ORGANIC LETTERS

2012
Vol. 14, No. 10
2536–2539

Palladium Catalyzed Carbonylative Heck Reaction Affording Monoprotected 1,3-Ketoaldehydes

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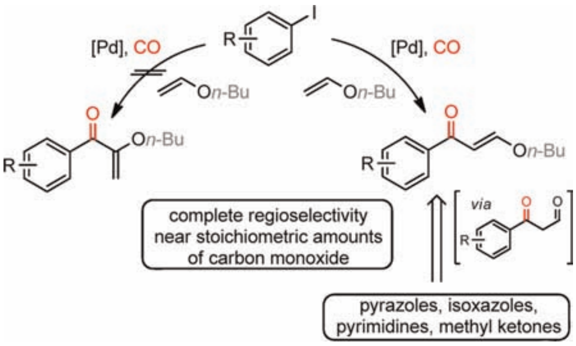
Received April 2, 2012

ABSTRACT



The direct carbonylative palladium catalyzed synthesis of monoprotected 1,3-ketoaldehydes is reported starting from aryl iodides applying near stoichiometric amounts of carbon monoxide. Besides representing platforms for a variety of heterocyclic structures, these motives serve as viable precursors for the highly relevant aryl methyl ketones. The presented strategy can also be adapted for the facile and efficient incorporation of ^{13}C-labeled carbon monoxide.

Olefins represent one of the most versatile functional groups in organic chemistry serving as an indispensible platform to a myriad of different chemical bond formations. The presence of C–C double bonds in bioactive compounds, fine chemicals, organic materials, etc. is vast, emphasizing the importance of this functional group and its functionalization.[1]

The palladium catalyzed direct substitution of the olefinic C–H bonds, also known as the Heck reaction, constitutes one of the most powerful Pd-catalyzed reactions owing to the exceptional functional group tolerance and mild conditions often applied.[2] Although the Heck reaction has been subjected to considerable investigations in recent decades, controlling regioselectivity still poses a significant challenge, especially when neutral- and electron-rich olefins are employed.[3] In order to gain full control of the regioselective outcome, it is essential to be able to differentiate between the two catalytic pathways, which are inherently competing during the catalytic cycle of the Heck reaction. Traditionally, bidentate ligands have been utilized in the regioselective arylation of electron-rich olefins resulting in the cationic pathway, thus producing

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10.1021/ol300837d

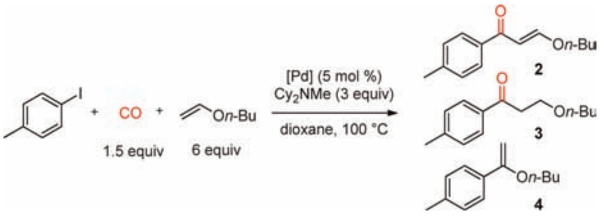
branched α-arylated alkenes.[4] On the other hand, introducing monodentate ligands tends to produce mixtures of the two regioisomers, when olefins such as butyl vinyl ether are employed indicating both pathways are operative.[3d,4a,5,6]

Recently, Beller and co-workers disclosed the carbonylative Heck reaction of aryl halides and styrenes or vinyl ethers relying on a catalytic system composed of palladium and a bidentate ligand.[7] Interestingly, in the couplings of vinyl ethers the linear α,*β*-unsaturated ketoethers were obtained exclusively implying that the insertion of carbon monoxide into the catalytic cycle reverses the regioselective outcome of the Heck reaction of electron-rich olefins.[8] In accordance to the literature, the relatively high pressures of CO (5−10 bar) applied in this protocol increase the demands imposed on the catalytic system. The employment of an imidazole-based phosphine developed by Beller and co-workers was found to be mandatory in order to secure an active catalytic system.[7b,8,9] Formation of carbonyl palladium clusters at high CO pressures slows the rate of the overall reaction as the concentration of the active catalyst is lowered, a hurdle which can be overcome by the addition of extra phosphine.[10] Hence, lowering of the applied CO pressures, thereby preventing the formation of palladium carbonyl clusters, would in general be beneficial in Pd-catalyzed carbonylation chemistry.[11]

Based on our recent work dealing with the Pd-catalyzed carbonylative Heck reaction of styrenes, we wish to report on the regioselective aroylation of butyl vinyl ether applying carbon monoxide in a slight excess.[12] The presented strategy describes the direct formation of monoprotected 1,3-ketoaldehydes starting from aryl iodides without using autoclaves and specialized safety equipment.[13] In particular, 1,3-ketoaldehydes serve as valuable precursors to a wide range of heterocyclic structures including pyrazoles, pyrimidines, isoxazoles, etc. Furthermore, we found α,*β*-unsaturated ketoethers to be immediate precursors to the corresponding aryl methyl ketones further demonstrating the applicability of these structures.

In order to secure a safe and efficient delivery of carbon monoxide, the diatomic gas was generated externally in a two-chamber system (COware) from 9-methyl-9-fluorene-9-carbonyl chloride **1** (COgen) in the presence of $Pd(dba)_2$ and $HBF_4P(t\text{-}Bu)_3$ combined with DIPEA (diisopropylethylamine) as previously reported.[14,15] In the parallel CO-consuming chamber preliminary investigations revealed $PdCl_2$ without the addition of phosphine ligands in the presence of tertiary amine base Cy_2NMe[16] at 100 °C to be a promising starting point facilitating the desired carbonylative Heck coupling of 4-iodotoluene and butyl vinyl ether (Table 1, entry 1). However, significant amounts of the reduced *β*-aroylated product were detected, which could be explained by the competing reductive Heck reaction.[17]

Table 1. Optimization of the Carbonylative Heck Reaction[a]



entry	[Pd]	ligand (mol %)	conversion (%)	ratio (**2**:**3**:**4**)	yield[b] (%)
1	$PdCl_2$	–	>95	20:10:1	–
2	$Pd(OAc)_2$	–	55	4:1:1	–
3	$[(allyl)PdCl]_2$	–	>95	10:3:1	–
4	$Pd(dba)_2$	–	50	20:3:1	–
5	$[(cinnamyl)PdCl]_2$	–	82	20:5:1-	–
6	$[(cinnamyl)PdCl]_2$	$P(o\text{-}tol)_3$ (5.0)	93	10:1:1	–
7	$[(cinnamyl)PdCl]_2$	$P(o\text{-}tol)_3$ (2.5)	>95	20:3:1	–
8	$[(cinnamyl)PdCl]_2$	cataCXium A (2.5)	85	20:1:5	–
9	$[(cinnamyl)PdCl]_2$	PPh_3 (2.5)	>95	20:1:4	–
10	$[(cinnamyl)PdCl]_2$	$P(Ph)_2Bn$ (2.5)	90	10:2:1	–
11	$[(cinnamyl)PdCl]_2$	X-Phos (2.5)	92	20:7:3	–
12	$[(cinnamyl)PdCl]_2$	$HBF_4P(t\text{-}Bu)_3$ (2.5)	>95	20:0:1	72
13	$[(cinnamyl)PdCl]_2$[c]	$HBF_4P(t\text{-}Bu)_3$ (2.5)	69	20:0:1	–
14[d]	$[(cinnamyl)PdCl]_2$	$HBF_4P(t\text{-}Bu)_3$ (2.5)	88	20:0:1	–
15[e,f]	$[(cinnamyl)PdCl]_2$	$HBF_4P(t\text{-}Bu)_3$ (2.5)	>95	20:0:1	81

[a] Chamber A: **1** (0.45 mmol), $Pd(dba)_2$ (5 mol %), $HBF_4P(t\text{-}Bu)_3$ (5 mol %), DIPEA (0.68 mmol) in dioxane (2 mL). Chamber B: 4-Iodotoluene (0.3 mmol), butyl vinyl ether (1.8 mmol), Cy_2NMe (0.9 mmol), ligand (5 mol %), [Pd] (5 mol %) in dioxane (2 mL). [b] Isolated yield. [c] [Pd] (1.25 mol %). [d] Reaction run at 90 °C. [e] In Chamber A: **1** (0.66 mmol). [f] In Chamber A: $Pd(dba)_2$ (1 mol %), $HBF_4P(t\text{-}Bu)_3$ (1 mol %).

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(4) (a) Ruan, J.; Xiao, J. *Acc. Chem. Res.* **2011**, *44*, 614.

(5) (a) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 79. (b) Datta, G. K.; von Schenk, H.; Hallberg, A.; Larhed, M. *J. Org. Chem.* **2006**, *71*, 3896.

(6) The existence of anionic palladium species in the catalytic cycle might also be responsible for the regioselective outcome of the Heck reaction using sterically encumbered alkyl phosphine ligands such as $P(t\text{-}Bu)_3$. See ref 5a.

(7) (a) Wu, X.-F.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5284. (b) Wu, X.-F.; Neumann, H.; Spannenberg, A.; Schulz, T.; Jiao, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 14596.

(8) During the preparation of this article, the group of Beller reported the carbonylative Heck reaction of aryl bromides using vinyl ethers applying a total pressure of 80 bar (5 bar of CO and 75 bar of N_2). See: Schranck, J.; Wu, X.-F.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2012**, *18*, 4827.

(9) It has been shown that high pressures of CO impedes the overall carbonylative reaction. See: (a) Barnard, C. F. J. *Org. Process Res. Dev.* **2008**, *12*, 566. (b) Kormos, C. M.; Leadbeater, N. E. *Synlett* **2007**, *13*, 2006. (c) Gaviño, R.; Pellegrini, S.; Castanet, Y.; Mortreux, A.; Mentré, O. *Appl. Catal., A* **2001**, *217*, 91.

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

(11) Alternatively, Hallberg and coworkers previously reported the palladium catalyzed regioselective *β*-aroylation of vinyl ethers using aroyl chlorides. See: Anderson, C.-M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4257.

(12) Hermange, P.; Gøgsig, T. M.; Lindhardt, A. T.; Taaning, R. H.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 2444.

(13) For the direct synthesis of 1,3-diketones starting from aryl iodides, see: Gøgsig, T. M.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 798.

(14) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061.

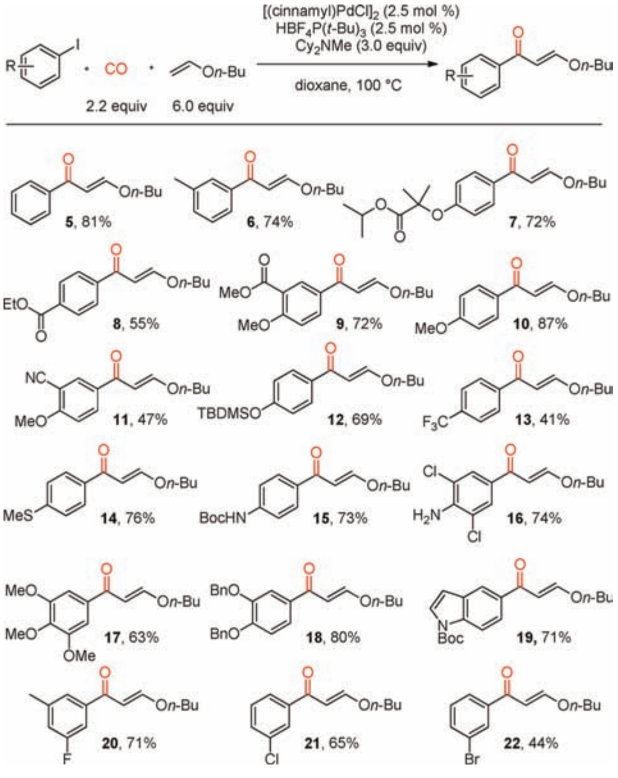
(15) COware and COgen are commercially available at sytracks.com.

(16) (a) Gürtler, C.; Buchwald, S. L. *Chem.—Eur. J.* **1999**, *5*, 3107. (b) Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178.

(17) Gottumukkala, A. L.; de Vries, J. G.; Minnaard, A. J. *Chem.—Eur. J.* **2011**, *17*, 3091.

Improved selectivity and comparable catalytic activity were observed when employing [(cinnamyl)PdCl]$_2$ as the catalyst precursor (entry 5). The addition of monodentate phosphine based ligands lowered the amount of reduced product, and the desired α,β-unsaturated ketoether was produced nearly exclusively when HBF$_4$(t-Bu)$_3$ was applied to the carbonylative β-arylation (entry 12).[18] The formation of a neutral tricoordinated T-shaped complex subsequent to the oxidative addition, securing the catalytic cycle to be operated by a neutral mechanism, could possibly explain the regioselective outcome of the reaction.[19] Interestingly, P(t-Bu)$_3$ proved ineffective in the carbonylative Heck reaction of styrenes neglecting the incorporation of carbon monoxide and providing the stilbene products.[12] On the other hand cataCXium A proved less effective promoting the direct α-arylated Heck product to a higher extent (entry 8). Importantly, a 2:1 ratio of the Pd precursor and the phosphine ligand proved mandatory in order to generate an efficient catalytic system (entries 6, 7, and 13). This effect corresponds with the kinetic data published by Heck and co-workers obtained on the basis of 13 discrete complexes, demonstrating that the addition of excess phosphine impeded the rate of carbon monoxide insertion.[20] This can be overcome by increasing the CO pressure, which in turn may require higher phosphine loadings as earlier described. Lowering the reaction temperature obstructed the catalytic turnover (entry 14). Finally, optimal reaction conditions were obtained when applying 2.2 equiv of carbon monoxide to the reaction mixture resulting in the monoprotected aryl ketoaldehyde in an 81% isolated yield (entry 15). Noteworthy, a catalyst loading of 1 mol % in Chamber A proved equally suitable for an efficient CO release (entry 15).

Scheme 1. Scope of the Carbonylative Heck Reaction[a,b]



[a] Chamber A: 1 (1.10 mmol), Pd(dba)$_2$ (1 mol %), HBF$_4$P(t-Bu)$_3$ (1 mol %), DIPEA (1.65 mmol) in dioxane (3 mL). Chamber B: Aryl iodide (0.50 mmol), butyl vinyl ether (3.0 mmol), Cy$_2$NMe (1.50 mmol), HBF$_4$P(t-Bu)$_3$ (2.5 mol %), [(cinnamyl)PdCl]$_2$ (2.5 mol %), dioxane (4 mL) for 17 h. [b] Isolated yields are given.

These results prompted us to explore the scope of the carbonylative β-arylation testing different aryl iodides. As depicted in Scheme 1 a wide variety of aryl iodides underwent a successful coupling using the optimized reaction conditions.

Aryl iodides displaying both electron-donating and -withdrawing groups provided the β-aroylated vinyl ethers effectively. Arenes carrying ester, cyano, silylether, sulfide, trifluoromethyl, carbamate, and amino groups coupled smoothly complementing the exceptional functional group tolerance typically observed in the Heck reaction (**7**–**9** and **11**–**16**). Protected catecholes and indoles also proved suitable and good yields could be secured after column chromatography (**18** and **19**). The presence of chloride and fluoride did not seem to influence the outcome of the carbonylative Heck reaction (**20** and **21**). On the other hand, activation of the bromide could potentially account for the moderate yield obtained employing 3-bromoiodobenzene (**22**). Aryl bromides proved less effective under the optimized conditions resulting in trace amounts of the desired products (results not shown).

Having established an efficient strategy for the direct synthesis of 1,3-ketoaldehyde surrogates, the applicability of these structures was studied (Scheme 2). Heterocyclic moieties such as pyrazole, isoxazole, and pyrimidine based structures were easily obtained treating the resulting keto vinyl ethers with the appropriate nucleophile. As an example, the 2,4-disubstituted pyrimidine **24** was assembled in an 83% yield starting from the monoprotected ketoaldehyde and benzamidine under basic conditions at 50 °C. Furthermore, hydrazine and hydroxylamine proved equally effective producing the pyrazole **23** and isoxazole **25** derivatives, respectively, in excellent yields.

The stoichiometric amounts of applied carbon monoxide allowed us to investigate the ^{13}C-isotope labeling of aryl methyl ketones obtained by hydrolysis of the initially formed keto vinyl ether with aqueous hydrogen chloride (Scheme 3).

This protocol represents a direct synthesis of carbon isotope labeled acetophenone derivatives and complements the synthesis of acetylated benzene derivatives obtained by the Heck reaction of aryl electrophiles and vinyl ethers using only a slight excess of ^{13}C-labeled carbon

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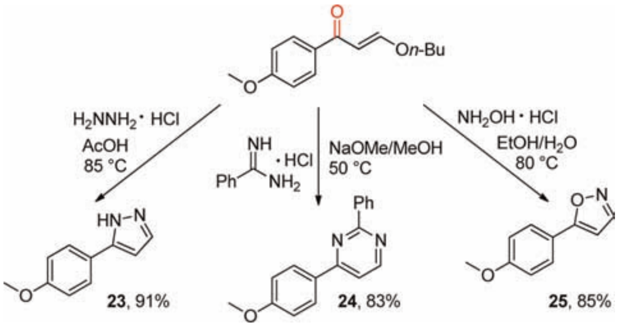
[18] A range of bidentate ligands were tested including DPPF, Xantphos, (±)BINAP, and PPF-t-Bu proved inferior generating significant amounts of the direct α-arylated vinyl ether.

[19] Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141.

[20] Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115.

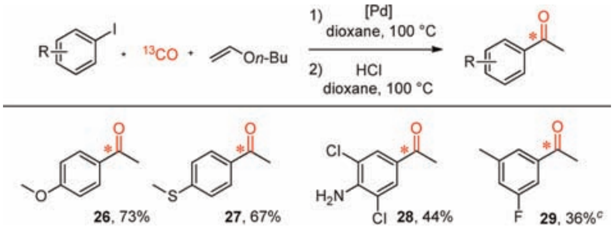
Scheme 2. Heterocyclic Compounds Obtained from a 1,3-Ketoaldehyde Synthon



monoxide. For instance, ^{13}C-labeled 4-methoxyacetophenone **26** was successfully produced in a 73% isolated yield illustrating the diversity and utility of Pd-catalyzed carbonylative chemistry when limited amounts of carbon monoxide are employed.

In conclusion, a simple approach for the synthesis of 1,3-ketoaldehyde synthons has been found starting from aryl iodides employing a palladium catalyst and near stoichiometric amounts of carbon monoxide. The monoprotected 1,3-ketoaldehydes were obtained with complete regioselectivity. This suggests that the formation of the intermediary aroylpalladium complex dictates the regioselective outcome of the reaction affording the linear products, when electron-rich olefins such as vinyl ethers are applied. Further investigations into this effect are en route and will be reported in due time.

Scheme 3. ^{13}C-Labeled Aryl Methyl Ketones Obtained from 1,3-Ketoaldehyde Synthons[a,b]



[a] For reaction procedures, see Supporting Information. [b] Overall yields are given. [c] Obtained in one pot.

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

Supporting Information Available. Experimental details and copies of the ^{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.

The authors declare no competing financial interest.