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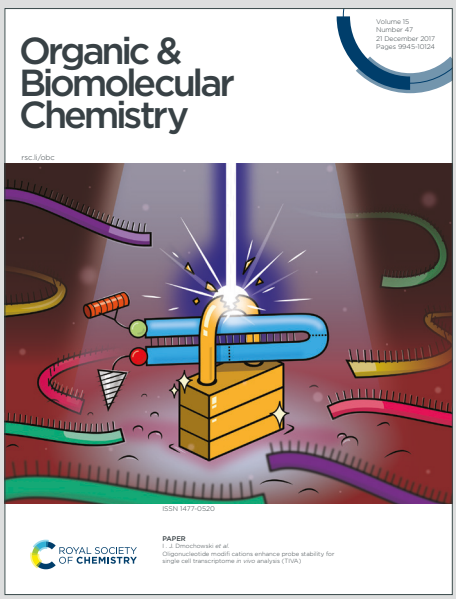

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Catalyst- and Solvent-Free Efficient Access to *N*-Alkylated Amines via Reductive Amination using HBpin

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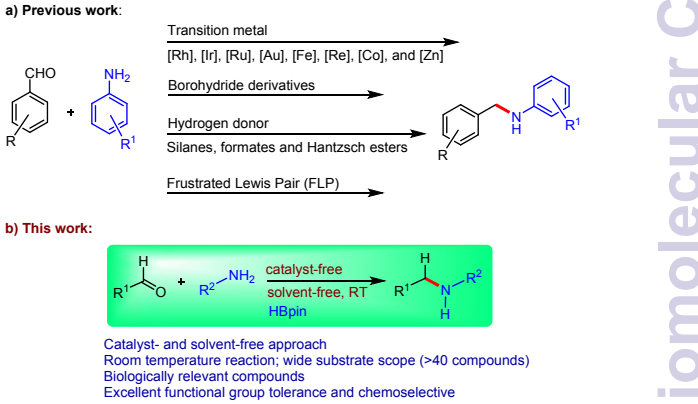
A sustainable approach which works under catalyst- and solvent-free conditions for the synthesis of structurally diverse secondary amines has been uncovered. This one-pot protocol works efficiently at room temperature and compatible with a wide range of sterically and electronically diverse aldehydes and primary amines. Notably, this simple process offers scalability, excellent functional group tolerance, chemoselectivity, and is also effective for the synthesis of biologically relevant molecules.

The widespread applications of the amines and their derivatives in natural products, pharmaceuticals, agrochemicals, dyes, and polymers have raised their demands globally.[1] Thus, developing more improved and efficient protocols to access the amine related compounds is a much demanding research area in synthetic chemistry. Several methods have been devised to access variety of *N*-alkylated amines such as nitrile reduction,[2a] Buchwald-Hartwig amination,[2b] alkylation of amine using alcohol,[2c,d] and the direct reductive amination (DRA).[2a,3] Among the above mentioned protocols, the direct reductive amination of aldehydes is the most acknowledged method for the synthesis of higher *N*-alkylated amines. This is due to the several advantages offered by this method over others such as milder reaction conditions, utilization of the readily available and affordable substrates, compatibility with various functionalities, simple experimental procedures etc.[3] Since the introduction, with the passage of time, reductive amination process has witnessed several modifications and upgradations.[4] Catalytic hydrogenation using H_2 and the use of reducing agents such as borohydrides are the two most familiar ways of performing the reductive amination (Scheme 1a).[3,5a,b-c] Several reports are available based on the precious transition metals (Rh, Ru, Ir)[6] driven reductive amination reactions involving catalytic hydrogenation pathway.[5a,6] However, the efficacy of this method is somewhat restricted as it is not compatible with the multifunctional substrates featuring unsaturated and other reducible functionalities such as nitro, cyano and furyl groups.[7] On the other hand, the commonly employed borohydride based reducing agents also have several limitations such as poor selectivity, generation of toxic byproducts, need of acidic medium and longer reaction duration.[4,5c] These limitations compelled the researchers to develop environment-friendly, economic, and modest catalytic systems for the reductive amination process which is applicable to a broad range of substrates. As a result, some metal-free *N*-alkylation reactions were evolved with reductants such as hydrosilatrane, Hantzsch ester, boranes etc. (Scheme 1a),[8] however, these methods also have certain demerits as they demand longer reaction duration and/or higher reaction temperature, additives, tedious purification methods etc.[7c,8] Recently, Ogoshi and co-workers have introduced a Frustrated Lewis Pair (FLP) system in the reductive amination (Scheme 1a) of poly-functionalized amines and aldehydes however, still using H_2 (practically inconvenient) and elevated reaction temperature.[9]



Scheme 1 Overview of the prior reductive amination and this work.

In recent years, catalyst- and/or solvent-free reactions involving diverse unsaturated functionalities such as carbonyls, carboxylic acid, imines etc., pioneered by the hydroboration of alkenes and alkynes, have gained enormous attention among the researchers.[10] This is mainly driven by the fact that a solvent as well as catalyst-free approach makes any process practically more convenient and greener by avoiding the use of organic solvents and minimizing the waste generation.[11] In line with these efforts, we delved ourselves in developing solvent- and catalyst-free mild reductive amination approaches. Herein, we present a one-pot catalyst- and solvent-free room temperature protocol to access diverse secondary amines via

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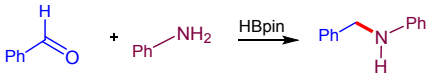
reductive amination using HBpin which offers impressive functional group tolerance as well as the compatibility to access a range of biologically relevant amines.

To find out the feasibility of reductive amination using HBpin, the reaction of benzaldehyde with aniline was chosen as a model reaction. The reaction under neat condition using 1.1 equiv. of HBpin at room temperature (entry 1; Table 1) led to the direct formation of *N*-benzylaniline in 74% yield. *N*-benzylaniline is obtained as the end product possibly via hydrolysis of the imine hydroboration product by H_2O, produced during the generation of the *N*-benzylideneaniline from aniline and benzaldehyde. To our delight, the use of 1.3 equiv. HBpin delivered the *N*-benzylaniline in excellent yield of 91% (entry 2) which, however, slightly reduced to 84% in the absence of molecular sieves (entry 3). Reaction at higher temperature (60 °C) by reducing the reaction duration was not helpful (entry 7). Further, the reactions in organic solvents (entries 4-6) delivered the *N*-benzylaniline in rather less yields of 82-87%. On the basis of these observations, reaction under neat condition using 1.3 equiv. of HBpin was set as optimized conditions for the reductive amination reaction at room temperature.

Table 1 Optimization of the reductive amination reaction [a]



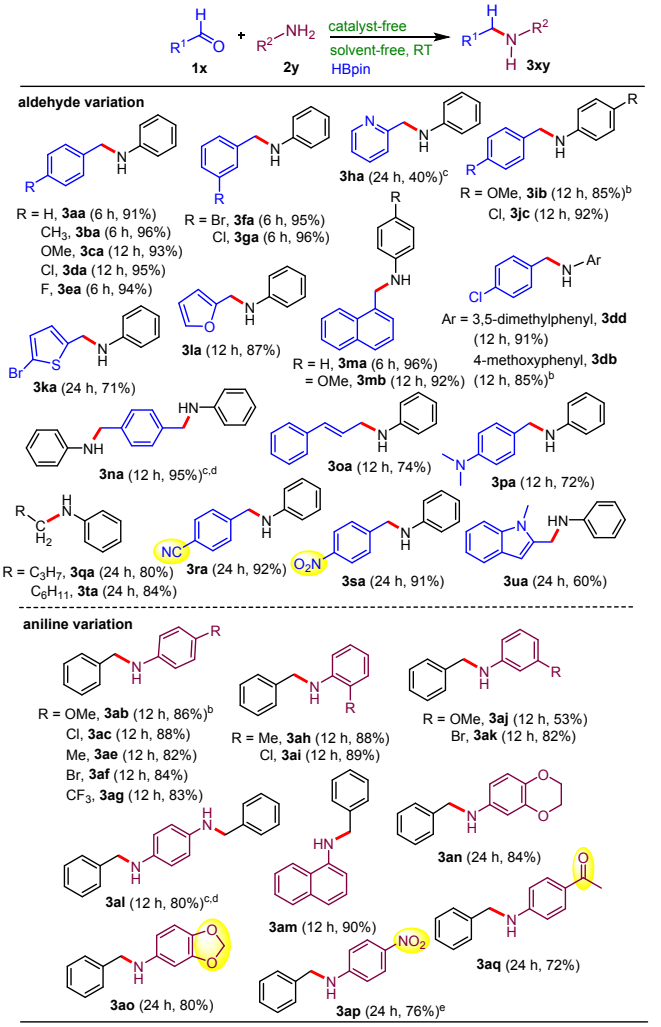
Entry	Solvent	Temperature	Time (h)	Yield (%)[b]
1[c]	-	RT	6	74
2	-	RT	6	91
3[d]	-	RT	6	84
4	Acetonitrile	RT	6	82
5	THF	RT	6	84
6	DCM	RT	6	87
7	-	60 °C	2	77

[a] Reaction condition: benzaldehyde (0.5 mmol), aniline (0.525 mmol), HBpin (0.65 mmol), 6 h, molecular sieves. [b] All are isolated yields. [c] 1.1 equiv. HBpin was used. [d] Without using molecular sieves.

With these optimized reaction conditions, we explored the substrate scope of our present reductive amination protocol. We were pleased to find that various sterically and electronically distinct amines and aldehydes which include aliphatic, (hetero)aromatic, and polyaromatic variants with a wide range of substituents are suitable for this method (Table 2). Notably, reaction proceeds smoothly at room temperature except for a few cases producing the secondary amines in good to excellent yields. First, the potential of this process was probed by reacting aniline with varying aldehydes. Both the electron-withdrawing as well as -donating substituents at the *para*-position of benzaldehyde (**1a-e**) are tolerated to provide the corresponding mono-alkylated amines (**3aa**-**3ea**) in more than 90% yields and importantly, our present method performs better for these substrates than those reported for the FLP, Zn^{II}, and Hantzsch ester based catalytic systems which require higher reaction temperature (60-150 °C) along with higher catalyst loadings.[7c,9,12a] Similarly, *meta*-halo substituted benzaldehydes (**1f-g**) also provided the desired products (**3fa**-**3ga**) in near quantitative yields.

Satisfyingly, the present protocol also enables the reductive amination for a range of heteroaromatic aldehydes such as 2-pyridinecarboxaldehyde (**1h**), 5-bromothiophene carboxaldehyde (**1k**), and furfural (**1l**). Heteroaromatic derived secondary amines **3ka** and **3la** were obtained in good yields (71-87%) at room temperature and it should be noted that our simple protocol is more effective for the synthesis of **3la** than the previous reports on the catalysed reactions which demand higher catalyst loadings, organic solvents, and in addition, higher temperature and/or longer reaction time.[9,12] The picolyl substituted amine **3ha** was obtained in moderate yield. Polyaromatic aldehyde naphthaldehyde (**3m**) is also compatible with our methodology as exemplified by the isolation of **3ma** and **3mb**, however, *p*-OMe substituted aniline requires longer reaction time than aniline to have comparable yield of the secondary amine.

Table 2 Substrate scope for the reductive amination reaction [a]



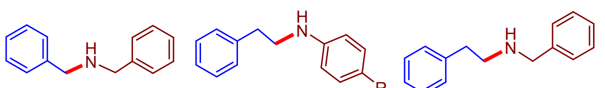
[a] Reaction condition: aldehyde (0.5 mmol), amine (0.525 mmol), HBpin (0.65 mmol), RT, 6-24 h, all are isolated yields. [b] 1.5 equiv. HBpin was used. [c] Reactions were performed at 60 °C. [d] 2.3 equiv. HBpin was used. [e] 0.3 mL DCM was used.

Furthermore, cinnamaldehyde (**1o**) and 1-methylindole-2-carboxyaldehyde (**1u**) which feature alkene functionality, noted to be intolerant towards reductive amination,[13a] also delivered the desired products **3oa** and **3ua**, respectively in good yields (60-74%). Gratifyingly, this approach can also be extended to the one-pot double reductive amination process and the diamine products (**3na** and **3al**) could be isolated in good to excellent yields although a slightly higher temperature of 60 °C is required. Next, the present protocol is also proved to be effective for the nucleophilic dimethylamino substituted benzaldehyde (**1p**) and the mono alkylated amine **3pa** was attained in good yield. It is worth

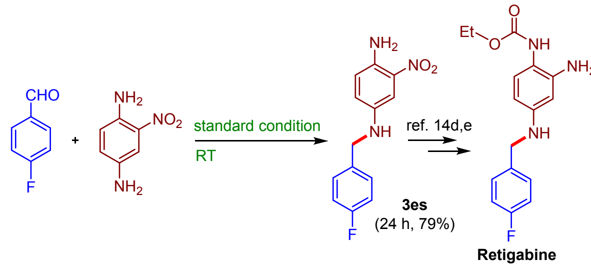
mentioning that *N*,*N*-dimethyl-*p*-toluidine rather than **3pa** was only detected in the previously described FLP mediated reductive amination reaction of **1p** and **2a**.[9] Acyclic longer chain aliphatic aldehydes have been noted to be problematic for some of the reported catalytic systems.[9,13b] However, our method is also suitable for the relatively less reactive aliphatic aldehydes such as *n*-butyraldehyde and cyclohexyl carboxaldehyde and provided the *N*-alkylated anilines **3qa** and **3ta**, respectively at room temperature in competing yields (80-84%) of the previous methods at higher temperature.[12] Remarkably, excellent tolerance towards the nitro and nitrile functionality was also observed and the secondary amines (**3ra** and **3sa**) featuring the nitro and nitrile groups unchanged were exclusively attained in excellent yields (91-92%) at room temperature. Substrates featuring substituents at the phenyl rings of both the aldehyde and aniline also operate well and the desired secondary amines (**3ib**, **3jc**, and **3db**) were realized in excellent yields of 85-92%.

Next, we investigated the substrate scope of the present reductive amination protocol by varying the amine counterparts (Table 2). Accordingly, anilines installed with both the electron-donating and -withdrawing groups at the *para*-position of the *N*-phenyl ring (**2b**-**c** and **2e**-**g**) were utilized and pleasingly, a range of secondary amines (**3ab-ac** and **3ae-ag**) were realized in good yields. The present protocol is found to be relatively more effective for the synthesis of the related secondary amines with variation of the *C*-phenyl ring substituents (**3aa**-**3ea**) than the *N*-phenyl ring substituted variants (**3ab-ac** and **3ae-ag**). Sterically congested anilines such as *o*-toluidine (**2h**) and *o*-chloroaniline (**2i**) are also active and delivered the secondary amines **3ah** and **3ai**, respectively in good yields (88-89%). Satisfyingly, other sterically hindered substrates such as 3,5-dimethylaniline (**2d**) and 1-naphthyl amine (**2m**) can also be utilized to afford the corresponding mono-alkylated amines (**3dd** and **3am**, respectively) in excellent yields of 90-91%. Further, the reaction also proceeds with the *meta*-substituted anilines (**3aj, 3ak**). Gratifyingly, ether-functionalized 1,4-benzodioxan-6-amine (**2n**) and 3,4-methylene-dioxyaniline (**2o**) are also proved to be effective to provide the mono-alkylated amines (**3an** and **3ao**) in good yields. Notably, strongly electron-withdrawing NO_2 group substituted aniline (**2p**) is also compatible and the secondary amine **3ap** was attained in 76% yield. It should be noted that **2p** was previously described to provide the amine **3ap** in lower yield because of the significant amount of benzaldehyde reduction due to less imine formation.[13b] 4-aminoacetophenone is also active and the secondary amine **3aq** with the ketone moiety intact was obtained in 72% yield.

Table 3 Substrate scope for biologically relevant molecules

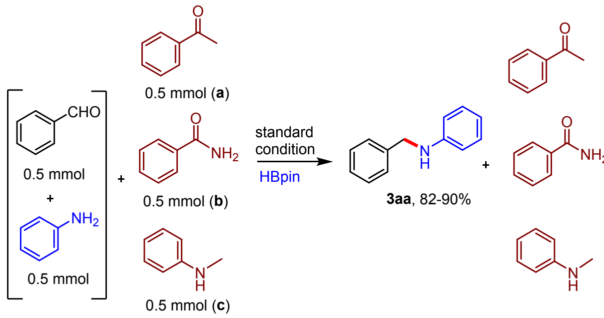


Further, we focused on the synthesis of biologically relevant amines using our present protocol. We were pleased to observe that various secondary amines containing either the 2-phenethylamine or benzylamine core (frequently found in the antiobesity and anticonvulsant drugs)[14a-b] can also be realized by using our mild reductive amination approach (Table 3). Several combinations of the phenylacetaldehyde or benzaldehyde and benzylamine or (substituted)aniline afforded the corresponding secondary amines (**3ar-3vr**) in moderate to excellent yields. The utility of our present protocol was further showcased by the effective synthesis of amine **3es**, precursor for the synthesis of Retigabine (an antileptic drug which mainly works towards the proper functioning of the potassium channel in brain neurons),[14c] at room temperature in good yield of 79% (Scheme 2). It is worth mentioning that the prior reports either demand the isolation of the imine intermediate using an ion exchange resin and/or the higher reaction temperature to produce the **3es** in comparable yield.[1a,14d-e]



Scheme 2 Synthesis of Retigabine.

Next, to explore the chemoselectivity of the present protocol, first, benzaldehyde, aniline, and acetophenone (in 1:1:1 ratio) were reacted and only the formation of *N*-benzylaniline **3aa** was observed (Figure S1) and 86% of acetophenone was also recovered from the reaction (Scheme 3a). This shows that the present protocol is selective to aldehyde over ketone functionality. Similarly, the reaction of benzaldehyde with a 1:1 mixture of aniline and benzamide was carried out and again selectively the *N*-benzylaniline was exclusively formed (Figure S2). Further, the primary amine is preferred over the secondary one (Figure S3) as exemplified by the isolation of *N*-benzylaniline in 82% yield (Scheme 3c) from the reaction of a 1:1 mixture of aniline and *N*-methylaniline with benzaldehyde.



Scheme 3 Chemoselective reductive amination reaction. All are isolated yields.

Satisfyingly, this protocol also works for the large scale synthesis as demonstrated by the one-pot gram scale synthesis of *N*-benzylaniline **3aa** in 82% yield under the optimized conditions (Scheme S1).

To understand the mechanism, a few control experiments were carried out. Reaction of the *N*-benzylideneaniline (intermediate of the reductive amination process) with HBpin at room temperature for 6 h which results in hydroboration of the imine moiety followed by the treatment with H_2O/D_2O produces the *N*-benzylaniline-(*d*), respectively (see supporting information). This demonstrates that H_2O/D_2O is capable of hydrolysing the *N*-Bpin bond justifying the one-pot direct formation of *N*-benzylaniline via in situ hydrolysis with H_2O (produced during imine formation). Along the same line, our standard protocol in presence of excess D_2O yielded *N*-benzylaniline-*d* (Figure S8). Further, the ^{11}B NMR analyses (~22.4/21.3 ppm)

indicate the presence of Bpin-OH/O(Bpin)$_2$ in the reaction mixtures (see supporting information).[15]

With the support of these preliminary studies and some reported literatures,[16] we propose a plausible mechanism of the present protocol as follows. Both the concerted and stepwise pathways are feasible (Scheme S2). First, the aldehyde and amine couple to generate the imine **A** under the removal of H_2O. In the case of concerted pathway, attachment of H_2O to HBpin in the form of a 1:1 Lewis acid-base adduct enhances the hydricity of the B-H bond[16] and thereby fostering the hydride transfer from HBpin to the imine function in **A**. Then the transfer of both the hydride (from HBpin) and hydrogen (from H_2O) to the imine moiety likely via a six-membered cyclic transition state (**C**)[16a] produces the corresponding secondary amines under the elimination of Bpin-OH. Conversely, the imine may also first undergo hydroboration with HBpin to yield the *N*-borylated amine (**B**) which further gets hydrolysed by H_2O presumably via a four membered transition state (**D**) (Scheme S2).

In conclusion, we have developed an efficient catalyst- and solvent-free room temperature reductive amination protocol which produces the secondary amines in one-pot. Our protocol is applicable to synthetically diverse amines, which include aliphatic, (hetero)aromatic, and polyaromatic substrates and importantly, provides excellent chemoselectivities (aldehyde over ketone, primary amine over the secondary amine and amide). Furthermore, the present protocol offers excellent functional group tolerance and can be used to access biologically relevant compounds.

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Conflicts of interest

There are no conflicts to declare.

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