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Transfer hydrogenative reductive amination of aldehydes in aqueous sodium formate solution

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ABSTRACT

A practical direct reductive amination reaction of aldehydes in aqueous sodium formate solution which produces amines in good yields under mild conditions is described. The amount and strength of the acid additives were critical factors to affect the reaction selectivities. This reductive amination method has great application potential for the synthesis of amine products given the mild conditions, short reaction time, the use of water as a solvent, and the use of benign hydrogen sources.

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Nitrogen containing molecules have important uses in such diverse areas as pharmaceuticals and manufacturing. Reductive amination of carbonyls is one of the powerful convergent strategies for synthesizing functionalized amine structures.[1–4] Aqueous reductive amination was not developed until the beginning of last decade. In 2002, Beller group[5] reported for the first time that direct reductive amination of aldehydes with aqueous ammonia can be performed using soluble transition metal catalysts. Afterward, several groups have developed different methods of aqueous reductive amination based on either hydride reagents or hydrogenation using gaseous H_2.[6–11] However, these reactions usually suffer some drawbacks, such as the requirement of high temperatures and moderate to high pressures, or poor atom economy.

Xiao and co-workers[12–16] have pioneered in the catalytic transfer hydrogenation reactions in water. They have used Noyori–Ikariya precatalyst RuCl(TsDPEN)(*p*-cymene) (**1**)[17–19] to hydrogenate ketones and quinolones in high yields. Other examples of catalytic transfer hydrogenation of ketones in aqueous mixed media have also been reported.[20–25] However, there is little information on transfer hydrogenative aqueous reductive amination in the literature.[26–29] This paper reports a practical and efficient catalytic transfer hydrogenative reductive amination of aldehydes using the Noyori–Ikariya precatalyst RuCl(TsDPEN)(*p*-cymene) (**1**) in aqueous sodium formate solution.

As shown in Scheme 1 where benzaldehyde and aniline are used as representatives, the key to aqueous reductive amination using transfer hydrogenation was finding the optimal reaction conditions of temperature and acidity under which selective hydrogenation of the intermediate imine was favored over the starting aldehyde. Also under the optimal conditions, the formylation of amine reagents as well as the reverse reaction of imine formation should be minimized if possible. The results of screening experiments for the reductive amination of benzaldehyde (**2**) with aniline (**3**) using in situ formed **1** as a precatalyst and HCO_2H as an acid additive are shown in Table 1.

Clearly, product *N*-benzylaniline (**5**) selectivity is sensitive to the amount of HCO_2H and temperature. Preliminary experiments on the reduction of *N*-benzylideneaniline (**4**) failed at room temperature due to its melting point (52–54 °C) and the low solubility in water, thus temperature screening began at 50 °C. Without the addition of HCO_2H (entry 1), no *N*-benzylaniline (**5**) but only 6% benzyl alcohol (**6**) was detected, even though all the rest of benzaldehyde was converted to the intermediate imine (**4**). This clearly shows the essential role of acid additive in reductive amination. Addition of 0.5 equiv of HCO_2H produced 40% of **5** and 19% of **6** (entry 2). Under these conditions, the selectivity toward the desired amine product over benzyl alcohol was inferior, however, delightful results were observed after adding additional HCO_2H. The selectivity of **5** versus **6** was enhanced as more HCO_2H was added, however, the tradeoff was that the conversion of benzaldehyde was reduced (entry 4–11). This phenomenon indicates that the hydrogenation of benzaldehyde was significantly suppressed at lower pH, whereas the reverse reaction of imine formation was accelerated under the same conditions. With 20 equiv HCO_2H,

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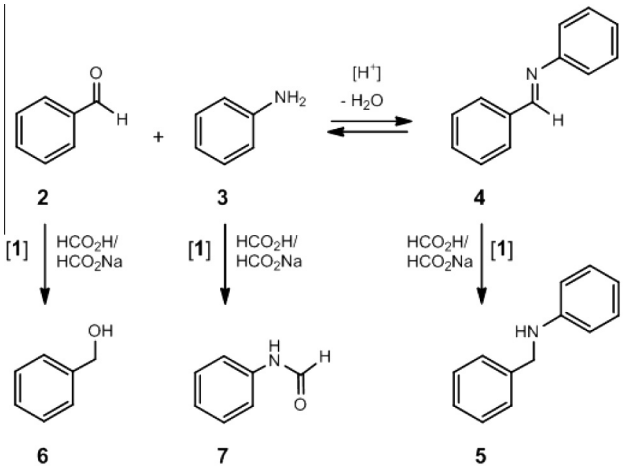

Scheme 1. Reaction scheme for **1**-catalyzed reductive amination.

25% yield of **5** was obtained and no yield of **6** was observed at 1 h reaction (entry 9). Under the same conditions, the extension of reaction time to 4 h increased the yield of **5** to 51% and 2% of **6** was formed (entry 10). Increasing the HCO_2H addition to 50 equiv maintained the high selectivity toward **5**, however, it further reduced the reactivity because of the fast reverse reaction of imine formation. Taking into account both selectivity and reactivity, 20 equiv of HCO_2H was selected to be further optimized. The temperature was then raised from 50 to 60 °C to enhance the reactivity. Delightedly, the reaction accomplished completion within two hours with 94% yield to *N*-benzylaniline (**5**), with only 6% yield loss due to the hydrogenation of benzaldehyde itself (entry 14). It was noted that unreacted aniline was transformed to *N*-phenylformamide (**7**) at 60 °C. It was also observed that insufficient mixing led to inferior results (entry 3). In short, complete conversion in 2 h for a reductive amination reaction performed in water at relatively low temperatures is the most significant finding of this work. Thus, 20 equiv of HCO_2H and 60 °C were chosen as the optimal reaction conditions.

Under the optimized conditions, aqueous direct reductive amination between benzaldehyde and a series of *para*-substituted aniline derivatives as well as aliphatic amines were carried out and results are summarized in Table 2.

Table 1
Screening results of catalytic reductive amination[‡]

Entry	HCO_2H[a] (equiv)	Time (h)	Temp (°C)	Distribution[b] (%)			
				2	**4**	**5**	**6**
1	0.0	0.3	50	0	94	**0**	6
2	0.5	1.0	50	0	41	**40**	19
3[c]	0.5	1.0	50	4	80	**8**	8
4	0.7	1.0	50	5	76	**13**	6
5	1.0	1.0	50	6	80	**11**	3
6	3.0	1.0	50	8	80	**11**	1
7	5.0	1.0	50	11	64	**23**	2
8	10	1.0	50	18	60	**20**	2
9	20	1.0	50	46	29	**25**	0
10	20	4.0	50	2	45	**51**	2
11	50	1.0	50	67	14	**19**	0
12	20	1.0	60	17	10	**71**	2
13	20	1.5	60	12	5	**81**	2
14	20	2.0	60	0	0	**94**	6

‡ Experimental conditions: **1**:**2**:**3**:HCO_2Na = 1:100:100:1000, 1 mmol **1**, 5 mL H_2O, 750 rpm stirrer speed.
[a] Relative to **2** and **3**.
[b] Determined from ^1H NMR or GC–MS analysis.
[c] Stirrer speed at 350 rpm.

Table 2
Reductive amination of benzaldehyde[‡]

Entry	Amine	Time (h)	Distribution (%)			
			2	**4**[c]	**5**[c]	**6**
15[a]	H_2N–C_6H_4(*p*-OCH_3)	2.0	0	0	**89**	0
16[a]	H_2N–C_6H_4(*p*-OC_2H_5)	2.0	0	0	**92**	0
17[a]	H_2N–C_6H_4(*p*-CH_3)	2.0	0	0	**95**	3
18	H_2N–C_6H_5	2.0	0	0	**94**	6
19	H_2N–C_6H_4(*p*-F)	2.0	0	0	**94**	6
20	H_2N–C_6H_4(*p*-Cl)	3.0	0	0	**92**	8
21	H_2N–C_6H_4(*p*-CN)	2.0	0	0	**68**	32
22	H_2N–C_6H_4(*p*-NO_2)	2.0	0	0	**22**	78
23	H_2N–CH_2Ph	2.0	69	0	**0**	31
24[b]	H_2N–CH_2Ph	1.5	0	0	**22**	78
25[b]	H_2N–$(CH_2)_3CH_3$	1.0	0	0	**0**	100

‡ Experimental conditions: **1**:**2**:**3**:HCO_2Na = 1:100:100:1000, 1 mmol **1**, 20 equiv HCO_2H relative to **2**, 5 mL H_2O, 60 °C, 750 rpm stirrer speed.
[a] Yield loss was due to N-formylation of **5**.
[b] 2 equiv HCO_2H relative to **2**, 50 °C.
[c] **4** and **5** refer to the corresponding imine and amine product.

For the reaction of benzaldehyde with aniline derivatives (entry 15–22), complete conversion of benzaldehyde occured within 2 or 3 h, however, selectivities toward **5** versus **6** decreased as the substituents in the *para* position went from electron-donating to electron-withdrawing. *N*-formylated side products (**7**) were detected at varying levels except for the reaction of *p*-nitroaniline. Notably, N-formylation of **5** was also observed for entry 15–17. When same reaction conditions were applied to the reaction between benzaldehyde and aliphatic amines, such as benzyl amine, only 31% of benzaldehyde was converted to **6** and neither **5** nor **4** was observed (entry 23). After screening different amounts of HCO_2H at varying temperature, the best condition was found to be with 2 equiv HCO_2H at 50 °C. However, the selectivity of **5** was still low (22%). With these modified conditions, the reaction between benzaldehyde and *n*-butylamine led to benzyl alcohol (**6**) exclusively (entry 25), suggesting that the reaction conditions involving aliphatic amines need to be further turned.

Valeraldehyde was chosen as the aliphatic aldehyde model to react with amine reagents, and results are shown in Table 3. Given the possible aldol condensation of aliphatic aldehydes under acidic conditions, the amount of HCO_2H used was screened and the temperature was adjusted to 50 °C. In the absence of HCO_2H, only imine was formed after 1 h reaction. In the presence of 1 equiv of HCO_2H, valeraldehyde was subjected to the aldol condensation, and the yield loss due to aldol condensation was 63% and only 27% of desired amine product was obtained (entry 27). Increasing the amount of HCO_2H further promoted the aldol condensation (entry 28). Therefore, the challenge with aliphatic aldehydes relies on suppressing acid-catalyzed self-condensation reactions. After

Table 3
Reductive amination of valeraldehyde[‡]

Entry	Amine	Acid	equiv	Time (h)	Distribution (%)			
					2[a]	**4**[a]	**5**[a]	**8**[b]
26	H_2N–C_6H_5	HCO_2H	0	1.0	0	100	**0**	0
27	H_2N–C_6H_5	HCO_2H	1	1.0	0	10	**27**	63
28	H_2N–C_6H_5	HCO_2H	2	1.0	0	10	**21**	69
29	H_2N–C_6H_5	NaH_2PO_4	1	1.0	0	49	**33**	18
30	H_2N–C_6H_5	NaH_2PO_4	1	4.0	0	6	**59**	35
31	H_2N–CH_2Ph	NaH_2PO_4	1	2.0	0	22	**11**	67
32	H_2N–$(CH_2)_3CH_3$	NaH_2PO_4	1	1.0	0	0	**0**	100

‡ Experimental conditions: **1**:**2**:**3**:HCO_2Na = 1:100:100:1000, 1 mmol **1**, 5 mL H_2O, 60 °C, 750 rpm stirrer speed.
[a] **2**, **4**, and **5** refer to valeraldehyde, the corresponding imine and amine product.
[b] Aldol condensation products of valeraldehyde.

varying different acid additives, NaH_2PO_4 was found the best in terms of minimizing the yield loss due to aldol condensation. Upon addition of 1 equiv NaH_2PO_4, the yield was improved to 33% after 1 h reaction and 59% after 4 h reaction. This is a substantial improvement over formic acid and a promising result that fine tuning of the acid can result in a widening of the scope of this reaction. Reactions between valeraldehyde and aliphatic amines were subjected to more severe aldol condensation. Reaction with benzyl amine only generated 11% of product after 2 h, and reaction with *n*-butylamine resulted in no desired product formation. Therefore the substrate scope of this method is limited to aromatic amines.

For (η^6-arene)Ru(II) piano stool complexes Ts-DPEN is considered the benchmark ligand for assessing the catalytic performance of bifunctional hydrogenation reactions, whether they are asymmetric transformations or not. For this reason the chiral (*S*,*S*)-Ts-DPEN ligand was employed in this study although none of the substrates included enantiomerically pure or racemic α-branched aldehydes. However, using the parent *N*-tosylethylenediamine ligand, lacking any substitution in the backbone, gave 79% of **5** which was inferior to the 94% yield when Ts-DPEN was used under the same conditions. Notedly, compared with the previously reported reductive amination using Noyori–Ikariya catalyst in $HCOOH/NEt_3$ mixture,[30] the aqueous catalytic method is limited to aromatic amines.

In conclusion, the optimal conditions for reductive amination of anilines with sodium formate in aqueous formic acid catalyzed by RuCl(TsDPEN)(*p*-cymene) (**1**) were found. The merits of this reductive amination are short reaction times, mild conditions, and the use of water as solvent.[31] The reactions are carried out under nitrogen but do not require degassing or high pressure gas handling. This reaction can be conducted on the bench top without specialized equipment. The active catalyst is used in 1 mol % and is generated in situ from commercially available reagents. This reaction is particularly suitable for rapid library synthesis, for modification of biological molecules, or for synthesis on a large scale.

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31. *A typical catalytic reaction was carried out in the following manner:* [$RuCl_2$(*p*-cymene)]$_2$ (3.1 mg, 0.005 mmol) and (1*S*,2*S*)-TsDPEN (4.4 mg, 0.012 mmol) were stirred in 3 mL distilled water at 50 °C under N_2 for 15 min. Meanwhile, aniline (91 μL, 1 mmol) was slowly added to 1 mL water solution containing benzaldehyde (102 μL, 1 mmol) at room temperature to immediately form a cloudy white mixture. After 5 min, the substrate mixture was combined with a 1 mL aqueous solution containing HCO_2Na (680 mg, 10 mmol) and HCO_2H (760 μL, 20 mmol). Under N_2, the yellowish catalyst solution was transferred to the substrate/formate/formic acid mixture via syringe and the mixture stirred (750 rpm) at 50 or 60 °C. After a given time interval, catalysis was quenched by cooling the reaction vial to room temperature. Around 3 mL of methylene chloride was added to the reaction vial and mixed thoroughly. Approximately 10 drops of the organic layer were removed and diluted in $CDCl_3$ to make NMR samples. The conversion was determined by NMR spectroscopy and/or GC–MS.