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Note

Organoiridium complexes: efficient catalysts for the formation of sugar acetals and ketals

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ABSTRACT

$[Cp^*IrCl_2]_2$ is used as an efficient promoter for the synthesis of sugar acetals and ketals with good to excellent yields. The catalyst is found to be general for a wide range of sugars.

Protecting group manipulations are the key to the success of oligosaccharide synthesis. With the ever-increasing growth in the demand for the medicinally relevant sugar molecules to determine their applications in elucidating various biological pathways and designing of future drugs or delivery agents,[1] development of smarter synthetic techniques is of constant requirement. Formation of acetals and ketals for the protection of *cis*-diols is very common and extremely useful for making building blocks for oligosaccharide synthesis.[2] Depending on the position of the *cis*-diols, acceptors can be synthesized by the formation of acetals/ketals. Moreover, cyclic ketals of sugars are often medicinally relevant, for example, 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose[3] is known for its antipyretic and anti-inflammatory activities with low toxicity. Due to the wide applications of cyclic acetals/ketals of sugars, considerable effort has been paid to develop strategies for the synthesis of these molecules in large quantities.

The most traditional method uses dry acetone in the presence of an acid for example, concd H_2SO_4,[4] $HClO_4$, or anhydrous $ZnCl_2$.[5] The corresponding dimethyl acetals,[6] ketals[7], or enol-ethers[8] have earned their applications owing to its better reactivity. However, the use of strong acids limits the scope of the application in the presence of other protecting groups. Therefore, several modifications are made to increase the compatibility with commonly used protecting groups. Literature evidences suggest a long list of catalysts that includes $FeCl_3$,[9] $AlCl_3$,[10] $CuSO_4$,[11] cerium(IV) ammonium nitrate (CAN),[12] $VO(OTf)_2{\cdot}xH_2O$,[13] bromodimethylsulfonium bromide (BDMS),[14] tetrabutylammonium tribromide (TBATB),[15] heterogeneous catalysts like montmorillonite clay, Zeolite-HY, supported catalysts like H_2SO_4 immobilized on silica,[16] polymer bound PPh_3 and I_2.[17] However, several drawbacks, such as harsh reaction conditions, extensive purification, requirement of inert atmosphere, and eventual loss in yields limit the use of the catalysts. Therefore, there is a clear need of a simple but versatile technique to make these important compounds in large scale.

Transition metal catalysts are often advantageous especially for acid-labile substrates and substrates with multiple functionalities where a mixture of products is possible. Thus, various complexes of platinum,[18] rhodium,[19] iridium,[20] ruthenium[19,20], and palladium[18] are employed as catalysts for different organic reactions including the synthesis of acetals. Recently, Crotti et al.[21] reported the use of $[Cp^*IrCl_2]_2$ as the catalyst for the synthesis of glycerol acetals and ketals with a range of aldehydes and ketones. To the best of our knowledge, there is no report on the use of transition metal catalysts for the synthesis of sugar acetals/ketals. The present report describes the results obtained from the $[Ir(cod)Cl]_2$ and $[Cp^*IrCl_2]_2$-catalyzed sugar acetal/ketal formation reactions.

To start with, commercially available D-glucose (1 mmol) was suspended in dry acetone (2 mL) in a Schlenk flask. After flashing the system with nitrogen, the catalyst (0.03 mmol) was introduced and the reaction mixture was allowed to stir at 40 °C and the progress of the reaction was monitored by TLC. With $[Ir(cod)Cl]_2$ as the catalyst, the reaction took 8 h to complete whereas in the presence of $[Cp^*IrCl_2]_2$, TLC showed complete conversion within 2 h. Purification of the product by flash chromatography using *n*-hexane–EtOAc (3:1) and characterization of the product by spectroscopic means revealed that 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose is the only product in both reactions, however, the yields are 53%

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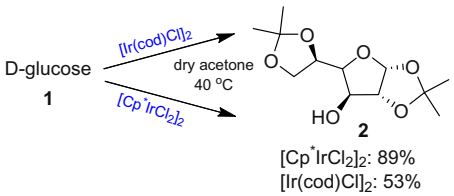


Scheme 1. Organoiridium catalyzed synthesis of sugar acetonides.

and 89%, respectively (Scheme 1). Hence, $[Cp^*IrCl_2]_2$ was chosen as the preferred catalyst to study further. Replacing acetone with more reactive 2,2-dimethoxypropane (2 equiv) in acetonitrile resulted in a faster reaction (45 min) without any significant change in the product yield.

Once the conditions are optimized $[Cp^*IrCl_2]_2$ was used for the acetonation of other hexoses: D-galactose and D-mannose; pentoses: L-arabinose, D-xylose and D-ribose; 6-deoxy hexoses: L-rhamnose and the results are summarized in Table 1. The yields

Table 1
$[Cp^*IrCl_2]_2$ catalyzed synthesis of isopropylidene and benzylidene derivatives of sugars and glycosides

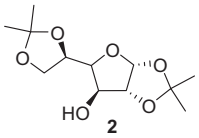
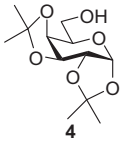
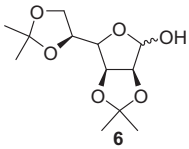
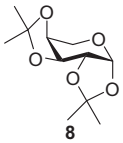
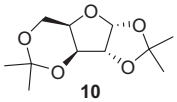
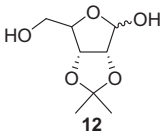
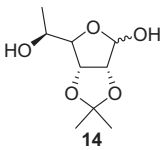
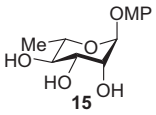
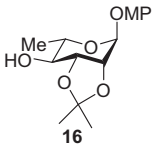
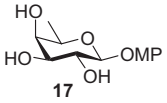
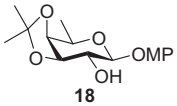
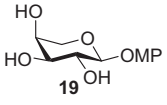
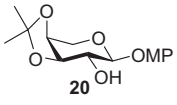
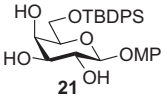
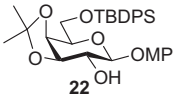
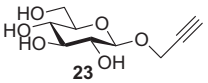
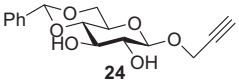
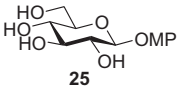
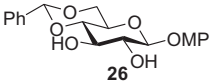
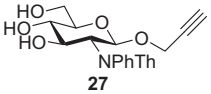
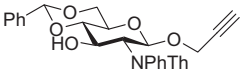
No.	Starting material[a]	Product	Method	Time (min)	Yield[b] (%)	Ref.
1	D-Glucose **1**	 **2**	A B	120 45	89 90	22
2	D-Galactose **3**	 **4**	A B	120 60	85 87	22
3	D-Mannose **5**	 **6**	A	120	81	17
4	L-Arabinose **7**	 **8**	A	90	82	22
5	D-Xylose **9**	 **10**	A	90	82	14
6	D-Ribose **11**	 **12**	A	90	85	17
7	L-Rhamnose **13**	 **14**	A	60	87	23
8	 **15**	 **16**	B	60	91	24
9	 **17**	 **18**	B	60	89	25
10	 **19**	 **20**	B	60	86	

Table 1 (*continued*)

No.	Starting material[a]	Product	Method	Time (min)	Yield[b] (%)	Ref.
11	 **21**	 **22**	B	90	83	
12	 **23**	 **24**	C	90	81	26
13	 **25**	 **26**	C	90	85	27
14	 **27**	 **28**	C	90	84	

[a] MP = *p*-methoxyphenyl, PhTh = phthalimido.
[b] Yields are those obtained after chromatographic purification.

are good in all cases. The glycosides of different sugars also ended up with the expected isopropylidene derivatives in good yields when subjected to $[Cp^*IrCl_2]_2$ catalyzed reaction (Table 1, entries 8–11).

The success with the isopropylidene formation triggered our attention to envisage the scope of the catalyst for the synthesis of benzylidene derivatives, another important and to some extent inevitable protecting group in oligosaccharide syntheses. To our satisfaction, the reaction of propargyl β-D-glucopyranoside (**23**) and benzaldehyde dimethylacetal in the presence of $[Cp^*IrCl_2]_2$ in dry CH_3CN afforded propargyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**24**) in 81% yield. Similarly, derivatives of galactose and mannose gave the desired benzylidene derivatives (Table 1, entries 12–14).

In conclusion, $[Cp^*IrCl_2]_2$ is an efficient organometallic catalyst for the syntheses of sugar isopropylidene and benzylidene derivatives in mild condition. It is potentially an effective alternative of the reported catalysts that require harsh reaction conditions and extra precautions.

1. Experimental section

1.1. General procedure for reactions

$[Ir(cod)Cl]_2$[28] and $[Cp^*IrCl_2]_2$[29] were prepared by following literature procedures and used directly for the reactions. Following appropriate literature procedure the solvents were dried prior to use in the reactions. All reactions were carried out in Schlenk apparatus under argon atmosphere. Following are the methods applied for the experiments described.

1.1.1. Method A

To a suspension of the sugar/glycoside (1 mmol) in dry acetone (2 mL), the organoiridium catalyst (0.03 mmol) was added and the mixture was allowed to stir at 40 °C under argon atmosphere till the TLC (*n*-hexane–EtOAc 2:1) showed complete conversion of the starting material. The mixture was evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (5 mL) and washed with brine (5 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated to afford the crude product that was further purified by flash chromatography using *n*-hexane–EtOAc 2:1 as the eluent.

1.1.2. Method B

To a suspension of the sugar/glycoside (1 mmol) in dry acetonitrile (3 mL) and 2,2-dimethoxypropane (2 mmol), the organoiridium catalyst (0.03 mmol) was added and the mixture was allowed to stir at 40 °C under argon atmosphere till the TLC (*n*-hexane–EtOAc 2:1) showed complete conversion of the starting material. The work-up and purification of the product was as above.

1.1.3. Method C

To a suspension of the sugar/glycoside (1 mmol) in dry acetonitrile (3 mL) and α,α-dimethoxytoluene (2 mmol), the organoiridium catalyst (0.03 mmol) was added and the mixture was allowed to stir at 40 °C under argon atmosphere till the TLC (*n*-hexane–EtOAc 2:1) showed complete conversion of the starting material. The work-up and purification of the product were same as Method A.

1.2. Spectroscopic data of new compounds

1.2.1. *p*-Methoxyphenyl 3,4-*O*-isopropylidene-α-L-arabino pyranoside (20)

$[\alpha]_D^{25}$ +102 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.93 (d, 2H, *J* 9.0 Hz, $C_6H_4OCH_3$), 6.77 (d, 2H, *J* 9.0 Hz, $C_6H_4OCH_3$), 4.73 (d, 1H, *J* 7.2 Hz, H-1), 4.29–4.26 (m, 1H, H-4), 4.10 (dd, 1H, *J* 7.2 Hz, H-2), 4.08 (dd, 1H, *J* 4.5 Hz, 7.2 Hz, H-3), 3.86 (dd, 1H, *J* 2.1 Hz, 12.9 Hz, H-5a), 3.82 (dd,1H, *J* 4.2 Hz, 12.9 Hz, H-5b), 3.75 (s, 3H, $C_6H_4OCH_3$), 2.94 (br s, 1H, O*H*), 1.54 (s, 3H, isopropylidene-CH_3), 1.36 (s, 3H, isopropylidene-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.8, 136.7, 118.7 (2 × C), 114.7 (2 × C), (ArC), 110.2 (isopropylidene-*C*), 101.5 (C-1), 77.9, 72.9, 72.4, 62.7 (C-5), 55.5 ($C_6H_4OCH_3$), 27.8 (isopropylidene-CH_3), 25.8 (isopropylidene-CH_3). HRMS calcd for $C_{15}H_{24}O_6N$ $[M+NH_4]^+$: 314.1604; found 314.1601.

1.2.2. *p*-Methoxyphenyl 6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (22)

$[\alpha]_D^{25}$ +122 (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.59–7.19 (m, 10H, ArH), 6.91 (d, 2H, *J* 9.0 Hz, $C_6H_4OCH_3$), 6.67 (d, 2H, *J* 9.0 Hz, $C_6H_4OCH_3$), 4.53 (d, 1H, *J* 8.1 Hz, H-1), 4.15 (br d, 1H, *J* 5.4 Hz, H-4), 4.04 (m, 1H, H-3), 3.87 (m, 3H, H-5, H-6[a], H-6b), 3.71 (dd, 1H, *J* 8.1 Hz, 9.3 Hz, H-2), 3.67 (s, 3H, $C_6H_4OCH_3$), 2.62 (br s, 1H, O*H*), 1.43, 1.28 (2s, 6H, 2 × isopropylidene CH_3), 1.01 (s, 9H, $SiC(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 155.5, 151.3, 135.7 (5 × C), 133.3, 129.8 (2 × C), 127.7 (4 × C), 118.7 (2 × C), 114.5 (2 × C) (ArC), 110.2 ($C(CH_3)_2$), 102.0 (C-1), 79.0, 74.2, 73.5, 73.4, 63.0 (C-6), 55.4 ($C_6H_4OCH_3$), 28.3, 26.5 (2 × isopropylidene *C*H_3), 27.0 (3 × C) ($SiC(CH_3)_3$), 19.4 ($SiC(CH_3)_3$). HRMS calcd for $C_{32}H_{40}O_7SiNa$ $[M+Na]^+$: 587.2441; found 587.2439.

1.2.3. Propargyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (28)

$[\alpha]_D^{25}$ +93 (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.87–7.72 (m, 9H, ArH), 5.58 (s, 1H, C*H*Ph), 5.50 (d, 1H, *J* 8.5 Hz, H-1), 4.72 (dd, 1H, *J* 8.5 Hz, 10.5 Hz, H-2), 4.40 (dd, 1H, *J* 5.0 Hz, 10.5 Hz, H-6a), 4.33, 4.28 (2dd, 2H, *J* 2.5 Hz, 16.0 Hz, CH_2–C≡CH), 4.26 (dd, 1H, *J* 2.5 Hz, 10.5 Hz, H-6b), 3.84 (t, 1H, *J* 10.5 Hz, H-3), 3.68 (m, 1H, H-5), 3.63 (t, 1H, *J* 10.5 Hz, H-4), 2.25 (t, 1H, *J* 1.5 Hz, CH_2–C≡C*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.5, 167.6 (2 × phthalimido C=O), 137.2, 135.9 (2 × C), 133.1 (2 × C), 130.8, 128.4 (3 × C), 127.4, 123.4, 123.2 (ArC), 101.0 (*C*HPh), 95.8 (C-1), 81.1, 74.3, 67.6, 67.4, 65.2, 55.3, 21.7 (CH_2–C≡CH), 21.7 (CH_2–C≡CH). HRMS calcd for $C_{24}H_{21}O_7NNa$ $[M+Na]^+$: 458.1216; found 458.1211.

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References

1. (a) Mansour, H. M.; Xu, Z.; Hickey, A. J. *J. Pharm. Sci.* **2010**, *99*, 3430–3441; (b) Chen, G.; Amajjahe, S.; Stenzel, M. H. *Chem. Commun.* **2009**, 1198–1200; (c) Sears, P.; Wong, C.-H. *Science* **2001**, *291*, 2344.
2. (a) Mukherjee, D.; Shah, B. A.; Gupta, P.; Taneja, S. C. *J. Org. Chem.* **2007**, *72*, 8965–8968; (b) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Chang, K.-L.; Hung, S.-C. *Nature* **2007**, *446*, 896–899.
3. Goi, A.; Bruzzese, T.; Notarianni, A. F.; Riva, M.; Ronchini, A. *Arzneim.-Forsch./Drug Res.* **1979**, *29*, 986–990.
4. (a) Stevens, J. D. *Chem. Commun.* **1969**, 1140–1141; (b) Hughes, N. A.; Speakman, P. R. H. *Carbohydr. Res.* **1965**, *1*, 171–175.
5. Wood, H. B., Jr.; Diehl, H. W.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 1986–1988.
6. Kihlberg, J.; Frejd, T.; Jansson, K.; Magnusson, G. *Carbohydr. Res.* **1986**, *152*, 113–130.
7. Barili, P. L.; Berti, G.; Catelani, G.; Colonna, F.; Marra, A. *Tetrahedron Lett.* **1986**, *27*, 2307–2310.
8. Hung, S.-C.; Chen, C.-S. *J. Chin. Chem. Soc.* **2000**, *47*, 1257–1262.
9. Singh, P. P.; Gharia, M. M.; Dasgupta, F.; Srivastava, H. C. *Tetrahedron Lett.* **1977**, 439–440.
10. Lal, B.; Gidwani, R. M.; Rupp, R. H. *Synthesis* **1989**, 711–713.
11. (a) Morgenlie, S. *Acta Chem. Scand.* **1973**, *27*, 3609–3610; (b) Morgenlie, S. *Acta Chem. Scand. Ser. B* **1975**, *29*, 367–372.
12. Manzo, E.; Barone, G.; Parrilli, M. *Synlett* **2000**, 887–889.
13. Lin, C.-C.; Jan, M.-D.; Weng, S.-S.; Lin, C.-C.; Chen, C.-T. *Carbohydr. Res.* **2006**, *341*, 1948–1953.
14. Khan, A. T.; Khan, M. M. *Carbohydr. Res.* **2010**, *345*, 154–159.
15. Khan, A. T.; Khan, M. M.; Adhikary, A. *Carbohydr. Res.* **2011**, *346*, 673–677.
16. Rajput, V. K.; Mukhopadhyay, B. *Tetrahedron Lett.* **2006**, *47*, 5939–5941.
17. Silvana, P.; Annalisa, G.; Daniele, D.; Mauro, D. N.; Giovanni, P. *Synthesis* **2006**, 305–308.
18. Cataldo, M.; Nieddu, E.; Gavagnin, R.; Pinna, F.; Strukul, G. *J. Mol. Catal. A: Chem.* **1999**, *142*, 305–316.
19. Barbaro, P.; Bianchini, C.; Oberhauser, W.; Togni, A. *J. Mol. Catal. A: Chem.* **1999**, *145*, 139–146.
20. Sulu, M.; Venanzi, L. M. *Helv. Chim.Acta* **2001**, *84*, 898–907.
21. Crotti, C.; Farnetti, E.; Guidolin, N. *Green Chem.* **2010**, *12*, 2225–2231.
22. Rauter, A. P.; Ramôa-Ribeiro, F.; Fernandes, A. C.; Figueiredo, J. A. *Tetrahedron* **1995**, *51*, 6529–6540.
23. Haines, A. H. *Carbohydr. Res.* **1965**, *1*, 214–217.
24. (a) Werz, D. B.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6315–6318; (b) Sarkar, K.; Mukherjee, I.; Roy, N. *J. Carbohydr. Chem.* **2003**, *22*, 95–108.
25. Roy, B.; Pramanik, K.; Mukhopadhyay, B. *Glycoconjugate J.* **2008**, *25*, 157–166.
26. Minoru, I.; Koichi, F.; Shoichi, K. *Synlett* **2002**, 1409–1416.
27. (a) Nitz, M.; Bundle, D. R. *J. Org. Chem.* **2000**, *65*, 3064–3073; (b) Meijer, A.; Ellervik, U. *J. Org. Chem.* **2004**, *69*, 6249–6256.
28. Herde, J. L.; Lambert, J. C.; Senoff, C. V. *Inorg. Synth.* **1974**, *15*, 18–20.
29. White, C.; Yates, A.; Maitlis, P. M. *Inorg. Synth.* **1992**, *29*, 228–234.