Organic LETTERS
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pubs.acs.org/OrgLett

Ligand-Free, Palladium-Catalyzed Dihydrogen Generation from TMDS: Dehalogenation of Aryl Halides on Water

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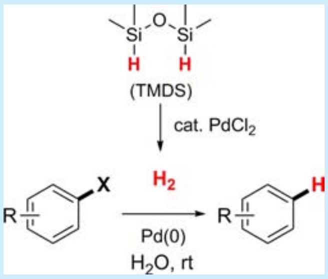
Supporting Information

ABSTRACT: A mild and environmentally attractive dehalogenation of functionalized aryl halides has been developed using nanoparticles formed from $PdCl_2$ in the presence of tetramethyldisiloxane (TMDS) on water. The active catalyst and reaction medium can be recycled. This method can also be applied to cascade reactions in a one-pot sequence.

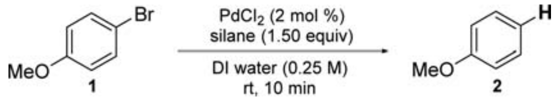


The direct dehydrogenative coupling of mono- and polyhydrosilanes can be catalyzed by group 4 metals as well as several lanthanide complexes for the synthesis of polysilanes. One outgrowth of these reactions is production of dihydrogen. If efficient, it might be utilized for a variety of tasks, such as fuel cells.[1] The poly- or oligosilanes produced may be recycled back to hydrosilanes (e.g., with LAH). In the course of our studies on Pd-catalyzed silylations of aryl halides, we had taken note of dihydrogen generation from silanes.[2] On the basis of these prior observations, it was anticipated that the H_2 so generated could be used synthetically. Herein, we present the results of hydrodehalogenation reactions of aryl halides, which can be performed in an environmentally attractive fashion: *on water at room temperature*, effected by dihydrogen generated in situ from tetramethyldisiloxane $(Me_2HSi)_2O$ (TMDS).

The reduction of a carbon−halogen bond represents a fundamental reaction in organic synthesis that still draws considerable attention.[3] It has also taken on added significance in light of environmental issues, in particular concerning polychlorinated biphenyls (PCBs), which are known to be health hazards.[4] New technologies that not only result in aromatic dehalogenation but also provide both economic and environmentally attractive processes remain in demand. Literature procedures that effect such reductions are commonly performed in organic solvents at high temperatures, thus adding to organic waste streams and use of external sources of energy.[5] A variety of reducing agents have been employed for this purpose, ranging from dihydrogen[6] to elemental metals,[7] and from intermediate organolithiums[8] to hydride transfer agents (e.g., alcohols,[9] alkoxides,[10] amines,[3] hydrazines[11] and borohydride[12] or LAH[13]). Palladium-catalyzed dehalogenations of organic halides with silanes have been described, albeit usually involving elevated temperatures in organic media.[14] With PMHS, fluoride-activated hydro-dehalogenations have also been reported in aqueous organic media.[14b,15]

Initially, testing *p*-bromoanisole as a model compound led within 2 h to debromination using 2 mol % of $PdCl_2$ and 1.5 equiv of Et_3SiH in deionized (DI) water at ambient temperature. The active reducing agent was shown to be dihydrogen (vide infra). Screening of silanes and siloxanes revealed variations in the rate of dihydrogen generation. The rate of dehalogenation for aryl bromides was highest for TMDS (1.5 equiv), where *p*-bromoanisole could be reduced in 10 min at room temperature (Table 1).

Table 1. Screening of Silanes for Halide Reductions



silane	conv (%) to **2**	silane	conv (%) to **2**
Et_3SiH	60	PMHS	46
Ph_2SiH_2	0	**TMDS**	**100**
$PhSiH_3$	43	DEMS	82

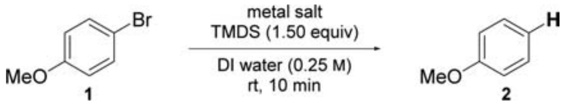
Other metal salts and their complexes were also tested (Table 2). Base metals did not lead to dihydrogen generation from the silane, at least visibly, and were ineffective for halide reduction. Precious metals other than Pd all generated dihydrogen efficiently but did not catalyze dehalogenation, presumably due to their inability to add oxidatively to the C−X bond.

A number of organic solvents (Table 3) could be used to effect this conversion, although deionized (DI) water provided an equally effective, or superior, medium. Use of the designer surfactant, Nok,[16] offered no advantage. Use of neat TMDS led to dehalogenation as well, as dihydrogen generation from this silane is independent of water. However, the absence of water

Received: December 27, 2014
Published: February 13, 2015

DOI: 10.1021/ol5037369
Org. Lett. 2015, 17, 1122−1125

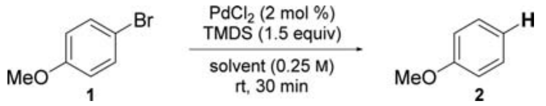
Table 2. Evaluation of Metal Salts as Precatalysts



catalyst	conv (%) to **2**
$NiCl_2{\cdot}6H_2O$ (4 mol %)	0.2
$CuCl_2{\cdot}2H_2O$ (4 mol %)	0
$CoCl_2{\cdot}6H_2O$ (4 mol %)	0.1
$FeCl_3{\cdot}6H_2O$ (4 mol %)	0
$PdCl_2$ (2 mol %)	**100**
$[Ir(COD)Cl]_2$ (2 mol %)	0
$[Rh(nbd)_2]BF_4$ (2 mol %)	2
$RuCl_3$ (2 mol %)	0
$Pt(COD)Cl_2$ (2 mol %)	0

🟥 does not generate H_2 from silane
🟩 produces H_2 from silane

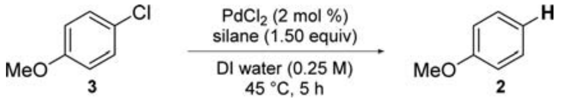
Table 3. Variation of the Reaction Medium



medium	conv (%) to **2**	medium	conv (%) to **2**
CH_2Cl_2	81	EtOAc	73
MeOH	66	acetone	8
EtOH	55	MeCN	11
toluene	86	2 wt % Nok, H_2O	98
Et_2O	99	**DI water**	**100**

resulted in a multitude of as yet unknown side products. While aryl bromides could be reduced at room temperature, aryl chlorides, in general, required longer reaction times and 45 °C reaction temperatures (Table 4). Again, TMDS afforded the best results. The reaction could be performed at room temperature if the scale was increased along with the global concentration (from 0.25 to 1.0 M). This may be a result of a greater buildup of dihydrogen pressure that facilitates reduction.

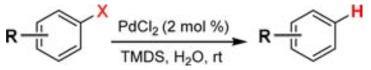
Table 4. Screening of Silanes

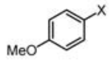
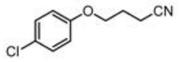
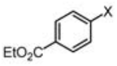
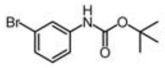
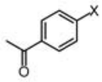
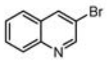
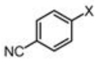
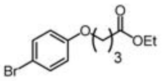
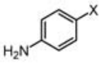
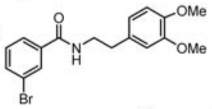
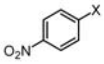
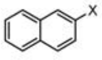
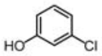
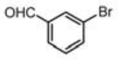
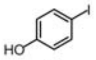
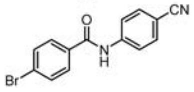
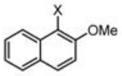
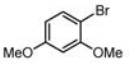
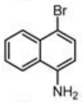
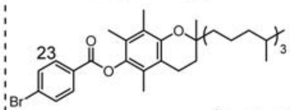
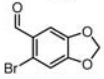
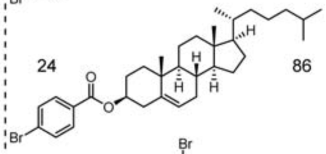
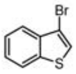
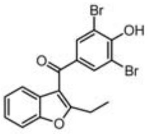
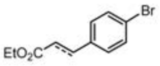


silane	conv (%) to **2**	silane	conv (%) to **2**
Et_3SiH	22	PMHS	0
Ph_2SiH_2	30	**TMDS**	**99**
$PhSiH_3$	25	DEMS	27

Several aryl halides were subjected to these optimized conditions (Table 5). In general, functional group compatibility is high. The carbonyl moieties found in an ester, carbamate, and amide were all tolerated. Other functional groups examined under these conditions (i.e., $PdCl_2$/TMDS) include aldehyde, ketone, nitro, and isolated, sterically available olefins. The endocyclic olefin, e.g., of cholesterol was untouched. Nitrile groups also survived. Products from the various nitro-substituted aromatic halides were isolated as their corresponding amine counterparts. If $PdCl_2$/TMDS was used, aldehydes and ketones (entries 3, 11, and 20) were reduced to the corresponding benzylic alcohols; e.g., entry 11 gave only piperonyl alcohol; no benzylic C−O hydrogenolysis was observed.[17] Reduction of the aldehyde or keto carbonyl groups could be prevented in large measure by switching to $PdCl_2$(dtbpf) as precatalyst, in the presence of triethylamine. In the same case of bromopiperonal (entry 11), neither the aldehyde nor acetal is affected, the latter presumably due to the alkaline pH of the aqueous medium. Heterocycle *m*-bromoquinoline (entry 16) underwent facile dehalogenation with $PdCl_2$ alone. Steric bulk inhibited the dehalogenation of bromo- and iodo- mesitylenes, while the dimethoxybromoarene (entry 22) underwent the anticipated halide reduction. Both bromo- and iodomethoxynaphthalene (entry 9) were reduced using either $PdCl_2$ or $PdCl_2$(dtbpf) as precatalyst, as long as triethylamine was present. In the absence

Table 5. Scope of Halide Reductions*



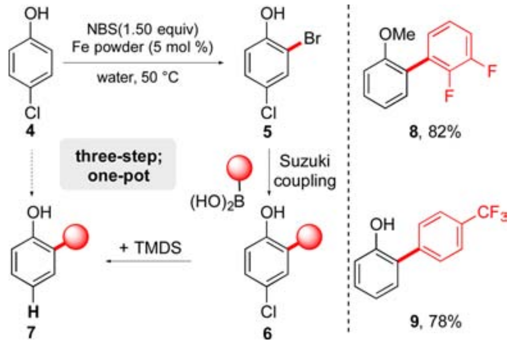
entry	substrate	isolated yield (%)	entry	substrate	isolated yield (%)
1		I; 79 Br; 78 Cl; 75[a], 83[b]	14		84[a]
2		I; 86 Br; 88	15		93
3		I; 80[c] Br; 77[c]	16		87
4		I; 89 Br; 91 Cl; 84[a]	17		89
5		Br; 79 Cl; 77[a]	18		77
6[d]		I; 83 Cl; 80[a]	19		I; 75 Br; 80
7		81[a]	20		85[c]
8		80	21		79
9		I; 85 Br; 90	22		81
10		85	23		80
11		88[c]	24		86
12		90	25		88[c,f,g]
13		86[e] 97[c]			

*Conditions (unless otherwise mentioned): $PdCl_2$ (5 μmol), Ar-X (0.25 mmol), DI water (1 mL), TMDS (0.375 mmol), rt; capped in a sample vial (4 mL). [a]At 50 °C. [b]Concn 1.0 M. [c]$PdCl_2$(dtbpf) (5 μmol), Ar-X (0.25 mmol), Et_3N (0.75 mmol), DI water (1 mL), TMDS (0.375 mmol), rt; capped in a sample vial (4 mL). [d]Reduced to the corresponding aniline. [e]The product was isolated as the alkane. [f]TMDS (0.75 mmol). [g]Double reduction.

of this base, no dehalogenation was observed, either in water or in 5 wt % aqueous solutions of surfactants Nok or TPGS-750-M.[18]

Use of halogens on aromatic rings as hydrogen equivalents is a common synthetic strategy.[19] We have been able to show that this approach could be used to advantage in a three-step sequence, performed in one pot at 50 °C, all in water (Scheme 1).

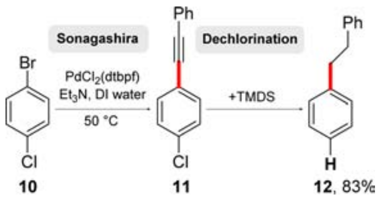
Scheme 1. Three-Step, One-Pot Sequence in Water



Starting with *p*-chloroanisole, bromination with NBS on water gave dihalide **5**, which without isolation was subjected to a Suzuki–Miyaura coupling to give **6** [using cat. $PdCl_2$(dtbpf) in the presence of an arylboronic acid]. Again, without isolation, the resulting biaryl could then be dechlorinated to **7** upon addition of TMDS. Following this three-step, one-pot sequence, products **8** and **9** could be isolated in good overall yields.

Since this cat. $PdCl_2$/TMDS combination in water can also be used to reduce isolated alkynes, a net aromatic alkylation could be effected using a Sonogashira/reduction. Starting with bromochlorobenzene, initial Pd-catalyzed Sonogashira cross-coupling at the C–Br bond to **11** could be followed by a simultaneous dechlorination/alkyne reduction to final product **12** (Scheme 2).

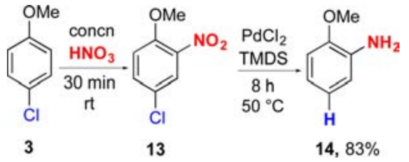
Scheme 2. Site-Selective Coupling Followed by Double Reduction



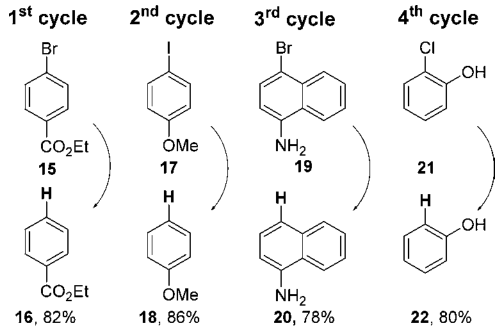
A simultaneous nitro group reduction/dehalogenation could be used to introduce an amino residue into the *ortho*-position of an aromatic ring (Scheme 3). Thus, following a standard nitration (e.g., of **3**), *o*-aminoanisole **14** could be formed in one pot upon exposure to cat. $PdCl_2$/TMDS in water at 50 °C.

Upon completion of a reduction and "in-flask" extraction of product using a minimum of organic solvent, the aqueous medium can be recycled *without additional catalyst being added*. Introduction of fresh TMDS after each recycle allowed at least four cycles (Scheme 4), using a different aryl halide in each. The reaction rate was somewhat slower with each recycle, as trace amounts of catalyst were inadvertently removed along with the organic solvent during extraction.

Scheme 3. Net *o*-Amination/Reduction of 4-Chloroanisole

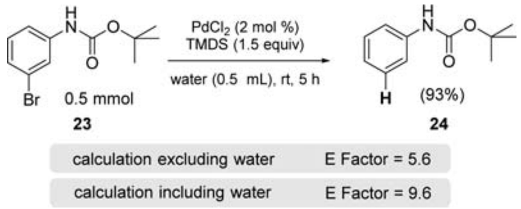


Scheme 4. Recycling of the Reaction Mixture



E Factors[20] were calculated to assess the level of waste generation based on the amounts of organic solvents involved. The model reaction shown in Scheme 5 was used, which led to an *E* Factor of only 5.6 using ether as the in-flask extraction solvent. Traditionally, water is excluded from the calculation of *E* Factors. Nonetheless, it often does become waste, and hence, we favor its inclusion in the calculation, albeit as a separate value. In this case, the *E* Factor for both water and organic solvent use is only 9.6. With recycling of the aqueous medium, the associated *E* factors would drop significantly.[5]

Scheme 5. *E* Factors for a Model Reduction



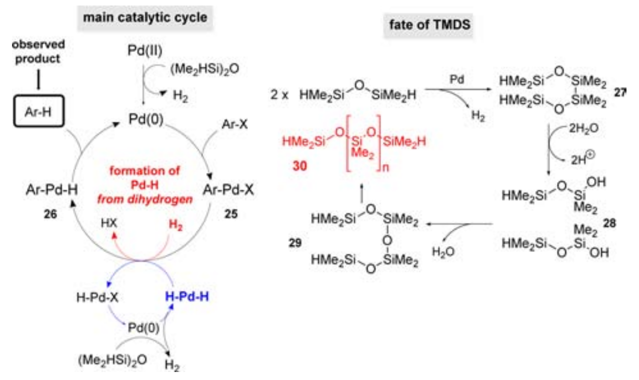
The nanoparticles formed from $PdCl_2$/TMDS were subjected to XPS analysis and found to have a binding energy characteristic of Pd(0) (ca. 336 eV; Table 6, entry 4). These Pd(0) nanoparticles catalyzed the desired reaction equally efficiently as Pd(0) generated in situ from $PdCl_2$/TMDS using our standard conditions (Table 5).

Table 6. XPS Experiments on Various Pd Sources

entry	Pd source	binding energy (eV)
1	$Pd(P\text{-}t\text{-}Bu_3)_2$	335.3
2	$(t\text{-}Bu_3P\text{-}PdBr)_2$	337.6
3	$PdCl_2$	338.0
4	$PdCl_2$/TMDS	335.9

Changing the solvent from H_2O to D_2O led to no deuterium incorporation in the resulting arene (see last entry, Table 3). Hence, water appears to have a minimal role in dihydrogen formation and likely provides just a medium for the process. Therefore, dihydrogen may be generated by metathesis between two Pd(II) species formed by oxidative addition of silane to Pd(0) (see the Supporting Information).

Scheme 6. Proposed Mechanistic Rationale



Based on the observations noted above, the following mechanistic scheme can be proposed (Scheme 6). The silane reduces Pd(II) to Pd(0), which leads to oxidative addition to the aryl halide. Either dihydrogen or a palladium hydride in the medium converts **25** to **26**. Palladium hydride can be generated from Pd(0) and TMDS or via dihydrogen. In either case, the resulting species Ar−Pd−H (**26**) undergoes reductive elimination to give the observed product Ar−H. GCMS analyses suggest formation of oligosiloxanes, rationalized by initial dehydrogenative coupling of TMDS[21] to give **27**, which can now be hydrolyzed in water to **28** which gives **29** upon dehydration. Siloxane **29** can polymerize to **30**.

In summary, an efficient and relatively environmentally benign method for dehalogenation of aryl halides has been uncovered using cat. $PdCl_2$/TMDS under mild conditions in water. Iodides and mainly aryl bromides can be reduced at ambient temperatures, while chlorides require gentle heating to 45−50 °C. Several functional groups tolerate these conditions, including aldehydes and ketones. This technology also exploits the hydrophobic aggregation of educts and catalysts[22] and serves as a synthetically valuable example of a process where recyclable water can provide a preferable medium to organic solvents.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization information for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support provided by the NIH (GM 86485) is warmly acknowledged with thanks. We acknowledge Johnson Matthey (Tom Colacot) for Pd catalysts, Dr. Tom Mates, Materials Research Laboratory, UCSB, and NSF DMR 1121053 for the XPS studies. P.K. also acknowledges the Royal Thai Government Fellowship for financial support.

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