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Palladium-catalyzed hydrodehalogenations by fluoride activated polymethylhydrosiloxane

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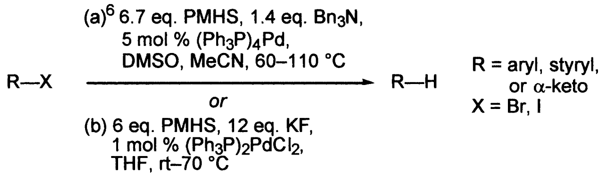
Abstract—A mild, selective, and efficient method for the Pd-catalyzed reduction of aryl bromides and iodides by hypercoordinate polymethylhydrosiloxane (PMHS) is reported. In contrast to related methods, the hydrodehalogenations described herein are amine free and can be carried out in THF with relatively low loads of catalyst. Furthermore, we have evidence to suggest that the reduction of bromostyrene proceeds differently than previously described. © 2002 Elsevier Science Ltd. All rights reserved.

The formation of arenes from aryl halides represents an important chemical transformation in organic synthesis.[1] Reduction under free radical conditions,[1,2] electrochemical means,[1,3] catalytic hydrogenation,[1,4] or metal catalyzed hydride delivery[1,5] are among the common ways to perform such hydrodehalogenations.

In 1986, Pri-Bar and Buchman[6] reported that polymethylhydrosiloxane (PMHS) in the presence of a Pd(0) catalyst could effectively reduce aryl, styryl, and α-keto halides (Scheme 1, conditions a). Milder than LAH, $NaBH_4$, etc., PMHS is air and moisture stable, soluble in a number of organic solvents, relatively non-toxic, and inexpensive.[7] Unfortunately, use of this attractive reductant in hydrodehalogenations also required the employment of excess tribenzylamine, relatively high boiling and polar solvents (DMSO/MeCN), elevated temperatures, and fairly high loads (5 mol%) of $(Ph_3P)_4Pd$. As fluoride activation of PMHS is known,[7a,8] we decided to investigate if a combination of PMHS and fluoride would facilitate aryl halide reductions and thereby minimize some of the disadvantages posed by the original protocol.



Scheme 1.

Screening various catalyst, solvent, stoichiometry, fluoride source, and reaction temperature combinations revealed that like the original conditions ~6 equiv. of PMHS worked best (Scheme 1, conditions b). Importantly though, adding 12 equiv. of KF (aq.) to the reaction obviated the need for tribenzylamine, allowed us to reduce the Pd-load from 5 to 1 mol%, and facilitated the reactions so that they could now be performed in THF at 70°C or lower (Table 1).[9] Fluoride clearly promoted these reductions. Control experiments run in the absence of KF saw yields diminish by ~80% for the aryl bromides to ~30% for the aryl iodides.[10]

As compared to the hydrodehalogenations described by Pri-Bar and Buchman, reduction with PMHS/KF in THF[11] tended to be higher yielding, though they often took longer to complete. Despite this increased reaction time, by avoiding the amine and polar high boiling solvents, reaction monitoring (GC or NMR) as well as product isolation and purification were made much easier. Furthermore, it needs to be noted that reductions under Pri-Bar and Buchman's conditions at 'our' temperatures and times were almost always incomplete.[12]

Table 1 details the results of our hydrodehalogenation experiments. Iodobenzene is efficiently reduced to benzene at room temperature (entry 1). In contrast, complete reduction of bromobenzene required heating to 70°C (entry 2). An iodide can be selectively reduced in the presence of a bromide and a bromide in the presence of a chloride (entries 3–4). However, with these dihalides Pd black tends to precipitate after reduction of the more facile halide. As illustrated in entries 5–9,

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Keywords: hydrodehalogenation; reduction; palladium; PMHS.

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Table 1. Pd-catalyzed hydrodehalogenations with fluoride activated PMHS[a]

Entry	Starting material	Temp. (°C)	Time (hours)	Product	% Yield[b]
1	Iodobenzene	Rt	24	Benzene	90[d]
2	Bromobenzene	70	36	Benzene	100[d]
3	1-Bromo-4-iodobenzene	Rt	26	Bromobenzene	100[c]
4	3-Bromochlorobenzene	70	48	Chlorobenzene	90[c]
5	1-Bromo-4-nitrobenzene	70	3.5	Nitrobenzene	66[e]
6	1-Iodo-2,4-dinitrobenzene	70	0.25	1,3-Dinitrobenzene	80[e]
7	4-Bromobenzaldehyde	70	48	Benzaldehyde	79[c]
8	4′-Bromoacetophenone	70	24	Acetophenone	99[c]
9	Methyl 4-bromobenzoate	70	18	Methyl benzoate	92[c]
10	2-Bromoacetophenone	Rt	24	Acetophenone	90[c]
11	2-Bromoacetophenone	70	15	Acetophenone	89[c]
12	Chlorobenzene	110	24	Benzene	Trace[d]
13	4′-Chloroacetophenone	110	72	Acetophenone	0
14	4-Bromobenzoic acid	70	24	Benzoic acid	0
15	α-Bromophenylacetic acid	70	48	Phenylacetic acid	0
16	4-Bromophenol	70	24	Phenol	17[c]

[a] See Ref. 9 for experimental details.
[b] Yields are an average of two runs.
[c] As determined by GC (calibration curve).
[d] As determined by NMR (internal standard).
[e] Isolated yield.

dehalogenation of bromo arenes bearing nitro, aldehyde, ketone, or ester groups takes place smoothly in good to near quantitative yields. α-Bromo-carbonyl compounds (entries 10–11) can also be reduced, albeit with minor side product formation.[13]

Though our protocol holds certain advantages over Pri-Bar and Buchman's original procedure, it is not superior for all substrates. Fluoride activation provides no advantage with arylchlorides (entries 12–13), as they are nearly inert under both conditions. Moreover, while Pri-Bar and Buchman could successfully hydrodehalogenate *p*-bromobenzoic acid and α-bromoacetic acids, in our system the presence of carboxylic acids or phenols spelled failure (entries 14–16).

The reduction of β-bromostyrene represents another *apparent* departure from reductions with PMHS, Bn_3N, and Pd(0) in DMSO/MeCN. Pri-Bar and Buchman reported the reduction of β-bromostyrene to styrene in 37% yield (Table 2, entry 8). Under our conditions, β-bromostyrene was reduced over 24 h at room temperature to PhEt in 92% yield (entry 1). Low yield (24%) reduction of styrene by Rh-mediated hydrogen transfer from PMHS has been described.[14] However, the efficiency of entry 1 led us to probe this over reduction further. Subjecting styrene to our conditions afforded some PhEt after 24 h at room temperature, but in only 12% yield (entry 3). Heating the reaction at 70°C for 24 h proved more efficient affording PhEt in 72% yield (entry 4).

Table 2. Reduction of β-bromostyrene, styrene, and control experiments[a]

Entry	Starting material	Temp. (°C)	Hours	Product	% Yield[b]
1	β-Bromostyrene	Rt	24	PhEt	92[c]
2	β-Bromostyrene	70	22	Styrene	42[c]
3	Styrene	Rt	24	PhEt	12[c,d]
4	Styrene	70	24	PhEt	72[c,d]
5	50/50 Styrene + 2-bromoacetophenone	Rt	24	PhEt	78[d]
6	50/50 Styrene + 2-bromoacetophenone	70	22	PhEt	43[d]
7	Styrene + KBr	Rt	24	PhEt	12[c,d]
	Under Pri-Bar and Buchman's conditions				
8	β-Bromostyrene	60	3	Styrene[e]	37[e]
9	β-Bromostyrene	60	3	PhEt[f]	25[d,f]
10	Styrene	60	3	No rxn[f]	–

[a] See Ref. 9 for experimental details (entries 1–7).
[b] Yields are an average of two runs.
[c] As determined by GC (calibration curve).
[d] As determined by NMR (internal standard).
[e] Per Ref. 6.
[f] Our data.

Returning to β-bromostyrene, we looked at its reduction at 70°C. To our surprise, after 22 h at this temperature a 42% yield of styrene was obtained along with 48% starting material and only a trace amount of PhEt (entry 2). Thus, it would appear that β-bromostyrene reduces first to styrene and then on to PhEt. However, if this were so then why would the reductions proceed further at room temperature than at 70°C, especially since the reduction of pure styrene is much more facile at 70°C than at room temperature?

A potential answer to this question may lie in our observation of a Pd-black precipitate during the 70°C reduction of β-bromostyrene. Perhaps, some combination of halide *and* styrene contributes to an active but thermally unstable Pd-complex. Thus, reduction of β-bromostyrene is complete at room temperature, but stops considerably short of completion at elevated temperatures. This hypothesis is supported by several additional experiments. Room temperature reduction of a 50/50 mixture of styrene and 2-bromoacetophenone afforded a 78% yield of PhEt after 24 h (entry 5). In contrast, at 70°C, styrene reduction was *retarded* by the presence of 2-bromoacetophenone. After 22 h, the reaction afforded some PhEt (43%) along with 52% unreacted styrene and 51% of the normally easy to reduce 2-bromoacetophenone (entry 6).

Substituting KBr for 2-bromoacetophenone failed to promote the reduction of styrene (entry 7); while adding 1 equiv. of n-Bu$_4$NBr turned the reaction into an intractable gel after 10 min. Decreasing the amount of added 2-bromoacetophenone met with a corresponding decrease in the yield of PhEt. So while our results indicate that the bromide plays a role in these reductions, the specifics of this involvement as well as the mechanism by which the alkene is saturated remain unclear.[14b]

These results prompted us to repeat[15] the reduction of β-bromostyrene using Pri-Bar and Buchman's procedure. In our hands, their conditions (60°C, 3 h) also reduced β-bromostyrene to PhEt (25% yield+38% unreacted β-bromostyrene), as judged by NMR analysis of the reaction mixture (entry 9).[16] No PhEt was observed when styrene was subjected to these conditions (entry 10), suggesting again an involvement of the halide in the over reduction.

In summary, the hydrodehalogenation of aryl- and α-keto-bromides are selectively reduced with KF (aq.), PMHS, and catalytic (Ph$_3$P)$_2$PdCl$_2$, in THF. This system tolerates nitro groups, aldehydes, ketones, and esters, however, carboxylic acids or phenols are incompatible. Under these conditions, β-bromostyrene reduces to PhEt with the bromide playing an important but undefined role in the transformation. Additional synthetic and mechanistic studies will be presented in due course.

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9. General reaction procedure: an oven dried round bottom flask was charged with 1.0 mmol of aryl halide in 5 mL THF (0.2 M solution) and 0.01 equiv. of $(Ph_3P)_2PdCl_2$. The flask was sealed with a septum and flushed with nitrogen. While flushing the reaction, 12 equiv. of KF in 2 mL of degassed water were introduced by syringe. PMHS (6 equiv.) was then injected into the reaction mixture. If the reaction mixture is heated, a reflux condensor is attached to the round bottom and placed in a preheated oil bath. 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 1 M solution of NaOH. After stirring overnight to hydrolyze unreacted PMHS, the mixture was extracted several times with Et_2O. The combined organics were dried over $MgSO_4$, concentrated, and purified by silica gel chromatography.
10. Fluoride free reductions of β-bromostyrene and 2-bromoacetophenone saw yields drop by 60 and 40%, respectively.
11. Substituting DMSO/MeCN for THF proved inefficient.
12. 2-Bromoacetophenone was an exception as its reduction was complete after 6 h at rt.
13. Byproduct isolation proved difficult, but analysis of crude reaction mixtures suggests these minor constituents to be the result of condensation reactions.
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15. β-Bromostyrene reductions under Pri-Bar and Buchman's conditions were repeated four times.
16. Pri-Bar and Buchman assigned their reaction products by GC analysis. Though we do not know their GC parameters, retention times for styrene and PhEt on a 30 M×0.32 mm SPB-5 fused silica GC column at 30–200°C (increased 10°C/min) are similar. Thus, absent additional analysis PhEt could be easily mis-assigned as styrene.