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Carbohydrate-Derived Organocatalysts for the Reduction of Imines with Trichlorosilane

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Abstract

The backbone of D-glucosamine hydrochloride was fine-tuned and modified by protecting the hydroxyl groups. In order to reduce imines with trichlorosilane, the carbohydrate-derived organocatalysts were prepared and screened. Methyl-4,6-O-benzylidene-2-amino-2-deoxy-α-D-glucopyranoside was found as the best catalyst. The reduction was proceeded under $CHCl_3$ as solvent at 40˚C, affording 68% - 94% yield.

Keywords

Carbohydrate, Organocatalyst, Reduction, Imine

1. Introduction

The reduction of imines is an attractive approach for preparing amines, which have a wide application in the pharmaceuticals, agricultural chemicals and bioactive compounds [1]. In addition to the reductive amination catalyzed by the transition metals [2], boranes [3] and borohydrides [4], an organocatalytic approach is a promising method to obtain amine compounds [1]. In the organocatalytic approach, trichlorosilane and Hantzsch dihydropyridine were separately used as reducing agents for the reduction of imines in the presence of organocatalyst. Moreover, organocatalysis has received hot attention to catalyze the reaction. In spite of the rapid development of organocatalysts, it is important to continue exploiting and developing more organocatalysts.

Until now, carbohydrates have been developed as organocatalysts for application in organic synthesis [5]. In 2007, Becker *et al.* [6] reported enantioselective Streck and Mannich reactions catalyzed by D glucosa-mine-derived bifunctional urea schiff base organocatalysts. Subsequently, Becker *et al.* [7] synthesized carbohydrate-derived bifunctional primary amine-thiourea catalysts to catalyze Michael addition of aromatic ketones with nitroolefins. In 2003, Dekamin *et al.* [8] used the chitosan as recoverable and reused catalyst for the expeditious synthesis of α-amino nitriles and imines under mild conditions. In our preliminary work, we developed the carbohydrate-derived amino alcohols [9] and novel carbohydrate-derived prolinamide [10] to catalyze asymmeteric

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aldol reaction. As a part of our continued interests in carbohydrates [9]-[16], herein we reported carbohydrate-derived organocatalysts for the reduction of imines with trichlorosilane.

2. Experimental Details

2.1. General Methods

Melting points were determined on an X4-Data microscopic melting point apparatus and were uncorrected. Optical rotation values were measured on a PerkinElmer P241 polarimeter operating at 589 nm. Nuclear magnetic resonance (NMR) spectra were measured at 400 MHz (^{1}H) or at 100 MHz (^{13}C) on a Bruker Avance DRX-400 spectrometer. All reactions were monitored by analytical thin-layer chromatography (TLC) from Merck with detection by spraying with 5% (w/v) phosphomolybdic acid in ethanol and subsequent heating or UV. All reagents and solvents were general reagent grade unless otherwise stated.

2.2. The Synthesis of Carbohydrate Derived Organocatalysts 4-5

The carbohydrate derived organocatalysts **4-5** were prepared by previously described methods. [9] [10] [17] [18]

2.3. Methyl-4,6-O-Benzylidene-2-Amino-2-Deoxy-α-D-Glucopyranoside 5a

White solide. M.p. 166˚C - 167˚C; $[\alpha]_D^{20}$ = +103.1 (c = 0.905, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.41 (m, 2H), 7.41 - 7.35 (m, 3H), 5.61 (s, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 4.18 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.76 3.56 (m, 3H), 3.48 (t, *J* = 9.2 Hz, 1H), 3.29 (s, 3H), 2.81 (dd, *J* = 9.7, 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ142.99, 134.09, 133.24, 131.63, 106.13, 103.97, 87.27, 73.27, 72.63, 67.68, 59.96, 59.35. Anal. Calcd. (%) for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98; O, 28.44. Found: C, 59.764; H, 6.75; N, 4.81.

2.4. Benzyl-4,6-O-Benzylidene-2-Amino-2-Deoxy-α-D-Glucopyranoside 5b

White solide. Mp 172.4˚C - 173.8˚C. $[\alpha]_D^{20}$ = +59.7 (c = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 - 6.91 (m, 10H), 5.53 (s, 1H), 4.90 (d, *J* = 3.6 Hz, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.24 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.88 (td, *J* = 9.9, 4.8 Hz, 1H), 3.83 - 3.66 (m, 2H), 3.49 (t, *J* = 9.3 Hz, 1H), 2.81 (dd, *J* = 9.7, 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.86, 137.67, 128.97, 128.42, 128.06, 127.89, 127.76, 126.62, 101.47, 99.58, 82.08, 71.70, 69.33, 68.74, 63.30, 57.06. Anal. Calcd. (%) for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; O, 22.38. Found: C, 67.12; H, 6.32; N, 3.81.

2.5. Methyl-4,6-O-Benzylidene-2-Acetylamino-2-Deoxy-α-D-Glucopyranoside 4a

White solide. M.p. 250˚C - 252˚C; $[\alpha]_D^{20}$ = +90 (c = 0.11, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 7.90 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 6.6, 3.2 Hz, 2H), 7.41 - 7.35 (m, 3H), 5.61 (s, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 4.18 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.89 - 3.80 (m, 1H), 3.74 (t, *J* = 10.1 Hz, 1H), 3.69 - 3.63 (m, 1H), 3.63 - 3.56 (m, 1H), 3.48 (t, *J* = 9.2 Hz, 1H), 3.29 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.43, 137.74, 128.84, 127.99, 126.37, 100.87, 98.71, 82.01, 68.02, 67.37, 62.43, 54.71, 54.10, 22.57. Anal. Calcd. (%) for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33; O, 29.69 Found: C, 59.67; H, 6.72; N, 4.21.

2.6. Benzyl-4,6-O-Benzylidene-2-Acetylamino-2-Deoxy-α-D-Glucopyranoside 4b

White solide. M.p. 189˚C - 192˚C; $[\alpha]_D^{20}$ = +56 (*c* = 0.21, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 8.00 (d, *J* = 8.2 Hz, 1H), 7.49 - 7.43 (m, 2H), 7.42 - 7.33 (m, 7H), 7.30 (ddd, *J* = 8.4, 3.6, 1.8 Hz, 1H), 5.62 (s, 1H), 5.19 (d, *J* = 5.8 Hz, 1H), 4.80 (d, *J* = 3.6 Hz, 1H), 4.70 (d, *J* = 12.6 Hz, 1H), 4.49 (d, *J* = 12.6 Hz, 1H), 4.18 - 4.11 (m, 1H), 3.86 (ddd, *J* = 10.6, 8.3, 3.7 Hz, 1H), 3.72 (ddd, *J* = 21.9, 12.6, 7.9 Hz, 3H), 3.51 (t, *J* = 9.0 Hz, 1H), 1.84 (d, *J* = 9.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 169.93, 138.19 (d, *J* = 3.3 Hz), 129.34, 128.7, 128.49, 128.07 (d, *J* = 7.3 Hz), 126.86, 101.34, 97.43, 69.06, 68.48, 67.73, 63.33 54.67, 23.00. Anal. Calcd. (%) for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51; O, 24.03. Found: C, 66.04; H, 6.15; N, 3.48.

2.7. General Experimental Procedure for the Reduction of Imines with Trichlorosilane Catalyzed by 5a

To a stirred solution of imine **6** (0.5 mmol) and catalyst **5a** (25 mg, 0.05 mmol) in dry $CHCl_3$ (2 mL) was added

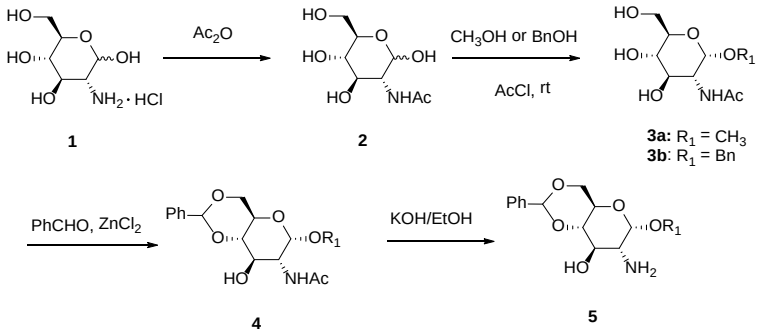
the trichlorosilane (0.1 ml, 1 mmol) at 0˚C and the reaction mixture was stirred at 0˚C for 24 h. Then, saturated $NaHCO_3$ (2 ml) was added and extracted with $CHCl_3$ (3 × 5 ml). The combined organic phases were washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. Then the crude product was purified by column chromatography through silica gel, eluting with 1:99 ethyl acetate/petroleum ether solvent mixture, to give the pure **7**.

***N*-Phenyl-1-phenylethylamine 7a** Yield 91%. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.18 (m, 4H), 7.14 (t, J = 7.1 Hz, 1H), 7.01 (t, J = 7.6 Hz, 2H), 6.56 (t, J = 7.2 Hz, 1H), 6.43 (d, J = 7.6 Hz, 2H), 4.41 (q, J = 6.6 Hz, 1H), 1.43 (d, J = 6.7 Hz, 3H). ^{13}C NMR (1010 MHz, $CDCl_3$) δ 146.26, 144.20, 128.07, 127.60, 125.83, 124.82, 116.21, 112.29, 52.43, 23.98.

3. Results and Discussion

First we attempted to synthesize the carbohydrate-derived organocatalysts (**Scheme 1**). The amino group in the position C-2 of D-glucosamine hydrochloride **1** was first protected by acetylation. The hydroxyl group in the position C-1 was modified by glycoside and benzyl glycoside. Then the hydroxyl groups in the position C-4 and C-6 were protected by benzylidene acetal. Finally, the acetyl group in the position C-2 was removed by alkaline alcohol solution. The carbohydrate-derived alcohols **5** were obtained.

In order to screen the catalysts (**Figure 1**), the reduction of imine **5a** with trichlorosilane was investigated as a model reaction. The results of the catalysts screening and condition optimizations are summarized in **Table 1**. In our initial practice, we attempted to use carbohydrate-derived amino alcohols **5a** and **5b** as catalysts at room temperature, affording 74% yield and 63% yield separately (**Table 1**, entries 1-2). Then, the carbohydrate-derived



Scheme 1. Synthesis of carbohydrate-derived alcohols.

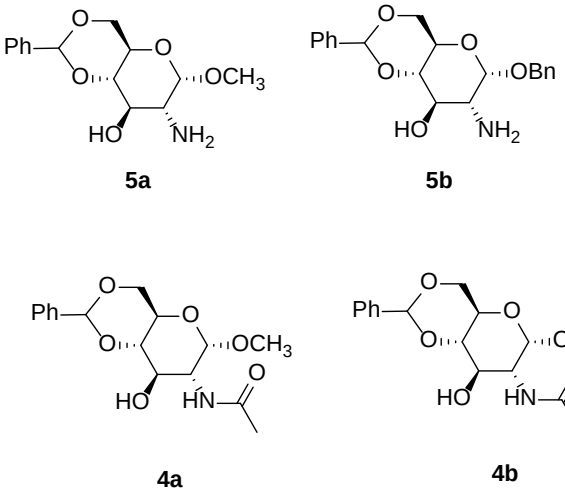
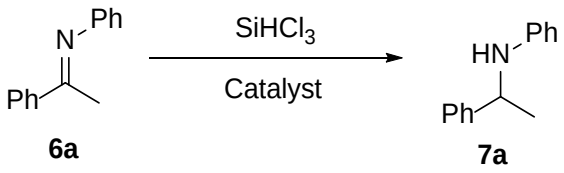


Figure 1. Structures of carbohydrate-derived organocatalysts evaluated in this study.

Table 1. Asymmetric reduction of imine **6a**[a].

Entry	Catalyst	Solvent	Temp (°C)	Yield (%)[b]
1	**5a**	CH_2Cl_2	rt	74
2	**5b**	CH_2Cl_2	rt	63
3	**4a**	CH_2Cl_2	rt	67
4	**4b**	CH_2Cl_2	rt	61
5	**5a**	Toluene	rt	34
6	**5a**	$CHCl_3$	rt	81
7	**5a**	$ClCH_2CH_2Cl$	rt	54
8	**5a**	$CHCl_3$	0	69
9	**5a**	$CHCl_3$	40	91

[a]The reactions were carried out with 10 mol % catalyst and 2.0 equiv of $SiHCl_3$ on a 0.5 mmol scale in 2.0 mL of solvent for 24 h. [b]Isolated yield based on the imine.



6a **7a**

acetamide alcohols **4a** and **4b** also could catalyze the reduction of imine **6a** (**Table 1**, entries 3-4). The 67% yield and 61% yield were obtained separately. Thus, the catalyst effect of carbohydrate-derived amino alcohols **5a** was best. Then the optimization of reaction conditions was studied. The effect of solvent was firstly investigated (**Table 1**, entries 1, 5-7). We found that trichloromethane was the best solvent affording the product with 81% yield (**Table 1**, entry 6). Therefor, the reaction temperature was further studied (**Table 1**, entries 1, 8-9). The best result was obtained at 40˚C, affording 91% yield (**Table 1**, entry 9). Thus, we selected 40˚C as the best temperature in this reaction.

Encouraged by these results, the substrate scope of the reduction of imines with trichlorosilane was further studied under the optimized conditions. The results were summarized in **Table 2**. For aromatic *N*-Ph imines **6b-6g** with electron-withdrawing groups, only 68-77% yields were obtained (**Table 2, entries 2-4**). When aromatic *N*-Ph imines **6c-6e** with electron-donating groups were reduced, the yields were increased to 94-95% (**Table 2, entries 5-6**). The benzyl *N*-Ph imine **6h** could afford the 91% yield (**Table 2, entry 7**). Phenyl *N*-aryl imines **6i-6k** with electron-withdrawing groups could be reduced in 78-82 yields (**Table 2, entries 9-11**). When the Phenyl *N*-aryl imine **6l** with electron-donating group, the yield was also increased (**Table 2, entry 12**). *N*-aryl propiophenone imines were similar to *N*-Ph acetophenone imines, affording the 78% - 89% yields (**Table 2, entries 13-15**).

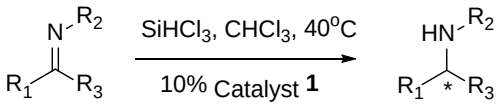
4. Conclusion

In sum, we have described carbohydrate-derived organocatalyst for the reduction of imines with trichlorosilane. The backbone of D-glucosamine hydrochloride was fine-tuned and modified. The amino group in the position C-2 was first protected by acetylation. The hydroxyl group in the position C-1 was modified by glycoside and benzyl glycoside. Then the hydroxyl groups in the position C-4 and C-6 were protected by benzylidene acetal. Finally, the acetyl group in the position C-2 was removed by alkaline alcohol solution. The carbohydrate-derived organocatalysts were screened. Methyl-4,6-O-benzylidene-2-amino-2-deoxy-α-D-glucopyranoside was selected as the best catalyst. This reduction reaction of imines with trichlorosilane could be carried out in $CHCl_3$ at 40˚C, affording 68% - 94% yield.

Table 2. Asymmetric reduction of imine **6** with catalyst **1**[a].

Entry	Imine	R_1	R_2	R_3	Yield (%)[b]
1	**6a**	C_6H_5	C_6H_5	CH_3	91
2	**6b**	C_6H_5	4-FC_6H_4	CH_3	74
3	**6d**	C_6H_5	4-ClC_6H_4	CH_3	68
4	**6f**	C_6H_5	3-ClC_6H_4	CH_3	76
5	**6g**	C_6H_5	3-BrC_6H_4	CH_3	77
6	**6c**	C_6H_5	2-$CH_3C_6H_4$	CH_3	95
7	**6e**	C_6H_5	4-$CH_3C_6H_4$	CH_3	94
8	**6h**	C_6H_5	$C_6H_4CH_2$	CH_3	91
9	**6i**	4-FC_6H_4	C_6H_5	CH_3	81
10	**6j**	4-ClC_6H_4	C_6H_5	CH_3	78
11	**6k**	4-$NO_2C_6H_4$	C_6H_5	CH_3	82
12	**6l**	4-$CH_3C_6H_4$	C_6H_5	CH_3	94
13	**6m**	C_6H_5	C_6H_5	CH_3CH_2	87
14	**6n**	4-ClC_6H_4	C_6H_5	CH_3CH_2	78
15	**6o**	4-$CH_3C_6H_4$	C_6H_5	CH_3CH_2	89

[a]The reactions were carried out with 10 mol % catalyst and 2.0 equiv of $SiHCl_3$ on a 0.5 mmol scale in 2.0 mL of $CHCl_3$ at 40 °C for 24 h. [b]Isolated yield based on the imine.



6 **7**

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