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Direct reductive amination of carbonyl compounds with primary/secondary amines using recyclable water-soluble Fe^{II}/EDTA complex as catalyst

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Abstract

Direct reductive amination of aliphatic, aromatic and heterocyclic carbonyl compounds with primary/secondary amines is reported with water-soluble Fe^{II}/EDTA complex as a catalyst using low-pressure molecular hydrogen in a biphasic media. The catalyst is highly selective, recyclable and is an excellent replacement for expensive noble metal catalysts or stoichiometric reducing agents.

Keywords: Water-soluble catalyst; Imines; Hydrogenation; Biphasic catalysis

Amines and their derivatives are used as versatile building blocks for organic compounds, precursors to biologically active compounds, pharmaceuticals,[1] such as tolterodine and agrochemicals.[2] They are synthesized using various methods including arylation of amines,[3] hydroamination of olefins,[4] reductive amination of carbonyl compounds,[5] nitro reduction followed by reductive amination,[6] hydrocyanation of imines,[7] etc. Direct reductive amination (DRA) of carbonyl compounds with amines is an elegant and powerful method for producing substituted amines. It is commonly carried out using borohydride based reducing agents such as $NaBH_4$,[8] $NaBH_3CN$,[9] $NaBH(OAc)_3$,[10] pyridine–BH_3,[11] $ZnBH_4$–$ZnCl_2$[12] and silica gel–$ZnBH_4$.[13] However, most of these methods suffer from the major drawback of requiring stoichiometric reductant. Also, the use of $NaBH_3CN$ has a risk of residual cyanide; pyridine borane is thermally unstable and involves handling risks. Hence, use of a cheaper reductant like molecular hydrogen, that is, catalytic hydrogenation is attractive from economical and ecological points of view. DRA is normally carried out using heterogeneous catalysts,[14] however, a few homogeneous catalysts have been reported.[15] Börner and co-workers[16] and Beller and co-workers[17] independently reported the first homogeneously catalyzed reductive amination of carbonyl compounds with amines using Rh(I) complexes as catalysts and Rh/TPPTS catalyst in organic solvents for the synthesis of primary amines using aq ammonia. Also, Nait Ajjou and Robichaud demonstrated the first example of DRA of aldehydes with amines using water-soluble transition metal catalysts[18] (Pd, Pt, Ir, Rh) along with water-soluble ligands such as TPPTS and BQC.

Recently, Chaudhari and co-workers[19] reported chemoselective hydrogenation of nitroaromatics using novel water-soluble Fe complex catalysts. The catalyst has several advantages including lower cost, high TON value and is an efficient alternative to stoichiometric reductions using metal catalysts for hydrogenation of nitroaromatics. Also, Casey and Guan[20] reported a chemoselective Fe catalyst for hydrogenation of ketones. In continuation of our work on amine synthesis via N-arylation,[21] DRA using $Cu(PPh_3)_2BH_4$ as the reducing agent in the presence of sulfamic acid[22] and chemoselective hydrogenation of

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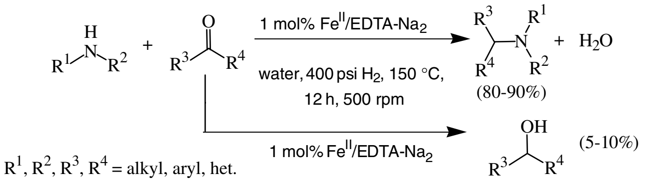


Scheme 1. DRA of carbonyl compounds with amines catalyzed by Fe^{II}/EDTA.

α,β-unsaturated nitriles,[23] we herein report a novel methodology for DRA of carbonyl compounds with primary and secondary amines using water-soluble Fe^{II}/EDTA-Na$_2$ complex as catalyst with molecular hydrogen (Scheme 1).

The reaction was carried out in water as a solvent and using molecular hydrogen. Moreover, the catalyst is air stable due to the absence of conventional air sensitive phosphine based ligands as in TPPTS.[24] Initially, DRA of benzaldehyde with aniline was chosen as a model reaction to test the catalytic activity of the water-soluble Fe/EDTA catalysts. The results are summarized in Table 1, which show the selective formation of *N*-benzylaniline. Formation of a small quantity of benzyl alcohol along with unreacted imine accounted for the products obtained indicating excellent material balance.

When Fe salts such as $FeNO_3{\cdot}9H_2O$ and $FeSO_4{\cdot}7H_2O$ were used as catalysts without any ligand, low yields of amine (52% and 66%, respectively) and reduced selectivity towards the amine as 10–15% of benzyl alcohol was also observed as a hydrogenation product of benzaldehyde. The use of ethylenediaminetetraacetic acid disodium salt dihydrate (EDTA-$Na_2{\cdot}2H_2O$) as a ligand in combination with Fe salts led to a significant increase in both selectivity and yields of amine. Reductive amination under biphasic conditions using toluene/water as a solvent gave a 60% yield but with a slower reaction rate without affecting the selectivity and supports the literature report that the reaction rate is lower in biphasic systems than the respective homogeneous systems.[24] In this context, we preferred not to use another solvent. In the current system, the reagents were added to the water phase directly containing the Fe/EDTA complex. Since, the reagents are liquid and insoluble in the aqueous phase, they form small droplets suspended in a continuous aqueous catalyst phase. This is typical of biphasic catalysis wherein the catalyst phase acts as a continuous phase and the reactants form another phase in the form of small-suspended droplets.[25] Due to elimination of the organic solvent phase, an increased concentration of reagents can be achieved leading to a higher reaction rate.[26] The products remained insoluble after reaction and could be separated by simple phase separation or using extraction techniques. The catalyst phase could be recycled (Table 1, entry 5). The role of temperature on the reductive amination was studied (entries 7 and 8). It was observed that at 100 °C and 120 °C, the reaction rate was much slower leading to just 62% and 79% yields of *N*-benzylaniline, respectively, whereas a better yield of 90% was obtained at 150 °C. EDTA is a well-known N-containing hexadentate chelating ligand, similarly the Fe(II) complex of the O-containing chelating ligand 2,2,6,6,-tetramethyl-3,5-heptanedione (TMHD)[21a] was also tested. The efficiency of the Fe/EDTA catalyst was also compared with the conventional Pd/C catalyst and found to give comparable results (entry 10).[5b] The best reaction conditions for DRA were 1 mol % of $FeSO_4{\cdot}7H_2O$ and EDTA-$Na_2{\cdot}2H_2O$ as ligand (Fe/EDTA ratio of 1:5), which gave a 90% yield of *N*-benzylaniline (entry 4).

Table 1
Reductive amination of aniline (A) with benzaldehyde (B)[a]

Entry	Catalyst	Ligand	Conversion		Yield	
			A[a]	B[a]	C[g]	D[g]
1	$FeNO_3{\cdot}9H_2O$	—	99	98	52	15
2	$FeSO_4{\cdot}7H_2O$	—	99	98	66	12
3	$FeNO_3{\cdot}9H_2O$	EDTA-Na_2	99	98	72	9
4	**$FeSO_4{\cdot}7H_2O$**	**EDTA-Na_2**	**99**	**98**	**90**	**5**
5[b]	$FeSO_4{\cdot}7H_2O$	EDTA-Na_2	97	96	85	4
6[c]	$FeSO_4{\cdot}7H_2O$	EDTA-Na_2	99	97	60	4
7[d]	$FeSO_4{\cdot}7H_2O$	EDTA-Na_2	95	93	62	3
8[e]	$FeSO_4{\cdot}7H_2O$	EDTA-Na_2	99	97	79	4
9[f]	Fe(II)TMHD	—	99	96	58	8
10[h]	10% Pd/C	—	99	99	94	4

[a] Aniline (A = 5 mmol), benzaldehyde (B = 6 mmol), catalyst (0.05 mmol), ligand (0.25 mmol), water (20 ml), H_2 (400 psi), 150 °C, 500 rpm, 12 h.

[b] 3rd recycle.

[c] Biphasic conditions (toluene 10 ml: water 10 ml).

[d] At 100 °C.

[e] At 120 °C.

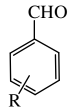
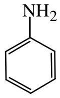
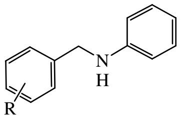
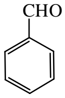
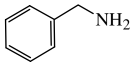
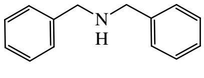
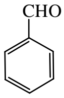
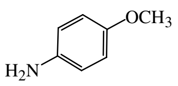
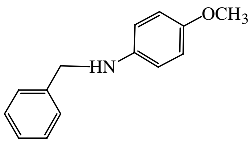
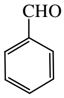
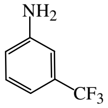
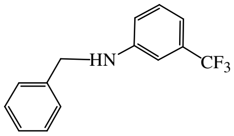
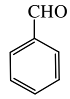
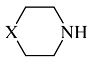
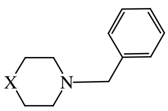
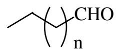
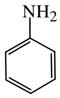
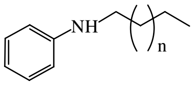
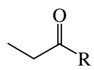
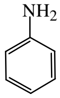
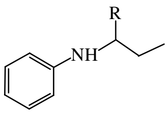
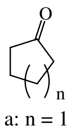
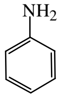
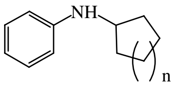
[f] Toluene (20 ml) as a solvent.

[g] GC yields of C = *N*-benzyl aniline; D = benzyl alcohol.

[h] Reaction condition as given in Ref. 5b.

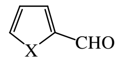
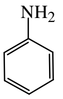
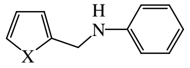
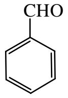
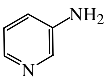
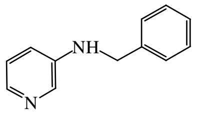
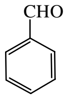
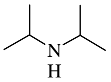
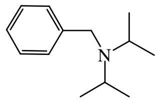
The present water-soluble catalyst system was applicable for DRA of a variety of aliphatic, aromatic and heterocyclic aldehydes as well as aliphatic and cyclic ketones with primary and secondary amines (Table 2).[27] Substituted benzaldehydes (4-methoxy, 4-chloro, 4-cyano) were reductively aminated with aniline to give N-alkylated amines in 81–84% yields. Formation of dechlorinated or cyano reduced products were not observed. The catalyst system was also effective for reductive amination of benzaldehyde with an aliphatic amine (entry 2) and substituted anilines (4-methoxy and 3-trifluoromethyl) resulting in N-alkylated amines in 78%, 86% and 82% yields, respectively. DRA of benzaldehyde with secondary amines such as piperidine, morpholine and *N*-benzylpiperazine was carried out using the Fe/EDTA catalyst and molecular hydrogen in good yields (70–74%, entry 5). Aliphatic aldehydes such as pentanal, hexanal and heptanal were found to undergo reductive amination with aniline with good selectivity towards amines (entry 6). Similarly, aliphatic or cyclic ketones were reductively aminated with aniline leading to good yields of amines (entries 7 and 8). N-Alkylated amines containing a heterocycle could also be obtained in moderate to good yields via reductive amination of furfural or thiophene-2-carboxaldehyde with aniline (entry 9) and benzaldehyde

Table 2
Reductive amination of carbonyl compounds with amines[a]

Entry	Carbonyl compound	Amine	Product	Alkylated amine yield (%)	Alcohol yield (%)
1	 a: R = -H b: R = 4 –OCH_3 c: R = 4 –Cl d: R = 4 –CN			88 84 83 81	5 6 6 5
2				78	8
3				86	4
4				82	5
5	 a: X = CH_2 b: X = O c: X = N-Bz			74 72 70	9 7 8
6	 a: n = 2 b: n = 3 c: n = 4			81 78 80	5 6 6
7	 a: R = -CH_3 b: R = -C_2H_5			70 66	6 4
8	 a: n = 1 b: n = 2			62 65	6 6

(*continued on next page*)

Table 2 (*continued*)

Entry	Carbonyl compound	Amine	Product	Alkylated amine yield (%)	Alcohol yield (%)
9	 a: X = O b: X = S			72 76	7 5
10				52	8
11				21	2

[a] Reaction conditions: carbonyl comp. (6 mmol), amine (5 mmol), $FeSO_4{\cdot}7H_2O$ (0.05 mmol), EDTA-Na_2 (0.25 mmol), water (20 ml), H_2 (400 psi), 150 °C, 500 rpm, 12 h.

with 3-aminopyridine (entry 10). Reductive amination of benzaldehyde with *N,N*-diisopropylamine gave only a 21% yield of the corresponding tertiary amine (entry 11).

In conclusion, we have developed a simple and eco-friendly method for direct reductive amination of aliphatic, aromatic and heterocyclic carbonyl compounds with primary and secondary amines. The catalyst system is an efficient alternative to the noble metal catalysts used in hydrogenation reactions. The method gives amines selectively and operates at a low pressure of molecular hydrogen and utilizes environmentally benign water as a solvent.

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27. *Typical procedure for reductive amination of aldehydes and ketones with amines*: To a 100 ml high pressure reactor were added aldehyde or ketone (6 mmol) and amine (5 mmol) resulting in a white opaque solution indicating the formation of an imine intermediate. In a 100 ml beaker, 14 mg (0.05 mmol) of $FeSO_4{\cdot}7H_2O$ (powder form) and 93 mg (0.25 mmol) of $EDTA\text{-}Na_2{\cdot}2H_2O$ were dissolved in water (20 ml). The resulting clear light green solution was then transferred to the high pressure reactor. The reaction was then pressurized to 400 psi of hydrogen, heated to 150 °C and stirred for 12 h at 500 rpm. The reactor was cooled to room temperature and the remaining hydrogen was carefully vented and the reactor opened. Ethyl acetate (2×15 ml) was added to the reactor and the reaction stirred for 15 min to extract the product. The aqueous layer containing the Fe/EDTA complex was recycled for the next run after phase separation. The combined extracts were dried over sodium sulfate and the solvent was evaporated in vacuo. The reaction mixture was analyzed by GC and the products were confirmed by GCMS. Compound **1a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$ (m, 5H), 7.30 (m, 2H), 6.83 (t, $J = 7.3$ Hz, 1H), 6.74 (d, $J = 7.7$ Hz, 2H), 4.32 (s, 2H), 4.06 (s, 1H). MS *m/z* (EI): M^+ 183 (68), 91 (100), 182 (28), 106 (20), 77 (19), 65 (18).