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Cp_2ZrCl_2-$AgBF_4$ in Benzene: A New Reagent System for Rapid and Highly Selective α-Mannoside Synthesis from Tetra-O-benzyl-D-mannosyl Fluoride

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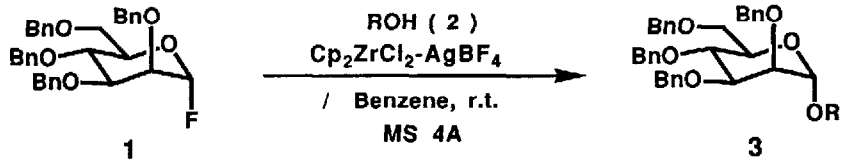
Summary: Combination of Cp_2ZrCl_2-$AgBF_4$ (molar ratio = 0.5 : 1) is highly effective in promoting rapid and high-yield glycosidation of tetra-O-benzyl-D-mannopyranosyl fluoride. Yields are excellent in all cases examined and high α-selectivity is achievable by the reaction in benzene at room temperature.

The efficiency of glycosidation — the yield and the stereoselectivity — casts decisive influence over the synthetic strategy toward a number of biologically significant glycosidic compounds such as glycoproteins.[1] The outcome of glycosidation reaction is, in many cases, quite sensitive to various reaction parameters, which must be carefully defined to gain utmost efficiency.

The synthesis of mannosyl glycosides, either α-selective or β-selective, finds special importance in relation to a class of glycoproteins, the high-mannose-type, the synthesis of which is under active investigations.[2] Besides the well-recognized difficulty in β-mannoside synthesis,[3] also the α-selective formation of mannoside linkages is not necessarily easy, even though which appears to be kinetically and thermodynamically favored. Such circumstance has been met for the mannosyl donor without neighboring-group participation, the stereocontrolled glycosidation of which is difficult *via* the conventional method.[2a]

Recently, we reported a novel method for the activation of glycosyl fluoride, utilizing the metallocene-based promoter (Cp_2MCl_2-$AgClO_4$: M=Zr, Hf), which enables the rapid and high-yield glycosidation.[4] Particularly notable feature of this method is the high reactivity, which is valid even for the substrates of high steric demand or high chemical sensitivity. As a part of our glycosidation study, we applied the method to tetra-O-benzyl-D-mannosyl fluoride (1)[5] in the specific problem of mannoside synthesis stated above, with a hope to extend the scope of this new glycosidic activation.



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In this communication, we wish to describe that the rapid and highly α-selective glycosidation of 1 is possible by employing a novel reagent system, Cp_2ZrCl_2-$AgBF_4$ in benzene at room temperature.

First, we surveyed the solvent effect by carrying out the reaction of 1 and cyclohexylmethanol in the presence of Cp_2ZrCl_2-$AgClO_4$ at room temperature. Some representative results are summarized in Table 1, which suggests that CH_2Cl_2 or benzene is the solvent of choice for gaining high α-selectivity.

In these solvents, the reaction proceeded almost instantaneously to afford the corresponding glycoside in excellent yields. Interestingly, the α-selectivity was lowered at -20 °C to give 1/1 anomeric mixture (Cf. runs 3 and 4).[6]

Table 1. Solvent Effect in Cp_2ZrCl_2-$AgClO_4$ Promoted Reaction.[a,b]

Run	Solvent	Temperature	Yield (%)	α / β[c]
1	Et_2O	r.t.	95	58 / 42
2	CH_3CN	r.t.	87	60 / 40
3	CH_2Cl_2	r.t.	96	97 / 3
4	CH_2Cl_2	- 20° C	92	50 / 50
5	benzene	r.t.	92	95 / 5

a) Cyclohexylmethanol was used as the glycosyl acceptor (ROH).
b) 1 / ROH / Cp_2ZrCl_2 / $AgClO_4$ = 1.0 / 2.0 / 0.5 / 1.0 (See ref. 7).
c) By HPLC (Zorbax-sil, Du Pont, 4.6x25; hexane-AcOEt=93/7).

Having found a potentially useful procedure for gaining α-selectivity, that is, Cp_2ZrCl_2-$AgClO_4$ in benzene (Method A), we applied it to the glycosylation of various alcohols as summarized in Table 2. The method is effective so long as the primary or secondary alcohols are concerned (runs 1, 3). However, the cases of sterically hindered alcohols resulted in the substantial decrease of the yield (runs 5, 7, 9, 11, 13) due to the competing formation of **4** *via* the intramolecular Friedel-Crafts closure of the 2-O-benzyl group. We reasoned that the level of glycosidic activation is so high that the side reaction competes, which would be suppressed by the modulation of activator.

With this reasoning in mind, we attempted to use several silver salts in combination with Cp_2ZrCl_2. Those are $AgBF_4$, AgOTf, $AgPF_6$, and $AgSbF_6$, all of which led to the rapid consumption of **1** with the comparable reaction rates to the case of $AgClO_4$. However, the extent of the formation of **4** were clearly different by the counter ions: The use of $AgPF_6$ or $AgSbF_6$ led to substantial formation of **4**. In contrast, the use of $AgBF_4$ or AgOTf is effective in suppressing the formation of **4** to afford the glycoside in excellent yields. The difference between the latter two reagents is the stereoselectivity and $AgBF_4$ is more excellent in view of the reactivity as well as the stereoselectivity.[8]

Employment of Cp_2ZrCl_2-$AgBF_4$ in benzene (Method B), thus found, led to uniformly clean and high-yield formation of the α-glycosides for all the cases listed in Table 2. Particularly noteworthy is that none of the byproduct **4** was detected even in the case of sterically hindered glycosyl acceptors, where also the high α-selectivity was retained. Considering the excellent yields and stereoselectivity as well as the simplicity of the procedure, the present method may be added to a method of choice for α-mannoside synthesis.

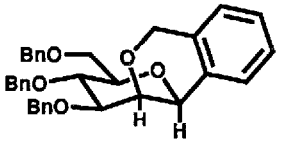

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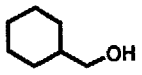
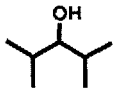
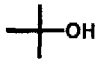
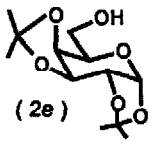
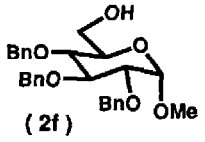
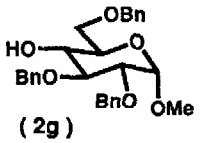
Table 2. α-Selective Glycosidation.[9)]

Run	ROH	Method[a)]	Product	Yield (%)	α / β[b)]
1	 (2a)	A	3a	91	98 / 2
2		B		95	86 / 14
3	3-β-cholestanol (2b)	A	3b	91	94 / 6
4		B		94	96 / 4
5	 (2c)	A	3c	70	97 / 3
6		B		92	96 / 4
7	 (2d)	A	3d	58	100 / 0
8		B		86	97 / 3
9	 (2e)	A	3e	56	85 / 15
10		B		92	96 / 4
11	 (2f)	A	3f	59	98 / 2
12		B		85	90 / 10
13	 (2g)	A	3g	64	96 / 4
14		B		91	100 / 0

a) Method A: Cp_2ZrCl_2-$AgClO_4$ in benzene.
Method B: Cp_2ZrCl_2-$AgBF_4$ in benzene.
Reactions were carried out at room temperature for 20 min (see typical procedure).
b) Determined by HPLC (Zorbax-sil, Du Pont, 4.6x20, hexane-AcOEt)

Typical procedure is described for the reaction of **1** and **2b**: To a mixture of **2b** (62.0 mg, 160 μmol) Cp_2ZrCl_2 (12.0 mg, 41.1 μmol), $AgBF_4$ (90%; 18.0 mg, 83.2 μmol) and powdered molecular sieves 4A (ca. 200 mg) in benzene (2 mL) was added glycosyl fluoride **1** (43.2 mg, 79.6 μmol) in benzene (1 mL) was added at room temperature and the mixture was stirred for 20 min. Usual work up[4] and purification by silica-gel TLC (hexane-AcOEt=80/20) gave **3b** (67.9 mg, 94%).

References and Notes

1) Review: a) K. Igarashi, *Adv. Carbohydr. Chem. Biochem.*, **34**, 243 (1977); b) H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, **21**, 155 (1982).

2) a) T. Ogawa & T. Nukada, *Carbohydr. Res.*, **136**, 135 (1985); b) H. Paulsen, M. Heume, Z. Györgydeak, & R. Lebuhn, *ibid*, **144**, 57 (1985).

3) H. Kunz & W. Gunther, *Angew. Chem., Int. Ed. Engl.*, **27**, 1086 (1988), and references cited therein.

4) a) T. Matsumoto, H. Maeta, K. Suzuki, & G. Tsuchihashi, *Tetrahedron Lett.*, **29**, 3567 (1988); b) K. Suzuki, H. Maeta, T. Matsumoto, & G. Tsuchihashi, *ibid.*, **29**, 3571 (1988).

5) M. Hayashi, S. Hashimoto, & R. Noyori, *Chem. Lett.*, **1984**, 1747.

6) Possibility of thermodynamic control is ruled out by that the α/β ratio showed no change upon subjection of a 1/1 anomeric mixture of **3** to the reaction conditions at room temperature.

7) Employment of Cp_2MCl_2-$AgClO_4$ in the 1:2-ratio leads to an enhancement of the reactivity in comparison with the original 1:1-ratio: see, K. Suzuki, H. Maeta, & T. Matsumoto, *Tetrahedron Lett.*, in press.

8) In the Cp_2ZrCl_2-$AgBF_4$-protocol (Method B), the active species could be BF_3, generated by the collapse of $Cp_2ZrX(BF_4)$ to Cp_2ZrXF. Control experiments by using $BF_3{\bullet}OEt_2$ in benzene actually showed similar reaction rate and stereoselectivity. The difference is the slightly decreased yields (ca. 80%) by the formation of **4** (ca. 10%), although not large enough to exclude the possibility. For the $BF_3{\bullet}OEt_2$ promotion, see K. C. Nicolaou, A. Chucholowski, R. E. Dolle, & J. L. Randall, *J. Chem. Soc., Chem. Commun.*, **1984**, 1155.

9) Data of ^{13}C NMR [δ, C1 / ($J_{C1\text{-}H1}$); 100 MHz, $CDCl_3$] of glycosides **3a-3g** follow; (Cf. K. Bock & C. Pedersen, *J. Chem. Soc., Perkin II*, **1974**, 293.)

	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
α	98.0	95.8	100.8	92.5	97.3	98.9	100.5
	(168.1)	(164.5)	(166.7)	(165.2)	(168.8)	(170.2)	(170.9)
β	102.0	99.3	102.7	96.1	-- a)	-- a)	-- a)
	(152.6)	(152.6)	(151.2)	(151.2)	-- a)	-- a)	-- a)

a) Not determined.

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