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Direct reductive amination of 5-hydroxymethylfurfural with primary/secondary amines *via* Ru-complex catalyzed hydrogenation†

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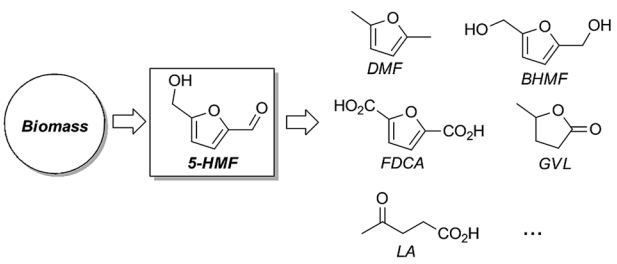
In this work, the complex dichlorobis(2,9-dimethyl-1,10-phenanthroline)ruthenium(II) ($Ru(DMP)_2Cl_2$) was found to effectively catalyze the direct reductive amination of bio-based 5-hydroxymethylfurfural (5-HMF) in the presence of H_2 (g) in ethanol solvent. Good product yields (66–95%) were obtained from a broad substrate scope of primary and secondary amines.

Carbohydrates are abundant organic materials from natural biomass. 5-Hydroxymethylfurfural (5-HMF) is among the top 10 bio-based platform chemicals[1] from carbohydrates,[2–5] such as fructose, glucose, mannose, sucrose, inulin, starch, and cellulose, according to the US Department of Energy.

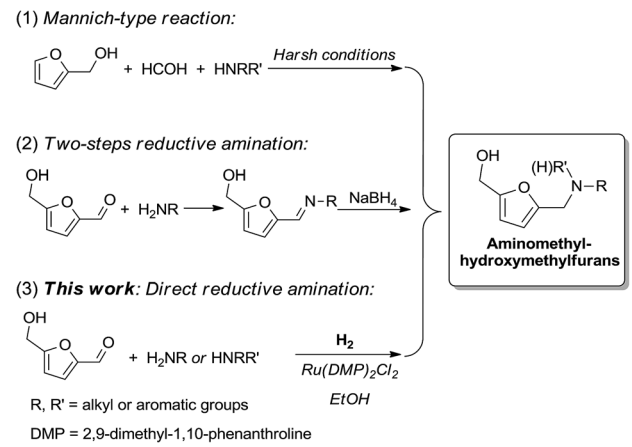
Starting with the versatile bio-based 5-HMF, numerous important chemicals have become available (Scheme 1).[6,7] For example, levulinic acid[8] (LA) is a starting material to prepare polymers, fuel additives, dyestuffs, and pharmaceutical compounds; 2,5-furandicarboxylic acid[9,10] (FDCA) is an alternative of terephthalic and isophthalic acid for polymer production; 2,5-bis(hydroxymethyl)furan[11] (BHMF) is already used to produce polyurethane foams; 2,5-dimethylfuran[12,13] (DMF) is a potential fuel additive; γ-valerolactone[14–16] (GVL) is a promising co-solvent to dissolve cellulose in aqueous phase and can serve directly as a gasoline blender.

Aminomethyl-hydroxymethylfuran derivatives (Scheme 2) are well known for their widely recognized pharmaceutical activities,[17–22] including muscarinic receptor agonist, *Pyricularia oryzae* inhibitory, calcium antagonistic activity, cholinergic agent. These structures are generally produced from furfural alcohol or furfural.[17,23] However, these reported procedures usually require harsh reaction conditions with lower selectivity.

Stevens reported a one-pot, two-steps reductive amination of 5-HMF in the absence of catalyst (Scheme 2).[24] However, this two-steps procedure starts with imine formation, which limits the scope of amine substrates, followed by the use of excess $NaBH_4$, which generates copious amounts of waste besides the costly hydrogenation reagent.



Scheme 1 5-HMF serves as a versatile platform for producing various valuable chemicals.



Scheme 2 Synthetic routes for preparing aminomethyl-hydroxymethylfurans.

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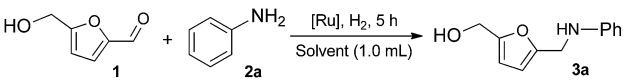
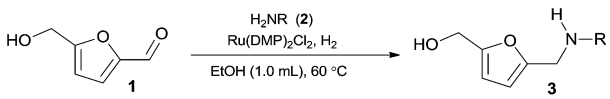
Table 1 Optimization of Ru-catalyzed direct reductive amination of 5-HMF[a]

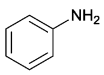
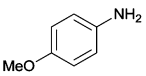
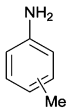
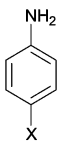
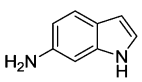
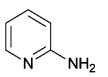
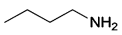


Entry	Catalyst	Temperature (°C)	Solvent	Pressure (psi)	Yield[b] (%)
1	$Ru(DMP)_2Cl_2$	100	EtOH	132	91
2	$Ru(Phen)_2Cl_2$	100	EtOH	132	0[c]
3	$Ru(Dmbp)_2Cl_2$	100	EtOH	132	54
4	$Ru(Bipy)_2Cl_2$	100	EtOH	132	0[c]
5[d]	$[Ru(p\text{-cymene})Cl_2]_2$	100	EtOH	132	20
6	$Ru(DMP)_2Cl_2$	100	MeOH	132	28
7	$Ru(DMP)_2Cl_2$	100	H_2O	173	28
8	$Ru(DMP)_2Cl_2$	100	EtOH	173	98
9	$Ru(DMP)_2Cl_2$	80	EtOH	173	98
10	$Ru(DMP)_2Cl_2$	60	EtOH	173	98
11	$Ru(DMP)_2Cl_2$	50	EtOH	173	68

[a] Reaction conditions: 5-HMF (0.5 mmol), aniline (1.1 equiv. to 5-HMF, 0.55 mmol), catalyst (0.0025 mmol, 0.5 mol% to 5-HMF), and solvent (1.0 mL), under H_2 for 5 hours. [b] GC-MS yield, anisole was the internal standard. [c] Imine was detected by GC-MS. [d] Catalyst (0.00125 mmol, 0.25 mol% to 5-HMF) was used.

Table 2 $Ru(DMP)_2Cl_2$-catalyzed direct reductive amination of 5-HMF with primary amines[a]



Entry	Amine		Product	Time (h)	Yield[b] (%)
1		**2a**	**3a**	5	93
2		**2b**	**3b**	5	89
3		*ortho*-Me (**2c**)	**3c**	4	43 (79)[c]
4		*meta*-Me (**2d**)	**3d**	4	90
5		*para*-Me (**2e**)	**3e**	4	91
6		X = F (**2f**)	**3f**	20	94
7		X = Cl (**2g**)	**3g**	20	95
8		X = Br (**2h**)	**3h**	20	95
9		X = CO_2Et (**2i**)	**3i**	24	69[d]
10		X = COMe (**2j**)	**3j**	20	66[d]
11		X = CN (**2k**)	**3k**	24	0[d]
12		X = $CONH_2$ (**2l**)	**3l**	24	0[d]
13		**2m**	**3m**	5	58[e]
14		**2n**	**3n**	20	0
15		**2o**	**3o**	20	0

[a] Reaction conditions: $Ru(DMP)_2Cl_2$ (0.5 mol% to 5-HMF), 5-HMF (0.5 mmol), amine (0.55 mmol), H_2 (173 psi), EtOH (1.0 mL), 60 °C. [b] Isolated yield. [c] The isolated yield of 20 h reaction was given in bracket. [d] 80 °C. [e] Yield of corresponding imine.

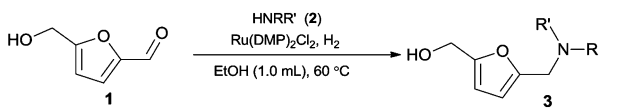
Ruthenium-catalyzed reductive amination has been well developed for the synthesis of functional amines.[25–29] Moreover, the direct reductive amination has been proven to be a much more environmentally friendly method.[30–36] For example, hydrogen gas or formic acid were used as the reductant for the synthesis of bioactive molecular dual orexin antagonist[37] and sitagliptin.[38] Surprisingly, the direct reductive amination route involving 5-HMF and amines was rarely reported.[39] In this paper, the direct reductive amination of 5-HMF with various primary and secondary amines by dichlorobis(2,9-dimethyl-1,10-phenanthroline)ruthenium(II) ($Ru(DMP)_2Cl_2$) catalyzed hydrogenation is reported (Scheme 2). To the best of our knowledge, this is the first example of applying the easily prepared $Ru(DMP)_2Cl_2$ as an efficient direct reductive amination catalyst. H_2 is employed as the reductant, which improves the atom economy of the reaction. Using bio-based ethanol (EtOH) solvent as the reaction media further improves the sustainability of the strategy.

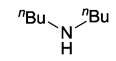
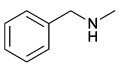
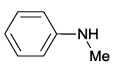
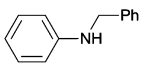
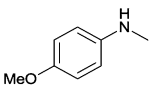
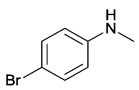
Initial studies began with the reaction of 5-HMF (**1**) with aniline (**2a**) as a model reaction for optimizing the reaction conditions. Easily prepared Ru(II)-based complexes, including dichlorobis(2,2′-bipyridine)ruthenium(II) ($Ru(Bipy)_2Cl_2$),[40] dichlorobis(6,6′-dimethyl-2,2′-bipyridine)ruthenium(II) ($Ru(Dmbp)_2Cl_2$), dichlorobis(1,10-phenanthroline)ruthenium(II) ($Ru(Phen)_2Cl_2$),[41] dichlorobis(2,9-dimethyl-1,10-phenanthroline)ruthenium(II) ($Ru(DMP)_2Cl_2$),[42] and dichloro(*p*-cymene)ruthenium(II) dimer ($[Ru(p\text{-cymene})Cl_2]_2$) were tested in EtOH solution. Bidentate ligand seems to play an important role to control reaction selectivity. $Ru(DMP)_2Cl_2$ and $Ru(Dmbp)_2Cl_2$ bearing sterically hindered ligands exhibited good catalytic activity (entries 1 and 3), while Phen or Bipy based catalysts gave no hydrogenation product and only imines were detected (entries 2 and 4). Probably the Ru-intermediate linked with sterically hindered ligand prefers *cis*-coordination mode,[43] which favours H_2 activation. Only 28% yield was achieved when the reaction was carried out in methanol (entry 6). Even at higher H_2 pressure, only 28% yield of product was obtained in water using $Ru(DMP)_2Cl_2$ as the catalyst (entry 7). It is possibly due to low-solubility of $Ru(DMP)_2Cl_2$ in water. Increasing H_2 pressure for the $Ru(DMP)_2Cl_2$ catalyst in EtOH from 132 psi (entry 1) to 173 psi was found to further improve the product yield (entry 8). Interestingly, $Ru(DMP)_2Cl_2$ remained high in catalytic reactivity when the temperature decreased to 60 °C (entry 10), while imine could be detected and the product yield decreased to 68% at 50 °C (entry 11). Under optimized conditions, subsequent direct reductive amination of 5-HMF with various amines was performed with $Ru(DMP)_2Cl_2$ as the catalyst in EtOH at 60 °C under a H_2 atmosphere (173 psi) (Table 1).

The direct reductive amination of bio-based 5-HMF with primary amines was performed under optimized conditions, and the results are shown in Table 2. Previous studies[24] on two-steps reductive amination have indicated that aromatic amines showed poor reactivities, while most of the aromatic amines showed very high reactivities by the combination of the $Ru(DMP)_2Cl_2$ catalyst, ethanol solvent under appropriate H_2 pressure in this work. The reactions of aromatic amines bearing electron-donating groups (**2b**, **2d**, and **2e**) smoothly proceeded to furnish the corresponding products **3b**, **3d**, and **3e** in high yields (89%, 90%, and 91%, respectively). Only a moderate yield (43%, entry 3) was obtained from the reaction of 5-HMF with **2c**, which bears the *ortho*-methyl on its benzene ring. The catalyst prefers *cis*-coordination mode in solvent as proposed by Collin and Sauvage[43] because of the unfavorable steric interactions for DMP ligand. This may explain why the sterically hindered substrate **2c** showed lower reactivity. However, the reaction yield could still be improved to 79% after a long reaction time (entry 3). The aromatic amines bearing electron-withdrawing groups (entries 6–10) required much longer reaction time or higher temperature to reach good yields (94%, 95%, 95%, 69%, and 66%, respectively). No desired products were obtained when aromatic amines bear nitrile and amide groups (entries 11 and 12). These results indicate that the reactivity is remarkably suppressed by the electron-withdrawing groups on the benzene ring of the aromatic amine. The reactivity of heteroaromatic amines was also studied (entries 13 and 14). For 6-aminoindole (**2m**), only corresponding imine was obtained (entry 13). The 2-aminopyridine (**2n**) could act as a potential ligand and strongly coordinate to the catalyst; therefore no desired product was obtained (entry 14). The reaction of primary alkylamines butylamine (**2o**) was carried out under the conditions (entry 15). However, no desired product was detected.

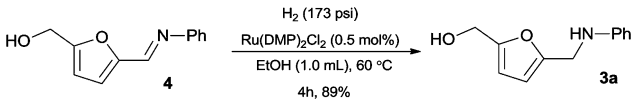
The above results prompted us to investigate the direct reductive amination of 5-HMF with secondary amines (Table 3).

Table 3 $Ru(DMP)_2Cl_2$ catalyzed direct reductive amination of 5-HMF with secondary amines[a]



Entry	Amine		Product	Time (h)	Yield[b] (%)
1[c]		**2p**	**3p**	6	83
2		**2q**	**3q**	5	67
3		**2r**	**3r**	5	87
4		**2s**	**3s**	6	79
5		**2t**	**3t**	19	74
6		**2u**	**3u**	6	72
7		**2v**	**3v**	19	67

[a] Reaction conditions: $Ru(DMP)_2Cl_2$ (0.5 mol% to 5-HMF), 5-HMF (0.5 mmol), amine (0.55 mmol), H_2 (173 psi), EtOH (1.0 mL), 60 °C. [b] Isolated yield. [c] The reaction was carried out at 30 °C.



Scheme 3 Reductive amination of imine catalyzed by $Ru(DMP)_2Cl_2$.

Interestingly, the reaction of 5-HMF with cyclic aliphatic morpholine (**2j**) could be carried out at 30 °C with high isolated yield (83%, entry 1). The reactions of dibutylamine (**2k**) and *N*-methyl-1-phenylmethanamine (**2l**) amines proceeded well at 60 °C (entries 2 and 3), while no desired products were detected at 30 °C. Aromatic secondary amines also showed good reactivity (entries 4–7). However, electron-deficiency aromatic secondary amine (entry 7) requires much longer reaction time to reach high yield.

The hydrogenation of imine **4** was studied, and 89% of **3a** was obtained (Scheme 3). This result supports our proposed mechanism that the direct reductive amination of 5-HMF with amines proceeds *via* imine formation, followed by hydrogenation of the imine. Steric effect and electronic effect may influence the coordination chemistry of the imine to Ru-complex, which may further impact the hydrogenation reactivity. Mechanism studies are under way as well as exploring new water-soluble Ru(II)-based catalysts to investigate the reactivity and recyclability in water.

Conclusions

In conclusion, a simple and efficient procedure to synthesize aminomethyl-hydroxymethylfurans by direct reductive amination of biomass derived 5-HMF has been developed. Using H_2 as reductant and EtOH as solvent should further improve sustainability of the reaction. Most of primary and secondary amines showed good reactivities and yields. The present method is efficient for synthesizing a number of new aminomethyl-hydroxymethylfurans for the pharmaceutical industry. The mechanism involves imine formation from the direct reductive amination of 5-HMF with amines, followed by hydrogenation of the imine.

Acknowledgements

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