Highly selective conversion of nitrobenzenes using a simple reducing system combined with a trivalent indium salt and a hydrosilane†

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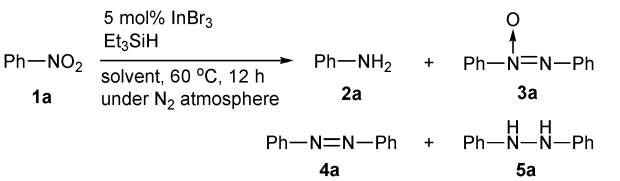
Controlling the type of indium salt and hydrosilane enables a highly selective reduction of aromatic nitro compounds into three coupling compounds, azoxybenzenes, azobenzenes and diphenylhydrazines, and one reductive compound, anilines.

Most nitrogen-containing compounds such as anilines, azoxybenzene compounds or azobenzene derivatives, are important and central building blocks in naturally occurring compounds and functional materials.[1] In general the reduction of nitrobenzenes with an appropriate reducing reagent is a straightforward method for the direct synthesis of these highly valuable compounds.[2–4] Currently, general conversion of either a nitro group into an amino group or the corresponding coupling product is most often achieved either by treatment with a reducing reagent, such as H_2 gas,[2b,2c,5] CO gas,[2a,6] NH_2NH_2,[7] or $NaBH_4$,[8] in the presence of a transition metal or by reduction with a zerovalent metal, such as Bi,[3d] Cr,[3e] Fe,[9] In,[2f] Mg,[4a] Sm,[2e] or Zn[3a] under acidic/basic/neutral conditions. However, these conventional procedures generally require excess amounts of a reducing metal, flammable gas and reagents, and the use of high-pressure equipment. Conventional methods that require the use of a strong reducing reagent often produce undesirable byproducts. Moreover, selective conversion of one aromatic nitro compound into more than one reductive product by use of a single reducing system has not been studied extensively.[10] During the last decade several groups have reported that a reducing system comprised of an indium salt and a hydrosilane, which is a mild reducing agent, is highly effective for the reductive conversion of functional groups.[11] Our ongoing studies on the reductive conversion of functional groups[12] have yielded unprecedented results.[13] The use of our simple reducing system resulted in the highly selective conversion of nitrobenzenes into four different reductive compounds, azoxybenzenes, azobenzenes, hydrazobenzenes and anilines. Herein we report the preliminary results of these studies.

We initially investigated the reductive conversion of nitrobenzene (**1a**) with $InBr_3$ and Et_3SiH (Table 1). Based on our previous work, when the reduction was carried out under $CHCl_3$ reflux, most of the nitrobenzene was recovered and four derivatives were formed: aniline (**2a**), azoxybenzene (**3a**), azobenzene (**4a**) and hydrazobenzene (**5a**) (run 1). Thus, several experiments were performed to evaluate the solvent effect. THF produced azoxybenzene (**3a**) in a nearly quantitative yield (run 2). Also, when the reduction was conducted with DMF, the hydrazine **5a** was obtained as the sole product in an excellent yield (run 3). Interestingly, addition of a small amount of H_2O to the reaction system accelerated the desired reduction, and the reaction was completed within 5 h (run 4). Unfortunately, the $InBr_3$–Et_3SiH system was ineffective for the preparation of azobenzene (**4a**). The use of $In(OTf)_3$ in place of $InBr_3$ allowed for the preparation of azobenzene (**4a**), but the product selectivity was rather low (run 5). Thus, in the first step, we attempted to produce the diphenylhydrazine derivative **5a** using the $In(OTf)_3$–Et_3SiH reducing system, followed by oxidative conversion of the hydrazine into the corresponding azobenzene **4a** under atmosphere. We also found that $In(OTf)_3$ promoted dehydrogenation of hydrazo derivatives under atmosphere (run 6).[14] Unfortunately, the reducing system that used either $InBr_3$ or $In(OTf)_3$ did not selectively convert nitrobenzene (**1a**) into aniline (**2a**).

Using the optimal conditions, the synthesis of azoxybenzene derivatives from a variety of nitrobenzenes was examined (Table 2). For instance, when *o*-nitrotoluene was used as the starting material, the reductive conversion was completed within 20 h, producing the corresponding azoxybenzene compound **3b** in 82% yield. The steric hindrance of the *ortho* methyl group was not effective for this reduction. We encountered problems in the solubility of the starting nitrobenzenes. Thus, the following reactions were carried out in DMF instead of THF. Nitrobenzenes with a halogen atom

Table 1 Examination of reaction conditions



Run	Solv.	Si–H /Equiv.	Yield/%[a] 2a	3a	4a	5a
1	$CHCl_3$	4	9	15	2	10
2	THF	2.2	ND	96	Trace	Trace
3	DMF	4	ND	ND	ND	94
4[b]	DMF	4	ND	ND	ND	95
5[c]	DMF	2.5	ND	ND	64	29
6[c,d]	DMF	2.5	—	—	(99)	—

[a] NMR(Isolated) yield. [b] Solvent: DMF–H_2O = 95/5, Reaction time: 5 h. [c] $In(OTf)_3$ (5 mol%) was used. [d] After the reduction, the resulting mixture was stirred at 60 °C for 15 h under atmosphere.

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Table 2 Synthesis of azoxybenzene derivatives **3**[a]

Entry	X	Time/h	Product	Yield/%
1	H	8	**3a**	96
2	2-Me	20	**3b**	82
3	3-Me	20	**3c**	74
4[b]	4-Me	12	**3d**	93
5[b]	4-Cl	15	**3e**	81
6[b]	4-Br	15	**3f**	62
7[b]	4-CN	12	**3g**	88
8[b]	4-MeCO	3	**3h**	97
9[b]	4-$MeCO_2$	12	**3i**	64

[a] $InBr_3$ (5 mol%)/Et_3SiH (2.2 equiv.) in THF at 60 °C. [b] $InBr_3$ (5 mol%)/Et_3SiH (1.1 equiv.) in DMF at 60 °C.

Table 4 Synthesis of diphenylhydrazine derivatives **5**[a]

Entry	X	Time/h	Product	Yield/%
1	H	8	**5a**	96
2	2-Me	15	**5b**	63[b]
3	3-Me	15	**5c**	41
4	4-Me	15	**5d**	82
5	4-Cl	8	**5e**	72
6	4-Br	8	**5f**	81
7	4-CN	20	**5g**	78
8	4-MeCO	20	**5h**	81
9	4-$MeCO_2$	20	**5i**	64

[a] $InBr_3$ (5 mol%)/Et_3SiH (4 equiv.) in DMF at 60 °C. [b] 2-Methylaniline was isolated in 22% yield.

instead of a cyano group were selectively and quantitatively converted into the corresponding azoxybenzene derivatives **3d–i**, if 1.1 equiv. of Et_3SiH in DMF was used.[15] In addition, we found that this reducing reagent did not affect either an acetyl group or an ester moiety.[16]

We next examined the synthesis of azobenzene derivatives (Table 3). In the first step, we used the In(OTf)$_3$–Et_3SiH reducing system to produce hydrazine **5**. In the second step, we successively and directly converted the hydrazine derivative into the corresponding azobenzene **4** by oxidation under atmosphere without isolation of the hydrazine. Most of the nitrobenzene derivatives with a functional group, such as a methyl group, halogen atom, cyano group, or ketone and ester moiety, were successfully converted into the corresponding azobenzene derivatives **4a–i** in good yields.

Then, when $InBr_3$ and 4 equiv. of Et_3SiH in DMF were used, nitrobenzenes were successfully converted into the corresponding diphenylhydrazine derivatives **5a–i** (Table 4). Unlike the preparation of azoxybenzenes and azobenzenes, substitution at the *ortho* position had an effect on the product ratio. When 2-nitrotoluene was used, 2-methylaniline was isolated in 22% yield as a by-product. When 2-(phenylethynyl)-nitrobenzene **6** was subjected to the standard conditions, no hydrazine derivative was produced, but 2-(phenylethynyl)-aniline **7** was obtained in 83% yield. As described in run 4 of Table 1, it is noteworthy that when 5 wt% of H_2O was added to the reaction system, the time required to complete the reduction and produce a hydrazine derivative was markedly reduced.[17] This acceleration of the reaction rate might occur because protic solvents are proton sources that trap the amide anions that form *in situ*, thus driving the reaction equilibrium to completion.

Table 3 Synthesis of azobenzene derivatives **4**[a,b]

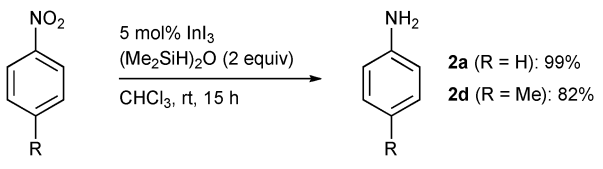
Entry	X	Time/h	Product	Yield/%
1	H	8	**4a**	99
2	2-Me	20	**4b**	62
3	3-Me	20	**4c**	78
4	4-Me	12	**4d**	72
5	4-Cl	6	**4e**	70
6	4-Br	6	**4f**	80
7	4-CN	5	**4g**	74
8	4-MeCO	12	**4h**	92
9	4-$MeCO_2$	5	**4i**	95

[a] In(OTf)$_3$ (5 mol%)/Et_3SiH (2.2 equiv.) in DMF at 60 °C. [b] After the first reduction, the resulting mixture was stirred at 60 °C for 15 h under atmosphere.

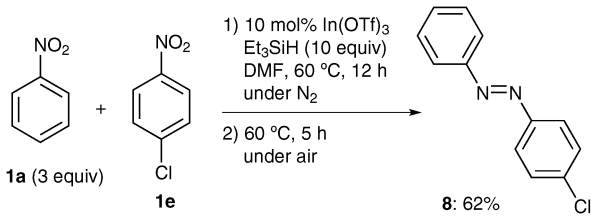
The results shown above prompted us to examine the selective preparation of aniline derivatives. After further examination, we finally found a novel reducing system that consisted of InI_3 (5 mol%) and 2 equiv. (4 equiv. as *Si-H*) of tetramethyldisiloxane (TMDS)[18] in $CHCl_3$ at room temperature, which successfully and selectively produced aniline (**2a**) in quantitative yield.[19] Moreover, when the reduction of *p*-methylnitrobenzene (**1d**) was carried out under reductive conditions, the desired *p*-toluidine (**2d**) was selectively obtained in 82% yield (Scheme 1).

It is noteworthy that this reducing method could be applied to the direct preparation of unsymmetrical azobenzene derivatives.[1,20] After tuning the reaction conditions, we found that when the DMF solution containing 3 equiv. of nitrobenzene (**1a**) and 1 equiv. of *p*-chloronitrobenzene (**1e**) was treated with 10 mol% of In(OTf)$_3$ and an excess (10 equiv.) of Et_3SiH, the desired unsymmetrical azobenzene derivative **8** was directly obtained in a practical yield (Scheme 2). Although the homo-coupling azobenzenes formed as by-products, silica gel column purification enabled us to isolate the desired unsymmetrical product from the mixture.

To understand the reaction path, we performed several control experiments. When nitrosobenzene was subjected to our standard reaction conditions, which consisted of 5 mol% of $InBr_3$ and 3 equiv. of Et_3SiH in DMF, the corresponding diphenylhydrazine (**5a**) was isolated in 94% yield. Also, when a Mills-type reaction of nitrosobenzene with *p*-chloroaniline was examined in the absence of an indium salt and/or a hydrosilane, no coupling products were obtained. Moreover, the reaction of nitrobenzene with *p*-chloroaniline gave diphenylhydrazine (**5a**) in 93% yield, and did not produce the crossed hydrazine derivative. Thus, these results showed that the combination of an indium salt and a hydrosilane was essential, and that generation of a nitrosobenzene derivative,



Scheme 1 Reductive conversion to anilines.



Scheme 2 Direct synthesis of an unsymmetrical azobenzene.

but not aniline, was required for the reductive coupling of nitrobenzene derivatives. Also, formation of an aniline derivative may proceed *via* direct reduction of nitrosobenzene, and not by further reductive cleavage of a hydrazine.

In summary, we demonstrated that a reducing system consisting of a trivalent indium salt and a hydrosilane allowed the highly selective conversion of aromatic nitro compounds into four derivatives. Azoxybenzenes [$InBr_3$–Et_3SiH (1.1–2.2 equiv.) in THF or DMF], azobenzenes [$In(OTf)_3$–Et_3SiH (2.5 equiv.) in DMF–oxidation step], diphenylhydrazines [$InBr_3$–Et_3SiH (4 equiv.) in DMF] and anilines [InI_3–$(Me_2SiH)_2O$ (2 equiv.) in $CHCl_3$] were produced by controlling the type of trivalent indium salt, hydrosilane and solvent, and the number of hydrosilane equivalents used in the reaction. We also found that this reducing system allowed for the direct preparation of an unsymmetrical azobenzene.

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