Are Heterogeneous Catalysts Precursors to Homogeneous Catalysts?

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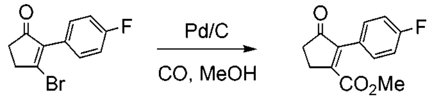
Homogeneous and heterogeneous catalysts offer their own distinct advantages.[1] Heterogeneous catalysts have an advantage that at the end of reaction the catalyst can be removed by simple filtration. In principle the product is un-contaminated with a transition metal or ligand and allows the catalyst to be recycled into the next reaction.[2] While the distinction between homogeneous and heterogeneous catalysis seems well-defined, in many cases there may be leaching of the transition metal into solution. In these instances the question that always remains is whether the catalytic activity resides with the leached metal. In other situations, it is unclear whether a "*release and capture*" of the transition metal catalyst has occurred. We report a simple unambiguous test to determine the presence of a homogeneous catalyst and demonstrate its application in three prototypical reactions. Not only does this method clarify the phase of the catalytically active species it also allows additional mechanistic information to be obtained regarding the system.

Our initial studies were prompted by the carbonylation of **1** to give the carbomethoxycyclopentenone **2** (eq 1). Although this transformation worked quite well with the conventional homogeneous catalyst $Pd(PPh_3)_2Cl_2$,[3] a heterogeneous catalyst was sought for this reaction to simplify product isolation. In many of our programs, the fate of the catalyst is especially important during processing since the acceptable level of transition metal residuals is highly regulated in pharmaceutical products. Pd/C has been used for a number of palladium-catalyzed reactions.[4,5] After parallel catalyst screening, the optimal conditions were identified at small scale.[6] Using these conditions at 1 mol scale (1 mol % Pd/C, 60 °C, 80 psig CO, 1 M DMA, 2 equiv Bu_3N, 5 equiv MeOH, 10 h) led to the formation of **2** in 98−99% yield.[7] There was no trace of reduction, dimerization, or amide formation[8] and mass balance was accounted for by two low-level impurities (see Supporting Information).[9] The product was isolated by crystallization from the reaction stream after removal of the carbon by filtration and typically contained 200 ppm of Pd as determined by ICP-AES analysis.

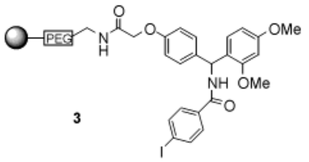


(1)

1 **2**

Analysis of the reaction mixture after filtration of the carbon demonstrated >125 ppm of Pd in the process stream, i.e. 25% of the initial catalyst charge. The addition of mercury limited the reaction to two turnovers providing circumstantial evidence regarding the phase of the active catalyst.[10,11] To unambiguously assign the role of a homogeneous catalyst we envisaged application of a *three-phase test*.[12]

Advances in the design of solid supports and the accompanying developments in analysis have been driven by the combinatorial revolution and a wide range of supports are now available. Since the carbonylation reaction is performed under basic conditions we chose to use a Novasyn TGR resin allowing the attachment of the substrate with an amide bond. The design features involving the use of an aryl iodide in addition to the presence of a para-electron-withdrawing group used as attachment ensure that the oxidative addition with a homogeneous catalyst would be extremely facile.



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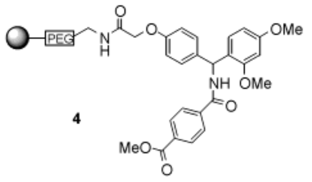

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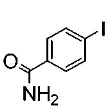
Control experiments with resin **3** under our standard conditions (1 mol % Pd/C, 60 °C, 80 psig CO, 1 M DMA, 2 equiv of Bu_3N, 5 equiv of MeOH, 10 h) resulted in quantitative recovery of **5** following cleavage with TFA, i.e. there was no catalytically active species present in solution. However, addition of resin **3** to the carbonylation reaction in the presence of **1** led to a 95% yield of **2** and a quantitative formation of ester **6** following TFA cleavage of the resin-bound product. Iodobenzene was equally effective at generating a homogeneous catalyst and was itself converted to methylbenzoate in 97% yield.



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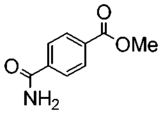

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The requirement for the organohalide in the generation of an active catalyst suggests that upon oxidative addition, desorption of the Pd(II) species, e.g. Ph−Pd−I, occurs which enters a conventional solution phase catalytic cycle generating a soluble

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[1] Gates, B. C. In *Catalytic Chemistry*; Wiley: New York, 1992.

[2] For the sake of simplicity, in this article we specifically address transition metal-catalyzed processes and we use palladium in particular to illustrate the approach. The principles and observations discussed should be broadly applicable.

[3] Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

[4] (a) Suzuki-Miyaura reaction: LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R. *Org. Lett.* **2001**, *3*, 1555. (b) Amidocarbonylation of imines: Beller, M.; Moradi, W. A.; Eckert, M.; Neumann, H. *Tetrahedron Lett.* **1999**, *40*, 4523. (c) Heck reaction: Augustine, R. A.; O'Leary, S. T. *J. Mol. Catal.* **1992**, *72*, 229. (d) Stille reaction: Liebeskind, L. S.; Penn-Cabrera, E. *Org. Synth.* **1999**, *77*, 135.

[5] For related Ni/C catalyzed reactions see: Lipshutz, B. H.; Ueda, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 4492.

[6] Parallel reaction screening using the Argonaut Endeavor.

[7] The iodide reacted with similar efficiency where as the chloride was unreactive even at higher temperatures.

[8] Schnyder A.; Beller, M.; Mehltretter, G.; Nsenda, T.; Studer, M.; Indolese, A. F. *J. Org. Chem.* **2001**, *66*, 4311.

[9] All new compounds were fully characterized. The identity of known compounds were confirmed by comparison (LCMS) with authentic samples.

[10] For suppression of a heterogeneous Pt-catalyzed reaction by Hg(0) see: Whitesides, G. M.; Hackett, M.; Brainard, R. L.; Lavalleye, J.-P. P. M.; Sowinski, A. F.; Izumi, A. N.; Moore, S. S.; Brown, D. W.; Staudt, E. M. *Organometallics* **1985**, *4*, 1819. Interpetation of the results from the Hg(0) test should be viewed with caution: Lin, Y.; Finke, R. G. *Inorg. Chem.* **1994**, *33*, 4891. The presence of Hg(0) may lead to suppression of catalysis via amalgamation, which inhibits the proposed oxidative addition/desorption mechanism.

[11] For application of dibenzo[*a*,*e*]cyclooctetraene as a potent poison for homogeneous catalysis see: Anton, D. R.; Crabtree, R. H. *Organometallics* **1983**, *2*, 855. For application of polymer substrates as a test in hydrogenation reactions see: Collman, J. P.; Kosydar, K. M.; Bressan, M.; Lamanna, W.; Garrett, T. *J. Am. Chem. Soc.* **1984**, *106*, 2569.

[12] Rebek J.; Gavina, F. *J. Am. Chem. Soc.* **1974**, *96*, 7112. Rebek, J.; Brown, D.; Zimmerman, S. *J. Am. Chem. Soc.* **1975**, *97*, 454. Rebek, J. *Tetrahedron* **1979**, *35*, 723.

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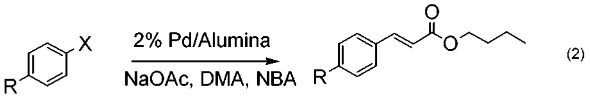
Pd(0) catalyst.[13] Carbon monoxide is not required for the generation of the active homogeneous catalyst. The homogeneous catalyst can be prepared by aging the reaction mixture under nitrogen followed by filtration of the carbon prior to the introduction of CO. The homogeneous catalyst prepared in this manner has a minimum turnover number (ton) of 850 and turnover frequency (tof) of 250/h for the conversion of **1** to **2**.[14]

A further illustration is provided by an investigation of the Heck reaction. Recently, indirect methods have implicated the involvement of a homogeneous catalyst involving Pd/alumina, Pd/C, or polystyrene-supported palladium.[15] In the case of Pd/C it has been suggested that a homogeneous mechanism may be in operation but is redeposited on the support.[16] Heck reaction of bromoacetophenone **7** and *n*-butylacrylate (NBA) promoted by Pd/alumina (2 mol %) proceeded to give cinnamate **8** in 98% yield (eq 2). Iodobenzene and the iodoamide **5** coupled with similar efficiency.



(2)

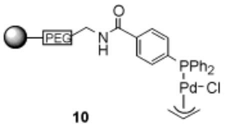
7 X = Br, R = COMe
5 X = I, R = $CONH_2$

8 R = COMe
9 R = $CONH_2$

Performing the Heck reaction in the presence of resin **3** led to quantitative formation of cinnamate **9** following TFA cleavage. Control experiments indicated that in the absence of the aryl halide low conversions of **3** were observed and the rate of reaction increased with the sodium acetate charge (2−5 equiv). Conversion and rate of reaction of **3** were greatly enhanced by the presence of both aryl halide **7** and sodium acetate, i.e. they act cooperatively. Surface oxidative addition occurs and desorption of the palladium(II) species is presumably accelerated by the formation of $ArPdBr(OAc)_n$[17] or $ArPd(OAc)_n$,[18] which are free to enter a conventional solution-phase reaction.[19] Our results firmly establish the involvement of a homogeneous catalyst.

Finally, a demonstration of the utility of this approach in a system that has direct implications for library generation involved the use of phosphine complexes. Polymer-supported phosphines have now been used in a growing number of transformations and a large number are now commercially available. The palladium complex **10**, prepared from triphenylphosphine-NovaGel and palladium π-allyl chloride dimer, has successfully been applied to Suzuki−Miyaura cross-coupling and arylation of allylic acetates.[20]

Performing the Suzuki−Miyaura coupling reaction of iodobenzene and phenylboronic acid (1.5 M KOH, 20 h, 25 °C) in the presence of resin **3** (0.5 mol %) and 10 (3 mol %) led to the clean formation of biphenyl. The biphenylamide **11** was obtained in 85% yield following TFA cleavage of the resin. The reaction stream contained 2.5 ppm Pd by ICP-AES analysis. Perhaps the most unsatisfactory shortcoming of the test is that the method offers unambiguous evidence for the existence of an intermediate but only inferences can be drawn concerning its structure. In this particular example further studies will be required to elucidate if all of the reactivity is associated with the homogeneous catalyst. However, the resin may serve as a convenient catalyst precursor for "*release*" and acts as a scavenger for palladium at the end of reaction—"*capture*".[21]



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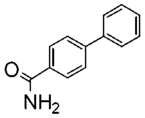

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In conclusion, we have unequivocally demonstrated in two reactions involving palladium on heterogeneous supports that the reaction proceeds via a homogeneous catalyst. In the case of the Suzuki−Miyaura coupling with a polymeric phosphine we have demonstrated the existence of a competent homogeneous catalyst. These examples clearly challenge the assumption that all heterogeneous catalysts operate in a well-defined regimen. The use of polymer supports that allow for designed, sequential, and multistep organic synthesis is a rapidly expanding arena.[22] Our observations emphasize that caution needs to be exercised in planning multistep synthesis involving transition metal resins since this endeavor relies upon the effective isolation of the reactive centers. The *three-phase test* should find renewed application in a wide range of reactions involving supported catalysts.[23]

Acknowledgment. We would like to thank Professor Barry Trost for his insightful suggestions regarding application of a three-phase test and his continued interest in our programs.

Supporting Information Available: Experimental procedures and characterization data for all new compounds, conversion vs CO uptake data as a function of pressure and temperature, a comparison of Pd/C vs $Pd(PPh_3)_2Cl_2$ as a function of temperature, and data to support the calculation of ton and tof (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) PhCl was unreactive even at higher temperatures. Similarly the chloro analogue of **1** was unreactive. These observations provide additional circumstantial evidence that the desorption mechanism is driven by surface oxidative or electron transfer.

(14) The catalyst was prepared by using 10 equiv of bromide **1** vs 5 wt % Pd/C. See Supporting Information for details.

(15) Biffis, A.; Zecca, M.; Basato, M. *Eur. J. Inorg. Chem.* **2001**, 1131.

(16) Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. *Chem. Eur.* **2000**, *6*, 843. Zhao, F.; Shirai, M.; Arai, M. *J. Mol. Catal.* **2000**, *154*, 39. Jayasaree, J.; Seayad, A.; Chaudhari, R. V. *Chem. Commun.* **1999**, 1067.

(17) For a discussion of the formation of anionic palladium(II) complexes in the Heck reaction see: Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

(18) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217.

(19) For an intriguing mechanistic proposal for the role of acetate ion and anionic palladium complexes in the Heck reaction see: Shaw, B. L. *New J. Chem.* **1998**, 77.

(20) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384.

(21) In the generally accepted mechanism, an 18-electron palladium(0) complex PdL_n must undergo a ligand loss to PdL_{n-2} prior to generation of a competent catalyst. In the case of a resin bound monodentate phosphine ($\otimes$-P) the complex $Pd(\otimes\text{-P})L_{n-1}$ may lose $\otimes$-P based on steric or electronic arguments (e.g. trans-effect) releasing a free PdL_{n-1} into the solution phase as a precursor to a conventional catalytic cycle. See ref 17 for an alternative mechanism involving anionic palladium complexes.

(22) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott. J. S.; Storer, I. R.; Taylor, S. J. *J. Chem. Soc., Perkin Trans 1* **2000**, 3815. For the first example of a sequential reaction see: Pittman, C. U.; Wuu, S. K.; Jacobsen, J. *J. Catal.* **1976**, *44*, 87.

(23) For example, Raney-Ni-tartaric acid methylacetoacetate reduction in the presence of bromide ion, see: Harada, T.; Yamamoto, M.; Onaka, S.; Imaida, M.; Tai, A.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2323. Pt-chinchona ketoester reduction, see: LeBlond, C.; Wang, J.; Liu, A.; Andrews, A. T.; Sun, Y.-K. *J. Am. Chem. Soc.* **1999**, *121*, 4920.