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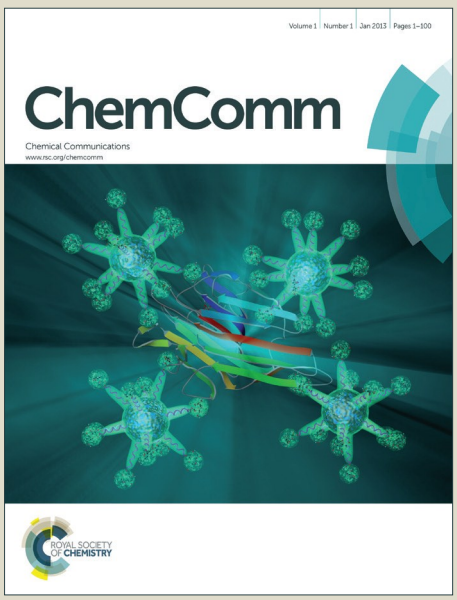

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DOI: 10.1039/C6CC04381J

Journal Name

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Synthesis of tertiary arylamines: Lewis acid-catalyzed direct reductive *N*-alkylation of secondary amines with ketones through an alternative pathway**

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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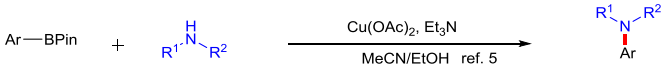
We report herein a highly efficient, tin(II)/PMHS catalyzed reductive *N*-alkylation of arylamines with ketones affording tertiary arylamines. Very wide substrate scope was observed for current catalytic method as all six permutations of ketones/aldehydes/heterocyclic carbonyls and primary/ secondary/ heterocyclic amines were well tolerated, enabling access to secondary, tertiary and heterocyclic amines. The method is also convenient for the synthesis of *N*-substituted isoindolinones and phthalazinones via tandem amination–amidation sequence. Mechanistic investigations revealed carbocationic pathway instead of ordinary direct reductive amination pathway.

Tertiary arylamines are one of the most important class of compounds, widely used in sensor designing,[1] catalysis,[2] nitrogen group insertion,[3] and as synthetic building blocks.[4] Among numerous methods used for the synthesis of tertiary amines, alkylation of amines,[5] direct reductive amination (DRA) of carbonyl compounds[6] and reductive hydroamination of alkynes[7] are the most common approaches (Scheme 1).

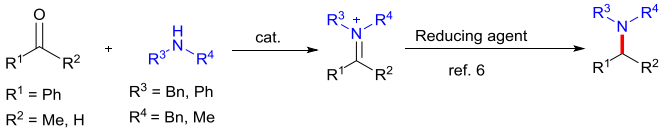
DRA of easily available and cost effective carbonyl compounds is a simple and effective approach for the functionalization of amines. DRA has been mainly used for synthesizing secondary amines,[8] however, the synthesis of tertiary arylamines *via* this pathway is still a challenge.[9] DRA of carbonyl compounds with secondary amines disfavours the formation of iminium ion/enamine product due to steric hindrance. Nevertheless, few reports of DRA of secondary arylamines are available,[6c,d,f] an alternate pathway that can overcome the above difficulties is needed. In our previous study, we found that tin(II) triflate showed specific interaction with arylamine to generate tin(II) amidinium complex, which restricted the enamine or iminium ion formation.[7a] Delighted with this observation, we questioned whether this strategy might be extended for an alternative pathway to DRA.

Previous work

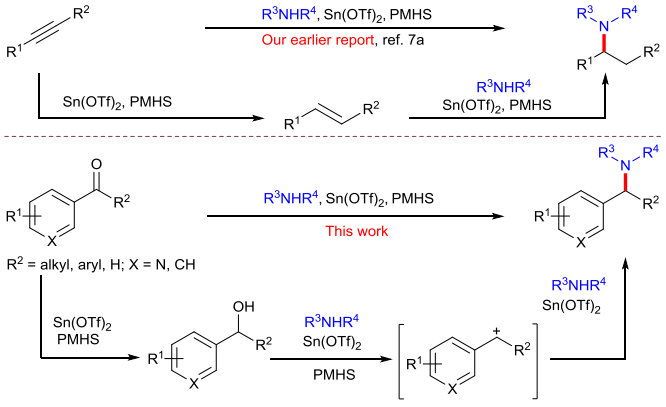
a) *N*-Alkylation of amines



b) Direct reductive amination



c) An alternative pathway



Scheme 1. Approaches for synthesis of tertiary amines.

Although, Chisholm group described Brønsted acid catalyzed *N*-alkylation of aniline by using trichloroacetimidate electrophiles *via* carbenium ion pathway, requirement for pre-activated substrate limit the scope of thismethod.[10] Herein, we report a tin-catalyzed reductive *N*-alkylation of unactivated secondary arylamines with ketones in the presence of polymethylhydrosiloxane (PMHS). PMHS is an economic and

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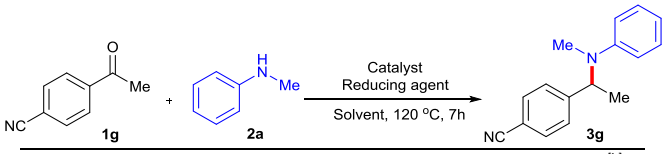
[$] This manuscript is dedicated to Dr. Neeraj Kumar, who deceased on 28th March 2016 while compiling the manuscript. He was a great advisor and a brilliant scientist who is missed by all who knew him.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here. See DOI: 10.1039/x0xx00000x

environment friendly reducing agent.[11] In addition, it is less air and moisture sensitive as compared to other silanes.

We initiated the investigation by using 4-acetylbenzonitrile (**1g**) with *N*-methylaniline (**2a**) as a model substrate (Table 1).

Table 1. Optimization of reaction condition.[a]



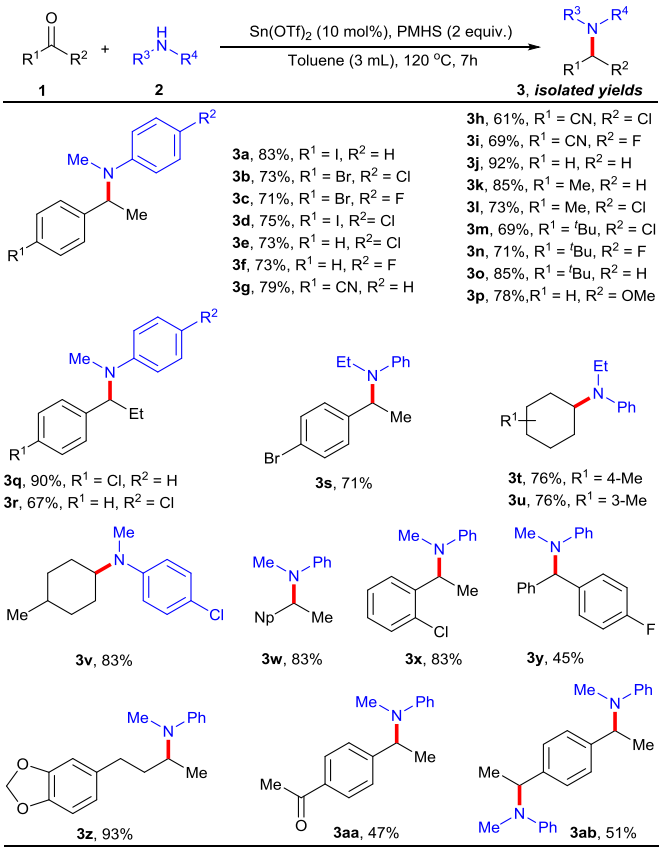
Entry	Catalsyt	Reducing agent	Solvent	Yield (%)[b]
1	**$Sn(OTf)_2$**	**PMHS**	**toluene**	**89**
2	$Sn(OTf)_2$	PMHS	toluene	50[c]
3	$Sn(OTf)_2$	PMHS	toluene	87[d]
4	--	PMHS	toluene	NR
5	$Sn(OTf)_2$	--	toluene	NR
6	$Sn(OTf)_2$	PMHS	toluene	35[e]

[a]Reaction conditions: **1g** (2 mmol), **2a** (1 mmol), catalyst (10 mol%), reducing agent (2 mmol), solvent (3 mL), 120 °C, 7h. [b]GC yield using hexadecane as an internal standard. [c]5 mol% of $Sn(OTf)_2$. [d]15 mol% of $Sn(OTf)_2$. [e]Dry toluene and N_2 atm. NR = no reaction.

When the reductive *N*-alkylation of **2a** was carried out with **1g** in presence of 10 mol% tin(II) triflate and 2.0 equivalent PMHS in toluene at 120 °C for 7h, **3g** was formed in 89% yield (Table 1, entry 1). Decreasing the catalyst loading led to low yield whereas no effect was observed on increasing the catalyst loading (Table 1, entries 2-3). Product was not detected in the absence of either tin(II) triflate or reducing agent PMHS (Table 1, entries 4-5).[12] To improve the reaction efficiency a range of Lewis acid catalysts, reducing agents and solvents were examined (for details, see the Supporting Information, Table S1). Surprisingly, when the reaction was carried out in substantially anhydrous condition under N_2 atmosphere, comparatively low yield was observed (Table 1, entry 6). This observation suggested that traces of water are crucial for the success of the reaction.[13]

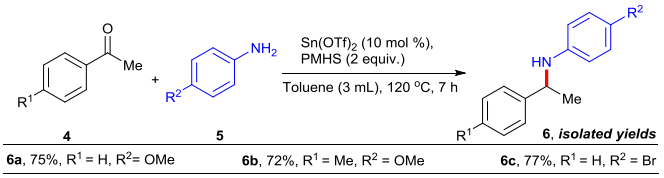
With the optimized reaction conditions substrate scope of the developed method was explored. A wide range of tertiary amines has been prepared in moderate to excellent yields (Table 2). Aromatic ketones bearing halogens and electron withdrawing groups such as cyano at different positions coupled smoothly with *N*-alkylaniline as well as electron deficient aniline (Table 2, **3a**-**3i** & **3x**). The reductive alkylation of *N*-methylaniline with acetophenone and 2-naphthylmethylketone proceeded well to afford the corresponding amines (Table 2, **3j** & **3w**). Alkyl substituents bearing acetophenone were well compatible with electron deficient as well as electron rich anilines providing the desired product in good to excellent yields (Table 2, **3k-3p**). Propiophenone derivatives and 4-Benzo[1,3]dioxol-5-yl-butan-2-one reacted smoothly with aniline moieties, providing good yields of corresponding amines (Table 2, **3q-3r**). Switching from *N*-methylaniline to *N*-ethylaniline and from acetophenone to aliphatic or cyclic ketones did not affect the outcome of the reaction (Table 2, amines **3s-3v & 3z**). 4-Fluorobenzophenone gave the moderate yield of the desired amines which may be due to steric hindrance (Table 2, **3y**). *N*-Methylaniline treated with 1,4-diacetylbenzene to afford both **3aa** and **3ab** in almost equivalent ratio (Table 2, **3aa-3ab**). Unfortunately, no reaction

Table 2. Direct reductive amination of secondary arylamines.[a]



[a]Reaction conditions: $Sn(OTf)_2$ (10 mol%), **1** (2 mmol), **2** (1 mmol), PMHS (2 mmol), Toluene (3 mL), 120 °C. NR = no reaction. Np=naphthyl.

Table 3. Direct reductive *N*-alylation of anilines.[a]



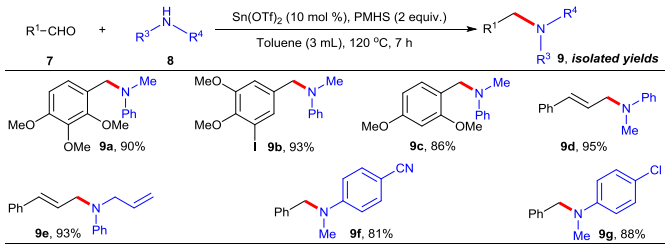
[a]Reaction conditions: $Sn(OTf)_2$ (10 mol%), **4** (2 mmol), **5** (1 mmol), PMHS (2 mmol), Toluene (3 mL), 120 °C.

was observed with secondary aliphatic amines (not shown). Anilines possessing electron donating or electron withdrawing substituents reacted efficiently with ketones to afford the corresponding secondary amines in good yields (Table 3).

Next, amination of aldehydes with secondary arylamines was studied (Table 4). Polysubstituted aldehydes were well tolerated with *N*-methylaniline and gave excellent yield of desired amines (Table 4, **9a-9c**). Excellent chemoselectivity (>99%) and yield was observed for the reaction of cinnamaldehyde with *N*-methylaniline (Table 4, **9d**). Cinnamaldehyde was also well compatible with *N*-allyl aniline (Table 4, **9e**). Furthermore, reductive amination of benzaldehyde proceeded smoothly with electron deficient

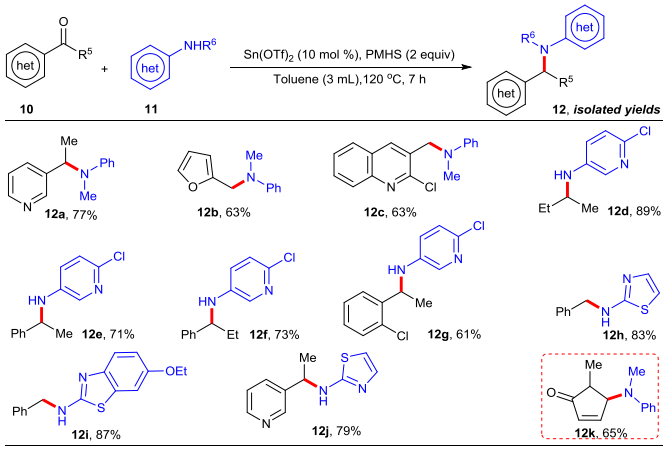
aniline to give products in good yields (Table 4, **9f-9g**). Heteroaromatic amines are common building blocks in the synthesis of drugs and agrochemicals [14] and also an important structural motif in many biologically active compounds, such

Table 4. Direct reductive *N*-alkylation of secondary arylamines with aldehydes.[a]



[a]Reaction conditions: $Sn(OTf)_2$ (10 mol%), **7** (2 mmol), **8** (1 mmol), PMHS (2 mmol), Toluene (3 mL), 120 °C.

Table 5. Synthesis of heterocyclic amines *via* direct reductive *N*-alkylation of amines with carbonyl compounds.[a]

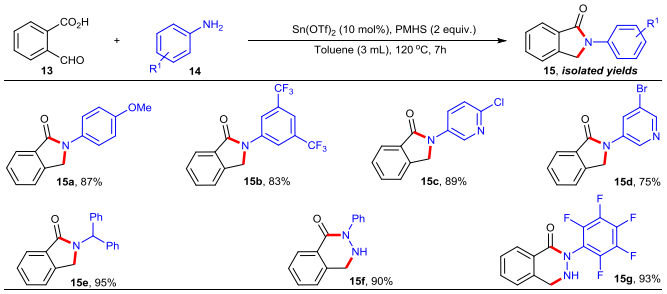


[a]Reaction conditions: $Sn(OTf)_2$ (10 mol%), **10** (2 mmol), **11** (1 mmol), PMHS (2 mmol), Toluene (3 mL), 120 °C.

as UDP-galactopyranose mutase inhibitor, fanetizole (anti-inflammatory agent) and small molecule somatostatin receptor subtype 5 (SST5R) antagonists.[15] Owing to the immense importance of these amines, synthesis ofheterocyclic amines was attempted (Table 5). The heterocyclic carbonyl compounds such as 3-acetylpyridine, furfural and 2-chloro-3-quinolinecarboxaldehyde reacted well with amine **2a** affording the corresponding products in good yields (Table 5, **12a-12c**). A heteroaryl substrate such as 5-amino-2-chloropyridine was also compatible with aliphatic as well as aromatic ketones providing the desired amines in excellent yields (Table 5, **12d-12g**). 2-Aminothiazole and its derivatives also reacted smoothly with benzaldehyde and 3-acetylpyridine to afford desired amines with excellent yields. These compounds are highly demandable in medicinal chemistry due to their antitumor, anticancer and antimicrobial activities (Table 5, **12h-12j**).[16] Surprisingly, the reaction carried out between 2-furylmethylketone and *N*-methylaniline, yielded the unexpected product **12k** (Table 5, **12k**). The formation of **12k** in this case might be proceeding through Aza-Piancatelli rearrgement involving ketone reduction to alcohol which reacted with amine in the presence of Lewis acid.[17]

Furthermore, the scope of the reaction was extended for the synthesis of biologically important[18] *N*-substituted isoindolinones *via* tandem amination–amidation of 2-carboxybenzaldehyde (Table 6). *N*-Substituted isoindolinones have demonstrated a remarkably wide variety of pharmacological activities, including antiinflammatory, antihypertensive, antipsychotic, vasodilatory and anticanceretc.[19] Interestingly, both electron rich and electron deficient anilines delivered the corresponding isoindolinones in excellent yields (Table 6, entries **15a**-**15b**).

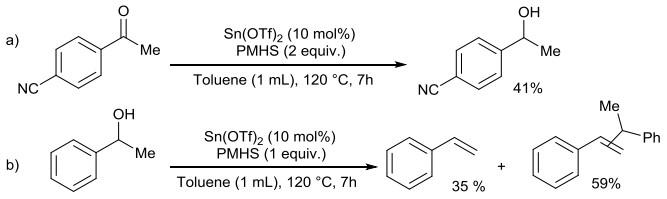
Table 6. Synthesis of *N*-substituted isoindolinones and phthalazinones *via* tandem amination–amidation of 2-carboxybenzaldehyde.[a]



[a]Reaction conditions: $Sn(OTf)_2$ (10 mol%), **13** (1 mmol), **14** (1 mmol), PMHS (2 mmol), Toluene (3 mL), 120 °C.

Heteroaromatic amines such as halogen substituted aminopyridine provided corresponding *N*-substituted isoindolinones in good yields (Table 6, entries **15c**-**15d**). Aliphatic amine also afforded excellent yield of the desired product (**15e**). Phthalazinones were obtained in excellent yields when phenyl hydrazine or substituted phenylhydrazine is used as the nitrogen source instead of amines under standard reaction conditions (**15f-15g**).

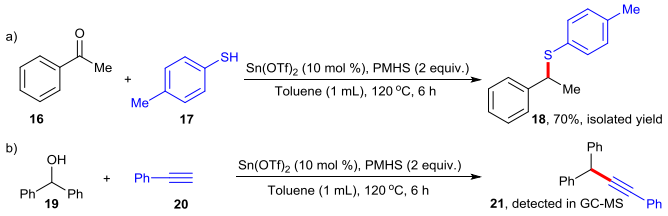
For understanding the reaction pathway various experiments were carried out, where we rule out the possibility of DRA (See SI). Standard reaction in the absence of *N*-methylaniline gave corresponding alcohol in 41% yield (Scheme 2a). When 1-phenylethanol was reacted in absence of *N*-methylaniline, styrene and stilbene derivate were detected, which indicates that reaction might involve carbocation intermediate (Scheme 2b).[20] The formation of **12K** in case of 2-acetylfuran under current reaction condition through Aza-Piancatelli rearrgement also supported the carbocation involvment.[17]



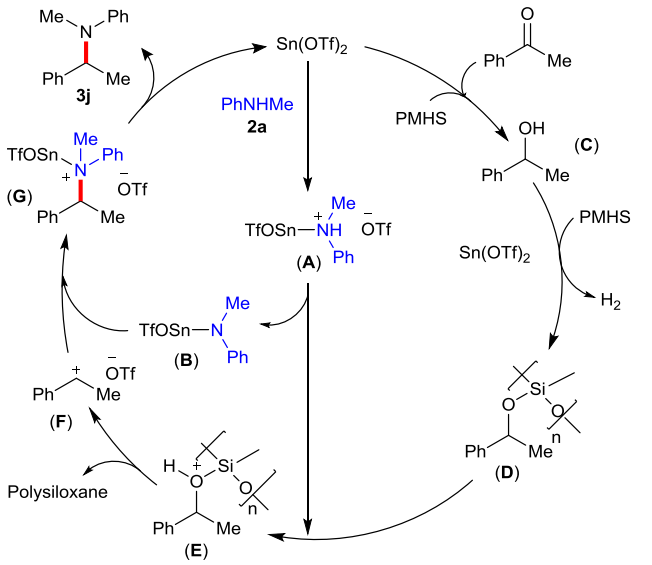
Scheme 2. Control experiments.

To trap carbocation intermediates upon reaction with suitable nucleophiles, substrates **16** and **19** were reacted under the optimized reaction conditions with nucleophiles such as thiol and alkyne (Scheme 3).[21,22] The formation of corresponding products in these cases clearly suggests that the current reaction is proceeding *via* a carbocationic pathway.

On the basis of above various control experiments and our previous study on the unique interaction between tin salts and aniline,[7a] we proposed a possible reaction pathway as depicted in scheme 4. Initially, ketone is reduced to corresponding



Scheme 3. Mechanistic probes for detection of carbocation.



Scheme 4. Proposed reaction mechanism.

alcohol (**C**) in the presence of $Sn(OTf)_2$ and PMHS. Subsequently the alcohol undergoes silylation with PMHS to form *O*-silylated product (**D**). Meanwhile, insertion of *N*-methylaniline into Sn(II) triflate would form tin(II) amidinium complex (**A**) which protonate **D** to form the benzylic cation (**F**) *via* desilylation of **E**. Further tin(II) amide (**B**) attacks the cationic centre of **F** to form **G**. Demetalation of complex **G**, resulted in the formation of product **3j** along with the regeneration of tin(II) triflate.

In conclusion, a novel $Sn(OTf)_2$ catalyzed method with wide substrate scope has been developed for the synthesis of tertiary as well as secondary amines by using PMHS as a reducing agent. Furthermore, the generality of the current catalytic method was demonstrated by the synthesis of biologically important isoindolinones and phthalazinones in good to excellent yields.

The authors are grateful to The Director, CSIR-IHBT for support. M.S.T, V.B. and M.K. thanks UGC for granting research fellowship. This work is inacially supported by CSIR-New Delhi (CSC-0108).

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DOI: 10.1039/C6CC04381J

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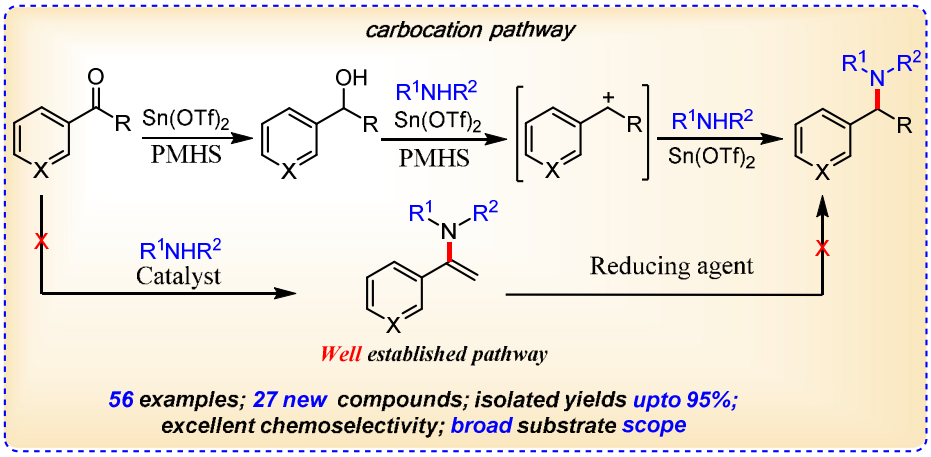

Reductive *N*-alkylation through carbocation pathway