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2, 4, 6-trichloro-1, 3, 5-triazine (TCT) catalysed direct reductive amination of aldehydes using hantzsch dihydropyridine ester as a reducing agent

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ABSTRACT

An efficient, rapid and environmentally benign approach for direct reductive amination of aldehydes and ketones is reported. The mild and economical process requires only catalytic amount of 2, 4, 6-trichloro-1, 3, 5-triazine (TCT) and utilizes Hantzsch ester for transfer hydrogenation and provides rapid access to the structurally diverse amines in high yields.

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KEYWORDS

Reductive amination;
Amines;
Hantzsch DHP;
Cyanuric chloride;
One-pot reaction.

Hydrogenation of double bond containing compounds such as carbonyls, olefins and imines are crucial for living organism as well as for the industrial production of the chemicals. If the double bond is imine, the resulting products are amines which are key structural element in a multitude of biologically active natural products and pharmaceuticals and therefore their synthesis has become an objective of high priority from the perspective of medicinal chemistry and organic synthesis.[1] One-pot multicomponent reactions have an obvious advantage of atom economy over their linear counterparts.[2] Reductive amination of aldehydes and ketones, in which a mixture of a carbonyl compound and an amine is treated with a reductant in a "one-pot" fashion, is one of the most useful methods for the preparation of secondary or tertiary amines and related functional compounds. Consequently, a number of methods have been developed to carry out this direct process.[3-14] Most of these procedures employ boranes or metal hydrides as reducing agents and rely on Brønsted and Lewis acids to facilitate formation of the intermediate imines and their subsequent activation for a preferential reduction in the presence of the carbonyl compound. However, many of these protocols suffer from the limitation such as incompatibility with acid labile functionalities, excessive use of amines, and production of toxic waste to the environment and inconvenience of handling. To circumvent these drawbacks, one of the best alternatives is to apply organo reductants that possess excellent reproducibility.[3]

In recent years, the natural product enzyme cofactor NAD(P) and NAD(P) H[15-20] have been a stimulus for the investigation of use of Hantzsch ester 1 and other 1,4dihydropyridine derivatives as attractive biomimetic reducing agent for the applications in synthetic and physical organic chemistry.[20-22] This conceptual blueprint of biochemical hydride reduction, wherein an enzyme and cofactor are replaced by catalysts and dihydropyridine analogues respectively, has been employed in chemical reduction of many double bond containing com-

pounds.[23-26] In recent years, synthetic chemists have made many efforts to develop DHP as a widely used reducing agent and have obtained good to excellent results. However, there are few reports on it's use for the direct reductive amination of imines.[26] The Lewis acids such as $Mg^{(II)}$,[27] SiO_2,[28] Al_2O_3[28] and $Sc(OTf)_3$[29] have been reported to promote such reductive amination of aldehydes and ketones. Recently, the group of Rueping,[30] List[31] and McMilllan[32] have independently reported the reduction of imines by Hantzsch ester using phosphoric acid as a catalyst. Very recently, Menche et al. reported the use of Hantzsch ester as a mild and selective reducing agent in the thiourea catalysed direct reductive amination of aldehyde[33] and ketones.[34] Although these methods provide an easy access to the structurally diverse amines under mild conditions but they suffer from the limitation such as use of expensive and hazardous Lewis or protic acid catalysts, excess use of amines, longer reaction time[33,34] and low yields of the products.

2, 4, 6-Trichloro1, 3, 5-Triazine (TCT) has been known for a long period of time. It is commercially available, inexpensive, relatively environmentally benign reagent. In the older literature, one can find examples of applications of 2, 4, 6-trichloro-1, 3, 5-triazine in synthesis.[35] Recently there has been a considerable growth of interest in the use of cyanuric chloride and its derivatives for functional group transformations.[36] However, to our knowledge, TCT has not hitherto tested as catalyst for the reductive amination of aldehydes with DHP ester as reducing agent. We envisaged that the use of cyanuric chloride in combination with Hantzsch ester for direct reductive amination of aldehydes and ketones could provide the environmentally benign and inexpensive protocol for the synthesis of diverse amines under mild conditions. Herein, we report that cyanuric chloride was found to be an efficient catalyst for direct reductive amination of adehydes and ketones in high yields and under mild conditions using Hantzsch ester as a biomimetic hydride source.

When the reaction between benzaldehyde, aniline and Hantzsch ester in equimolar proportion in the presence of 10 mol % cyanuric chloride in THF at room temperature was performed, the corresponding amine was obtained in quantitative yields within 3.5h. In the absence of catalyst the reaction hardly proceeded. To check the efficacy of the present catalyst, the comparative study using other Lewis and protic acid catalysts were performed and results are summarized in TABLE 1. As shown in TABLE 1, amongst all the catalysts screened, cyanuric chloride was found to be the best catalyst for the present reaction. Bismuth nitrate also proved to be effective catalyst but the yield were little lower than with TCT. Boronic acids have been previously reported by ourselves[35a,35b] and others[35c-d] as an efficient and "green" Lewis acid catalysts in organic synthesis and they also proved to be effective catalysts for the present reaction. However, relatively high cost of these boronic acids limits their applications. Obviously, TCT becomes the catalyst of choice for the present reaction. Thus, the present study revealed that the best reaction conditions were 1, equiv. of aldehyde, 1 equiv. of amine and 1 equiv of Hantzsch ester in the presence of 0.1 equiv of TCT in THF at room temperature for 5h.

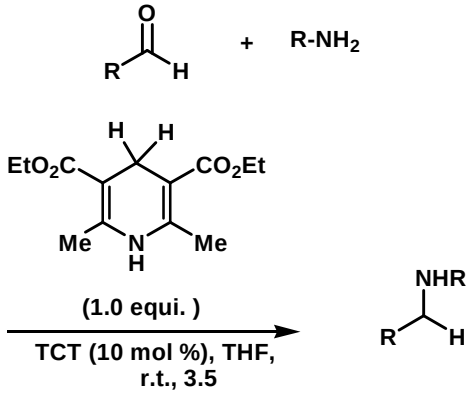
TABLE 1 : One-pot reductive amination of benzaldehyde using different catalysts.[a]

Entry	Catalyst	Yield (%)[b]
1	--------	Trace
2	cyanuric chloride	96
3	pTSA	84
4	$Bi(NO_3)_3$	94
5	CF_3SO_3H	41
6	$Ph\text{-}B(OH)_2$	trace
7	$3\text{-}NO_2C_6H_4B(OH)_2$	45
8	cyanuric chloride	98[c]

[a] **Reaction condition: 1 equiv. of benzaldehyde, 1 equiv. of aniline and 1 equiv of Hantzsch ester in the presence of 10 mol % of catalyst in THF at room temperature for 3.5 h.**

[b] **Ioslated yields**

[c] **500 mg of freshly activated 4 A molecular sieves were used.**



Scheme 1

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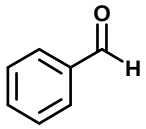
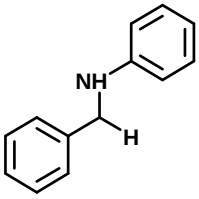
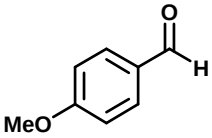
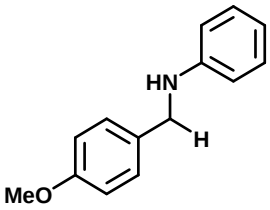
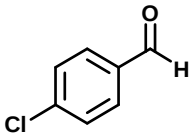
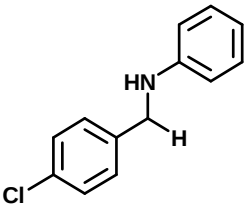
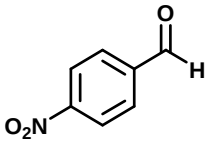
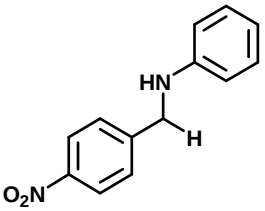
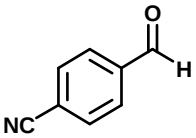
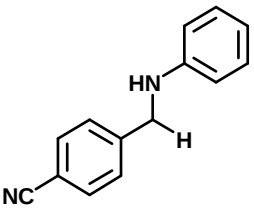
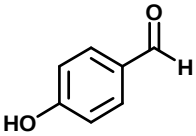
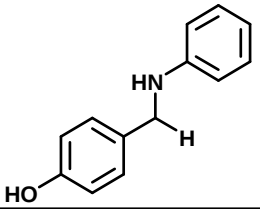
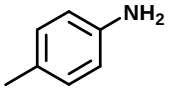
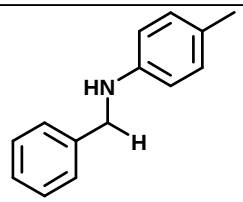
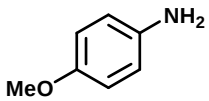
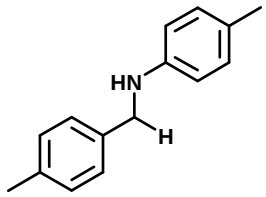
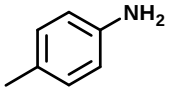
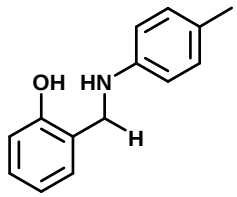
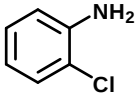
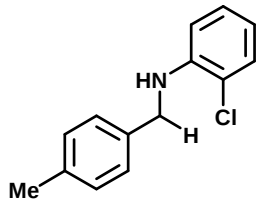
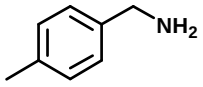
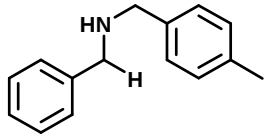
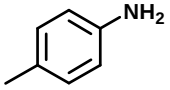
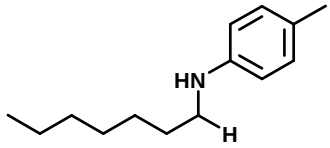
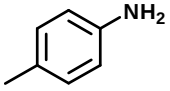
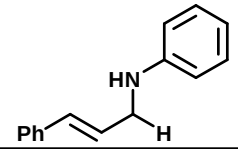
With good result being obtained in the reaction between benzaldehyde and aniline, next to gauge scope and applicability of this protocol, structurally diverse aldehydes and amines were subjected to reductive amination using our optimized reaction conditions, Scheme 1.

TABLE 2 : Scope of various aldehyde in one-pot reductive amination catalysed by TCT[a]

Entry	Aldehyde	Product	Yield (%)[b]
1			96
2			94
3			95
4			>99
5			98
6			95

[a] Reaction conditions: 1.0 mmol. of aldehyde, 1.0 mmol. of amine and 1.0 mmol. of hantzsch in the presence of 10 mol % of TCT in THF at room temperature for 3.5h.
[b] Colum purified yields.

TABLE 3: Scope of various amines in one-pot reductive amination catalysed by TCT[a]

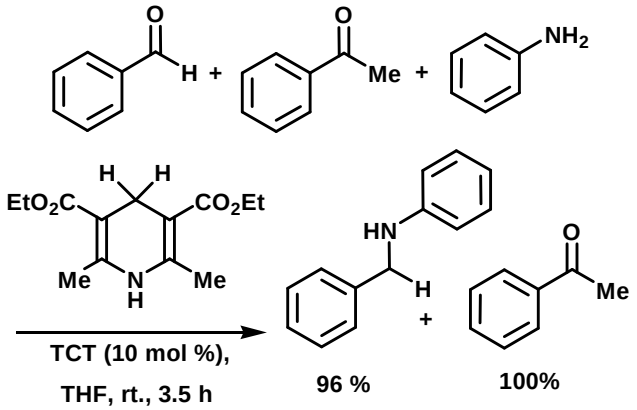
Entry	Amine	Product	Yield (%)[b]
7			96
8			>99
9			90
10			92
11			98
12			95
13			82[c]

[a] Reaction conditions: 1.0 mmol. of aldehyde, 1.0 mmol. of amine and 1.0 mmol. of hantzsch DHP ester in the presence of 10 mol % of TCT in THF at room temperature for 3.5 h.
[b] Colum purified yields.
[c] Concommitant reduction of conjugated double bond was observed.[12]

In all the example studied, the desired amines were obtained in high, and in some cases in quantitative yields in short reaction times. Aromatic and aldehydes bearing both electron releasing as well as electron withdrawing group participated successfully in

the reductive amination. In addition to aromatic aldehydes, aliphatic aldehydes were also readily aminated under present reaction conditions to give high yields of the corresponding amines. Not only aldehydes but structurally diverse aromatic amines including ortho substituted anilines reacted efficiently under present reaction conditions to give high yields of the amination products. The mild reaction conditions described herein are evident by the fact that acid sensitive functionalities such as nitro, cyano, halides, hydroxyl and alkoxy group both on aldehydes as well as amines were well tolerated.

Having successfully applied the present reaction condition for the reductive amination of aldehydes, next, we decided to explore the possibility of applying the present reaction conditions to the reductive amination of ketone. Accordingly, the reaction of acetophenone and aniline was carried out under above reaction conditions. Though reaction proceeded under these conditions, but relatively lower yield of the product was obtained within same reaction time. However, when the reaction time was increased from 3.5 to 7h., the high yield of the corresponding aminated product was obtained. This clearly indicates that the reductive amination of aldehyde is faster that that of ketone under present reducing system. This finding prompted us to explore the possibility of selective reduction of aldimine in the presence of ketimine. Thus when the reaction of benzaldehyde, acetophenone, aniline in equimolar proportion was carried out under our optimized reaction conditions, to our pleasure, reductive amination of benzaldehyde was found to be selective as the acetophenone was recovered unchanged almost quantitatively, Scheme 2.



Scheme 2

Thus, Hantzsch ester 1 in the presence of TCT was found to be selective reducing agent for the one-pot reductive amination of aldehyde in the presence of ketone.

The Hantzsch 1, 4-Dihydropyridine can be synthesized at a great ease on large scale by Hantzsch condensation reaction.[36] It is to be noted that TCT reacts with 'incipient' moisture and produces anhydrous HCl in reaction media.[37] The HCl generated *in situ* acts as a protic acid which make the present protocol much convenient and practical than the direct HCl catalysed reductive amination protocol.

The catalyst, TCT employed herein is inexpensive and an environmentally benign compound and is used in catalytic amount. The reactions were carried out at room temperature and reach to completion in short time to give high yields of the secondary and tertiary amines without the need for excess amines.

In conclusion, we have developed a mild, high yielding and selective protocol for the direct reductive amination of aldehydes using readily available Hantzsch ester as a biomemitic reducing agent in the presence of catalytic amount of TCT. Though currently we have investigated the reductive amination of acetophenone only, the detail investigation as regard to applicability of the reaction conditions for other ketones would be undertaken soon.

GENERAL PROCEDURE

For reductive amination of aldimines

To a mixture of aldehyde, amine and Hantzsch dihydropyridine ester 1 in the molar ratio of 1:1:1 in THF was added cyanuric chloride 0.1 m mol and resulting mixture was stirred at room temperature for 3.5 h. After completion of rection (TLC), the mixture was washed washed with $NaHCO_3$ and brine and finally with water. After drying over anhydrous $MgSO_4$, solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (60-120 mesh, CH_2Cl_2/ Ethylacetate = 20) to give analytically pure products in 84 ->99 % yields.

For reductive amination of ketimine

Same as for a except that reaction mixture was stirred for 10 h and chromatographed with eluent, Ethylacetae/hexanne = 2)

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