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Sonogashira Coupling of Aryl Halides Catalyzed by Palladium on Charcoal

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Abstract: With the proper choice of solvent, palladium on charcoal acts as an efficient catalyst in the Sonogashira cross-coupling reaction of aryl bromides. The catalytically active species in the process is probably palladium, which leaches into the solution but returns onto the surface of the charcoal at the end of the reaction.

The palladium-catalyzed coupling of terminal acetylenes with aryl and vinyl halides (the Sonogashira reaction) is one of the important and widely used carbon−carbon bond-forming reactions in organic synthesis.[1] The reaction generally proceeds in the presence of a homogeneous palladium catalyst, which makes the recovery of the metal tedious if not impossible and might result in high palladium contamination of the product. A way to overcome these difficulties would be the use of a heterogeneous palladium catalyst such as a solid-supported metal. The most readily available form of supported catalyst is palladium on charcoal, which is widely used in heterogeneous hydrogenation processes and also has a growing importance in carbon−carbon bond-forming reactions.[2,3] To the best of our knowledge, there is only one comprehensive publication on the use of palladium/charcoal in the Sonogashira coupling,[4] where the authors claim that Pd/C serves only as a source of soluble palladium and the active species is a dissolved palladium−triphenylphosphane complex. There are also a number of papers that report the use of Pd/C as a catalyst in singular reactions, but they are usually limited to the more reactive aryl iodides and 2-halopyridines.[5,6]

The potential advantages of the Pd/C catalyst system, the ease of separation and facile recycling of the metal and the low level (usually below 1 ppm) of metal contamination[3d] in the product, suggest that an efficient Sonogashira coupling protocol based on the use of the Pd/C catalyst system and utilizing aromatic halides other than iodides would be of major interest for both industrial and academic applications.

Of the factors governing the catalytic efficiency of the Pd/C system in coupling reactions, the choice of solvent was found to be crucial,[3d,5e] although its influence was not examined in detail; therefore, our first reactions were designed to study the effect of the solvent on the Pd/C-catalyzed Sonogashira coupling. Electron-rich 4-bromotoluene (**1**) and the more reactive 3-bromopyridine (**2**) were chosen as aryl halides,[7] and the acetylene derivatives included 3-butyne-1-ol (**3a**), 1-hexyne (**3b**), and 2-methyl-3-butyn-2-ol (**3c**). The solvents used ranged from the apolar toluene through dioxane to water, and our base of choice was diisopropylamine. The aryl halide, 1.2 equiv of the alkyne, 5 mol % Pd (10 wt % on charcoal), 10 mol % PPh_3,[8] 10 mol % CuI, and 1.2 equiv of diisopropylamine were heated in an 80 °C oil bath for 24 h, and the conversions were determined by GC analysis (Table 1).

The results clearly demonstrate the expected reactivity difference between 4-bromotoluene (**1**) and 3-bromopyridine (**2**), where the latter reached high conversion in most cases. The comparison of the results in the bromotoluene (**1**) series, on the other hand, shows some interesting trends. The polarity of the solvent seems to play an important role in the process. Addition of 5% water to dioxane led to a significant increase in the conversion, while in the dimethyl acetamide (DMA) series, the effect was similar but less marked. It is also interesting to note that reasonable conversions were achieved also in water, except for the apolar 1-hexyne, where the limited solubility of the reagent might hinder

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[1] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470. (b) Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 2.4, pp 521−549 and references therein. (c) Bumagin, N. A.; Sukhomlinova, L. I.; Luzikova, E. V.; Tolstaya, T. P.; Beletskaya, I. P. *Tetrahedron Lett.* **1996**, *37*, 897−900. (d) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731. (e) Erdelyi, M.; Gogoll, A. *J. Org. Chem.* **2001**, *66*, 4165−4169.

[2] Heck reaction: (a) Mehnert, C. P.; Weaver, D. W.; Ying, J. Y. *J. Am. Chem. Soc.* **1998**, *120*, 12289−12296. (b) Khan, S. I.; Grinstaff, M. W. *J. Org. Chem.* **1999**, *64*, 1077−1078. (c) Whitcombe, N., J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449−7476. (d) Hagiwara, H.; Shimizu, Y.; Hoshi, T.; Suzuki, T.; Ando, M.; Ohkubo, K.; Yokoyama, C. *Tetrahedron Lett.* **2001**, *42*, 4349−4351. (e) Djakovitch, L.; Koehler, K. *J. Am. Chem. Soc.* **2001**, *123*, 5990−5999.

[3] Pd on charcoal in the Suzuki reaction: (a) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277−3280. (b) Gala, D.; Stamford, A.; Jenkins, J.; Kugelman, M. *Org. Process Res. Dev.* **1997**, *1*, 163−164. (c) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G. E.; Carstairs, A. *Org. Process Res. Dev.* **1999**, *3*, 248−252. (d) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R., Jr. *Org. Lett.* **2001**, *3*, 1555−1557. (e) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, *67*, 2721−2722.

[4] De la Rosa, M. A.; Velarde, E.; Guzman, A. *Synth. Commun.* **1990**, *20*, 2059−2064.

[5] Other examples of singular Pd/C-catalyzed Sonogashira reactions based on ref 4 are: (a) Potts, K. T.; Horwitz, C. P.; Fessak, A.; Keshavarz-K, M.; Nash, K. E.; Toscano, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 10444−10445. (b) Bleicher, L.; Cosford, N. D. P. *Synlett* **1995**, 1115−1116. (c) Cosford, N. D. P. et al. *J. Med. Chem.* **1996**, *39*, 3235−3237. (d) Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109−1118. (e) Felpin, F.-X.; Vo-Thanh, G.; Villiéras, J.; Lebreton, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1121−1124. (f) Bates, R. W.; Boonsombat, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 654−657. (g) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118−1122. (h) Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571−1574.

[6] For a solvent-free Sonogashira reaction catalyzed by Pd on alumina, see: Kabalka, G. W.; Wang, L.; Namboodiri, V.; Pagni, R. M. *Tetrahedron Lett.* **2000**, *41*, 5151−5154.

[7] Reagents were selected to provide a representative example both in terms of reactivity and utility. Although aromatic iodides react more readily under the applied conditions, aryl bromides are available in far greater numbers and their use is more economical.

[8] Preliminary screening of common phosphorous-based ligands showed that the catalytic system containing triphenylphosphine is not inferior in terms of activity to phosphites, dppe, dppp, dppb, or dppf.

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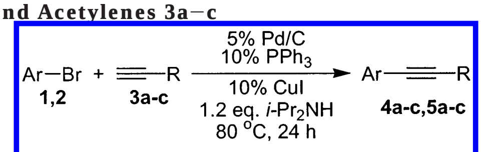
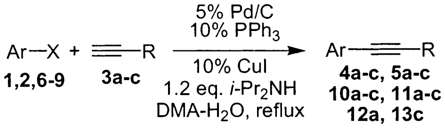
TABLE 1. Solvent-Dependent Conversions in the Pd/C-Catalyzed Sonogashira Coupling of Aryl Bromides (1, 2) and Acetylenes 3a−c

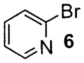
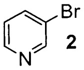
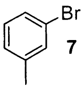
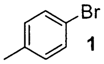
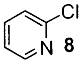
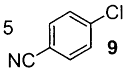


1,**4**: Ar=4-tolyl; **2**,**5**: Ar=3-pyridyl
a: R=C_2H_4OH; **b**: R=C_4H_9; **c**: R=$C(CH_3)_2OH$

		toluene	dioxane	aqueous dioxane	DMA	aqueous DMA	H_2O
1	**3a**	74	20	44	85	84	69
1	**3b**	16	13	39	73	71	37
1	**3c**	4	6	34	76	100	98
2	**3a**	100	99	100	86	100	96
2	**3b**	100	53	93	90	84	54
2	**3c**	46	15	97	100	92	92

TABLE 2. Pd/C-Catalyzed Sonogashira Coupling of Aryl Halides and Acetylenes in DMA−Water



Entry	Reagents		Product	Conversion[a]%
1	 **6**	**3a**	**10a**	100 (58)
2		**3b**	**10b**	100 (62)
3		**3c**	**10c**	100 (65)
4	 **2**	**3a**	**5a**	100 (77)
5		**3b**	**5b**	100 (81)
6		**3c**	**5c**	100 (69)
7	 **7**	**3a**	**11a**	95 (44)
8		**3b**	**11b**	95[b] (26)
9		**3c**	**11c**	99 (48)
10	 **1**	**3a**	**4a**	94[b] (46)
11		**3b**	**4b**	96[b] (31)
12		**3c**	**4c**	93 (51)
13	 **8**	**3b**	**10b**	93 (54)
14		**3c**	**10c**	85 (51)
15	 **9**	**3b**	**12b**	42[b] (--)

[a] Isolated yields are given in parenthesis. [b] 0.6 equiv of alkyne added after 24 h.

the process. Our solvent of choice for further studies was DMA containing 5% water, in which the observed reaction rates were comparable to the analogous homogeneous reactions.

To check the applicability of the DMA−water solvent system, a range of aromatic halides, from the highly reactive 2-bromopyridine (**6**) to the least reactive 4-chlorobenzonitrile (**9**), were reacted with simple alkynes (**3a**−**c**) (Table 2). The reactions were run on a 10 mmol scale and driven to (near) completion. In cases where conversion did not reach 90% after 24 h (entries 8, 10, 11, and 14), another 0.6 equiv of the alkyne was added,[9] which achieved the desired effect in all but one case (entry 15). Following an aqueous workup, the desired products were isolated by column chromatography. The isolated yields varied considerably from good in the case of 3-pyridylacetylenes (**5a**−**c**)[10] to moderate to poor in the case of tolylacetylenes. The change of 2-bromopyridine to 2-chloropyridine led only to a minor decrease in the isolated yields (cf. entries 1, 3, 13, and 14). This result suggests that the significant difference between conversions and yields in the bromotoluene series might be attributed to the enhanced lability of the intermediate arylpalladium species rather than the decomposition of the product on elongated heating. Despite its presence and identification by GC-MS, we were unable to isolate any of the 4-cyanophenyl-acetylene **12b** (entry 15).

After the demonstration of the applicability of palladium on charcoal in the Sonogashira coupling of aryl bromides, there are still a number of questions to be answered about the process. (i) Can we recycle the catalyst without the deterioration of its activity? (ii) What is the optimal palladium-to-ligand ratio? (iii) Where does the catalytic cycle work, on the surface or in solution?

2-Bromopyridine (**6**) and 2-methyl-3-butyn-2-ol (**3c**) were reacted for 24 h using the standard conditions,[11] and after the reaction mixture was allowed to cool to ambient temperature, the amount of the palladium in the solution was established as only 1.8% of the original by atomic absorption measurements.[12] After filtration, washing with water, acetone, and DCM, and drying, the catalyst was mixed with the reagents, base, ligand, and cocatalyst and the process was repeated four more times giving 100, 86, 82, 72, and 68% conversions, respectively.

Another question we addressed is the optimal ligand-to-catalyst ratio in the process. Study of the reaction of **6** and **3c** under standard conditions demonstrated, that the conversion depends markedly on the amount of ligand added: from the 0.5, 1, 2, 3, 4, and 5 equiv of PPh_3 to Pd used, the first three runs (0.5, 1, and 2 equiv) gave significantly higher rates with the maximal efficiency observed with a P:Pd ratio of 1:1. Increasing the phosphine level above a certain “saturation” limit (P:Pd > 2:1) leads to no major change in the activity; only the “free phosphine” concentration of the solution increases sharply, as observed by the increase of its GC signal.

The mechanism of catalytic processes utilizing a heterogeneous palladium source has frequently been disputed in the literature recently.[12,13] The central question of the debate is whether the palladium stays on the support or dissolves before the catalytically active species is formed. Examination of the homogeneous equivalent of our process by changing Pd/C to palladium acetate under the same reaction conditions shows a similar behavior: variation of the amount of phosphine between 0 and 5 equiv leads to a maximum in efficiency at a P:Pd

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(9) In slower reactions, the competing copper-catalyzed dimerization of the alkyne consumes the reagent before the completion of the Sonogashira coupling.

(10) In certain cases, the reactions were also repeated on a 100 mmol scale and the products were isolated in similar yield using distillation.

(11) For details, see Supporting Information.

(12) Recent results suggest that the amount of palladium in solution might further be reduced by the addition of sodium formate at the end of the process. For details, see: Köhler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. *Chem. Eur. J.* **2002**, *8*, 622−631.

(13) (a) Zhao, F.; Shirai, M.; Ikushima, Y.; Arai, M. *J. Mol. Catal. A: Chem.* **2002**, *180*, 211−219. (b) Augustine, R. L.; O'Leary, S. T. *J. Mol. Catal. A: Chem.* **1995**, *95*, 277−285 and references therein.

ratio of 2, and reactions run with a higher phosphine ratio than 2 are significantly slower.[11] Contrary to the Pd/C-catalyzed processes, we see a slow coupling in the absence of phosphine, too.

A series of experiments were run using 5 mol % Pd/C and 10 mol % PPh_3, and the solids in the reaction mixtures were separated from the hot solutions by filtration under argon after 1, 4, and 10 min reaction times, respectively. The filtrates were returned to the oil bath, while a mixture of starting materials, base, cocatalyst, and ligand was added to each filtered sample.[11,14] All of the isolated Pd/C samples showed catalytic activity, although slightly smaller than the original catalyst, showing that minor amounts of palladium might have leached from the support.[11] The catalytic activity of the filtrates, on the other hand, was not affected by the removal of the solid-supported palladium. The reactions proceeded uninterrupted, although they stopped at around 80% conversion.[11]

These results unambiguously prove that the palladium that leaches into the solution is catalytically active, which means that Pd/C is most likely not the active form but the source of palladium in the process. The comparable catalytic activity of the filtered Pd/C and the solution also suggests that only a minor portion of the bound palladium is released into the solution.

In summary, we established that palladium on charcoal is an efficient catalyst in the Sonogashira coupling of aryl bromides in polar solvents. By using this supported form of palladium, the metal contamination of the reaction mixture was less than 2% and we were able to reuse the catalyst (although with limited success). Our studies also revealed that the catalytic cycle runs in the solution and that Pd/C acts most likely only as a source of palladium in the process. These findings suggest that by using solid-supported palladium in coupling reactions, one might be able to exploit the benefits of homogeneous catalysis but still retain the ease of heterogeneous catalyst separation.

Experimental Section

General Procedure for the Pd/C-Catalyzed Sonogashira Coupling of Aryl Halides. A dry Schlenk flask was charged with 0.512 g of Pd/C (0.5 mmol Pd), 0.192 g (1 mmol) of CuI, and 0.262 g (1 mmol) of PPh_3, followed by 9.5 mL of DMA and 0.5 mL of water. After the addition of 10 mmol of aryl halide, 2.1 mL of diisopropylamine, and 12.8 mmol of the appropriate acetylene, the reaction mixture was purged with argon, sealed, and placed in an 80 °C oil bath for 24 h. After the mixture was cooled to ambient temperature, the charcoal was filtered off and water was added to the solution. The aqueous phase was extracted with diethyl ether, and the combined organic phases were dried over magnesium sulfate. After removal of the solvent in a vacuum, the crude products were purified by column chromatography.

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Supporting Information Available: Details of the mechanistic studies as well as characterization data and literature references for the products illustrated in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Sheldon, R. A.; Wallau, M.; Arends, I. W. C. E.; Schuchardt, U. *Acc. Chem. Res.* **1998**, *31*, 485−493.