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Remarkably efficient activation of glycosyl trichloro- and (*N*-phenyl)trifluoroacetimidates with bismuth(III) triflate

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Abstract—Easily handled and nontoxic $Bi(OTf)_3$ is a powerful activator for trichloro- and (*N*-phenyl)trifluoroacetimidate glycosyl donors. This catalyst allows glycosidations to be performed at low temperatures in very short times. Rewarding yields were obtained from a wide range of donors of varying reactivity.

An impressive progress has been registered over the last years in oligosaccharide synthesis with the development of automated procedures[1] and the development of a programmable one-pot approach enabling the construction of more than one glycosidic bond in a single synthetic operation.[2] Despite these advances, oligosaccharide synthesis is still presenting a variety of problems partly related to the inherent structural complexity of saccharidic molecules with a great number of possible glycosidic connections. As a matter of fact, there is not yet a 'universal' glycosidation procedure which serves at best in every possible case of connection. In addition, the most adopted protocols are experimentally demanding as strictly anhydrous conditions are necessary for good yields to be attained.[3] Furthermore, harsh acidic agents (TMSOTf, $BF_3{\cdot}OEt_2$, triflic anhydride, triflic acid, etc.) are routinely included in the promoter systems. These agents are either moisture sensitive or highly hygroscopic, and special caution is thereby necessary for their handling and storage. A further drawback is represented by the problems of chemical compatibility occasionally observed in glycosidations conducted in the presence of acid labile functional groups.

Glycosyl trichloroacetimidates are broadly used glycosyl donors whose activation is typically accomplished with catalytic amounts of TMSOTf or $BF_3{\cdot}OEt_2$,[4] whereas alternative acidic promoters have occasionally been used.[5] Very recently two independent reports described the use of perchloric acid supported on silica gel as an operationally simpler alternative to conventional promoters.[6] Along this line, in the last years we have been devoting a wide interest toward the development of alternative glycosidation promoters featuring moisture stability and $Yb(OTf)_3$ turned out to be a rather versatile promoter in glycosidations conducted with glycosyl trichloroacetimidates and the recently introduced (*N*-phenyl)trifluoroacetimidate[7] analogues.[8,9] This lanthanide salt was found able to activate both 'armed' and 'disarmed'[10] donors, and was applied in the construction of biologically interesting oligosaccharide antigene sequences or glycoconjugates.[9] The commercial availability of several metal triflates prompted us to search for even improved results.[11]

From a literature survey we have realized that bismuth(III) triflate is often serving better than lanthanide triflates in acid promoted transformations of organic synthesis,[12] and therefore this nontoxic and cheap salt has been examined as a potential activator of glycosyl trihaloacetimidates. To the best of our knowledge, the only reported application of this salt in glycosidation chemistry concerns its use in combination with $BF_3{\cdot}OEt_2$ (both agents in exceeding stoichiometric amount) for effecting the activation of sialyl acetates donors.[13]

In a preliminary screening, a dramatic influence exerted by the nature of the solvent on the reactivity of this salt was observed. Armed perbenzylated trifluoroacetimidate and trichloroacetimidate **1** and **2** (Table 1) of glucose were smoothly activated in solvent mixtures

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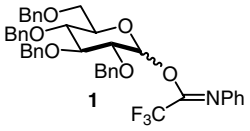
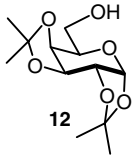
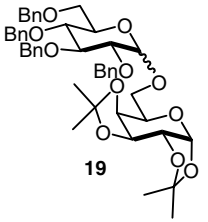
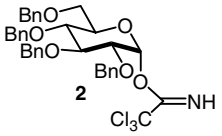
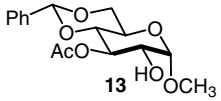
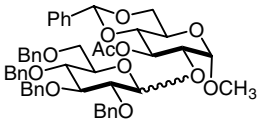
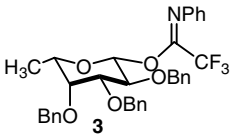
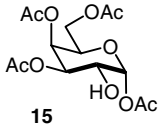
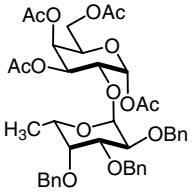
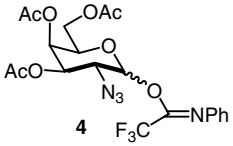
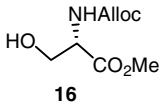
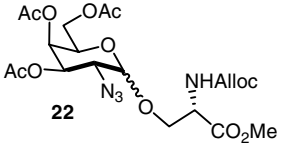
Table 1. $Bi(OTf)_3$ promoted glycosidations with donors devoid of participating groups[a]

Entry	Donor	Acceptor	Solvent	% $Bi(OTf)_3$	T (°C)	Product	Yield (%) (α:β)
1	 **1**	 **12**	$PhCH_3$/DME 2:1	5[b]	−70 to −50	 **19**	97 (1.8)
2	 **2**	**12**	$PhCH_3$/DME 2:1	1.5[b]	−70 to −50	**19**	97 (1.2)
3	**1**	 **13**	$PhCH_3$/DME 2:1	5[b]	−50 to −30	 **20**	86 (6.0)
4	**2**	**13**	$PhCH_3$/DME 2:1	1.5[b]	−70	**20**	77 (4.0)
5	 **3**	 **15**	DCM/dioxane/Et_2O 4:1:1	5[c]	−50	 **21**	75 (>10)
6	 **4**	 **16**	Dioxane/$PhCH_3$/DME 3:1:1	10[c]	−10	 **22**	72 (5.5)

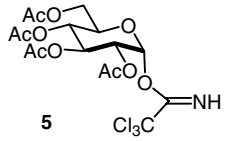
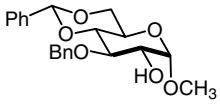
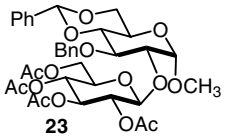
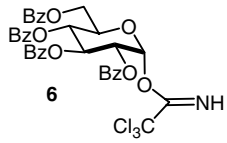
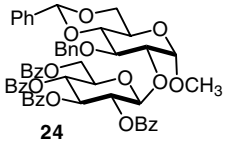
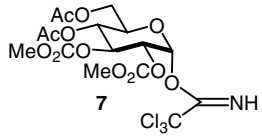
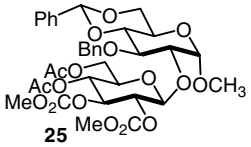
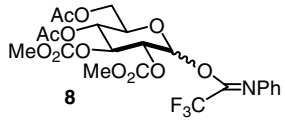
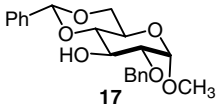
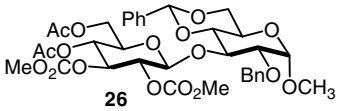
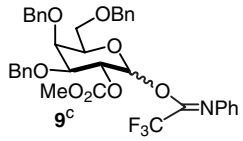
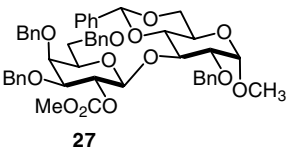
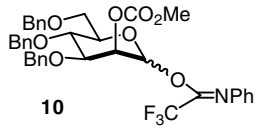
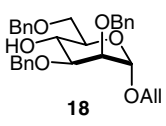
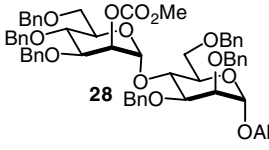
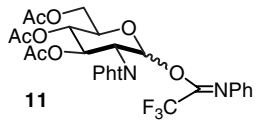
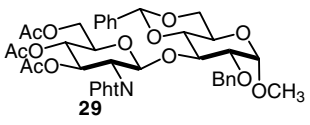
[a] General conditions: acceptor (1 equiv), donor (1.2–1.4 equiv) (entries 1–5). For entry 6: acceptor (1.3 equiv), donor (1.0 equiv).
[b] The promoter was added as a solution in dioxane (10–20 mg/mL).
[c] The promoter was added as a solution in the reaction solvent mixture.

containing toluene, 1,2-dimethoxyethane and dioxane, previously found to provide a remarkable α-selectivity under $Yb(OTf)_3$ activation (Table 1, entries 1–4).[8c]

Notably, reactions took very short times (less than 45 min) and could be performed in higher yields at sensibly lower temperatures as well as with a lower catalytic amount than in the case of the lanthanide activation.[8c] α-Stereoselectivity was found to be lower but similarly influenced by both the nature of the donor leaving group and the reactivity of the acceptor hydroxyl group. Good results were obtained also with fucosyl donor **3** and the azido galactose derivative **4** (entries 5 and 6). Improved α-stereoselectivity was reached in the case of the fucosylation.[9a] As for entry 6, it should be noted that the coupling of **4**, when performed under $Yb(OTf)_3$ activation, took several days at room temperature for a comparable overall yield to be achieved.[14]

In contrast, reactions in nitrile solvents, usefully adopted with armed donors for β-selective $Yb(OTf)_3$ promoted glycosidations[8b,9b] gave disappointing results under $Bi(OTf)_3$ activation due to their extreme sluggishness. This result might be ascribed to the ability of

Table 2. $Bi(OTf)_3$ promoted glycosidations with donors equipped with participating groups[a]

Entry	Donor	Acceptor	% $Bi(OTf)_3$[b]	T (°C)	Product	Yield (%)
1	 **5**	 **14**	5	−30 to rt	 **23**	87
2	 **6**	**14**	5	−30 to rt	 **24**	90
3	 **7**	**14**	5	−30 to rt	 **25**	85
4	 **8**	**14**	10	0	**25**	88
5	**8**	 **17**	10	0	 **26**	79
6	 **9**[c]	**17**	5	−30 to rt	 **27**	91
7	 **10**	 **18**	8	−20	 **28**	92
8	 **11**	**17**	10	−10	 **29**	88

[a] General conditions: acceptor (1 equiv), donor (1.2–1.4 equiv), DCE.
[b] The promoter was added as a solution in dioxane (10–20 mg/mL).
[c] 1.6 equiv of donor were used.

trivalent bismuth to form complexes committing several nitrile molecules.[15]

Activation of disarmed donors was even more sensitive to the reaction solvents and the best results were obtained in mixtures of 1,2-dichloroethane and dioxane. The efficacy of the promoter was tested on donors derived from glucose (**5**–**8**), galactose (**9**), mannose (**10**) and glucosamine (**11**) as shown in Table 2.

Excellent yields were obtained with trichloroacetimidates **5** and **6**, protected with conventional acetyl and benzoyl groups which are prone to give orthoester coupling products.[3] As a matter of fact, TLC analysis of the mixture of entry 2 displayed the fast consumption at low temperature of both donor and acceptor and the preponderant generation of an initial intermediate which was converted, upon warming to room temperature, to the desired β-linked disaccharide. This evidence strongly suggests that an orthoester intermediate might be initially formed as the preponderant coupling product that subsequently rearranges to the corresponding 1,2-*trans* glycoside.

Also the disarmed donors reacted smoothly and in high yields (generally less than 30 min were sufficient and in no case reactions were worked-up after more than 3 h).

In contrast to lanthanide triflates,[16] $Bi(OTf)_3$ cannot be completely dried[12] and therefore it was simply coevaporated with dry toluene prior to its use. The observed results demonstrate that the residual amounts of water contained in the salt were not detrimental to the achievement of high coupling yields.

In conclusion, $Bi(OTf)_3$ has been found to act as a powerful activator for trichloro- and (*N*-phenyl)trifluoroacetimidate glycosyl donors. Glycosidations are efficiently conducted at low temperature and in very short times,[17] comparably with the standard protocols involving strong Lewis or protic acids as activators. In addition, use of $Bi(OTf)_3$ appears at least advantageous in that the storage and the handling of this nontoxic agent does not entail special precautions. The activation protocol was successfully applied to a variety of both armed and disarmed donors from a wide range of saccharidic precursors. Use of this promoter is now being investigated with other glycosidation approaches as well as in the assemblage of more complex oligosaccharide sequences.

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17. Typical procedure: A mixture of donor **8** (58 mg, 0.105 mmol) and acceptor **17** (32 mg, 0.086 mmol) was coevaporated three times with anhydrous toluene and then kept for 30 min under vacuum. The mixture of donor and acceptor was dissolved at 0 °C under argon in anhydrous 1,2-dichloroethane (1.2 mL) in the presence of activated 4 Å acid washed molecular sieves (AW 300 MS). Bismuth(III) triflate was also coevaporated three times with anhydrous toluene and dissolved in dioxane (20 mg/mL) in the presence of activated 4 Å molecular sieves (ultrasonication favours solubilization). An aliquot of this solution (280 μL, 8.5 μmol of promoter) was added at 0 °C to the mixture of the donor and the acceptor. After 10 min TLC analysis displayed complete consumption of the donor. A few drops of pyridine were added and the mixture was filtered on a short plug of silica gel. The resulting crude product was then chromatographed on a silica gel column eluted with hexane/ethyl acetate mixtures to yield disaccharide **26** (48 mg, yield 79%). Spectroscopic

data of **26**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.60 (aromatic protons), 5.52 (1H, s), 5.03 (1H, t, $J_{2,3} = J_{3,4} = 10.0$ Hz, H-4′), 5.00–4.90 (2H, overlapped signals, H-2′ and H-3′), 4.85 (1H, d, $J_{gem} = 11.2$ Hz, –OCH_aH$_b$Ph), 4.48 (1H, d, –OCH$_a$$H_b$Ph), 4.45 (1H, $J_{1,2} = 3.6$ Hz, H-1), 4.22 (1H, d, $J_{1,2} = 8.0$ Hz, H-1′), 4.20 (1H, dd, $J_{5,6eq} = 2.8$ Hz, $J_{6ax,6eq} = 10.0$ Hz, H-6eq), 4.11 (1H, $J_{5,6a} = 4.4$ Hz, $J_{6a,6b} = 12.0$ Hz, H-6a′), 3.93 (1H, $J_{5,6b} = 2.4$ Hz, H-6b′), 3.85–3.75 (2H, overlapped signals, H-3 and H-5), 3.77 and 3.76 (6H, 2 × s, 2 × –OCO_2CH_3), 3.72 (1H, t, $J_{5,6ax} = J_{5,6eq} = 10.0$ Hz, H-6ax), 3.56 (1H, $J_{3,4} = J_{4,5} = 10.0$ Hz, H-4), 3.52–3.49 (2H, overlapped signals, H-2 and H-5′), 3.34 (3H, s, 1-OCH_3), 2.01 and 1.98 (6H, 2 × s, 2 × –$COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7 and 169.4 (–COCH_3), 155.1 and 154.9 (–OCO$_2$$CH_3$), 138.0 and 137.2 (aromatic C), 129.0–126.0 (aromatic CH), 101.2 (benzylidene acetal CH), 100.5 (C-1′), 98.7 (C-1), 55.3 (–OCH_3), 20.7 and 20.6 (–COCH_3). Other signals at δ 79.7, 79.6, 75.4, 74.2, 71.4, 68.9, 68.3, 62.2, 61.9.