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A Convenient Synthesis of Glycals Employing *In-Situ* Generated Cp_2TiCl

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Abstract: Reductive elimination of acetylated glycosyl bromides to the corresponding glycal is easily achieved by mixing the bromide with Cp_2TiCl_2 and Mn in THF, and hence does not require the separate preparation of Cp_2TiCl using glove-box techniques.

Glycals have become important building blocks for the construction of oligosaccharides, *C*-glycosides and noncarbohydrate-based natural products.[1] In addition, glycals can easily be transformed to 2-amino-2-deoxy sugars, which are not easily obtained by other means.[2] The standard protocol for the preparation of glycals involves the reduction of peracetylated glycosyl bromides with zinc dust in acetic acid.[3] This method is not always compatible with other hydroxyl protecting groups used and in general gives product mixtures not easily separable. Other methods have therefore been devised for the conversion of glycosyl halides to glycals such as Zn/Ag,[4] Cr(II) salts,[5] SmI_2[6] and Zn/base,[7] but most are simply not practical or are expensive.

Recently, Schwartz and coworkers reported on an extremely mild and efficient means for achieving the reduction of glycosyl bromides using the dimeric titanium(III) reagent, $(Cp_2TiCl)_2$ in THF.[8] This reagent promotes a fast electron transfer to the bromide to give an anomeric radical species which is subsequently reduced by another Cp_2TiCl to the corresponding anion with concomitant elimination of the C2-acetate (Figure 1). Its compatibility with other hydroxyl protecting groups such as benzyl and silyl ethers as well as acetals makes this reducing agent ideal for glycal synthesis. The only drawback with this reagent is the necessity for glove-box techniques for its preparation and isolation making it impractical for normal laboratory use. In this paper, we show that by simple *in-situ* generation of the Ti(III) species from Cp_2TiCl_2 using a metal reductant, these reactions can be easily performed in high yields without the necessity of glove-box techniques.

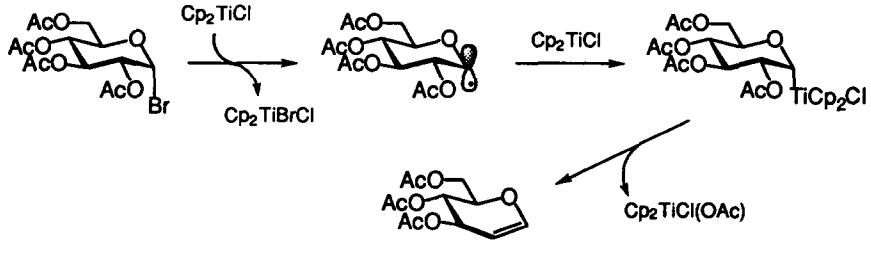

Figure 1

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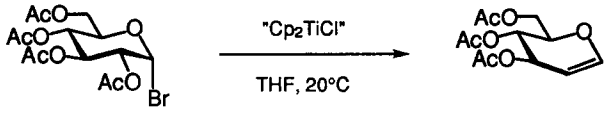
The preparation of the trivalent titanium species from Cp_2TiCl_2 can be achieved by various means such as with metals (Zn, Al and Mn),[9] or by direct electrochemical reduction.[10] However, cyclic voltammetry investigations recently performed by us reveal that the oxidation potential of the Ti(III) species differs considerably depending on the choice of the metal reductant.[10b] It is therefore not irrelevant which method is employed for reducing Cp_2TiCl_2, as was also confirmed in our attempts to simplify the Ti(III) induced glycal synthesis.[11]

Preliminary studies were performed with acetobromoglucose, where solutions of "Cp_2TiCl" were prepared by simply mixing Cp_2TiCl_2 with either metal Al, Mn or Zn as the reductant in THF, and then syringing over the green solution of the reducing agent to the bromide (Scheme 1). A large rate difference was immediately noticed between the different Ti(III) species as monitored by the color change. With the Cp_2TiCl_2/Zn solution the reaction was terminated after 15 min. though resulting in the formation of a complex mixture with only traces of the glycal as seen in the ^1H NMR spectrum. Similarly, with aluminum metal as the reductant the reaction was fast but only a 44% yield of the glycal was obtained in addition to 1-deoxy-2,3,4,6-tetra-*O*-acetyl-D-glucopyranose. In complete contrast, the Cp_2TiCl_2/Mn combination was a much slower reaction but led to almost quantitative conversion of acetobromoglucose to the desired product. Further studies were therefore continued with this pair.



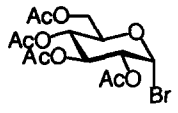
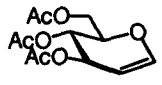
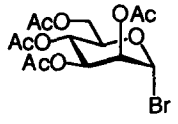
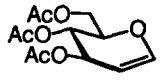
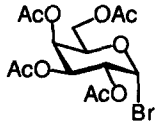
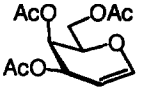
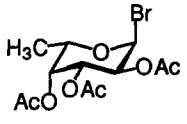
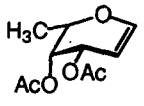
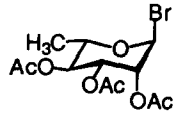
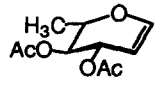
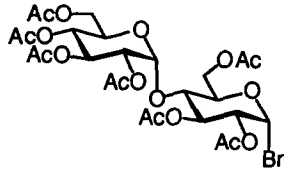
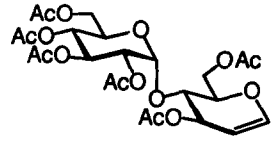
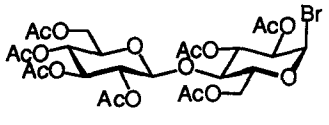
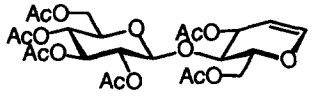
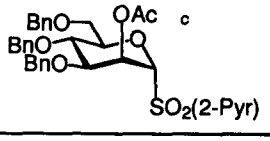
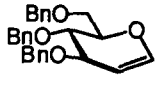
Metal Reductant	Reaction time	Yield
Cp_2TiCl_2/Zn	15 min.	trace
Cp_2TiCl_2/Al	15 min.	44%
Cp_2TiCl_2/Mn	12 h	94%
Mn	12 h	0%

Scheme 1

As manganese itself shows no reactivity with acetobromoglucose (Scheme 1), the procedure for glycal formation was simplified even further. Hence, in a typical procedure THF (2 ml) was added to a deaerated mixture of the bromide (102 mg, 0.25 mmol), Cp_2TiCl_2 (131 mg, 0.53 mmol) and Mn (55 mg, 1.0 mmol, 325 mesh). Stirring overnight at room temperature then led to a 91% yield of D-glucal after work up and column chromatography (Table 1, entry 1). Other monosaccharides (entries 2-5) and disaccharides (entries 6 and 7) work equally well where yields of the glycal range from 77-94%, underlining the generality of this method.[12] In the final case (entry 8), we show that glycosyl pyridyl sulfones, which have previously been employed in SmI_2 promoted reductions,[13] may also undergo reductive elimination in the presence of the Ti(III) species.[14] The use of the in situ generation of "Cp_2TiCl" from manganese therefore represents a simple and efficacious procedure for the preparation of glycals.

Further work is now underway to make this method catalytic with respect to the titanium-based reductant[15] and to understand the influence of the metal reductant on the rates of the electron transfer observed.

Table 1: Cp_2TiCl_2/Mn mediated synthesis of glycals from the corresponding glycosyl bromide[a]

Entry	Glycosyl bromide	Glycal	Yield[b]
1			91%
2			87%
3			77%
4			82%
5			84%
6			94%
7			91%
8	 [c]		70%

[a]See text for experimental procedure. [b]Yields are based on isolated glycal after column chromatography. [c]For the preparation of the mannosyl pyridyl sulfone, see ref. 13a.

Acknowledgements

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References and Notes

1. For a review on the use of glycals in organic synthesis, see: Danishefsky, S.J.; Bilodeau, M.T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

2. a) Lemieux, R.U.; Ratcliffe, R.M. *Can. J. Chem.* **1979**, *57*, 1244; b) Griffith, D.A.; Danishefsky, S.J. *J. Am. Chem. Soc.* **1991**, *113*, 5863; c) Czernecki, S.; Ayadi, E.; Randriamandimby, D. *J. Chem. Soc., Chem. Commun.* **1994**, 35.

3. Roth, W.; Pigman, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405.

4. Csuk, R.; Fürstner, A; Glänzer, B.I.; Weidmann, H. *J. Chem. Soc., Chem. Commun.* **1986**, 1149.

5. Pollon, J.H.P.; Llewellyn, G.; Williams, J.M. *Synthesis* **1989**, 758.

6. de Pouilly, P.; Chénedé, A.; Mallet, J.-M.; Sinaÿ, P. *Bull. Soc. Chim. Fr.* **1993**, *130*, 256.

7. Somsák, L.; Németh, I. *J. Carbohydr. Chem.* **1993**, *12*, 679.

8. a) Cavallaro, C.L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055; b) Spencer, R. P.; Schwartz, J. *Tetrahedron Lett.* **1996**, *37*, 4357. $(Cp_2TiCl)_2$ dissociates in THF to the monomeric species.

9. a) Sekutowski, D.; Jungst, R.; Stucky, G.D. *Inorg. Chem.* **1978**, *17*, 1848; b) Stephan, D.W. *Organometallics* **1992**, *11*, 996; c) Green, M.L.H.; Lucas, C.R. *J. Chem. Soc., Dalton Trans.* **1972**, 1000; d) RajanBabu, T.V.; Nugent, W.A. *J. Am. Chem. Soc.* **1994**, *116*, 986.

10. a) Anderson, J.E.; Sawtelle, S.M. *Inorg. Chem.* **1992**, *31*, 5345; b) Enemærke, R.J.; Daasbjerg, K.; Skrydstrup, T., manuscript in preparation.

11. The reduction of Cp_2TiCl_2 with a metal reductant can lead to the formation of dinuclear or trinuclear complexes of Cp_2TiCl in solution (see ref. 9a and b).

12. It is interesting to note that in the case of acetobromogalactose and acetobromofucose as substrates (Table 1, entries 3 and 4), approximately 10% of 1-deoxy-2,3,4,6-tetra-*O*-acetyl-D-galactopyranose and to 1-deoxy-2,3,4-tri-*O*-acetyl-L-fucopyranose, resp., were isolated as side-products.

13. a) Skrydstrup, T.; Mazéas, D.; Elmouchir, M.; Doisneau, G.; Beau, J.-M.; *Chem. Eur. J.* **1997**, *8*, 1342; b) Skrydstrup, T.; Jarreton, O.; Mazéas, D.; Urban, D.; Beau, J.-M.; *Chem. Eur. J.*, **1998**, *4*, 655; c) Urban, D.; Skrydstrup, T.; Beau, J.-M.; *J. Org. Chem.*, **1998**, *63*, 2507; d) Urban, D.; Skrydstrup, T.; Beau, J.-M.; *Chem. Commun.* **1998**, 955; e) Andersen, L.; Mikkelsen, L.M.; Beau, J.-M.; Skrydstrup, T. *Synlett* **1998**, 1393; f) Jarreton, O.; Skrydstrup,T.; Espinosa, J.-F.; Jiménez-Barbero,J.; Beau, J.-M. *Chem. Eur. J.*, **1999**, *5*, 430.

14. For examples of the reductive samariation of glycosyl phenylsulfones for the preparation of glycals, see, de Pouilly, P.; Chénedé, A.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1992**, *33*, 8065.

15. Gansäuer and coworkers have recently developed a catalytic system for promoting the pinacol coupling and reductive opening of epoxides using Cp_2TiCl_2 as the catalyst and manganese as the stoichiometric reductant. a) Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 1923; b) Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 2673; c) Gansäuer, A.; Bluhm, H.; Pierobon, M.; *J. Am. Chem. Soc.* **1998**, *120*, 12849.