino)-1-(naphthalen-1-yl)-1*H*-pyrrole together with [(cinnamyl)PdCl]$_2$ and aryl bromides can be transformed into the corresponding chalcones. Best results are obtained at a slightly increased reaction temperature (120 °C) and a CO pressure (10 bar) (Table 2, entries 16−22). Both electron-rich (methoxy- and dimethylamino-substituted bromobenzenes) as well as electron-poor (ester- and fluoride-substituted bromobenzenes) aryl bromides gave good isolated yields of the corresponding products (Table 2, entries 21, 22; 60−72%).

Next, we turned our attention to carbonylative vinylations with other olefins. Notably, not only styrene but substituted styrenes and acrylates as well as enol ethers worked well in our protocol (Table 3)! For example, *p*-*tert*-butyl-, *p*-methoxy-, *m*-methyl-, *p*-fluoro-, and *p*-chloro-substituted styrenes gave 51−88% of the corresponding chalcone products (Table 3, entries 1−5). In the case of expensive styrenes, the excess of olefin can easily be separated from the reaction mixture either by column chromatography or by distillation. However, even

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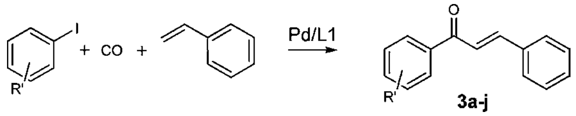
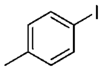
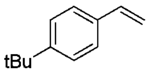
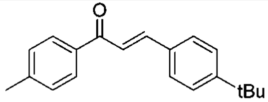
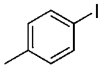
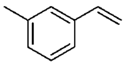
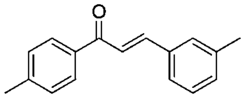
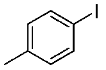
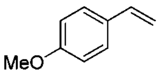
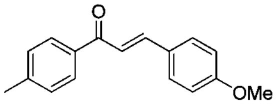
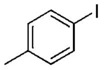
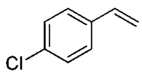
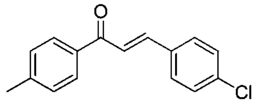
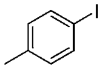
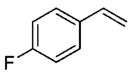
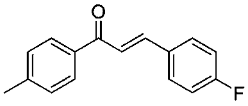
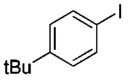
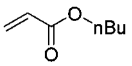
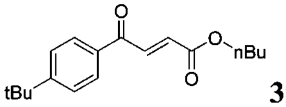
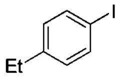
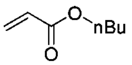
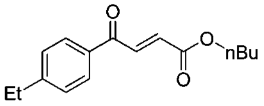
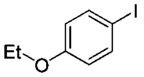
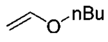
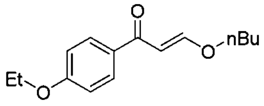
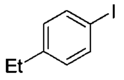
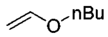
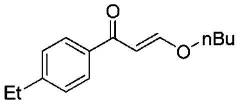
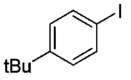
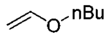
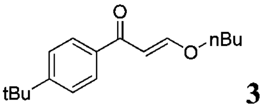
(12) For some other application of this ligand see: (a) Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 918. (b) Sergeev, A. G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7595. (c) Hu, T.; Schulz, T.; Torborg, C.; Chen, X.; Wang, J.; Beller, M.; Huang, J. *Chem. Commun.* **2009**, 7330. (d) Schulz, T.; Torborg, C.; Enthaler, S.; Schaffner, B.; Dumrath, A.; Spannenberg, A.; Neumann, H.; Börner, A.; Beller, M. *Chem.—Eur. J.* **2009**, *15*, 4528.

(13) Neumann, H.; Sergeev, A.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4887.

(14) For reviews and recent selected examples of Heck coupling see: (a) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345. (c) Jeffery, T. *Adv. Met. Org. Chem.* **1996**, *5*, 153. (d) Stark, G.; Riermeier, T. H.; Beller, M. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 1; p 208. (e) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (f) Ludwig, M.; Stroemberg, S.; Svensson, M.; Akermark, B. *Organometallics* **1999**, *18*, 970. (g) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, *11*, 1589. (h) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (i) Amatore, C.; Godin, B.; Jutand, A.; Lemaitre, F. *Organometallics* **2007**, *26*, 1757. (j) Lee, M. T.; Lee, H. M.; Hu, C. H. *Organometallics* **2007**, *26*, 1317. (k) Amatone, C.; Godin, B.; Jutand, A.; Lemaitre, F. *Chem.—Eur. J.* **2007**, *13*, 2002. (l) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31. (m) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 79. (n) Wang, D.; Engle, K. M.; Shi, B.; Yu, J. *Science* **2010**, *327*, 315.

Table 3. Variation of Alkenes[a]



Entry	Aryl halide	Alkene	Product	Yield [%][b]
1			 **3a**	68
2			 **3b**	82
3			 **3c**	85
4			 **3d**	51
5			 **3e**	88
6			 **3f**	72 47[d]
7			 **3g**	70
8			 **3h**	77[c]
9			 **3i**	69[c]
10			 **3j**	78[c] 55[d]

[a] Aryl iodide (1 mmol), styrene (6 mmol), [(cinnamyl)PdCl]$_2$ (1 mol %), **L1** (4 mol %), NEt$_3$ (2 mmol), dioxane (0.5 mL), CO (5 bar), 100 °C, 20 h. [b] Isolated yield. [c] Trans product was isolated with >99% selectivity. [d] 3 equiv of alkene.

with a lower amount of alkene (3 equiv), the corresponding carbonylative products are isolated in 47−55% yield (Table 3, entries 6, 10). Reactions of inexpensive butyl acrylate and butyl vinyl ether with aryl iodides in the presence of carbon monoxide led to interesting functionalized building blocks in 69−78% yields (Table 3, entries 6−10).[15] Notably, all products are isolated with >99% trans selectivity. To the best of our knowledge none of these reactions have been described before and it is clear that they represent valuable extensions of currently known carbonylation reactions.

The proposed mechanism of the palladium-catalyzed carbonylative vinylation is shown in Scheme 3. In agreement with previous studies on catalytic carbonylations of aryl halides,[16] we suppose that oxidative addition of the aryl halide to Pd(0), which is easily generated by reduction of Pd(II) with CO, forms complex **1**.[17] This complex could be isolated as a stable intermediate, and the structure was confirmed by NMR and X-ray studies (Figure 1). Subsequent coordination and insertion of carbon monoxide leads to the respective acylpalladium

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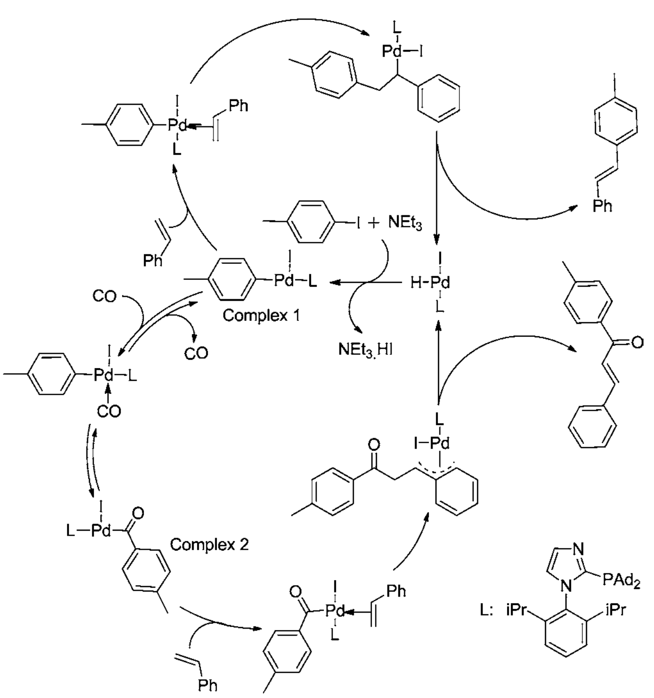
(15) Nilsson, P.; Olofsson, K.; Larhed, M. Focus on Regioselectivity and Product Outcome in Organic Synthesis. In *The Heck Reaction*; Oestreich, M., Ed.; John Wiley and Sons: New York, 2009; p 133.

Scheme 3. Proposed Mechanism



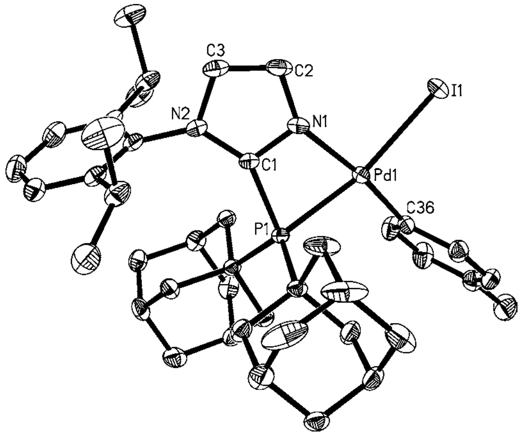


Figure 1. Molecular structure of complex **1**. Thermal ellipsoids correspond to 30% probability. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd1−I1, 2.6140(3); Pd1−P1, 2.2977(8); Pd1−N1, 2.151(2); Pd1−C36, 2.000(3); C36−Pd1−P1, 103.68(8); N1−Pd1−P1, 69.12(7); C36−Pd1−I1, 90.26(8); N1−Pd1−I1, 96.94(6).[17]

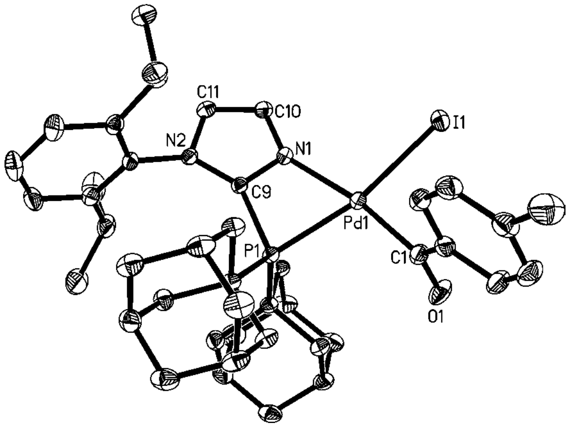


Figure 2. Molecular structure of complex **2**. Thermal ellipsoids correspond to 30% probability. Selected bond lengths (Å) and angles (deg): C1−Pd1, 1.952(4); N1−Pd1, 2.201(2); P1−Pd1, 2.3198(6); Pd1−I1, 2.6300(2); C1−Pd1−P1, 103.63(11); N1−Pd1−P1, 68.10(5); C1−Pd1−I1, 88.74(11); N1−Pd1−I1, 99.72(5).[18]

intermediate **2**. Indeed, reaction of complex **1** under 5 bar of CO gave **2** as a brown solid within one hour at room temperature (Figure 2).[18] Coordination and insertion of the alkene followed by β-hydride elimination produces the desired chalcone.[19] Finally, the active palladium species is regenerated by reaction with NEt_3 to complete the catalytic cycle. Most likely, formation of benzoic acid amide and acid anhydride proceeds via decomposition reactions of NEt_3[20] and reactions with trace amounts of water. The formation of stilbene (Table 2, entries 6 and 7) can be explained either by direct insertion of the olefin into complex **1** or by reversible decarbonylation of **2** and subsequent olefin insertion. However, reaction of complex **2** with styrene in between room temperature and 100 °C did not result in the formation of stilbene. Notably, at room temperature no chalcone is detected even after 24 h; however, at 100 °C the product is formed after 30 min. Apparently, insertion of styrene into the benzoylpalladium species constitutes the rate-determining step under these conditions.

Conclusion

In summary, we have developed a general and efficient protocol for carbonylative Heck reactions of aryl iodides and bromides. This methodology represents a useful extension of the established carbonylative Suzuki and carbonylative Sonogashira reactions. For the first time, various aromatic and aliphatic alkenes work well in our system and afford good yields of the corresponding α,β-unsaturated ketones (41−90%). Start-

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(16) For selected examples of mechanistic studies of palladium-catalyzed carbonylations see: (a) Sergeev, A. G.; Spannenberg, A.; Matthias, M. *J. Am. Chem. Soc.* **2008**, *130*, 15549. (b) Trzeciak, A. M.; Ziolkowski, J. J. *Coord. Chem. Rev.* **2005**, *249*, 2308.

(17) Crystal data of complex 1: $C_{46}H_{66}IN_2OPPd$, $M_r = 927.28$, monoclinic, space group $P2_1/n$, $a = 13.7393(3)$ Å, $b = 18.4558(4)$ Å, $c = 17.0955(4)$ Å, $\beta = 90.225(2)°$, $V = 4334.9(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.421$ g·cm^{-3}, $\mu = 1.213$ mm^{-1}, $T = 200$ K, 60956 reflections collected, 8511 independent ($R_{int} = 0.0503$) and 5820 observed [$I > 2\sigma(I)$] reflections, final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0301$, $wR_2 = 0.0542$, R indices (all data): $R_1 = 0.0556$, $wR_2 = 0.0577$, 476 refined parameters. Crystal of the compound contained diethylether as solvent, which is not depicted in Figure 1.

(18) Crystal data of complex 2: $C_{46.2}H_{65.3}I_{1.1}N_2O_{1.9}PPd$, $M_r = 956.06$, monoclinic, space group $P2_1/c$, $a = 12.7752(2)$ Å, $b = 14.9793(3)$ Å, $c = 23.3956(4)$ Å, $\beta = 102.3919(14)°$, $V = 4372.76(13)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.452$ g·cm^{-3}, $\mu = 1.276$ mm^{-1}, $T = 200$ K, 69762 reflections collected, 10055 independent ($R_{int} = 0.0463$) and 7119 observed [$I > 2\sigma(I)$] reflections, final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0255$, $wR_2 = 0.0474$, R indices (all data): $R_1 = 0.0476$, $wR_2 = 0.0501$, 491 refined parameters. Crystal of the compound contained diethylether as solvent, which is not depicted in Figure 2. 10% of $L1PdI_2$ besides the desired complex 2 was obtained in the solid state. The I ligand with a side occupancy factor of 0.1 is omitted in Figure 2.

(19) For some examples of insertion of olefins into acylpalladium complexes see: (a) Hamada, A.; Braunstein, P. *Organometallics* **2009**, *28*, 1688. (b) Zuidema, E.; Bo, C.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2007**, *129*, 3989. (c) Agostinho, M.; Braunstein, P. *Chem. Commun.* **2007**, 58. (d) Takeuchi, D.; Yasuda, A.; Osakada, K. *J. Chem. Soc., Dalton Trans.* **2003**, 2029. (e) Schwarz, J.; Herdtweck, E.; Herrmann, W. A.; Gardiner, M. G. *Organometallics* **2000**, *19*, 3154.

(20) Negishi, E.-I.; Coperet, C.; Ma, S.; Mita, T.; Sugihara, T.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5904.

ing from easily available aryl iodides and bromides, interesting building blocks are obtained under mild conditions.

Experimental Section

General Comments. All reactions were carried out under argon atmosphere. Dioxane, triethylamine, THF, diethyl ether, and heptane were distilled from sodium ketyl or CaH and stored in Aldrich Sure/Stor flasks under argon. Aryl iodides and styrenes were purchased from Aldrich or ABCR and used as received. 2-(Di-1-adamantylphosphino)-1-(2,6-diisopropylphenyl)-1*H*-imidazole,[12] Pd(COD)-$(CH_2SiMe_3)_2$,[21] and $[(cinnamyl)PdCl]_2$[22] were synthesized according to reported procedures. Column chromatography was performed using Merck Silicagel 60 (0.043−0.06 mm). NMR data were recorded on Bruker ARX 300 and Bruker ARX 400 spectrometers. ^{13}C and ^{1}H NMR spectra were referenced to signals of deutero solvents and residual protiated solvents, respectively. ^{31}P NMR chemical shifts are reported relative to 85% H_3PO_4. Gas chromatography analysis was performed on an Agilent HP-5890 instrument with a FID detector and HP-5 capillary column (polydimethylsiloxane with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 μm film thickness) using argon as carrier gas. Gas chromatography−mass analysis was carried out on an Agilent HP-5890 instrument with an Agilent HP-5973 Mass Selective Detector (EI) and HP-5 capillary column (polydimethylsiloxane with 5% phenyl groups, 30 m, 0.25 mm i.d., 0.25 μm film thickness) using helium carrier gas. ESI and HR-MS measurements were performed on an Agilent 1969A TOF mass spectrometer. Melting points were measured by GalenTMIII. X-ray crystal structure analysis of complexes: data were collected on a STOE IPDS II diffractometer using graphite-monochromated Mo Kα radiation. The structures were solved by direct methods (SHELXS-97: Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112) and refined by full-matrix least-squares techniques on F^2 (SHELXL-97: Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112). XP (Bruker AXS) was used for graphical representations.

General Procedure for Catalytic Reactions. A 10 mL Schlenk flask was charged with $[(cinnamyl)PdCl]_2$ (26 mg, 1 mol %), 2-(di-1-adamantylphosphino)-1-(2,6-diisopropylphenyl)-1*H*-imidazole (105.8 mg, 4 mol %), NEt_3 (1.4 mL, 2 equiv), and dioxane (2.5 mL). Then, hexadecane (1 mL, internal GC standard) and 0.98 mL of this clear, brown stock solution were transferred into four vials (12 mL reaction volume) equipped with a septum, a small cannula, a stirring bar, 1 mmol of the corresponding aryl iodides and 6 mmol of styrenes. The vials were placed in an alloy plate, which was transferred into a 300-mL autoclave of the 4560 series from Parr Instruments under argon atmosphere. After flushing the autoclave three times with CO and adjusting the pressure to 5 bar, the reaction was performed for 20 h at 100 °C. After the reaction, the autoclave was cooled down to room temperature, and the pressure was released carefully. The product was washed with water and extracted with 2 mL of ethyl acetate three times; after being concentrated under reduced pressure, the product was purified by silica gel chromatography using *n*-heptane/AcOEt (40:1) as an eluent.

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Supporting Information Available: Optimization data, NMR data for all products, X-ray crystallographic and NMR studies for complexes **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Pan, Y.; Young, G. B. *J. Organomet. Chem.* **1999**, *577*, 257.

(22) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2003.