ORGANIC LETTERS
2011
Vol. 13, No. 4
584–587

C–O Hydrogenolysis Catalyzed by Pd-PMHS Nanoparticles in the Company of Chloroarenes

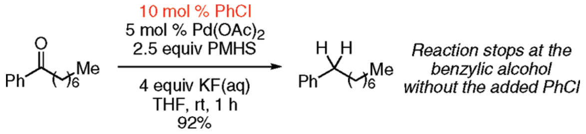
Ronald J. Rahaim Jr.[‡] and Robert E. Maleczka Jr.*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States

maleczka@chemistry.msu.edu

Received November 13, 2010

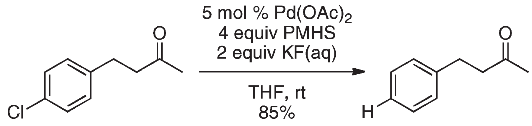
ABSTRACT



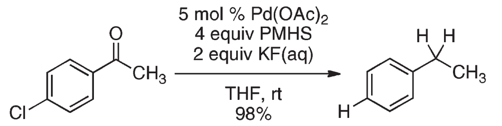
Catalytic $Pd(OAc)_2$ and polymethylhydrosiloxane (PMHS), in conjunction with aqueous KF, and a catalytic amount of an aromatic chloride, effects the chemo-, regio-, and stereoselective deoxygenation of benzylic oxygenated substrates at room temperature in THF. Preliminary mechanistic experiments suggest the process to involve palladium–nanoparticle-catalyzed hydrosilylation followed by C–O reduction. The chloroarene additive appears to facilitate the hydrogenolysis process through the slow controlled release of HCl.

In the early 1990s, Tour[1] and Crabtree[2] independently reported on how dispersing palladium throughout a siloxane polymer matrix raises the catalytic activity of the metal. Originally termed Pd-colloids, in 2004 Chauhan[3] unequivocally showed that mixing $Pd(OAc)_2$ with polymethylhydrosiloxane (PMHS) formed polysiloxane-encapsulated Pd-nanoclusters.

We had previously reported that $Pd(OAc)_2$/PMHS in the presence of aqueous KF rapidly hydrodehalogenated chloroarenes.[4] Despite PMHS' ability to reduce ketones to alcohols,[5] this system chemoselectively dechlorinated 4-(4-chlorophenyl)-2-butanone (eq 1). In contrast, when 4′-chloroacetophenone was placed under the same conditions, it was fully reduced to ethylbenzene (eq 2).



(1)



(2)

Since transfer hydrogenolysis of activated C–O bonds by PMHS are known,[6] we were not entirely surprised by this result, until we examined the reactivity of acetophenone. After being exposed to the $Pd(OAc)_2/PMHS/KF_{(aq)}$

[‡] Current address: Scripps Florida, Department of Chemistry, Jupiter, Florida 33458, United States

[1] (a) Tour, J. M.; Cooper, J. P.; Pendalwar, S. L. *J. Org. Chem.* **1990**, *55*, 3452–3453. (b) Tour, J. M.; Pendalwar, S. L.; Cooper, J. P. *Chem. Mater.* **1990**, *2*, 647–649.

[2] Fowley, L. A.; Michos, D.; Luo, X.-L.; Crabtree, R. H. *Tetrahedron Lett.* **1993**, *34*, 3075–3078.

[3] Chauhan, B. P. S.; Rathore, J. S.; Bandoo, T. *J. Am. Chem. Soc.* **2004**, *126*, 8493–8500.

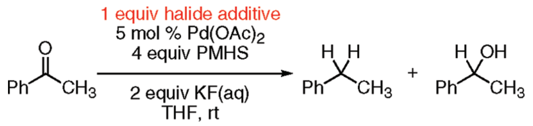
[4] Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **2002**, *43*, 8823–8826.

[5] (a) Larson, G. L.; Fry, J. L. *Org. React.* **2008**, *71*, 1–771. (b) Mimoun, H. *J. Org. Chem.* **1999**, *64*, 2582–2589. (c) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381–3391.

[6] (a) Blum, J.; Bitan, G.; Marx, S.; Vollhardt, K. P. C. *J. Mol. Catal.* **1991**, *66*, 313–319. (b) Blum, J.; Pri-Bar, I.; Alper, H. *J. Mol. Catal.* **1986**, *37*, 359–367.

10.1021/ol102757v

Table 1. Screening Halides as Deoxygenation Additives



entry	halide source	time (h)	% yield[a] of PhEt	% yield[a] of alcohol
1	none	24	0	98
2	PhCl	1	100	0
3	PhBr	2	22	78
4	PhI	16	0	25
5	Bu_4NCl	3.5	trace[b]	30
6	CsCl	24	trace[b]	98
7	LiCl	24	trace[b]	100
8	PhONf	1	trace[b]	99
9	PhONf + LiCl	1	97	0
10	HCl	1	15	40
11	1-chlorobutane	1	trace[b]	22
12	TMS-Cl	1	95	0

[a] Average of two runs as determined by ^{1}H NMR with CH_2Cl_2 as an internal standard. [b] Determined by GC.

conditions for 24 h, the acetophenone afforded no visible amounts of ethyl benzene, stopping instead at 1-phenylethanol (Table 1, entry 1).

Empirically, the presence of a chloro group was influencing the reactivity of the benzylic ketone/alcohol. Yet, GC monitoring of the 4′-chloroacetophenone reduction indicated the intermediacy of acetophenone. Thus the chloro group of 4-chloroacetophenone was not directly enhancing its reactivity. An investigation was undertaken to uncover why in situ generated acetophenone undergoes full deoxygenation, while subjecting acetophenone starting material to the "same" reduction conditions stopped at the alcohol. Through experimentation, we found that by simply starting the reaction in the company of chlorobenzene, acetophenone was quantitatively reduced to ethylbenzene after 1 h at room temperature. Moreover, 10 mol % chlorobenzene[7] proved equally effective at facilitating the reaction.

To the best of our knowledge this is the first example of chlorobenzene serving as a productive additive in Pd-mediated reductions.[8−10] To explore this curious finding further, we surveyed a variety of chlorides and related additives against the reaction of acetophenone with $Pd(OAc)_2/PMHS/KF_{(aq)}$.

Where chlorobenzene efficiently facilitated deoxygenation, among bromobenzene, iodobenzene, and phenyl nonaflate (entries 3−4 and 8), only PhBr showed any effectiveness as an additive with its reaction affording ethylbenzene in 22% yield. With PhI and PhONf, the reductions stopped at 1-phenylethanol. It was also noted that relative to chlorobenzene, PhBr, PhI, and PhONf were themselves reduced very rapidly to benzene. A number of chloride salts were also tested (entries 5−7), but only trace amounts of ethylbenzene were formed in their presence. Interestingly though, while LiCl (entry 7) and PhONf (entry 8) were ineffective additives on their own, when both were added to the reaction (entry 9) acetophenone was quantitatively converted to ethylbenzene.

These data pointed to the possible participation of an Ar-Pd-Cl species.[11] Such an intermediate could play many roles. Among the possibilities, the aromatic chloride might serve as a ligand on the active Pd catalyst or in some other way (e.g., transmetalation) positively alter the reactivity of the polysiloxane matrix. It could also be that Ar-Pd(II)-Cl in the presence of PMHS and water simply serves as a source of HCl.[12] Indeed, adding 1 equiv of HCl to the acetophenone reaction (entry 10) gave 15% of PhEt.

Though certainly speculation, we were of the opinion that these preliminary results best fit a scenario where chlorobenzene provided for a controlled release of HCl. Supposing this to be the case, entries 2 vs 10 would indicate that the rate at which HCl enters the reaction affects the efficiency of the overall reaction. As such, we deemed it useful to examine other additives that could generate HCl in situ. However, 1-chlorobutane (entry 11), which could afford HCl via β-hydride elimination, was not an effective additive. On the other hand, adding TMSCl to the reaction was beneficial, with deoxygenation of the ketone occurring in 95% (entry 12). We also screened various chloroarenes under the assumption that they would form Ar-Pd(II)-Cl species and in turn release HCl at different rates. Anticipating subtle differences between chloroarenes, we chose the relatively slow reacting methyl 4-acetylbenzoate as the starting ketone (Table 2). In the presence of 10 mol % of PhCl, this substrate afforded 21% of methyl 4-ethylbenzoate (**A**) and 77% of methyl 4-(1-hydroxyethyl)benzoate (**B**). A set of sterically and electronically varied chloroarenes was then assessed. As seen in Table 2, the ratio of **A**/**B** was highest with 4-chloroanisole (entry 3). To further test the hypothesis that chloroarene derived HCl was the deoxygenation promoter, the reduction of methyl 4-acetylbenzoate was performed in the presence of both 4-chloroanisole and various acid scavengers. In all instances (entries 8−11) the deoxygenations were suppressed, albeit to unequal extents.

---

(7) As little as 1 mol % of chlorobenzene facilitated deoxygenation, but reactions stopped at the alcohol with < 1 mol % of PhCl.

(8) For the productive use of stoichiometric PhCl in Pd-mediated oxidations, see: (a) Bei, X.; Hagemeyer, A.; Volpe, A.; Saxton, R.; Turner, H.; Guram, A. S. *J. Org. Chem.* **2004**, *69*, 8626–8633. (b) Guram, A. S.; Bei, X.; Turner, H. W. *Org. Lett.* **2003**, *5*, 2485–2487.

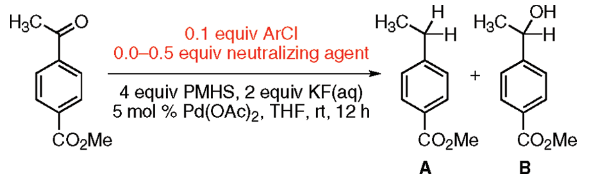
(9) For related observations, see: (a) Maleczka, R E., Jr.; Rahaim, R J., Jr.; Teixeira, R. R. *Tetrahedron Lett.* **2002**, *43*, 7087–7090. (b) Zigterman, J. L.; Woo, J. C. S.; Walker, S. D.; Tedrow, J. S.; Borths, C. J.; Bunel, E. E.; Faul, M. M. *J. Org. Chem.* **2007**, *72*, 8870–8876.

(10) For other surprising aryl halide and halide effects in transition-metal catalysis, see:(a) Chrovian, C. C.; Montgomery, J. *Org. Lett.* **2007**, *9*, 537–540. (b) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47.

(11) Note: Using $PdCl_2$ in place of $Pd(OAc)_2$ with no additives only yielded 8% of ethylbenzene along with 71% benzyl alcohol.

(12) Rylander, P. *Catalytic Hydrogenation in Organic Synthesis*; Academic: New York, 1979; p 274.

Table 2. Screening Halides as Deoxgyenation Additives



entry	ArCl	neutralizing agent	% yield[a] (**A**/**B**/sm)
1	chlorobenzene		21/77/−
2	2-chloro-*m*-xylene		13/74/−
3	4-chloroanisole		39/46/ −
4	4-chlorobenzo-trifluoride		32/28/10
5	2-chloropyridine		−/13/85
6	*o*-dichlorobenzene		38/61/−
7	hexachlorobenzene		30/66/2
8	4-chloroanisole	2,6-lutidine[b]	−/94/1
9	4-chloroanisole	DTBMP[c,d]	28/65/−
10	4-chloroanisole	proton-sponge[d]	−/98/−
11	4-chloroanisole	propylene oxide[d]	37/57/−

[a] Average isolated yield over two runs. [b] 0.1 equiv. [c] 2,6-di-*tert*-butyl-4-methylpyridine. [d] 0.5 equiv.

In addition to these reactions being mechanistically curious, chlorobenzene represents a unique and attractive additive. Even relative to TMSCl, chlorobenzene is cheap, stable, and otherwise inert. For these reasons we presented these conditions to a variety of substrates bearing benzylic C−O bonds (Table 3). Substrate screening was carried out with 10 mol % of PhCl, 5 mol % of Pd(OAc)$_2$, 1.5−4.0 equiv of PMHS, and 4 equiv of KF in 5:2 THF/H$_2$O at room temperature for 1 h.[13,14] We found that increasing the steric environment about the carbonyl hindered the deoxygenation (entries 6, 10, and 12−14), with substitution at both ortho positions completely shutting down a second reduction (entries 15 and 16). To evaluate the chemoselectivity of the system, 4-(4-acetylphenyl)butan-2-one (entries 18−21) was prepared and subjected to the reaction conditions, resulting in reduction of only the benzylic ketone. Likewise, subjecting 1-phenylbutane-1,3-dione to the reaction conditions (entries 22−24) resulted in deoxygenation of the benzylic carbonyl, along with some reduction of the 3-carbonyl to the alcohol. Similar chemoselectivity was also seen with methyl 4-acethylbenzoate (entry 25).

Entries 27−32 show that the chlorobenzene effect can be seen during the hydrogenolysis of a variety of C−O bonds.[15] In the presence of PhCl, benzyl bornyl ether (entry 29) underwent deprotection in 67% yield in less than 1 h. In the absence of PhCl, only 15% of isobornyl alcohol was formed in 1 h, and over 8 h was needed for the reaction to give a comparable yield. Not surprisingly, the rate acceleration that occurs courtesy of PhCl could impact the reactions negatively. For example, the benzyl ether of 1-phenylethanol (entry 27) undergoes hydrogenolysis of both C−O bonds when PhCl is present, whereas without PhCl the reaction was regioselective for hydride delivery to the least substituted benzyl, affording toluene and *sec*-phenethyl alcohol in nearly quantitative yields. It should also be noted that the presence of a basic nitrogen inhibited the deoxygenation (entry 17), affording only the alcohol, presumably due to HCl sequestration.

To evaluate the regio- and stereoselectivity of the reduction, a stereodefined benzylic epoxide (entry 31) was subjected to the conditions. Here, the 1,2-diol was generated in high yield and 95% de.[16] Reaction of the epoxide without PhCl also afforded the 1,2-diol quantitatively, but with decreased de (entry 32). A stereodefined[17] tertiary benzylic alcohol (entry 33) afforded (*S*)-3-phenyl-1-butanol with no loss of enantiomeric excess and retention of configuration.[18] Finally, as evidenced by entries 8 vs 7, 11 vs 10, 20 vs 19, and 26 vs 25, changing the aryl chloride additive from chlorobenzene to 4-chloroanisole enabled the deoxygenation of some of the more difficult substrates.

More work is needed to secure a mechanism for this process, as well as to determine how the additives impact the nature of the Pd nanoparticles. That said, the observed memory of chirality (Table 3, entry 33) and cyclobutane stability (Table 3, entries 6−9) argue against the presence of benzyl radicals. On the basis of these and other data, we favor a mechanism were the ketone is first reduced to the alcohol by Pd-catalyzed hydrosilylation. In the interim, a reduction of chlorobenzene affords benzene and a chlorosiloxane. The chlorosiloxane is then hydrolyzed by water present in the reaction to form HCl and the silanol. The HCl then facilitates[12,19] Pd-catalyzed transfer hydrogenolysis of the benzylic C−O bond, where the hydrogen is in part formed from the PMHS and water.[6] This last step is

---

(13) Typical procedure: Into a 25 mL round-bottom flask that had been purged with nitrogen was charged Pd(OAc)$_2$ (0.05 mmol, 11 mg), freshly distilled THF (5 mL), and then the ketone (1.0 mmol). The flask was fitted with a balloon of nitrogen. A solution of potassium fluoride (4 mmol, 232 mg) in degassed water (2 mL) was added via syringe into the reaction, followed by chlorobenzene (0.1 mmol, 0.01 mL). PMHS (2.5 mmol, 0.15 mL) was then dropwise added via syringe into the reaction mixture. The resulting reaction was stirred for one hour. Ether was added to the reaction mixture, the layers were separated, and the aqueous layer was back-extracted with ether. The combined organics were concentrated and subjected to flash chromatography. (**Caution**: *Rapid addition of PMHS can result in vigorous gas evolution! For reactions run on large scale, it is recommended that the reaction flask be fitted with a reflux condenser*.)

(14) As little as 1 mol % of Pd(OAc)$_2$ can be used provided the amounts of PMHS and KF are raised to 5 and 10 equiv, respectively. However, increasing the amount of PMHS can make purifications more difficult as PMHS can undergo sol−gel processes.

(15) For other Pd-mediated reductions of benzylic C−O bonds, see: (a) Felpin, F.-X.; Fouquet, E. *Chem.—Eur. J.* **2010**, *16*, 12440–12445. (b) Mirza-Aghayan, M.; Boukherroub, R.; Rahimifard, M. *Tetrahedron Lett.* **2009**, *50*, 5930–5932. (c) Thiery, E.; Le Bras, J.; Muzart, J. *Green Chem.* **2007**, *9*, 326–327. (d) Coleman, R. S.; Shah, J. A. *Synthesis* **1999**, 1399–1400. (e) Keinan, E.; Greenspoon, N. *J. Org. Chem.* **1983**, *48*, 3545–3548. (f) Lipowitz, J; Bowman, S. A. *J. Org. Chem.* **1973**, *38*, 162–165.

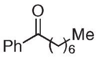
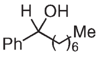
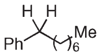
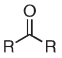
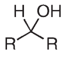
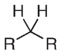
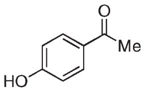
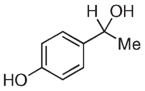
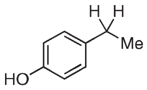
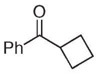
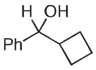
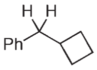
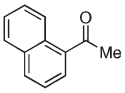
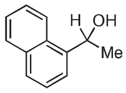
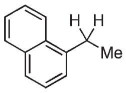
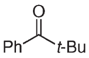
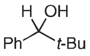
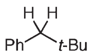
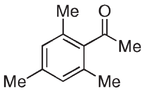
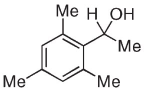
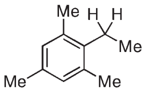
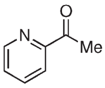
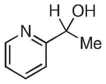
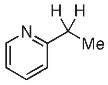
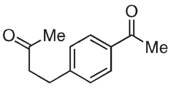
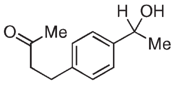
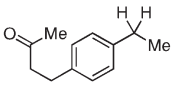
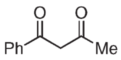
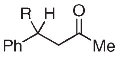
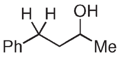
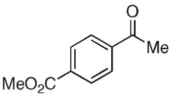
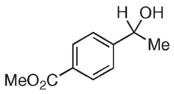
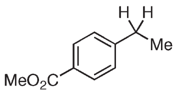
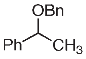
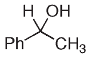
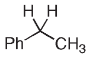
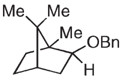
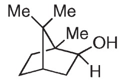
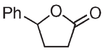
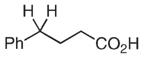
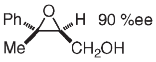
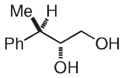
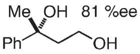
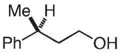
(16) 3-Phenyl-1-butanol (3%) was also isolated.

(17) The % ee and absolute configuration of the starting material were determined by derivation to Mosher's ester with (*S*)-(+)-MTPA-Cl. See: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

(18) The % ee and absolute configuration of the product were determined by derivation with (*R*)-MPA. See: Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929–4932.

(19) Consistent with this proposal is the quantitative deoxygenation of *sec*-phenethyl alcohol and its TBS ether in the presence of catalytic HCl.

Table 3. Deoxygenation Substrate Screening[a]

entry	starting material	equiv PMHS	Ar-Cl added	product(s) %yield[b]			
1		2.5	Ph–Cl		0%		92%
2		1.5	none		88%		0%
3	 R = 4-MeOC$_6$H$_4$	2.5	Ph–Cl	 R = 4-MeOC$_6$H$_4$	0%	 R = 4-MeOC$_6$H$_4$	95%
4		2.5	Ph–Cl		0%		86%
5[c]		1.5	none		67%		0%
6		2.5	Ph–Cl		21%		72%
7		4.0	Ph–Cl		12%		83%
8		4.0	4-chloroanisole		0%		94%
9[c]		1.5	none		99%		0%
10		2.5	Ph–Cl		20%		80%
11		2.5	4-chloroanisole		0%		99%
12		4.0	Ph–Cl		97%		0%
13		4.0	4-chloroanisole		96%		0%
14[c]		1.5	none		99%		0%
15		4.0	Ph–Cl		0%		0%
16[c]		4.0	none		0%		0%
17[d]		2.5	Ph–Cl		98%		0%
18		2.5	Ph–Cl		44%		52%
19		4.0	Ph–Cl		41%		57%
20		4.0	4-chloroanisole		25%		72%
21[c]		3.0	none		94%		0%
22		2.5	Ph–Cl		48% (R = OH)[e]		11%
23		4.0	Ph–Cl		33% (R = H)		46%
24[c]		1.5	none		42% (R = OH)		0%
25		4.0	Ph–Cl		73%		25%
26		4.0	4-chloroanisole		46%		52%
27[d]		2.5	Ph–Cl		0%		94%[f]
28[c,d]		1.5	none		98%[f]		0%
29[g]		2.5	Ph–Cl		67%		
30[c]		1.5	Ph–Cl		90%		
31		2.5	Ph–Cl		97% (95 %de)		
32[c]		1.5	none		99% (79 %de)		
33[h]		2.5	Ph–Cl		62% (81 %ee)		

[a] Conditions: 1 equiv of substrate (1 mmol), 5 mol % of Pd(OAc)$_2$, 10 mol % of PhCl, 2.5 equiv of PMHS, 4 equiv of KF, 5 mL of THF, 2 mL of H$_2$O, rt, 1 h. [b] Average isolated yield of two runs. [c] Reaction run with 2 equiv of KF. [d] Determined by ^{1}H NMR with CH$_2$Cl$_2$ as an internal standard. [e] Plus 7% (R = H). [f] Toluene was also observed in >95% yield. [g] 31% recovered starting material. [h] 38% recovered starting material.

supported by reactions run in D$_2$O, which saw ~37% deuterium incorporation at the newly formed benzylic methylene.[20]

Acknowledgment. We thank the NSF, NIH, and the Astellas USA Foundation for generous support.

Supporting Information Available. Experimental details and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

---

[20] A description of the deuterium labeling and silicon hydride screening experiments can be found in the Supporting Information.