

New Mechanistic Insights Regarding Pd/Cu Catalysts for the Sonogashira Reaction: HRMAS NMR Studies of Silica-Immobilized Systems

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Palladium catalysts are indispensable in organic chemistry,¹ especially for Sonogashira reactions, where terminal alkynes are cross-coupled with aryl halides (Scheme 1).² Here, we report on the Cu(I)-assisted Pd(II) Sonogashira cross-coupling catalyst.³ Despite its importance, the reaction mechanism is still not quite clear. Having gained experience in immobilized catalysts over the past decade,⁴ we sought to explore mechanistic aspects using surface-bound versions of the Sonogashira catalyst system. We demonstrate that solid-state NMR of the dry supports (CP/MAS),⁵ and HRMAS NMR,⁶ where the material is suspended in solvents and spun at 2 kHz in a rotor equipped with inserts,^{6a} can give crucial insights into the nature and behavior of catalysts in all phases.

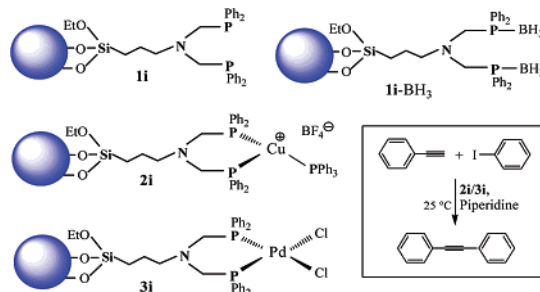
Reaction of the linker (EtO)₃Si(CH₂)₃N(CH₂PPh₂)₂ (**1**)⁷ and silica under our standard conditions⁸ cleanly gives **1i** (Scheme 1).⁹ The supported Cu(I) complex **2i** (Scheme 1) is best generated directly on the surface. In the optimal procedure, (CH₃CN)₄CuBF₄ is treated with 2 equiv of PPh₃ (acetone, 2 h) and then combined with **1i** (2 h, 50 °C). After washing the material (acetone) and drying (in vacuo), a broad and unstructured ³¹P CP/MAS signal results (Figure 1, top). However, recording the HRMAS spectrum with the parameters described previously,^{6a} even at 2 kHz, two well-resolved signals with an intensity ratio of 1:2 are obtained (Figure 1, bottom). These can be assigned to the PPh₃ (5.7 ppm) and PPh₂ (−17.8 ppm) moieties of **2i**. Thus, the structure of **2i** (Scheme 1) is in accord with the analogue Cu(PPh₃)₃(BF₄).¹⁰ Dimeric forms or higher aggregates are ruled out by a NOESY spectrum of the suspension (Figure 2). The cross-peak proves that the two ³¹P nuclei must be in close proximity to each other, in accord with **2i** as represented in Scheme 1.

The Pd(II) complex **3**, obtained by reacting **1** with an equimolar amount of (PhCN)₂PdCl₂, can be immobilized cleanly on silica.⁸ Figure 3 displays the ³¹P CP/MAS spectrum of **3i** (bottom). Again, the residual line width and the CSA are large even at 4 kHz. Fortunately, the HRMAS spectra in most solvents give narrow signals (Figure 3), especially with acetone, as for the Cu system. Only nonpolar solvents, such as pentane or cyclooctane, are not mobilizing the complex sufficiently and therefore give no ³¹P signals.^{8c}

Neither the immobilized Pd complex **3i** nor the Cu complex **2i** on their own catalyze the Sonogashira coupling (Scheme 1) at ambient temperature.

Next, we sought to immobilize **2i** and **3i** on the same silica support. However, regardless of whether we started from **2i** and then tried to attach **3**, or vice versa, only unassignable HRMAS signals in the region from −20 to +30 ppm were obtained from the material, although it was highly reactive with respect to the Sonogashira coupling, giving toluene as the only product. Therefore, as a new point of view joining the controversial literature,¹² we conclude that the catalytically active species is not a well-defined molecular species but some Pd–Cu aggregate or nanoparticles that give complex ³¹P HRMAS spectra. Fortunately, immobilizing the Cu component first, with CH₃CN as the third ligand instead of PPh₃,

Scheme 1. The Silica-Immobilized Versions of Linker **1** (**1i**, **1i**·BH₃) and Complex **3** (**3i**, **2i**), and the Sonogashira Reaction for **2i/3i**



prevents the attack of the Pd complex during the immobilization step, and thus the immediate formation of Pd–Cu aggregates and the narrow ³¹P HRMAS signals of the immobilized molecular Pd and Cu species on the same silica result.

Interestingly, when recording the HRMAS spectrum of silica with a 50% loading of **3i**⁹ and 50% of **1i**,⁹ the ³¹P signal of **1i** becomes very broad, and it is shifted to ca. −7 ppm (Figure 4, middle), although **1i** alone gives a narrow resonance at −31.4 ppm (Figure 4, bottom) at any surface coverage. Therefore, we conclude that Pd can “hop” or migrate over the lawn of uncomplexed linkers, thus leading to an averaged phosphine signal. To support this thesis, we manufactured a “hopping barrier” for Pd; that is, we protected the surface-bound phosphine linkers (surface coverage 50%)⁹ with BH₃, leading to **1i**·BH₃.¹¹ When **3** is added, the ³¹P HRMAS

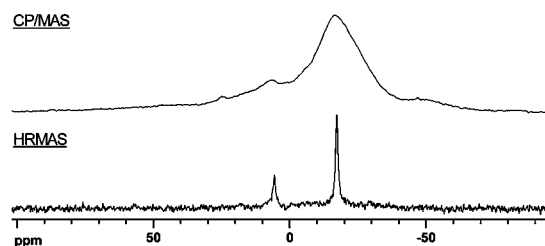


Figure 1. ³¹P CP/MAS (top, 4 kHz) and ³¹P HRMAS (bottom, acetone-*d*₆, 2 kHz) spectra of immobilized Cu complex **2i**.

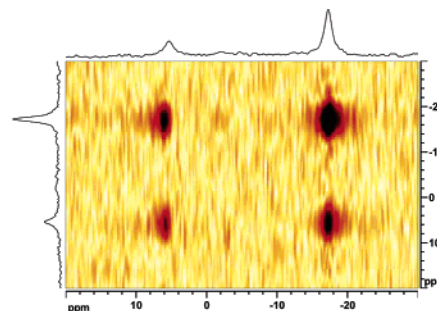


Figure 2. ³¹P, ³¹P NOESY spectrum of **2i** (mixing time 1 s, acetone-*d*₆).

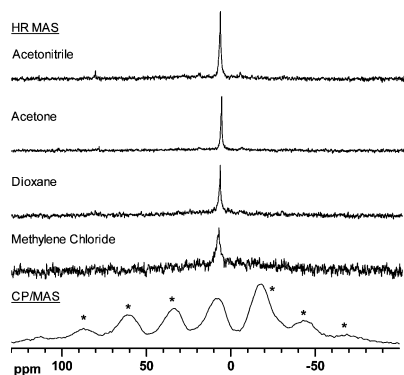


Figure 3. ^{31}P CP/MAS (bottom, 4 kHz, *rotational sidebands) and ^{31}P HRMAS spectra of **3i** (1000 scans, 2 kHz) with the indicated solvents.

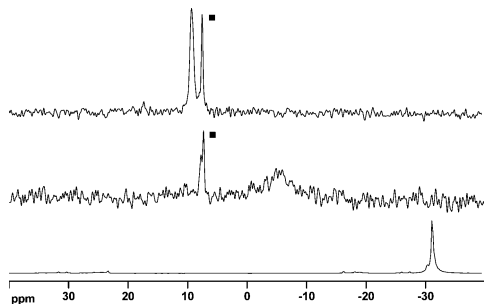


Figure 4. ^{31}P HRMAS spectra (1000 scans, acetone): linker **1i** (bottom), Pd complex **3i** with 1 equiv of uncomplexed phosphine linker **1i** (middle), and **3i** in the presence of **1i**· BH_3 (top). The square indicates **3i**.

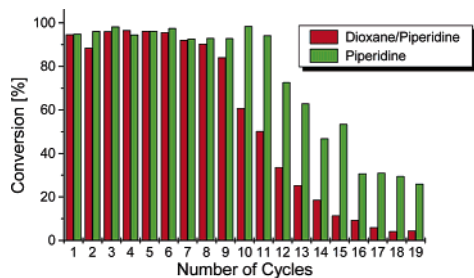


Figure 5. Recycling characteristics of immobilized Cu catalyst **2i** (reaction time 6 h for each run) with $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ added batchwise.

spectrum displays the narrow signals of **3i** at 7.4 ppm and of **1i**· BH_3 at 9.1 ppm (Figure 4, top). Obviously, this previously unrecognized dynamic effect of Pd hopping is important when considering heterobimetallic immobilized catalyst systems.

HRMAS investigations provide insight into the various immobilized Cu/Pd systems and help to obtain catalysts with prolonged lifetimes. Importantly, while organic solvents only remove trace amounts of Pd from the surface,¹³ $\text{C}_6\text{H}_5\text{I}$ quantitatively transfers Pd into the solution¹³ and finally to the immobilized Cu complex. Therefore, irrespective of the immobilization sequence for **2i** and **3i** and whether they are on the same silica batch or not, the initial catalytic activity is high, but the system as a whole loses activity quickly during recycling steps, and in the fourth run the toluene yield is typically only 20%. Immobilizing the Pd complex with the thiol linker $(\text{MeO})_3\text{Si}(\text{CH}_2)_3\text{SH}$ ^{3c} impedes the surface mobility of Pd, and its detachment from the support and thus the toluene yield is merely 7% in the first cycle.

The immobilized Cu complex **2i** does not leach into solution: **2i** does not catalyze the Sonogashira reaction, even with added **3**

or $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$, when the phenyl iodide is covalently bound to a different batch of support as described by Crudden.^{3c} The negative result of this three-phase test shows that the Sonogashira reaction does indeed take place on the surface, but with $\text{C}_6\text{H}_5\text{I}$, the Pd complex always acts as a homogeneous component. Any Cu/Pd aggregate that might form in the catalytic step is not persistent, and the Pd leaches during subsequent recycling steps.

With HRMAS, the optimal Sonogashira coupling system is quickly identified. As shown in Figure 5, **2i**, together with freshly added $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$, gives high yields of the Sonogashira coupling product toluene in piperidine at room temperature even after 19 cycles.

In summary, we have demonstrated that HRMAS constitutes a powerful new tool for investigating the structures and mobilities of immobilized species and thus enables us to understand and quickly optimize heterobimetallic catalyst systems.

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References

- (1) (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) *Handbook of Organopalladium Chemistry*; Negishi, E., de Meijere, A., Eds.; Wiley: New York, 2002.
- (2) (a) Cheng, J.; Sun, Y.; Wang, F.; Guo, M.; Xu, J.-H.; Pan, Y.; Zhang, Z. *J. Org. Chem.* **2004**, *69*, 5428–5432. (b) Méry, D.; Heuzé, K.; Astruc, D. *Chem. Commun.* **2003**, 1934–1935. (c) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679–3681.
- (3) Selected lead references: (a) Heuzé, K.; Méry, D.; Gauss, D.; Astruc, D. *Chem. Commun.* **2003**, 2274–2275. (b) Heuzé, K.; Méry, D.; Gauss, D.; Blais, J.-C.; Astruc, D. *Chem.—Eur. J.* **2004**, *10*, 3936–3944. (c) Crudden, C. M.; Sateesh, M.; Lewis, R. *J. Am. Chem. Soc.* **2005**, *127*, 10045–10050. (d) Pears, D. A.; Smith, S. C. *Aldrichimica Acta* **2005**, *38*, 24–34. (e) Lohmann, S.; Andrews, S. P.; Burke, B. J.; Smith, M. D.; Attfield, J. P.; Tanaka, H.; Kaneko, K.; Ley, S. V. *Synlett* **2005**, 1291–1295. (f) Stevens, P. D.; Li, G.; Fan, J.; Yen, M.; Gao, Y. *Chem. Commun.* **2005**, 4435–4437. (g) Garg, N. K.; Woodroffe, C. C.; Lacenere, C. J.; Quake, S. R.; Stoltz, B. M. *Chem. Commun.* **2005**, 4551–4553. (h) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391–393. (i) Park, S. B.; Alper, H. *Chem. Commun.* **2004**, 1306–1307. (j) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
- (4) (a) Merckle, C.; Blümel, J. *Top. Catal.* **2005**, *34*, 5–15. (b) Reinhard, S.; Soba, P.; Rominger, F.; Blümel, J. *Adv. Synth. Catal.* **2003**, *345*, 589–602.
- (5) Reinhard, S.; Blümel, J. *Magn. Reson. Chem.* **2003**, *41*, 406–416.
- (6) (a) Posset, T.; Rominger, F.; Blümel, J. *Chem. Mater.* **2005**, *17*, 586–595. (b) Bogza, M.; Oeser, T.; Blümel, J. *J. Organomet. Chem.* **2005**, *690*, 3383–3389. (c) Brenna, S.; Posset, T.; Furrer, J.; Blümel, J. *Chem.—Eur. J.* **2006**, *12*, 2880–2888.
- (7) Linker **1** was prepared by reaction of $(\text{EtO})_3\text{Si}(\text{CH}_2)_3\text{NH}_2$ with Ph_2PH and paraformaldehyde (12 h, toluene, 60 °C).
- (8) (a) Blümel, J. *J. Am. Chem. Soc.* **1995**, *117*, 2112–2113. (b) Behringer, K. D.; Blümel, J. *J. Liquid Chromatogr.* **1996**, *19*, 2753–2765. (c) Merckle, Ch.; Blümel, J. *Chem. Mater.* **2001**, *13*, 3617–3623.
- (9) The surface coverage is determined by weighing the excess of linker or metal complex in the supernatant solution after removal of the solvent. Maximal surface coverage (100%) of **1** corresponds, for example, to 82 mg of **1** on 1 g of silica (Merck, 40 Å average pore diameter, 750 m²/g).
- (10) Gaughan, A. P.; Dori, Z.; Ibers, J. A. *Inorg. Chem.* **1974**, *13*, 1657–1667.
- (11) No reduction of Pd(II) to Pd(0) by treatment of **3i** with BH_3 was observed.
- (12) (a) Cassol, C. C.; Umpierre, A. P.; Machado, G.; Wolke, S. I.; Dupont, J. *J. Am. Chem. Soc.* **2005**, *127*, 3298–3299. (b) Hagen, C. M.; Widgren, J. A.; Maitlis, P. M.; Finke, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 4423–4432. (c) Thathagar, M. B.; Kooyman, P. J.; Boerleider, R.; Jansen, E.; Elsevier, C. J.; Rothenberg, G. *Adv. Synth. Catal.* **2005**, *347*, 1965–1968. (d) Köhler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. *Chem.—Eur. J.* **2002**, *8*, 622–630. (e) Rocaboy, C.; Gladysz, J. A. *Org. Lett.* **2002**, *4*, 1993–1996.
- (13) When **3i** is stirred overnight with an excess of acetone, trace amounts of Pd ($3 \pm 2\%$) can be detected in the supernatant solution by AAS. When **3i** is stirred with $\text{C}_6\text{H}_5\text{I}$ (1:1) in THF, $(\text{THF})\text{C}_6\text{H}_5\text{Pd}(\mu\text{-I})_2\text{PdC}_6\text{H}_5(\text{THF})$ is obtained quantitatively, as determined by weighing the residue after removal of the solvent from the supernatant solution.

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