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Room temperature dehalogenation of chloroarenes by polymethylhydrosiloxane (PMHS) under palladium catalysis

Ronald J. Rahaim, Jr. and Robert E. Maleczka, Jr.*

Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA

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Abstract—The first method for the reduction of chloroarenes by polymethylhydrosiloxane (PMHS) is reported. Catalytic amounts of palladium(II) acetate in combination with PMHS and aqueous KF will rapidly hydrodehalogenate aryl chlorides at room temperature. The mildness of the method is demonstrated by its tolerance of ketones, amides, esters, nitriles, ethers, borate esters, and amines. © 2002 Elsevier Science Ltd. All rights reserved.

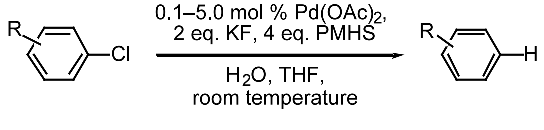
Polymethylhydrosiloxane (PMHS) is an easily handled, inexpensive, non-toxic, and mild reducing agent. Although relatively inert towards organic functionality, PMHS can transfer its hydride to a variety of metal catalysts (including Sn, Ti, Zn, Cu, and Pd) that can then participate in a wide range of reductions.[1]

PMHS hydrodehalogenates aryl bromides and iodides under palladium catalysis.[2] However, to the best of our knowledge, all attempts to reduce chlorides by such conditions have failed. This is unfortunate as the formation of arenes from aryl chlorides is an important chemical transformation.[3] The reduction of chloroarenes has been studied under a variety of conditions including free radical,[4] catalytic and transfer hydrogenation,[5] oxidative,[6] and metal-catalyzed hydride delivery.[2,7–9] Several of these methods employ relatively expensive silanes[7c,e,9b,c] or hazardous stannanes,[4] for which PMHS would be an attractive alternative.

Recently, phosphine free palladium catalysts have seen considerable success in reactions with aryl chlorides.[7a,10] Thus, we decided to explore if related systems could solve the problem of reducing chloroarenes with PMHS.[4] This investigation revealed that catalytic palladium(II) acetate with PMHS in the presence of potassium fluoride reduced chlorobenzene to benzene.[11,12] Impressively, this transformation could take place at room temperature in a matter of minutes (Scheme 1).

Reaction optimization experiments carried out on 4-chlorotoluene indicated that fluoride was essential for rapid reaction as only trace quantities of toluene were produced upon reaction with 5 mol% $Pd(OAc)_2$ and 6 equiv. of PMHS (relative to chloroarene) at room temperature for 24 h. While the presence of fluoride was beneficial, too much (>50 mol% based on PMHS) decreased the efficiency of the reaction. As for the amount of PMHS required, increasing the equivalency of PMHS increased the rate of dehalogenation. The reaction of equal molar amounts of PMHS and 4-chlorotoluene was complete after 24 h. Using a sixfold excess of PMHS allowed for near complete reduction after only 2 h. Upon factoring in the low cost and mildness of PMHS[1] and our desire to maximize reaction efficiency as well as ease of purification and workup, we settled on 4 equiv. of PMHS and 2 equiv. of KF as the conditions of choice (Scheme 1).

A variety of haloarenes were reacted with 4 equiv. of PMHS, 2 equiv. of an aqueous solution of KF, and 5 mol% $Pd(OAc)_2$[12] in THF (Table 1).[11] Chlorobenzene was efficiently reduced to benzene in 20 min (entry 1). Chloroarenes bearing electron neutral, donating or releasing groups were all reduced smoothly. Most reductions were complete in less than 4 h. Even sterically hindered 2-chloro-*m*-xylene (entry 12) was quanti-



Scheme 1.

Keywords: hydrodehalogenation; chlorides; reduction; palladium; PMHS.

* Corresponding author.

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Table 1. Room temperature Pd-catalyzed hydrodehalogenations with 2 equiv. KF and 4 equiv. PMHS[11]

Entry	Starting material	Pd-catalyst	Time (h)	Product	% Yield[a]
1	Chlorobenzene	5 mol% $Pd(OAc)_2$	0.3	Benzene	95
2	4-Chlorotoluene	5 mol% $Pd(OAc)_2$	3	Toluene	95
3	4-Chlorotoluene	1 mol% $Pd(OAc)_2$	10	Toluene	96
4	4-Chlorotoluene	0.1 mol% $Pd(OAc)_2$	54	Toluene	24
5	4-Chlorotoluene	5 mol% $Pd(CN)_2$	3	Toluene	0
6	4-Chlorotoluene	5 mol% $Pd(NH_2)Cl_2$	3	Toluene	0
7	4-Chlorotoluene	5 mol% $Pd(acac)_2$	3	Toluene	73
8	4-Chlorotoluene	5 mol% Pd black	3	Toluene	94
9	4-Chlorotoluene	5 mol% $PdCl_2$	3	Toluene	78
10	4-Chlorotoluene	5 mol% $Pd_2(dba)_3$	3	Toluene	96
11	2-Chlorotoluene	5 mol% $Pd(OAc)_2$	3	Toluene	100
12	2-Chloro-*m*-xylene	5 mol% $Pd(OAc)_2$	8	*m*-Xylene	100
13	2-Chloro-*m*-xylene	5 mol% $PdCl_2$	14	*m*-Xylene	0
14	2-Chloro-*m*-xylene	5 mol% $Pd_2(dba)_3$	17	*m*-Xylene	50
15	1-Chloronaphthalene	5 mol% $Pd(OAc)_2$	4	Naphthalene	96, 82[b]
16	4-Chlorophenol	5 mol% $Pd(OAc)_2$	17	Phenol	0
17	4-Chloroanisole	5 mol% $Pd(OAc)_2$	1.5	Anisole	100
18	4-Chloroaniline	5 mol% $Pd(OAc)_2$	0.5	Aniline	99, 87[b]
19	4-Chloroaniline	1 mol% $Pd(OAc)_2$	1	Aniline	98
20	4-Chloroaniline	0.1 mol% $Pd(OAc)_2$	29	Aniline	97
21	3-Chloroaniline	5 mol% $Pd(OAc)_2$	0.75	Aniline	94
22	2-Chloroaniline	5 mol% $Pd(OAc)_2$	0.75	Aniline	99
23	4-Chlorobenzoic acid	5 mol% $Pd(OAc)_2$	24	Benzoic acid	0
24	Methyl 4-chlorobenzoate	5 mol% $Pd(OAc)_2$	3	Methyl benzoate	84
25	Methyl 2-chlorobenzoate	5 mol% $Pd(OAc)_2$	1	Methyl benzoate	98, 76[b]
26	Methyl 2-chlorobenzoate	1 mol% $Pd(OAc)_2$	9	Methyl benzoate	100
27	Methyl 2-chlorobenzoate	0.1 mol% $Pd(OAc)_2$	54	Methyl benzoate	100
28	4-Chlorobenzamide	5 mol% $Pd(OAc)_2$	1.5	Benzamide	99, 83[b]
29	2-Chlorobenzamide	5 mol% $Pd(OAc)_2$	0.75	Benzamide	89
30	4-Chlorobenzonitrile	5 mol% $Pd(OAc)_2$	0.5	Benzonitrile	81
31	2-Chlorobenzonitrile	5 mol% $Pd(OAc)_2$	1	Benzonitrile	90
32	4-Chlorobenzotrifluoride	5 mol% $Pd(OAc)_2$	4	Trifluorotoluene	96
33	2-Chlorobenzotrifluoride	5 mol% $Pd(OAc)_2$	4	Trifluorotoluene	99
34	4-Chloropyridine·HCl	5 mol% $Pd(OAc)_2$	1.5	Pyridine	96
35	3-Chloropyridine	5 mol% $Pd(OAc)_2$	1	Pyridine	97
36	2-Chloropyridine	5 mol% $Pd(OAc)_2$	1.5	Pyridine	94
37	2-Chloropyridine	5 mol% Pd black	1.5	Pyridine	0
38	4-(4-Chlorophenyl)-2-butanone	5 mol% $Pd(OAc)_2$	18	4-Phenyl-2-butanone	95, 85[b]
39	1-Chloro-4-fluorobenzene	5 mol% $Pd(OAc)_2$	20	Fluorobenzene	92
40	1,2-Dichlorobenzene[c]	5 mol% $Pd(OAc)_2$	18	Benzene	98
41	1,3-Dichlorobenzene[c]	5 mol% $Pd(OAc)_2$	6	Benzene	98
42	1,4-Dichlorobenzene[c]	5 mol% $Pd(OAc)_2$	3	Benzene	98
43	1-Chloro-4-iodobenzene[c]	5 mol% $Pd(OAc)_2$	3	Chlorobenzene	93
44	3-Chloro-5-methylphenylpinacolborane	5 mol% $Pd(OAc)_2$	6	3-Methylphenylpinacolborane	85[b]

[a] Yields are an average of two runs and unless otherwise noted were determined by NMR (internal standard).

[b] Isolated yield.

[c] Run with 4 equiv. of PMHS and 2 equiv. of KF per halogen.

tatively reduced at room temperature, albeit after a somewhat extended (8 h) reaction time. Substituted pyridines (entries 34–36) also perform well under the reaction conditions, including 2-chloropyridine which has afforded poor yields in other systems.[8a] Dihalogenated arenes can also be reduced with 4 equiv. of PMHS per halogen[13] (entries 40–43).

These conditions are compatible with a variety of functional groups including ethers (entry 17), amines (entries 18–22), esters (entries 24–27), amides (entries 28–29), nitriles (entries 30–31), ketones (entry 38[14]), aryl fluorides (entry 39), and borate esters (entry 44[15]). Of the substrates studied only 4-chlorophenol (entry 16) and 4-chlorobenzoic acid (entry 23) did not reduce.[16]

The presence of additional substituents can retard the reaction. For example, certain *para*-substituted aryl chlorides proved surprisingly sluggish. The reduction of 1-chloro-4-fluorobenzene (entry 39) was only 78% complete by GC after 12 h and required 20 h before the reaction was complete. Likewise, entry 38 required 18 h for full consumption of 4-(4-chlorophenyl)-2-butanone. Most unusual was the hydrodehalogenation of 1-chloro-4-iodobenzene (entry 43), which after 3 h afforded only chlorobenzene.[17] In contrast, chlorobenzene and iodobenzene were reduced to benzene in 20 min.

Having proved the reduction of chloroarenes by hypercoordinate PMHS under Pd-catalysis to be mild, rapid, and general, we looked to see if the palladium loading could be lowered below 5 mol%. Though longer reaction times were required, the hydrodehalogenations of 4-chlorotoluene, 4-chloroaniline, and methyl 2-chlorobenzoate in the presence of only 1 mol% $Pd(OAc)_2$ were all high yielding (entries 3, 19, and 26, respectively). Decreasing the catalyst loading by another order of magnitude (0.1 mol%) still allowed for the efficient, though slow, dechlorination of 4-chloroaniline and methyl 2-chlorobenzoate (entries 20 and 27, respectively). However, for 4-chlorotoluene (entry 4) diminishing returns set in at this loading.

We also screened the efficacy of other phosphine free[18] palladium sources. In these experiments $Pd(CN)_2$ and $Pd(NH_2)Cl_2$ failed to reduce 4-chlorotoluene (entries 5–6). While $Pd(acac)_2$, palladium black, $PdCl_2$, and $Pd_2(dba)_3$ dechlorinated 4-chlorotoluene (entries 7–10), these catalysts proved considerably less efficient than $Pd(OAc)_2$ with other substrates (e.g. entries 13, 14, and 37). Thus, on balance, $Pd(OAc)_2$[12] appears to be the most universal catalyst for room temperature hydrodehalogenations with KF/PMHS.

Finally, a limited investigation suggests that the ratio of water to THF can influence the course of these reductions. Increasing the water/THF ratio from 2/5 to 3/5 decreased the required reaction time for the reduction of 4-chlorotoluene from 3 h to 1. However, this proved a delicate balance as any further increase in the amount of water prohibited the reaction from going to completion. Additional studies on this water effect and other aspects of these reductions, including mechanism, continue and will be reported elsewhere.

In summary $KF_{(aq)}$, PMHS, and catalytic $Pd(OAc)_2$ in THF is a mild and efficient system for the room temperature[19] dechlorination of aryl chlorides. Under these conditions, electron neutral, rich, or poor chloroarenes can be rapidly hydrodechlorinated at room temperature. Ketones, amides, esters, nitriles, ethers, borate esters and amines are tolerated by the reaction, whereas phenols and carboxylic acids are not. Dehalogenations can be accomplished with as low as 0.1 mol%, however 1–5 mol% $Pd(OAc)_2$ represent a more general catalyst loading.

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11. An oven dried round bottom flask was charged with 1.0 mmol of aryl chloride in 5 mL THF (0.2 M solution) and 0.05 equiv. of $Pd(OAc)_2$.[12] The flask was sealed with a septum and flushed with nitrogen. While flushing the reaction, 2 equiv. of KF in 2 mL of degassed water were introduced by syringe. PMHS (4 equiv.) was then injected dropwise into the reaction mixture. The reaction was stirred until complete as judged by disappearance of the starting material (GC analysis). Upon complete reduction, the reaction mixture was added to a 3 M solution of NaOH. After stirring 5 h to hydrolyze unreacted PMHS, the mixture was extracted several times with Et_2O. The combined organics were dried over $MgSO_4$ and concentrated. The crude material was then either distilled or purified by silica gel chromatography. (When column chromatography was needed, initial elution with CCl_4/hexanes (1:1) was useful in removing silane byproducts.)
12. Palladium(II) acetate purchased from Strem or Aldrich's 99.9+% $Pd(OAc)_2$ performed well in this study, however, the reactions were much less efficient when run with Aldrich's 98% $Pd(OAc)_2$.
13. These substrates could be reduced with 4 equiv. of PMHS per equivalent of arene, however, these reactions took 2–4 times longer.
14. 4-(4-Chlorophenyl)butan-2-one was prepared according to: Buntin, S. A.; Heck, R. F. *Org. Synth.* **1983**, *61*, 82–84.
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16. This failure was not entirely surprising as 4-bromophenol and 4-bromobenzoic acid were not reduced with PMHS, KF, and catalytic $(Ph_3P)_2PdCl_2$ (Ref. 2a).
17. Even after 48 h only chlorobenzene was present. Similar observations were made by Tashiro and co-workers during dehalogenations with metallic calcium in ethanol. See: Mitoma, Y.; Nagashima, S.; Simion, C.; Simion, A. M.; Yamada, T.; Mimura, K.; Ishimoto, K.; Tashiro, M. *Environ. Sci. Technol.* **2001**, *35*, 4145–4148.
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