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Stereoselective 1,2-*cis*-galactosylation assisted by remote neighboring group participation and solvent effects

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Abstract

Iodonium-ion promoted glycosylations in 1,4-dioxane/toluene with galactosyl donors having an electron-donating neighboring group participating functionality at C-4 give exceptional high α-anomeric selectivities.
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The last 10 years have witnessed a dramatic improvement in the methods used for complex oligosaccharide assembly.[1] Many new leaving groups for the anomeric center, which can be introduced under mild reaction conditions and are sufficiently stable to be purified and stored for a considerable period of time, have been developed. Convergent synthetic strategies enabling the convenient assembly of complex oligosaccharides from properly protected building units, involving a minimum number of synthetic steps, have become available. Methods for solid-phase oligosaccharide synthesis have been reported and these procedures shorten oligosaccharide synthesis by removing the need to purify intermediate derivatives. However, all these developments are off-set by the difficulties of stereoselective introduction of 1,2-*cis* glycosides.

Recently, we reported[2] that iodonium-ion mediated glycosylations of thioglucosides in 1,4-dioxane/toluene give significantly higher α-anomeric selectivities compared to similar couplings in 1,2-dichloroethane (DCE)/diethyl ether (1/5, v/v). It was proposed that this effect is derived from the superior donating effect of 1,4-dioxane and the relatively low polarity of the solvent mixture. Here, we report parameters for the reliable introduction of α-galactosides.

N-Iodosuccinimide (NIS)/trimethylsilyl triflate (TMSOTf) promoted glycosylation[3] of **1a** with **2** in 1,2-dichloroethane (DCE)/diethyl ether (1/5, v/v) gave disaccharide **3a** as a mixture of anomers (α/β=1.2/1) (Table 1).[4] A slightly higher anomeric selectivity (α/β=2.2/1) was obtained when the same glycosylation was performed in 1,4-dioxane/toluene. The α-anomeric selectivity could be further improved by using iodonium dicollidine perchlorate (IDCP) as the promoter.[2,5]

Despite the higher α-anomeric selectivity in the new solvent mixture, the results are far from being satisfactory. In general, couplings with galactosyl donors give significantly lower anomeric outcomes

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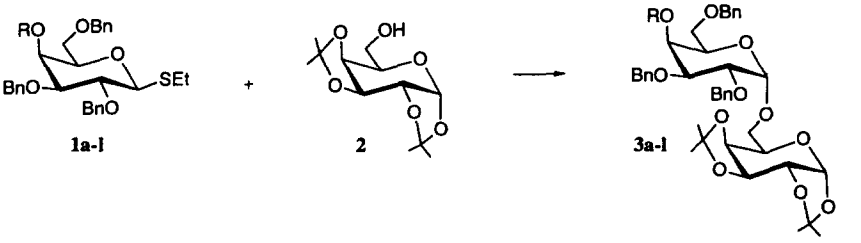
Table 1
Glycosylations of galactosyl donors **1a–1l** with **2**



	R	Diethyl ether/DCE (5/1, v/v)		1,4-Dioxane/Toluene (3/1, v/v)	
		NIS/TMSOTf	IDCP	NIS/TMSOTf	IDCP
		α/β Ratio of **3a-3l** (Yield %)			
a	$CH_2C_6H_5$	1.2/1 (83)	2.1/1 (77)	2.2/1 (91)	2.6/1 (74)
b	CH_3	1.4/1 (78)	1.6/1 (75)	2.3/1 (90)	2.9/1 (83)
c	*H*	1/1.9 (65)	1/1.8 (53)	1.7/1 (68)	2.0/1 (62)
d	$COCH_3$	3.6/1 (74)	6.0/1 (62)	7.2/1 (76)	14/1 (68)
e	COC_6H_5	9.5/1 (79)	12.5/1 (66)	17/1 (72)	32/1 (74)
f	CH_2CF_3			2.3/1 (58)	*
g	$COCCl_3$			4.5/1 (72)	*
h	$COCF_3$			3.0/1 (71)	*
i	$COC_6H_4(p\text{-}NO_2)$			14/1 (87)	*
j	$COCMe_3$			16/1 (74)	*
k	$COC_6H_4(p\text{-}CH_3)$			18/1 (82)	*
l	$COC_6H_4(p\text{-}OCH_3)$			33/1 (85)	only α (75)

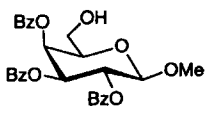
* Glycosylation which were too sluggish when promoted with IDCP

than glycosylations with similarly-protected glucosyl donors.[6] One possible explanation of the low anomeric selectivities in the galactosyl series may be unfavorable steric effects of the axially orientated substituent at C-4. To minimize these influences, glycosylations were performed with the 4-*O*-methyl derivative **1b**.[7] Coupling **1b** with **2** in the presence of NIS/TMSOTf or IDCP in DCE/diethyl ether (1/5, v/v) afforded disaccharide **3b** with modest anomeric selectivity, whereas coupling in 1,4-dioxane/toluene gave the same disaccharide with a slightly higher α-anomeric outcome. When the same glycosylations were performed with glycosyl donor **1c**, which has no protection at C-4, slight preferences for the β-anomer were observed. These experiments indicate that the bulkiness at C-4 of a galactosyl donor has only a marginal effect on the anomeric selectivity.

Several reports[8,9] have highlighted that the nature of a protecting group remote to the anomeric center may influence the stereochemical outcome of glycosylations. For example, it has been postulated[8] that ester-protecting groups at C-4 of fucosyl donors can perform remote neighboring group participation to give glycosides with high α-anomeric selectivities.

Galactosyl donors **1d** and **1e**, which have, respectively, an acetyl and benzoyl ester at C-4, were coupled with **2** to probe possible inductive, through-bond or neighboring group participating effects arising from C-4 of galactosyl donors. As can be seen in Table 1, the ester functionalities significantly increase the anomeric selectivities and very promising results were obtained with 4-*O*-benzoylated derivative **1e** especially when 1,4-dioxane/toluene was used as the solvent.

Table 2
Glycosylation of **4–7** with 4-*O*-(*p*-anisoyl) donor **1l** in the presence of NIS/TMSOTf



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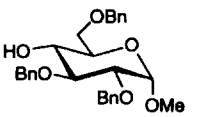

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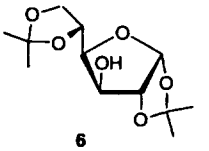

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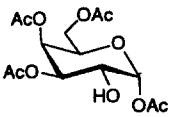

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Entry	Acceptor	Solvent	Time, h	Yield, %	α/β Ratio
1	4	Diethyl ether/DCE	2	87	Only α
2	4	1,4-Dioxane/Toluene	16	78	Only α
3	5	Diethyl ether/DCE	2	67	57/1
4	5	1,4-Dioxane/Toluene	16	80	Only α
5	6	Diethyl ether/DCE	2	84	34/1
6	6	1,4-Dioxane/Toluene	16	75	58/1
7	7	Diethyl ether/DCE	2	80	41/1
8	7	1,4-Dioxane/Toluene	16	72	Only α

To reveal the mechanism of α-galactosylation, we prepared the glycosyl donors **1f–h** and used these compounds in NIS/TMSOTf-promoted glycosylations in 1,4-dioxane/toluene with acceptor **2**. The 2,2,2-trifluoroethyl (**f**), trifluoroacetyl (**g**) and trichloroacetyl (**h**) share in common their strongly electron-withdrawing properties but will not perform neighboring group participation during glycosylations.[10] The results summarized in Table 1 (**f–h**) show that, in each case a modest α-anomeric selectivity was obtained. It can be concluded that the electron-withdrawing nature of a protecting group at C-4 of a galactosyl donor has only a marginal effect on the anomeric ratio of a glycosylation. Therefore, it is reasonable to assume that an *O*-acetyl or *O*-benzoyl at C-4 of a galactosyl donor can perform remote neighboring group participation during a glycosylation, which improves α-anomeric selectivity.

Based on these results, it was anticipated that ester functionalities with general R^DCOO structure, where R^D is an electron-donating moiety, will be an effective neighboring group participant and as a result should give high α-anomeric selectivities. To confirm this postulate, we synthesized donors with an *O*-nitrobenzoyl (**1i**), *O*-pivaloyl (**1j**), *O*-toluoyl (**1k**) and *O*-*p*-anisoyl (**1l**) moiety at C-4. As illustrated in Table 1 (**i–l**), more electron-withdrawing *p*-nitrobenzoyl group (**1i**) gave a lower anomeric selectivity than the benzoyl group (**1e**). On the other hand, the pivaloyl (**1j**), *p*-toluoyl (**1k**) and *p*-anisoyl (**1l**) containing derivatives gave higher α/β-ratios and the best results were obtained with the most electron-donating *p*-anisoyl moiety. These results strongly indicate that a 4-*O*-acyl protecting group of a galactosyl donor can perform neighboring group participation and derivatives with strongly electron-donating substituents are the most effective ones.

The glycosyl donor **1l** was used for the synthesis of various disaccharides. In all cases, excellent anomeric stereoselectivities were achieved especially when 1,4-dioxane/toluene was used as the solvent mixture (Table 2).

In conclusion, we have shown that the α-selectivity in glycosylations with D-galactosyl donors can be significantly improved by using a neighboring group participating-functionality at C-4 and the best results were obtained with ester functionalities of general R^DCOO structure, R^D being an electron-donating moiety. The α-selectivity can be further improved if 1,4-dioxane/toluene is used as the reaction solvent. Probably, this donating solvent system stabilizes the oxo-carbenium ion intermediate form during

neighboring group participation. In some cases, the yields in the new solvent mixture were slightly lower than the yields for the same glycosylations in diethyl ether/DCE.

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