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SmI_2/H_2O/amine promoted reductive cleavage of benzyl-heteroatom bonds: optimization and mechanism

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ABSTRACT

The SmI_2/H_2O/pyrrolidine mediated cleavage of benzylic alcohols and benzyl groups was studied and found to be a viable alternative to the Birch reduction yielding the corresponding deoxygenated product in excellent yield. The reaction has been investigated by kinetic methods, and a mechanism involving a pre-complexation of the alcohol to SmI_2 followed by an amine mediated electron transfer and subsequent bond cleavage and transfer of a second electron and proton to yield the toluene product has been proposed. The reaction is strongly inhibited at higher concentrations of water, indicating that it proceeds via an inner-sphere electron transfer from samarium(II) to the benzyl group, and excess of water prevents coordination of benzyl alcohol to samarium.

1. Introduction

The Birch reduction, employing alkali metals in ammonia, is a widely used reaction for a number of transformations in organic synthesis.[1] Although the reduction conditions are considered cumbersome and dangerous, it retains an important role for a number of reduction processes including deoxygenation[2] and deprotection[3] of benzylic amines, alcohols, and thiols. Alkali metals have a very high reduction potential that even enable facile reduction of benzene, which results in low functional group tolerance. In this respect it is desirable to find alternatives that are more tolerant toward other functional groups.[4] We have discovered that the addition of an amine to a SmI_2/H_2O mixture have a dramatic effect on the rate of reduction of ketones[5] and that it is capable of reducing conjugated double and triple bonds[6] as well as polyaromatics[7] (Fig. 1a–b). The SmI_2/H_2O/amine mixture also mediates deallylation[8] and detosylation[9] (Fig. 1c–d). In addition, we have found that benzylic alcohols and amines are reduced yielding toluene. The above mentioned reactions all share properties with the Birch reaction, and this encouraged us to explore the scope and limitation of this reaction as well as studying the underlying mechanism. Although it has been demonstrated that SmI_2 can mediate cleavage of activated benzyl groups,[10] there are no reports on the reduction of benzylic alcohols and amines.

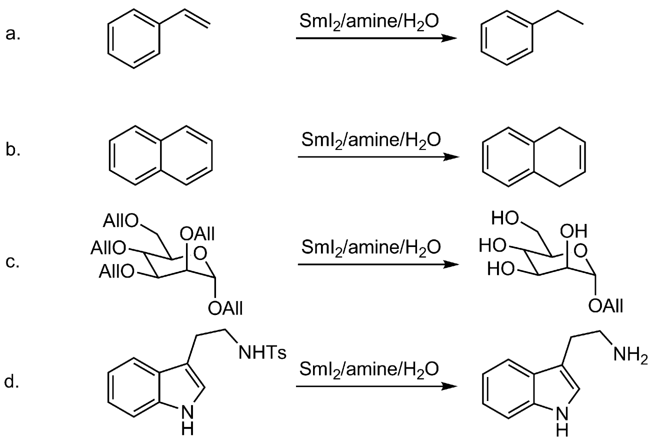

Figure 1. a) Reduction of conjugated olefins, b) Reduction of polyaromatics, c) Efficient cleavage of allylprotected carbohydrates, d) Detosylation of primary amines.

Herein we now wish to report on the SmI_2/H_2O/amine mediated reduction of the benzyl heteroatom bond along with mechanistic studies of the reduction of benzyl alcohol.

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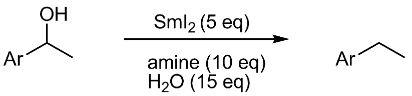
2. Results and discussion

2.1. Cleavage of the benzyl-heteroatom bond

Preliminary studies in our lab have revealed that benzyl alcohol is reduced to toluene upon exposure to SmI_2/H_2O/amine in THF at room temperature. Good conversion (85%) was achieved in 2 h at room temperature (Table 1, entry 1), and prolonged reaction time (24 h) resulted in marginal improvements (Table 1, entry 2). Higher yields could be achieved when pyrrolidine was used instead of triethylamine (Table 1, entry 3). Considerably lower yields were obtained with an α-substituted substrate, 1-phenyl ethanol (entries 4–7). The use of more reactive amines, e.g., isopropyl amine or pyrrolidine, resulted in a faster reaction, however the breakdown of the reagent was also accelerated[11] explaining why there was only a modest increase in chemical yield (entries 5 and 6). Fortunately, this unwanted reaction could be suppressed when the reaction was carried out at −20 °C (entry 7). This is in accordance with our previously reported results where reductions of the nitro group to the amine with SmI_2/H_2O/amine proceeds in much better yields when carried out at −20 °C.[12]

Table 1
Optimization study for the reduction of benzyl alcohols



Entry	Substrate	Time (h)	Temp (°C)	Amine	Yield[a] (%)
1	Benzyl alcohol	2	RT	Et_3N	85
2	Benzyl alcohol	24	RT	Et_3N	90
3	Benzyl alcohol	12	RT	Pyrrolidine	95
4	1-Phenyl ethanol	20	RT	Et_3N	28
5	1-Phenyl ethanol	24	RT	Isopropylamine	37
6	1-Phenyl ethanol	24	RT	Pyrrolidine	37
7	1-Phenyl ethanol	24	−20	Pyrrolidine	62

[a] Yields were determined by GC/MS analysis using dodecane as internal standard and authentic samples as references.

Several alkyl and aryl substituted benzyl alcohols were efficiently reduced by SmI_2/H_2O/amine in high yields (Table 2). From these results we conclude that both the steric bulk around the benzylic carbon (Table 2, entries 2–4) as well as the electronic properties (Table 2, entries 5 and 6) of the substrate is important for the success of the reaction.

Amazingly the introduction of one or two trifluoromethyl groups (entries 5 and 6) facilitates the reductive cleavage considerably, yielding the respective toluene derivatives seemingly instantaneously using the less reactive triethylamine in the reduction mixture. In contrast, the reaction almost halted upon substitution on the phenyl ring with a 4-methoxy group, resulting in low conversion (38%) after 48 h. The major products observed were cyclohexadiene derivatives, which are characteristic of the Birch reduction (Fig. 2).

In addition, benzyl substituted primary or secondary amines and thiols also undergo smooth reduction under these conditions (entries 8–10). Benzyl amines were efficiently reduced using SmI_2/H_2O/pyrrolidine yielding toluene and the corresponding debenzylated amines in 76 and 95% yields after 24 h (entries 9 and 10).

It is well known from the literature that derivatization of benzylic alcohols with acetate greatly facilitates the deoxygenation.[13] Thus we prepared a selection of 1-phenyl ethanol esters and exposed them to the reagent mixture (Table 2, entries 11–14). The reaction was instantaneous at RT and afforded the deoxygenated product in excellent to nearly quantitative yields. The trifluoroacetate derivatized alcohol (entry 14) gave a lower conversion to ethyl benzene. Closer inspection of the product distribution revealed that 2,3-diphenylbutane was formed via a reductive coupling reaction in a 60% yield (Fig. 3).

2.2. Electronic and steric effects in the reduction of various benzylic alcohols

The kinetic studies revealed that the relative rate was not only dependent on the steric hindrance, but the electronic properties of the benzylic moiety also affected the rate to a very high degree. Electron-withdrawing groups on the aromatic ring enhanced the rate considerably (Table 3). A Hammett plot (log k vs σ_X^-) reveals a correlation with a slope of 4.0 (Fig. 4). This result should be taken with some caution due to the relatively low number of substrates (Table 3, entries 1–5). In addition, the substrates with p-F and p-H, which has approximately the same σ_X, proceeds with different rates.

The use of Crearýs $\sigma*$ (often yielding better results for radicals) or any linear combination of the three Hammett values (σ, σ^- and $\sigma*$) did not result in any improvement of the correlation. We also conclude that both p-F and p-OMe yields surprisingly low rates. It should be noted that these substituents may destabilize a radical anion intermediate via resonance thus lowering the rate.

The introduction of α-substituents was also investigated (Table 3, entries 6–8). The rate of reduction was lowered by a factor of two upon the introduction of a methyl group. A second methyl group almost stopped the reduction and the rate was almost two orders of magnitude lower (Table 3, entry 7). Surprisingly, benzhydrol (Table 3, entry 8) reacts very slowly; it is almost six times less reactive than benzyl alcohol. These latter results indicate that steric hindrance affects the rate of reduction significantly.

Both the benzyl amines and the thiol undergo clean reduction by SmI_2/H_2O/amine (Table 2, entries 8 and 9). Thus the rates of reduction in these cases were investigated in a similar fashion (Table 4). Benzyl amine (entry 2) is eight times less reactive than benzyl alcohol itself, and the highest rate of reduction is obtained with N-methyl substitution (entry 3). However, with the introduction of a second methyl group on the nitrogen (entry 4), the relative rate dropped slightly. Again, further substitution at the α-position with a methyl group lowers the rate approximately two times (entry 5). There is no clear trend among the benzyl amines investigated, but the difference in reactivity could possibly be due to the presence of the electron-donating methyl groups that is somewhat overshadowed by an increase in steric hindrance.

Converting the alcohol to an methyl ether (entry 6) also lowers the rate considerably and it is 40 times less reactive. Benzyl thiol (entry 7) is approximately 1.5 times more reactive than benzyl alcohol supporting the fact that the yield for this substrate is excellent.

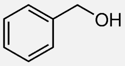
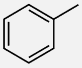
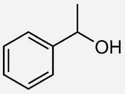
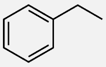
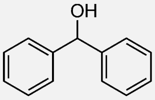
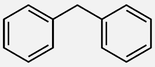
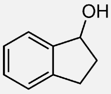
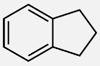
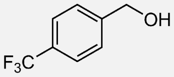
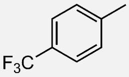
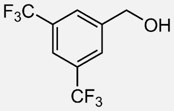
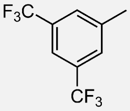
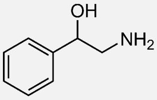
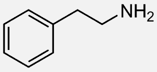
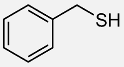
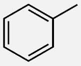
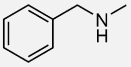
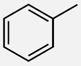
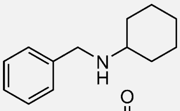
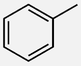
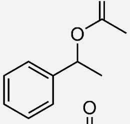
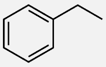
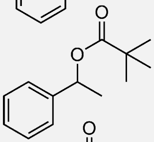
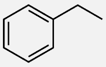
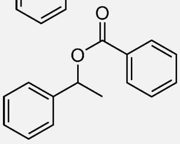
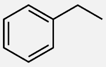
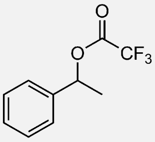
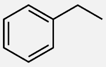
2.3. Determination of the rate orders for the reduction of benzyl alcohol

The method of initial rates can be used for precise and convenient determination of the reaction orders in a complex system, as long as the reaction follows the same kinetics throughout the course of the reaction.[14]

By individually varying the component concentrations over at least an eightfold range the reaction order in each component SmI_2, amine, water, and benzyl alcohol was obtained from the slope of the plots of log[initial rate] vs log[component]. The rate order in SmI_2 was determined by measuring the rate constant at different concentrations of SmI_2 from 12 to 955 mM, (Fig. 5). In contrast to our previous findings in the reduction of alkyl halides with SmI_2/H_2O/amine where the reaction order for SmI_2 was found to be two, benzyl alcohol reduction yields a rate order of one. This clearly indicates that a different mechanism is operating.

Table 2

$SmI_2/H_2O/R_3N$ mediated cleavage of benzyl heteroatom bonds[a]

Entry	Alcohol	Time	Temp (°C)	Amine	Product	Yield[b] (%)
1		22 h	−20	Pyrrolidine		95
2		24 h	−20	Pyrrolidine		62
3		5 h	−20	Pyrrolidine		85[c]
4		22 h	−20	Pyrrolidine		80
5		>1 min	20	Triethylamine		99
6		>1 min	20	Triethylamine		99
7		20 h	−20	Pyrrolidine		88
8		20 h	−20	Pyrrolidine		95
9		20 h	−20	Pyrrolidine		95
10		20 h	−20	Pyrrolidine		76
11		>1 min	20	Pyrrolidine		73
12		>1 min	20	Pyrrolidine		84
13		>1 min	20	Pyrrolidine		91
14		>1 min	20	Triethylamine		31

[a] The benzylic substrate (0.04 mmol) was added to a mixture of amine (0.4 mmol) and water (0.6 mmol) in a 0.1 M solution of SmI_2 (0.2 mmol) in THF at −20 °C. See experimental section for more details.

[b] Yields determined with GC/MS analysis, except entry 7, which was determined with HPLC. Yields were calculated using internal standard and authentic samples as reference.

[c] Isolated yield.

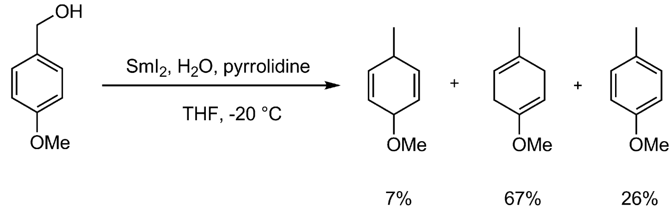


Figure 2. Product distribution in the reduction of anisyl alcohol.

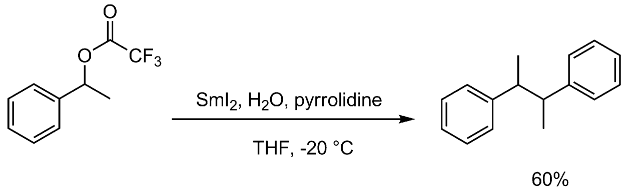
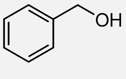
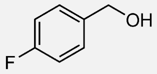
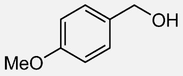
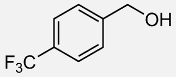
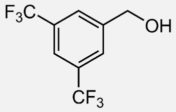
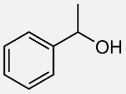
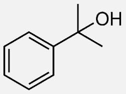
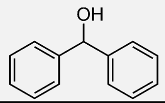


Figure 3. Reductive coupling of benzylic trifluoroacetate.

Table 3
Relative rates in the reduction of benzyl alcohol derivatives to the respective toluenes determined by the initial rate method

Entry	Alcohol	k_{rel}
1		1
2		0.012
3		0.012
4		93
5		>500
6		0.5
7		0.012
8		0.18

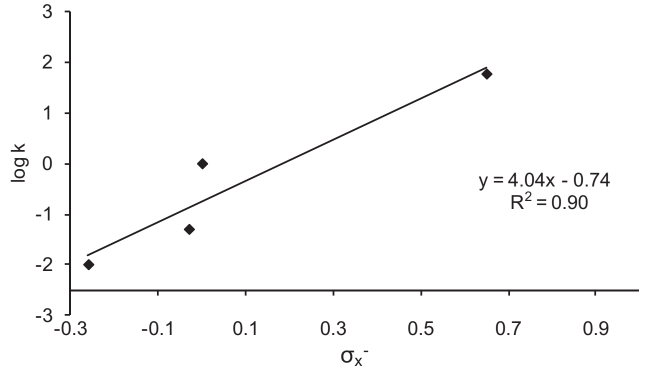
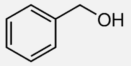
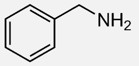
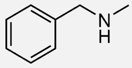
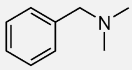
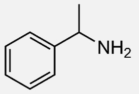
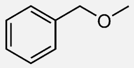
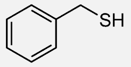


Figure 4. Hammett plot (log *k* vs σ_x^-) for the SmI_2/amine/water mediated reduction of benzyl alcohol in THF.

Table 4
Relative rates in the reduction of various benzylic heteroatoms, determined by the initial rate method

Entry	Substrate	k_{rel}
1		1
2		0.125
3		0.25
4		0.18
5		0.05
6		0.025
7		1.5

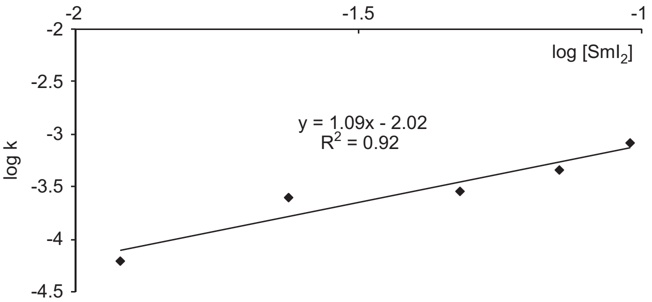


Figure 5. Initial log(rate) vs log (concentration) of SmI_2 (12–955 mM). Reaction conditions; 200 mM Et_3N, 300 mM H_2O, 14 mM benzyl alcohol studied at 20 °C in THF.

Similarly the rate order in benzyl alcohol was determined to be unity at concentrations below 19 mM, while at higher concentrations it gradually increased toward 0.5 (Fig. 6). There can be several explanations for this behavior. It can indicate that benzyl alcohol is a monomer at lower concentrations and that it dimerizes at higher concentrations in THF at room temperature. Another explanation can be that at higher concentrations the benzyl alcohol begins to effectively compete with water at the metal center thus altering the mechanism.

The rate order in triethylamine was found to be unity between in the range 18 and 388 mM (Figs. 7 and 8).

To our surprise the rate dependence for water in the reaction was found to be non-linear. At lower concentrations (24 mM to approx 300 mM) the rate appears to increase linearly with a slope corresponding to rate order 1. It then reaches a plateau (300 mM), and at yet higher concentrations the rate dropped dramatically, with a slope of −4 in the log–log plot.

Although there is no reaction at this point the solution remains dark, indicating that SmI_2 is still intact. Notably, in control experiments the reaction mixture containing large excess of H_2O is still

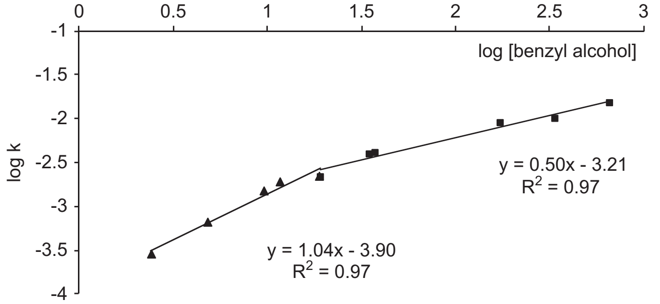


Figure 6. Initial rate vs concentration of benzyl alcohol (2.4–654 mM). Reaction conditions; 100 mM SmI_2, 200 mM H_2O, 300 mM H_2O studied at 20 °C in THF.

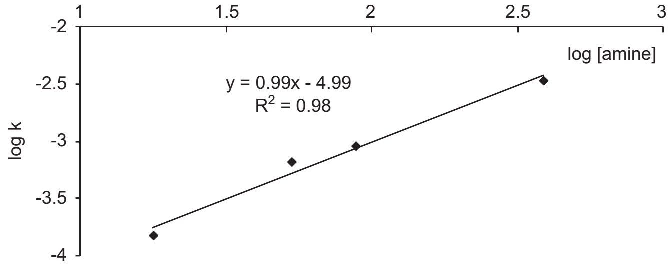


Figure 7. Initial rate vs concentration of amine (18–388 mM). Reaction conditions; 100 mM SmI_2, 300 mM H_2O, 14 mM benzyl alcohol studied at 20 °C in THF.

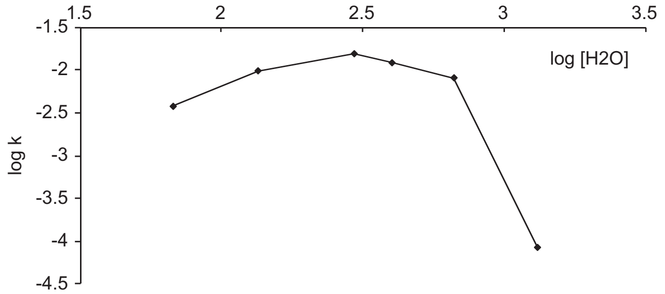


Figure 8. Initial log (rate) vs log (concentration) of water (67–1316 mM). Reaction conditions; 100 mM SmI_2, 200 mM Et_3N, 14 mM benzyl alcohol studied at 20 °C in THF.

a powerful reductant that instantaneously reduces ketones quantitatively to alcohols. Such dependence indicates that the coordination of the substrate, i.e., benzyl alcohol to the metal center is of paramount importance for the electron transfer step of the reaction, which would be inhibited at higher water concentrations since water is a better ligand for SmI_2 than benzyl alcohol. The reductive cleavage of the benzyl group thus appears to be an inner-sphere electron transfer process and if the water concentration is high it will occupy all available coordinating sites around samarium. Ketones on the other hand are much stronger Lewis bases and they might compete effectively with water at the coordination sites on samarium. Flowers has previously observed that large excess of the very powerful Lewis base HMPA may indeed inhibit reduction reactions with SmI_2.[15] Alternatively, it is also possible that reduction of a ketone, which can proceed with a much weaker reducing agent, may proceed via an alternative outer-sphere electron transfer.

2.4. Activation parameters

The temperature dependence of the reduction of benzyl alcohol with $SmI_2/H_2O/Et_3N$ was studied at temperatures from 0 °C to 50 °C at temperature increments of 10 °C. The values for k_{obs} was obtained by determining the initial rates at concentrations where the rate order is unity in each component,[16] and with the assumption that the concentration of each component is approximately equal to their initial concentration (pseudo-first order rate condition). An Eyring plot was obtained by plotting $\ln(k_{obs}h/k_BT)$ vs $1/T$ (Figs. 9–11).

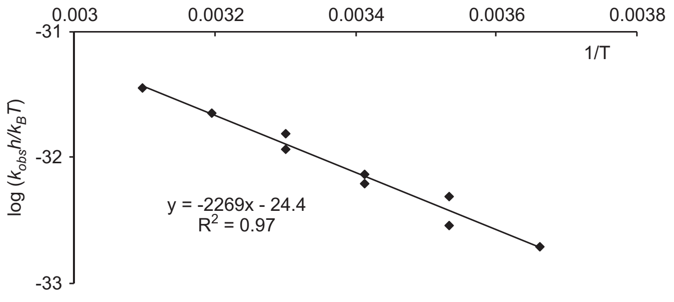


Figure 9. The Eyring plot ($\ln[k_{obs}h/k_BT]$ vs $1/T$, T=273–323) for the reduction of benzyl alcohol in THF.

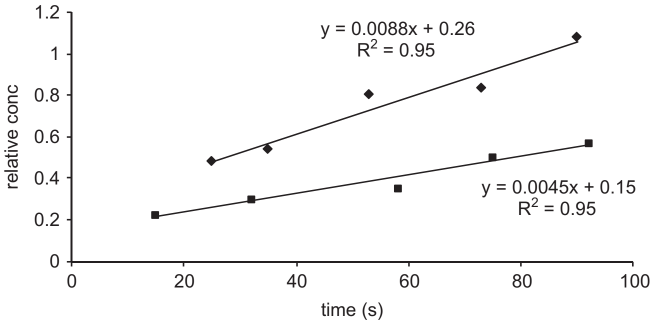


Figure 10. Initial rates of the reduction of benzyl alcohol with SmI_2 with H_2O and D_2O, the kinetic isotope effect was calculated to be 1.9. Reaction conditions; 100 mM SmI_2, 200 mM Et_3N, 130 mM L_2O and 14 mM benzyl alcohol at 20 °C in THF.

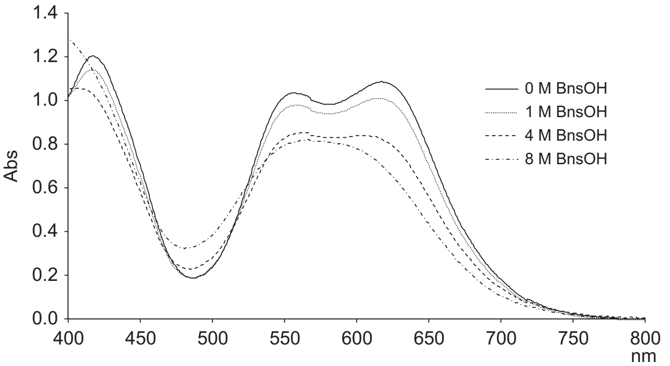


Figure 11. Absorption spectra of SmI_2 (2 mM) in the presence of increasing amount of benzyl alcohol (0, 0.5, 1, 2, 4, 8 M). Several lines are omitted for clarity.

Activation parameters for the reduction reaction were obtained from the linear correlation according to the Eyring equation $[\ln(k_{obs}h/k_BT)=-\Delta H^{\ddagger}/RT+\Delta S^{\ddagger}/R]$, i.e. $\Delta H^{\ddagger}=18.9\pm1.0\ \mathrm{kJ\ mol^{-1}}$, $\Delta S^{\ddagger}=-260\pm30\ \mathrm{J\ K^{-1}\ mol^{-1}}$ and $\Delta G^{\ddagger}{}_{298K}=97\pm10\ \mathrm{kJ\ mol^{-1}}$.

The large negative entropy of activation is obviously a result of the observed high order in the reaction components.

2.5. The amine influences the rate of reaction

The rate of reduction was also found to be dependent on the amine, and there is a clear Brønsted correlation between pK_{BH} and rate (Table 5).

Table 5
Relative rates

Entry	Amine	Rate	Log rate	pK_{BH}[a]
1	Pyrrolidine	0.029	−1.53	11.26
2	Isopropylamine	0.029	−1.54	10.68
3	Et_3N	0.0050	−2.31	10.62
4	Tributylamine	0.0005	−3.30	9.99

[a] The values were predicted using ACD Lab software for THF.

2.6. Kinetic isotope effect studies

The rate of reduction of benzyl alcohol with SmI_2/amine/water shows a substantial kinetic isotope effect $k^{H_2O}/k^{D_2O} = 1.9$. The isotope effect were found to be independent of the water concentrations, $[L_2O]=130$ or 667 mM.

The result is expected as the water is of first order in the rate expression (Eq. 1) and the proton transfer therefore is part of the rate determining step. The incorporation of deuterium was complete as only α-deuterium toluene could be detected in the reaction mixture.

2.7. Spectroscopic investigation UV

The UV–Vis spectrum of dilute SmI_2 solution with added benzyl alcohol reveals a 50 nm hypochromic shift. The UV–Vis band at 617 nm from the THF complex of SmI_2 shifts to 567 nm upon addition of MeOH. ($[SmI_2]=2$ mM, $[Bn\text{–}OH]=0.5\text{–}8$ M).

From this data it is possible to obtain the equilibrium constant between SmI_2 and benzyl alcohol. Regression analysis of the UV–Vis data for benzyl alcohol gave a complex equilibrium constant of 0.095 M^{-1}.[17,18]

This proves that there is an equilibrium between SmI_2 and benzyl alcohol in THF. The UV–Vis spectra of SmI_2 and aliphatic amines were also studied; Et_3N, isopropyl amine, pyrrolidine. Et_3N gave no effect on the UV spectra while isopropylamine and pyrrolidine additions gave rise to a strong bathochromic shift.

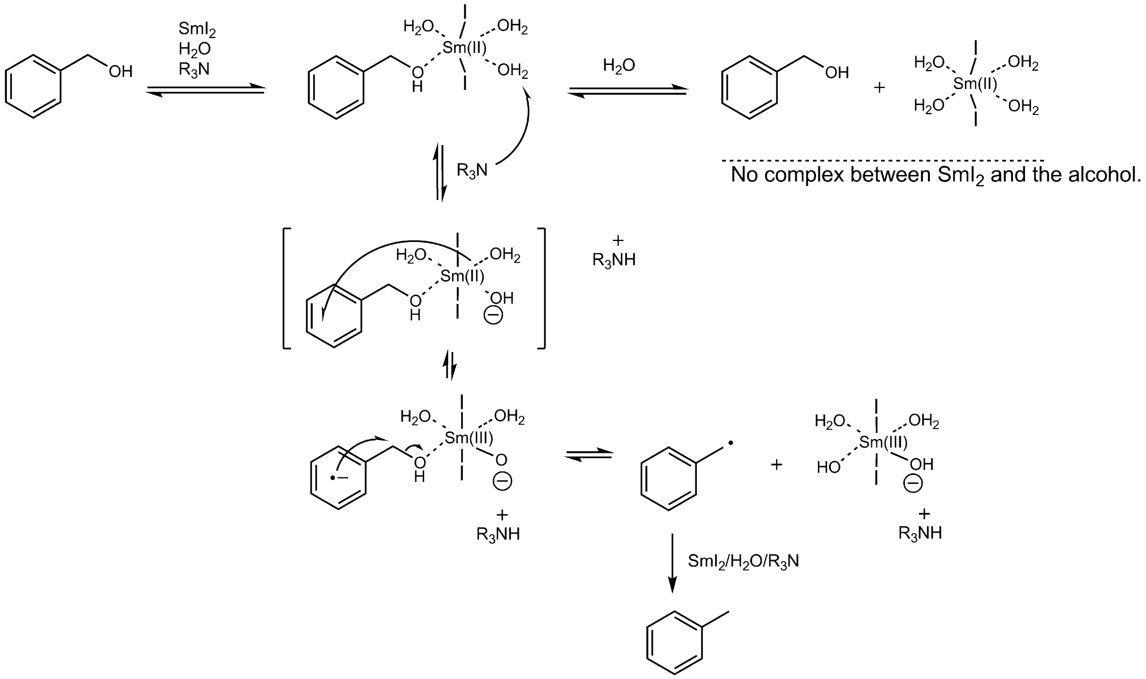
2.8. Mechanism proposal

The evidence collected indicates that the first electron is transferred to the aromatic ring forming a radical anion. This is presumably destabilized by substituents capable of donating electrons (–OMe and –F) thus lowering the reaction rate. On the contrary, electron withdrawing substituents will enhance the rate, and this is also the case as the difference in rate between 4-methoxy benzyl alcohol and 4-trifluoromethyl benzyl alcohol is approximately three orders of magnitude. We can also conclude that the rate of reduction is highest when three equivalents of water are present. Higher amounts of water will effectively displace coordinated benzyl alcohol leading to a lower rate. This proves that the alcohol must coordinate to the metal center in order to receive an electron and this strongly indicates that it occurs via an inner-sphere mechanism.

The strong dependency on electronic effects indicate that the reaction proceeds likely through a radical anion intermediate that rearranges to a benzyl radical intermediate (Scheme 1) followed by transfer of another electron and proton to yield the reduced product, toluene. The role of the amine is similar to that reported for the $SmI_2/H_2O/R_3N$ mediated reduction of alkyl halides, i.e. the amine deprotonates the $SmI_2(H_2O)x$ complex, yielding a much more powerful reducing agent.[19]

3. Conclusion

The reactivity pattern displayed by $SmI_2/H_2O/R_3N$ is in close resemblance with that of the Birch reaction, but in contrast to this reaction the reduction is shut down once the heteroatom is cleaved off and the aromaticity is preserved. The reactions proceeds smoothly and the reaction do not involve any hazardous reagents or conditions and no precautions is required for its use. We have shown that $SmI_2/H_2O/R_3N$ has potential use as deoxygenation and debenzylation reagent. Furthermore, as a result of the detailed mechanistic studies we have revealed that the amount of coordinating water can have a dramatic effect on the reactivity of $SmI_2/H_2O/R_3N$, possibly by inhibiting an inner-sphere electron transfer pathway. This behavior was not observed during our previous studies on the reduction of benzyl halides, which most likely proceeds via an outer-sphere mechanism. It is thus possible that excess of water can inhibit other inner-sphere reactions mediated by $SmI_2/H_2O/R_3N$, i.e., the amount of water can possibly



Scheme 1. A suggested mechanism for the reduction of benzyl alcohol derivatives by $SmI_2/H_2O/R_3N$.

control the functional group selectivity of this reagent. We are currently exploring similar reactions in our laboratory with the aim of developing selective reactions mediated by $SmI_2/H_2O/R_3N$.

4. Experimental

4.1. General

All chemicals were purchased from Aldrich except samarium (Alfa) and used without further purification unless stated otherwise. All handling of the samarium(II) iodide solutions were done in a nitrogen glovebox.

Column chromatography: SiO_2 Kiselgel 60 (Merck flash chromatography grade). TLC: Merck pre-coated SiO_2 plates $60F_{254}$. ^1H NMR and ^{13}C NMR were recorded on a Varian Unity 400, chemical shifts is given in ppm relative to $CDCl_3$. GC/MS analysis used for identification and kinetics were recorded on a Varian 3400 GC with a Varian Saturn 2000 MS, column: SB-5 MS, and Helium was used as carrier gas. Temperature program: 40–330 °C (12 °C/min), hold time 4 min. UV–Vis was recorded on a Varian Cary Bio 100.

4.2. General procedure for the reductive cleavage of the benzyl heteroatom bond (Table 2)

SmI_2 (0.52 mmol, 4 mL, 0.13 M in THF containing decane as internal standard), pyrrolidine (1.04 mmol, 90 μL) and the substrate (0.104 mmol) was cooled to −20 °C (if specified) and water was added (1.56 mmol, 28 μL). The reaction was left to stir for the specified time. The reaction mixture was quenched with the addition of diethyl ether (4 mL) followed by dilute hydrochloric acid (4 mL, 0.5 M) and one drop saturated sodium thiosulfate solution. The organic phase was analyzed on GC/MS comparing with authentic samples and using the internal standard for quantification.

On large scale exemplified for benzhydrol: Benzhydrol (0.42 mmol, 77 mg) was added to SmI_2 (2.08 mmol, 16 mL 0.13 M in THF) followed by pyrrolidine (4.16 mmol, 360 μL) and the mixture was cooled to −20 °C. Water was added and the reaction was allowed to proceed for 21 h. The reaction was quenched with diethyl ether (20 mL) and shaken with hydrochloric acid (30 mL 0.5 M). The organic phase was dried over $MgSO_4$ and evaporated to yield crude diphenylmethane (70 mg). This was purified with column chromatography to yield 59 mg (85%) product identical to an authentic sample diphenylmethane.

4.3. General procedure for the kinetic experiments

SmI_2 (0.4 mmol, 4 mL containing decane as internal standard) was added to a Schlenck tube and equilibrated in a water bath at 20.0 °C. Water and amine was added and after a short period of time benzyl alcohol was added. Five aliquots (200 μL) was withdrawn and quenched in hexane saturated with iodine (0.5 mL). Dilute hydrochloric acid (0.5 mL 0.1 M) and diethyl ether (0.5 mL) was added and the organic phase was analyzed using GC/MS.

4.4. UV–Vis experiments

The benzyl alcohol was distilled under nitrogen using a column packed with small glass helices and a variable take off distillation head and subsequently dried with 4 Å molecular sieves. Use of dried benzyl alcohol from the bottle was not pure enough and immediately quenched the dilute SmI_2 solution used. Measurements were recorded between 400 and 800 nm.

Acknowledgements

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