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Chemoselective nitro reduction and hydroamination using a single iron catalyst†

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The reduction and reductive addition (formal hydroamination) of functionalised nitroarenes is reported using a simple and bench-stable iron(III) catalyst and silane. The reduction is chemoselective for nitro groups over an array of reactive functionalities (ketone, ester, amide, nitrile, sulfonyl and aryl halide). The high activity of this earth-abundant metal catalyst also facilitates a follow-on reaction in the reductive addition of nitroarenes to alkenes, giving efficient formal hydroamination of olefins under mild conditions. Both reactions offer significant improvements in catalytic activity and chemoselectivity and the utility of these catalysts in facilitating two challenging reactions supports an important mechanistic overlap.

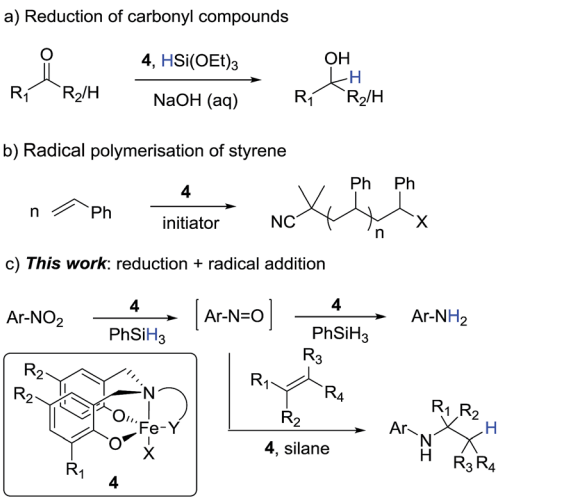
Introduction

The chemoselective production of aniline and aniline derivatives is a cornerstone of modern industrial chemistry. The global aniline market was valued at £6.25 billion in 2013 and will reach a gross market value of £10.17 billion by 2020.[1] Aniline and aniline derivatives find use in polymers and materials (*e.g.* polyurethane and rubber), herbicides, bulk chemicals and dyes and pigments (*e.g.* indigo).[2] Current preparation methods rely on the precious metal-catalysed reduction of nitroarenes using high pressures of hydrogen gas, and suffer from low chemoselectivity.[3] Silanes have emerged as a hydrogen gas alternative.[4]

Earth abundant metal catalysis is at the fore of academic and industrial research due to the inherent availability, sustainability, low cost and low toxicity of these metals. Iron holds a unique position, offering the lowest environmental and societal impact as it is the most abundant transition metal, non-toxic and environmentally benign. Although great strides have been made in the use of iron catalysts in organic synthesis,[5] the reduction of nitro groups has received relatively little attention.[6] The current state-of-the-art methods often require high catalyst loadings and long reaction times to transform a limited scope of substrates with low chemoselectivity.

We recently reported the reduction of carbonyl compounds using an iron(III)-amine-bis(phenolate) catalyst **4b** and silane as the stoichiometric reductant (Scheme 1a).[7] While these complexes were originally used as mediators of controlled radical polymerisations,[8] (Scheme 1b) we were surprised that they also showed excellent activity and chemoselectivity for the hydrosilylation of aldehydes and ketones over a wide range of other functionalities.

Inspired by this ability of the amine-bis(phenolate) catalyst to mediate both radical and reduction events we sought to extend this reaction manifold to the reduction and reductive functionalisation of nitroarenes. If the chemoselectivity and high catalyst activity observed in the carbonyl reductions could be transferred to nitroarene reductions, the amine-bis(phenolate) system would represent a clear advance of the current iron-based reduction manifolds. Moreover, if nitro reduction is combined with radical hydrogen-atom transfer (HAT) to an alkene,[9] a formal hydroamination would be possible. As



Scheme 1 Iron-catalysed reduction and radical reactions supported by Fe(III) amine-bis(phenolate) catalysts and the extension of these reactions to the reduction and reductive addition of nitroarenes.

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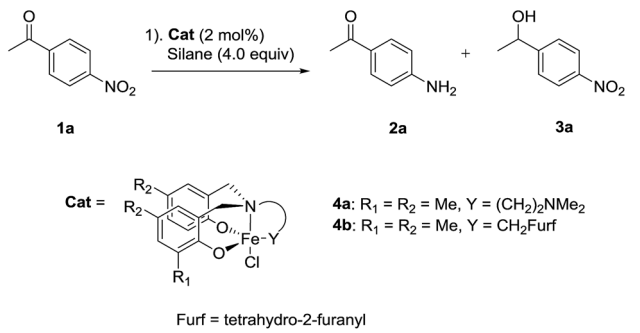
recently reported,[9] the iron-catalysed formal hydroamination of alkenes is an extremely powerful reaction accessible with high iron catalyst loadings (>30 mol%) and elevated reaction temperatures (60 °C) to achieve moderate yields. We postulated that increasing the rate of nitroarene reduction, and thus increasing the concentration of the intermediate nitrosoarene, the overall efficiency of this process could be increased and the catalyst loading lowered significantly.

In the context of the catalytic flexibility of the Fe(III) amine-bis(phenolate) framework, there is an obvious opportunity to develop a single catalytic system that is able to both reduce nitro compounds under mild conditions with high chemoselectivity and access a formal hydroamination of olefins at low catalyst loadings and temperatures (Scheme 1c).

Results and discussion

Our investigations began with the development of the chemoselective nitro reduction of 4-nitroacetophenone **1a** (Table 1). Triethoxysilane was selected as the stoichiometric reductant due to its low cost, ease of handling and wide availability.[10] Amine-bis(phenolate) iron(III) catalysts **4a** gave amine **2a** in 79% yield with 7% reduction of the ketone to give alcohol **3a** (entry 1). Catalyst **4b**, bearing the tetrahydro-2-furanyl donating group gave both high reactivity and chemoselectivity for amine **2a** (entry 2). Solvent had a significant influence on the reaction in terms of both reactivity and selectivity. Replacing MeCN with toluene gave a significant drop in both conversion and chemoselectivity (entry 3). Using THF gave an even lower conversion and reduction of the carbonyl group was observed (entry 4). Ethyl acetate gave a similar result to that of toluene with regard to conversion and selectivity (entry 5). The use of $PhSiH_3$ or Ph_2SiH_2 as the reducing agent, significantly reduced conversion and chemoselectivity (entries 6 and 7). The sterically bulky silanes Ph_2MeSiH and $(Me_3SiO)_2MeSiH$ showed no reactivity towards either the nitro or carbonyl groups (entries 8 and 9). Reducing the amount of silane from 4.0 equivalents to 3.0 equivalents led to a longer reaction time of 8 h in order to obtain comparable reduction (entry 10). Using diethoxymethylsilane, a widely used surrogate for triethoxysilane with greater thermal stability, gave product **2a** in 90% yield together with 5% of **3a** using 5 mol% catalyst (entry 11).

Table 1 Optimisation of reaction condition[a]

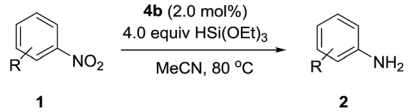


Entry	Cat.	Solvent	Silane	SM[b] (%)	2a[b] (%)	3a[b] (%)
1	**4a**	MeCN	$HSi(OEt)_3$	7	79	7
2	**4b**	MeCN	$HSi(OEt)_3$	Trace	>95(91)[c]	Trace
3	**4b**	PhMe	$HSi(OEt)_3$	46	40	14
4	**4b**	THF	$HSi(OEt)_3$	84	14	2
5	**4b**	EtOAc	$HSi(OEt)_3$	51	35	14
6	**4b**	MeCN	$PhSiH_3$	22	60	11
7	**4b**	MeCN	Ph_2SiH_2	55	26	10
8	**4b**	MeCN	Ph_2MeSiH	>95	0	0
9	**4b**	MeCN	$(Me_3SiO)_2MeSiH$	>95	0	0
10[d]	**4b**	MeCN	$HSi(OEt)_3$	Trace	>95	Trace
11[e]	**4b**	MeCN	$HSiMe(OEt)_2$	Trace	90	5

[a] Unless otherwise noted, all reactions were carried out using 4.0 eq. of hydrosilane (1.20 mmol), 1.0 eq. of 4-nitroacetophenone (0.3 mmol), 0.02 eq. of catalyst **4** (0.006 mmol) in 0.3 mL solvent at 80 °C for 4 h. [b] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield. [d] 3.0 eq. of triethoxysilane was used, 8 h. [e] 0.05 eq. of catalyst was used.

The substrate scope of this newly developed catalytic system was investigated using the optimised reaction conditions of 2 mol% catalyst **4b**, 4.0 equivalents of triethoxysilane in MeCN (1.0 M) at 80 °C (Table 2). In all cases, good to excellent yield and chemoselectivity were obtained, demonstrating the utility of this methodology in synthesis. Industrially important aniline could be prepared from nitrobenzene in 84% isolated yield (entry 1). *o*-Methyl, *m*-methyl and, in contrast to other methods,[6] even the sterically hindered 2,6-dimethyl nitrobenzene were all successfully reduced in good yields (entries 2, 3 and 4). *p*-(Methylthio) aniline **2f** was produced from the corresponding nitroarene in excellent yield, although an 8 hour reaction time was needed (entry 5). The selective reduction of the nitro group in the presence of an ester functionality proceeded smoothly in all cases with excellent yields (entries 6, 7, 8, and 9), indicating the complete chemoselectivity and reactivity of the developed system for these challenging substrates.[11] Methylsulfonyl substituted nitrobenzene **1k** was also reduced with excellent chemoselectivity for the NO_2 group (entry 10). In the case of 4-nitrobenzonitrile, 65% yield of amine **2l** was obtained; however, 30% of the starting material was recovered, once again demonstrating the high chemoselectivity of the catalyst for the nitro group over nitrile (entry 11). The low yield in the reaction of 4-nitrobenzonitrile is attributed to the strong coordination of the nitrile group to the catalyst which inhibits catalyst activity. To demonstrate this, a standard reduction of ethyl 4-nitrobenzoate was doped with 4-nitrobenzonitrile (1 : 1) and the yield of nitro reduction at ethyl 4-nitrobenzoate **1h** dropped from 98% to 30%.[12] Halogenated nitrobenzene derivatives were also reduced chemoselectively and in good yield without any protodehalogenation[13] or homocoupling[14] observed (entries 12, 13 and 14). Nitroarenes **1p** and **1q**, bearing the strongly electron-withdrawing CF_3 group, were reduced to the corresponding anilines, **2p** and **2q**, in 90% and 85% yield, respectively (entries 15 and 16). Nitro-substituted benzoxazole **1r** was selectively reduced to corresponding amine **2r** in 88% yield without any ring-

Table 2 Substrate scope of nitroarene reduction[a]



1 2

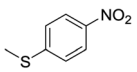
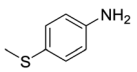
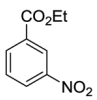
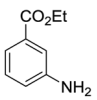
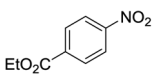
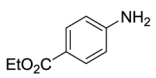
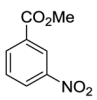
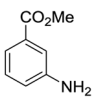
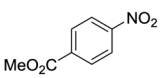
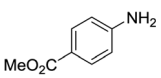
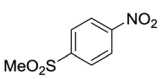
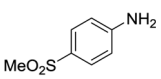
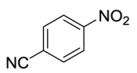
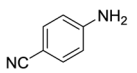
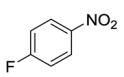
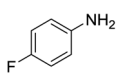
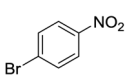
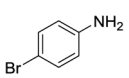
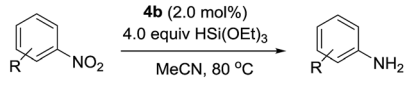
Entry	Substrate	Product	Time	Yield[b]
1	 **1b**	 **2b**	4 h	84%
2	 **1c**	 **2c**	6 h	84%
3	 **1d**	 **2d**	6 h	70%
4	 **1e**	 **2e**	6 h	82%
5	 **1f**	 **2f**	8 h	93%
6	 **1g**	 **2g**	5 h	91%
7	 **1h**	 **2h**	5 h	98%(85%)[c]
8	 **1i**	 **2i**	5 h	94%
9	 **1j**	 **2j**	5 h	93%
10	 **1k**	 **2k**	4 h	80%(15%)[d]
11	 **1l**	 **2l**	6 h	65%(30%)[d]
12	 **1m**	 **2m**	5 h	82%
13	 **1n**	 **2n**	8 h	87%[e]
14	 **1o**	 **2o**	5 h	90%

Table 2 (*Contd.*)



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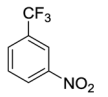
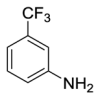
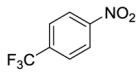
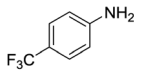
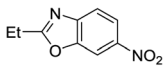
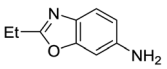
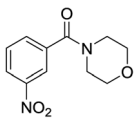
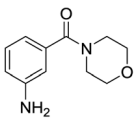
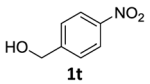
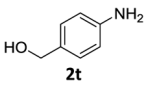
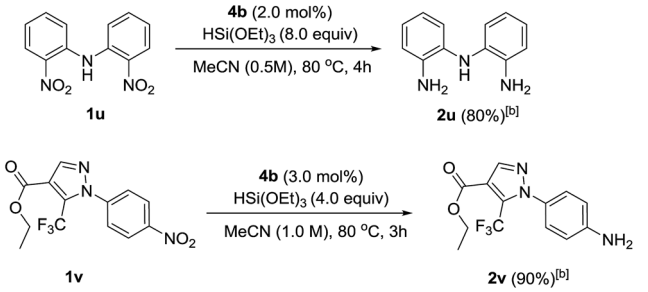
Entry	Substrate	Product	Time	Yield[b]
15	 **1p**	 **2p**	3 h	90%
16	 **1q**	 **2q**	3 h	85%
17	 **1r**	 **2r**	6 h	88%
18[f]	 **1s**	 **2s**	4 h	98%
19	 **1t**	 **2t**	6 h	55%

[a] Unless otherwise noted, all reactions were carried out using 4.0 eq. of triethoxysilane (2.40 mmol), 1.0 eq. of nitro substrate (0.6 mmol), 0.02 eq. of catalyst (0.012 mmol) in 0.6 mL MeCN at 80 °C. [b] Isolated yield. [c] Using 4.0 eq. of $HSiMe(OEt)_2$, 0.05 eq. of **4b**, 5 h. [d] Starting material recovered. [e] Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [f] 0.04 eq of catalyst was used.

opening or arene hydrogenation observed (entry 17).[15] Nitrobenzene **1s**, bearing an amide functionality, was also well tolerated to give the product in excellent yield (entry 18). When a substrate bearing a free alcohol was used, decreased catalytic activity was observed (entry 19).

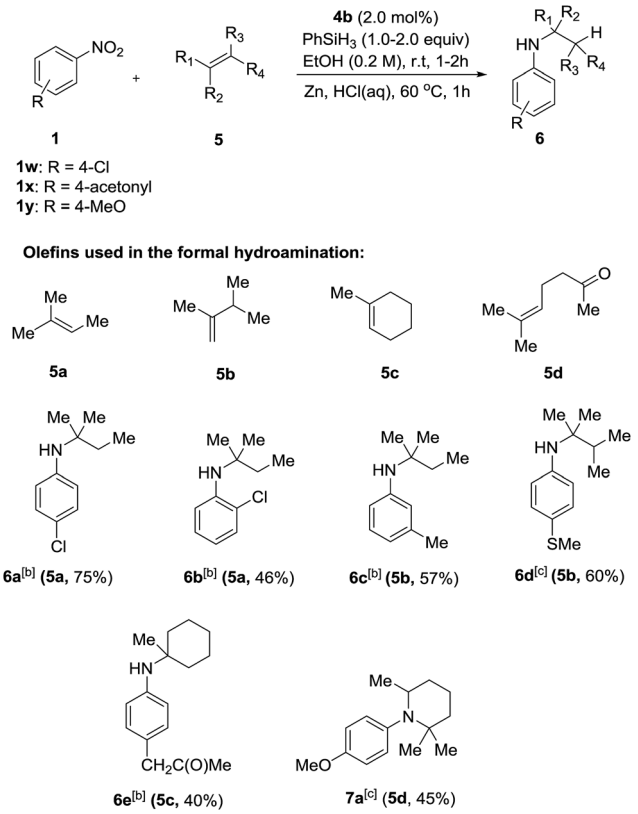
To showcase the applicability of the developed nitro reduction, we explored the reduction of academically- and industrially-relevant targets. Bis(2-aminophenyl)amine **2u**, which is widely used in the synthesis of *N*,*N*,*N*-type pincer[16] or triamido[17] ligands, was obtained in 80% isolated yield. This was directly comparable to the yield reported using palladium-catalysed reduction with H_2.[16] Drug precursor **1v** was chemoselectively reduced to amine **2v** in 90% yield. This late stage reduction with a non-toxic metal greatly simplifies purification and trace metal removal, so making the developed method ideal for targets to be tested *in vivo*.[18] Amidation of **2v** would give 4-(pyrazole-1-yl) carboxanilides, a family of drugs that tune the activity of canonical transient receptor potential channels (TRPC) and thus control the influx of intracellular Ca^{2+} into a plethora of mammalian cell types (Scheme 2).[19]

Having successfully developed a highly efficient silane-mediated reduction of nitroarenes, we were keen to explore if



Scheme 2 Selective nitro reduction in the synthesis of 'real-world' targets. [a] Reactions were carried out using 0.6 mmol of nitro compounds. [b] Isolated yield.

this could be combined with radical HAT for a formal hydroamination.[9,20] We hypothesised that the high reactivity of **4b** for nitroarene reduction would increased rates of reactions with alkenes. Strikingly, application of catalyst **4b** in the formal hydroamination of alkenes using nitroarene **1w** and alkene **5a** gave amine **6a** in 75% isolated yield after Zn/HCl work-up[21] using just 2.0 mol% catalyst, a 15-fold reduction in catalyst loading compared to the previous system.[20] Additionally, the starting nitro substrate was fully consumed at room temperature in just 2 h. 1-Chloro-2-nitrobenzene **1n** gave the corresponding amine product **6b** in relatively lower yield, potentially due to the halogenophilicity of the parent Fe complexes.[8] A methyl substituted nitroarene **1c** was well tolerated to give the formal hydroamination product **6c** while nitroarene **1f**, bearing a methyl thioester group, gave the corresponding amine **6d**, both in good yields. Nitroarene **1x** with a free carbonyl group was also well tolerated to give the product **6e** in lower yield but with the carbonyl functionality unchanged. Importantly, the formal hydroamination of olefin **5d** could be further extended under the same reaction conditions. Reaction with 4-nitroanisole **1y** followed by an intramolecular reductive amination gave the *N*-arylpiperidine **7a** in 45% yield, indicating the potential application of this method in the preparation of *N*-heterocycles (Scheme 3). Deprotection of the *para*-methoxyphenyl (PMP) group of **7a** would give 2,2,6-trimethyl piperidine which is a useful reagent for the α-alkylation of aldehydes.[22]



Scheme 3 Formal hydroamination of olefins with catalyst **4b**. [a] Reactions were carried out using 0.3 mmol of nitro compounds and 0.9 mmol of alkene. [b] 2.0 equiv. of silane, 2 h. [c] 1.0 equiv. of silane, 1 h. Isolated yield are shown in parentheses together with the donor olefin used.

Conclusions

We have developed a highly chemoselective, efficient and operationally simple amine-bis(phenolate) iron(III)-catalysed reduction of nitro compounds using triethoxysilane as the reducing agent. The system chemoselectively reduces aryl nitro groups over carbonyl, ester, imine, sulfonyl and cyano functionalities. The highly efficient formal hydroamination of alkenes has also been developed with excellent activity observed at room temperature with low iron catalyst loadings. Mechanistic studies and the investigation into the scope of catalyst **4b** for reductive functionalisation continue.

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