Acyl Sulfonamide Catalysts for Glycosylation Reactions with Trichloroacetimidate Donors

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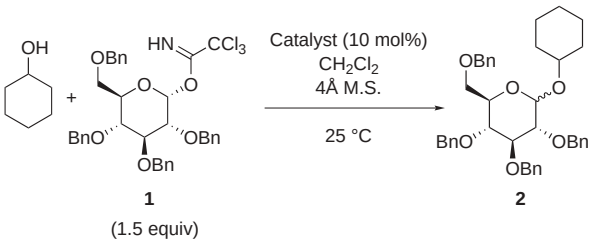
Abstract: The acyl sulfonamide functional group has been found to serve as a catalytic moiety for the glycosylation of several alcohols when glycosyl donors based on trichloroacetimidates are employed.

Key words: glycosylation, hydrogen bond, trichloroacetimidate, organocatalysis

The glycosylation reaction is a fundamental process at the heart of carbohydrate assembly. Among the challenges in the field is the issue of regioselectivity when glycosylation reactions are carried out with polyfunctional glycosyl acceptors. This is partially due to the fact that unprotected hydroxyl groups within the monosaccharide acceptor often possess comparable electronic and steric properties.[1] However, their relative reactivity differences are difficult to predict and are often complicated by the fact that their nucleophilicity is dependent on the monosaccharide structure and the specific reaction conditions. In the context of carbohydrate synthesis, enzymatic approaches certainly represent one form of the state of the art.[2] However, variation in substrate structure may result in significant loss of selectivity for such enzymatic reactions. In terms of nonenzymatic chemistry, the field has seen a tremendous range of approaches to chemical glycosylation to meet the myriad of challenges presented by carbohydrate structures.[3]

In an effort to develop small-molecule catalysts for glycosylation reactions, we were intrigued by the possibility of pursuing an organocatalytic approach since so many of the known protocols are based on Lewis-acid activation of the glycosyl donor. In particular, we were interested in developing catalysts that might allow for binding of coupling partners through host-guest interactions during the bond-forming step of a more complicated mechanism. Given that the hydrogen bond represents an effective Brønsted acid, and in fact may catalyze a number of reactions that are better known to proceed under Lewis acid catalysis,[4] we sought to define the range of hydrogen bond-containing functional groups that could catalyze a given glycosylation reaction.

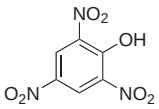
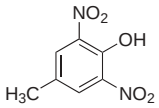
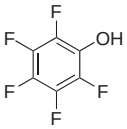
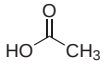
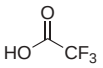
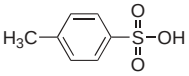
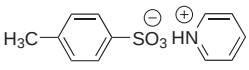
Our studies began with the coupling of cyclohexanol to trichloroacetimidate donor **1** (Equation 1, Table 1).[5] We explored the efficiency of glycosidic bond formation under a variety of conditions, finding in accord with literature precedent,[6] that the coupling is acid-catalyzed. Thus, when cyclohexanol and **1** are comixed in dichloromethane, in the presence of a variety of acidic additives, appreciable amounts of product are obtained.



1 (1.5 equiv) **2**

Equation 1

Table 1 Catalyst Screen for the Coupling of **1** to Cyclohexanol[a]

Entry	Catalyst	Reaction time (h)	Yield (%)[b]	α/β[c]
1		1.5	Quantitative	60:40
2		24	<5	N.D.
3		24	70	57:43
4		24	<5	N.D.
5		24	<5	N.D.
6		1.5	92	46:54
7		24	54	53:47

[a] All reactions conducted at 25°C in CH_2Cl_2 in the presence of 4 Å sieves. Catalyst loadings are 12 mol% with respect to alcohol.
[b] Yields refer to isolated yield after silica gel chromatography.
[c] As determined by ^1H NMR (400 MHz).

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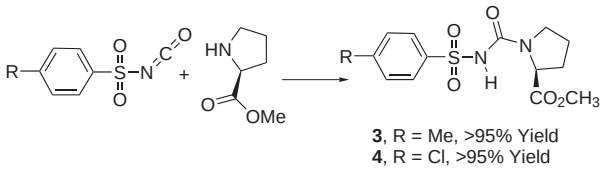
Among the acids screened, picric acid[7] proved to be among the most efficient, delivering coupled product **2** in quantitative yield after only 90 minutes as a 3:2 mixture of anomers (entry 1). In striking contrast, replacement of but one of the nitro groups with a methyl group reduces the efficiency of the reaction. Thus, use of 2,6-dinitro-4-methyl phenol as the intended catalyst results in less than 5% yield of the desired product (entry 2). Pentafluorophenol (PFP) provides intermediate catalytic activity, delivering product **2** in 70% isolated yield (α/β = 57:43) after 24 hours (entry 3). Given the pK_a range of PFP (ca 6.0)[8] and picric acid (ca 0.3),[9] we sought to establish whether simple carboxylic acids provided efficient catalytic reactions. Of note, neither acetic acid (entry 4) nor trifluoroacetic acid (entry 5) is effective. It appears that in these cases, donor **1** is activated by the catalyst, but the conjugate base may outcompete the glycosyl acceptor for the activated donor. Surmising that acid catalysts with non-nucleophilic conjugate bases may be optimal catalysts for this process, we found that toluenesulfonic acid was comparable to picric acid as a catalyst (entry 6), affording **2** in 92% isolated yield after 90 minutes, albeit as a nearly 1:1 mixture of anomers. The buffered version, PPTS was also competent, but resulted in attenuated reactivity (54% yield after 24 h, entry 7).

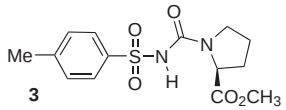
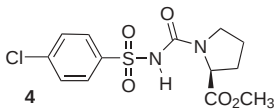
We then sought to extend these findings to other classes of Brønsted acids that might be amenable to structural modification, and ultimately the tuning of catalytic activity. For this purpose, we turned our attention to acyl sulfonamides, a class of compounds that have been relatively unexplored as catalysts for organic reactions. We chose acyl sulfonamides for this purpose since they possess a proton with acidity that might be readily tuned through alteration of the structure. In addition, we speculated that the acyl sulfonamide-derived conjugate base would be a poor nucleophile. Acyl sulfonamides are readily available through condensation of an amine and a sulfonyl isocyanate.[10] Accordingly, we prepared compounds **3** and **4** through coupling of Pro-OMe to various sulfonyl isocyanates under mild conditions (Equation 2).[11]



Equation 2

Compounds **3** and **4** do indeed prove to be catalysts for glycosylation of cyclohexanol with a trichloroacetimidate donor such as **1**. As shown in Table 2, the tolyl substituted compound **3** catalyzes a sluggish reaction, but it affords a 60% isolated yield of the product as a 2:3 mixture of anomers (α/β) over the course of 43 hours (entry 1). However, changing the *para*-substituent on the aromatic ring has a significant impact on the catalytic activity. For example, *para*-chloro-substituted catalyst **4** provides a faster reaction, delivering product **2** in 80% yield within a 24 hour period (entry 2).

Table 2 Catalyst Screen for the Coupling of **1** to Cyclohexanol under the Influence of Acyl Sulfonamide Catalysts[a]

Entry	Catalyst	Reaction time (h)	Yield (%)[b]	α/β[c]
1	 **3**	43	60	40:60
2	 **4**	24	80	40:60

[a] All reactions conducted at 25 °C in CH_2Cl_2 in the prescence of 4 Å sieves. Catalyst loadings are 10 mol% with respect to alcohol.
[b] Yields refer to isolated yield after silica gel chromatography.
[c] As determined by ^1H NMR (400 MHz).

While a more complete data set would allow a more definitive explanation of the apparant rate difference, it appears at this time that the more electron deficient compound may be more active due to heightened acidity of the sulfonamide proton. Of note, control experiments show that the catalyst does not undergo hydrolysis under the reaction conditions to afford the corresponding catalytically active sulfonic acid. For example, when the reaction is conducted in a deuterated solvent, no catalyst decomposition is observed by NMR (<2%, 400 MHz, ^1H NMR). In addition, the catalyst can be recovered in >90% yield by silica gel chromatography after the reaction has been run to completion. Of course, a very minor degree of hydrolysis cannot be rigorously excluded.

With an acyl sulfonamide-based catalyst on hand that provided convenient reaction times, we sought to examine its behavior with additional glycosyl acceptors. As shown in Table 3, catalyst **4** mediates glycosidic bond formation with a variety of alcohol acceptors.[12,13] In addition to cyclohexanol,[14] *n*-octanol participates as an acceptor; glycoside **6** may be obtained in 60% yield (α/β = 60:40, entry 2).[15] Phenyl glycoside **7** is obtained in somewhat lower yield (49%, α/β = 40:60, entry 3). In addition, glucose derivatives may be employed as the acceptor, as illustrated by the formation of **8** (67%, α/β = 42:58, entry 4).[16] In contrast, a BOC-protected serine derived acceptor was a less efficient coupling partner, delivering glycoside **9** in a low 28% isolated yield over 48 h. The reasons for the low yield are a matter of further study, as the possibility of competitive hydrogen bonding between acceptor and catalyst may play a role.[17]

In summary, we have found that an appropriately functionalized acyl sulfonamide can function as a catalyst for glycosylation of trichloroacetimidate donors. The next phase of this research will endeavor to explore the tunability of these catalysts as a function of further

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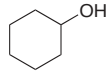
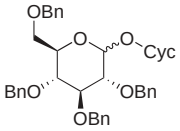
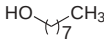
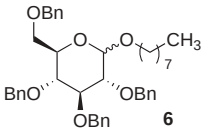
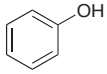
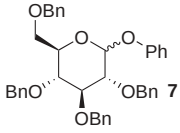
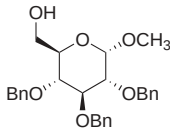
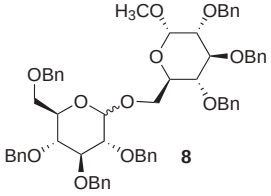
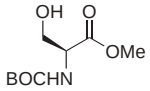
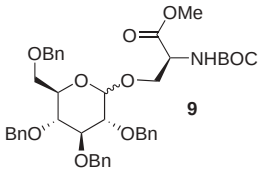
Table 3 Glycosylation Reactions Performed with Acyl Sulfonamide **4** as the Catalyst[a]

Entry	Acceptor	Product	Time (h)	Yield (%)[b]	α/β[c]
1			24	92	58:42
2		 **6**	40	60	60:40
3		 **7**	48	49	40:60
4		 **8**	48	67	42:58
5		 **9**	48	28	57:43

[a] All reactions conducted at 25 °C in CH_2Cl_2 in the prescence of 4 Å sieves. Catalyst loadings are 15 mol% with respect to alcohol.
[b] Yields refer to isolated yield after silica gel chromatography.
[c] As determined by ^1H NMR (400 MHz).

variations of both the aryl moiety, and also the amino acid (and peptide) coupling partner introduced during the acyl sulfonamide synthesis.

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(7) Caution: picric acid is a potentially explosive compound when thoroughly dried (water content <10%). We did not observe any difficulties of this type during these experiments.
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(9) (a) Iwachido, T.; Oosawa, S.; Toei, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2415. (b) Kolthoff, I. M.; Chantooni, M. K.; Bhomik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23.
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(11) Compounds **3** and **4** were prepared by the reaction of L-proline methylester with either 4-chlorophenylsulfonyl isocyanate or *p*-toluenesulfonyl isocyanate according to the following procedure: To a solution of L-proline methylester hydrogen chloride (48.0 mg, 0.289 mmol) in CH_2Cl_2 (720 μL) stirring at 0 °C was added Et_3N (40.0 μL, 0.289 mmol). Isocyanate was then added dropwise and the reaction was allowed to warm to 25 °C. The reaction was allowed to stir for 30 min at 25 °C and was then diluted with 5 mL of CH_2Cl_2 and washed with 1 N HCl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was chromatographed on silica gel with 0–5% MeOH/CH_2Cl_2 (>95% yield). Data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 4.40 (dd, *J* = 8.4, 3.9 Hz, 1 H), 3.70 (s, 3 H), 3.56–3.34 (m, 2 H), 2.43 (s, 3 H), 2.20–1.81 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 150.5, 144.4, 136.3, 129.4, 128.3, 59.1, 52.5, 46.5, 29.5, 24.5, 21.6. IR (film): 3245, 2948, 1747, 1676, 1456, 1379, 1325, 1171 cm^{-1}. TLC: R_f = 0.50 (10% MeOH/CH_2Cl_2). Exact mass calcd for [$C_{14}H_{18}N_2O_5NaS$] requires *m/z* 349.0834. Found: 349.0827 (ESI+). Data for compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.9 Hz, 2 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 4.41 (dd, *J* = 8.7, 3.8 Hz, 1 H), 3.82–3.63 (m, 1 H), 3.72 (s, 3 H), 3.54–3.34 (m, 1 H), 2.20–1.86 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 150.4, 139.7, 137.4, 129.5, 128.8, 59.1, 52.3, 46.5, 29.4, 24.1. IR(film): 3245, 2954, 1747, 1670, 1456, 1379, 1183 cm^{-1}. TLC: R_f = 0.40 (10% MeOH/CH_2Cl_2). Exact mass calcd for [$C_{13}H_{15}N_2O_5Na_1S_1C_{l1}$] requires *m/z* 369.0288. Found: 369.0282 (ESI+).

(12) All compounds gave satisfactory analytical data.

(13) The general experimental procedure is as follows: Trichloroacetimidate **1** (50.0 mg, 0.0730 mmol) was suspended in methylene chloride (300 μL). The glycosyl acceptor (0.0487 mmol) was then introduced, followed by the addition of activated 4 Å molecular sieves (50.0 mg). The solution was allowed to stir at 25 °C for 10 min upon which a stock solution of catalyst was added (50.0 μL**,** 0.00730 mmol). When the reaction was judged to be finished by TLC, the suspension was filtered through a layer of celite and concentrated in vacuo. The resulting residue was subjected to flash chromatography on silica gel, eluting with 5% EtOAc/hexanes. The products are isolated as a mixture of α/β anomers, which could be assigned by ^{1}H NMR spectroscopy.

(14) Compound **2** has been characterized previously: Hosono, S.; Kim, W.-S.; Sasai, H.; Shibisaki, M. *J. Org. Chem.* **1995**, *60*, 4.

(15) (a) Characterization data for compound **6**: α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.12 (m, 20 H), 4.99 (d, *J* = 11.0 Hz, 1 H), 4.84–4.75 (m, 4 H), 4.66–4.59 (m, 2 H), 4.47 (d, *J* = 12.1 Hz, 2 H), 3.99 (t, *J* = 9.3 Hz, 1 H), 3.79–3.72 (m, 2 H), 3.65–3.54 (m, 4 H), 3.44–3.39 (m, 1 H), 1.64–1.58 (m, 2 H), 1.23 (bs, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 138.2, 138.1, 137.8, 128.2, 127.9, 127.8, 127.7, 127.5, 127.4, 96.8, 82.1, 80.1, 77.8, 75.7, 75,1, 73.5, 73.1, 70.1, 68.6, 68.3, 32.0, 29.5, 29.4, 26.3, 22.8, 14.3. IR(film): 3089, 3063, 3030, 2926, 2856 cm^{-1}. TLC: R_f = 0.39 (20% EtOAc/hexanes). Anal. Calcd for $C_{42}H_{52}O_6$: C, 77.27; H, 8.03. Found: C, 76.94; H, 8.05. β-Anomer ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.14 (m, 20 H), 4.95 (t, *J* = 11.0 Hz, 2 H), 4 .80 (t, *J* = 11.4 Hz, 2 H), 4.72 (d, *J* = 11.0 Hz, 1 H), 4.63–4.51 (m, 3 H), 4.39 (d, *J* = 7.7 Hz, 1 H), 3.99–3.94 (m, 1 H), 3.75 (dd, *J* = 10.8, 2.0 Hz, 1 H), 3.69–3.43 (m, 6 H), 1.68–1.62 (m, 2 H), 1.42–1.26 (m, 10 H), 0.87 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.5, 138.3, 138.0, 137.9, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 123.6, 84.7, 82.8, 77.9, 75.7, 75.0, 74.8, 73.4, 70.1, 69.0, 31.9, 29.9, 29.5, 29.4, 26.3, 22.8, 14.2. IR (film): 3087, 3063, 3032, 2927, 2857 cm^{-1}. TLC: R_f = 0.50 (20% EtOAc/hexanes). Anal. Calcd for $C_{42}H_{52}O_6$: C, 77.27; H, 8.03. Found: C, 77.00; H, 8.00.

(16) For compounds **7** and **8**, see: Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269.

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