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Development of a catalytic cycle for the generation of C1-glycosyl carbanions with Cp_2TiCl_2: application to glycal synthesis

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Abstract

A catalytic cycle has been developed for the conversion of glycosyl halides to their corresponding glycals using Cp_2TiCl_2. This process can be effectively used with only 30% of the in situ generated single electron reducing agent in contrast to the 2 equivalents normally employed. © 2000 Published by Elsevier Science Ltd.

Keywords: electron transfer; glycosyl halides; anomeric radicals; anions; titanium.

The single electron reducing agent, bis(cyclopentadienyl)titanium chloride (Cp_2TiCl), has currently attracted much interest due to its ability to promote a variety of selective radical and anionic reactions, such as highly diastereoselective pinacol coupling,[1] reductive epoxide opening and subsequent radical addition reactions,[2] as well as reduction of glycosyl halides[3] and *vic*-dibromides.[4] Particularly attractive for the radical based reactions are the recent developments of catalytic protocols with respect to the low valent metal complex. Gansäuer and co-workers have nicely demonstrated that both pinacol coupling and reductive epoxide opening may effectively be achieved with 5 mol% Cp_2TiCl_2 employing a stoichiometric reductant such as manganese, and either a trialkylsilyl chloride or collidinium chloride for the liberation of the Ti^{IV} species from the product.[1d–h,2g–j,5] Whereas such a protocol works well for radical reactions, it may be anticipated that in reactions where the corresponding anion is of interest, the second reduction step would be less favored owing to competitive hydrogen abstraction, rearrangement and fast dimerization reactions.[6] This is explained by the increased effective lifetime of the generated radical due to the decreased quantities and hence low concentration of the $titanium^{III}$ reagent compared to the stoichiometric version.

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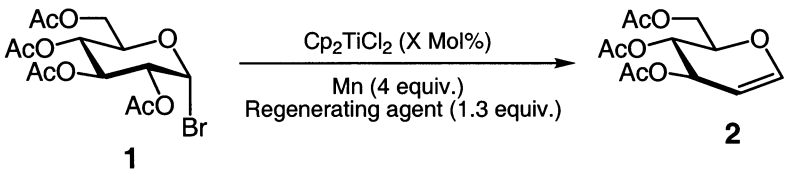
In this communication, we show that counterintuitively glycosyl C1-carbanions are effectively prepared employing only 30 mol% of Cp_2TiCl_2 with manganese as the metal reductant compared to the two equivalents of the Ti^{IV} complex, which has previously been reported. This catalytic cycle has been adapted to the preparation of the synthetically useful glycals[7] from protected glycosyl halides.[8]

Initial experiments were carried out with acetobromoglucose (**1**) as shown in Table 1. Reactions were run exactly as described earlier with manganese as the stoichiometric reductant[9] though with varying quantities of Cp_2TiCl_2 and the addition of 1.3 equivalents of Me_3SiCl or collidinium chloride. Best results were obtained with Me_3SiCl as the regenerating agent (entry 2), as in its absence or with collidinium chloride (entries 3 and 4) the yield of triacetylglucal **2** was low, suggesting that regeneration of Cp_2TiCl was slow or not taking place. As expected, the catalyst loading has a clear effect on the efficiency of the glycal formation. The yields of the glycal steadily improved with increasing mol% of Cp_2TiCl_2 reaching a plateau at approximately 40 mol% (entry 6).[10] The importance of the catalyst is shown in entry 9, as in its absence no glycal formation was obtained.[11]

Table 1
Effect of the catalyst loading on the formation of triacetylglucal[a]



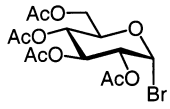
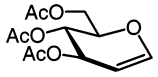
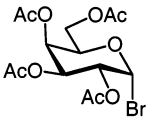
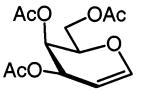
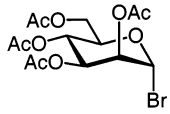
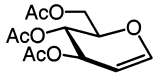
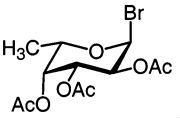
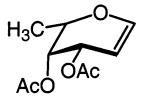
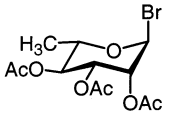
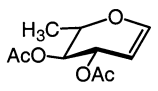
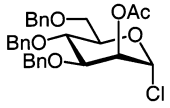
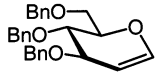
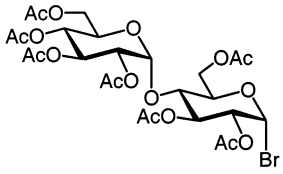
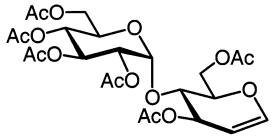
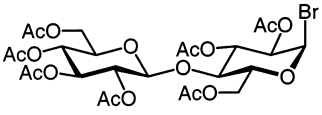
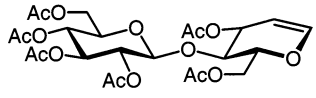
1 **2**

Entry	Quantity of Cp_2TiCl_2 (mol%)	Regenerating agent	Yield of triacetylglucal
1	10	Me_3SiCl	59%
2	20	Me_3SiCl	62%
3	20	–	17%
4	20	Collidinium chloride	31%
5	30	Me_3SiCl	65%
6	40	Me_3SiCl	77%
7	80	Me_3SiCl	83%
8	160	Me_3SiCl	82%
9	0	Me_3SiCl	0%

[a] Isolated yields after chromatography on silica gel.

In order to diminish the quantity of the titanium catalyst without effecting the yield, the solvent volume was reduced by two-fold.[12] In this way, the catalyst loading could be decreased to 30% without a noteworthy influence on the product yield. The results are shown in Table 2 with a variety of glycosyl bromides and one chloride. The reaction with the monosaccharide and disaccharide derivatives in entries 1–8 work well and are basically as good as seen with that employing stoichiometric amounts of Cp_2TiCl_2.[3e] Even the less reactive glycosyl chloride could be used affording the tri-*O*-benzylglucal in 72% yield (entry 8).[13]

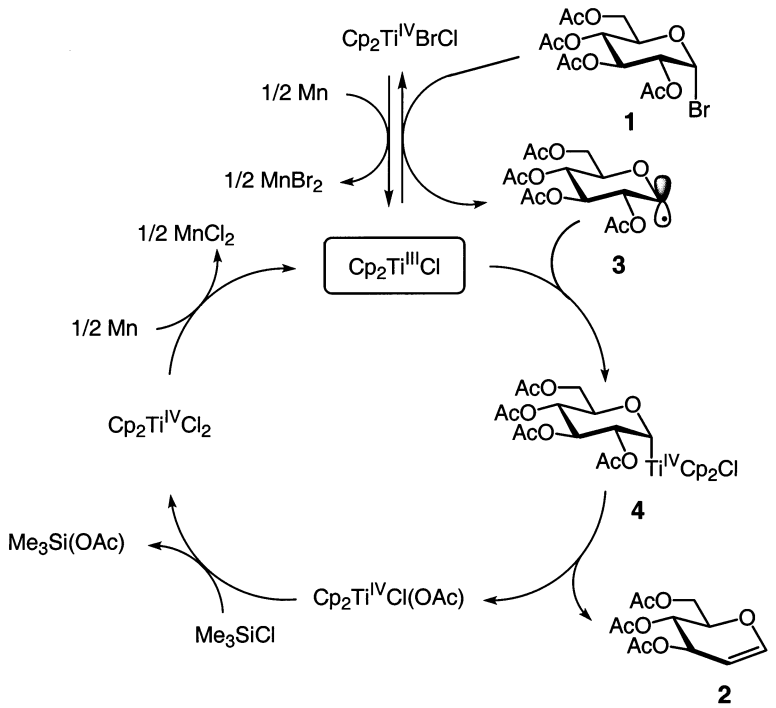
Table 2
Glycal synthesis using 30 mol% Cp_2TiCl_2[a]

Entry	Glycosyl halide	Glycal (Yield[b])	Entry	Glycosyl halide	Glycal (Yield[b])
1		 75%	6		 77%
2		 86%	7		 66%
3		 87%	8		 72%
4		 92%			
5		 94%			

[a] For the reaction conditions see Ref. 13.
[b] Isolated yields after chromatography on silica gel.

In Scheme 1, we propose a mechanism for the catalytic cycle developed to generate carbohydrate C1-carbanions. Reduction of Cp_2TiCl_2 with manganese powder affords Cp_2TiCl which participates in a dissociative electron transfer step with the glycosyl halide **1**. This produces the anomeric radical **3** and $Cp_2TiBrCl$, which is reduced to Cp_2TiCl with the excess manganese. Further reduction of **3** then gives the anomeric anion **4**, which undergoes concomitant β-elimination with the C2-substituent affording the glycal **2** and $Cp_2TiCl(OAc)$. Liberation of the Ti^{IV} complex from acetate with Me_3SiCl then completes the catalytic cycle.

In conclusion, we have successfully applied the catalytic protocol with Cp_2TiCl_2, previously employed in radical reactions, for the generation of C1-sugar anions. Although the amount of catalyst is still higher than for other Ti^{III}-catalyzed radical reactions, the above-described work has lowered the amount of Cp_2TiCl_2 required for glycal formation from 200 to 30 mol%, which is a considerable reduction. Further work is now in progress to employ such anions in other reactions.



Scheme 1. A mechanistic proposal for the catalytic cycle with Cp_2TiCl_2

Acknowledgements

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6. For example, Cavallaro and Schwartz have previously attempted the preparation of glycals from glycosyl halides using catalytic Cp_2TiCl_2 with aluminum or zinc. In both cases, the product obtained from direct reduction of the halide was observed as the major product, see Ref. 3d.
7. For recent reviews on the use of glycals in organic synthesis, see: (a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380. (b) Seeberger, P. H.; Danishefsky, S. J. *Acc. Chem. Res.* **1998**, *31*, 685.
8. For a recent account on the different methods used for the preparation of glycals, see: Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103.
9. Replacement of the manganese metal, by aluminum or zinc led to reduced or no yield of the expected glycals, respectively (Ref. 3e).
10. The major byproduct in the reactions with low catalyst loading is the compound of simple reduction; 1-deoxy-2,3,4,6-tetra-*O*-acetyl-D-glucopyranose.
11. Several attempts to reduce the catalyst loading by the syringe pump addition of the glycosyl halide to the Cp_2TiCl_2/Mn/Me_3SiCl mixture lead to a low yield of the glycal in addition to the 1-deoxy derivative (Ref. 10).
12. Further reduction of the solvent volume led to a slurry which afforded reduced yields of the triacetylglucal.
13. *Representative example:* a solution of acetobromocellobiose (170 mg, 0.24 mmol), Cp_2TiCl_2 (18 mg, 0.073 mmol), Mn (50 mg, 0.91 mmol) and Me_3SiCl (40 μl, 0.31 mmol) in THF (1 ml) was stirred for 12 h at 20°C under argon. The reaction was evaporated to dryness and the residue was purified by column chromatography (CH_2Cl_2:acetone, 24:1). This afforded the corresponding glycal as a colorless syrup (128 mg, 94%).