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Assessing the effectiveness of different chiral and achiral phosphoric acids in presence of thiourea co-catalyst in co-operative organocatalytic stereoselective glycosylation reactions

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Organocatalytic glycosylation reactions were attempted with an aim to achieve stereoselectivity using chiral TRIP (Binol derived phosphoric acid) and achiral biphenyl phosphoric acids as catalyst and a thiourea derivative as co-catalyst, based on the transition model suggested by Schmidt group[1] during co-operative organocatalysis. Though the stereoselectivity as reported by the Schmidt was not observed, but it was found that the thiourea co-catalyst assisted the catalyst in making the reaction faster, especially in the cases where the catalyst was itself not a strong enough acid.

Keywords: Chiral, achiral, thiourea, phosphoric, acids, glycosylation, organocatalysis

Organocatalysis, or the use of small organic molecules to catalyze organic transformations, is a relatively new and popular field within the domain of asymmetric synthesis[2]. The regioselective and stereoselective synthesis of glycosidic bonds still remains as one of the most challenging areas within organic synthesis. Despite the broad use of organocatalysis within asymmetric synthesis, its application towards oligosaccharide synthesis by diastereoselective glycosylation is still in its infancy[3].

However recent developments in the growing field of organocatalysis[4] have provideda section of new asymmetric process that may be more applicable to the control of the diastereoslectivity of glycosylation reactions. In particular, the potential use of chiral Brønsted acids for the activation of glycosyl donors represents an attractive prospect for controlling the stereochemistry of the glycosylation product[5].

Chiral organocatalysts

Fairbanks *et al*. reported that *β*-selective glycosylations of glycosyltrichloroacetamidates can be achieved using a chiral BINOL-derived phosphoric acid catalyst[5] .

Chiral thioureas have been employed by Jacobsen *et al*. for the catalytic enantioselective addition of silyl ketene acetals to oxocarbenium ions and preliminary results of the application of this methodology towards glycosylation reactions were also reported[6].

Following on from the work of Fairbanks, the Toshima group[7] used the same chiral phosphoric acid as an organocatalyst, and demonstrated that glycosylation using a racemic mixture of a chiral alcohol as the acceptor was selective for one enantiomer and in addition was *β*-selective.

Achiral organocatalysts

The catalytic use of phenylboron difluoride, diphenylboron fluoride, and phenylsilyltrifluoride as activators for glycosylation reactions of glycosyltrichloroacetimidates was demonstrated by Schmidt *et al*[8]. Good to excellent yields and useful *β*-selectivities were achieved in many of the reported examples.

Schreiner *et al*. had reported organocatalytictetrahydropyranylation of alcohols, using thiourea derivative as the organocatalyst leading to tetrahydropyranylation of alcohols[9].

Later McGarrigle *et al*. adopted the same methodology and organocatalyst to develop a glycosylation method[10]. Dihydropyran was replaced with glycols to achieve glycosylation reactions affording 2-deoxyglycosides.

Cooperative catalysis in glycosylation reactions with *O*-glycosyltrichloroacetimidates as glycosyl donors

The use of thioureas for the catalysis of glycosylation reactions using various kinds of donors

has been reported by several research groups[3] Schmidt[1] group reported a series of β stereoselective glycosylation reactions by activation of trichloroacetamidate donors with an achiral phosphoric acid and an achiral thiourea as organocatalysts. However, when the reactions were carried out without the thiourea co-catalyst, the selectivities observed were extremely poor.

Schmidt proposed that the observed stereoselectivity arose from a co-operative effect between the thiourea and the acid catalyst as shown in Scheme I.

Interestingly, even when TMSOTf and thiourea derivative were used as the catalyst and co-catalyst respectively, much higher stereoselectivity was seen when compared to the reaction that was performed without the co-catalyst.

Results and Discussions

Glycosylation reactions were carried out with α-2,3,4,6-tetra-*O*-benzyl-D-galactopyranose trichloro-acetimidate1 as donor, and 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose asacceptor 2, and the BINOL derived phosphoric acid catalyst, "TRIP" (Figure 1) as the acid catalyst, which is similar in structure to those used previously by the Fairbanks' group[5] and the thiourea derived co-catalyst 5, used by Schmidt[1]. The choice of TRIP was based on the fact that, it has been used as a powerful Brønsted acid catalyst for asymmetric synthesis[11]. Both (*R*)-TRIP (3) and (*S*)-TRIP (4) were used as catalysts to observe any effect of catalyst stereochemistry on the stereoselectivivity of glycosylation.

The (*R*) and (*S*) TRIP organocatalysts were purchased and the co-catalyst thiourea derivative (**5**) was synthesized starting from thiocarbonyldiimidazole and *bis*-trifluoromethylaniline as shown in Scheme II[12].

Synthesis of the donor

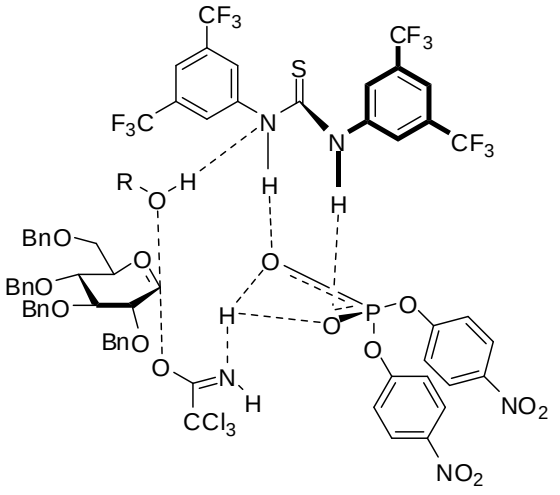
The trichloroacetimidate donor **1**,chosen for direct comparison with Schmidt's[1] and Fairbanks[5] work,was synthesized by reaction of tetrabenzylgalactopyranose with trichloroacetonitrile in presence of catalytic amount of DBU (Scheme III)[13]

Results and Discussion

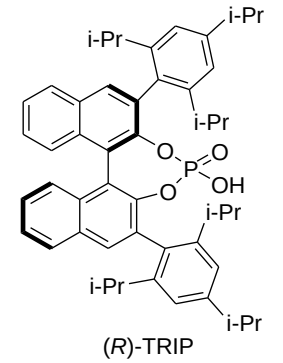
Organocatalytic stereoselective synthesis of DAG glycoside

The glycosylation reaction that was studied is shown in Scheme IV.

When diacetone galactose **2**was glycosylated with the donor **1**,using TMSOTf as the catalyst, in the absence of co-catalyst **5**, the disaccharide **6** was obtained as a mixture of diastereomers in a ratio of β:α = 3.9:1. However, in contrast to the report of Schmidt, the addition of co-catalyst **5**did *not* lead to any improvement in the stereoselectivity of the



Scheme I



(*R*)-TRIP

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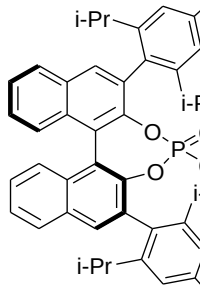

(*S*)-TRIP

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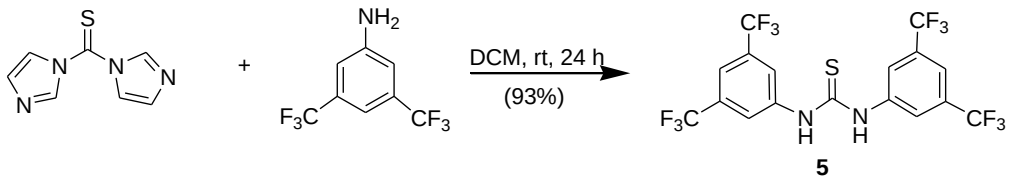
Figure 1



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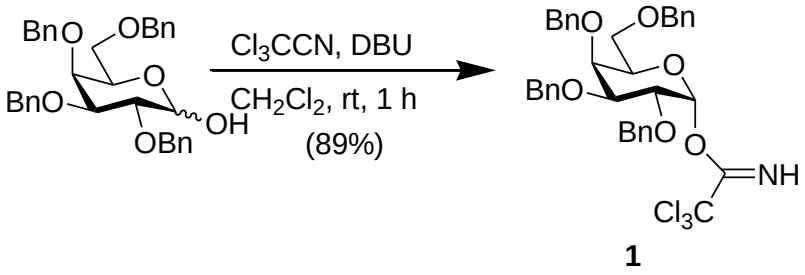
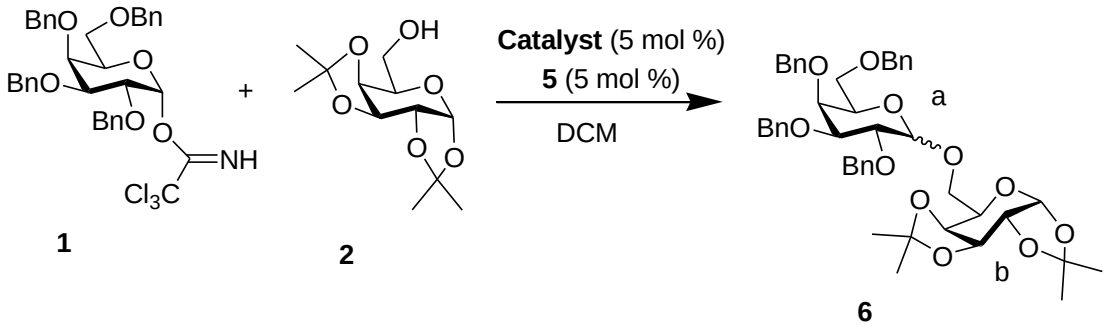
Scheme II



Scheme III



Scheme IV

reaction (β:α = 3.7:1)). When the asymmetric organocatalysts, (*R*)-TRIP **3** and (*S*)-TRIP **4** were used along with the co-catalyst **5**, both gave very poor stereoselectivity (β:α = 1.5:1) respectively. Furthermore, in the absence of co-catalyst **5**, no stereoselectivity was observed when (*R*)-TRIP **3** was used as the catalyst. However, interestingly, when (*S*)-TRIP **4** was used as catalyst in absence of the co-catalyst **5** an improvement was observed in β stereoselectivity (β:α = 1.5:1). These results raise serious doubts about any co-operative effect between the catalyst and co-catalyst during the glycosylation reaction. Since only very modest stereoselectivity has been observed further investigations were required.

Interestingly, in terms of product formation it was observed that reactions carried out in the presence of co-catalyst **5** proceeded to completion. In the absence of the co-catalyst, reactions did not reach completion even after stirring for 96 h. It was concluded that TRIP alone is not acidic enough to efficiently catalyze the reaction for the reaction to undergo completion, and the co-catalyst certainly improved the catalytic efficiency by some form of synergistic interaction.

In order to investigate the effect of co-catalyst **5**, the glycosylation reaction was carried out using only a catalytic amount of **5** without using any additional acid catalyst. However,**5** proved to be a very inefficient catalyst as the maximum yield of disaccharide obtained was only 9%. However, the stereoselectivity of this reaction was found to be the same (1.5:1, β:α) as when the reactions were carried out using both (*R*)-TRIP **3** and (*S*)-TRIP **4** together with the co-catalyst **5**.

Since the stereoselectivity of the glycosylation reactions investigated so far was poor, glycosylations were attempted with the catalyst *bis*(4-nitrophenyl)phosphoric acid **7**, which had shown the best results in stereoselectivity in the experiments reported out by the Schmidt group[1]. This acid [pK_a 2.79 (H_2O)] was found to be more effective as the reaction always went to completion either with or without any added co-catalyst. In contrast to the report by Schmidt the stereoselectivity was slightly higher (β:α = 2.3:1) when the reaction was carried out without using the co-catalyst **5**, as compared to the reaction performed with the co-catalyst (β:α = 2:1). Similar observations were made when the reaction was carried out using diphenyl phosphoric acid **8** as catalyst. These results directly contradict the report by Schmidt and we can conclude that the transition state suggested by Schmidt is not applicable for reactions with diacetone galactose **2** as the acceptor.

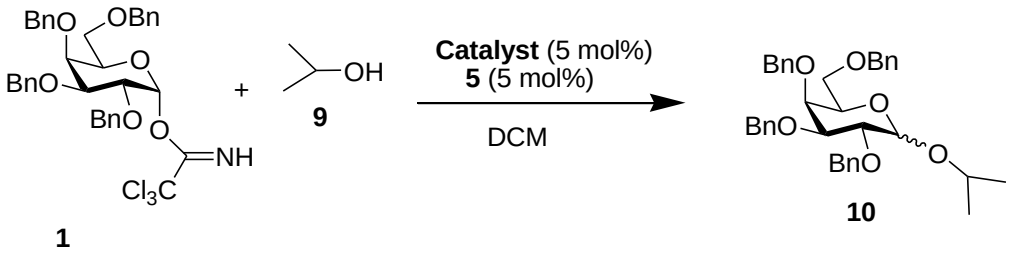
The outcomes of glycosylation[a] reactions performed with donor **1** and acceptor **2** to yield the disaccharide **6** are summarized in Table I.

Table I — Organocatalytic stereoselective synthesis of DAG glycoside

Entry	Catalyst	Co-Catalyst (5)	Reaction Status	Time (h)	Temp.	Yield (%)	β:α ratio [b]
1.	TMSOTf	+	Complete	6	-78 °C	74	3.7:1
2.	TMSOTf	-	Complete	6	-78°C	70	3.9:1
3.	(*R*)-TRIP 3	+	Complete	72	rt	60	1.5:1
4.	(*R*)-TRIP 3	-	Incomplete	96	rt	18	2.5:1
5.	(*S*)-TRIP 4	+	Complete	72	rt	64	1.5:1
6.	(*S*)-TRIP 4	-	Incomplete	96	rt	28	1.1:1
7.	-	+	Incomplete	96	rt	9	1.5:1
8.	Diphenyl phosphoric acid8	+	Complete	72	rt	65	1.1:1
9.	Diphenyl phosphoric acid8	-	Incomplete	96	rt	19	1.9:1
10.	*Bis*(4-nitrophenyl) phosphoric acid 7	+	Complete	72	rt	74	2:1
11.	*Bis*(4-nitrophenyl) phosphoric acid 7	-	Complete	72	rt	60	2.3:1

[a] Reaction conditions: acceptor (1.2 equiv.), Catalyst (0.025 equiv.), Co-Catalyst (0.05 equiv.), DCM.

[b] Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H NMR spectra. Glycosylation reactions were carried out in duplicate to confirm the reproducibility of results.



Scheme V

Organocatalytic stereoselective synthesis of isopropyl glycoside

After obtaining unsatisfactory results using diacetone galactose **2** as acceptor, the focus was shifted to using isopropyl alcohol **9** as the acceptor to determine the stereochemical outcome of these glycosylation reactions. Again the catalysts were varied, in a search for more stereoselective processes catalysts.

The glycosylation reaction is shown below (Scheme V). The glycosylation reaction shown in Scheme 4.15 using donor **1**, isopropyl alcohol **9** as acceptor, TMSOTf as the catalyst, and **5** as the co-catalyst, yielded the isopropyl galactoside**10** in a 25:1 β:α ratio, exactly as reported by the Schmidt group. However when the reaction was carried out without the addition of the co-catalyst, the observed stereoselectivity was (β:α = 23:1), which was significantly higher than that reported by the Schmidt group (12:1).

When the glycosylation was carried out using *bis*(4-nitrophenyl)phosphoric acid **7** as catalyst and co-catalyst **5**, the isopropyl galactoside **10** was formed in an anomeric ratio that was exactly as reported by Schmidt's group (β:α = 7:1). When the same reaction was carried out without using the co-catalyst **5**, there was a slight reduction in the stereoselectivity of the reaction (β:α = 5:1). the use of diphenyl phosphoric acid **8** as the catalyst gave very similar results as compared to catalyst **7**, *viz* a stereoselectivity of (β:α = 6:1) when the reaction was carried with the co-catalyst **5**, and a stereoselectivity of (β:α = 4:1) when reaction was carried on without the co-catalyst **5**.

To evaluate the efficiency of the asymmetric phosphoric acid catalyst, (*R*)-TRIP **3** and (*S*)-TRIP **4** were used as catalysts for the glycosylation reaction. Both (*R*)-TRIP **3**and (*S*)-TRIP **4**, when used with the co-catalyst **5**, gave very similar stereoselectivities to those observed by the use of other two organocatalysts*viz* **7** and **8**. However, when (*S*)-TRIP **4** was used in absence of co-catalyst **5**, an unprecedented improvement in stereoselectivity (β:α = 20:1) was observed, though the yield of the process was poor (25%) (. When the reaction was carried out in the presence of only the co-catalyst **5**, the lowest stereoselectivity was observed (3:1).

The glycosylation[c] reactions performed with donor **1** and acceptor **9** to yield the isopropyl glycoside **10** are summarized in Table II.

Table II — Organocatalytic stereoselective synthesis of isopropyl glycoside

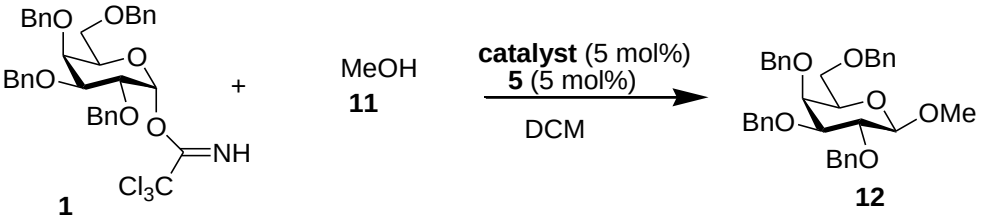
Entry	Catalyst	Co-Catalyst (5)	Reaction Status	Time (h)	Temp.	Yield (%)	β:α ratio [d]
1.	TMSOTf	+	Complete	6	-78 °C	67	25:1
2.	TMSOTf	-	Complete	6	-78 °C	67	23:1
3.	(*R*)-TRIP 3	+	Complete	72	rt	61	6:1
4.	(*R*)-TRIP 3	-	Incomplete	96	rt	28[e]	7:1
5.	(*S*)-TRIP 4	+	Complete	72	rt	64	6:1
6.	(*S*)-TRIP 4	-	Incomplete	96	rt	25[e]	20:1
7.	-	+	Incomplete	96	rt	16[e]	3:1
8.	Diphenyl phosphoric acid 8	+	Complete	72	rt	65	6:1
9.	Diphenyl phosphoric acid 8	-	Incomplete	96	rt	22[e]	4:1
10.	*Bis*(4-nitrophenyl) phosphoric acid 7	+	Complete	72	rt	72	7:1
11.	*Bis*(4-nitrophenyl) phosphoric acid 7	-	Complete	72	rt	71	7:1
12.	*Bis*(4-nitrophenyl) phosphoric acid 7	+	Complete	3	rt	73	5:1

[c] Reaction conditions: acceptor (1.2 equiv.), Catalyst (0.025 equiv.), Co-Catalyst (0.05 equiv.), DCM.
[d] Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H NMR spectra. Glycosylation reactions were carried out in duplicate to confirm the reproducibility of results.
[e] Determined by ^{1}H-NMR

Table III — Organocatalytic stereoselective synthesis of methyl glycoside

Entry	Catalyst	Co-Catalyst 5	Reaction Status	Time (h)	Temp.	Yield (%)	β:α[g]
1.	TMSOTf	+	Complete	0.5	-78 °C	71	1:0
2.	TMSOTf	-	Complete	0.5	-78 °C	71	1:0
3.	*Bis*(4-nitrophenyl) phosphoric acid7	+	Complete	4	rt	65	1:0
4.	*Bis*(4-nitrophenyl) phosphoric acid 7	+	Complete	72	rt	64	1:0
5.	*Bis*(4-nitrophenyl) phosphoric acid 7	-	Complete	48 h	rt	60	1:0

[f] Reaction conditions: acceptor (1.2 equiv.), Catalyst (0.025 equiv.), Co-Catalyst 5 (0.05 equiv.), DCM.
[g] Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H NMR spectra. Glycosylation reactions were carried out in duplicate to confirm the reproducibility of results.



Scheme VI

Organocatalytic stereoselective synthesis of methyl glycoside

Finally theorganocatalytic glycosylation was carried out using methanol **11** as the acceptor and either TMSOTf or *bis*(4-nitrophenyl) phosphoric acid **7** as catalyst, both with and without co-catalyst **5** as shown in Scheme VI.

Strangely, all the reaction conditions investigated led exclusively to the β-product. A summary of glycosylation[f] reactions performed with donor **1** and methanol **11** as acceptor to yield the methyl glycoside **12** is shown in Table III.

Verification of anomerization under reaction conditions

Since the reaction times for most of the glycosylation reactions were very long (up to 72 h), there was also a need to verify whether any anomerization of the product occurred in the acidic conditions provided by the catalyst. Therefore a pure α disaccharide **13** (Figure 2) (20 mg) was stirred in DCM along with (i) catalysts (5 mol%) **7**, **8**, **3** and **4** along with co-catalyst (5 mol%) **5**in different reaction vessels, (ii) with co-catalyst **5** (5 mol%) alone. ^{1}H-NMRs of the aliquots of all the reaction vessels

were recorded at intervals of 1 h, 3 h, 6 h, 24 h, 48 h and 72 h, however there was no isomerization of the *α* diastereomer to *β*diastereomer seen at any time, it was concluded that the observed anomeric stereochemistry is not a result of product equilibration.

Experimental Section

All reactions involving moisture sensitive reagents were performed under an atmosphere of argon or nitrogen *via* standard vacuum Schlenk line techniques. All glassware for such reactions was flame-dried and cooled under an atmosphere of argon. Reactions conducted at -78°C were cooled by means of an acetone/dry ice bath; those conducted at 0°C were cooled by means of an ice bath. Solvent was removed under reduced pressure using a BuchiTM rotary evaporator. HPLC–grade solvents were used for reactions and in case of moisture–sensitive reactions; solvents were dried by literature procedures and freshly distilled as required. Petroleum ether (Petrol) refers to the fraction of light petroleum ether boiling in the range 40-60°C. Reagents were used as supplied without further purification unless otherwise stated. Thin Layer Chromatography (t.l.c.) was carried out on Merck Silica Gel 60F254 aluminium-backed plates. Visualisation of the plates was achieved using a UV lamp (λmax = 254 or 365 nm), and/or ammonium molybdate (5% in 2M H2SO4). Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. Proton and carbon nuclear magnetic resonance (^{1}H, ^{13}C) spectra were recorded on Agilent 400–MR instrument operating for ^{1}H NMR at 400 MHz, and at 100 MHz, for ^{13}C NMR. All chemical shifts are quoted on the δ-scale in ppm using residual solvent as an internal standard. ^{1}H and ^{13}C NMR spectra were assigned using COSY, DEPT, HSQC, HMBC, TOCSY and DPFGSE-TOCSY. High resolution mass spectra were recorded by Dr. Marie Squire and Dr. Alexander on either a DIONEX Ultimate 3000 or Bruker Ma Xis 4G spectrometer, operated in high resolution positive ion electrospray mode. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a water-jacketed 1 cm3 cell with a path length of 1 dm, and are quoted in units of °cm^2.g-1. Concentrations (*c*) are given in g / 100 cm3, solvent and temperature are recorded. Infrared spectra were recorded on a Perkin–Elmer Spectrum One FTIR instrument operating in diffuse reflectance mode with samples prepared as KBr pellets (KBr) or on a Bruker FTIR spectrometer with Alpha's Platinum ATR single reflection diamond where the neat samples were recorded.

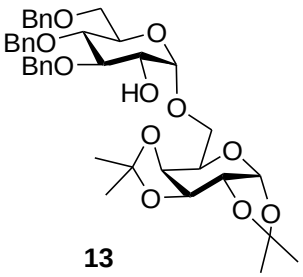


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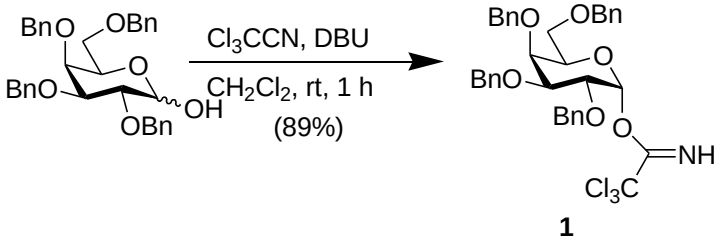
Figure 2

2,3,4,6-Tetrabenzyl-*α*-D-glucopyranosyltrichloro-acetimidate[50]1 (Scheme VII).

To a solution of tetrabenzylglucopyranose (800 mg, 1.48 mmol) in anhydrous DCM (10 mL) were added trichloroacetonitrile (1.7 mL, 12.3 mmol) and DBU (0.090 mL, 0.59 mmol) and the mixture was stirred at rt. After 1 h, t.l.c. (petrol: ethylacetalte, 4:1, with 1% TEA) indicated the formation of a major product (R_f 0.6) and a minor product (R_f 0.4), and complete disappearance of starting material (R_f 0.1). The solvent was then concentrated *in vacuo* and the residue was purified by flash column chromatography (petrol:ethyl acetate, 10:1, with 1% TEA) and the major product was isolated to afford 2,3,4,5-terabenzyl-*α*-D-glucopyranosyltrichloroacetimidate **1** as a colorless oil (900 mg, 89%); ν_{max} (KBr) 3336 (w, N-H), 1673 (s, C=N) cm^{-1}; δ_H (400 MHz,



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Scheme VII

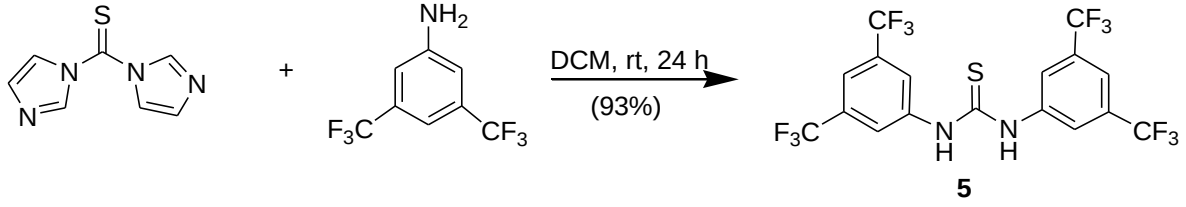
$CDCl_3$):[50] 3.48-3.63 (2H, m, H-6, H-6'), 3.96-4.08 (2H, m, H-3, H-2), 4.10-4.19 (1H, m, H-5), 4.19-4.24 (1H, m, H-4), 4.38-4.50 (8H, m, 4 x OCH_2Ph), 6.53 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1), 7.24-7.34 (20H, m, Ar-CH), 8.51 (1H, s, N-H); δ_C (100 MHz, $CDCl_3$): 68.3 (t, C-6), 72.2, 72.9, 72.9, 73.4 (4 x t, 4 x OCH_2Ph), 74.6, 74.9, 75.9 (3 x d, C-2, C-4, C-5), 78.0 (d, C-3), 95.2 (d, C-1), 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3 (9 x d, ArCH), 137.8, 138.4, 138.5, 138.6 (4 x s, 4 x ArC), 161.2 (s, C=NH).

N,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea[51] 5 (Scheme VIII)

To a mixture of 1,1' – thiocarbonyldiimidazole (500 mg, 2.81 mmol) in DCM (3 mL) was added 3, 5 – bis(trifluoromethyl)aniline (0.91 mL, 5.90 mmol) under a nitrogen atmosphere. The resulting solution was stirred for 24 h at rt. The solvent was evaporated and diethyl ether (25 mL) was then added. The organic phase was washed with aq. HCl (1 M, 3 x 10 mL), saturated aq. sodium bicarbonate solution (3 x 10 mL), and brine (3 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallized ($CHCl_3$) to afford *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea **5** as white crystalline solid (1.13 g, 93%); m. p. 167 – 168°C ($CHCl_3$) (lit.[51]172 – 173°C); δ_H (400 MHz, $CDCl_3$): [51] 1.55 (2H, s, 2 x N-H), 7.78 (2H, s, C-H_{para}), 7.87 (4H, s, C-H_{ortho}); δ_C (100 MHz, [d_4] methanol): 120.47 (d, CH), 123.17 (s, C_q), 125.87 (d, CH), 132.67 (s, C_q), 142.51 (s, C_q), 182.20 (s, C=S); δ_F (380 MHz, $CDCl_3$): -63.06; HRMS (ES^+) calculated for $C_{17}H_9F_{12}N_2S$ (MH^+) 501.0297, found 501.0300.

2,3,4,6-Tetra-*O*-benzyl-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-glucopyranoside[52] 6 (Scheme IX)

O-(2,3,4,6-Tetra-*O*-benzyl-*α*-D-galactopyranosyl) trichloroacetimidate **1** (100 mg, 0.14 mmol), 1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranoside **2** (50 mg, 0.18 mmol) and the cocatalyst **5** (3.5 mg, 0.007 mmol) were dissolved in freshly distilled DCM (2 mL) and stirred at rt for 5 min under a nitrogen atmosphere. The phosphoric acid derived catalyst (0.0035 mmol) was then added. aftert.l.c. (petrol: ethyl acetate, 5:1) indicated the complete consumption of the trichloroacetimidate starting material (R_f 0.7) and the formation of product (R_f 0.5), the reaction was quenched by the addition of triethylamine and filtered through Celite®. The mixture was then concentrated *in vacuo* and the residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford 2,3,4,6-tetra-*O*-benzyl-*α*/*β*-D-galactopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **6** as a pale yellow oil; δ_H (400 MHz, $CDCl_3$)[53] [Data provided for 1:1 mixture of *α*:*β*anomers] 1.26, 1.30, 1.32, 1.40, 1.43, 1.49, 1.51, 1.63 (24H, 8 x s, 4 x $CH_3\alpha$, 4 x $CH_3\beta$), 3.50-3.59



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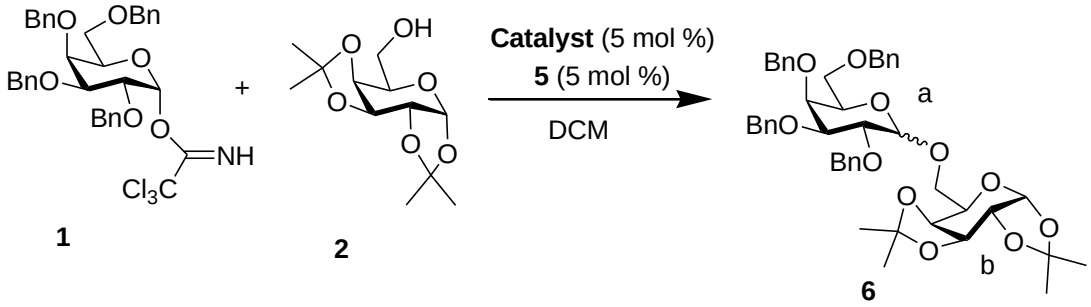
Scheme VIII



1 **2** **6**

Scheme IX

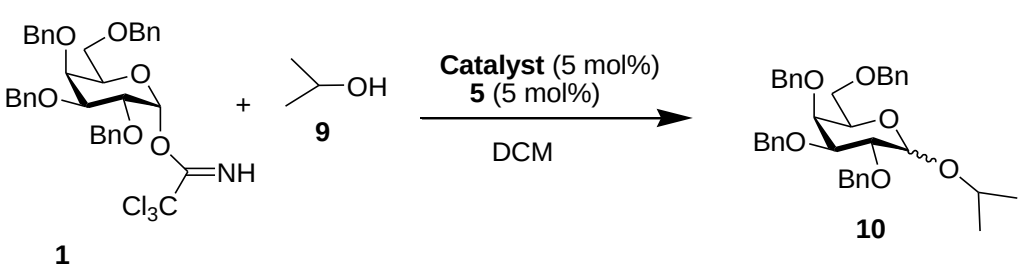
(6H, m, H-$6_a\alpha$, H-$6_a\beta$, H-$6'_a\alpha$, H-$6'_a\beta$, H-$3_b\alpha$, H-$3_b\beta$), 3.68-3.84 (4H, m, H-$4_b\alpha$, H-$4_b\beta$, H-$5_b\alpha$, H-$5_b\beta$), 3.88 (1H, br d, J = 2.7 Hz, H-$2_a\alpha$), 3.98-4.16 (7H, m, H-$4_a\alpha$, H-$4_a\beta$, H-$5_a\alpha$, H-$5_a\beta$, H-$2_a\beta$, H-$3_a\alpha$, H-$2_b\alpha/\beta$), 4.22 (1H, dd, J = 7.9 Hz, J = 2.1 Hz, H-$3_a\beta$), 4.30-4.34 (3H, m, H-$6_b\alpha$, H-$6_b\beta$, H-$2_b\alpha/\beta$), 4.39-4.52 (5H, m, H-$1_a\beta$, CH_2Ph α, CH_2Ph β), 4.60 (2H, m, H-$6'_b\alpha$, H-$6'_b\beta$), 4.59-5.06 (12H, m, 3 x CH_2Ph α, 3 x CH_2Ph β), 5.01 (1H, d, $J_{1,2}$ = 3.4 Hz, H-$1_a\alpha$), 5.50 (1H, d, $J_{1,2}$ = 5.1 Hz, H-$1_a\alpha$), 5.55 (1H, d, $J_{1,2}$ = 4.8 Hz, H-1aβ), 7.23-7.45 (40H, m, 20 x ArC-H α, 20 x ArC-H β); δ_C (100 MHz, $CDCl_3$) 24.4, 24.5, 24.9, 25.0, 25.1, 25.9, 26.0, 26.1 (8 x q, 4 x $CH_3\alpha$, 4 x $CH_3\beta$), 65.8 (d, C-$5_b\alpha/\beta$), 66.3 (t, C-$6_a\alpha$), 67.4 (t, C-6_a β), 68.6 (d, C-$5_b\alpha/\beta$), 68.7, 69.1 (2 x d, C-$2_a\alpha$, C-$2_a\beta$), 69.6, 70.5 (C-$2_b\alpha$, C-$2_b\beta$), 70.6, 70.7, 70.8, 70.9 (4 x d, C-$3_b\alpha$, C-$3_b\beta$, C-$4_b\alpha$, C-$4_b\beta$), 71.4, 72.7, 72.8, 73.0, 73.1, 73.2, 73.3, 73.4, 73.5, 73.6 (10 x t, C-$6_b\alpha$, C-$6_b\beta$, 4 x CH_2Ph α, 4 x CH_2Ph β), 74.5, 74.8 (2 x d, C-$4_b\alpha$, C-$4_b\beta$), 74.9 (d, C-$3_a\alpha/\beta$), 78.9, 79.1 (2 x d, C-$5_a\alpha$, C-$5_a\beta$), 81.9 (d, C-$3_a\alpha/\beta$), 96.3, 96.4 (2 x d, C-$1_b\alpha$, C-$1_b\beta$), 97.5 (d, C-$1_a\alpha$), 104.6 (d, C-$1_a\beta$), 108.5, 108.6, 109.2, 109.3 (4 x s, 2 x *C*$(CH_3)_2\alpha$, 2 x *C*$(CH_3)_2\beta$), 127.3, 127.4, 127.4, 127.5, 127.6, 127.6, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.7 (24 x d, 12 x Ar*C*-H α, 12 x Ar*C*-H β) 137.9, 138.0, 138.5, 138.6, 138.8, 138.9, 139.0, 139.1 (8 x s, 4 x Ar-C α, 4 x Ar-C β); HRMS (ES^+) calculated for $C_{46}H_{54}O_{11}Na$ (MNa^+) 805.3558, found 805.3568.

Isopropyl 2,3,4,6-Tetra-*O*-benzyl-*α*/*β*-D-galactopyranoside10 (Scheme X)

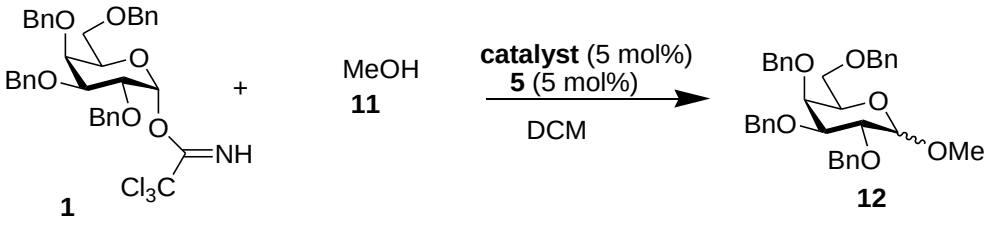
O-(2,3,4,6-Tetra-*O*-benzyl-*α*-D-galactopyranosyl) trichloroacetimidate **1** (100 mg, 0.14 mmol), propan-2-ol **9** (14 µL, 0.18 mol) and the cocatalyst **5** (3.5 mg, 0.007 mmol) were dissolved in freshly distilled DCM (2 mL) and stirred at rt for 5 min in a nitrogen atmosphere. The phosphoric acid catalyst (0.0035 mol) was then added. Aftert.l.c. (toluene: ethyl acetate, 9:1) indicated the complete consumption of starting material (R_f 0.7) and the formation of product (R_f 0.68) the reaction was quenched by the addition of triethyl amine and filtered through Celite®. Then the reaction was allowed to run for 72 h. The mixture was then concentrated *in vacuo* and the residue was purified by flash column chromatography (petrol: ethyl acetate, 6:1) to afford isopropyl 2,3,4,6-tetra-*O*-benzyl-*α*/*β*-D-galactopyranoside**10** as a pale yellow oil; δ_H (400 MHz, CD_3CN) [Data provided for 1:3 mixture of *α*:*β*anomers] 1.15-1.23 (24H, m, CH $(CH_3)_2\alpha$, 3 x CH $(CH_3)_2\beta$), 3.49-3.64 (16H, m, H-2*α*, 3 x H-2 *β*, H-5*α*, 3 x H-5 *β*, H-6 *α*, 3 x H-6 *β*, H-6' *α*, 3 x H-6 *β*), 3.88-4.04 (12H, m, H-3 *α*, 3 x H-3 *β*, H-4 *α*, 3 x H-4 *β*, *CH* $(CH_3)_2\alpha$, 3 x *CH* $(CH_3)_2\beta$), 4.45 (3H, d, $J_{1,2}$ = 8.0 Hz, 3 x H-1 *β*), 4.48-4.89 (32H, m, 4 x CH_2Ph *α*, 12 x CH_2Ph *β*), 5.07 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1 *α*), 7.26-7.50 (80H, m, 20 x ArC-H *α*, 60 x ArC-H *β*); δ_C (100 MHz, CD_3CN) 20.8, 21.4, 22.8, 23.0 (4 x q, CH $(CH_3)_2\alpha$, CH $(CH_3)_2\beta$), 68.9 (t, C-6 *β*), 69.1 (t, C-6 *α*), 69.3 (d, C-3*α*), 71.4 (d, C-3 *β*), 72.0, 72.2 (2 x d, C-4 *α*, C-4 *β*), 72.3, 72.8, 72.9, 74.3, 74.4, 74.5, 74.6, 75.6 (8 x t, 4 x *C*H_2Ph *α*, 4 x *C*H_2Ph *β*), 74.3,74.3 (2 x d, *C*H $(CH_3)_2\alpha$, *C*H $(CH_3)_2\beta$), 76.1 (d, C-5 *α*), 78.5 (d, C-2 *α*), 79.3 (d, C-5 *β*), 79.3 (d, C-2 *β*), 95.3 (d, C-1 *α*), 101.9 (d, C-1 *β*), 127.3, 127.3, 127.4, 127.4, 127.5, 127.5, 127.6, 127.6, 127.7, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.2, 128.2, 128.3, 128.3, 128.4 (24 x d, 12 x Ar*C*-H *α*, 12 x Ar*C*-H *β*) 138.6, 138.8, 138.9, 139.0, 139.1, 139.1, 139.2, 139.3 (8 x s, 4 x Ar-C *α*, 4 x Ar-C *β*); HRMS (ES^+) calculated for $C_{37}H_{42}O_6Na$ (MNa^+) 605.2861, found 605.2867.

Methyl 2,3,4,6-Tetra-*O*-benzyl-*α*/*β*-D-galactopyranoside 12 (Scheme XI)

O-(2,3,4,6-Tetra-*O*-benzyl-*α*-D-galactopyranosyl) trichloroacetimidate**1**(100 mg, 0.14 mmol), methanol **11** (6 µL, 0.18 mmol) and the cocatalyst **5** (3.5 mg, 0.007 mol) were dissolved in freshly distilled DCM (2 mL) and stirred at rt for 5 min in a nitrogen atmosphere. The phosphoric acid derived catalyst



Scheme X



Scheme XI

(0.0035 mmol) was then added. When t.l.c. (petrol: ethyl acetate, 5:2) indicated the complete consumption of starting material (R_f 0.7) and the formation of product (R_f 0.65) the reaction was quenched by the addition of triethyl amine and filtered through Celite®. The mixture was then concentrated *in vacuo* and the residue was purified by flash column chromatography (petrol: ethyl acetate, 6:1) to afford methyl 2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranoside **12** as a pale yellow oil, $[\alpha]_D^{20}$ – 1.4(*c*, 1.0 in $CHCl_3$), lit[54] $[\alpha]_D^{20}$ – 0.9(*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 3.52-3.63 (5H, m, CH_3, H-3,H-5), 3.82 (1H, at, J = 8.4 Hz, H-2), 3.91 (1H, m, H-4), 4.29 (1H, d, $J_{1,2}$ = 7.2 Hz), 4.41-4.46 (2H, m, H-6, H-6'), 4.61-4.97 (8H, m, 4 x CH_2Ph), 7.25-7.39 (20H, m, ArC-H); δ_C (100 MHz, $CDCl_3$) 57.0 (q, OCH_3), 68.9 (d, C-3), 73.2 (d, C-4), 73.4 (t, C-6), 73.5, 73.6, 74.5, 75.1 (4 x t, 4 x *C*H_2Ph), 79.6 (d, C-2), 82.1 (d, C-5), 105.0 (d, C-1), 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.4, 128.5 (12 x d, 12 x Ar*C*-H) 137.9, 138.5, 138.6, 138.8 (4 x s, 4 x Ar-C); HRMS (ES^+) calculated for $C_{35}H_{38}O_6Na$ (MNa^+) 577.2560, found 577.2569.

Conclusions

It is well-established that the stereochemical outcome of glycosylation reactions can be highly dependent on the acceptor used in glycosylation step. In particular, a match or mis-match of donor and acceptor may occur[14]. In these studies, it was found that the smaller the acceptor that was used, the higher the *β*-stereoselectivity that was obtained. Undoubtedly, the thiourea derivative co-catalyst **5** assisted the catalyst in making the reaction faster, especially in the cases where the catalyst was itself not acidic enough, and thus reactions performed in its presence was not effective in improving the stereochemical outcome of the reaction, and in many cases the reaction gave better selectivity when the co-catalyst was not used. The *β*-stereoselectivity observed when using TMSOTf, either with or without the co-catalyst **5**, was always higher than when the organocatalysts were used, either with or without the co-catalyst. So, the existence and role of the transition state suggested by Schmidt's group in their explanation of the high stereoselectivity they observed appears to be ambiguous. In the transition state suggested by the Schmidt group, thiourea nitrogen's lone pair of electron was involved in hydrogen bonding with the acceptor molecule. However, the lone pair of electron of nitrogen is in conjugation with C=S of thiourea, thus reducing the availability of nitrogen lone pair for hydrogen bonding. So probably that's the reason, it holds smaller acceptors much strongly compared to larger one and thus better stereoselectivity is seen with smaller acceptors. Indeed their stereoselectivtites were highly acceptor specific, casting significant doubt on the utility of their work. The co-operative effect between the catalyst and co-catalyst needs to be investigated further.

Conflict of Interest

The authors declare no competing financial interest.

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