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$B(C_6F_5)_3$-Catalyzed Highly Chemoselective Reduction of Isatins: Synthesis of Indolin-3-ones and Indolines

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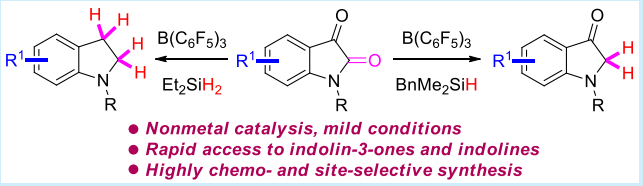
ABSTRACT: A chemo- and site-selective reduction reaction of isatin derivatives using catalyst $B(C_6F_5)_3$ and hydrosilanes is described. This transformation is operationally simple, proceeds under mild conditions, and is resistant to various functional groups. Thus, this efficient reaction using a combination of $B(C_6F_5)_3$ and $BnMe_2SiH$ or $B(C_6F_5)_3$ and Et_2SiH_2 could potentially be utilized to produce various indolin-3-ones and indolines, without the need for multistep procedures and metal catalysis conditions.



Indolin-3-ones are attractive target motifs, as they are important building blocks for the synthesis of numerous pharmaceutical compounds and natural products (Figure 1).[1]

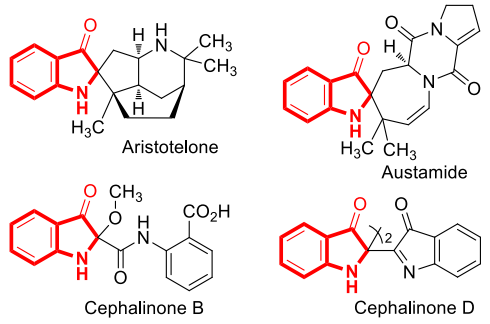


Figure 1. Representative examples of natural products containing the indolin-3-one motif.

In addition, the indolin-3-one scaffold is widely studied as a crucial starting material for the development of new synthetic methodologies, as it exhibits varied reactivity and enables high stereoselective transformations. However, despite their utility and interesting structure, a few synthetic routes[2] have been developed for the construction of indolin-3-ones. Traditional methods to construct indolin-3-ones involve several steps consisting of 2-aminobenzoic acid alkylation, cyclization to afford indole, and finally indole oxidation. In addition to the conventional methods, recent approaches include visible-light-induced radical-mediated processes,[2a] gold-catalyzed cyclization,[2b] and mercury-catalyzed enolate umpolung reactions.[2c] Consequently, practical and efficient synthetic strategies for developing the indolin-3-one framework remain desirable.

Recently, the reduction of amide groups to amines via catalytic hydrosilylation has received immense attention owing to its desirable chemoselectivity. Particularly, selective amide reduction using attractive boron Lewis acids has been investigated by several research groups because of their low cost, benign environmental impact, and high Lewis acid strength (Scheme 1).[3] Zhang and co-workers first used $B(C_6F_5)_3$ as the catalyst and Ph_2SiH_2 as the reductant for the reduction of amides to amines.[3b] *N*-Phenylamide was successfully reduced using this catalyst system while benzamide did not undergo reduction. Later, the reduction of benzamides to amines, catalyzed by $B(C_6F_5)_3$ in the presence of tetramethyldisiloxane or polymethylhydrosiloxane, was independently realized by the research groups of Cantat and Adronov.[3c,d] The reduction of diverse secondary and tertiary benzamides to the corresponding amines was accomplished by treatment with this catalyst system. In 2018, Gagné and co-workers reported a new (3-hexyl)$B(C_6F_5)_2$ catalyst with modified steric and electronic properties for chemoselective amide reduction at the later stage, with no competing reaction at other positions.[3e,f] A new deoxygenative reduction of amide using the $B(C_6F_5)_3/BF_3{\cdot}O(C_2H_5)_2/H_3N{\cdot}BH_3$ combination was disclosed by Xiao et al. last year.[3g] In addition to reduction using the strong Lewis acid $B(C_6F_5)_3$, the selective reduction of amide using the moderately strong Lewis acid BPh_3 was realized by Okuda et al.[3h] In this catalytic reaction, tertiary amides reacted with BPh_3 and $PhMeSiH_2$ and were transformed into amines with good chemoselectivity. The Beller group first used a combination of boronic acid, which is a mild Lewis acid, and hydrosilane for the synthesis of amines from amides.[3i] Primary, secondary, and tertiary amides were

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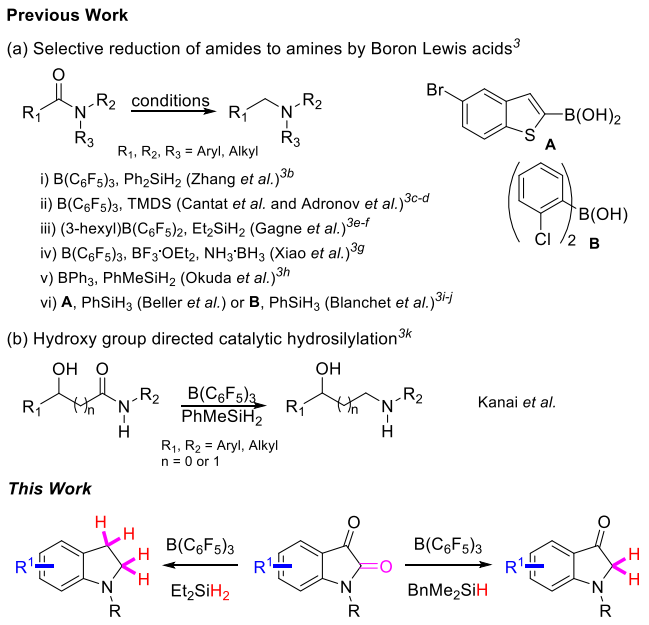
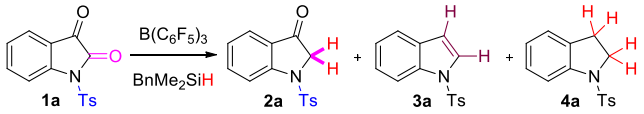
Scheme 1. Synthetic Strategies for the Development of Indolin-3-one and Indoline Derivatives



gradually reduced using benzothiophene-derived boronic acid and $PhSiH_3$ to produce the desired amines. More recently, the chemo- and site-selective reduction of α- or β-hydroxy amides using a combination of $B(C_6F_5)_3$ and $PhMeSiH_2$ was described by Kanai et al.[3k] The hydroxy group of hydroxy amides reacted with $PhMeSiH_2$ to form silyl ether, and another hydride from hydrosilane attacked the amide to synthesize amines with functional group tolerance. Inspired by the previous study that utilizes $B(C_6F_5)_3$ and hydrosilanes, we envisioned that isatin, which is less expensive and commercially available, is suitable as a substrate to synthesize indolin-3-ones via chemoselective amide reduction. Thus, we decided to investigate the chemo- and site-selective reduction of isatins for the preparation of indolin-3-ones. Herein, we report the first $B(C_6F_5)_3$-catalyzed selective reduction of isatins using hydrosilanes to produce useful indolin-3-ones and indolines.

Initially, we used tosyl-protected isatin **1a**[4] as the standard substrate to screen various reaction conditions, and the results are summarized in Table 1. First, the reaction of isatin **1a**, $BnMe_2SiH$, and 10 mol % $B(C_6F_5)_3$ was performed in DCM, chloroform, DCE, or benzene at temperatures ranging from 60 to 100 °C (entries 1−4). With the use of DCM, only indoline **4a** was isolated in 29% yield (entry 1), while no desirable products were detected in the other three solvents (entries 2−4). Pleasingly, the expected site-selective reduction of tosyl-protected isatin **1a** occurred in chlorobenzene at 120 °C, affording **2a**,[2b,c] **3a**,[2b,8b,14] and **4a** in yields of 80%, 12%, and 5%, respectively (entry 5). Several solvents were screened to minimize the production of **3a** and **4a** (entries 6 and 7); moreover, a shortening of the reaction time from 84 to 48 h was only possible in toluene (entry 7). Next, the utility of various hydrosilanes was evaluated; however, the yields of **2a** could not be improved (entries 8−11). Additionally, the reaction was attempted with 2 and 4 equiv of $BnMe_2SiH$ in toluene, where **2a** was obtained in yields of 75% and 76%, respectively (entries 12 and 13). When 2 equiv of a structurally similar $PhMe_2SiH$ was used in toluene, **2a** was produced in 83% yield without any byproducts (entry 14). Based on this

Table 1. Optimization of Reaction Conditions[a]



entry	solvent/temp (°C)/time (h)	2a/3a/4a[b] (%)
1	DCM/60 °C/60 h	0/0/29
2	chloroform/60 °C/84 h	N.D.
3	DCE/80 °C/60 h	N.D.
4	benzene/100 °C/96 h	N.D.
5	chlorobenzene/120 °C/84 h	80/12/5
6	dichlorobenzene/120 °C/48 h	57/15/8
7	toluene/120 °C/48 h	78/6/3
8[c]	toluene/120 °C/60 h	48/12/0
9[d]	toluene/120 °C/120 h	48/27/1
10[e]	toluene/120 °C/120 h	31/0/0
11[f]	toluene/120 °C/60 h	N.D.
12[g]	toluene/120 °C/12 h	75/21/0
13[h]	toluene/120 °C/7 h	76/13/0
14[i]	toluene/120 °C/3 h	83/0/0
15[h]	dichlorobenzene/120 °C/2 h	92/2/0
16[h,j]	dichlorobenzene/120 °C/12 h	no rex
17[k]	dichlorobenzene/120 °C/12 h	no rex
18[l]	toluene/120 °C/1.5 h	0/1/98
19[l,m]	solvent/60 °C/2 h	0/5/93
20[l,n]	toluene/60 °C/1.5 h	0/3/94

[a]Reactions were carried out with **1a** (0.2 mmol), 10 mol % $B(C_6F_5)_3$, and $BnMe_2SiH$ (1.2 mmol) in solvent (0.1 M). [b]Isolated yield. [c]Ph_2MeSiH. [d]Et_3SiH. [e]Ph_3SiH. [f]Ph_2SiH_2. [g]$BnMe_2SiH$ (0.8 mmol). [h]$BnMe_2SiH$ (0.4 mmol). [i]$PhMe_2SiH$ (0.4 mmol). [j]No $B(C_6F_5)_3$. [k]No silane. [l]Et_2SiH_2 (0.4 mmol). [m]DCE, chloroform, chlorobenzene, or dichlorobenzene. [n]5 mol % $B(C_6F_5)_3$.

result, the reaction of **1a** with 2 equiv of $BnMe_2SiH$ in the presence of 10 mol % $B(C_6F_5)_3$ was performed in dichlorobenzene at 120 °C for 2 h to provide the highest yield of **2a** (92%) and a trace amount of **3a** (entry 15). Furthermore, various catalysts such as BPh_3, BEt_3, and $BF_3{\cdot}O(C_2H_5)_2$ have been investigated, but the decomposition of **1a** was observed in all cases. The control reaction, performed without $B(C_6F_5)_3$ or $BnMe_2SiH$, did not yield any adducts (entries 16 and 17), and the use of Et_2SiH_2 instead of $BnMe_2SiH$ allowed the formation of **4a**[8] in an excellent yield of 98% (entry 18). Even at a lower temperature of 60 °C, the reactions worked well in various solvents to afford **4a** (entry 19). We further examined the reaction to achieve a lower $B(C_6F_5)_3$ catalyst loading. Surprisingly, the reaction of **1a**, with Et_2SiH_2 in the presence of 5 mol % $B(C_6F_5)_3$ in toluene at 60 °C for 1.5 h, afforded indoline **4a** and indole **3a** in yields of 94% and 3%, respectively (entry 20).

With the optimized reaction conditions in hand, we explored the substrate scope of indolin-3-one synthesis, as shown in Scheme 2. The reaction with 5-methyl-1-tosylisatin **1b**,[4b,5] prepared using tosyl chloride and TEA, proceeded well to deliver **2b**[2b,c] in a yield of 88%, while 5-methyl-1-tosylindole **3b**[14b,c] was isolated in 7% yield by column chromatography. Analogues **1c**, **1d**,[5] and **1e**[4b,5] produced the corresponding products **2c**,[2b,c] **2d**,[2b,c] and **2e**[2b,c] in 85%, 84%, and 76% yields, respectively; at the same time, undesired indoles **3c**,[14b,d,15] **3d**,[14d,16] and **3e**[14b,d,15] were generated in low yields. 5-Bromo-1-tosylisatin **1f**[4c] reacted smoothly to deliver the desired product **2f**[2b,c] in 74% yield without the formation of indole

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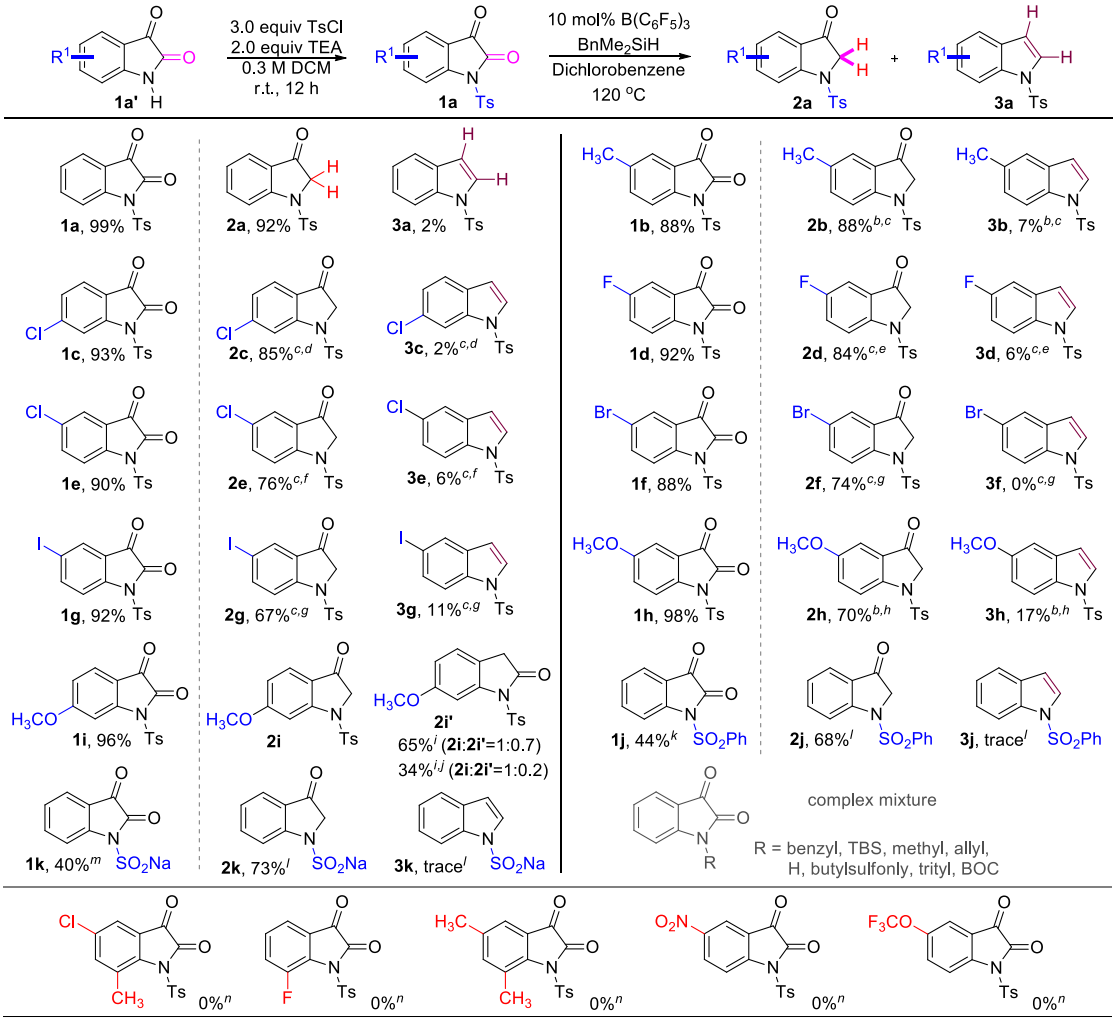
Scheme 2. Substrate Scope of Indolin-3-one Synthesis[a]



[a]Reaction conditions: tosyl isatin **1a** (0.2 mmol), $BnMe_2SiH$ (2.0 equiv), $B(C_6F_5)_3$ (10 mol %), dichlorobenzene (0.1 M), 120 °C, 2 h. The yields are isolated yields. [b]24 h. [c]$BnMe_2SiH$ (4.0 equiv). [d]72 h. [e]84 h. [f]36 h. [g]48 h. [h]$BnMe_2SiH$ (5.0 equiv). [i]6 h. [j]$BnMe_2SiH$ (3.0 equiv). [k]Benzenesulfonyl chloride was used instead of tosyl chloride. [l]1.5 h. [m]Naphthalenesulfonyl chloride was used instead of tosyl chloride. [n]No tosylation reaction.

3f.[14b,17] 5-Iodo-1-tosylisatin **1g** was also tolerated and yielded the adducts **2g** and **3g**[18] in yields of 67% and 11%, respectively. Similarly, utilizing 5-methoxy-1-tosylisatin **1h**[6] as the substrate furnished **2h**[2b,c] and **3h**[14b,c,15] in yields of 70% and 17%, respectively. Interestingly, 6-methoxy-1-tosylisatin **1i** produced a mixture of regioisomers, **2i** and **2i′** with **2i**:**2i′** = 1:0.7, which were completely isolated by column chromatography, with a combined yield of 65% without indole. When **1i** was treated with 3 equiv of $BnMe_2SiH$ and 10 mol % $B(C_6F_5)_3$, a mixture of regioisomers **2i** and **2i′** was obtained in 34% yield with **2i**:**2i′** = 1:0.2. In addition to the tosyl protecting group, *N*-benzenesulfonyl- and *N*-naphthalenesulfonylisatin generated the desired products **2j**[19] and **2k** in the yields of 68% and 73%, respectively. In contrast, isatin derivatives with diverse protecting groups such as benzyl, TBS, methyl, allyl, butylsulfonyl, trityl, or BOC could not be converted to the expected products. Notably, the selective reduction of isatins was attributed to electronic effects, whereby strongly electron withdrawing protecting groups like tosyl, benzenesulfonyl, or naphthalenesulfonyl increased the reactivity of the substrates. Unfortunately, 1-tosylisatin containing a methyl or fluoro substituent at the C7 position or a nitro or trifluoromethoxy substituent at the C5 position could not be synthesized under various tosylation conditions due to unfavorable steric and electronic effects.

Next, we focused on the substrate scope of the indoline synthesis, as represented in Scheme 3. Under the optimized reaction conditions detailed in entry 20 of Table 1, the reaction of 5-methyl-1-tosylisatin **1b** gave rise to the corresponding product **4b**[8b,9] in 69% yield, without the generation of **3b**. With the use of chloro-substituted tosylisatins **1c** and **1e**, the desired products **4c** and **4e**[8b] were furnished in good yields of 71% and 75%, respectively. Similarly, the expected products **4d**[8b] and **4f**[8b] were obtained in 76% and 71% yields, respectively, from their respective precursors under these reaction conditions. The reaction with **1g** furnished the product **4g**[10] in 77% yield, even though **3g** was isolated in 17% yield. In the case of 1-tosylisatins bearing a methoxy group at the C5 or C6 position, the targeted products **4h**[11] and **4i**[8c] were prepared in moderate yields of 32% and 56%, respectively, while in contrast to other substrates, the yields of indoles **3h** and **3i**[15] were higher (66% and 22%, respectively)

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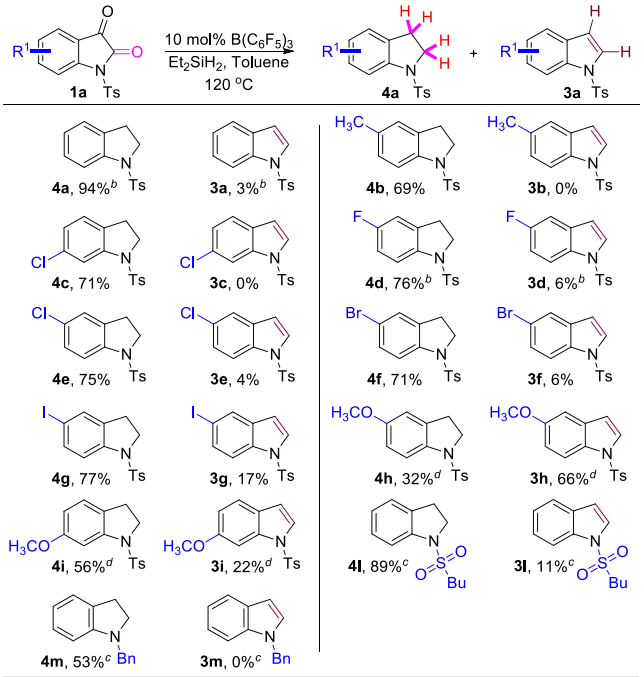
Scheme 3. Substrate Scope of Indoline Synthesis[a]

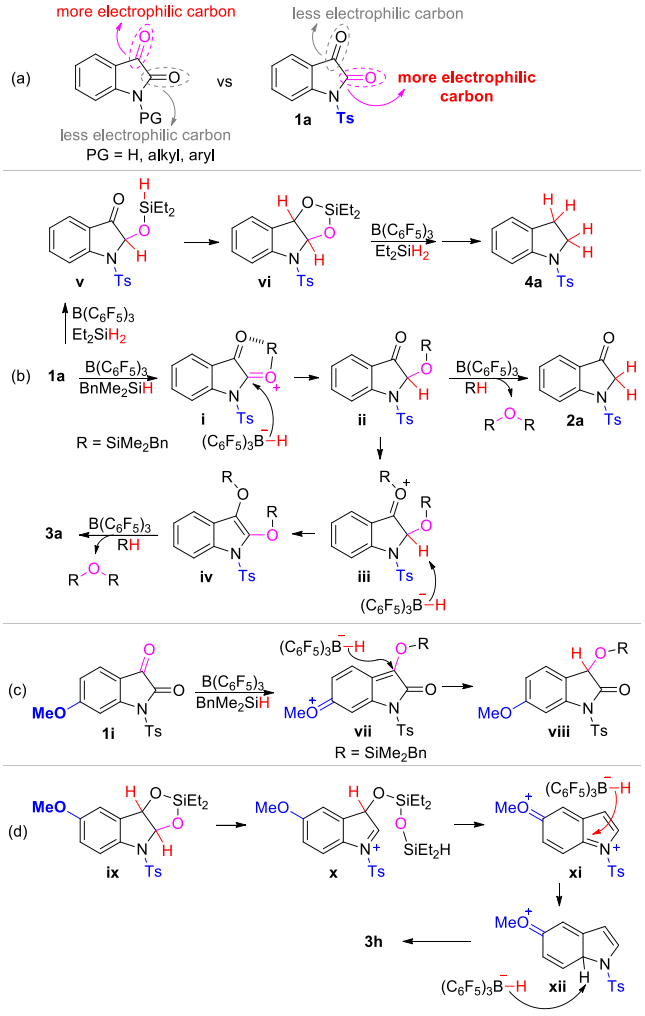


[a]Reaction conditions: tosyl isatin (0.2 mmol), Et_2SiH_2 (2.0 equiv), $B(C_6F_5)_3$ (10 mol %), toluene (0.1 M), 120 °C, 2 h. Above shown yields are the isolated yields. [b]$B(C_6F_5)_3$ (5 mol %), 60 °C, 1.5 h. [c]60 °C. [d]Et_2SiH_2 (4.0 equiv).

for these substrates. The reaction with *N*-butylsulfonyl- and *N*-benzyl-protected isatins **1l**[4c] and **1m**[7] led to give the corresponding products **4l**[12] and **4m**[8b,13] in yields of 89% and 53%, respectively.

Based on the experimental results, we propose a possible reaction mechanism for the formation of **2a** from isatin **1a** via a selective reduction reaction shown in Scheme 4. Generally, the electrophilicities of the carbonyl groups at the C2 and C3 positions of isatin are known to be different; the carbonyl at C3 of diverse isatins is more electrophilic than the carbonyl at C2 (Scheme 4a). Thus, several reactions, such as reduction, nucleophilic addition, or condensation reactions, occur at the C3 position carbonyl group to generate the corresponding adducts. In contrast, reversed reactivities of the carbonyl groups in isatin toward the $B(C_6F_5)_3/BnMe_2SiH$ catalytic system were observed because of the introduction of a tosyl-protecting group in nitrogen. Remarkably, the strong electron-withdrawing protecting group had changed the distribution of electron density in isatin, which resulted in higher reactivity at the C2 position carbonyl group. Taking into account the distribution of the electron density in isatin, we proposed that the electrophilic silane associated with $B(C_6F_5)_3$ coordinates with the carbonyl groups at C2 and C3 positions to produce intermediate **i**, which is attacked by the hydride from borohydride at the more electrophilic C2 position (Scheme 4b). The generated intermediate **ii**[20] reacts with $B(C_6F_5)_3/BnMe_2SiH$ again to transform **2a** by releasing silyl ether. The trace amounts of intermediate **ii** react with electrophilic silylium cations at the C3 position carbonyl group to produce **iii**, which is converted to **iv** by the abstraction of vicinal hydrogen from hydride. Finally, **3a** is synthesized by hydrosilylation and silicon-assisted β-elimination.[21] Similarly, intermediate **v** is formed by treating with $B(C_6F_5)_3/Et_2SiH_2$,

Scheme 4. Proposed Reaction Mechanism



which allows continuous intramolecular hydrosilylation to give *O*-silyl hemiaminal species **vi**. Further reaction of **vi** with $B(C_6F_5)_3/Et_2SiH_2$ produces **4a**. In the case of 6-methoxy-1-tosylisatin **1i**, the unanticipated oxindole **2i′**, in which the C3 position is reduced, is obtained (Scheme 4c). We believe that the 6-methoxy substituent donates a lone-pair electron to the isatin backbone, which activates the C3 position for reacting with the electrophilic silylium cation. The activated species **vii** is easily reduced by hydride to produce **viii**, which converts to oxindole **2i′**. In another possible pathway, **3h** is obtained as a major product from **1h** utilizing $B(C_6F_5)_3/Et_2SiH_2$, as illustrated in Scheme 4d. Intermediate **ix** reacts with the electrophilic silylium cation, followed by the release of silyl ether, which is triggered by electron-donation from nitrogen. Next, silyl ether is completely released by the activation of the methoxy group in **x**; simultaneously, hydride addition occurs to the carbon of iminium **xi**. Finally, to reform the aromatic compound, benzene, a hydrogen from **xii** is abstracted by borohydride, resulting in the formation of **3h**.

In conclusion, we have demonstrated the first $B(C_6F_5)_3$-catalyzed selective reduction of isatins for the synthesis of indolin-3-one and indoline derivatives. The indolin-3-one skeleton, which is ubiquitous in pharmaceutical and natural products, is a material of interest requiring facile, efficient, and general synthetic approaches for its development. The developed synthetic strategy features a simple single-step

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reaction with metal-free conditions and broad functional group tolerance and does not require lengthy synthetic steps to generate the key reaction precursors. Moreover, the acidic α-hydrogen of indolin-3-ones enables various further transformations, such as aldol, carbonyl α-substitution, and oxime formation reactions. Further investigations aimed at expanding the substrates of this methodology are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03150.

Experimental procedures, characterization data, and copies of all ^{1}H and ^{13}C NMR spectra for all isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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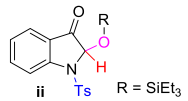

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