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Carbon dioxide promoted reductive amination of aldehydes in water mediated by iron powder and catalytic palladium on activated carbon

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ABSTRACT

A mixture of iron powder and catalytic palladium on activated carbon has been developed for reductive amination of various aromatic aldehydes, including 2-pyridinecarboxaldehyde, in water under CO_2 atmosphere. The reversible reaction of CO_2 with water could form carbonic acid and hydrogen transfer from water to Pd(0) took place with the presence of iron powder, leading to formation of high-active Pd hydrides for the reductive amination process. On the other hand, the reaction system could be inherently neutralized by ready removal of CO_2, thus resulting in facile post-processing.

1. Introduction

Preparation of functionalized amines in an effective way has always been necessary especially in medicinal chemistry and modern organic synthesis. In this context, direct reductive amination of carbonyl compounds represents a powerful tool for the preparation of amine derivatives, which generally includes two steps: the formation of imines *via* the reaction of aldehydes or ketones with amines and subsequent hydrogenation [1–3]. Ecological and economic benefits of this kind protocol are obvious since the amount of solvents, reagents and energy consumption would be dramatically reduced compared with the stepwise processes. However, despite being a reaction of proven efficiency, it presents a large drawback related with the handling of hydrogen gas (flammable and explosive). For this reason, numerous alternative reducing agents that are mainly rely on precious metals (*e.g.*, Ir, Pt, Rh, Ru) have been developed, such as active boranes or tin compounds, iso-propanol, formates, silanes, and so-called Hanztsch esters [4–8]. Recently, Beller et al. reported the nanostructured iron-catalyst for the tandem reductive amination between nitroarenes and aldehydes using hydrogen as reductant [9]. While, there is still much room for improvement in terms of environmentally benign hydrogen source and easily operated processes with less expensive and less toxic metals.

The efficient reduction of water for generation of hydrogen is one of the most challenging transformations in chemistry and water is the ultimate hydrogen source, being both safe and plentiful. In the CO_2–H_2O two phase system, water is thought to behave as the terminal hydrogen source with the presence of the reducing metal such as Fe or Zn because the reversible reaction between CO_2 and H_2O could form the carbonic acid with a pH value as low as 3 [10]. And this CO_2/H_2O system could be inherently neutralized by readily remove of CO_2. As an extension of our previous works on the use of *in situ* carbonic acid-promoted organic reactions [11], we herein would like to apply such self-neutralizing acid for the synthesis of various amine derivatives by the direct reductive amination of aldehydes, thus avoiding isolating the imines intermediate (Scheme 1). Pd/C and iron powder mixture in the CO_2/H_2O system has been revealed to be an efficient methodology for the reductive amination process and satisfactory yields of the one-pot formed amines were achieved with facilitated post-processing procedures.

2. Experimental

Aldehydes and amines were purchased from Aladdin Reagent Inc. Pd/C and iron powder was purchased from Alfa Aesar China Co., Ltd. Distilled water and all other reagents were obtained

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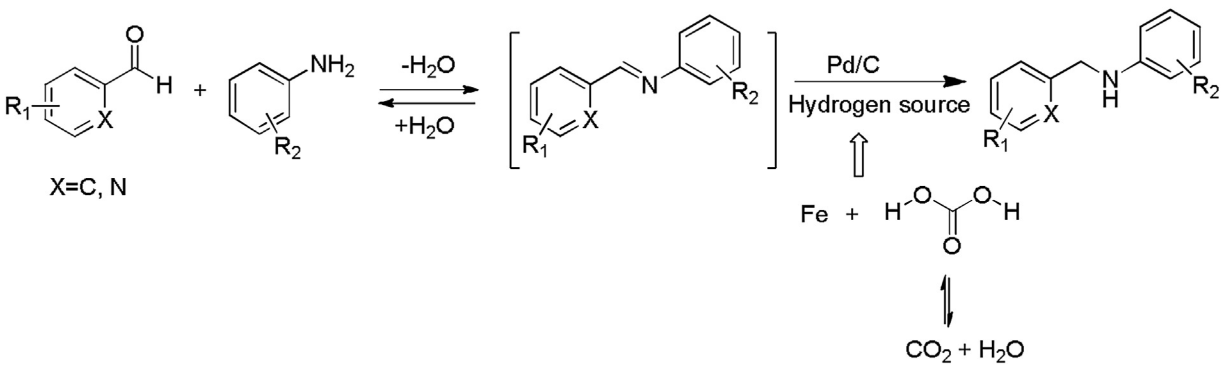
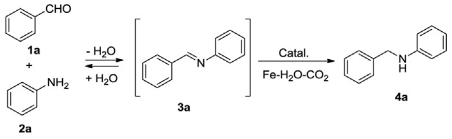


Scheme 1. Pd/C-catalyzed reductive amination of aldehydes with Fe in CO_2/H_2O system.

Table 1
Reductive amination with Fe in CO_2/H_2O system[a].



Entry	Catal.	CO_2 (MPa)	Conv.[b] (%)	Yield (%)	
				3a[b]	**4a**[b]
1	–	8	93	92	–
2	$ZnCl_2$	8	88	84	–
3	$FeCl_2$	8	94	93	–
4	$FeBr_3$	8	58	54	–
5	$RuCl_3$	8	57	53	–
6	$Cu(OTf)_2$	8	50	39	6
7	$RhCl_3$	8	33	26	4
8	$IrCl_3$	8	66	57	4
9	$PdCl_2$	8	92	73	19
10	Pd/C	8	86	50	33
11	$PdBr_2$	8	55	41	11
12	$Pd(OAc)_2$	8	57	50	1
13[c]	Pd/C	8	84	84	–
14	Pd/C	–	88	76	–
15[d]	Pd/C	–	–	–	–

[a] Reaction conditions: benzaldehyde (1.1 mmol, 116.7 mg), aniline (1 mmol, 93.1 mg), catalyst 5 mol%, H_2O (2 mL), Fe (2 mmol, 111.7 mg), 80 °C, 10 h.
[b] Conversion and yield were relative to primary amine and determined by GC with biphenyl as the internal standard.
[c] Without Fe.
[d] H_2 balloon, toluene was detected.

commercially from Tianjin Guangfu Fine Chemical Research Institute and used without further purification. ^{1}H NMR spectra was recorded with a Bruker 400 spectrometer in $CDCl_3$ and $CDCl_3$ (7.26 ppm) was used as the internal reference. ^{13}C NMR was recorded at 100.6 MHz in $CDCl_3$ and $CDCl_3$ (77.0 ppm) was used as the internal reference. GC–MS datas were collected on a Finnigan HPG1800 A. GC analyses were performed on a Shimadzu GC-2014, equipped with a capillary column (RTX-17, 30 m × 0.25 μm) using a flame ionization detector.

2.1. *Reduction amination of aldehydes with Fe powder in CO_2/H_2O*

A mixture of aldehyde (1.1 mmol), amine (1 mmol), Fe (3 mmol, 167.5 mg), Pd/C (Palladium on activated carbon 5% Pd, 106.4 mg), H_2O (3 mL) was placed in a 50 mL stainless steel autoclave equipped with an inner glass tube at room temperature. The vessel was sealed and CO_2 was subsequently introduced into the autoclave, which was then heated under the predetermined reaction temperature for 25 min to reach the equilibration. The final pressure was adjusted to the desired pressure by introducing the correct amount of CO_2. After the reaction was finished, the vessel was cooled within an ice-bath and the pressure was released slowly to atmospheric pressure. The products were diluted with ethyl acetate and analyzed by GC. The residue was purified by column chromatography on silica gel (200–300 mesh, eluting with *n*-hexane and ethyl acetate) to afford the desired product. The isolated products were further identified with NMR spectra and GC–MS, which are consistent with those reported in the literature.

Table 2
Optimization of the reaction parameters[a].

Entry	CO_2 (MPa)	H_2O (mL)	Temp. (°C)	Conv.[b] (%)	Yield **4a**[b] (%)
1	8	2	80	86	33
2	8	3	80	85	45
3	12	3	80	81	17
4	4	3	80	87	34
5[c]	8	3	80	84	52
6[c,d]	8	3	80	93	75

[a] Unless otherwise stated, all the reactions were carried out with 1.1 mmol **1a** and 1.0 mmol **2a** in 2 mL solvent in the presence of Pd/C and Fe, at 80 °C for 10 h.
[b] Conversion and yield were based on primary amines and determined by GC with biphenyl as the internal standard.
[c] Fe (3 mmol, 167.5 mg).
[d] 15 h.

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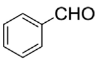
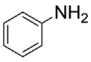
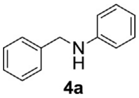
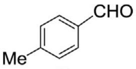
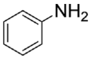
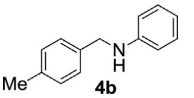
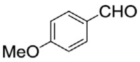
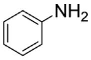
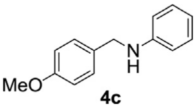
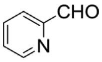
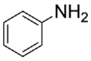
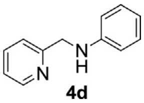
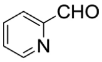
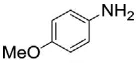
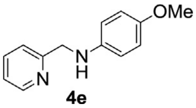
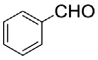
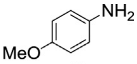
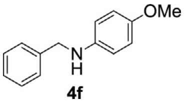
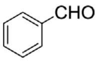
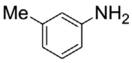
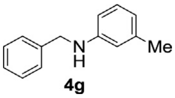
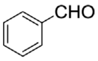
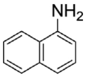
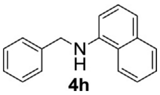
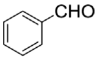
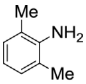
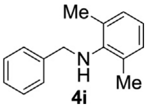
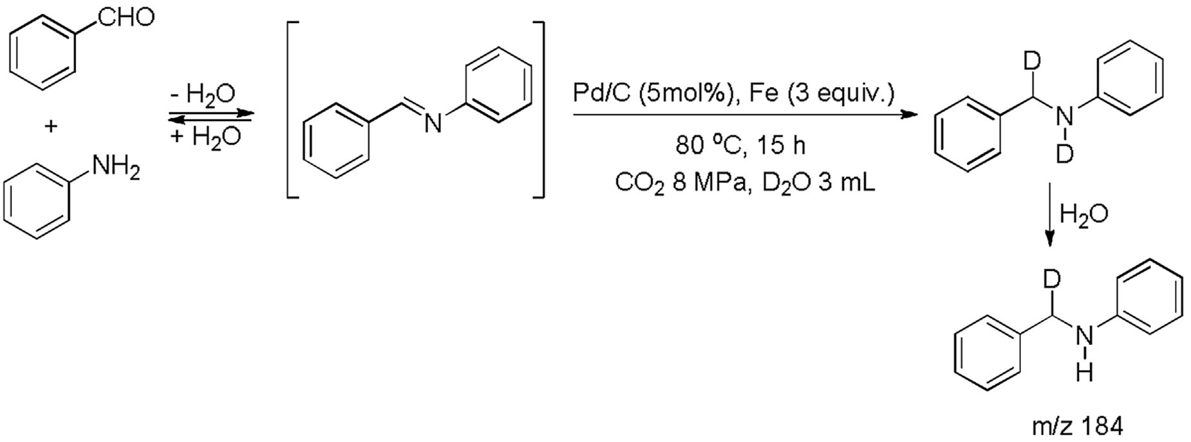
Table 3
Reductive amination of aromatic aldehydes with different amines[a].

Entry	Aldehyde	Amine	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **4a**	75
2	 **1b**	 **2a**	 **4b**	82
3	 **1c**	 **2a**	 **4c**	74
4	 **1d**	 **2a**	 **4d**	60
5	 **1d**	 **2b**	 **4e**	44
6	 **1a**	 **2b**	 **4f**	60
7	 **1a**	 **2c**	 **4g**	63
8[c]	 **1a**	 **2d**	 **4h**	37
9	 **1a**	 **2e**	 **4i**	11

[a] Reaction conditions: aldehyde (1.1 mmol), amine (1 mmol), Pd/C (Palladium on activated carbon, 5% Pd, 106.4 mg), Fe (3 mmol, 167.5 mg), H_2O 3 mL, CO_2 8 MPa, 80 °C, 15 h.
[b] Yield was based on primary amines and determined by ^1H NMR yield with 1,1,2,2-tetrachloroethane as the internal standard.
[c] 100 °C.



Scheme 2. Isotope labeling experiments.

3. Results and discussion

In our initial investigation, the reductive amination of benzaldehyde **1a** with aniline **2a** in reversible CO_2/H_2O system was carried out (Table 1). No desired product **4a** was detected in the absence of any catalyst, and imine **3a** was obtained in high yield with or without CO_2 (entry 1) [12]. Then, a series of catalysts were screened. As a result, Lewis acid catalysts such as zinc(II), iron(II) or iron(III), Ru(III) salts were almost inactive for the formation of **4a**, but were favorable for **3a** formation in moderate to high yield (entries 2–5). The

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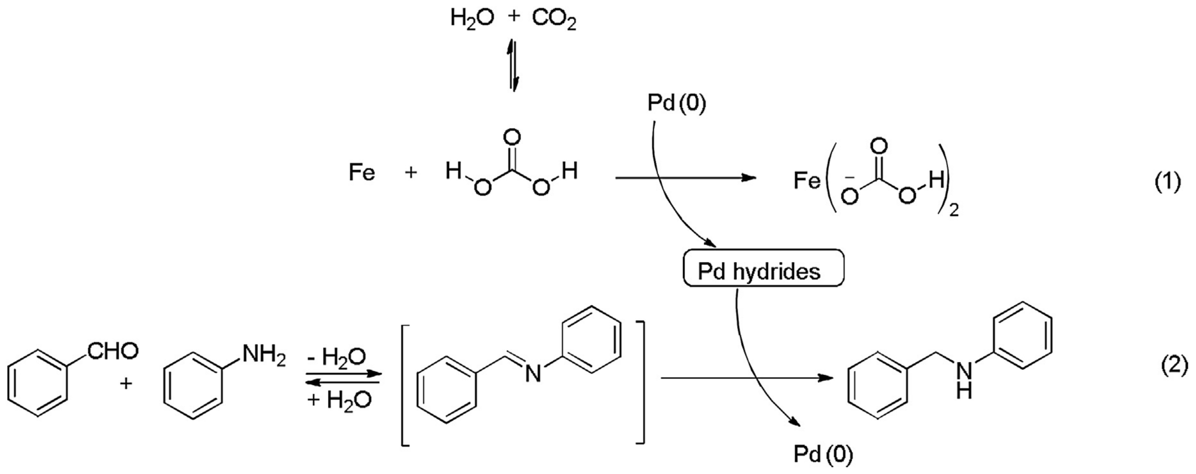

Scheme 3. Suggested mechanism for the reductive amination.

possible reason is that these Lewis acidic metal catalysts may have an influence on the formation of imines from the primary amine and aldehydes or promote the imine hydrolysis. Trace amount of **4a** was just detected when Cu(II), Rh(III) and Ir(III) salts were employed (entries 6–8). Notably, surplus benzaldehyde was hydrogenated to benzyl alcohol in this Fe/CO_2/H_2O system detected by GC–MS. [10a] Pd catalysts such as Pd/C and $PdCl_2$, gave the target amine **4a** in significant yields. Whereas, $PdBr_2$ just exhibited poorer performance and $Pd(OAc)_2$ was inactive in terms of producing **4a** (entries 9–12). Control experiments were turned out to prove the synergistic effect between the iron powder and carbonic acid *in situ* formed (entries 13–14). No amine product **4a** was detected in the absence of either iron powder or CO_2, thus demonstrating the promotion effect of CO_2 and iron powder in the hydrogen transfer from water to imine intermediate (entries 13–14). On the other hand, when H_2 (balloon) was used as direct hydrogen resource, only toluene was observed as a hydrogenation product of benzaldehyde (entry 15).

Water was used as the terminal hydrogen source and solvent in this CO_2 promoted reductive amination process, and 3 mL of water could reach an adequate point for better yield with sufficient proton donor (Table 2, entries 1 *vs* 2). On the other hand, CO_2 pressure certainly has a significant influence on the reduction reaction through tuning the acidity of the CO_2/H_2O biphasic system [13]. In this context, the optimal CO_2 pressure was screened out as listed in Table 2. As expected, lower CO_2 pressure would cause deficient proton concentration (entry 4) and an optimal productivity of **4a** was attained at the supercritical state of 8 MPa. But further pumping CO_2 to 12 MPa would be unfavorable (entry 3), probably owing to the dilution effect by high density CO_2, thereby would cause inefficiency of reductive amination. Increasing the amount of iron powder revealed feasible, leading to a remarkably enhanced **4a** yield (entry 5). Finally, good yields (> 70%) of **4a** was obtained with the extending the reaction time to 15 h (entries 6).

The generality and feasibility of the present protocol were then evaluated by performing the reductive amination with a broad range of aldehydes with various amines under optimal reaction conditions. As shown in Table 3, a variety of substituted benzaldehydes were smoothly aminated and hydrogenated in good to excellent yields. Aldehydes with —CH_3 or —OCH_3 at *para*-position successfully gave the amine **4b,c** in up to 82% yield (Table 3, entries 2–3). Heteroaromatic aldehyde, *i.e.*, 2-pyridinecarboxaldehyde was also readily converted to the corresponding amines through the reductive amination with aniline **2a** or *p*-anisidine **2b** (entries 4–5). Then, the reductive amination of different aromatic amines with benzaldehyde **1a** was investigated. Aniline with electron-donating group **2b** was transformed into the desired amines in 60% yield (entry 6). Satisfactory yield of **4g** was obtained through reductive amination of benzaldehyde **1a** with *m*-toluidine **2c** (entry 7). 1-naphthylamine **2d** showed poorer performance even at an elevated temperature, providing low yield of **4h** (entry 8). While, 2,6-dimethylaniline only furnished 11% yield of **4i**, probably due to the steric hindrance (entry 9).

In order to illuminate the actual proton donator of water, isotope-labeling experiment was run in D_2O instead of H_2O as depicted in Scheme 2. The deuterium position at the C—N double bond of final hydrolytic product (NMR and MS, see supporting information), suggesting the hydrogen transfer from water to the imine, followed by solvolysis with a trace amount of water ($m/z = 184$).

At this point we can propose a mechanism in which water can act as hydrogen donor in the presence of CO_2 promoted reductive amination with metals mixture Pd/C/Fe (Scheme 3). In this mechanism two sequential paths for the hydrogen transference from water to imine intermediate are proposed. The first step implies a hydrogen transfer from water to Pd(0), leading to the formation of the high-active Pd hydrides (Scheme 1) [14]. Then, the generated Pd hydrides are able to hydrogenate the imine intermediate to amine product, accompanied by the regeneration of Pd(0) catalyst.

4. Conclusion

In summary, we have developed an effective process for the reductive amination of aldehydes mediated by Pd/C/Fe mixture. With the promotion of CO_2, water serves as solvent and terminal hydrogen source. The work-up process could be inherently neutralized by simple depressurization. Various amine derivatives were obtained in good to excellent yield through the reductive amination of aromatic, 2-pyridinecarboxaldehyde with different substituted aromatic amines. Accordingly, the findings uncovered in the present study could provide an industrially feasible route for amines, and would also broaden the application of CO_2 in green chemical processes as a reaction medium and promoter.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cattod.2016.01.048.

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