ORGANIC
LETTERS

2003
Vol. 5, No. 18
3285−3288

Homeopathic Ligand-Free Palladium as a Catalyst in the Heck Reaction. A Comparison with a Palladacycle

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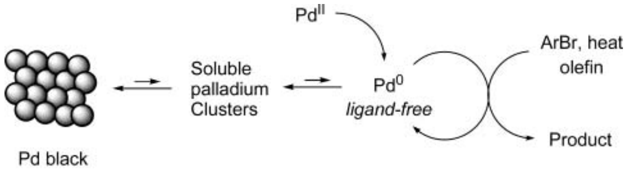
Received June 26, 2003

ABSTRACT



The lower the [Pd] the higher the TOF's

Ligand-free Pd(OAc)$_2$ can be used as a catalyst in the Heck reaction of aryl bromides as long as the amount of catalyst is kept between 0.01 and 0.1 mol %. At higher concentrations palladium black forms and the reaction stops. The actual catalyst is monomeric. Palladacycles merely serve as a source of ligand-free palladium in Heck reactions of aryl bromides.

The Heck reaction has recently been the focus of attention in both the academic[1] and industrial[2] community. This has been fuelled by the discovery of new generations of catalysts, such as palladacycles and pincers, and more recently the bulky electron-rich ligands for coupling reactions on aryl chlorides.[3]

Our research has focused on the reduction of costs of these reactions by the creation of highly active catalysts,[4] and on the reduction of waste by developing a halide-free Heck reaction based on the use of aromatic anhydrides as arylating agents.[5] From the perspective of process development, there is a strong drive to simplify these reactions as much as possible. In this respect, the presence of phosphine ligands can be a nuisance, particularly at high catalyst loadings, as they are often hard to separate from the product.

Mainly due to the work of Jeffery,[6] it is known that ligand-free palladium[7] can be used for the Heck reaction on aryl iodides. It is also possible to apply ligand-free palladium for Heck reactions in water,[8] or on less usual leaving groups such as diazonium salts, aroyl halides, anhydrides, and other

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[4] van Strijdonck, G. P. F.; Boele, M. D. K.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1999**, 1073.

[5] (a) Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 662. (b) Stephan, M. S.; de Vries, J. G. In *Chemical Industries 82*, *Catalysis of Organic Reactions*; Ford, M. E., Ed.; Marcel Dekker Inc.: New York, 2000, p 379. For further work on this concept see: Goossen, L. J.; Paetzold, J.; Ghosh, K. *Synlett* **2002**, 1721 and references therein.

[6] Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1996; Vol 5, p 153. See also: Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.

[7] The phrase "ligand-free" is used when no additional ligand, e.g., a phosphine, is added to the reaction mixture to keep the palladium in solution.

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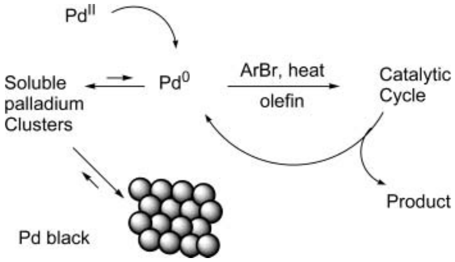
10.1021/ol035184b CCC: $25.00

carboxylic acid derivatives.[1f] Recently, we developed a practical ligand-free palladium recycle for Heck reactions on aryl iodides, which can be used on-site in the same vessel where the Heck reaction has been performed.[9]

However, ligand-free approaches usually do not work for the preferred aryl bromides.[10] In most cases a precipitate of palladium black forms in the early stages of the reaction and the reaction usually stops well before full conversion. The reason for this probably lies in the kinetics of these reactions. Whereas with the aryl iodides olefin insertion is presumably the rate-determining step, with aryl bromides it is most likely the oxidative addition of this substrate to palladium that is rate determining. This has great implications for the stability of the resting state. Whereas with the aryl iodides most of the palladium is in the form of palladium(II) complexes,[9] with aryl bromides the resting state is most likely a less stable palladium(0) complex.[11] The Pd(0) species is subject to two competing processes (Scheme 1). The catalyst can either enter the catalytic cycle or aggregate to form initially soluble palladium clusters, which at some point will turn into insoluble palladium black. The latter process is self-catalyzed and rapidly leads to the withdrawal of all palladium from the catalytic cycle.

Scheme 1. Fate of Palladium in Ligand-Free Heck Reactions on Aryl Bromides



It has been shown that palladium clusters stabilized by quaternary ammonium salts are active catalysts in the Heck reaction on aryl bromides.[12] Recently, several systems have been described based on palladium particles stabilized by coordinating polymers,[13] dendrimers,[14] or polyoxometalates.[15] Optimized Jeffery conditions with use of MeNCy$_2$ or HNCy$_2$ as base in conjunction with Et$_4$NCl also work in the ligand-free palladium Heck reaction on aryl bromides, but these reactions are rather slow.[16]

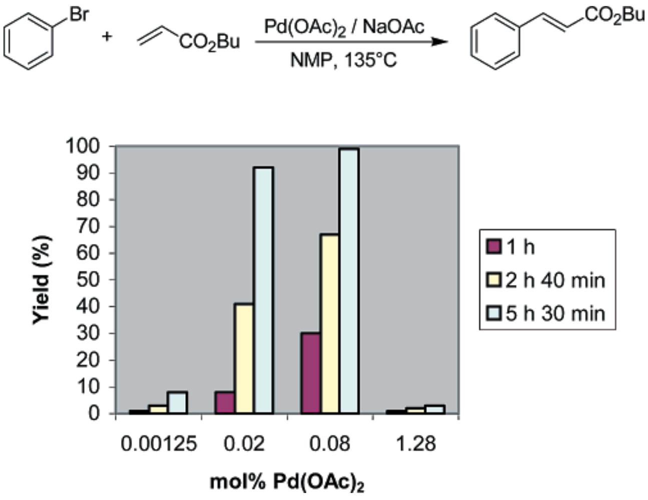


Figure 1. Effect of palladium/substrate ratio on the yield of the Heck reaction between PhBr and *n*-butyl acrylate at 135 °C.

Whereas these ligand-free solutions function well they defeat the purpose of our attempts to simplify the reaction mixture. Based on the picture in Scheme 1 a more simple solution presents itself. Whereas the Heck reaction presumably is first order in palladium concentration, the aggregation process must be higher order. Thus it would seem that by lowering the catalyst-to-substrate ratio the point can be reached where the oxidative addition outruns the aggregation process. In practice, this concept works beautifully: use of ligand-free Pd(OAc)$_2$ in the range between 0.01 and 0.10 mol % leads to very acceptable reaction rates in the Heck reaction of bromobenzene with butyl acrylate (NMP, NaOAc, 135 °C) (Figure 1).[17,18] As shown in Figure 1 the reaction stops at an early stage at a palladium-to-substrate ratio of 1.28 mol %. In this reaction the presence of palladium black is clearly visible. No palladium black was observed at the lower concentrations, nor did the reaction stop halfway. When the catalyst-to-substrate ratio is further lowered to 0.00125 mol % the catalysis still functions very well, but the conversion is too slow to be practical.[19] It is also clear from Figure 1 that the turnover frequency increases going

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(9) de Vries, A. H. M.; Parlevliet, F. J.; Schmieder-van de Vondervoort, L.; Mommers, J. H. M.; Henderickx, H. J. W.; Walet, M. A. N.; de Vries, J. G. *Adv. Synth. Catal.* **2002**, *344*, 996.

(10) Although aryl chlorides are cheaper than aryl bromides, the TON numbers attained for aryl chlorides are much lower than those for aryl bromides, so overall, a process based on an aryl bromide with low-loading palladium is cheaper. See also the concluding paragraph in ref 3.

(11) As evidenced by the absence of Ar−Pd species in the MS (vide infra). Also see: Jutand, A.; Negri, S.; de Vries, J. G. *Eur. J. Inorg. Chem.* **2002**, 1711.

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(18) The low loading of ligand-free palladium (in our examples 0.01−0.1 mol %) has been dubbed as homeopathic doses, a phrase also used by Beletskaya and Cheprakov, see ref 1f, p 3009.

(19) Reetz has noted in his work on the use of dimethylglycine as promotor for the Heck reaction that the promoting effect disappears at very low palladium-to-substrate ratios, ligand-free Pd(OAc)$_2$ at 0.009 mol % sufficing for 77% conversion after 24 h. Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449.

from 0.08 to 0.00125 mol %.[20] This can be explained by the equilibrium between the palladium present in the clusters and the palladium that is taking part in the catalytic cycle. At lower concentrations this equilibrium is shifted away from the clusters leading to a higher percentage of active catalyst.

To gauge the generality of this phenomenon and also to establish the scope of the method we have screened a large number of substrates in parallel, using the automated synthesizer ASW 2000 of Chemspeed. Conversions and selectivities were determined by GC-MS of samples of the reaction mixtures taken after 1, 2, 5, and 15 h. (See Table 1 and Figure 2.) A broad range of aryl bromides with electron-withdrawing as well as electron-donating substituents showed very high conversions with butyl acrylate (entries 1−20). Reaction times range from 1 to 15 h depending on the reactivity of the aryl bromide. Styrene also undergoes the ligand-free Heck reaction smoothly (entries 21−24). The selectivity of these reactions follows the general rules given in Figure 2 and is similar to those found for ligand-containing catalysts.[1] Electron-rich olefins convert nicely too but show the usual poor selectivity (entries 25−30),[21] except for 3-buten-2-ol, which forms the ketone adduct in more than 90% (entries 31−32).

Table 1. Heck Reactions with 0.05 mol % Pd(OAc)$_2$ as a Catalyst[a]

entry	aryl bromide	olefin	time (h)	conv (%)
1	PhBr	*n*-Bu-acrylate	5	96
2	4-CHO-PhBr	*n*-Bu-acrylate	1	100
3	4-CN-PhBr	*n*-Bu-acrylate	1	100
4	4-CH$_3$CO-PhBr	*n*-Bu-acrylate	1	100
5	4-O$_2$N-PhBr	*n*-Bu-acrylate	1	100
6	2-CHO-PhBr	*n*-Bu-acrylate	5	95
7	2-CN-PhBr	*n*-Bu-acrylate	1	100
8	1-Br-naphthalene	*n*-Bu-acrylate	2	100
9	9-Br-phenanthrene	*n*-Bu-acrylate	2	100
10	2-Br,6-MeO-naphthalene	*n*-Bu-acrylate	1	100
11	4-Br-biphenyl	*n*-Bu-acrylate	2	95
12	2-Br-biphenyl	*n*-Bu-acrylate	15	94
13	3-Br-pyridine	*n*-Bu-acrylate	15	100
14[b]	4-HO$_2$C-PhBr	*n*-Bu-acrylate	15	100
15	2-F-PhBr	*t*-Bu-acrylate	1	100
16	3-F-PhBr	*t*-Bu-acrylate	1	100
17	4-F-PhBr	*t*-Bu-acrylate	1	100
18	4-Cl-PhBr	*t*-Bu-acrylate	2	99
19	4-MeO-PhBr	*t*-Bu-acrylate	5	91
20	4-Me$_2$N-PhBr	*t*-Bu-acrylate	15	92
21	PhBr	styrene	15	99
22	4-CH$_3$CO-PhBr	styrene	15	99
23	2-Br,6-MeO-naphthalene	styrene	15	>95
24	4-Cl-PhBr	styrene	15	99
25	PhBr	CH$_2$=CHOCy[c]	15	85
26	4-CH$_3$CO-PhBr	CH$_2$=CHOCy[c]	15	99
27	2-Br,6-MeO-naphthalene	CH$_2$=CHOCy[c]	15	>95
28	4-Cl-PhBr	CH$_2$=CHOCy[c]	15	>95
29	PhBr	*N*-vinyl-acetamide	15	>90
30[d]	4-CH$_3$CO-PhBr	*N*-vinyl-acetamide	2	100
31	PhBr	3-buten-2-ol	15	80[e]
32	4-CH$_3$CO-PhBr	3-buten-2-ol	5	99[e]

[a] General conditions: 2 mmol of ArBr, 2.3 mmol of olefin, 0.05 mol % of Pd(OAc)$_2$, 2.4 mmol of NaOAc, NMP, 135 °C (total volume: 5 mL). Conversion and selectivity (see Figure 2 and text) were determined by GC-MS, using an internal standard. [b] 4.8 mmol of NaOAc. [c] Cy = cyclohexyl. [d] Octyl$_3$N as base. [e] Selectivity of more than 90% to 1-aryl-3-butanone.

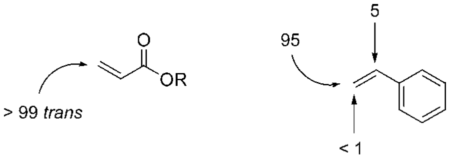

Figure 2. Observed selectivity in the ligand-free Heck reaction for electron-poor olefins.

To benchmark the method, we compared our ligand-free palladium system with the palladacycle developed by Herrmann, Beller, and co-workers[22] (both at 0.02 mol % of palladium). As shown in Figure 3, the two catalysts have a very similar kinetic profile in the Heck reaction between bromobenzene and *n*-butyl acrylate.[23]

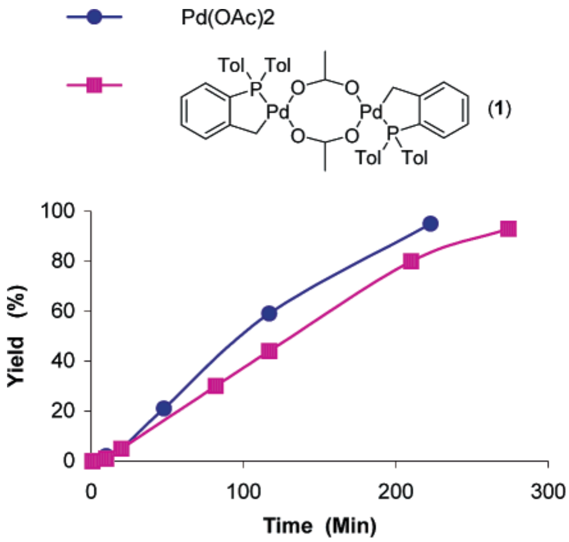

Figure 3. Rate comparison of catalysts in the reaction of PhBr with *n*-butyl acrylate in NMP and NaOAc as base (140 °C).

This intriguing result made us hypothesize that the active catalyst in the palladacycle-catalyzed reaction also is a ligand-

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[20] TOF values at 2 h 40 min are the following: 309 (0.08 mol %), 787 (0.02mol %), 900 (0.00125 mol %) h^{-1}.

[21] A mixture of a β-*trans*- and β-*cis*-arylated product was found, see also: Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1987**, *52*, 3529.

[22] (a) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844. (b) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357. (c) Böhm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2001**, *7*, 4191.

[23] The observed TOF values for the palladacycle in NMP correspond nicely with the ones reported in DMF, see ref 22.

free palladium species. Recently, Nowotny et al. showed that when using an immobilized palladacycle in a Heck reaction the catalytic activity remained in the filtered solution, whereas no activity remained in the solid.[24] Similar findings were reported by Rocaboy and Gladysz[25] and by Beletskaya et al.[26] These authors refer to the intervention of nanoparticles or clusters as catalysts in these Heck reactions. However, the phenomenon of increasing TOF with decreasing catalyst concentration, which seems to be generally associated with the use of palladacycles as catalysts,[25−27] can only be explained by an equilibrium between a higher order palladium species and a monomeric species.[28]

We next tried to confirm our suspicion through an ES-MS study of the catalyst during the reaction. Indeed in both reactions the only palladium species found was $PdBr_3^-$. Neither in negative mode nor in positive mode did we detect any phosphine-ligated palladium species during the reaction.

Mechanisms based on anionic species have been proposed by Amatore and Jutand for phosphine-ligated species[29] and by Evans et al.[30] and us[9] for ligand-free palladium in Heck reactions on aryl iodides. The MS experiment seems to confirm the fact that in Heck reactions of aryl bromides catalyzed by palladacycles the actual catalyst is the same monomeric ligand-free palladium as in the ligand-free system. The absence of arylated palladium species in the MS, which is in contrast with the findings for aryl iodides, seems to confirm that the oxidative addition is the rate-determining step. We presume that the $PdBr_3^-$ is merely a reservoir from which the Pd(0) is generated.[31] The higher activity at lower palladium concentrations is explained by a preequilibrium between palladium clusters and monomeric palladium that is contained in the catalytic cycle (Scheme 1), which shifts to the highly active monomeric palladium at lower palladium concentrations.

Several ligand-free heterogeneous catalysts have been reported for the Heck reaction on aryl bromides. These include heterogeneous palladium on grafted molecular sieves,[32] zeolites,[33] layered double hydroxides,[34] hydroxyapatites,[35] or just activated carbon or Al_2O_3.[36] We assume that these systems also work via a monomeric Pd(0) species that may be in solution,[36] where it becomes equivalent to our method, or it may be contained in the framework of the inorganic material.

In conclusion, Heck reactions on aryl bromides can conveniently be performed with ligand-free palladium, added as $Pd(OAc)_2$ as long as the amount is kept as low as 0.01−0.1 mol %. This procedure is more reliable than previous methods using higher concentrations of palladium catalysts. There is no need for extra added ligands or preformed palladacycles; in fact most ligands retard the reaction. This method is extremely attractive for large-scale production in view of the low catalysts costs and the easy workup procedure. The method has been scaled up by us to Kg size.

Acknowledgment. We thank the Dutch Ministry of Economic affairs for a subsidy under the EET Scheme (grant nos. EETK97107 and EETK99104).

Supporting Information Available: Experimental details and ES-MS data on catalytic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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[28] Pfaltz and Blackmond, in their study on the kinetics of a Heck reaction catalyzed by a palladacycle, assumed that this phenomenon is due to a preequilibrium between a dimeric and a monomeric aryl-Pd(II) species. They found half-order in [Pd]. See: Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 1848. For the cluster case an order between 0 and 1 is expected.

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