Covalent Catalysis

Sulfoxide Covalent Catalysis: Application to Glycosidic Bond Formation**

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The discovery of novel catalyst systems for hydroxy group functionalization has significant implications in synthesis, both in terms of functional group interconversions as well as fragment-coupling reactions. The development of nonmetallic catalysts for hydroxy group derivatization is an active area of investigation, with the bulk of the work focusing on the discovery of nucleophilic catalysts derived from either nitrogen or phosphorus(III) to enhance acylation or alkylation reactions.[1] On the other hand, the paucity of methods for hydroxy group activation by sulfoxide catalysts is notable despite the diverse reactivity profile of this functional group. Although sulfoxides have been employed as ligands in metal-centered catalysis[2] and as additives to effect coordinative rate acceleration,[3] the use of substoichiometric sulfoxide reagents as stand-alone covalent catalysts has not been exploited.[4] Herein we describe the development of a method for hemiacetal hydroxy sulfonylation that not only establishes the feasibility of sulfoxide turnover in covalent catalysis but also proceeds by a mechanism distinct from the traditional pathway for nucleophilic catalysis. As a demonstration of its practical utility in synthesis, this transformation is applied in conjunction with a subsequent nucleophilic substitution event to effect anomeric bond construction.[5]

We have previously demonstrated that activated sulfoxide reagents (i.e., Ph_2SO and Tf_2O) can effect efficient hemiacetal activation and anomeric bond formation with C1-hydroxy carbohydrates, although the process is only possible when excess sulfoxide reagent is employed in the coupling process.[6] As a result, this glycosylation reaction serves as an ideal setting to establish sulfoxide covalent catalysis, in which the process of hemiacetal sulfonylation is explored. A reasonable pathway for sulfoxide-catalyzed C1-hydroxy sulfonylation (Scheme 1) is envisioned to involve initial *O*-sulfonylation of a sulfoxide catalyst (R^2_2SO, **1**) by an appropriate sulfonic anhydride $(R^1SO_2)_2O$ to generate the sulfonyloxysulfonium sulfonate **2**. Ideally, activation of the hemiacetal **3** by **2** leads to the formation of the anomeric sulfonate **4** with concomitant regeneration of the sulfoxide catalyst (R^2_2SO, **1**) for subsequent turnovers. The feasibility of sulfoxide turnover is

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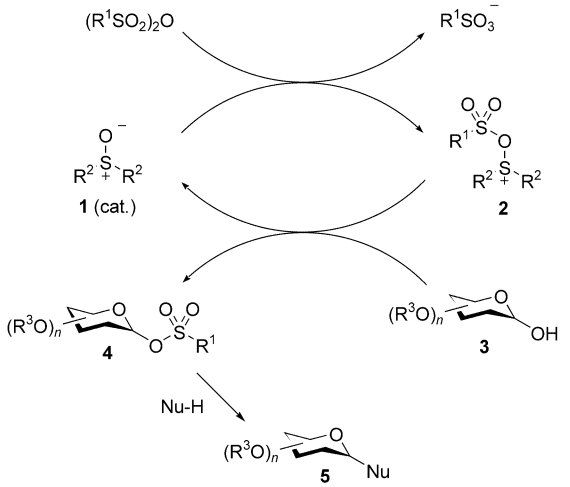
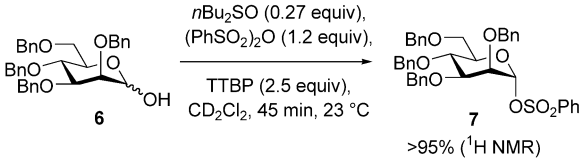


Scheme 1. Proposed pathway for sulfoxide-catalyzed C1-hydroxy sulfonylation (cat. = catalyst).

governed by the requirement that the sulfonate anion derived in the activation process ($R^1SO_3^-$) be of sufficient nucleophilicity so that the glycosyl sulfonate **4** serves as the resting state for the activated hemiacetal.[7] In addition, the anomeric sulfonate **4** must exhibit the desired balance between stability and reactivity if such a process is to be useful for further fragment couplings in glycoconjugate synthesis. For example, unproductive condensation of **4** with unconverted hemiacetal (**4**+**3**) must be avoided in the activation stage,[8] yet substitution at C1 with an external nucleophile (Nu–H, **4**→**5**) must proceed efficiently in the subsequent coupling stage in the absence of additional activating agents.

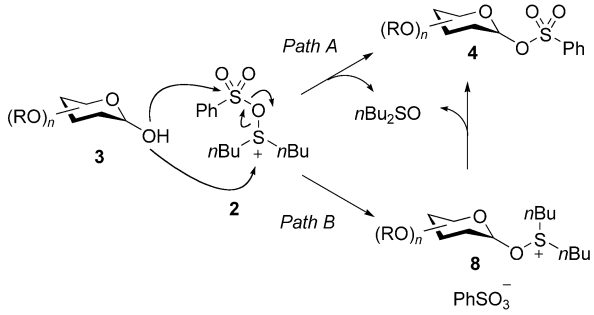
Screening of various sulfonic anhydrides and potential sulfoxide catalysts revealed the combination of nBu$_2$SO and $(PhSO_2)_2O$ to be a suitable system to effect efficient formation of the glycosyl sulfonate **4** by the catalytic turnover of substoichiometric quantities of sulfoxide (Scheme 2).



Scheme 2. Formation of α-mannosyl sulfonate **7** with nBu$_2$SO catalyst and $(PhSO_2)_2O$.

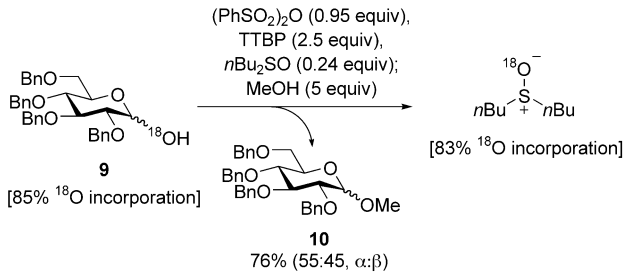
When 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**6**) is treated with $(PhSO_2)_2O$ (1.2 equiv) and nBu$_2$SO (0.27 equiv) in the presence of 2,4,6-tri-*tert*-butylpyridine (TTBP; 2.5 equiv) in CD_2Cl_2 at 23 °C, near quantitative formation (> 95 %) of the corresponding α-mannosyl sulfonate **7** is observed by ^{1}H NMR within 45 min. Importantly, hemiacetal sulfonylation does not proceed in the absence of the sulfoxide when the reaction is performed under otherwise-identical conditions,[9] thereby establishing the critical catalytic role of the sulfoxide species.

Mechanistic consideration of the hemiacetal activation and sulfoxide turnover events suggests two reasonable pathways (Scheme 3), including: (1) Lewis base nucleophilic catalysis[1] to form glycosyl sulfonate **4** (Scheme 3 path A) in



Scheme 3. Two possible pathways for the formation of **4**.

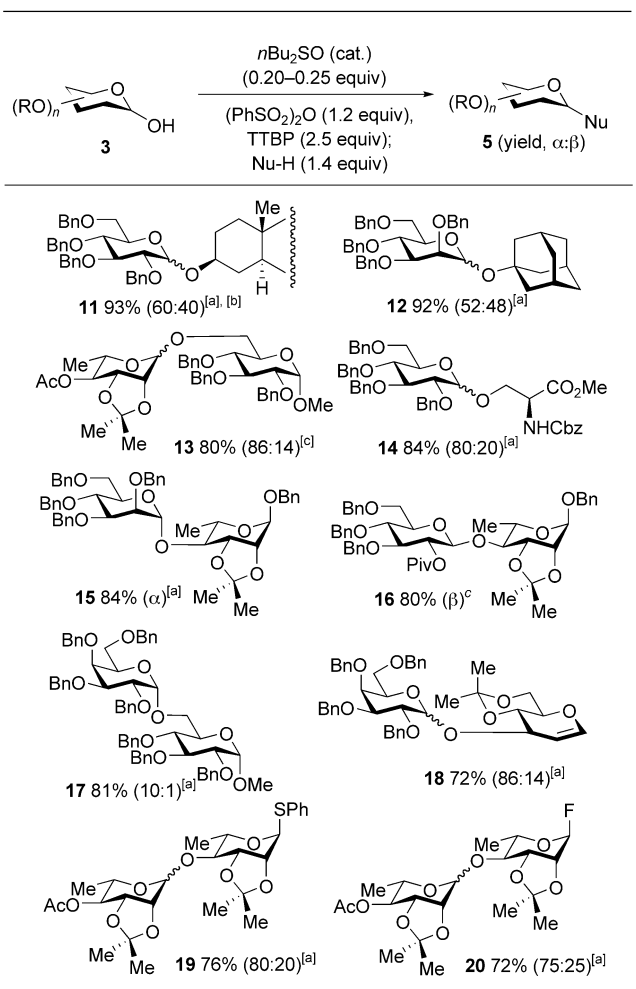
which the sulfoxide species functions sequentially as a transient nucleophile and leaving group; and (2) hemiacetal addition at the sulfonium center of **2** (Scheme 3 path B) to generate the glycosyl oxosulfonium **8**, which then undergoes expulsion/regeneration of the sulfoxide catalyst by nucleophilic substitution by $PhSO_3^-$ to form **4**. A key isotope-labeling experiment (Scheme 4) reveals that addition of



Scheme 4. Isotope-labeling experiment.

methyl alcohol to the glycosyl sulfonate derived from C1–^{18}O-labeled 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**9**, 85 % ^{18}O-atom incorporation) by the sulfoxide-catalyzed sulfonylation protocol led to isolation of the recovered sulfoxide catalyst with 83 % ^{18}O-incorporation, along with methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**10**, 76 %). Factors such as sulfoxide turnover and sulfonate exchange notwithstanding, this level of hemiacetal-to-sulfoxide ^{18}O-atom transfer indicates that C1–OH activation and sulfoxide turnover proceed at least in part (if not exclusively) through path B of Scheme 3[10,11] in which the sulfur(IV) center serves as a conduit for oxygen-atom transfer, a pathway markedly distinct from both traditional nucleophilic catalysis[1] and simple coordinative rate acceleration.[4]

The production of the methyl glycoside **10** in this experiment also highlights the potential utility of sulfoxide-catalyzed hemiacetal sulfonylation in glycosylation through the introduction of an external nucleophile following hemiacetal activation. Thus, this nBu$_2$SO-catalyzed activation and cou-



Scheme 5. Glycoconjugates obtainable by the described reaction; [a] 0.25 equivalents of nBu$_2$SO; [b] Nu–H = dihydrocholesterol; [c] 0.20 equivalents of nBu$_2$SO.

pling is amenable to the construction of a diverse array of glycoconjugates (Scheme 5) in a procedure conveniently conducted entirely at room temperature. In terms of nucleophile variability, primary, secondary, and tertiary alcohols are glycosylated in good yields.[12,13] The range of α:β ratios in the glycoconjugates indicates that the anomeric selectivities vary with the nature of the substrate, although the process does appear to respond to the effects of neighboring group participation (i.e., **16**). Notably, the method tolerates acid-sensitive functionalities such as those present in glycal nucleophiles (**18**). Moreover, the successful couplings with glycals (**18**) as well as nucleophiles bearing latent leaving groups such as sulfide (**19**) and fluoride (**20**) underscore the potential of this reaction to engage in orthogonal glycosylation approaches to oligosaccharide construction.[14]

In summary, the process of sulfoxide turnover in covalent catalysis has been achieved through the development of a versatile glycosylation reaction that employs a simple, commercially available, nonmetallic catalyst for anomeric hydroxy activation and subsequent coupling. The sulfoxide catalyst functions uniquely in three capacities, first as an O nucleophile, then as a S^+-electrophile, and finally as a leaving group to fulfill turnover. Investigations are currently underway to further probe the scope and mechanism of this novel mode of sulfoxide catalysis as well as expand it to other oxygen activation/substitution reactions in synthesis.[15]

Experimental Section

General glycosylation procedure with nBu$_2$SO catalyst/(PhSO$_2$)$_2$O: **15**: Benzenesulfonic anhydride (59.9 mg, 0.20 mmol) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (92.1 mg, 0.17 mmol), *n*-butyl sulfoxide (7.0 mg, 0.04 mmol), and 2,4,6-tri-*tert*-butylpyridine (104.6 mg, 0.42 mmol) in dichloromethane (1.3 mL) at 23 °C. After the reaction mixture had stirred for 1 h, a solution of benzyl 2,3-di-*O*-isopropylidene-α-L-rhamnopyranoside (70.3 mg, 0.24 mmol) in dichloromethane (400 μL) was added by syringe and the reaction mixture was then allowed to stir for an additional 19 h. The reaction was then quenched with triethylamine (235 μL, 1.69 mmol), concentrated under high vacuum, and purified by silica gel flash chromatography (5% → 17% ethyl acetate in benzene) to afford the (1→4) α-disaccharide **15** (116.3 mg, 84%) as a single anomer. $R_f = 0.19$ (5% ethyl acetate in benzene); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.18$–7.42 (m, 25H), 5.03 (s, 1H), 4.96 (d, 1H, $J = 1.5$ Hz), 4.92 (d, 1H, $J = 10.5$ Hz), 4.80 (d, 1H, $J = 12.6$ Hz), 4.77 (d, 1H, $J = 12.2$ Hz), 4.72 (d, 1H, $J = 12.6$ Hz), 4.69 (d, 1H, $J = 11.7$ Hz), 4.68 (d, 1H, $J = 11.9$ Hz), 4.65 (d, 1H, $J = 11.8$ Hz), 4.57 (d, 1H, $J = 10.6$ Hz), 4.52 (d, 1H, $J = 12.8$ Hz), 4.50 (d, 1H, $J = 12.1$ Hz), 4.24 (t, 1H, $J = 9.7$ Hz), 4.12 (d, 1H, $J = 5.7$ Hz), 4.05 (m, 1H), 4.02 (dd, 1H, $J = 5.8$, 7.3 Hz), 3.92 (dd, 1H, $J = 3.0$, 10.9 Hz), 3.87 (dd, 1H, $J = 3.0$, 9.8 Hz), 3.76 (dd, 1H, $J = 2.0$, 3.0 Hz), 3.70 (dd, 1H, $J = 1.9$, 10.7 Hz), 3.64 (qd, 1H, $J = 6.3$, 10.1 Hz), 3.36 (dd, 1H, $J = 7.4$, 9.9 Hz), 1.49 (s, 3H, CH_3), 1.27 (s, 3H), 1.06 ppm (d, 3H, $J = 6.3$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 138.7$, 138.7, 138.5, 138.3, 137.0, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 109.0, 98.9, 96.1, 80.2, 80.0, 76.0, 75.2, 74.7, 74.0, 73.4, 72.6, 72.3, 71.8, 69.0, 68.6, 65.0, 28.1, 26.3, 17.2 ppm; FTIR (neat film): $\tilde{\nu} = 2932$ (w), 1496 (w), 1454 (w), 1381 (w), 1220 (w), 1093 (s), 1052 (s), 1028 cm^{-1} (m); HRMS (FAB) m/z: calcd for $C_{50}H_{56}O_{10}Na$ $[M+Na]^+$ 839.3771; found 839.3770.

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Keywords: glycosylation · homogeneous catalysis · reaction mechanisms · sulfonylation · synthetic methods

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[8] Dehydrative glycosylations mediated by Ph_2SO and Tf_2O require the use of excess sulfoxide to minimize self-condensation of the hemiacetal donor since highly reactive glycosyl triflates would necessarily serve as the resting state during the initial activation process with substoichiometric quantities of sulfoxide.

[9] In the absence of sulfoxide catalyst, activation of hemiacetal **6** (1.2 equiv $(PhSO_2)_2O$, 2.5 equiv TTBP) does not occur even after 4 h at 23 °C as evidenced by ^{1}H NMR analysis.

[10] Approach of nucleophiles to the sulfonium center of **2** is consistent with the reactivity of oxosulfonium species with nucleophiles: T. T. Tidwell, *Synthesis* **1990**, 857 – 870.

[11] Partial ^{18}O-atom transfer to the sulfoxide catalyst by way of exclusive reaction through path A of Scheme 3 is possible only if rapid exchange of sulfonate anions with both the sulfonium intermediate **2** and the glycosyl sulfonate **4** occur throughout the activation process. However, participation of the other pseudoequivalent ^{16}O atoms (present in five-fold excess of the lone hemiacetal ^{18}O atom) within the sulfonate anions in this exchange process would result in at most a statistical incorporation of ^{18}O atoms into sulfoxide, even in the limiting case where sulfonate exchange in **2** and **4** might be extremely fast.

[12] Glycosylations to form disaccharide **15** with lower catalyst loadings of Bu_2SO resulted in lower yields of **15** accompanied by some self-condendensation of the hemiacetal donor. With 10 mol% catalyst loading, 75% of **15** and 11% of the corresponding 1,1′-α,α′-symmetrical mannodisaccharide was isolated. At 4 mol% catalyst, 60% of **15** and 20% of the 1,1′-α,α′-symmetrical disaccharide were isolated. Glycosylations to form disaccharide **15** with catalytic 4-dimethylaminopyridine (4-DMAP; 0.25 equiv) instead of nBu$_2$SO under otherwise identical conditions led to 18% yield.

[13] Glycosylation to form disaccharide **15** with catalytic dimethyl sulfoxide (DMSO; 0.25 equiv) instead of nBu$_2$SO under otherwise identical conditions led to 56% yield. An attempted nBu$_2$SO-catalyzed glycosylation to form **15** with Tf_2O (1.2 equiv) instead of $(PhSO_2)_2O$ produced a complex mixture that does not contain **15**.

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