Azide and Cyanide Displacements via Hypervalent Silicate Intermediates†

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Hypervalent azido- and cyanosilicate derivatives, prepared in situ by the reaction of trimethylsilyl azide or trimethylsilyl cyanide, respectively, with tetrabutylammonium fluoride, are effective sources of nucleophilic azide or cyanide. Primary and secondary alkyl halides and sulfonates undergo rapid and efficient azide or cyanide displacement in the absence of phase transfer catalysts with the silicate derivatives. Application of these reagents to the stereoselective synthesis of glycosyl azide derivatives is reported.

Nucleophilic substitution is one of the most prized and useful transformations in the chemical arsenal. At the practical level, however, nucleophilic displacements often require relatively harsh reaction conditions with high reaction temperatures, polar solvents such as DMSO, HMPA, or DMF, and a large excess of the nucleophile if high yields of product are to be achieved. Recently, we reported the use of tetrabutylammonium triphenyldifluorosilicate (TBAT, **1a**) as a source of nucleophilic fluoride for S_N2 displacement of primary and secondary alkyl substrates (Scheme 1)[1] and for silicon−carbon bond cleavage.[2] TBAT is an excellent fluoride surrogate when compared to alkali metal fluorides or tetraalkylammonium fluorides because TBAT is crystalline, soluble in a wide range of organic solvents, nonbasic, and nonhygroscopic. Having demonstrated that hypervalent silicate derivatives are practical reagents for the delivery of fluoride anion,[1−3] extension of this strategy to deliver other nucleophiles was investigated. In this paper, we report that trimethylsilyl azide (TMS-N_3) and trimethylsilyl cyanide (TMS-CN) underwent reaction with tetrabutylammonium fluoride (TBAF) to generate the respective hypervalent trimethylfluorosilicate (**1b** or **1c**) in situ. Analogous with the observations using TBAT, silicates **1b** and **1c** were extremely reactive alternates of azide and cyanide anion, respectively, for S_N2 displacement (Scheme 1). Using the in situ generated silicates, it was possible to perform displacements under milder conditions than typically required (vide infra). Takaya has also published a preliminary report in which azides are prepared in this manner.[4]

As noted in Scheme 2, silicates **1b** and **1c** are potent azide and cyanide anion surrogates. Comparison of the reaction conditions for nucleophilic displacement with those typically employed demonstrate the effectiveness of the silicate strategy. Especially noteworthy is the reaction of silicates **1b**/**1c** with phenethyl bromide because the substrate is prone to base-catalyzed elimination to afford styrene. Displacements employing alkali metal salts in polar solvents consistently afforded more elimination products than the silicate method (vide supra).

Cyanide Displacements

The major advantage of the silicate method with these substrates was the rate of cyanide displacement in acetonitrile. The silicate-based displacements occurred rapidly, whereas the displacements using alkali metal salts of cyanide were sluggish (typically >12 h) (Scheme 2). For example, the silicate-based displacement of benzyl bromide occurred *in less than 5 min* in refluxing acetonitrile, compared with the crown ether procedure that required 24 h under identical conditions (eq 1, Scheme 2). Results for the cyanide displacement with a variety of primary and secondary substrates bearing halide or sulfonate leaving groups are summarized in Table 1.

Several features of the results in Table 1 are noteworthy; although displacement was predictably longer for benzyl chloride (Table 1, entry b) than for the bromo analogue (entry a), the chloride underwent cyanide displacement in comparable yield. Previous methods, while achieving similar yield, required longer reaction times, painstakingly dried reagents, DMSO as the solvent, or toxic 18-crown-6 as a phase transfer catalyst.[5−7] Primary alkyl iodide (entry c), bromide (entry d), chloride (entry e), and mesylate (entry f) were efficiently converted to the corresponding nitrile **3**, where the relative order of reactivity was as follows: I ≈ OMs > Br > Cl. Again, the yield of displacement product was comparable to traditional methodologies; however, these more traditional methods employed either high temperatures and lengthy reaction time or required DMF as the solvent.[8,9] Phen-

† This paper is dedicated to Professor Jack Baldwin on the occasion of his 60th birthday.

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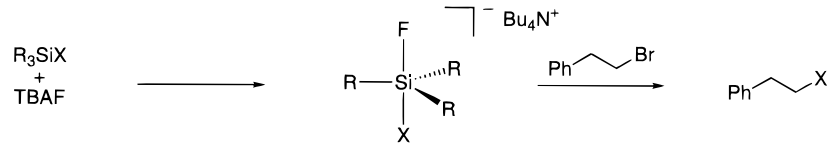
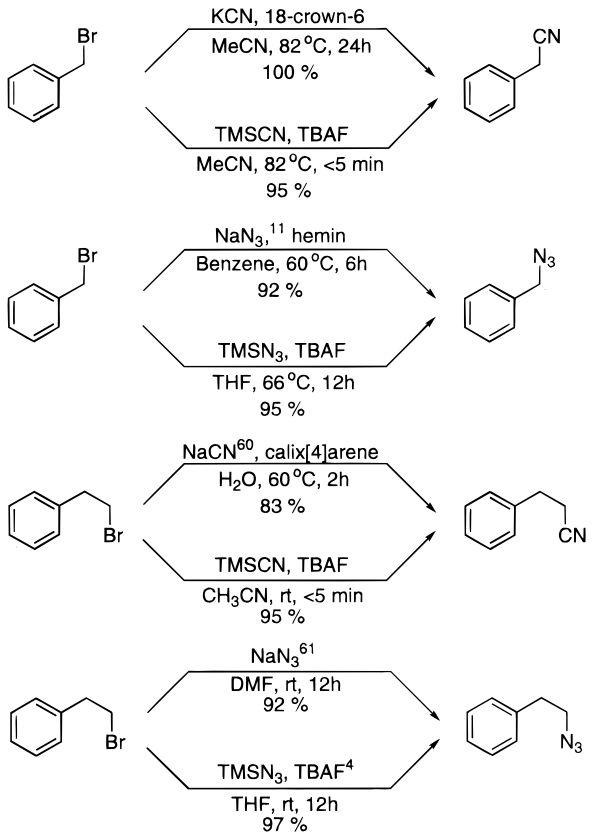
Scheme 1



1a: R = Ph, X = F (TBAT)
1b: R = Me, X = N_3
1c: R = Me, X= CN

Scheme 2



ethyl bromide (entry g), which should be more prone to elimination than the dodecyl substrates, gave no elimination products with silicate **1c**, again attesting to the nonbasic nature of the reagent. Predictably, secondary halides and sulfonates reacted slower with competing elimination, lowering the yields of nitrile. For example, silicate **1c** rapidly converted 2-iodooctane (entry h), bromide (entry i), and tosylate (entry j) to the nitrile in good yield (76−83%), although the alkene byproduct was also observed.

For secondary substrates, the silicate methodology is superior to prior methods with regard to yield and reaction conditions. Regen and co-workers reported the displacement of the primary bromide in entry d in quantitative yield using NaCN-coated alumina in refluxing toluene for 24 h. However, under the same conditions, Regen reported that the secondary bromide in entry i gave only 27% of the corresponding nitrile after 40 h.[8] The Bram group was able to perform the same transformation in 72% yield, but only under aqueous phase-transfer conditions.[10] Finally, secondary benzylic bromide (entry k) underwent smooth conversion to the corresponding nitrile upon treatment with cyanosilicate without the formation of the elimination product. Again the yield was superior to that previously reported.[11] In refluxing acetonitrile, no appreciable amount of nitrile product formed from *exo*-norbornyl bromide (entry l); however, in refluxing dioxane, displacement of the *exo*-bromide occurred in good yield to give *endo*-nitrile, albeit sluggishly. This reaction occurred predominantly with inversion of configuration, supporting our proposed S_N2 displacement mechanism. We have not yet been able to determine whether the small amount of *exo*-nitrile obtained is the result of epimerization of the halide prior to displacement or is due to an S_N1-like process. As expected, the cyclohexyl halides were less ideal substrates for the displacement reaction even with the silicate derivative. Cyclohexyl bromide (entry m) failed to give the displacement product and gave the alkene instead, mirroring the results of previous researchers.[6,12,13] (−)-Menthyl chloride (entry n) was similarly unreactive, presumably due to steric hindrance. However, it is noteworthy that the reagent did not induce elimination under these reaction conditions.

Cyanide is an ambident nucleophile and is known to react as a carbon nucleophile to give nitriles (R-CN) or as a nitrogen nucleophile to yield isocyanides (R-NC).[14] Traditionally, NaCN or KCN has been used to form nitriles, and AgCN has been used to form isocyanides.[15] It has been rationalized that alkali metal cyanide dissociates to give "free" CN ion which attacks with its more basic carbon end, whereas AgCN does not entirely dissociate, leaving Ag^+ complexed to the carbon of the nucleophile, so that only nitrogen is available for nucleophilic attack.[16] We hypothesized that the silicon would function analogously, so that C-complexation to silicon would leave the cyano nitrogen available to act as a nucleophile. However, no traces of isonitrile products were detected in the reaction mixtures. Whether this result is an indication of the bonding in the hypervalent species or a function of reaction conditions is under investigation.

Azide Displacements

Our primary interest in the azide displacement was for the synthesis of glycosyl azide derivatives, which are important precursors of *N*-linked glycoconjugates.[17] For

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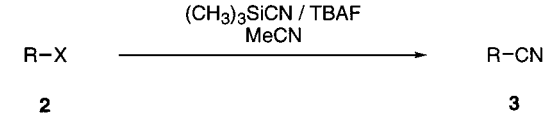
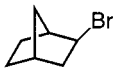
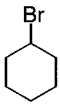
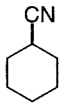
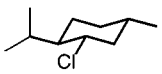
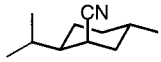
Table 1. Reaction of Silicate Anion 1c with Alkyl Halides[a]



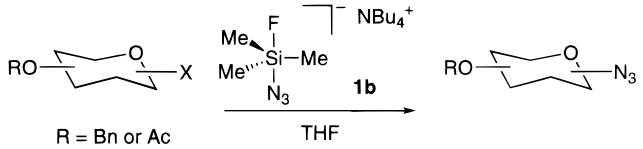
2 **3**

	Substrate (**2**)	Product (**3**)	Temp (°C)	Time (h)	Yield[b]
a	$(C_6H_5)CH_2Br$	$(C_6H_5)CH_2CN$	82	0.1	95
			25	1	(>95)
b	$(C_6H_5)CH_2Cl$	$(C_6H_5)CH_2CN$	82	2	(>95)
			25	72	(>95)
c	$CH_3(CH_2)_{11}I$	$CH_3(CH_2)_{11}CN$	82	0.1	95
			25	6	(95)
d	$CH_3(CH_2)_{11}Br$	$CH_3(CH_2)_{11}CN$	82	2	95
			25	36	(>95)
e	$CH_3(CH_2)_{11}Cl$	$CH_3(CH_2)_{11}CN$	82	3	95
			25	96	(33)
f	$CH_3(CH_2)_{11}OMs$	$CH_3(CH_2)_{11}CN$	82	0.1	95
g	$(C_6H_5)CH_2CH_2Br$	$(C_6H_5)CH_2CH_2CN$	82	0.1	95
			25	32	(>95)
h	$CH_3(CH_2)_5CHICH_3$	$CH_3(CH_2)_5CH(CN)CH_3$	82	1	(83)
			25	72	(68)
i	$CH_3(CH_2)_5CHBrCH_3$	$CH_3(CH_2)_5CH(CN)CH_3$	82	2	(82)
			25	120	(79)
j	$CH_3(CH_2)_5CHOTsCH_3$	$CH_3(CH_2)_5CH(CN)CH_3$	82	1	(76)
			25	48	(70)
k	$(C_6H_5)CHBrCH_3$	$(C_6H_5)CH(CN)CH_3$	82	1	92
			25	5	(>95)
l		 7:1 *endo : exo*	82	48	(0)[c]
			101[d]	96	70
m			82	48	(<5)
n			82	48	(0)[c]
			101[d]	96	(0)[c]

[a] The indicated substrate, Me_3SiCN, and TBAF (1:1.5:1.5 molar ratio) in acetonitrile were allowed to react at the given temperature, unless otherwise noted. [b] Isolated yield after purification. The yield determined by gas chromatographic analysis of the crude reaction mixture (vs an internal standard) is reported in parentheses. [c] No reaction was observed. [d] Reaction was performed in dioxane.

example, glycosylamines,[17,18] glycolipids,[19−22] glycopeptides,[23−25] heterocyclic *N*-glycosides,[26,27] and combinatorial libraries[28,29] have been prepared from glycosyl azide derivatives. It was found that a wide variety of glycosyl analogues underwent reaction with the silicate generated in situ from trimethylsilyl azide in the presence of a fluoride source, affording the corresponding glycosyl azides in high yield. The yield of azides obtained by this methodology exceed or are comparable to those reported by other

Scheme 3



methods while avoiding the use of toxic reagents or activating agents such as: tin(IV),[30,31] hexamethylphosphorictriamide,[32,33] in situ brominating reagents,[34] or large excess of alkali metal azide salt.[35,36]

The general transformation for azide displacement is outlined in Scheme 3 and involved nucleophilic displacement of bromide, chloride, triflate, tosylate, trichloroimidate, and isoxazoline leaving groups. Of particular concern was the ability to retain the protecting groups of the glycosyl derivatives during the displacement. Previous studies in our group had demonstrated that azide

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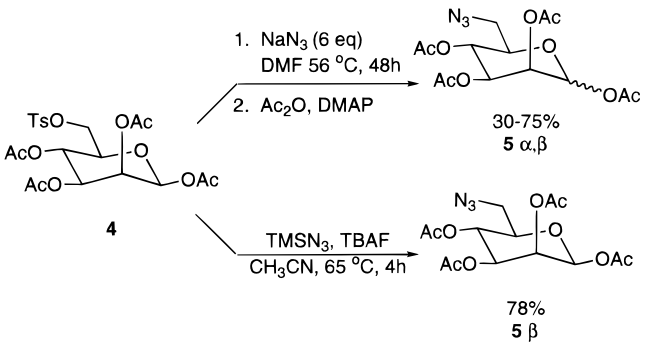
Scheme 4



displacements using the alkali metal salts resulted in removal of acetoxy groups under the strongly basic and nucleophilic reaction conditions (see Scheme 4).[37] Acetoxy or benzyl ether protected sugars bearing an appropriate leaving group underwent efficient azide displacement with a slight excess of silicate **1b** in THF at moderate temperatures to afford glycosyl azides in good to excellent yield. As noted in Table 2, the displacement occurred predominately with inversion of configuration and no deprotected or glycal elimination products were observed.

Peracetylmannose 6-tosylate **4** was prepared and subjected to typical azide displacement conditions (Scheme 4). Even under optimized conditions, the displacement required 6 equiv of sodium azide for 48 h in warm DMF. The yields were unreliable at best, and the azidation was accompanied by loss of the anomeric acetate and anomerization.[37] In addition, a second acetate was lost (presumably from the C-2 position). In contrast, when tosylate **4** was treated with TMS-N_3/TBAF, the displacement proceeded in dramatically improved yield and all the protecting groups as well as the configuration at the anomeric center were preserved. In addition, as was observed in cyanide displacements noted above, the rate of the displacement of tosylate by azide was enhanced by comparison with typical azide displacement conditions.

In addition to primary leaving groups, displacement at a more hindered secondary center occurred with equal facility (Table 2). For example, mannosyl triflate **6**[38] (entry a) gave 2-azidoglucopyranose **7** in 73% yield with complete inversion of configuration. Again, the anomeric configuration and integrity of the protecting groups were unaffected using these conditions.

Silicate **1b** could also be employed for the synthesis of 1-azido glycosyl derivatives from the corresponding precursors. For example, azide **9**β, which serves as a precursor to glycopeptide derivatives, was prepared from commercially available α-bromide **8**.[39] Similarly, α-chloride **10**[40] underwent displacement to afford **9**β. Note that the reactions occurred by S_N2 displacement, as evidenced by complete inversion at the reaction center. On the other hand, displacement of β-chloro anomer **11**[41] was not completely stereoselective and gave azide **9**α,β in 95% yield as a mixture of anomers ($\alpha:\beta = 85:10$).

Perbenzylated glycosyl donors are known to be more reactive than their acetylated counterparts and the α-chloro derivative gave the β-azido product stereoselectively (entry f). However, the much less stable α-trichloroimidate analogue **16** underwent azide displacement with silicate **1b** to afford a 1:1 mixture of anomeric azides.

The final glycosyl derivatives investigated was the *N*-acetylglucosamine family (entries h and i). Treatment of oxazoline **17** with silicate **1b** afforded exclusively β-azide **18** in good yield. This result was particularly pleasing since the oxazoline derivative is known to be hydrolytically unstable. Alternatively, α-chloride **19**, a much more robust analogue of *N*-acetylglucosamine, underwent azide displacement in only 1.5 h to give exclusively **18**.

The advantage of the silicate-based displacements is demonstrated in the following example from the Hirshmann−Smith laboratory (Scheme 5). Standard methods for direct conversion of the primary neopentyl carbinol (−)-**20** to its corresponding azide proved to be ineffective.[41−43] The most promising of these methods appeared to be the Mitsunobu conditions with diphenyl phosphoryl azide (DPPA) as the azide source.[43] On one occasion, these conditions afforded desired azide (−)-**21** in a low 30% yield, but this result was irreproducible. However, treatment of triflate **22** with the in situ generated azidosilicate **1b** in acetonitrile afforded azide (−)-**21** in 60% yield.

Conclusion

Treatment of trimethylsilyl cyanide and azide with TBAF resulted in the in situ generation of silicates **1c** and **1b**, respectively. The resulting silicates have been shown to be highly effective as nucleophilic cyanide and azide donors under extremely mild conditions. Extension of this strategy for the nucleophilic transfer of other groups will be reported in due course.

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in parts per million (δ), and coupling constants (*J* values) are given in hertz (Hz). Infrared absorbances are reported in reciprocal centimeters (cm^{-1}). Gas chromatography was performed on an instrument equipped with a flame ionization detector using a 25 m capillary column coated with cross linked methyl silicone.

Tetrahydrofuran (THF) and dioxane were distilled from sodium/benzophenone ketyl. Pyridine, acetonitrile (MeCN), and methylene chloride (CH_2Cl_2) were distilled from calcium hydride. Dimethylformamide (DMF) was distilled from molecular sieves. Methanol (MeOH) was dried and stored over molecular sieves. Glassware used in the reactions was dried overnight in an oven at 120 °C. All reactions were performed under an atmosphere of nitrogen unless noted otherwise.

Tetrabutylammonium fluoride (TBAF) was used as a 1.0 M solution in THF. All materials were purchase from Aldrich and used as received, with the following exceptions. 2-Iodooctane (Table 1, entry h) was synthesized from the corresponding alcohol using Olah's method.[44] In the case of sulfonates (Table

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(38) 1,3,4,6-Tetra-*O*-acetyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranose [cat. no. 31,025-5] was purchased from Aldrich Chemical Co. and used without further purification.

(39) 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide [cat. no. 27093-0100] was purchased from Acros Organics and recrystallized from diisopropyl ether prior to use.

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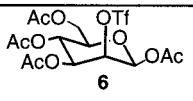
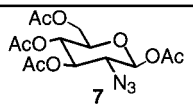
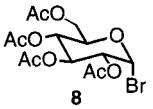
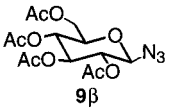
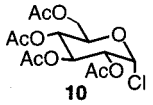
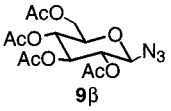
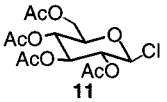
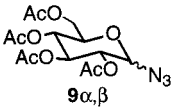
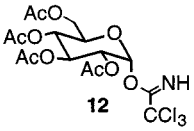
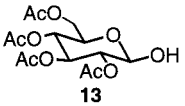
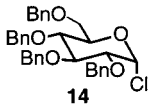
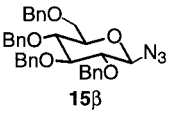
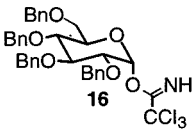
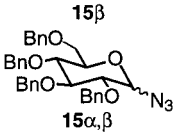
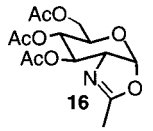
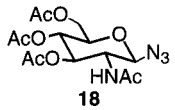
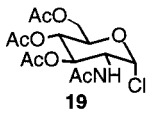
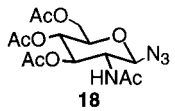
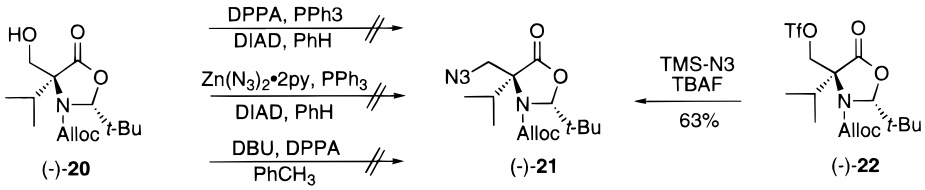
Table 2. Reaction of Silicate Anion 1b with Glycosyl Acceptors[a]

Entry	Substrate	Product	Temp. (°C)	Time (h)	Yield[b] (%)
a	 **6**	 **7**	25	22	73
b	 **8**	 **9β**	25	3	93
c	 **10**	 **9β**	65	29	85
d	 **11**	 **9α,β**	65	46	95 (α:β = 9:1)
e	 **12**	 **13**	65	22	88
f	 **14**	 **15β**	65	5	92
g	 **16**	 **15α,β**	65	48	48 (α:β=1:1)
h	 **16**	 **18**	65	22	73
i	 **19**	 **18**	65	1.5	89

[a] All reactions were performed using 1.2 equiv of silicate **1b**, generated in situ, in THF at the indicated temperature. [b] Isolated material. All known compounds exhibited physical and spectroscopic properties identical to those reported in the literature. See Experimental Section for details.

Scheme 5



1, entries f and j) the appropriate sulfonate was synthesized from the alcohol immediately before use using the literature method,[45,46] and the crude isolated sulfonate was used without further purification. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**8**) was purchased from Acros Organics and recrystallized from diisopropyl ether prior to use. All compounds were determined to be >95% pure by GC and ^{1}H NMR spectroscopy.

General Procedure for Synthesis of Nitriles 3. Nitrile preparations and product isolations were performed under identical reaction conditions, the only variable being the reaction time and solvent as outlined in Table 1. The following example is illustrative.

Phenylacetonitrile (Table 1, entries a and b). Trimethylsilyl cyanide (200 μL, 1.50 mmol) and TBAF (1.5 mL, 1.5 mmol) were added to a stirring solution of benzyl bromide (119μL, 1.00 mmol) in 10 mL of acetonitrile under an atmosphere of nitrogen. The reaction was complete by GC analysis in 0.1 h. The light yellow reaction mixture was concentrated in vacuo, and the resulting syrup was purified by flash chromatography (9:1, pentane/CH_2Cl_2) to afford 111 mg (95%) of phenylacetonitrile as a colorless oil. The IR and ^{1}H and ^{13}C NMR data were identical to those of an authentic sample purchased from Aldrich, as well as published spectral data.[47,48]

(45) Wawzonek, S.; Klimstra, P. D.; Kallio, R. E. *J. Org. Chem.* **1960**, *25*, 621−623.
(46) Schleyer, P. v. R. In *Reagents for Organic Synthesis*; Fieser, L. F., Fieser, M., Eds.; John Wiley and Sons: New York, 1967; Vol. 1, pp 1180−1181.
(47) Pouchert, C. J. *The Aldrich Library of FT-IR Spectra*, 1st ed.; Aldrich Chemical Company: Milwaukee, 1985; Vol. 2.
(48) Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra*, 1st ed.; Aldrich Chemical Co.: Milwaukee, 1993; Vol. 2.

Tridecanenitrile (Table 1, entries c−f): colorless oil.; IR (thin film) 2246; ^{1}H NMR, 400 MHz ($CDCl_3$) δ 2.33 (t, J = 7.2, 2H), 1.62 (p, 2H), 1.51−1.39 (m, 2H), 1.38−1.17 (m, 16H), 0.84 (t, J = 7.6, 3H); ^{13}C NMR ($CDCl_3$) δ 120.1, 32.1, 29.8, 29.7, 29.5, 29.0, 28.9, 25.6, 22.8, 17.3, 14.3. The IR was identical to the published spectrum.[49]

Hydrocinnamonitrile (Table 1, entry g): colorless oil. The IR and ^{1}H and ^{13}C NMR data were identical to those of an authentic sample purchased from Aldrich, as well as published spectral data.[48,49]

2-Phenylpropionitrile (Table 1, entry k): colorless oil. The IR and ^{1}H and ^{13}C NMR data were identical to those of an authentic sample purchased from Aldrich, as well as published spectral data.[48,49]

***endo/exo*-2-Norbornane Carbonitrile** (Table 1, entry l). The IR and ^{1}H and ^{13}C NMR data were identical, except for the *endo/exo* ratio, to those of an authentic sample purchased from Aldrich, as well as published spectral data.[47,48,50] The *endo/exo* ratio was determined by integration of the ^{13}C NMR spectrum.

1,2,3,4-Tetra-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranose (5α). Tosylate **4** (500 mg, 1.24 mmol) was dissolved in 10 mL of anhydrous DMF. Sodium azide (810 mg, 12.5 mmol) was added, and the solution was stirred at 56 °C for 48 h. The reaction mixture was poured into brine and extracted with ethyl acetate 5 times. The combined ethyl acetate extracts were concentrated in vacuo. The residue was dissolved in 10 mL of anhydrous pyridine, DMAP (20 mg, 0.16 mmol) and acetic anhydride (500 μL, 5.30 mmol) were added, and the mixture was stirred at room temperature for 4 h. The reaction was poured into 10 mL of ice water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed (1:9, EtOAc/CH_2Cl_2) to yield 262 mg (55%) of azide **5**α as an oil: IR (neat) 2106, 1756;^{1}H NMR ($CDCl_3$) δ 6.08 (d, J = 1.6 Hz, 1H), 5.35−5.21 (m, 3H), 4.03−3.92(m, 1H), 3.43−3.22 (m, 2H), 2.16 (s, 3H), 2.15 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.8, 169.5, 169.4, 167.8, 90.1, 71.7, 68.4, 66.1, 66.3, 50.5, 20.8, 20.7, 20.6, 20.4; LRMS (EI), *m/z* (rel int) 314 (M^+ − OAc) (18), 286 (10), 214 (5), 97 (100); HRMS (M^+ − OAc) *m/z* calcd for $C_{12}H_{16}O_7N_3$ 314.0988, found 314.0989.

1,2,3,4-Tetra-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranose (5β). Trimethylsilyl azide (40 μL, 0.300 mmol) and TBAF (300 μL, 0.310 mmol) were added to an argon-blanketed solution of tosylate **4** (109 mg, 0.217 mmol) in 4 mL of CH_3CN. The reaction was heated at reflux for 6 h. Over this time, the solution turned from colorless to clear yellow. The mixture was allowed to return to room temperature, and 10 mL of water was added. This material was extracted with ethyl acetate. The organic extracts were combined, dried over Na_2SO_4, and filtered. Solvent was removed in vacuo to afford a light yellow oil. The oil was purified by flash chromatography (2:1, EtOAc/hexane) to yield 62 mg (77%) of azide **5**β as a colorless oil: IR (CCl_4) 2106, 17569; ^{1}H NMR ($CDCl_3$) δ 5.84 (d, J = 1.2 Hz, 1H), 5.46 (dd, J = 3.1, 1.2, 1H), 5.24 (dd, J = 9.6, 9.6, 1H), 5.09 (dd, J = 9.6, 3.1, 1H), 3.74 (ddd, J = 9.6, 5.5, 3.5, 1H), 3.42−3.34 (m, 2H), 2.20 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H),1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.2, 169.8, 169.7, 168.4, 90.1, 74.4, 70.5, 68.0, 66.4, 50.7, 20.8, 20.7, 20.6, 20.5.

1,3,4,6-Tetra-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranose (7). 1,3,4,6-Tetra-*O*-acetyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranose (**6**) (53 mg, 0.11 mmol) was dissolved at 25 °C in 3 mL of THF. Trimethylsilyl azide (19 μL, 0.15 mmol) was added via syringe followed by TBAF (150 μL, 0.15 mmol). The solution was stirred at 25 °C for 22 h. The reaction mixture was filtered through a plug of silica gel and concentrated in vacuo to give a yellow oil which was chromatographed (2:1, hexanes/EtOAc) to afford 30 mg (73%) of β-anomer **7** as a colorless oil.: IR (CCl_4) 2113, 1762; ^{1}H NMR ($CDCl_3$) 5.56 (d, J = 8.8), 5.10 (t, J = 9.5), 5.05 (t, J = 9.5), 4.31 (dd, J = 4.8, 12.5), 4.09 (dd, J = 2.0, 12.5), 3.79 (ddd, J = 9.5, 4.8, 2.0), 3.65 (dd, J = 9.5, 8.8), 2.18 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H). The spectra for the anomeric mixture has been previously reported.[51]

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl Azide (9β). Method a (Entry b, Table 2). 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**8**) (89 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Trimethylsilyl azide (40 μL, 0.3 mmol) was added via syringe followed by TBAF (0.3 mL, 0.3 mmol). The solution was stirred at 25 °C for 3 h. The organic solution was filtered through a plug of silica gel, dried over Na_2SO_4, and concentrated in vacuo to give a yellow amorphous solid. The residue was crystallized from absolute ethanol to afford 75 mg (93%) of azide **9**β as a white solid: mp 126−127 °C (lit.[33] mp 126−128 °C). Physical and spectroscopic properties of **9**β were identical to previously reported data.[33,36]

Method b (Entry c, Table 2). 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride[40] (**10**) (80 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Trimethylsilyl azide (40 μL, 0.3 mmol) was added via syringe followed by TBAF (0.3 mL, 0.3 mmol). The solution was stirred for 29 h at 65 °C. The reaction was cooled to ambient temperature, filtered through a plug of silica gel, dried over Na_2SO_4, and concentrated in vacuo to give a yellow oil. The oil was crystallized from absolute ethanol to afford 69 mg (85%) of azide **9**β as a white solid: mp 126−126.5 °C (lit.[33] mp 126−128 °C). Physical and spectroscopic properties of **9**β were in agreement with previously reported values.[33,36]

Method c (Entry e, Table 2). 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl trichloroimidate[52] (**12**) (240 mg, 0.49 mmol) was dissolved at 25 °C in 4 mL of THF. Trimethylsilyl azide (90 μL, 0.68 mmol) was added via syringe followed by TBAF (0.68 mL, 0.68 mmol). The solution was stirred for 22 h at 65 °C. The reaction was cooled to ambient temperature, filtered through a plug of silica gel, dried over Na_2SO_4, and concentrated in vacuo to give a yellow oil. The oil was crystallized from acetone and recrystallized from Et_2O/petroleum ether (1:1) to afford 150 mg (88%) of hydrolyzed sugar **13** as a white solid with no traces of sugar azide. **13**: mp 130−132 °C (lit.[53] mp 132−134 °C); IR (CCl_4) 3462, 1759; ^{1}H NMR ($CDCl_3$) 5.27 (t, J = 9.7), 5.09 (t, J = 9.7), 4.89 (dd, J = 9.7, 8.2), 4.75 (dd, J = 8.7, 8.2), 4.26 (dd, J = 12.3, 4.7), 4.15 (dd, J = 12.3, 2.3), 4.75 (ddd, J = 9.7, 4.7, 2.4), 3.62 (d J = 8.7), 2.07 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H).

2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl Azide (9α/β). 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl chloride[54] (**11**) (80 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Trimethylsilyl azide (40 μL, 0.3 mmol) was added via syringe followed by TBAF (0.3 mL, 0.3 mmol). The solution was stirred for 46 h at 65 °C. The reaction was cooled to ambient temperature, filtered through a plug of silica gel, dried over Na_2SO_4, and concentrated in vacuo to give a yellow amorphous material which was crystallized from absolute ethanol. The crude reaction mixture was a 9:1 (α/β) anomeric mixture of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl azide as determined by ^{1}H NMR. The anomeric mixture was separated by column chromatography (4:1, hexanes/EtOAc) and crystallized from absolute ethanol to afford 8 mg (10%) of azide **9**β as a white solid and 69 mg (90%) of azide **9**α as a white solid (overall yield of 95%) with melting point of 98−99 °C (lit.[2] mp 98−99.5 °C). Physical and spectroscopic properties of azide **9**α were identical to previously reported values.[33,36]

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl Azide (15β). Method a (Entry f, Table 2). 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride[55] (**14**) (100 mg, 0.18 mmol) was dis-

(49) Pouchert, C. J. *The Aldrich Library of Infrared Spectra*, 3rd ed.; Aldrich Chemical Co.: Milwaukee, 1981.

(50) Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 7107−7120.

(51) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073−2077.

(52) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249−1256.

(53) McCloskey, C. M.; Pyle, R. E.; Coleman, G. H. *J. Am. Chem. Soc.* **1944**, *66*, 349−350.

(54) Lemieux, R. U. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfram, M. L., BeMiller, J. N., Eds.; Academic Press: New York, 1963; Vol. 2, pp 224−225.

solved at 25 °C in 3 mL of THF. Trimethylsilyl azide (32 μL, 0.25 mmol) was added via syringe followed by TBAF (0.25 mL, 0.25 mmol). The solution was stirred for 5 h at 65 °C. The reaction was cooled to ambient temperature, filtered through a plug of silica gel, dried over Na_2SO_4, and concentrated in vacuo to give a yellow oil. The oil was chromatographed (9:1, hexanes/EtOAc) to afford 94 mg (92%) of azide **15**β as a colorless oil. Physical and spectroscopic properties of azide **15**β were identical to previously reported values.[33]

Method b (Entry g, Table 2). 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl trichloroimidate[56] (**16**) (790 mg, 0.1.15 mmol) was dissolved at 25 °C in 30 mL of THF. Trimethylsilyl azide (0.21 mL, 1.58 mmol) was added via syringe followed by TBAF (1.58 mL, 1.58 mmol). The solution was stirred for 48 h at 65 °C. The reaction was cooled to ambient temperature, filtered through a plug of silica gel, dried over Na_2SO_4, and concentrated in vacuo to give a yellow oil. The oil was chromatographed (9:1, hexanes/EtOAc) to give 310 mg (48%) of an inseparable anomeric mixture (1:1, α/β) of azide **15** as a colorless oil. Spectroscopic and physical properties of the anomeric mixture were in agreement with previously reported values.[33]

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl Azide (18). **Method a** (Entry h, Table 2). 2-Methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline[57,58] (**17**) (110 mg, 0.33 mmol) was dissolved at 25 °C in 3 mL of THF. Trimethylsilyl azide (60 μL, 0.44 mmol) was added via syringe followed by TBAF (0.44 mL, 0.44 mmol). The solution was stirred for 22 h at 65 °C. The reaction was cooled to ambient temperature, filtered through a plug of silica gel, dried over Na_2SO_4, and concentrated in vacuo to give a yellow oil. The oil was crystallized from EtOAc/petroleum ether to afford 89 mg (73%) of azide **18** as a white solid. Physical and spectroscopic properties of **18** were identical to previously reported data.[36]

Method b (Entry i, Table 2). 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[59] (**19**) (79 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Trimethylsilyl azide (58 μL, 0.43 mmol) was added via syringe followed by TBAF (0.43 mL, 0.43 mmol). The solution was stirred for 1.5 h at 65 °C. The reaction was cooled to ambient temperature, filtered through a plug of silica gel, dried over Na_2SO_4, and concentrated in vacuo to give a yellow-brown oil. The oil was chromatographed (10:1, CH_2Cl_2/MeOH) to afford a white solid which was recrystallized from EtOAc/petroleum ether to afford 72 mg (89%) of azide **18** as a white solid. Physical and spectroscopic properties of **18** were identical to previously reported data.[36]

Oxazolidinone Azide (−)-21. Carbinol (−)-**20**[62] (1.01 mL, 3.36 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.17 g, 5.71 mmol) were dissolved in 34 mL of CH_2Cl_2. Trifluoromethanesulfonic anhydride (0.79 mL, 4.70 mmol) was added at 0 °C. After 1 h at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), washed with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (4:1, hexanes/EtOAc) to gave 1.23 g (85%) of triflate (−)-**22** as a clear coloress oil. This was used immediately in the following step. Triflate (−)-**22** (1.23 g, 2.85 mmol) was dissolved in dry CH_3CN (20 mL). Trimethylsilyl azide (508 μL, 4.41 mmol) was added via syringe followed by TBAF (4.13 mL, 4.13 mmol). The solution was stirred at reflux for 12 h. The reaction was cooled to room temperature, water was added (30 mL), the solution was extracted with EtOAc, and the combined organics were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (4:1, hexanes/EtOAc) to afford 590 mg (63%) of azide (−)-**21** as a white solid: mp 35−36 °C; $[\alpha]^{20}_D$ −9.7° (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 3020, 2980, 2110, 1785, 1715; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (ddt, J = 17.1, 10.5, 6.2, 1 H), 5.60 (s, 1 H), 5.35 (dd, J = 17.1, 1.2, 1 H), 5.28 (d, J = 10.4, 1 H), 4.68 (dd, J = 12.8, 6.0, 1 H), 4.58 (dd, J = 12.6, 6.3, 1 H), 2.26 (septet, J = 7.0, 1 H), 1.13 (d, J = 7.0, 6 H), 0.98 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 155.0, 131.6, 119.6, 95.6, 68.8, 67.1, 51.2, 37.4, 34.6, 25.8, 18.7, 17.8; high-resolution mass spectrum (CI, NH_3) *m*/*z* 325.1879 [(M + H)$^+$; calcd for $C_{15}H_{25}O_4N_4$ 325.1876].

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