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Carbonylative Heck Reactions Using CO Generated *ex Situ* in a Two-Chamber System

Philippe Hermange, Thomas M. Gøgsig, Anders T. Lindhardt, Rolf H. Taaning, and Troels Skrydstrup*

Center for Insoluble Protein Structures (inSPIN), Department of Chemistry and the Interdisciplinary Nanoscience Center, Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark

ts@chem.au.dk

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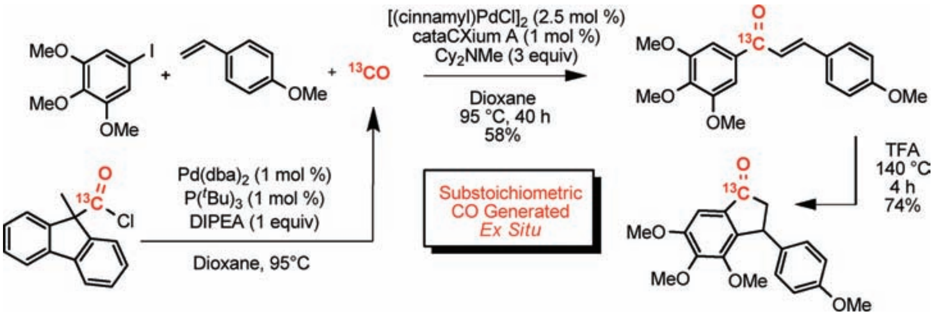
ABSTRACT



A carbonylative Heck reaction of aryl iodides and styrene derivatives employing a two-chamber system using a stable, crystalline, and nontransition metal based carbon monoxide source is reported. By applying near-stoichiometric amounts of the carbon monoxide precursor, an effective exploitation of the hazardous CO gas is obtained affording chalcone derivatives in good yields. Application to isotope labeling, incorporating ^{13}CO, was further established.

Since its discovery in 1968, the Heck reaction has proved itself to be one of the most useful palladium catalyzed reactions for C–C bond formation.[1] Due to the impressive functional group tolerance and vast applications, the Heck reaction has recently been decorated with the Nobel Prize together with the Suzuki and Negishi cross couplings. Nevertheless, improvements, new variations, and mechanistic insights are reported on a regular basis further illustrating the importance of this reaction.[2]

To make catalysis even more efficient and diverse, focus has been aimed on the introduction of multiple components to catalytic processes forming several bonds in a one-step procedure.[3] In particular, the direct incorporation of carbon monoxide as a one carbon fragment into the established palladium catalyzed reactions has received much attention. The resulting carbonylated product often acts as an entry point to further manipulations or serves as a valuable motif in itself. These transformations include amino-, thio-, and alkoxycarbonylations, carbonylative Suzuki and Sonogashira reactions, formylations, and carboxamidations to address a few.[4]

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(1) (a) Hartwig, J. F. In *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: 2010. (b) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5538. (c) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (d) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. (e) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133.

(2) (a) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 79. (b) Henriksen, S. T.; Norrby, P.-O.; Kaukoranta, P.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 10414. (c) Ebran, J.-P.; Hansen, A. L.; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *127*, 6931. (d) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (e) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751. (f) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349.

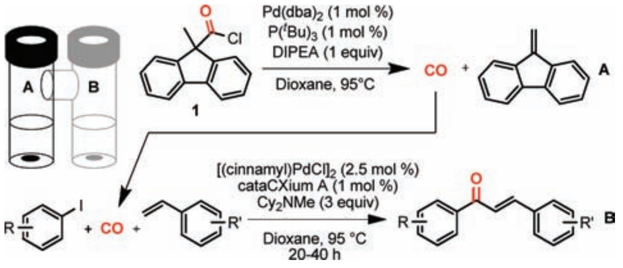
(3) (a) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050. (b) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 1644. (c) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 7439.

(4) (a) For review, see: Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114 and references herein. (b) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2010**, *16*, 9750.

10.1021/ol200686h

On the other hand, intermolecular carbonylative Heck couplings, introduced by Miura and co-workers in 1995, have been described to a lesser extent.[5,6] Recently, Beller and co-workers expanded this process disclosing a general strategy for the synthesis of pharmaceutical attractive chalcone related compounds starting from aryl halides in combination with carbon monoxide and acyclic olefins. Relatively high pressures (5−10 bar) of CO ensured by the use of an autoclave and a specially designed ligand proved mandatory.[7] The handling of high pressure carbon monoxide, being a flammable, toxic, and teratogenic gas, requires specific safety precautions hereby limiting its applicability in both industry and academia.

Scheme 1. *Ex Situ* CO Generation from the Two-Chamber System



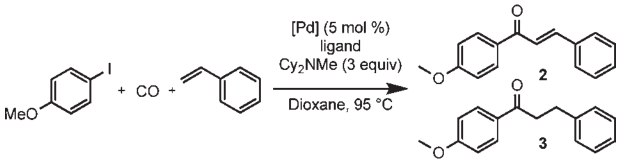
As illustrated in Scheme 1 we wish to report on a newly developed two-chamber system enabling a measured amount of CO, generated *ex situ* from a stable, crystalline, and nontransition metal based CO source (Chamber **A**), to be consumed in a parallel carbonylative Heck reaction (Chamber **B**). Furthermore, the unique setup unlocks a new efficient technique for carbon isotope labeling with mild reaction conditions.[8]

Based on previous work done by our group, an α-quaternary substituted acid chloride with the capability to undergo decarbonylation and subsequent β-hydride elimination when subjected to an appropriate palladium complex was chosen as the CO source (see Supporting Information).

In this regard, 9-methyl-fluorene-9-carbonyl chloride **1** in combination with Pd(dba)$_2$ and the sterical encumbered ligand P(tBu)$_3$ together with *N*-diisopropyl-*N*-ethylamine (DIPEA) as base proved effective (Scheme 1, **A**).[8c,9,10]

Preliminary investigations revealed PdCl$_2$ as a promising catalyst for the carbonylative Heck coupling of 4-iodoanisole and styrene in the presence of *N*,*N*-dicyclohexylmethylamine (Cy$_2$NMe) in dioxane using a slight excess of carbon monoxide (Table 1, entry 1). Noteworthy, *no ligand* was needed for completion of the reaction, but unfortunately substantial amounts of the reduced chalcone were detected.[11] Changing the catalyst to [(cinnamyl)PdCl]$_2$ gave a homogeneous reaction mixture, but similar conversions and ratios of the desired and reduced product were obtained.

Table 1. Optimization of the Carbonylative Heck Reaction in the Two-Chamber System[a]



entry	[Pd]	ligand	ratio **2:3**	conversion [%][b] (isolated yield) [%]
1	PdCl$_2$	-	4:1	>95
2	Pd(OAc)$_2$	-	7:2	94
3	[(allyl)PdCl]$_2$	-	4:1	>95
4	[(cinnamyl)PdCl]$_2$	-	4:1	>95 (82)
5[c]	[(cinnamyl)PdCl]$_2$	PPh$_3$	5:1	62
6[c]	[(cinnamyl)PdCl]$_2$	PCy$_3$HBF$_4$	3:1	38
7[c,d]	[(cinnamyl)PdCl]$_2$	P(t-Bu)$_3$	0:0	>95
8[c]	[(cinnamyl)PdCl]$_2$	cataCXium A	>95:5	51
9[e]	[(cinnamyl)PdCl]$_2$	cataCXium A	>95:5	90
10[f]	[(cinnamyl)PdCl]$_2$	cataCXium A	>95:5	>95 (74)
11[g]	[(cinnamyl)PdCl]$_2$	cataCXium A	95:5	>95

[a] Chamber A: **1** (0.75 mmol), Pd(dba)$_2$ (1 mol %), P(t-Bu)$_3$ (1 mol %), DIPEA (0.75 mmol) in dioxane (3 mL) for 20 h. Chamber B: Iodoanisole (0.5 mmol), styrene (3.0 mmol), Cy$_2$NMe (1.5 mmol), [Pd] (5 mol %) in dioxane (3 mL) for 20 h. [b] Determined by ^{1}H NMR analysis. [c] Ligand (7.5 mol %). [d] Only the direct Heck coupling product was observed. [e] Ligand (2.5 mol %). [f] Ligand (1 mol %). [g] Ligand (0.5 mol %).

Addition of a phosphine ligand at 7.5 mol % such as PPh$_3$, PCy$_3$, P(tBu)$_3$, and cataCXium A influenced both the conversions and ratios (Table 1, entries 5−8). With P(tBu)$_3$ only direct coupling and the formation of stilbene were surprisingly observed.[12,13] On the other hand, employing cataCXium A resulted in excellent selectivity

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

(6) For intramolecular Heck reactions, see: (a) Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804. (b) Wu, X.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 346.

(7) (a) Wu, X.-F.; Neumann, H.; Spannenberg, A.; Schulz, T.; Jiao, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 14596. (b) For aryl triflates, see: Wu, X.-F.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010***49*, 5284. (c) For DFT computations, see: Wu, X.-F.; Jiao, H.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 726.

(8) (a) For carbonylation reactions using Mo(CO)$_6$, and Co$_2$(CO)$_8$, see: Wannberg, J.; Larhed, M. In *Modern Carbonylation Methods*; Kollár, L., Ed.; Wiley-VCH: 2008; pp 93−112. (b) For carbonylation reactions using W(CO)$_6$, see: Więckowska, A.; Fransson, R.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2011**, *76*, 978. (c) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**ASAP (DOI: 10.1021/ja200818w). (d) Patent application currently proceeding: Taaning, R. H.; Hermange P.; Lindhardt, A. T.; Skrydstrup, T. (Aarhus University, DK) System providing controlled delivery of gaseous CO for carbonylation reactions. PA 2010 70546, December 15, 2010.

(9) Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. *J. Am. Chem. Soc.* **2010**, *132*, 7998.

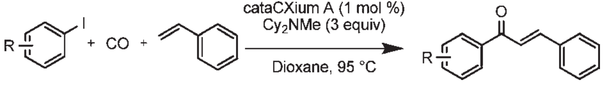
(10) The air- and moisture-stable HBF$_4$P(tBu)$_3$ salt performed equally well.

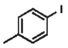
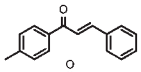
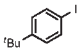
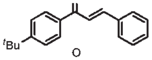
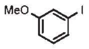
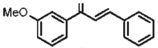
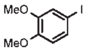
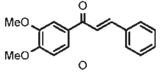
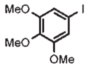
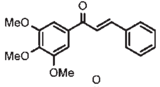
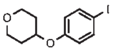
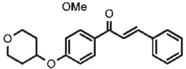
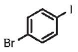
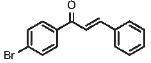
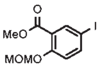
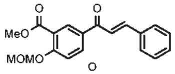
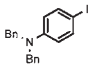
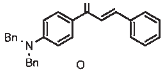
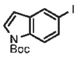
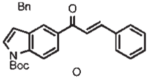
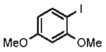
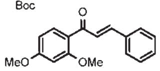
(11) Ether based solvents or trialkylamines are known to act as reducing agents: (a) Martins, A.; Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 5186. (b) Coquerel, Y.; Brémond, P.; Rodriguez, J. *J. Organomet. Chem.* **2007**, *692*, 4805.

(12) A similar effect was noted by the group of Beller in the formylation of aryl halides; see ref 8 and: 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.

generating the α,β-unsaturated ketone exclusively (Table 1, entry 8).[14] Under the assumption that excess ligand decreased the amount of the catalytically active species, the Pd/phosphine ratio was next investigated using this ligand (Table 1, entries 9−11). We were pleased to see that reducing the amount of cataCXium A to 1 mol % restored full conversion while maintaining an excellent selectivity, and a 74% yield of **2** could be secured upon column chromatography (Table 1, entry 10). In contrast, decreasing both palladium and phosphine loadings resulted in a detrimental effect (See Supporting Information).

Table 2. Scope of the Carbonylative Heck Reaction in the Two-Chamber System

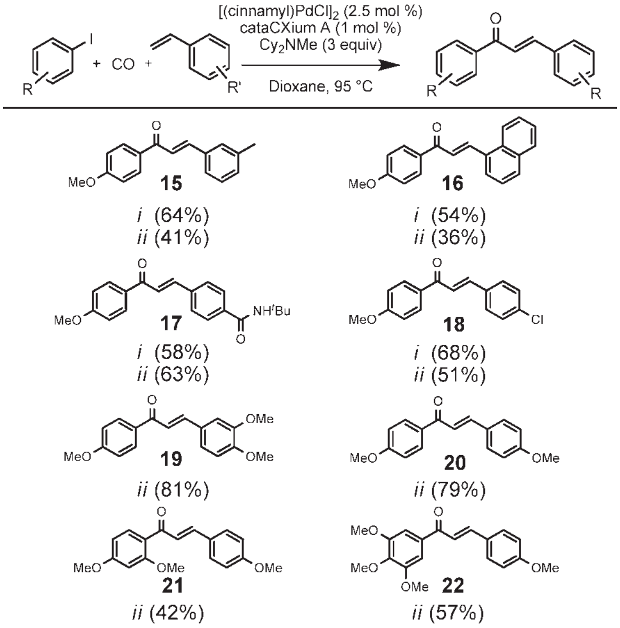


entry	aryl iodide	product		yield [%][b]
1			**4**	59
2			**5**	67
3			**6**	58
4			**7**	69
5			**8**	64
6			**9**	79
7			**10**	41
8			**11**	34
9			**12**	52
10			**13**	55
11			**14**	41

[a] Chamber **A**: **1** (0.75 mmol), Pd(dba)$_2$ (1 mol %), P(t-Bu)$_3$ (1 mol %), DIPEA (0.75 mmol) in dioxane (3 mL) for 20 h. Chamber **B**: Iodoanisole (0.5 mmol), styrene (3.0 mmol), Cy$_2$NMe (1.5 mmol), cataCXium A (1 mol %), [(cinnamyl)PdCl]$_2$ (2.5 mol %) in dioxane (3 mL) for 20 h. [b] Isolated by flash column chromatography.

Next, the scope of the two-chamber carbonylative Heck reaction using only 1.5 equiv of carbon monoxide was tested (Table 2). In general, moderate to good yields of the desired chalcone derivatives were obtained. In accordance with the literature, electron-rich arenes revealed themselves to be the most effective in facilitating CO incorporation and good yields were secured (entries 1−6).[8,15] Furthermore, heterocyclic compounds were well tolerated, and perfect chemoselectivities are attained in the coupling of 4-bromoiodobenzene allowing further functionalization (entries 6, 7, 10). Ortho-substituents and electron-withdrawing groups lowered the outcome of the carbonylative reaction, and increased amounts of the stilbene derivative were observed (entries 8, 11).[15]

Scheme 2. Scope of the Carbonylative Heck Reaction in the Two-Chamber System[a]



[a] Conditions *i*: Chamber A: **1** (0.75 mmol), Pd(dba)$_2$ (1 mol %), P(t-Bu)$_3$ (1 mol %), DIPEA (0.75 mmol) in dioxane (3 mL) for 20 h. Chamber B: Iodoanisole (0.5 mmol), olefin (3.0 mmol), Cy$_2$NMe (1.5 mmol), cataCXium A (1 mol %), [(cinnamyl)PdCl]$_2$ (2.5 mol %) in dioxane (3 mL) for 20 h. Conditions *ii*: Same as *i* using olefin (1 mmol) for 40 h in Chamber B.

Carbonylative vinylation of 4-iodoanisole exploiting different styrene derivatives was then studied using the described reaction conditions (Scheme 2). Alternatively, only 2 equiv of the olefin and prolonged reaction times could successfully be applied obtaining comparable yields. Gratifyingly, various substituted styrenes coupled effectively to 4-iodoanisole employing the two-chamber system forming the corresponding carbonylated stilbene in good yields. Both electron-rich and -deficient styrenes performed well using only a small excess of carbon monoxide. Again, ortho-substituents on the aryl iodide lowered the yield. However, an acceptable 42% isolated yield of the diuretic metochalcone **21** was accomplished, also being a precursor to a flavone derived compound.[16]

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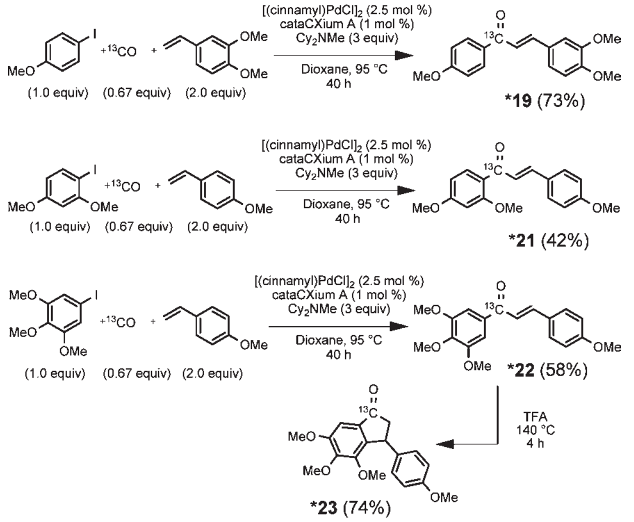
(13) Low incorporation of CO in the carbonylative Heck reaction was reported by the group of Beller using P(tBu)$_3$. The higher CO pressure employed could potentially acount for this observation; see ref 7a.

(14) Sergeev, A. G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2008**, *130*, 15549.

(15) Studies on the electronic properties of organopalladium complexes affecting the CO capture have been described revealing electron-donating groups to enhance the CO incorporation. See: (a) Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115. (b) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726.

Scheme 3. Isotope Labeling Using the Two-Chamber System



Finally, we decided to test the two-chamber system in ^{13}C isotope labeling. 9-Methyl-fluorene-9-[^{13}C] carbonyl chloride ***1**, readily obtained from 9-fluorenone, was utilized as the ^{13}CO source in substoichiometric amounts. To our delight, the two-chamber system proved effective facilitating the ^{13}C insertion, employing the described conditions (Scheme 3). The ^{13}C labeled chalcone ***19** and [^{13}C]metochalcone ***21** were secured in good yields based on the carbon monoxide precursor. Additionally, ^{13}CO was smoothly assimilated into an indanone scaffold ***23** in a two-step procedure starting from 3,4,5-trimethoxyiodobenzene.

In conclusion, carbonylative Heck reactions of various aryl iodides and styrene derivatives using only slight excess of carbon monoxide in a two-chamber system are reported. The described method demonstrates it to be a powerful tool for the isotope labeling of chalcone derived compounds. This technology opens a new method for carbonylative isotope chemistry, and further applications are en route in our laboratories.

Acknowledgment. We are deeply appreciative of the generous financial support from the Danish National Research Foundation, the Danish Natural Science Research Council, and Aarhus University.

Supporting Information Available. Experimental details and copies of ^{1}H and ^{13}C NMR spectra for all the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Yao, N.; Song, A.; Wang, X.; Dixon, S.; Lam, K. S. *J. Comb. Chem.* **2007**, *9*, 668.