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Activation of glycosyl trichloroacetimidates with perchloric acid on silica ($HClO_4$–SiO_2) provides enhanced α-selectivity

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Abstract

Obtaining high stereoselectivity in glycosylation reactions is often challenging in the absence of neighboring group participation. In this study, we demonstrate that activation of glycosyl trichloroacetimidate donors with immobilized perchloric acid on silica ($HClO_4$–SiO_2) provides higher α-selectivity than trimethylsilyl triflate (TMSOTf) for reactions that do not involve neighboring group participation.

Keywords

Glycosylation; Trichloroacetimidates; Stereoselectivity; Perchloric acid on silica

Carbohydrates play an important role in a variety of biological processes and are important constituents of many natural products and drugs.[1] Studies on this class of biopolymers require access to structurally-defined, homogeneous compounds; however, carbohydrates are notoriously difficult to isolate from natural sources and, when available, are typically only available in small quantities. Chemical and chemo-enzymatic methods provide a useful alternative for obtaining carbohydrates.[2–4] Both natural and unnatural carbohydrates can be obtained, and much larger quantities of pure material can be prepared.

The key step in the synthesis of carbohydrates is formation of the glycosidic linkages between monosaccharide units.[2–4] Both α and β linkages are possible, and control of stereochemistry is critical. In some cases, stereochemistry can be controlled by use of protecting groups that are capable of neighboring group participation. For example, esters at the C-2 position of a glycosyl donor typically provide high selectivity for the 1,2-*trans* glycoside product. Stereocontrol in the absence of neighboring group participation is considerably more challenging.[5] Many factors, such as steric hindrance of protecting groups, reaction solvent, and temperature, can affect the stereochemical outcome of a glycosylation reaction, and these effects are typically difficult to predict for any given donor-acceptor pair. Better methods to control stereoselectivity in the absence of neighboring group participation are needed.

Perchloric acid on silica ($HClO_4$–SiO_2) has recently been introduced as a user-friendly acid catalyst for a variety of organic transformations, such as protection–deprotection reactions,[6–8] rearrangements[9, 10] and esterifications.[11] $HClO_4$–SiO_2 is an air stable powder that is

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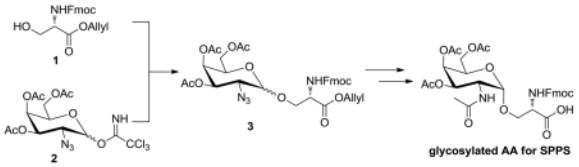
easily prepared, is conveniently handled, and can readily be removed from reaction mixtures by filtration. $HClO_4$–SiO_2 has been examined previously as a catalyst for glycosylation reactions.[12, 13] In particular, it was used as an alternative to the highly moisture sensitive trimethylsilyl triflate (TMSOTf) for the activation of trichloroacetimidate glycosyl donors. $HClO_4$–SiO_2 performed in all cases as well as TMSOTf for the activation of C-2 acylated donors, leading to the desired β-products for the Glc/Gal-series and α-products for Man-series compounds with high chemical yields. Much less was known about the effects of $HClO_4$–SiO_2 activation on the stereochemical outcome in the absence of neighboring group participation. In this study, we demonstrate that activation of glycosyl trichloroacetimidate donors with $HClO_4$–SiO_2 provides enhanced α-selectivity relative to TMSOTf in the absence of neighboring group participation.

Our initial studies focused on the synthesis of glycopeptides. Glycopeptides are typically prepared via solid phase peptide synthesis with incorporation of suitably protected glyco-amino acids at the appropriate position(s). For most *O*-linked glycans, the central connection between the glycan portion and peptide involves an α linkage between a GalNAc residue and a serine or threonine. Therefore, stereoselective formation of the requisite α-linkage between protected GalNAc derivatives and either serine or threonine is critical for the synthesis of this family of carbohydrates.

The synthesis of the key glycosidic linkage between GalNAc and serine/threonine has been studied in detail previously, and a variety of anomeric leaving groups have been investigated. Most frequently, glycosyl bromides,[14–17] trichloroacetimidates (TCA),[18–20] phenylsulfides,[21, 22] sulfoxides,[23] and phenylselenides[24] have been used as glycosyl donors with adequately protected acceptor amino acids. In general, many glycosylation methods and conditions will give good α-selectivity when the secondary alcohol of threonine is used as the acceptor. With primary alcohols, such as serine derivatives, stereoselectivities are typically much lower. For example, glycosylation of Fmoc-protected serine acceptor **1** with 2-azido-2-deoxygalactose imidate **2**[25] provided the corresponding glycoside **3** with an α to β ratio of only 1.4.[20] Therefore, better methods for preparing these compounds were needed.



To improve the α-selectivity when glycosylating serine derivatives, we varied a number of reaction parameters. We started by optimizing the reaction conditions for the standard TMSOTf activated glycosylation of the TCA-donor **2** and serine acceptor **4** with respect to α-selectivity and overall chemical yield. Because the reaction solvent and temperature can have a dramatic influence, both factors were tested systematically for their ability to drive the reaction to form predominantly the desired α-product. The reaction media chosen in this study were based on solvents and solvent systems that were reported to successfully lead to α-glycosylation, regardless of the anomeric leaving group.[26, 27] The results of these experiments are summarized in Table 1. The product ratios were determined by ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$).

Variation of the solvent had a minor influence on the stereoselectivity of the glycosylation reaction at −30°C (entries 1–9). α:β ratios ranged from slightly favoring the β-product (toluene, entry 7) to modest α-selectivity (toluene–dioxane, entry 8 and DCM–dioxane, entry 9). In accordance with the literature, reaction media containing the participating solvents ether or dioxane showed an increased α-selectivity, compared to the

nonparticipating solvents DCM and toluene. However, no selectivity was observed for the participating solvent THF. Interestingly, when the participating solvents ether and THF were paired with the nonparticipating DCM to form binary solutions, a marked increase in chemical yield was observed, without affecting the stereoselectivity (entries 2–5). Due to the high melting point of dioxane, no data could be obtained for the pure solvent at −30 °C. However, when paired with toluene or DCM (entries 8 and 9), the highest α-selectivities (α:β = 2.0) and chemical yields (94% and 97%, respectively) within this set of experiments were reached. Although both solvent systems behaved quite similar in these experiments, we continued our study with the mixture of DCM–dioxane, due to the low solubility of certain acceptors and donors in toluene based solvents, allowing a more general approach. Raising the reaction temperature from −30°C to 0 °C (entry 10) and room temperature (entry 11) resulted in additional increases in α-selectivity from 2.0 to 3.8 and 5.3, respectively, without a significant loss in overall chemical yield.

Next, we turned our attention to the influence of the catalyst on the α/β-product distribution of this reaction. Glycosylations were performed at 0 °C and room temperature with the same concentrations of donor and acceptor and employing an equal mol% of catalyst as compared to the TMSOTf-catalyzed reaction (Table 2).

Under the same reaction conditions, the use of $HClO_4$–SiO_2 consistently resulted in higher ratios of α/β-selectivity for the serine acceptor **4**, compared to the standard TMSOTf catalyzed reactions (entries 1,2: 3.8 to 8.0 and entries 5,6: 5.3 to 24.0). To determine whether this effect is related solely to the presence of solid SiO_2 in the reaction mixture, a control experiment with TMSOTf as catalyst and additional silica was performed under the optimized conditions (entry 3). No change of selectivity was observed compared to the reaction without the additive, ruling out an exclusive effect of the silica. Additionally, we performed a control experiment with TMSOTf as catalyst and 1.5 equivalents of $LiClO_4$ present in the reaction mixture (entry 4). Again, no change in selectivity was observed, indicating that the enhanced α-selectivity is not simply due to the presence of the perchlorate ion. When performed at room temperature, a significant decrease in overall yield was observed for the $HClO_4$–SiO_2 activated glycosylation (entry 6). This was due to partial cleavage of the acid labile *tert*-butyl ester moiety on the amino acid **4**. Therefore, this set of experiment was repeated with an acid stable benzyl ester (**6**), resulting again in a significant increase in α-selectivity for the $HClO_4$–SiO_2 activated reaction (entries 7,8: 3.7 to 12.0), while maintaining very good chemical yields.

These results encouraged us to look into a more general application of the $HClO_4$–SiO_2 catalyst for α-selective glycosylations. Therefore, a set of representative and easily accessible trichloroacetimidate glycosyl donors, bearing non-participating protecting groups at C-2, were selected. Besides the previously introduced disarmed galactosyl donor **2**, we also performed glycosylations with glucose (**15**)[28] and mannose (**18**)[29] donors. The hydroxyl groups on these donors are protected with benzyl ethers, giving rise to more reactive, or "armed",[30] donors relative to ester-protected donors. To cover a variety of representative acceptors, glycosylations were performed with the commercially-available 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**11**) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**13**). To complete our investigations on the Tn-antigen, the benzyl protected threonine **9** was also studied as acceptor. Reactions were performed under optimized conditions at either 0 °C or room temperature. The results from these experiments are listed in Table 3.

In all of the studied glycosylation reactions with representative donors and acceptors, the $HClO_4$–SiO_2 performed better, or at least as well as, the standard activator, TMSOTf, under the same reaction conditions. As noted before, the less reactive secondary acceptors tended

to show a higher selectivity for the α-product, as compared to the more reactive primary alcohols. Therefore, using threonine based acceptors (**9**) for constructing glycosylated amino acids resulted in better α/β-ratios, as compared to acceptors of the serine type (entries 1, 2). Nonetheless, the α-selectivities achieved with serine **4** under the presented reaction conditions (*vide supra*) are sufficiently high for efficient syntheses and were readily applied by us for the multi-gram scale preparation of the Tn-antigen.

In the case of the armed glucose donor **15** and the highly reactive acceptor **11**, no difference in glycosylation selectivity was observed for both catalysts (α/β = 3.0, entries 7,8). Raising the temperature from 0 °C to room temperature led to a slight increase in α-selectivity to 4.0 (entry 9), as already observed for donor–acceptor pair **2** and **4**. The epimeric mannose donor **18**, on the other hand, showed a marked increase in α-selectivity in the glycosylation with acceptor **11** after changing the catalyst from TMSOTf to $HClO_4$–SiO_2. The enhanced α-selectivity is especially interesting in light of the fact that activation of mannosyl bromides with silver silicate, a heterogeneous activator, produces primarily β-mannose products.[36]

In summary, we have demonstrated that the heterogeneous catalyst, $HClO_4$–SiO_2, provides enhanced α-selectivity in glycosylations involving trichloroacetimidate donors with non-participating protecting groups. The chemical yields are comparable to those achieved by TMSOTf activation, and the catalyst and conditions are applicable to a range of donor and acceptor pairs. Given the improved selectivity and ease of handling, $HClO_4$–SiO_2 is a useful alternative to TMSOTf for activation of trichloroacetimidates.

1. Experimental

1.1 General methods

All experiments involving water-sensitive compounds were conducted under dry conditions (positive argon pressure) using standard syringe, cannula and septa apparatus. Solvents: All solvents were purchased anhydrous (Aldrich) and stored over activated molecular sieves. Hexanes, ethyl acetate, methylene chloride, and methanol employed in chromatography were purchased HPLC-grade. Chromatography: Flash chromatography was performed with Teledyne ISCO CombiFlash Companion. TLC: analytical thin layer chromatography was performed on Analtech precoated plates (Uniplate, silica gel GHLF, 250 microns) containing a fluorescence indicator; sugar-containing compounds were visualized with the sugar spray reagent (5 mL of 4-methoxybenzaldehyde, 90 mL of ethanol, 5 mL of concentrated sulfuric acid, and 10 mL of glacial acectic acid) by heating with a heat gun. NMR spectra were recorded using a Varian Inova 400 MHz spectrometer. The coupling constants are reported in Hertz, and the peak shifts are reported in the delta (ppm) scale; abbreviations s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectra (ESI-MS) were obtained on an Agilent Technologies multimode ion source (LC/MSD SL) using the loop injection mode. Optical rotations were measured on a Jasco P-1010 polarimeter at 589 nm. Infrared spectroscopy data was obtained neat with a Jasco FT-IR/615 spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia, 30091.

1.2 Preparation of perchloric acid immobilized on silica gel ($HClO_4$-SiO_2)

To a suspension of silica gel (20.0 g, SiliaFlash F60, 230 – 400 mesh, Silicycle, Quebec City, Canada) in Et_2O (100 mL) was added $HClO_4$ (70% aq solution, 690 μL, 8.00 mmol) and the suspension was stirred for 2h at rt. The solvent was removed under reduced pressure and the crude catalyst was dried under vacuum overnight at 80 °C to afford $HClO_4$–SiO_2 (0.4 mmol/g) as a free-flowing colourless powder. The catalyst is light sensitive and should be stored under argon in the dark to maintain activity.

1.3 General procedure for TMSOTf-activated glycosylations

Trichloroacetimidate donor (1.3 equiv.) and glycosyl acceptor (1.0 equiv.) were dissolved in anhyd. CH_2Cl_2 (5.0 mL/mmol donor) and anhyd. dioxane (5.0 mL/mmol donor). Activated molecular sieves (4Å, 50 mg/mL solvent) were added and the mixture was stirred for 0.5 h at rt. The reaction mixture was adjusted to the desired temperature and TMSOTf (0.075 mmol/mmol donor) was added dropwise. The reaction was stirred at the indicated temperature until TLC-analysis revealed reaction completion. All reactions with the armed donors, **15** and **18**, were complete within 0.5 h. Reactions with the disarmed donor, **2**, were complete within 0.5 h when carried out at r.t. and within 1 h when carried out at 0 °C. After neutralization with DIPEA, the solids were filtered off and the solvent was removed under reduced pressure. The crude was purified by silica-gel flash chromatography (EtOAc in hexanes) and product containing fractions were pooled, concentrated and subjected to ^{1}H NMR-analysis for α/β-ratio determination. Additional chromatography provided pure compounds with spectroscopic data identical to those reported.

1.4 General procedure for $HClO_4$-SiO_2 -activated glycosylations

Trichloroacetimidate donor (1.3 equiv.) and glycosyl acceptor (1.0 equiv.) were dissolved in anhyd. CH_2Cl_2 (5.0 mL/mmol donor) and anhyd. dioxane (5.0 mL/mmol donor). Activated molecular sieves (4Å, 50 mg/mL solvent) were added and the mixture was stirred for 0.5 h at rt. The reaction mixture was adjusted to the desired temperature and $HClO_4$–SiO_2 (0.075 mmol/mmol donor) was added in one portion. The reaction was stirred at the indicated temperature until TLC-analysis revealed reaction completion. The solids were filtered off and the solvent was removed under reduced pressure. The crude was purified by silica-gel flash chromatography (EtOAc in hexanes) and product containing fractions were pooled, concentrated and subjected to ^{1}H NMR-analysis for α/β-ratio determination. Additional chromatography provided pure compounds with spectroscopic data identical to those reported.

1.5 Determination of the product ratio

20 mg of pre-purified product was dissolved in 0.75 mL of $CDCl_3$ and the ^{1}H NMR was recorded at 400 MHz at 25 °C. The ratio was determined by integration of fully isolated peaks of each diastereomer. The diagnostic protons of each compound are listed in Table 4.

1.6 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(3′,4′,6′-tri-*O*-acetyl-2′-azido-2′-deoxy-α-D-galactopyranosyl)-α-D-glucofuranose (14)

The reaction was carried out according to the general procedure for $HClO_4$-SiO_2-activated glycosylations with 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl trichloro-acetimidate donor **2** (100 mg, 0.210 mmol), diacetone-D-glucose acceptor **13** (42.1 mg, 0.162 mmol), activated molecular sieves (4A, 100 mg) and immobilized $HClO_4$ on silica (40.0 mg) in CH_2Cl_2–dioxane (1:1, 2.0 mL) at 0 °C. The crude was purified by chromatography on silica gel (EtOAc in hexanes 20–40%) to yield the α glycosylated disaccharide **14** (79.9 mg, 86%) as a colourless foam. $[\alpha]_D^{20}$ = +59.1 (c = 0.5, $CHCl_3$); IR (neat): 2990, 2109 (N_3), 1748, 1372, 1214, 1148, 1031, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1); 5.42 (dd, 1H, $J_{3'4'}$ 3.1 Hz, $J_{4'5'}$ 1.0 Hz, H-4′); 5.32 (d, 1H, $J_{1'2'}$ 3.7 Hz, H-1′); 5.20 (dd, 1H, $J_{2'3'}$ 11.1 Hz, $J_{3'4'}$ 3.7 Hz, H-3′); 4.53 (d, 1H, $J_{1,2}$ 3.6 Hz H-2); 4.39 (ddd, 1H, $J_{4,5}$ 8.9 Hz, $J_{5,6a}$ 6.0Hz, $J_{5,6b}$ 5.2Hz, H-5); 4.24 (d, 1H, $J_{3,4}$ 2.7 Hz, H-3); 4.23 – 4.19 (m, 1H, H-6′a); 4.14 (dd, 1H, $J_{6a,6b}$ 8.6Hz, $J_{5,6a}$ 6.0 Hz, H-6a); 4.10 (s, 1H, H-6′b); 4.08 (d, 1H, $J_{4'5'}$ 1.0 Hz, H-5′); 4.02 (dd, 1H, $J_{4,5}$ 8.9 Hz, $J_{3,4}$ 2.7 Hz, H-4); 3.94 (dd, 1H, $J_{6a,6b}$ 8.6 Hz, $J_{5,6b}$ 5.2 Hz, H-6b); 3.82 (dd, 1H, $J_{2'3'}$ 11.1 Hz, $J_{1'2'}$ 3.7 Hz, H-2′); 2.12 (s, 3H, OAc); 2.04 (s, 3H, OAc); 2.02 (s, 3H, OAc); 1.47 (s, 3H, CH_3, isoprop.); 1.39 (s, 3H, CH_3, isoprop.); 1.32 (s, 3H, CH_3, isoprop.); 1.30 (s, 3H, CH_3, isoprop.)

ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 170.49, 169.94, 169.77 (3 × *C*=O, Ac); 112.02, 109.30 (2 × *C*$(CH_3)_2$, isoprop.); 83.78 (C-2); 81.41 (C-3); 80.47 (C-4); 71.28 (C-5); 68.51 (C-4′); 67.88 (C-3′); 67.43 (C-6′); 67.24 (C-5′); 61.98 (C-6); 57.93, (C-2′); 26.83, 26.77, 26.23, 25.14, 20.59 (*C*H_3, OAc/isoporop.) ppm.; ESI-MS: 596.05 ($M+Na^+$); Elemental Analysis for $C_{24}H_{35}N_3O_{13}$: Calculated: C, 50.26; H, 6.15; N, 7.33. Found: C, 50.10; H, 6.06; N, 7.32.

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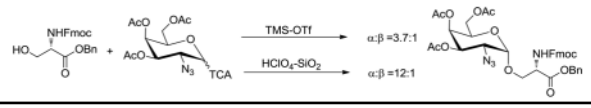
Table 1

Effects of solvent and temperature on stereoselectivity



Entry	Solvent	Catalyst	Temperature [°C]	Yield[a]	Ratio[b] (α/β)
1	DCM	TMSOTf	−30	98%	1.4
2	ether	TMSOTf	−30	71%	1.9
3	DCM–ether (1:1)	TMSOTf	−30	97%	1.9
4	THF	TMSOTf	−30	76%	1.0
5	DCM–THF (1:1)	TMSOTf	−30	90%	1.0
6	nitromethane–ether (1:1)	TMSOTf	−30	77%	1.6
7	toluene	TMSOTf	−30	78%	0.8
8	toluene–dioxane (1:1)	TMSOTf	−30	94%	2.0
9	DCM–dioxane (1:1)	TMSOTf	−30	97%	2.0
10	DCM–dioxane (1:1)	TMSOTf	0	96%	3.8
11	DCM–dioxane (1:1)	TMSOTf	rt	86%	5.3

[a] Combined yield of both anomers after purification

[b] Determined by ^{1}H NMR spectroscopy

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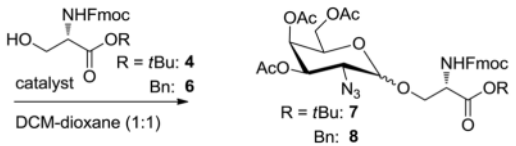
Table 2

Influence of catalyst and additives on stereoselectivity



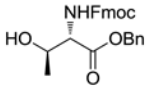
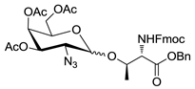
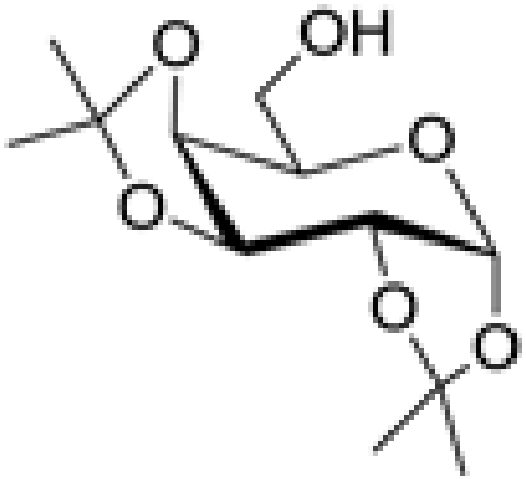
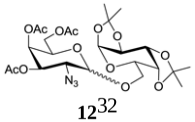
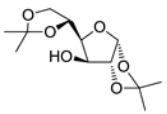
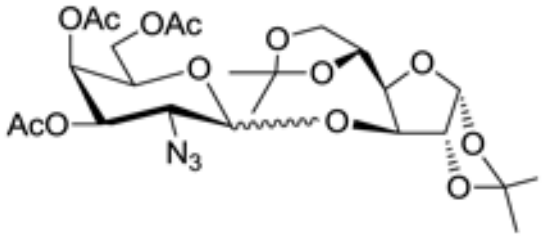
Entry	Acceptor	Catalyst	Temperature [°C]	Yield[a]	Ratio[b] (α/β)
1	**4**	TMSOTf	0	96%	3.8
2	**4**	$HClO_4$–SiO_2	0	93%	8.0
3	**4**	TMSOTf + SiO_2	0	91%	3.8
4	**4**	TMSOTf + $LiClO_4$	0	96%	3.9
5	**4**	TMSOTf	rt	86%	5.3
6	**4**	$HClO_4$–SiO_2	rt	42%	24.0
7	**6**	TMSOTf	rt	98%	3.7
8	**6**	$HClO_4$–SiO_2	rt	95%	12.0

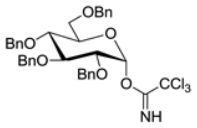
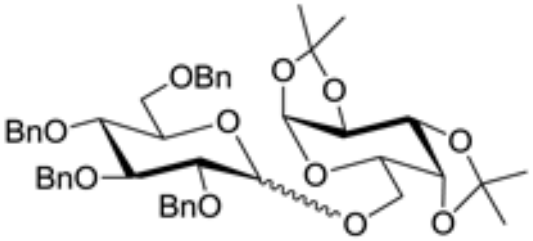
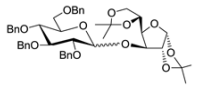
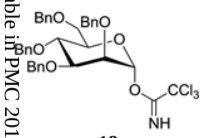
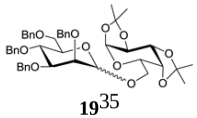
[a] Combined yield of both anomers after purification

[b] Determined by ^{1}H NMR spectroscopy

Table 3

Comparisons of α selectivities for various donor-acceptor pairs

Entry	Donor	Acceptor	Product	Conditions	Yield[a]	Ratio[b] (α/β)
1	**2**	 **9**	 **10**[31]	TMSOTf rt	79%	8.2
2	**2**	**9**	**10**	$HClO_4$-SiO_2 rt	81%	19
3	**2**	 **11**	 **12**[32]	TMSOTf 0°C	96%	6.1
4	**2**	**11**	**12**	$HClO_4$-SiO_2 0°C	94%	8.1
5	**2**	 **13**	 **14**	TMSOTf 0°C	84%	13

Entry	Donor	Acceptor	Product	Conditions	Yield[a]	Ratio[b] (α/β)
6	**2**	**13**	**14**	$HClO_4$-SiO_2 0°C	86%	32
7	 **15**	**11**	 **16**[33]	TMSOTf 0°C	93%	3.0
8	**15**	**11**	**16**	$HClO_4$-SiO_2 0°C	90%	3.0
9	**15**	**11**	**16**	$HClO_4$-SiO_2 rt	85%	4.0
10	**15**	**13**	 **17**[34]	TMSOTf 0°C	84%	4.0
11	**15**	**13**	**17**	$HClO_4$-SiO_2 0°C	88%	9.3
12	 **18**	**11**	 **19**[35]	TMSOTf 0°C	85%	3.0
13	**18**	**11**	**19**	$HClO_4$-SiO_2 0°C	88%	10

[a] Combined yield of both anomers after purification

[b] Determined by ^{1}H NMR spectroscopy

Table 4

Diagnostic protons for determining α/β product ratios

	Diagnostic Protons	
Compound	**δ_α [ppm]**	**δ_β [ppm]**
5	5.85 (d, 1H, *J* = 8.5 Hz, N*H*Fmoc) 2.12 (s, 3H, CH_3, OAc)	5.75 (d, 1H, *J* = 8.5 Hz, N*H*Fmoc) 2.10 (s, 3H, CH_3, OAc)
10	3.55 (dd, 1H, *J* = 11.2, 3.7 H-2)	4.63 (dd, 1H, *J* = 10.8, 3.2 Hz, H-3)
12	4.99 (d, 1H, *J* = 3.5 Hz, H-1)	4.50 (d, 1H, *J* = 8.0 Hz, H-1)
14	4.53 (d, 1H, *J* = 3.6 Hz, H-2)	4.55 (d, 1H, *J* = 3.6 Hz, H-2)
16	5.53 (d, 1H, *J* = 5.0 Hz, H-1) 1.53 (s, 3H, CH_3, isoprop.)	5.57 (d, 1H, *J* = 5.0 Hz, H-1) 1.50 (s, 3H, CH_3, isoprop.)
17	5.80 (d, 1H, *J* = 3.6 Hz, H-1)	5.68 (d, 1H, *J* = 3.6 Hz, H-1)
19	5.50 (d, 1H, *J* = 5.0 Hz, H-1) 1.48 (s, 3H, CH_3, isoprop.)	5.57 (d, 1H, *J* = 5.0 Hz, H-1) 1.46 (s, 3H, CH_3, isoprop.)