

Pd-Catalyzed Silicon Hydride Reductions
of Aromatic and Aliphatic Nitro Groups

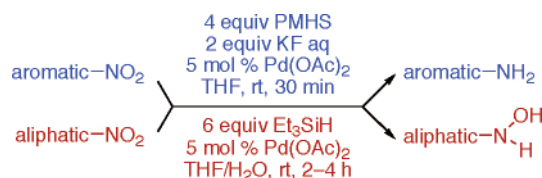
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ABSTRACT



Room-temperature reduction of aromatic nitro groups to amines can be accomplished in high yield, with wide functional group tolerance and short reaction times (30 min) using a combination of palladium(II) acetate, aqueous potassium fluoride, and polymethylhydrosiloxane (PMHS). Replacing PMHS/KF with triethylsilane allows aliphatic nitro groups to be reduced to their hydroxylamines.

Nitro compounds are important building blocks in organic synthesis¹ and routinely serve as precursors to amines. A vast number of nitroaromatics are commercially available or easily prepared,² while recent advances in the Michael³ and Henry⁴ reactions have made for easy access to new stereodefined aliphatic nitro compounds. A plethora of methods have been developed for the reduction of nitro compounds to amines,^{1,5} including those that involve hydrogenation, electron transfer, and hydride reductions. While several of these methods have seen wide use, chemists continue to seek⁶ or call upon⁷ new protocols to carry out such reductions.

The search for new nitro reduction methods has largely ignored the potential of silanes and siloxanes as reducing agents.⁸ During the 1970s, Andrianov and co-workers⁹ used several silanes for nitroarene reductions, but incomplete reactions and low yields were their norm. During this same period, Lipowitz and Bowman¹⁰ reported a single Pd/C-catalyzed reduction of nitrobenzene by polymethylhydrosiloxane (PMHS). To the best of our knowledge, this is the sole example of PMHS being used in such a capacity.^{11,12} Two decades later, Brinkman and Miles¹³ showed how

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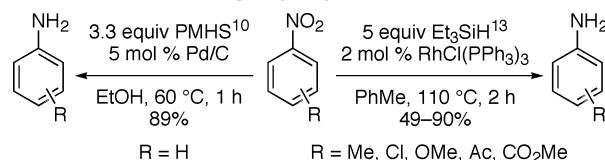
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Et₃SiH and Wilkinson's catalyst effect the efficient reduction of nitrobenzenes (Scheme 1).

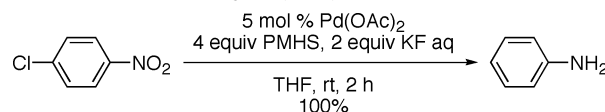
Scheme 1. Previous Examples of Nitroarene Reductions Using Silyl Hydrides^{10,13}



Recent studies of PMHS as a reagent for organic synthesis suggest that additional opportunities may exist for its use in nitro reductions. Prior work on the reactivity of PMHS in the presence of transition-metal catalysts revealed that the combination of catalytic Pd(OAc)₂, PMHS, and aqueous KF will efficiently and mildly hydrodehalogenate aryl chlorides,¹⁴ allow for 1,4-reduction of enones,¹⁵ and facilitate the reductive cleavage of benzylic C–O bonds, all at room temperature.¹⁶ The reactivity of this reduction system is likely due in part to the formation of palladium nanoparticles, as recognized by Chauhan.¹⁷

While screening substrates in Pd(OAc)₂/PMHS/KF dehalogenations,¹⁴ we found that 1-chloro-4-nitrobenzene was converted to aniline (Scheme 2). Given this result, the limited

Scheme 2. Preliminary Pd(OAc)₂/PMHS/KF Nitro Reduction



nature of prior works, and the low toxicity and cost of PMHS¹² and related silyl hydrides, a full study on nitro reductions using Pd(OAc)₂/PMHS/KF was warranted.

To begin, we simply subjected nitrobenzene to our dehalogenation conditions. Gratifyingly, these conditions

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quantitatively afforded aniline within 30 min. To build from this result, the reduction of 2-nitrotoluene was screened against a variety of palladium and fluoride sources, solvents, and siloxanes/silanes. In the absence of a palladium catalyst no amine formation was seen after 1 day. With the necessity of palladium established, a number of catalysts were tested in the reaction. Of these, Pd(OAc)₂ and Pd/C gave the highest yields (70 and 62%, respectively). In contrast, added Ph₃P or the use of phosphine-bearing catalysts shut down the reductions. Pd(OAc)₂ was selected for further optimization studies owing to its relatively low cost and previously noted¹⁴ functional group tolerance.

To learn the importance of fluoride in the reductions, reactions were run fluoride free. Under such conditions, no amine products were observed after 1 h, but at 24 h 2-aminotoluene was obtained in 50% yield. Presumably, fluoride aids formation of polycordinate siloxane intermediates, allowing for facile transfer of the hydride.^{8b} In this role, most simple anhydrous alkaline fluoride salts (LiF, NaF, KF, CsF) proved equally effective. TBAF could also be employed, but only when used in substoichiometric amounts (10 mol %) and under cryogenic (–78 °C) conditions. Use of 1 equiv of TBAF at –78 °C or in any amount at room temperature caused the reaction mixtures to turn into a solid mass via sol–gel formation.

Changing the reaction solvent dramatically affected reaction efficiency. Reductions in THF and EtOAc gave the highest yields, whereas only starting material was recovered with reactions run in DMF or NMP. Perhaps most surprisingly, catalyst insolubility and gel formation upon prolonged stirring in Et₂O were observed.

Nearly all silanes and siloxanes screened (Table 1) were able to efficiently reduce 2-nitrotoluene to 2-aminotoluene

Table 1. Silane/Siloxane Screening

entry	Si-H species	% yield ^a	entry	Si-H species	% yield ^a
1	PHMS	100	6	Me(MeO) ₂ SiH	97
2	Et ₃ SiH	100	7	Me(TMSO) ₂ SiH	90
3	TMS ₃ SiH	23	8	(TMSO) ₃ SiH	0
4	EtO(Me) ₂ SiH	100	9	bis-siloxane ^b	100
5	TMSO(Me) ₂ SiH	100	10	methyhydro-cyclosiloxanes	30

^a Determined by ¹H NMR with CH₂Cl₂ as an internal standard (two run average). ^b 1,3-Bis(trimethylsiloxy)-1,3-dimethyldisiloxane.

with the Pd(OAc)₂/KF aq/THF combination. Nonetheless, PMHS remained the silyl hydride of choice. A byproduct of the silicone industry, PMHS is inexpensive and tends to be much more air and moisture stable than other silanes.^{12,18} Indeed, PMHS can be stored on the bench for long periods of time (years), and no extraordinary measures are needed

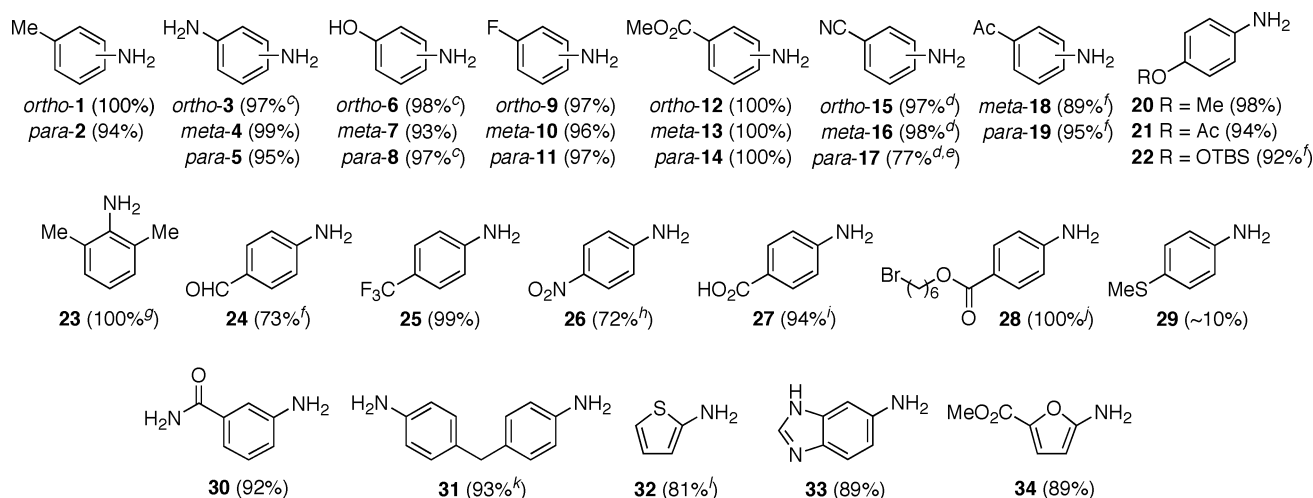


Figure 1. Anilines formed by the reduction of nitroarenes with Pd(OAc)₂/PMHS/KF.^{a,b} Key: (a) Conditions: 1 mmol of nitroarene, 5 mol % of Pd(OAc)₂, 4 equiv of PMHS, 2 equiv of KF, 2 mL of degassed H₂O, 5 mL of THF, rt, 30 min. (b) Isolated yields were determined after flash chromatography. (c) Isolated as the acetamide. (d) Stirred for 12 or 4 h with 4 equiv of KF. (e) Isolated as 4-(hydroxyamino)-benzonitrile. (f) Run with 3 equiv of PMHS. (g) Stirred for 3 h. (h) 20% 1,4-Diamine also isolated. (i) Isolated as 4-acetylamino benzoic acid. (j) Run with 3.5 equiv of PMHS. (k) Run with 8 equiv of PMHS and 4 equiv of KF. (l) Isolated as the BOC-protected amine.

when measuring out or using this reagent. Thus, after much investigation, our optimal conditions were determined to be the first conditions examined, namely, 5 mol % of Pd(OAc)₂, 4 equiv of PMHS, and 2 equiv of aqueous KF in THF at room temperature.

Substrate screening of a variety of nitro-substituted arenes and heteroarenes was thus initiated (Figure 1). In practice, the reaction system tolerated substituents irrespective of their ring position. The steric hindrance of one ortho functional group did not appreciably affect reaction times, but the presence of two substituents ortho to the nitro group slowed the formation of 2-amino-*m*-xylene (**23**) considerably (180 vs 30 min). Electron-donating functional groups were well tolerated with quantitative formation of the corresponding anilines (**3–8**, **20–22**) typically observed. One exception to this rule was 4-nitrothioanisole, which gave a complex mixture of products containing ~10% of the expected amine (**29**). Since sulfur is a well-known Pd scavenger and poison, we assume this was a factor in that negative result. In terms of electron-withdrawing functional groups the system tolerated carboxylic acid **27**, esters (**12–14**), amide **30**, benzylic ketones (**18–19**), and trifluorotoluene **25**. Reduction of the nitro was favored with 4-nitrobenzaldehyde affording **24** in 73% yield, but intrusive reduction of the aldehyde to the alcohol (27%) was unavoidable (reductive amination was not witnessed). Again, reactions were typically complete within 30 min, with formation of the amino-substituted benzonitriles (**15–17**) being notable exceptions. For these substrates 12 h reaction times were necessary, unless KF concentrations were increased. With 4 equiv of KF the 2- and 3-nitrobenzonitriles could be quantitatively reduced to their aniline derivatives within 4 h. However, even under these more

forcing conditions the reduction of 4-nitrobenzonitrile primarily stopped at the *N*-hydroxylamine (77%). The sluggish reactivity of this substrate may be attributable to increased resonance stabilization of its intermediates.

In addition to the functional group tolerances mentioned above, it should be noted that despite the presence of KF the TBS-protected aminophenol **22** was isolated in high yield accompanied by only 7% of the desilylated phenol. That said, chemoselective nitro reductions were not achieved in the presence of an aromatic bromide or chloride. On the other hand, aromatic fluorides (**9–11**) and an aliphatic bromide (**28**) were not dehalogenated under these conditions.

Attempted monoreduction of 1,4-dinitrobenzene afforded 4-nitroaniline (**26**) in 72% yield along with 20% of the diamine. A similar result was seen with bis(4-nitrophenyl)-methane, where doubling the PMHS and KF amounts gave diamine **31** in high yield after 30 min.

Extension of the methodology to nitro-substituted heteroarenes afforded the expected amines in high yields, but not without some nuances. Whereas thioanisole was a problem substrate, 2-nitrothiophene was easily reduced to **32**. However, isolation of the product was difficult and could only be achieved after its in situ protection as a Boc carbamate. For 5-nitrobenzimidazole, our standard procedure, where PMHS is added last, produced an atypical color change and only afforded starting material. We hypothesized that formation of the active Pd–PMHS complex was hindered by coordination of the substrate to the metal. To overcome this problem, we simply premixed the reagents, so as to allow nanoparticle formation in advance of exposure to 5-nitrobenzimidazole. This protocol, where the substrate was added last, gave the expected amine in high yield (**33**). In contrast to the aforementioned heterocycles, methyl 5-nitro-2-furanoate

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reduced to **34** (89% isolated yield) without modification of the standard conditions.

Our first attempts to reduce aliphatic nitro compounds met with little success. Subjection of 1-nitrodecane to the conditions yielded a small amount of *N*-hydroxyl-1-aminodecane (**35**) (15–20%), the corresponding nitroso compound (40%), and unreacted starting material (23%). Adjustments to the catalyst loading, PMHS concentration, fluoride source, and temperature afforded small increases in the product yield but not to desirable levels.

Here it was evident that the slower reacting aliphatics allowed for competing side reactions that consumed the hydride. To balance the reactivities and overcome this side reaction, we sought to lower the activity of the silyl hydride group by removing the fluoride. This significantly increased the yield of **35**; however, conversions topped out at ~60% as concomitantly formed sol–gels encapsulated the catalyst and shut down the reaction. To avoid sol–gel formation, three nonpolymeric silyl hydrides previously tested in the nitroarene reductions (see Table 1) were rescreened in reactions with the nitroalkane. Et₃SiH proved best, converting 85% of 1-nitrodecane to *N*-hydroxyl-1-aminodecane (**35**) in 2 h. It is worth noting that, even though the fluoride was eliminated, the addition of water remained critical to the reaction's success as anhydrous conditions gave low product yields. Also, to drive the reduction to completion and ensure its reproducibility, we found six equivalents of silane optimal.

As seen in Figure 2, a set of aliphatic nitro compounds responded favorably to these final reduction conditions (5 mol % of Pd(OAc)₂, 6 equiv of Et₃SiH, in THF/H₂O). Primary and secondary nitro groups were efficiently reduced within 2 h. In contrast, tertiary nitro aliphatics reacted poorly. Formation of the highly oxygenated **38** was only modestly successful, and the yields of **39** were trace at best. Exposure of **40**, prepared by a diastereoselective Henry reaction,^{4c} to the reaction conditions afforded the reduction product (**41**) in high yield and with complete retention of the stereochemistry. In this example and others we also found that the nitro reductions could also be followed by subsequent chemical events. For example, the hydroxylamine products could be intra- or intermolecularly trapped by electrophiles. In the case of **42**, prepared by a stereoselective Michael reaction,^{3d} a Reissig nitron synthesis¹⁹ occurred, where the intermediate hydroxylamine cyclized on the ketone, forming **43** with no loss of stereochemistry.

With regards to mechanism, the findings herein and from our previous studies^{14–16} led us to surmise that these reductions advance via nitroso and then hydroxylamine intermediates/products. The precise method by which these intermediates are formed and subsequently reduced is not

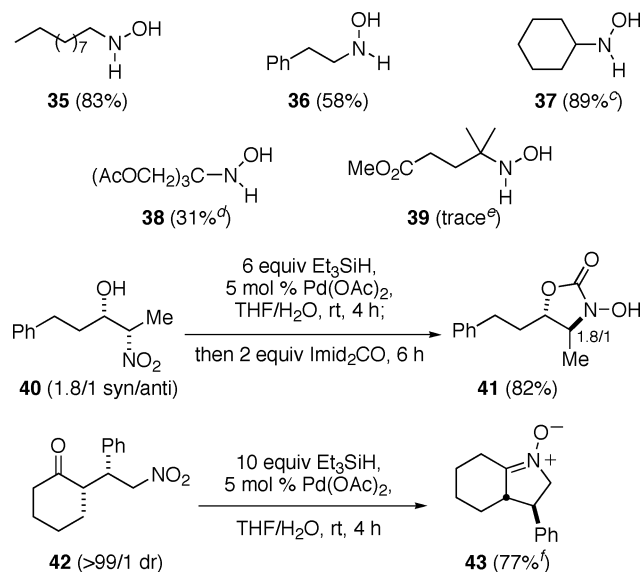


Figure 2. Hydroxylamines formed by the reduction of aliphatic nitro compounds with Pd(OAc)₂/Et₃SiH.^{a,b} Key: (a) Conditions: 1 mmol of substrate, 5 mol % of Pd(OAc)₂, 6 equiv of Et₃SiH, 2 mL of degassed H₂O, 5 mL of THF, rt, 2–4 h. (b) Isolated yield after chromatography. (c) Isolated as the sulfonamide. (d) 66% starting material recovered. (e) 64% starting material recovered. (f) 19% starting material recovered.

entirely clear. The need for water in these reactions could be indicative of a transfer hydrogenation process where hydrogen gas is formed from the silicon hydride and water via σ bond metathesis on the palladium. Other pathways including those that involve palladium-catalyzed hydrosilylations are also being considered. Our ongoing assessments of such possibilities will be reported later.

In summary, nanoparticles from Pd(OAc)₂ and PMHS, in combination with aqueous KF, rapidly and mildly reduce nitro-substituted arenes and heteroarenes to their corresponding amines in high yields. By substituting PMHS/KF with Et₃SiH, room-temperature reductions of aliphatic nitro groups are also viable. Both variations of the method exhibit good functional group compatibility and can be combined with other in situ reactions.

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

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