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Iron-catalyzed protodehalogenation of alkyl and aryl halides using hydrosilanes†

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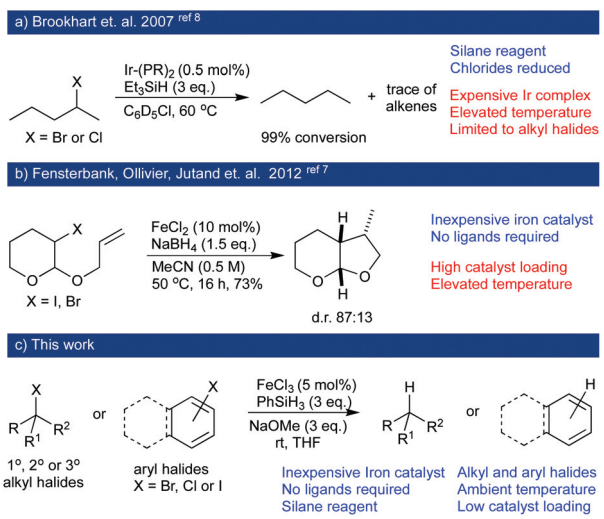
A simple and efficient iron-catalyzed protodehalogenation of alkyl and aryl halides using phenylhydrosilane is disclosed. The reaction utilizes $FeCl_3$ without the requirement of ligands. Unactivated alkyl and aryl halides were successfully reduced in good yields; sterically hindered tertiary halides were also reduced including the less reactive chlorides. The scalability of this methodology was demonstrated by a gram-scale synthesis with a catalyst loading as low as 0.5 mol%. Notably, disproportionation of phenylsilane leads to diphenylsilane that further reduces the halides. Preliminary mechanistic studies revealed a non-radical pathway and the source of hydrogen is $PhSiH_3$ *via* deuterium labeling studies. Our methodology represents simplicity and provides a good alternative to typical tin, aluminum and boron hydride reagents.

Introduction

Protodehalogenation is being utilized in various fields including organic synthesis, biochemistry and environmental protection.[1] In organic synthesis, bromo-cyclization followed by protodehalogenation to cyclic molecules[2] and the reduction of carbonyl compounds to an alkane *via* alkyl halides are routinely utilized.[3] A most common method for protodehalogenation is the tributyltin hydride mediated free radical transformations. However, the toxic nature of tin reagents makes them less attractive in the pharmaceutical industries due to the fact that they are hard to be removed from the desired product. There have been numerous efforts to circumvent the issue including the immobilization of tin reagents,[4] the use of photocatalysis (limited to iodides and activated halides),[5] and metal hydrides.[6–9]

The robustness of metal hydrides attracted several research groups. Baba *et al.* reported that indium hydride (10 mol%) generated from $NaBH_4/InCl_3$ efficiently reduces alkyl iodides and bromides *via* a radical intermediate; however the chloride was ineffective.[6] Recently, Fensterbank, Ollivier, Jutand *et al.* have reported the reductive cyclization of alkyl halides at elevated temperature that proceeds *via* a radical intermediate (10 mol% of $FeCl_2$ and $NaBH_4$) (Scheme 1b).[7,10,11] The above-mentioned methods are expected to undergo metal–halogen exchange followed by a reductive protodehalogenation. Though the majority of these reactions are reported to proceed through a radical intermediate, Brookhart *et al.* reported a cationic Ir(III)hydride–phosphine complex that does not follow a radical pathway and it can reduce a broad range of alkyl halides including chlorides (Scheme 1a).[8] Other transition metal complexes including palladium,[12,13] ruthenium,[3,14] and iron/Grignard[11] are reported to be effective for protodehalogenation.

In our ongoing studies, in the field of iron mediated cross-coupling reactions, we found that 1-(3-bromobutyl)-4-methoxy-



Scheme 1 Catalytic reduction of organic halides.

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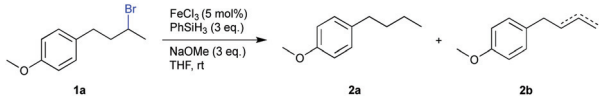
benzene **1a** was efficiently reduced (protodehalogenated) to alkane. In this context, we became interested in exploring the iron mediated protodehalogenation since it is economical, environmentally benign, and naturally abundant,[15] and the use of iron catalysis in the reduction of alkyl halides is very limited. Moreover, hydrosilanes are not much explored in iron catalysis. Hydrosilanes, being less toxic, can be an attractive alternative to tin-hydrides; however the activation towards the reduction of halides is challenging, $In(OAc)_3/PhSiH_3$ in combination with Et_3B and oxygen is reported to reduce the alkyl halides that proceed through a radical intermediate.[18] $AlCl_3$,[16] $PdCl_2$,[17] and Ir(III)phosphine complexes[8] have also been used in the formation of metal-hydrides that subsequently reduce alkyl halides.

Herein, we report a simple $FeCl_3/PhSiH_3$ system that does not require additional ligands but is highly efficient to reduce alkyl as well as aryl halides at room temperature in a shorter time with moderate to excellent yields; even the unreactive chlorides, sterically crowded tertiary halides, were also reduced seamlessly (Scheme 1c). Studies began with the focus of improving the yield of the reduced product that we observed in iron mediated coupling reactions (see the ESI† for more details). The major challenge was to avoid the formation of **2b** that is inseparable from the product and also to find a suitable hydrogen donor to improve the yield of **2a**.

We found that $PhSiH_3$ was very effective and observed no detectable amount of the eliminated product. $FeCl_3$ proved to be a better catalyst over $FeCl_2$ and $Fe(acac)_3$ (Table 1, entries 5 and 6). The inorganic bases and sodium methoxide offered a quantitative yield (99%, entry 1) in 5 h whereas phosphate, carbonate (see the ESI†), fluorides (entry 11) and an organic base (entry 13) were poor yielding. While NaOMe as a base offered a quantitative yield, KOMe gave traces of the product (entry 12). Hydrosilanes other than $PhSiH_3$ were ineffective (entries 3 and 4). Having an excess of $PhSiH_3$ and NaOMe (3 eq.) was useful in driving the reaction to completion in a shorter time, although stoichiometric reagents proved to be sufficient to obtain a similar yield provided that the reaction was allowed to run for a longer time (10 h, Scheme 2, **1d**). While THF offered a quantitative yield, the reaction was sluggish in Et_2O (see the ESI†) and CH_3CN gave only 31% of **2a** along with the eliminated product **2b** in 15 h (entry 17).

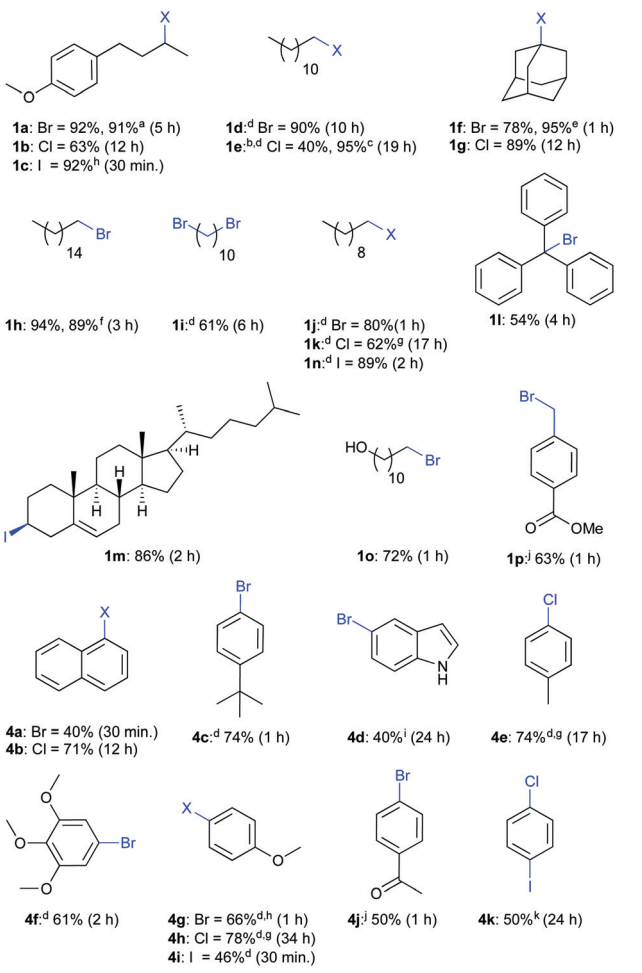
With the optimized reaction conditions in hand, we explored the scope of the substrates. As expected, the secondary alkyl iodide **1c** took only 30 minutes for the complete con-

Table 1 Optimization of the reaction conditions



Entry	Deviation from the standard conditions	Time (h)	Yield **2a**[a] (%)
1	None	5	99 (92)
2	^{t}BuOH instead of $PhSiH_3$	32	ND
3[b]	Me_2PhSiH or Et_3SiH	15	ND
4	Ph_3SiH	15	5
5	10 mol% $FeCl_2$	15	59
6	10 mol% $Fe(acac)_3$	15	62
7[c,d]	1.8 eq. NaO^{t}Bu	32	82
8[b,c,d]	1.8 eq. KO^{t}Bu	32	53
9	2 eq. $PhSiH_3$	15	83 (78)
10[e]	0.3 eq. NaOMe	5	12
11[d]	1.8 eq. CsF	32	<5
12[d,e]	1.8 eq. KOMe	15	<5
13	Lutidine	12	ND
14	Without $FeCl_3$	4	7
15	Without NaOMe	12	ND
16	Without $PhSiH_3$	12	ND
17[b]	CH_3CN	15	31

General reaction conditions: 0.36 mmol of **1a**, 2 mL of THF, 5 mol% $FeCl_3$, 1.08 mmol of $PhSiH_3$ and NaOMe. [a] Determined by GC analysis using dodecane as an internal standard, values in parentheses are the isolated yields. [b] Elimination to **2b** was observed. [c] 1.5 eq. of $PhSiH_3$. [d] Instead of NaOMe (3 eq.). [e] 10 mol% of $FeCl_3$. ND: not detectable.



Scheme 2 Substrate scope. Reaction conditions: 0.36 mmol of halide, 2 mL of THF, 5 mol% $FeCl_3$, 1.08 mmol of $PhSiH_3$ and NaOMe, the yields are isolated; [a]2.04 mmol of **1a**, 1 mol% $FeCl_3$, 15 h; [b]75 °C; [c]1.9 mmol of **1e**; [d]GC yield; [e]1.9 mmol of **1f**, 1 mol% $FeCl_3$, 1.5 eq. $PhSiH_3$ and 1.7 eq. NaOMe, 19 h; [f]6.04 mmol of 1 h, 0.5 mol% of $FeCl_3$; [g]100 °C; [h]0 °C; [i]60 °C; [j]carbonyl group also got reduced to alcohol; [k]10 mol% $FeCl_3$, 6 eq. of $PhSiH_3$ and NaOMe.

version with 92% isolated yield (Scheme 2); the corresponding bromide **1a** offered a similar yield in 5 h, and chloride **1b** took overnight for the complete conversion with 63% isolated yield. While the primary alkyl bromides **1d**, **1h** and **1j** were also reduced efficiently at room temperature in 90%, 94% and 80% isolated yield (Scheme 2), the corresponding chlorides exhibited reduced reactivity and required elevated temperature. Chloride **1e** took 19 h to offer the reduced product in 40% yield at 75 °C and chloride **1k** took 17 h at 100 °C for the complete conversion with 62% yield (Scheme 2). A double protodehalogenation of substrate **1i** was also effected with 61% yield.

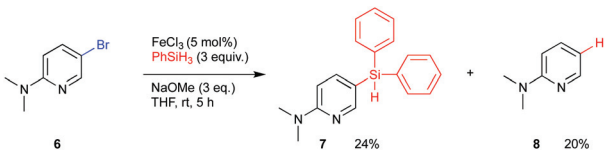
Sterically crowded and challenging tertiary alkyl bromides **1f** and **1l** were successfully reduced with 78% and 54% yields respectively; even 1-chloroadamantane **1g** was reduced with 89% yield. Cholesteryl iodide **1m** offered the protodeiodinated cholest-5-ene in 86% yield. Competitive experiments were conducted to determine the order of reactivity, chlorodecane **1j**, bromide **1k** and iodide were subjected to the standard reaction conditions in a single pot, the complete consumption of iodide was observed within 20 minutes, bromide **1k** took 24 h to get completely consumed; however, the chloride **1j** was intact even after 48 h (see the ESI† for more details). We carried out a gram-scale synthesis to demonstrate the practicability of this iron mediated protodehalogenation; it is worth noting that 0.5 mol% of $FeCl_3$ offered **2a** in 89% isolated yield. The moderate yield of certain substrates can be attributed to the low volatile nature of the product, for example, the substrates **1a**, **1e**, and **1f** were obtained in 91%, 95%, and 95% yields (Scheme 2) when the synthesis was carried out on a large scale (~2 mmol). Even 1.5 eq. of $PhSiH_3$ and NaOMe were sufficient to obtain an excellent yield (substrate **1f**, Scheme 2). These examples clearly illustrate the simplicity of the methodology and the results obtained are comparable to that of tin, aluminum and boron hydride reagents. Interestingly, the above optimized reaction conditions for alkyl halides are also applicable for the reduction of aryl halides. Notably, the reported metal hydrides ($FeCl_3$/$NaBH_4$, In(OAc)/$PhSiH_3$ and $InCl_3$/Et_3SiH) for the reduction of alkyl halides are known to follow a radical pathway that does not reduce aryl halides and it was usually carried out with $PdCl_2$,[12] $[RuCl_2X]_2$,[14] (PNN)RuHCl(CO),[3,7] and Fe(acac)$_3$/RMgX.[11]

1-Bromonaphthalene **4a** was reduced with 40% yield in 30 minutes and 1-chloronaphthalene **4b** took 12 h to complete the reaction with 71% isolated yield (Scheme 2). While 1-bromo-4-(*tert*-butyl)benzene **4c** offered 74% yield in 1 h, 1-chloro-4-methylbenzene **4e** and 5-bromoindole **4d** required elevated temperature and gave 74% and 40% yields respectively (Scheme 2). 5-Bromo-1,2,3-trimethoxybenzene **4f** and 4-chloro, bromo and iodo anisole **4g–i** offered 61%, 78%, 66% and 46% yields respectively; 1-chloro-4-iodobenzene **4k** was also reduced in 50% yield. The functional groups that are susceptible to reductions (ketone **4j** and ester **1p**) were also reduced (Scheme 2). Both the alkyl and aryl fluorides were intact under the reaction conditions.

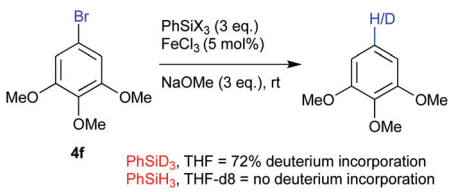
Despite the successful reduction of aryl halides, certain substrates offered poor yields (Scheme 2; see the ESI†) and this can be attributed to the formation of a silyl-coupled side product. When 5-bromo-*N*,*N*-dimethylpyridin-2-amine **6** was subjected to the optimized reaction conditions, we observed the formation of silane coupled product **7** in 24% isolated yield along with the expected reduced product **8** in 20% yield (Scheme 3). A similar coupled product was also observed with 1-bromonaphthalene **4a**. Our efforts to suppress the formation of the silylated product were not successful.

Deuterium labeled experiments were conducted in order to find the source of the hydrogen atom. When $PhSiD_3$ (>99% D, synthesized from $PhSiCl_3$ and $LiAlD_4$) was used, we observed 72% of deuterium incorporation in the product; however when the reaction was conducted in THF-d8, we observed no incorporation of deuterium in the product (Scheme 4). These results clearly indicate that the source of the hydrogen atom is $PhSiH_3$. Based on the earlier studies,[7] our initial expectation was the formation of a radical intermediate and the subsequent reduction to the product; however, our mechanistic studies revealed a non-radical pathway. When we introduced either a TEMPO or galvinoxyl radical inhibitor in the reaction medium, the reaction was not inhibited and we obtained the reduced product (**1a** to **2a**) in 72% and 92% yields respectively. Moreover, the alkene substrate **9a** is expected to undergo cyclization if the reaction proceeds through a radical intermediate; however we observed the formation of uncyclized reduced product **10b** (Scheme 5).

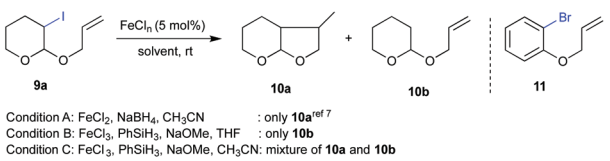
When the reaction was carried out in CH_3CN (a favorable solvent for the radical reaction) instead of THF (no reaction in



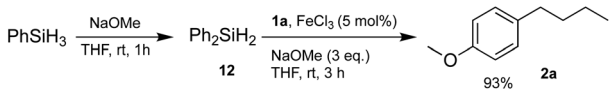
Scheme 3 Formation of a silyl-coupled side product.



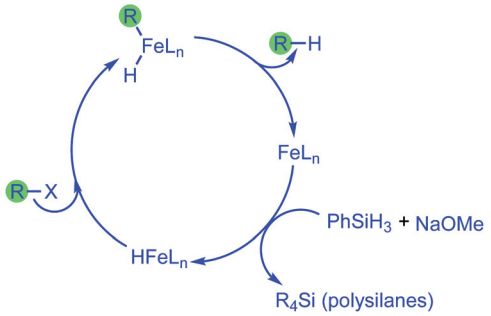
Scheme 4 Deuterium labeling studies.



Scheme 5 Cyclization of iodoalkene.



Scheme 6 Disproportionation of phenylsilane.



Scheme 7 Mechanistic hypothesis.

DMF), the reaction was sluggish and produced a mixture of cyclized **10a** and uncyclized **10b** products (based on crude NMR and GC-MS); further efforts to improve the selective formation of the cyclized product in CH_3CN were not successful. Similarly, an un-cyclized product was observed with substrate **11** and a carbonyl trap experiment also led to the uncyclized product.[10d] These experiments clearly demonstrate a non-radical mechanistic pathway under the established conditions.

The exposure of phenylsilane to NaOMe in THF resulted in the formation of diphenylsilane **12** *via* disproportionation (Scheme 6).[19] The isolated diphenylsilane **12** was subjected to protodehalogenation that offered **2a** in 93% yield. Based on our observation, a mechanistic hypothesis is represented in Scheme 7. A rapid disproportionation of phenylsilane leads to the formation of diphenylsilane that reduces $FeCl_3$ (in the presence of NaOMe) to $HFeL_n$; subsequent oxidative addition of halides followed by reductive elimination could lead to the protodehalogenated product. Additional investigation is necessary to completely elucidate the mechanism.

Conclusions

In summary, we have demonstrated a simple catalytic system based on $FeCl_3$ that can efficiently reduce both the alkyl and aryl halides. The loading of $FeCl_3$ can be reduced to as low as 0.5 mol%. The moderate yield obtained for aryl halides can be attributed to the formation of silylated side products; furthermore, mechanistic studies revealed that the reaction does not proceed through a radical intermediate.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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