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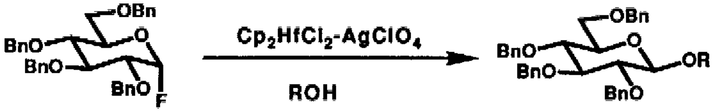
An Improved Procedure for Metallocene-Promoted Glycosidation. Enhanced Reactivity by Employing 1:2-Ratio of Cp_2HfCl_2-$AgClO_4$

Keisuke Suzuki*, Hideki Maeta, and Takashi Matsumoto

Department of Chemistry, Keio University, Hiyoshi, Yokohama 223, Japan

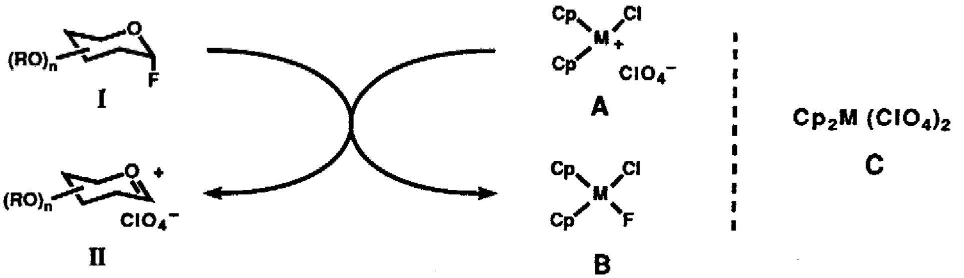
Summary: Use of Cp_2HfCl_2-$AgClO_4$ in 1:2-ratio rather than 1:1-ratio provides much higher reactivity for the activation of glycosyl fluoride, where some implication for the involvement of $Cp_2Hf(ClO_4)_2$ is obtained. β-Glucoside synthesis without resort to neighboring-group assistance is documented.

Recently, we reported a new glycosidation reaction by employing a novel activator of glycosyl fluoride, *i.e.*, the <u>equimolar</u> combination of Cp_2MCl_2 and $AgClO_4$ (M = Zr or Hf), the efficiency of which was shown in macrolide synthesis.[1] For the general use in O-glycoside synthesis,[2] we sought further improvement of the process through the model experiments shown in Eq. 1.



1 2 3 (Eq. 1)

Our attention was centered around the modification of the ratio of Cp_2MCl_2 and $AgClO_4$, the idea of which stemmed from the following mechanistic insight. Our postulate for the origin of present activation is the high "fluorophilicity" of early transition elements,[3] particularly at the stage of cationic complex **A**[4] which is capable of activating glycosyl fluoride **I** to produce oxonium species **II**. Conversion of **A** to **B** receives a profit of forming a strong M-F bond. With this hypothesis in mind, we attempted to use diperchlorato complex **C** which may be generated by mixing Cp_2MCl_2 and $AgClO_4$ in 1 : 2 ratio.[4] We hoped the enhanced reactivity of **C** in comparison with **A**.

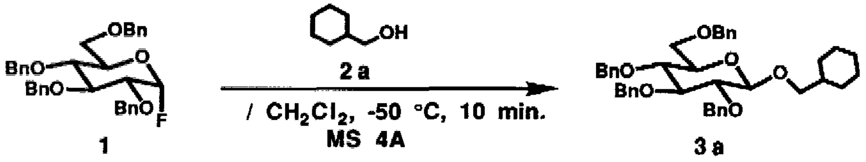


We were pleased to find *this simple modification of the ratio (Cp_2HfCl_2 : $AgClO_4$ = 1 : 2) actually provides an impressively enhanced reactivity than the former 1:1 ratio.* In this communication, we wish to describe an improved procedure based on this finding as well as some other experimental modifications,[2] which has considerable promise in glycoside synthesis.

Superior reactivity provided by the new ratio (Cp_2HfCl_2 : $AgClO_4$ = 1 : 2) is clearly illustrated by the following experiments.

A mixture of Cp_2HfCl_2 (2.0 equiv.) and $AgClO_4$ (2.0 equiv.) in CH_2Cl_2 was stirred at room temperature for 10 min, to which was added alcohol **2a** (2.0 equiv.). After cooling to -50 °C, fluoride **1** (1.0 equiv.) was added and the reaction was stopped after 10 min. The reaction was still halfway.

The same reaction was carried out by employing Cp_2HfCl_2 (1.0 equiv.) and $AgClO_4$ (2.0 equiv.) with carefully keeping other reaction parameters the same as above. Remarkably, the reaction was almost complete after 10 min to give 88 % yield of glycoside **3a** and the recovery of **1** was as little as 4 %.



Molar Ratio Cp_2HfCl_2 : $AgClO_4$ [a)]	**3a** (%)	Recovery of **1** (%)
2.0 : 2.0	50	43
1.0 : 2.0	88	4

a) Molar equivalent per one mole of **1** (see text).

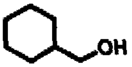
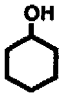
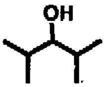
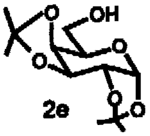
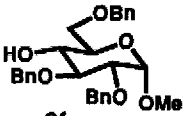
These results clearly show that the reaction proceeds faster by employing Cp_2HfCl_2-$AgClO_4$ in 1:2-ratio rather than by employing the 1:1-ratio. Note that *the reaction proceeds faster by reducing the amount of Cp_2HfCl_2*. This marked fact strongly suggests the involvement of different active species. At present, we tentatively assume the formation of diperchlorato complex, $Cp_2Hf(ClO_4)_2$, which seems reasonable by considering the preparation of "dicationic" complexes of titanocene or zirconocene derivatives by essentially the same technique.4) Although we made no attempts to isolate and characterize the complex by potential hazard, supporting data was obtained from NMR study which shows, at least, that the alteration of the ratio of Cp_2HfCl_2-$AgClO_4$ gives rise to a change of the dominant species in solution.5) More of the study is needed to understand the factors affecting the mode of activation. For example, although being set aside for the present discussion, the interaction of the metallocene complex with the glycosyl acceptor (ROH) may have a potential significance.

In any event, this new procedure offers generally higher reactivity than the original one, which is also illustrated by the reactions of **1** with various alcohols as shown in Table 1. Reactions were carried out in CH_2Cl_2 at -50 °C and quenched after the complete consumption of **1** was assured (TLC-monitoring). Although either procedure gave glycosides **3** in excellent yields, the new procedure by the 1:2-ratio invariably leads to faster reaction as recognized by comparing the reaction periods.

Synthetically notable is the high β-selectivity without resort to neighboring-group assistance. Although not detailed here, the β-selectivity can be further improved by lowering the temperature.

In summary, the use of Cp_2HfCl_2-$AgClO_4$ in 1:2 ratio offers an enhanced reactivity for the activation of glycosyl fluoride. The improved procedure described here will find wide applicability in various stages in glycoside synthesis. Further study on the mechanism as well as the application of the method is now under way in this laboratory.

Table 1. β-Selective Glycosidation

Run	ROH	Ratio a)	Time (hr) b)	Yield (%)	α / β c)
1	 **2a**	A	2	94	1 / 13
2		B	1	93	1 / 11
3	 **2b**	A	1.5	95	1 / 10
4		B	1	93	1 / 11
5	 **2c**	A	2	95	1 / 6
6		B	1	98	1 / 5
7	 **2d**	A	2.5	92	1 / 8
8		B	1.5	95	1 / 7
9	 **2e**	A	2.5	97	1 / 4
10		B	1	92	1 / 4
11	 **2f**	A	3	96	1 / 2
12		B	0.5	99	1 / 1.5

a) Ratio A: Cp_2HfCl_2 / $AgClO_4$ / **1** = 2.0 / 2.0 / 1.0 (the original procedure).
Ratio B: Cp_2HfCl_2 / $AgClO_4$ / **1** = 1.0 / 2.0 / 1.0 (the new procedure).
Alcohol (ROH) was used in 2.0 equiv. in both procedures.

b) Roughly corresponds to the time of complete consumption of **1** (See text).

c) Determined by HPLC (Zorbax-sil, Du Pont, 4.6x20, hexane-AcOEt) and/or ^1H NMR (400 MHz).

Typical procedure is described for the reaction of **1** and cyclohexanol (**2b**): A mixture of Cp_2HfCl_2 (43.0 mg, 113 μmol), $AgClO_4$ (47.0 mg, 227 μmol) and powdered molecular sieves 4A (ca. 100 mg) in CH_2Cl_2 (0.5 mL) was stirred at room temperature for 10 min, to which was added **2b** (22.6 mg, 226 μmol) in CH_2Cl_2 (0.5 mL). After cooling to -50 °C, fluoride **1** (61.2 mg, 113 μmol) in CH_2Cl_2 (1 mL) was added to the mixture and stirred for 1 hr. Usual workup[1] gave glycoside **3b** (65.2 mg, 93%).

As an additional comment, the order of mixing the reactants is also changed from the original procedure as described above, that is, the premixing of Cp_2HfCl_2 and $AgClO_4$ at room temperature before the addition of alcohol or glycosyl fluoride. We recommend this precaution to ensure the effective generation of active complex *in situ*, which is crucial for low-temperature reactions, otherwise substantial decrease in the yield may result.

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References and Notes

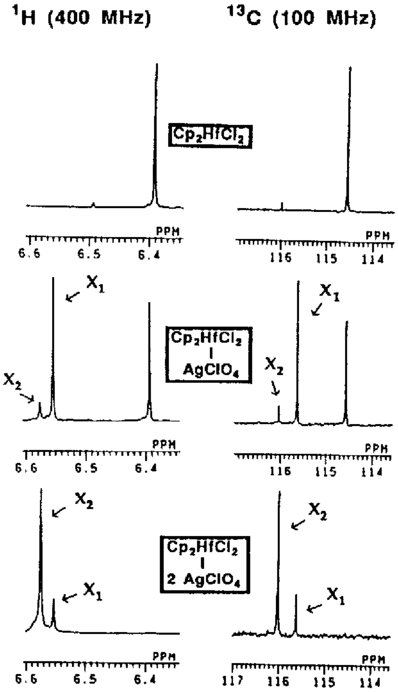
1) T. Matsumoto, H. Maeta, K. Suzuki, & G. Tsuchihashi, Tetrahedron Lett., **29**, 3567, 3571, 3575 (1988).

2) In our original procedure, Cp_2MCl_2 and $AgClO_4$ were used in large excess (each 5 equiv.) in order to facilitate rapid glycosidation of poorly reactive yet sensitive macrolide aglycon at low temperature. Such excess is unnecessary in the case of *usual* glycosyl acceptors (see typical procedure).

3) Bond strength of metal-halogen (M-X) bonds in the group IVa metals is in the order of F >> Cl > Br > I for the halide sequence. The M-F bond strength in MF_4 is in the order of Hf > Zr >> Ti, which agrees with the reactivity sequence of Cp_2MCl_2-$AgClO_4$ (M: Hf > Zr >> Ti): J. H. Canterford & R. Colton, "Halides of the Second and Third Row Transition Metals," Wiley, London (1968). See also, L. E. Schock and T. J. Marks, J. Am. Chem. Soc., **110**, 7701 (1988).

4) Preparation and structure of related "dicationic" complexes were studied by Thewalt et al.: $[Cp_2Ti(H_2O)_2](ClO_4)_2{\cdot}3THF$: U. Thewalt & H.-P. Klein, J. Organomet. Chem., **194**, 297 (1980); $[Cp_2Ti(bipyr)]^{2+}(OTf)_2$: U. Thewalt & K. Berhalter, *ibid.*, **302**, 193 (1986); $Cp_2Zr(OTf)_2{\cdot}(THF)$: U. Thewalt & W. Lasser, Z. Naturforsch., B. Anorg., Org. Chem., **38B**, 1501 (1983). Also see R. F. Jordan, C. S. Bajgur, R. Willett, & B. Scott, J. Am. Chem. Soc., **108**, 7410 (1986); R. F. Jordan, W. E. Dasher, & S. F. Echols, *ibid.*, **108**, 1718 (1986); R. F. Jordan & S. F. Echols, Inorg. Chem., **26**, 383 (1987).

5) ^1H (400 MHz) and ^{13}C (100 MHz) NMR were measured for various ratio of Cp_2HfCl_2-$AgClO_4$ mixture. Besides Cp_2HfCl_2 [6.39 (^1H); 114.5 (^{13}C)], formation of two new species X_1 [6.55 (^1H); 115.6 (^{13}C)] and X_2 [6.58 (^1H); 116.0 (^{13}C)] were observed in varying ratio. Starting from Cp_2HfCl_2, gradual addition of $AgClO_4$ leads to the appearance of X_1. On further addition, the second new species X_2 appears, which predominates at the stage of Cp_2HfCl_2-$AgClO_4$ = 1 : 2 or more. Samples were prepared by stirring Cp_2HfCl_2 and $AgClO_4$ in $CDCl_3$ followed by the filtration to remove AgCl. Details will be described elsewhere.



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