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ISSN: 2096-3246
Volume 58, Issue 01, 2026

# $SC(OTF)_3$ AND ACIDIC SILICA INDUCED A MILD AND EFFICIENT REDUCTIVE AMINATION USING AN ORGANOREDUCING AGENT

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**Abstract**

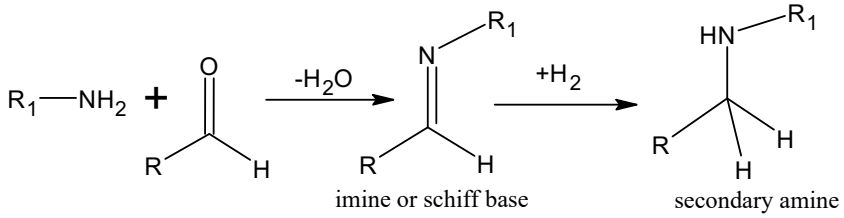
Reductive amination of carbonyl compounds continues to be a fundamental strategy for the synthesis of structurally diverse amines, which are key intermediates in medicinal chemistry and the preparation of complex natural products. In this study, we present an efficient protocol for the reductive amination of aldehydes with aryl amines using a dual catalytic system based on Scandium(III) triflate [$Sc(OTf)_3$] supported on acidic silica. The Lewis acid–mediated activation of the carbonyl group is coupled with Hantzsch-1,4-dihydropyridine (HEH) as a biomimetic organic hydride donor. Under optimized conditions in toluene at room temperature, a wide range of secondary amines were obtained with excellent chemoselectivity and high isolated yields. The protocol proceeds under mild conditions, avoids harsh reagents, and exhibits broad functional-group tolerance, highlighting its potential as a practical and environmentally benign approach for amine synthesis.

**Keywords:** Reductive Amination, Hantzsch-1,4-dihydropyridine (HEH), Scandium triflate, acidic silica, organo reducing agent, room temperature.

## Introduction

In both biological and chemical systems, reductive amination[1-3] is a very successful method for creating secondary or tertiary amines. This procedure usually consists of two steps: first, an intermediate (imine) is synthesized, and then, in the second step, the imine is reduced (see Scheme 1). The intermediate imine is frequently neither stable nor isolable. Therefore, the in situ formation and subsequent reduction of imines is the most practical and preferred method for producing saturated amines from carbonyl compounds and amines.

Reductive amination is also used in nature, where pyridoxal phosphate serves as a coenzyme in all transamination reactions. The natural conversion of pyridoxal phosphate into pyridoxamine phosphate in the presence of aminotransferase further exemplifies this process. [4-5]




**Scheme 1:** Reductive amination.

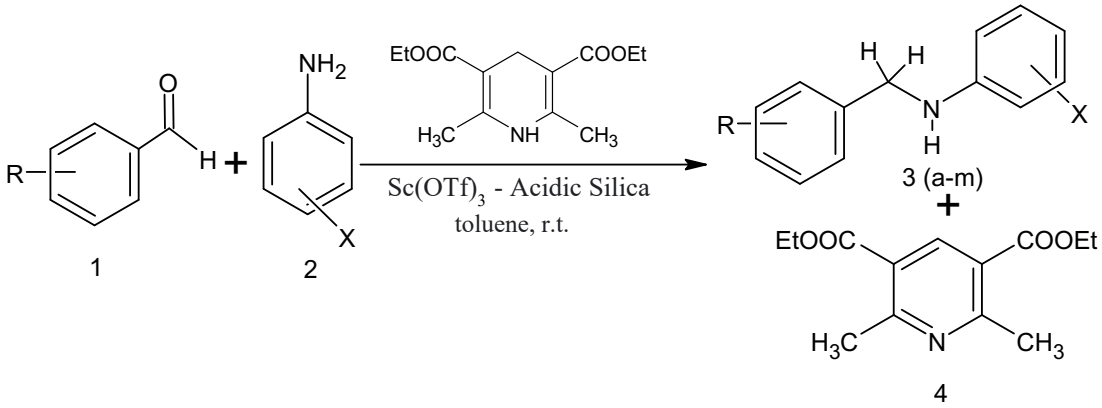
Therefore, there are numerous methods in the literature to perform this direct process, including $NaBH_3CN$, borohydride derivatives $NaBH(OAc)_3$, $Ti(O^i\text{-}Pr)_4$-$NaBH_4$, $NaBH_4$-$ZnCl_2$, $NaBH_4$-$NiCl_2$, $NaBH_4$-$H_3PW_{12}O_{40}$, $NaBH_4$ silica phosphoric acid, and N-methylpyrrolidine zinc borohydride, $NaBH_4$-$Mg(ClO_4)_2$, $NaBH_4$–wet clay, silica gel–$Zn(BH_4)_2$, $[Zr(BH_4)_2Cl_2(dabco)_2]$, $NaBH_4$ in micellar media, N–methylpiperidine zinc borohydride, Sodium cyanoborohydride and tin hydride[6-20] etc. Several previously reported methods have drabacks, including dependence on catalytic hydrogenation, incompatibility with compounds that contain C=C or C≡C bonds, and sensitivity to other reducible functional groups. Additionally, some reported procedures require severe reaction conditions and an atmosphere of argon or nitrogen, which raises the cost of the process.[21-24] Therefore, the development of novel and simple catalytic method for a mild direct reductive amination is still an important research objective for researchers.

Triflate salts offer several clear advantages as catalysts. They are more stable than many traditional catalysts, can be easily recovered and reused, and they also work well even in the presence of water. Because of these useful features, triflates have been widely applied in different organic reactions, including important transformations such as Aldol reactions, Diels-Alder reactions, Mukaiyama aldol reactions, Ugi condensation reactions, alkylations, Prins-type cyclization reactions, and the synthesis of benzodiazepines, Friedel-Crafts Acylation Reactions, Michael additions, among others.[25-31] Metal triflate catalyzed reductive amination procedures are also well documented in.[32-33] Keeping these points in mind, the present method uses scandium triflate $[Sc(OTf)_3]$ supported on acidic silica as the catalyst, along with Hantzsch-1,4-dihydropyridine (HEH) as a mild organic reducing agent. The reaction is carried out in toluene at room temperature under gentle conditions. A key highlight of this approach is its excellent selectivity: only the C=N bond is reduced, while other functional groups such as C=C double bonds and aldehyde (–CHO) groups remain unchanged. As a result, the desired amines are obtained in very good yields.

**Results and Discussion**

First, we prepared fresh Hantzsch 1,4-dihydropyridine (HEH) following the standard procedure reported in the literature. After that, we began our study by testing a direct reductive amination between benzaldehyde and aniline. For this reaction, scandium triflate $[Sc(OTf)_3]$ supported on acidic silica was used as the catalyst, while the freshly prepared and well-dried HEH served as the reducing agent. The reaction was performed by simply mixing benzaldehyde, aniline, and HEH in a 1:1:1.2 ratio, along with a catalytic amount of the $Sc(OTf)_3$–acidic silica system (0.1:0.5), in 20.0 mL of toluene at room temperature. The progress of the reaction was monitored by TLC until benzaldehyde was completely consumed. Under these mild conditions, the desired product, N-

benzylaniline (3a), was obtained in very good yield, without reduction of benzaldehyde and HEH was oxidized quantitatively to the corresponding pyridine derivative (**Scheme 2**).




**Scheme 2:** Reductive Amination using HEH and $Sc(OTf)_3$-Acidic silica at Ambient Temperature.

The use of a less amount of catalyst led to a decrease in product yield. On the other hand, increasing the catalyst loading beyond the optimized amount did not lead to any significant improvement in either the reaction rate or the overall yield. Similarly, we found that the best results were obtained when 1.2 mmol of Hantzsch 1,4-dihydropyridine (HEH) was used for every 1.0 mmol of aldehyde. Once the reaction conditions were optimized, the scope of the method was explored with a wide variety of aldehydes and amines. As shown in Table 1, this protocol successfully produced a broad range of structurally diverse secondary amines. Importantly, the reaction proceeded smoothly regardless of whether the aromatic ring contained electron-withdrawing or electron-donating substituents. Even sensitive functional groups such as –CHO, C=C, –OMe, and $–NO_2$ were well tolerated under these mild conditions.

**Table 1:** Synthesis of secondary amines via Reductive Amination using HEH and $Sc(OTf)_3$-Acidic silica at Ambient Temperature.

| S.N. | R | X | Product[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H | H | **3a** | 45 | 86 |
| 2 | 4-MeO | H | **3b** | 55 | 83 |
| 3 | 2-Cl | H | **3c** | 50 | 86 |
| 4 | 4-Cl | H | **3d** | 50 | 82 |
| 5 | 2-$NO_2$ | H | **3e** | 55 | 80 |
| 6 | 4-$NO_2$ | H | **3f** | 55 | 82 |
| 7 | H | 4-Cl | **3g** | 50 | 83 |
| 8 | H | 4-$NO_2$ | **3h** | 55 | 80 |
| 9 | H | 4-MeO | **3i** | 55 | 84 |
| 10 | H | 4-Me | **3j** | 40 | 83 |
| 11 | 4-$NO_2$ | 4-MeO | **3k** | 55 | 84 |
| 12 | 2-Me | 4-Cl | **3l** | 45 | 84 |
| 13 | H | 2-OH | **3m** | 55 | 80 |

[a]All the products were identified by comparison of their physical and spectral data with those of authentic samples.
[b]Isolated yields.

Overall, the clean reaction profile and the gentle reducing nature of HEH provided excellent chemoselectivity, with reduction occurring exclusively at the C=N bond. As a result, the desired amines were obtained in high yields without affecting other sensitive functional groups.

**Experimental**

All experiments were carried out using oven-dried glassware. Reagent-grade chemicals were obtained from commercial suppliers and used as received without additional purification. Melting points were measured using a Labotech melting point apparatus MPA350. Infrared (IR) spectra were recorded in KBr discs on a Perkin-Elmer FTIR spectrometer. $^1$H NMR spectra were recorded on a BRUKER AVANCE II 400 NMR spectrometer in $CDCl_3$/DMSO-$d_6$ using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck).

**General procedure for the synthesis of secondary amines (3a-m).**

In a typical procedure, an aldehyde (1.0 mmol), aniline (1.0 mmol), freshly prepared and well-dried Hantzsch 1,4-dihydropyridine (HEH, 1.2 mmol), and scandium triflate (0.1 mmol) supported on acidic silica (0.5 mol) were stirred in dry toluene (20.0 mL) at room temperature for the appropriate time (see Table 1) to afford the corresponding secondary amines (3a–m). The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was filtered, and the solid residue was washed with $CH_2Cl_2$ (2 × 10 mL). The solvent was then removed under reduced pressure to obtain the crude product. Purification was carried out by column chromatography on silica gel (60–120 mesh), using a mixture of ethyl acetate and petroleum ether containing 1% triethylamine as the eluent, to yield the pure amine products. The synthesized secondary amines were further characterized by comparing their physical properties and spectral data with those of authentic samples.

**Physical and spectral data of some selected compounds:**

**N-Benzylaniline 3a**: Liquid. IR (KBr): 1320, 1496, 1590, 2921, 3418 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 4.05 (br s, 1H), 4.36 (s, 2H), 6.56-6.91 (m, 3H), 7.08-7.36 (m, 7H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 46.20, 113.39, 117.40, 126.61, 127.30, 128.41, 139.90, 142.11, 149.81. ESI-MS: m/z 184 $(M+H)^+$.

**N-(4-Chlorobenzyl)benzenamine 3d**: Liquid. IR (KBr): 1100, 1318, 1468, 1600, 2925, 3681 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 4.03 (br s, 1H), 4.31 (s, 2H), 6.63-6.88 (m, 3H), 7.01-7.25 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 47.69, 112.86, 117.47, 128.96, 129.04, 138.06, 147.81. ESI-MS: m/z 218, 220 $(M+H)^+$.

**N-(4-Nitrobenzyl)benzenamine 3f**: Liquid. $^1$H NMR (400 MHz, $CDCl_3$): δ 4.33 (s, 2H), 5.11 (br s, 1H), 6.45-6.61 (m, 3H), 7.01-7.29 (m, 4H), 8.04-8.09 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 46.22, 113.46, 117.23, 120.87, 127.86, 129.60, 146.46, 148.94. ESI-MS: m/z 229 $(M+H)^+$.

**N-Benzyl-4-methoxybenzenamine 3i**: White solid, m.p. 46-47°C. IR (KBr): 1320, 1451, 1598, 2935, 3432 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 4.03 (br s, 1H), 4.23 (s, 2H), 6.61-6.75 (m, 4H), 7.25-7.41 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 49.71, 56.88, 114.37, 127.51, 128.73, 140.16, 144.12, 152.18. ESI-MS: m/z 214 $(M+H)^+$.

**N-Benzyl-2-hydroxybenzenamine 6m**: White solid, m.p. 79-80°C. IR (KBr): 1320, 1480, 1595, 2946, 3410 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 4.01 (br s, 1H), 4.30 (s, 2H), 5.17 (br s, 1H), 6.58-6.67 (m, 3H), 6.96–7.25 (m, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 48.50, 112.41, 113.53, 118.09, 121.67, 127.44, 127.70, 129.58, 136.69, 140.31, 144.76. ESI-MS: m/z 200 $(M+H)^+$.

## Conclusions

In conclusion, the present protocol provides a mild, efficient, and highly selective approach for the reductive amination of aldehydes with amines under convenient reaction conditions. The transformation is effectively mediated by scandium triflate supported on acidic silica in toluene at ambient temperature. This method offers several practical advantages, including the use of inexpensive reagents, a simple operational procedure, excellent product yields, and an easy work-up process. Moreover, Hantzsch 1,4-dihydropyridine (HEH) serves as an efficient, safe, and environmentally benign reducing agent for the direct reduction of imines. Overall, this protocol represents a clean and straightforward strategy for the synthesis of secondary amines, making it attractive not only from a synthetic standpoint but also from the viewpoint of ecological sustainability and green chemistry.

## Acknowledgements

The authors gratefully acknowledge the Sophisticated Analytical Instrument Facility (SAIF), Central Instrument Laboratory, Panjab University, Chandigarh, for providing spectral analysis support. The authors also express their sincere thanks to Guru Nanak College Budhlada and Mata Gujri College, Fatehgarh Sahib for their assistance and facilities.

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