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# Tin-Catalyzed Selective Reductive Hydroamination of Alkynes for the Synthesis of Tertiary Amines

Onkar S. Nayal,[a,b] Maheshwar S. Thakur,[a,b] Manoranjan Kumar,[a,b]
Sushila Sharma,[a,b] and Neeraj Kumar[a,b,*]

[a] Department of Natural Product Chemistry and Process Development, CSIR-Institute of Himalayan Bioresource Technology, Palampur, Himachal Pradesh 176 061, India
[b] Academy of Scientific and Innovative Research, Anusandhan Bhawan, 2 Rafi Marg, New Delhi 110001, India
E-mail: neerajnpp@rediffmail.com or neeraj@ihbt.res.in

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**Abstract:** A unique preference of tin(II) for aniline activation is disclosed. In the present work tin(II) triflate-catalyzed highly selective Markovnikov reductive hydroamination of internal as well as terminal alkynes is reported. The mechanistic study revealed the involvement of two steps in one pot wherein alkyne reduces to corresponding alkene in presence of PMHS as reducing agent followed by hydroamination of alkene. A broad range of alkynes transformed into tertiary amines with good to excellent yield. This method is equally applicable in synthesis of secondary amines.

**Keywords:** alkynes; C–N cross coupling; hydroamination; secondary amines; tertiary amines

## Introduction

Tertiary amines are widely present in biologically active natural products,[1] pharmaceuticals,[2] agrochemicals, dyes and polymers (Figure 1). The most convenient methods used for the synthesis and functionalization of amines mainly include reductive amination,[3] C–N cross-coupling,[4] nucleophilic addition to imines,[5] and C–H nitrogen insertion.[6] Hydroamination, wherein addition of an N–H bond occurred across an unsaturated C–C bond, is an alternative, simple, atom-economic and synthetically more efficient route to the functionalization of amines.

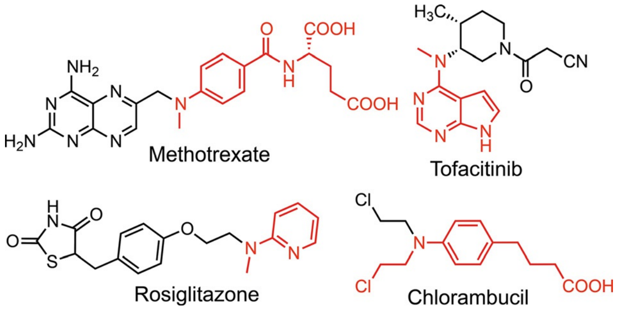


**Figure 1.** Pharmaceutical agents that feature tertiary amine motif.

Hydroamination/reductive hydroamination of alkynes with primary amines are generally reported with heterogeneous as well as homogeneous catalysts such as early transition[7] and late transition metals,[8] lanthanides and actinides metal complexes.[9] In recent years a selective number of researchers have contributed to the synthesis of tertiary amines through hydroamination of alkenes. The Lalic,[10] Hartwig,[11] Miura,[12a] and Buchwald groups[12b] demonstrated transition metal-catalyzed hydroamination of alkenes with secondary amines for the synthesis of tertiary amines. All these methods were more focused on the functionalization of aliphatic amines. Though metal-catalyzed hydroamination of alkynes for the synthesis of secondary amines are reported,[13,14] these methods included few examples of tertiary amines. Recently, Taillefer, Monnier and co-workers described the synthesis of tertiary amines from terminal alkynes and aliphatic secondary amines, using copper cyanide catalyst and $NaBH_3CN$ as a reducing agent,[15] and Yuan, Yao and co-workers reported zirconium catalyzed reductive hydroamination of alkynes with tetrahydroquinoline and its derivatives in presence of $LiAlH_4$ as a reducing agent.[16a] The Stradiotto group described the ligand-assisted gold-catalyzed intermolecular hydroamination of alkyne with dialkylamines.[16b] Despite the progress, however, to the best of our knowledge, reductive hydroamination of alkynes with secondary arylamines for the synthesis of tertiary amines is not reported to date. The challenges associated with the non-reactivity of secondary arylamines towards reductive hydroamination can be ascribed to their higher nucleophilicity that makes them strongly coordinated with metal salt, and the electrostatic repulsion between the more electron rich secondary arylamines and π-electrons of alkyne. We recently reported a catalytic method for the synthesis of tertiary amines featuring tin-catalyzed reductive amination of carbonyl compounds with secondary arylamines.[3c] During this work, a unique compatibility of tin salts with secondary arylamines was observed. Keeping in view the existing challenges of reductive hydroamination using secondary arylamines, we thought to explore the possibility of developing tin-catalyzed reductive hydroamination of alkynes for the synthesis of tertiary amines. To our delight, tin(II) triflate/PMHS/ethanol was found to be an efficient catalyst system for the hydroamination of alkynes with *N*-alkylanilines. Tin(II) triflate is readily available and insensitive to water and air. Similarly PMHS is a cheap, easy to handle, air and moisture stable, environment friendly reducing agent, and its by-product, polysiliconate, is used in silicon industries as an absorbent.[17]

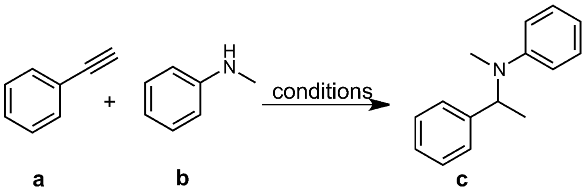
## Results and Discussion

The work was initiated by using phenylacetylene (**a**) and *N*-methylaniline (**b**) as model substrates for reductive hydroamination in presence of Lewis acidic tin(II) chloride as a catalyst (Table 1). With tin(II) chloride, a 17% GC yield of desired amine was obtained (Table 1, entry 1). A previous study has shown that the counter ions play an important role in the feasibility of this type of reaction.[18] After evaluation of various Lewis salts, we found that triflate counter anion showed excellent activity with tin as compared to other counter ions (Table 1, entries 2–4). Zinc, iron, copper, bismuth and other metal salts did not catalyze the reaction (Table 1, entries 5–11). During the optimization of the catalyst loading, 10 mol% of tin salt showed excellent activity (Table 1, entry 2). Further increase or decrease in the catalyst loading led to reduced yield (Table 1, entries 13–16). The reaction did not proceed in the absence of catalyst (Table 1, entry 12). Among the solvents screened, aprotic solvents such as toluene and benzene proved to be the most effective in facilitating the transformation (Table 1, entries 17–21). Although EtOH and water alone did not favor the formation of desired product (Table 1, entry 22-23), their additive role in enhancing the reaction rate is observed (Table 1, entry 2 and SI, Table S1, entries 6–8), EtOH was found to be a suitable additive, with enhanced rate of reaction and yield (SI, Table S1, entries 9–11). However methanol and *n*-propanol as additive gave comparable yield of the amine (Table 1, entries 24–25). The investigation of different silanes as a reducing agent such as triethylsilane, phenylsilane, diphenylsilane and triphenylsilane showed very low yield of desired amine (Table 1, entries 26–30). PMHS was revealed to be most effective reducing agent with enhanced yield (97%) of desired amine (Table 1, entry 2). A decrease in temperature from 120 to 110 °C resulted a sluggish reaction and only trace amount of product was observed, while no change in the yield was observed above 120 °C (Table 1, entries 33–34).

With an optimized set of conditions in hand, the scope of both the alkynes and secondary amine partners were evaluated. A range of tertiary amines have been prepared in moderate to excellent yields (Table 2). Easily available halogen substituted alkynes were well tolerated and corresponding amines obtained in good to excellent yields (Table 2, **3a**–**3d**, **3i** and **3j**). Fluorine substituted alkynes and amines smoothly gave good yields (Table 2, **3b**–**3e**), which are highly used in pharma industry.[19] In addition to substituted aromatic alkynes, we found that 4-*tert*-butyl and 4-methyl substituted aromatic alkynes readily participated in catalytic reductive hydroamination to deliver the respective product in high yields (Table 2, **3e**–**3g**). *N*-Ethylaniline was also well tolerated with both electron withdrawing as well as electron donating group substituted alkynes (Table 2, **3i**–**3l**). Terminal aliphatic alkynes such as 3-cyclohexyl-1-propyne, cyclohexylacetylene and cyclopentylacetylene with *N*-ethylaniline and *N*-methylaniline gave excellent yield of respective amines in shorter reaction time (Table 2, **3m**–**3p**). 4-Fluoro-*N*-methylaniline with cyclopentylacetylene gave excellent yield of desired amine and 4-trifluoromethoxyphenylacetylene with *N*-methylaniline achieved good yield of amine (Table 2, **3q**–**3s**). Hindered secondary amine such as *N*-benzyl-4-methoxyaniline also gave good yield of corresponding amines with phenylacetylene (Table 2, **3t**). Electron withdrawing group substituted aliphatic alkyne such as ethyl propiolate with secondary anilines, 4-fluoro-*N*-methylaniline, *N*-methyl- and *N*-ethylaniline afforded anti-Markovnikov products (Table 2, **3u**–**3w**). The observation of inverse regioselectivity indicated the involvement of conjugate addition–reduction pathway in these reactions. The formation of stable enamine intermediate in absence of PMHS further supported this pathway (See SI, Scheme S1).

Internal alkynes such as diphenylacetylene gave moderate yields of desired amine with *N*-methyl- as well as *N*-ethylaniline (Table 2, **3x** and **3y**) without formation of any side product. *N*-Methyl- and *N*-ethylaniline were well compatible with 9-ethynylphenan-

**Table 1.** Optimization of reaction conditions for reductive hydroamination of phenylacetylene with *N*-methylaniline.[a]



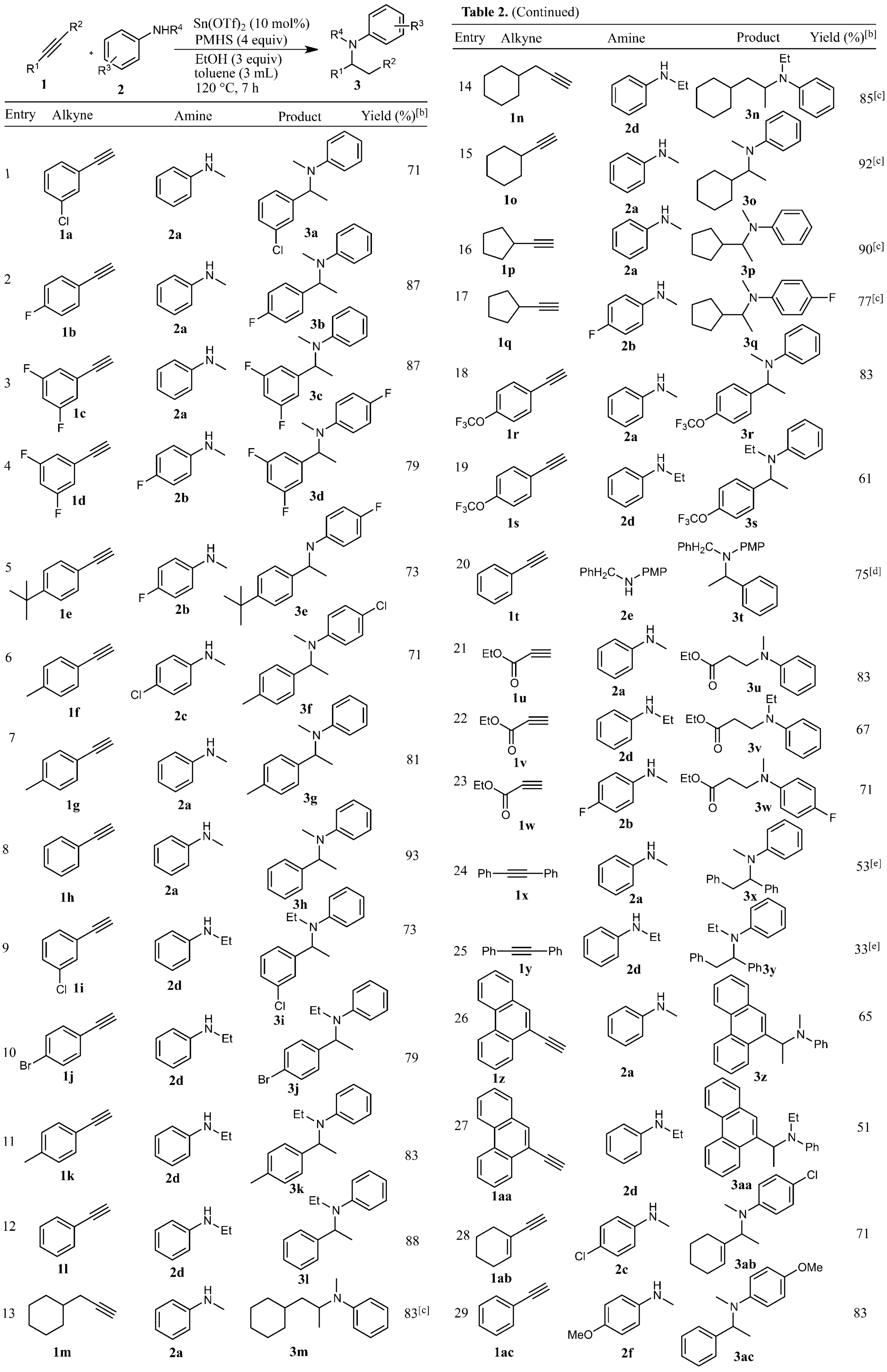
| Entry | Catalyst | Hydride source | Additive | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $SnCl_2$ | PMHS | EtOH | Toluene | 17 |
| **2** | $Sn(OTf)_2$ | PMHS | EtOH | Toluene | 97 |
| 3 | $SnBr_2$ | PMHS | EtOH | Toluene | 10 |
| 4 | $Sn(OAc)_2$ | PMHS | EtOH | Toluene | NR |
| 5 | $ZnCl_2$ | PMHS | EtOH | Toluene | NR |
| 6 | $FeCl_2$ | PMHS | EtOH | Toluene | NR |
| 7 | $CuCl_2$ | PMHS | EtOH | Toluene | NR |
| 8 | $Cu(OTf)_2$ | PMHS | EtOH | Toluene | NR |
| 9 | $Bi(OTf)_3$ | PMHS | EtOH | Toluene | NR |
| 10 | $CoCl_2$ | PMHS | EtOH | Toluene | NR |
| 11 | $AlCl_3$ | PMHS | EtOH | Toluene | NR |
| 12 | – | PMHS | EtOH | Toluene | NR |
| 13 | $Sn(OTf)_2$ | PMHS | EtOH | Toluene | 78[c] |
| 14 | $Sn(OTf)_2$ | PMHS | EtOH | Toluene | 77[d] |
| 15 | $Sn(OTf)_2$ | PMHS | EtOH | Toluene | 64[e] |
| 16 | $Sn(OTf)_2$ | PMHS | EtOH | Toluene | 73[f] |
| 17 | $Sn(OTf)_2$ | PMHS | EtOH | Benzene | 90 |
| 18 | $Sn(OTf)_2$ | PMHS | EtOH | THF | NR |
| 19 | $Sn(OTf)_2$ | PMHS | EtOH | ACN | NR |
| 20 | $Sn(OTf)_2$ | PMHS | EtOH | DMF | NR |
| 21 | $Sn(OTf)_2$ | PMHS | EtOH | DMSO | NR |
| 22 | $Sn(OTf)_2$ | PMHS | – | Ethanol | NR |
| 23 | $Sn(OTf)_2$ | PMHS | – | $H_2O$ | NR |
| 24 | $Sn(OTf)_2$ | PMHS | MeOH | Toluene | 92 |
| 25 | $Sn(OTf)_2$ | PMHS | *n*PrOH | Toluene | 86 |
| 26 | $Sn(OTf)_2$ | $Et_3SiH$ | EtOH | Toluene | 47 |
| 27 | $Sn(OTf)_2$ | $PhSiH_3$ | EtOH | Toluene | 35 |
| 28 | $Sn(OTf)_2$ | $Ph_2SiH_2$ | EtOH | Toluene | 27 |
| 29 | $Sn(OTf)_2$ | $Ph_3SiH$ | EtOH | Toluene | – |
| 30 | $Sn(OTf)_2$ | $MeSiH(OEt)_2$ | EtOH | Toluene | 75 |
| 31 | $Sn(OTf)_2$ | – | EtOH | Toluene | NR |
| 32 | $Sn(OTf)_2$ | PMHS | – | Toluene | 88 |
| 33 | $Sn(OTf)_2$ | PMHS | EtOH | Toluene | NR[g] |
| 34 | $Sn(OTf)_2$ | PMHS | EtOH | Toluene | 97[h] |

[a] Reaction conditions: Catalyst (10 mol%), **a** (1 mmol), **b** (1 mmol), reducing agent (4 mmol), EtOH (3 mmol), solvent (3 mL), 120 °C, 7 h, under air.
[b] GC yield using hexadecane as internal standard.
[c] Quantity of catalyst used was 5 mol%.
[d] Quantity of catalyst used was 15 mol%.
[e] Quantity of catalyst used was 3 mol%.
[f] Quantity of catalyst used was 20 mol%.
[g] The reaction was carried out at 110 °C.
[h] The reaction was carried out at 130 °C.

threne to form desired amines in good yields (Table 2, **3z** and **3aa**). Unsaturated aliphatic alkyne such as cyclohexenylacetylene afforded good yield of desired aniline with *N*-methylaniline (Table 2, **3ab**). Phenylacetylene was well tolerated with 4-methoxy-*N*-methylaniline to give excellent yield of desired amine (Table 2, **3ac**).

The scope of the method was further extended for the reductive hydroamination of terminal alkynes with primary amines which afforded excellent yields of the corresponding secondary amines with high chemoselectivity (Table 3). Recently, Sakai and co-workers reported indium-catalyzed reductive hydroamination of terminal alkyne.[14] The Beller group also de-

**Table 2.** Reductive hydroamination of alkynes with secondary amines.[a]



| Entry | Alkyne | Amine | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | **2a** | **3a** | 71 |
| 2 | **1b** | **2a** | **3b** | 87 |
| 3 | **1c** | **2a** | **3c** | 87 |
| 4 | **1d** | **2b** | **3d** | 79 |
| 5 | **1e** | **2b** | **3e** | 73 |
| 6 | **1f** | **2c** | **3f** | 71 |
| 7 | **1g** | **2a** | **3g** | 81 |
| 8 | **1h** | **2a** | **3h** | 93 |
| 9 | **1i** | **2d** | **3i** | 73 |
| 10 | **1j** | **2d** | **3j** | 79 |
| 11 | **1k** | **2d** | **3k** | 83 |
| 12 | **1l** | **2d** | **3l** | 88 |
| 13 | **1m** | **2a** | **3m** | 83[c] |
| 14 | **1n** | **2d** | **3n** | 85[c] |
| 15 | **1o** | **2a** | **3o** | 92[c] |
| 16 | **1p** | **2a** | **3p** | 90[c] |
| 17 | **1q** | **2b** | **3q** | 77[c] |
| 18 | **1r** | **2a** | **3r** | 83 |
| 19 | **1s** | **2d** | **3s** | 61 |
| 20 | **1t** | **2e** | **3t** | 75[d] |
| 21 | **1u** | **2a** | **3u** | 83 |
| 22 | **1v** | **2d** | **3v** | 67 |
| 23 | **1w** | **2b** | **3w** | 71 |
| 24 | **1x** | **2a** | **3x** | 53[e] |
| 25 | **1y** | **2d** | **3y** | 33[e] |
| 26 | **1z** | **2a** | **3z** | 65 |
| 27 | **1aa** | **2d** | **3aa** | 51 |
| 28 | **1ab** | **2c** | **3ab** | 71 |
| 29 | **1ac** | **2f** | **3ac** | 83 |

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[a] Reaction conditions: Sn(OTf)$_2$ (10 mol%), **1** (1 mmol), **2** (1 mmol), PMHS (4 mmol), EtOH (3 mmol), toluene (3 mL), 120 °C under air.

[b] Isolated yield.

[c] The reaction completed in 4 h.

[d] The reaction completed in 6 h.

[e] The reaction was carried out using 15 mol% catalyst and completed in 9 h.

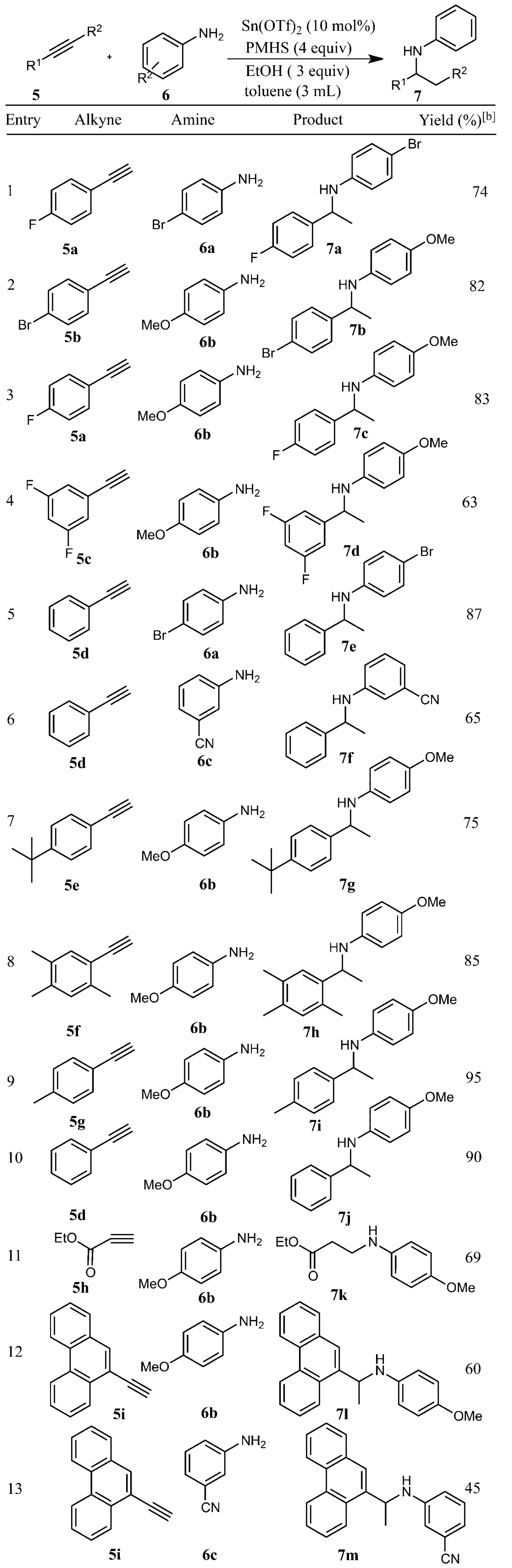
veloped an efficient method for reductive hydroamination of terminal alkyne using zinc triflate and hydrogen.[20] Li et al. described reductive hydroamination of alkyne with primary aniline using gallium trichloride as catalyst with $LiAlH_4$ as a reducing agent.[13]

In the present method, halogen substituted alkynes were well tolerated without dehalogenation of substrate and gave good to excellent yield of secondary amines (Table 3, **7a**–**7d**). Electron withdrawing substituted amines such as 4-bromoaniline and 3-cyanoaniline were also well tolerated to give good yield of desired amine (Table 3, **7e** and **7f**). The reaction of 4-anisidine with substituted aromatic alkynes such as 4-*tert*-butylphenylacetylene and 2,4,5-trimethylphenylacetylene proceeded smoothly to give desired amines in good to excellent yield (Table 3, **7g**–**7h**). 4-Anisidine also reacted efficiently with phenylacetylene (Table 3, **7j**). 4-Anisidine was well tolerated with ethyl propiolate and gave good yield of desired amine (Table 3, **7k**). 9-Ethynylphenanthrene gave good yield of desired amines with the primary amines substituted with an electron donating group as well as with an electron withdrawing group (Table 3, **7l** and **7m**), and no other by-product was observed. Unfortunately the present method was unsuccessful with primary and secondary aliphatic amines.

To investigate the mechanistic pathway different control experiments were carried out (Scheme 1). Under standard reaction conditions (Scheme 1a), *N*-1-phenylethyl-*N*-methylaniline was observed as sole product, while decreasing the quantity of PMHS from 4 to 2 equivalent resulted in the formation of the desired amine (67%) along with alkene as minor product (29%) (Scheme 1b). Additionally when 4-ethynyltoluene was heated under standard reaction conditions in the absence of aniline, corresponding alkene was observed as major product (45% GC–MS yield) (Scheme 1g). These experiments clearly indicated the intermediacy of alkene in present reaction condition. To rule out the involvement of enamine pathway, the model reaction was carried out in the absence of PMHS. As expected, the susbstrate remained as such and no enamine intermediate formation was observed (Scheme 1c). However, in case of electron deficient aliphatic alkyne such as ethyl propiolate, conjugate addition product i.e., corresponding enamine was observed in the absence of PMHS (Scheme 1e). So we speculate conjugate addition-reduction pathway is followed in this particular case.

Further we assumed that $Sn(OTf)_2$ plays an important role in the activation of *N*-methylaniline through the formation of tin amidinium complex (**A**). To find out the formation of **A**, $^{1}H$ and $^{13}C$ NMR of the mixture of $Sn(OTf)_2$ and *N*-methylaniline was studied (See, SI, Figures S1a to S1d). $^{1}H$ NMR clearly showed the downfield shift in *ortho*/*para* ($\Delta\delta \approx 0.81$),

**Table 3.** Reductive Hydroamination of Alkynes with Primary Amines.[a]



| Entry | Alkyne | Amine | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 5a | 6a | 7a | 74 |
| 2 | 5b | 6b | 7b | 82 |
| 3 | 5a | 6b | 7c | 83 |
| 4 | 5c | 6b | 7d | 63 |
| 5 | 5d | 6a | 7e | 87 |
| 6 | 5d | 6c | 7f | 65 |
| 7 | 5e | 6b | 7g | 75 |
| 8 | 5f | 6b | 7h | 85 |
| 9 | 5g | 6b | 7i | 95 |
| 10 | 5d | 6b | 7j | 90 |
| 11 | 5h | 6b | 7k | 69 |
| 12 | 5i | 6b | 7l | 60 |
| 13 | 5i | 6c | 7m | 45 |

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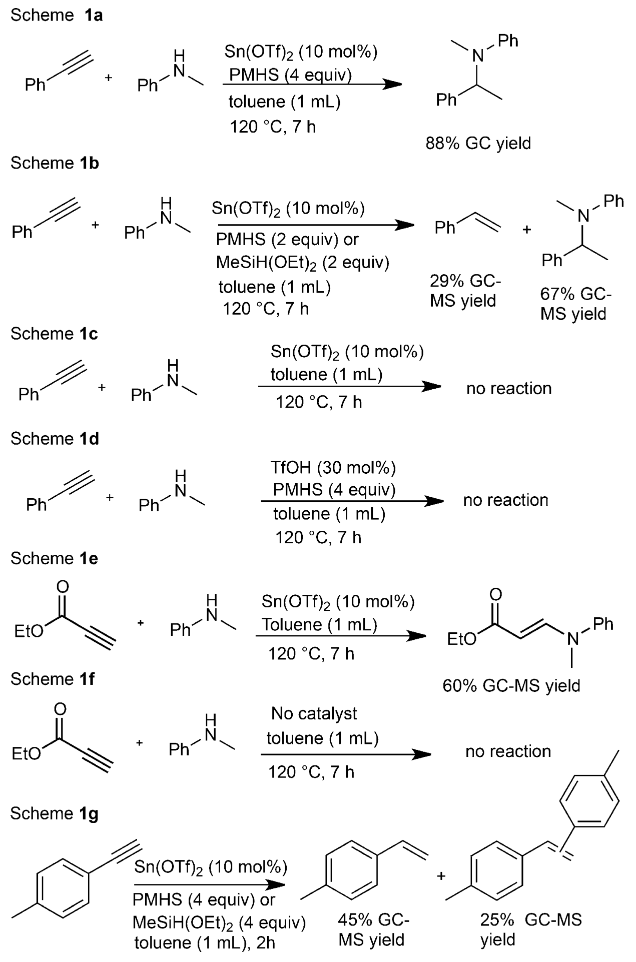
[a] Reaction conditions: $Sn(OTf)_2$ (10 mol%), **1** (1 mmol), **4** (1 mmol), PMHS (4 mmol), EtOH (3 mmol), toluene (3 mL), 120 °C under air for 7 h.

[b] Isolated yield.



**Scheme 1.** Controlled experiments.

*meta* ($\Delta\delta \approx 0.47$) and methyl protons ($\Delta\delta \approx 0.37$) of *N*-methylaniline. Similarly in $^{13}$C NMR, while other carbons are shifted downfield, significant upfield shift in aromatic carbon ($\alpha$-carbon) directly attached to nitrogen atom (17.7 ppm) and $\gamma$-carbon (2.3 ppm) is observed due to the formation of anilinium complex.

Next the UV-vis study of the mixture of $Sn(OTf)_2$ and *N*-methylaniline showed a hypsochromic shift in the $\lambda_{max}$ of *N*-methyaniline from 297 to 283 nm, which further supported the formation of **A** (see SI, Figure S2a and S2b). Moreover the $^{19}$F NMR study of mixture of $Sn(OTf)_2$ and *N*-methylaniline showed a slight downfield shift from $\delta$ −79.2 to −78.9 (Figure 2 and see SI, Figures S3a, S3b and S3c) due to interaction of $Sn(OTf)_2$ with *N*-methylaniline. Also during this experiment, in $^{19}$F NMR, peak corresponding to triflic acid was not observed which ruled out the in situ formation of triflic acid.

On the basis of above experiments and literature findings,[21] a plausible mechanim is proposed (Scheme 2).

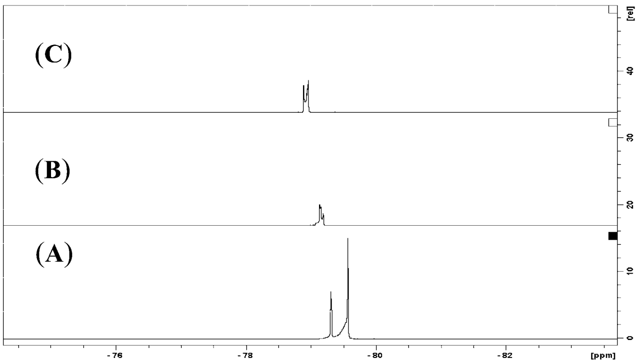
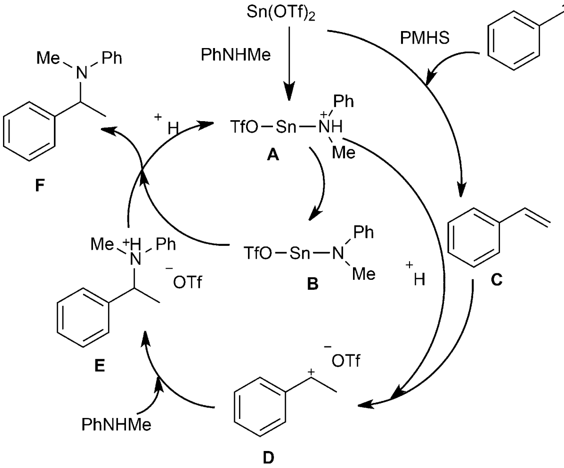


**Figure 2.** $^{19}$F NMR spectras of triflic acid (**A**), tin (II) triflate (**B**) and mixture of tin(II) triflate and *N*-methylaniline (**C**) in equivalent ratio of $C_6D_5CD_3/CD_3OD$.



**Scheme 2.** Proposed Mechanism.

Initially phenylacetylene is reduced to styrene (C) in the presence of $Sn(OTf)_2$ and PMHS. Meanwhile $Sn(OTf)_2$ interacts with *N*-methylaniline to form tin(II) amidinium complex (A) which protonate the styrene (C) to form the benzylic cation D. Further *N*-methylaniline attacks the cationic centre of D to form E which is deprotonated in the presence of B to form the product along with the regeneration of A.

## Conclusions

In conclusion, a novel $Sn(OTf)_2$ catalyzed reductive hydroamination reaction of terminal as well as internal alkynes using secondary aniline as a nucleophile was developed. The method provides an economical synthesis of a series of tertiary amines as well as secondary amines by using inexpensive, stable and easy to handle PMHS as reducing agent.

## Experimental Section

All reagents and solvents were obtained from commercial suppliers and were used without further purification for all reaction. Column chromatography was carried out with 60–120, 100–200 and 230–400 mesh silica gel and monitored with TLC on silica gel 60 F254 plates using UV light as visualizing agent. $^1$H and $^{13}$C NMR spectra were obtained on 300 MHz and 600 MHz instruments. Chemical shifts are reported in ppm relative to $CHCl_3$ downfield from an internal standard. UV-Vis spectra were recorded on UV-Vis spectrophotometer and Mass spectra were recorded on electrospray ionization quadrupole time of flight (ESI-QTOF-MS) mass spectrometer. The GC analysis was carried out on Gas Chromatogram, an AOC-20i autosampler coupled, and BP 20 capillary column (30 m × 0.25 mm i.d. 0.25 μm). The initial temperature of the column was held at 70 °C for 5 min and was programmed to 230 °C at 4 °C $min^{-1}$, then held for 15 min at 230 °C, the sample injection volume was 1 μL in GC grade dichloromethane. Nitrogen was used as the carrier gas at a flow rate of 1.1 mL $min^{-1}$.

General Procedure for Reductive Hydroamination of alkynes.

To an oven dried 15 mL test tube was added $Sn(OTf)_2$ (0.1 mmol), aniline or *N*-alkylaniline (1.0 mmol), alkyne (1.0 mmol), toluene (3 mL), EtOH (3.0 mmol) and PMHS (4.0 mmol). The test tube was capped and the reaction mixture was then heated to 120 °C under air in an oil bath. After completion of the reaction as observed by TLC, the reaction mixture was allowed to cool, filtered and passed through anhydrous sodium sulphate. The crude product was purified by column chromatography over silica gel (60–120, 100–200 and 230–400 mesh) with *n*-hexane or *n*-heptane and an appropriate mixture of *n*-hexane and ethyl acetate.

**Caution**: tin(II) triflate causes severe skin burns and eye damage. Wear protective gloves, protective clothing, eye protection and face protection.

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