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Efficient activation of armed glycosyl trichloroacetimidates with $Sm(OTf)_3$ in the stereoselective glycosidation of saccharidic acceptors

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Abstract

Catalytic amounts of $Sm(OTf)_3$ activate armed glycosyl trichloroacetimidates under very mild conditions. This reagent proved effective in promoting the glucosylation of saccharidic acceptors **2**, **3**, **4**, and **5**, possessing primary or secondary hydroxyls, with the model donor **1**. The stereoselectivity of these glycosidations can be controlled by a suitable choice of solvent. © 2000 Elsevier Science Ltd. All rights reserved.

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Recently we have reported on the conversion of glycosyl trichloroacetimidates into iodo- and iodobutyl-glycosides mediated by air oxidised samarium diiodide in THF.[1] This peculiar reactivity led us to anticipate the feasible activation of anomeric trichloroacetimidates in ordinary glycosidation reactions[2] by using different trivalent samarium species with a non-nucleophilic counterion. Herein we describe our first results concerning the efficiency of $Sm(OTf)_3$ in promoting the smooth glycosidation of primary and secondary saccharidic hydroxyls under very mild conditions. Very recently[3] this salt was reported to promote glycosidation reactions using 'armed'[4] anomeric sulfones as glycosidation donors. These reactions required the use of stoichiometric amounts of promoter, prolonged reaction times, and high temperatures to provide high yields. For our investigations we chose perbenzylated glucosyl trichloroacetimidate **1** as a model donor, and saccharidic compounds **2**, **3**, **4** and **5** as model acceptors.

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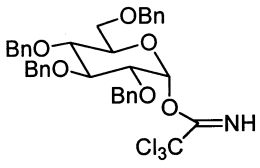

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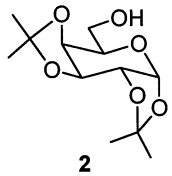
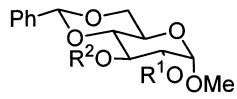
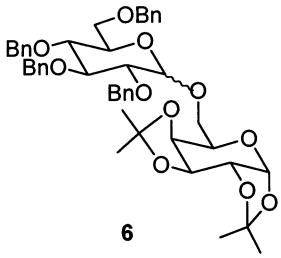


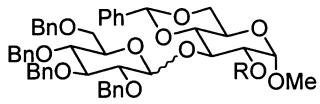
2



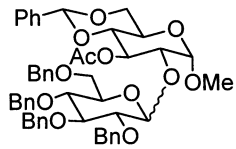
3: R^1= Ac R^2= H
4: R^1= H R^2= Ac
5: R^1= Bn R^2= H



6



7: R: Ac
9: R: Bn



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Initially we examined the reactivity of the donor with acceptor **2**, possessing a primary alcoholic function, in a variety of solvent mixtures. In all cases (Table 1, entries 1–8) glycosidation occurred smoothly (within one hour), at low temperature and in the presence of catalytic amounts of the lanthanide salt (10% or less) to provide disaccharide **6** (anomeric mixture). In all the reported reactions the promoter was added as a solution in the minor cosolvent (THF, acetonitrile or dioxane). As expected,[5] the use of acetonitrile afforded high β-selectivity (entry 4), while in 4:1 diethyl ether/dioxane α-selectivity was observed (entry 8). A predominance of the β anomer was nearly always observed in the other cases. The noteworthy

Table 1
Reaction of **1** with sugar acceptors promoted by $Sm(OTf)_3$

Entry	Acceptor	Solvent	Temp./°C	$Sm(OTf)_3$/% mol	Yield[a]/%	α:β ratio[b]
1	**2**	4:1 CH_2Cl_2/THF	−78	10	75	1:1.5
2	**2**	THF	−78	10[c]	57	1:2
3	**2**	4:1 CH_3CN/THF	−25	10	81	1:3
4	**2**	CH_3CN	−25	2	88	1:10
5	**2**	4:1 toluene/THF	−25	2	80	1:2
6	**2**	4:1 toluene/dioxane	−25	2	73	1:1
7	**2**	4:1 Et_2O/THF	−25	2	76	1:1
8	**2**	4:1 Et_2O/dioxane	−15 to 0	2	83	3.5:1
9	**3**	CH_3CN	−25	2	47 (55)	1:2
10	**3**	4:1 Et_2O/dioxane	−15 to 0	2	51 (60)	9:1
11	**4**	CH_3CN	−25	2	58 (70)	1:4
12	**4**	4:1 Et_2O/dioxane	−15 to 0	2	61 (70)	3.5:1
13	**5**	CH_3CN	−25	2	77 (90)	1:5.5
14	**5**	4:1 Et_2O/dioxane	−15 to 0	2	69 (80)	4:1

[a] Isolated yields. In parentheses: yields evaluated by NMR analysis of the crude reaction mixture. All disaccharides were identified by ^1H NMR spectroscopy.

[b] Determined by integration of the relevant ^1H NMR signals.

[c] Commercial $Sm(OTf)_3$ without previous dehydration (see text) was used.

activating power of $Sm(OTf)_3$ having been established, we examined the reactivity of **1** toward the less nucleophilic acceptors **3** and **4**.[6] In these cases as well, coupling reactions occurred smoothly (within 60–90 minutes) under very mild conditions affording disaccharides **7** and **8** in satisfying yields (entries 9–12). On the basis of evidence gained in the synthesis of disaccharide **6**, we modulated the glycosidation stereoselectivity through the choice of the solvent mixture (compare entries 9 and 11 to entries 10 and 12, respectively). Interestingly, a sensible increase of yield was observed in the synthesis of the 3-*O*-linked disaccharides utilising a 2-*O*-benzylated rather than a 2-*O*-acetylated acceptor (compare entries 9, 10 to 13, 14, respectively).[7]

These results highlight the potential of $Sm(OTf)_3$ in oligosaccharide synthesis. Although the hygroscopic nature of this white solid requires a careful dehydration procedure (heating at 190°C under vacuum for one night)[8] prior to its use, this reagent offers several advantages over the traditional activators of glycosyl trichloroacetimidates ($BF_3{\cdot}OEt_2$, TMSOTf, TfOH),[2] since it is chemically stable to prolonged storage under air, easy to handle and highly active under very mild conditions.[9] In a typical procedure for reactions in solvent mixtures, donor **1** (0.07 mmol) and the acceptor (0.05 mmol) were dissolved in the major cosolvent (0.8 mL) (see Table 1) in the presence of 4 Å molecular sieves. The mixture was cooled to the reaction temperature and then a solution of $Sm(OTf)_3$ in the minor cosolvent (0.2 mL) was added dropwise (temperature and promoter amounts as in Table 1). After 60–90 min the reaction is generally completed (TLC) and the mixture is diluted with $CHCl_3$ and washed with water. Concentration of the organic phase affords a crude product, which is purified by silica gel PLC (eluent: 7:3 or 3:1 hexane–ethyl acetate). We are currently investigating the extension of this approach to disarmed[4] glycosyl donors and the application to solid phase oligosaccharides synthesis.[10]

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