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# Iron triflate catalyzed reductive amination of aldehydes using sodium borohydride

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ence of catalytic amount of Fe(OTf)<sub>3</sub> is described.

#### ARTICLE INFO

# ABSTRACT

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Direct reductive amination of aldehydes in one pot is an important transformation in organic synthesis from process efficiency standpoint. Wherein, alternatively, indirect or two step reductive amination involves isolation of imine derivative with impeded efficiency (Scheme 1).

There are two types of reducing agents employed for direct reductive amination of aldehydes with amines. These two strategies are mainly based on metal catalyzed hydrogenation and hydride reducing agents. The metal catalyzed hydrogenation has limitations to many substrates which has reducible functionalities apart from imines.<sup>1</sup> There is another excellent Borch reduction approach, one of the early methods that involves sodium cyanoborohydride.<sup>2a</sup> In addition to this, derivatives of cyano borohydride in combination with other reagents<sup>2b-f</sup> are also being used but the cyanoborohydride derivatives suffer from the formation of highly toxic byproducts such as HCN and NaCN. Numerous alternative reagents such as NaBH(OAc)<sub>3</sub>,<sup>3a</sup> TiCl(OiPr)<sub>3</sub>/NaBH(OAc)<sub>3</sub>,<sup>3b</sup> NiCl<sub>2</sub>/ NaBH<sub>4</sub>,<sup>4a</sup> NaBH<sub>4</sub>/ZnCl<sub>2</sub>,<sup>4b</sup> NaBH<sub>4</sub>/ZrCl<sub>4</sub>,<sup>4c</sup> Ti(OiPr)<sub>4</sub>/NaBH<sub>4</sub>,<sup>4c</sup> NaBH<sub>4</sub>/ H<sub>2</sub>SO<sub>4</sub>,<sup>4d</sup> NaBH<sub>4</sub>/wet clay,<sup>4e</sup> solid acid activated NaBH<sub>4</sub>,<sup>4f</sup> NaBH<sub>4</sub>/ H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>,<sup>4g</sup> NaBH<sub>4</sub>/Bronsted acidic ionic liquid,<sup>4h</sup> NaBH<sub>4</sub>/(GuH-Cl),<sup>4i</sup> borohydride exchange resin,<sup>5</sup> pyridine/borane,<sup>6</sup> picoline/borane,<sup>7</sup> diborane/MeOH,<sup>8</sup> decaborane,<sup>9</sup> ZnBH<sub>4</sub>,<sup>10a</sup> ZnBH<sub>4</sub>/ZnCl<sub>2</sub>,<sup>10b</sup> ZnBH<sub>4</sub>/SiO<sub>2</sub>,<sup>10c</sup> Zn/AcOH,<sup>11</sup> PMHS/Ti(O'Pr)<sub>4</sub>,<sup>12a</sup> PMHS/ZnCl<sub>2</sub>,<sup>12b</sup> PMHS/BuSn(OCOR)<sub>3</sub>,<sup>12c</sup> Et<sub>3</sub>SiH/CF<sub>3</sub>CO<sub>2</sub>H,<sup>12d</sup> PhMe<sub>2</sub>SiH/(C<sub>6</sub>F<sub>6</sub>)<sub>3</sub>,<sup>12e</sup> Cl<sub>3</sub>SiH/DMF,<sup>12f</sup> PhSiH<sub>3</sub>/Bu<sub>2</sub>SnCl<sub>2</sub>,<sup>12g</sup> PMHS/TFA,<sup>12h</sup> <sup>n</sup>Bu<sub>3</sub>SnH/DMF or HMPA,<sup>13a</sup> <sup>n</sup>Bu<sub>3</sub>SnH/SiO<sub>2</sub><sup>13b</sup> and <sup>n</sup>Bu<sub>2</sub>SnIH or <sup>n</sup>Bu<sub>2</sub>/SnClH,<sup>13c,d</sup> Zr(BH<sub>4</sub>)<sub>4</sub>/piperazine,<sup>14</sup> hydrio-iridium(III) complex,<sup>1</sup> <sup>5</sup> iridium

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0040-4039/\$ - see front matter @ 2012 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tetlet.2012.06.018 complex,<sup>16</sup> Fe<sup>II</sup>/EDTA complex,<sup>17</sup> LiBH<sub>4</sub>,<sup>18</sup> ammoniaborane/ Ti(O<sup>i</sup>Pr)4,<sup>19</sup> bis(triphenylphosphine)copper(I) tetrahydroborate,<sup>20</sup> molybdenum dioxide dichloride and phenylsilane<sup>21</sup> etc. have been reported.<sup>4f</sup> Moreover, reagents containing zinc and Ti(O<sup>i</sup>Pr)<sub>4</sub> mediated are not suitable for chemoselective reductions.<sup>22</sup> Usage of tin hydrides is not suitable due to toxicity in large scale production as the removal of residual tin is found to be extremely difficult. Recently, Hantzsch method that involves dihydropyridine as reductant (removal of toxic pyridine is found to be extremely difficult) in the presence of scandium triflate as a catalyst,<sup>23</sup> S-benzyl isothiouronium chloride as a recoverable organocatalyst along with dihydropyridine,<sup>24</sup> Pd(PhCN)<sub>2</sub>Cl<sub>2</sub>/2,2'-biquinoline-4,4'-dicarboxylic acid dipotassium salt (BQC)<sup>25</sup> and Leuckart type reductive amination<sup>26</sup> are also reported for reductive amination.

An efficient and convenient procedure for the reductive amination of aldehydes using NaBH<sub>4</sub> in the pres-

Metal triflate catalyzed reductive amination procedures are well documented. In most of the cases, the metals as part of catalysts are not suitable for the synthesis of active pharmaceutical ingredients (APIs) due to regulatory requirements as one has to limit the traces of them in the order of ppms (parts per millions).<sup>27</sup>



Scheme 1. Direct and indirect reductive amination.





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Figure 1. Comparative toxicological classification of the metals.



Scheme 2. Fe(OTf)<sub>3</sub> catalyzed reductive amination of carbonyl compounds.

In order to do so, a tedious workup is required that becomes costly affair due to material loss. Therefore, we attempted to develop non- or less toxic metal triflate which is readily and cheaply available in the market. In comparison to other metals (Fig. 1),<sup>27</sup> Fe is



Scheme 3. Possible mechanism for direct amination.

most widely recommended due to its non-toxic nature. Such a strategy that features  $Fe(OTf)_3/NaBH_4$  reducing system provides very efficient and workable protocol to address the associated industrial problems up to great extent from three standpoints; (1) reduced duration of the reaction, (2) high conversion and (3) relaxed specification for metal content as Fe in pharmaceutical products is relatively much safer as per the US FDA guidelines.<sup>27</sup> This adds to a better process efficiency as one can avoid purifications and thereby increase the isolated yield in comparison to hitherto known procedures.

In our endeavor, catalytic quantity of iron triflate  $(Fe(OTf)_3 along with NaBH_4 was opted for direct reductive amination.$ 

Sodium borohydride is an inexpensive reducing agent which stands alone known to reduce imines and other functionalities limiting its application in broader sense. Moreover, it is understood that the poor electrophilic carbonyls, poor nucleophilic amines, and sterically crowded reactive centers do not favor the completion of imine formation. Thus, it is quite apparent that NaBH<sub>4</sub> alone may not afford excellent yields. Strategically, we employed the combination of 1 mol % Fe(OTf)<sub>3</sub> along with stoichiometric amount of NaBH<sub>4</sub> for the first time in the direct reductive amination. This strategy was demonstrated with various aldehydes and amines.

The reaction of aldehydes **1** with amines **2** proceeded smoothly in  $CH_2Cl_2$  with excellent yields as shown in Scheme 2.<sup>30</sup> In most of the cases, we obtained pure products hence there was no need to involve column chromatography. The catalytic activity of  $Fe(OTf)_3$ in reductive amination, was probed by conducting the control experiment without the catalyst. In this control experiment, we found that only NaBH<sub>4</sub> did not afford clean imine rather we encountered incomplete reaction as well as alcohol as a byproduct.

This strategy was extended not only to model substrates but it has found application in the synthesis of pharmaceutically relevant intermediates for example, Cinacalcet  $(3s)^{28}$  and Aliskiren (3t).<sup>29</sup>

Mechanistically, iron triflate as a Lewis acid activates the carbonyl functionality and provides very reactive electrophile source. Amine that was used as substrate reacts with the activated aldehyde to afford hemiaminol equivalent. Thereafter, dehydration event regenerates the catalyst. In situ generated imine can further be reduced with sodium borohydride affording the products as shown in Scheme 3. Our approach allowed us to have quick access of the products as the rate of the reaction was found to be very fast (in the order of minutes) in comparison with the non-catalytic reactions for example, NaBH(OAC)<sub>3</sub>,<sup>3a</sup> mediated reactions take 2 h–10 d for such type of reductive amination.

We have developed and demonstrated novel method by involving catalytic quantity of iron triflate and sodium borohyderide (1 equiv) which can be considered as synthetically useful reagent system for reductive amination in one pot.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.018.

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- 30. In a typical experimental procedure, sodium borohydride (0.001 mol) and  $Fe(OTF)_3$  (1 mol %) was added to a solution of benzaldehyde (0.001 mol) and aniline (0.001 mol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and the mixture was allowed to stir for 5–10 min. at room temperature. Thereafter, methanol (1 mL) was added to drive the reaction to completion. After completion of reaction (TLC), the reaction mass was distilled at 40 °C and the reaction mixture residue was quenched with 5% aqueous NaHCO<sub>3</sub> solution and reaction mixture was extracted with dichloromethane twice (2 × 10 mL). The organic layers were combined, washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure to obtain substantially pure products without column chromatography.