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Using In(III) as a Promoter for Glycosylation

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Abstract

$InCl_3$, $InBr_3$, and $In(OTf)_3$ were tested as promoters in the preparation of glycosides from trichloroacetimidate precursors. A range of protecting groups and of alcohol acceptors were used to determine the versatility of these promoters. Disaccharide formation was demonstrated. In most cases, the In(III) compounds were shown to promote glycosylation better than the widely used promoter BF_3•OEt_2.

Keywords

Glycosylation; Trichloroacetimidate; Indium(III) promotion; $InBr_3$; $InCl_3$; $In(OTf)_3$

Glycosylation is one of the most widely used processes in carbohydrate chemistry. It is one of the most common post translational modifications[1] and thus is an important reaction in the synthesis and study of biologically relevant molecules. Synthetic methods of glycosylation require activation of the carbohydrate donor.[2] These reactions have been researched and reviewed extensively,[3-8] and promotion of a trichloroacetimidate donor with a Lewis acid is common.[2,8] Due to the broad scope of glycosylation reactions, there is a constant need for new promoters to fine tune the reaction for specific donors and acceptors. Several of these promoters are heavy metal based, which can be impractical due to the waste generated.[9-11] BF_3•OEt_2 and TMSOTf are common alternatives as they avoid heavy metal waste,[2,8] however these promoters are hygroscopic, and BF_3•OEt_2 requires distillation prior to use, which creates difficulty in utility.

This paper describes the use of indium(III) as an alternative to current promoters. In(III) is desirable when compared to other Lewis acids due to its stability in air and water[12,13] and relatively low toxicity.[14] Since it is a weaker Lewis acid than the other heavy metal promoters, In(III) should be compatible with a wider range of substrates.[15] In carbohydrate synthesis, In(III) has been reported to catalyze peracetylation,[16] acetolysis, formation and hydrolysis of acetals, and formation of thioglycosides.[17,18] In addition, $InCl_3$ has been reported as a glycosylation promoter using glycohalide donors,[19,20] as well as peracetylated trichloroacetimidates.[21] While these sources focused on $InCl_3$, this paper broadens the scope to include other In(III) glycosylation promoters in the presence of a variety of protecting groups and alcohol acceptors.

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Supplementary Data
Supplementary data associated with this article can be found, in the online version, at

To investigate glycosylation reactions with In(III), $InBr_3$, $InCl_3$, and $In(OTf)_3$ were used as promoters for the glycosylation of three trichloroacetimidate donors with four alcohol acceptors. The strategy for reaction development is shown in Scheme 1. Acetyl, benzyl, and acetonide protecting groups were chosen to provide a stability range that tested the limitations of the In(III) promoters. Primary, tertiary, and benzylic alcohols were chosen as glycosyl acceptors to demonstrate the steric range through which the varying In(III) compounds should be effective. The promoter BF_3•OEt_2 was used for comparison with In(III) reagents. Overall, this paper describes a simple reaction procedure for In(III) promoted glycosylation reactions.

To identify optimal reaction conditions for each promoter, reactions were performed at a variety of different temperatures and with varying amounts of promoter. Reactions were monitored by ^{1}H NMR for the presence of the trichloroacetimidate starting material to determine how long the reactions should be performed. For acetyl protected mannosyl donor **1**, reactions at 0 °C were found to be optimal. As shown in Table 1, using alcohols **5** and **7** as the acceptor, 0.5 equivalents of $InCl_3$ was necessary with this Lewis acid. Only 10 mol % of $InBr_3$ was required (with decomposition becoming increasingly significant as larger amounts of $InBr_3$ were added). A trace amount of $In(OTf)_3$ was sufficient for glycosylation to occur in good yield. Thus, reactions using trichloroacetimidates **1-3** with alcohols **4-7** are reported using 0.1 equivalents of $InBr_3$, 0.25-0.5 equivalents of $InCl_3$, and 0.05 equivalents or a trace amount of $In(OTf)_3$. Additional optimization reactions are summarized in Table S1 of the Supplementary Data.

A series of experiments were performed to compare In(III) promoters against the standard method of BF_3•OEt_2 in glycosylation promotion, and these studies are summarized in Tables 2-4. Reactions using the peracetylated mannosyl trichloroacetimidate **1** are reported in Table 2. In general, $InBr_3$ and $InCl_3$ were shown to perform better than BF_3•OEt_2, with preference toward $InBr_3$ or $InCl_3$ being acceptor dependant. With alcohols **4-6**, $In(OTf)_3$ afforded lower yields of glycosylation products, but this trend is not observed with trichloroacetimidates **2** and **3** (*vide infra*). NMR yields with alcohol **4** were so low that no isolated yield was attempted. Only the alpha product was observed, presumably due to the neighboring group participation of the acetyl group at C2 on the mannoside and due to the anomeric effect.

The yields for reactions using the perbenzylated galactosyl trichloroacetimidate **2** are summarized in Table 3. Used in these catalytic amounts, In(III) was shown to be an effective promoter in all cases tested, with $In(OTf)_3$ giving yields of product formation consistently better than the BF_3•OEt_2 control. Yields for reactions with $InBr_3$ were generally higher than those for reactions using $InCl_3$, with the exception of the more hindered alcohol 7, which gave lower yields overall.

The experiments that are summarized in Table 3 using the perbenzylated galactosyl trichloroacetimidate **2** indicate that In(III) promoters can be catalytically used to effectively promote glycosylation reactions. However, since In(III) has been reported as a promoter of Friedel Crafts chemistry,[22,23] formation of side products is likely to detrimentally affect reaction yields. Although the side products were not characterized, the increased complexity of the aromatic region in the ^{13}C and ^{1}H NMR spectra of crude product mixtures from **2** indicates their formation.

For reactions using benzylated donor **2**, the β isomer is the major product in every case tested, and the most easily isolated, but α:β ratios vary depending on the acceptor used. Using $In(OTf)_3$ afforded the best results, but the conditions were optimized based on overall yield rather than anomeric ratios. It should be noted that time and strength of the acid

promoter (as well as reaction temperature) may have a significant effect on the anomeric ratio of products. While the α product gains some anomeric stability, electrostatic interactions in the oxocarbenium ion half-chair intermediates should have a strong effect on product formation.[24] For **2**, since some unfavorable interactions are likely in both half-chairs, mixtures of α and β products form. For **3**, only one oxocarbenium ion can form, and only the α product is ovserved (see results below and Figure S1 in the Supplementary Data for half-chair diagrams).

Products **14** and **15** were independently resubjected to the reaction conditions using one equivalent of $InBr_3$, $InCl_3$, or $BF_3{\bullet}OEt_2$, and interconversion of the α and β isomers was not observed. The α:β ratio did change over time for **14** (see Table S3 in the Supplementary Data), but the ^1H NMR spectrum clearly indicated decomposition of **14**, and the α:β ratio doesn't reliably shift toward the ratio that was obtained in the reaction (in two trials, the α:β ratio shifts away from rather than toward the reaction ratio). These experiments indicate that the reaction occurs under kinetic control.

Glycosylation reactions using acetonide-protected mannoside **3** are summarized in Table 4. Optimization of these reactions requires a balance between the strength and quantity of the promoter that is present and the length of time that is required for the reaction to achieve completion. Reactions comparing temperatures and times were performed using alcohol **5**, and details are provided in Table S1 in the Supplementary Data. Above 20 mol% for $InBr_3$ and above trace amounts for $In(OTf)_3$, significant product degradation was observed. The length of reaction time required when using $InCl_3$ lead to significant product degradation. Removal of acetonide protecting groups using $InCl_3$ has been reported,[25] and deprotection is apparently a competitive reaction as the length of reaction and the quantity of promoter are increased, as seen by loss of protecting group peaks in the NMR spectra. Trace amounts of $In(OTf)_3$ proved to be the most effective catalyst for glycosylation of **3** and required no column chromatography for purification. No beta product was observed for reactions using acetonide-protected mannoside **3**, presumably due to the anomeric effect in conjunction with steric hindrance at the C2 position (see Figure S1 in the Supplementary Information for diagrams).

Overall, glycosylation of peracetylated mannosyl trichloroacetimidate **1** with simple alcohols afforded the highest yields using $InBr_3$ or $InCl_3$. $In(OTf)_3$ was the best promoter for reactions with perbenzylated galactosyl trichloroacetimidate **2** and acetonide protected mannosyl trichloroacetimidate **3**. Using these results, disaccharide-forming reactions were explored using **1-3** and acceptor **20**. Initial tests with $InBr_3$ afforded significant amounts of unreacted **1** even when 20 mol % was used (rather than the 10 mol % that was used with **4-7**) and the reaction time was extended six-fold. $In(OTf)_3$ proved to be the preferred promoter for all three donors in disaccharide formation with **20**, and the results are shown in Table 5. Acetyl and acetonide protected mannosyl trichloroacetimidates gave high yields of disaccharides (78% and 94%, respectively) with only α-linked products observed and no column chromatography required in the case of acetonide protected mannosyl **3**. Benzylated galactosyl trichloroacetimidate **2** afforded a lower yield of α-linked product (27% yield) due to β product also being formed.

In conclusion, $InBr_3$, $InCl_3$ and $In(OTf)_3$ were effective promoters of glycosylation reactions when used with the variety of protecting groups tested. With respect to acetylated mannosyl trichloroacetimidate **1**, $InBr_3$ or $InCl_3$ afforded the highest yields. All three of the In(III) promoters that were tested worked well with benzylated galactosyl trichloroacetimidate **2**, with $In(OTf)_3$ giving slightly higher yields. When using acetonide protected mannosyl trichloroacetimidate **3**, trace amounts of $In(OTf)_3$ gave the highest yields and required no column chromatography for purification, while $InBr_3$ and $InCl_3$ gave lower yields equivalent

to BF_3•OEt_2. A glycoside acceptor was also successfully added to the trichloroacetimidates using $In(OTf)_3$ as the promoter. Overall, In(III) afforded good to excellent yields of products without the requirement of distillation or an inert reaction atmosphere. The ability to vary ligands on In(III) also provides a broad range of promotion strength, enabling optimization of the conditions for desired reactions.

1. Experimental

1.1. General Methods

To obtain pure products, crude products were purified by column chromatography on 60 Å silica gel for acetyl protected mannosyls and benzyl protected galactosyls with hexane: ethyl acetate mobile phase in the indicated ratio. Acetonide protected manosyls were purified by column chromatography on 32-63μm neutral alumina with hexane: ethyl acetate mobile phase. An ice bath was used for reactions run at 0 °C. ^{13}C and ^{1}H NMR were recorded for purified compounds on a Bruker DRX 500 MHz Spectrometer using TMS as an internal standard. Mass spectra were obtained using a high-resolution Bruker micro-TOF system with electrospray ionization. Yields are either isolated yields. or were calculated from crude ^{1}H NMR spectra using an internal mesitylene standard as specified. Ratios of alpha to beta diastereomers were determined using integrations of resonances in the ^{1}H NMR spectra or (for equivalent carbons) in the ^{13}C NMR spectra.[26] Trichloroacetimidate starting materials[27] and acceptor **20**[28] were synthesized using previously described methods. Trace additions of $In(OTf)_3$ were performed by the addition of a visible amount of $In(OTf)_3$ that weighed less than 0.1mg.

1.2. General procedure for optimization of reaction conditions

Duplicate reactions were performed in parallel. A dry 4 mL scintillation vial was charged with the trichloroacetimidate starting material with a slight excess of alcohol and dissolved in enough dry CH_2Cl_2 to obtain a 50 mM solution of the trichloroacetimidate. The mixture was cooled if specified, and the promoter was added. BF_3•OEt_2 reactions were run under an argon atmosphere. Aliquots were taken from vial 1 and evaluated by ^{1}H NMR for reaction completion. When no starting material was observed, vial 2 was quenched with approximately 0.2 g dry $NaHCO_3$ for 20 min, diluted with 2 mL CH_2Cl_2 and filtered. The solvent was removed under reduced pressure. Yields of vial 2 were obtained from ^{1}H NMR spectra using an internal mesitylene standard. Reaction conditions for vial 2 reactions are provided in Table S1.

1.3. General procedure for the preparation of mannopyranoside and galactopyranoside derivatives

A dry 4 mL scintillation vial was charged with the trichloroacetimidate starting material with a slight excess of alcohol and dissolved in enough dry CH_2Cl_2 to obtain a 50 mM solution of the trichloroacetimidate. The mixture was cooled if specified, and the promoter was added. BF_3•OEt_2 reactions were run under an argon atmosphere. The reaction stirred for the specified time, quenched with approximately 0.2 g dry $NaHCO_3$ for 20 min, diluted with 2 mL CH_2Cl_2 and filtered. The solvent was removed under reduced pressure. Chromatographic purification was performed (galactopyranoside products 8:2 hexane : EtOAc; acetyl protected mannopyranoside products either 7:3 hexane : EtOAc or 1:1 hexane : EtOAc; acetonide protected mannopyranoside products 7:3 hexane : EtOAc + 0.5% DCM) to obtain pure samples. Exact reaction conditions are provided in Table S2 of the Supplementary Data.

1.4. General procedure for evaluation of the reversibility of the reaction

A dry 2 mL scintillation vial was charged with the glycoside and a slight excess of alcohol and dissolved in enough dry CH_2Cl_2 to obtain a 50 mM solution of the trichloroacetimidate. The mixture was cooled to 0 °C, and the promoter was added. Reactions run with BF_3•OEt_2 were additionally purged with Ar. The reaction then stirred for 2h, then was diluted with 2 mL CH_2Cl_2 and quenched with 4 mL saturated $NaHCO_3$, washed with 4 mL brine, then dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The α:β ratios of crude products were obtained from ^{1}H NMR spectra. These reactions are summarized in Table S3 of the Supplementary Data.

1.5. General procedure for the preparation of acetonide protected mannopyranoside derivatives using $In(OTf)_3$

A dry 4 mL scintillation vial was charged with the trichloroacetimidate **3** with a slight excess of alcohol and dissolved in enough dry CH_2Cl_2 to obtain a 50 mM solution of the trichloroacetimidate. Less than 0.1 mg $In(OTf)_3$ was added, and reaction was stirred for 25 min. The reaction was quenched with approximately 0.2 g dry $NaHCO_3$ for 20 min. The solution was then filtered over a medium-sized plug of alumina using CH_2Cl_2 as the eluent. The solvent was removed under reduced pressure affording clean product.

1.6. General procedure for preparation of disaccharides

A dry 4 mL scintillation vial was charged with the trichloroacetimidate starting material with a slight excess of **20** and dissolved in enough dry CH_2Cl_2 to obtain a 50 mM solution of the trichloroacetimidate. The mixture was cooled if specified, and the promoter was added. The reaction then stirred for the specified time, was quenched with 2 mL of saturated $NaHCO_3$ for 20 min, diluted with 2 mL CH_2Cl_2 and filtered. The solvent was removed under reduced pressure. Chromatographic purification was performed (galactopyranoside product 6:4 hexane : EtOAc; acetyl protected mannopyranoside product 4:6 hexane : EtOAc). Acetonide protected mannopyranoside **23** was prepared via procedure 1.5 above. Exact reaction conditions are provided in Table S4 of the Supplementary Data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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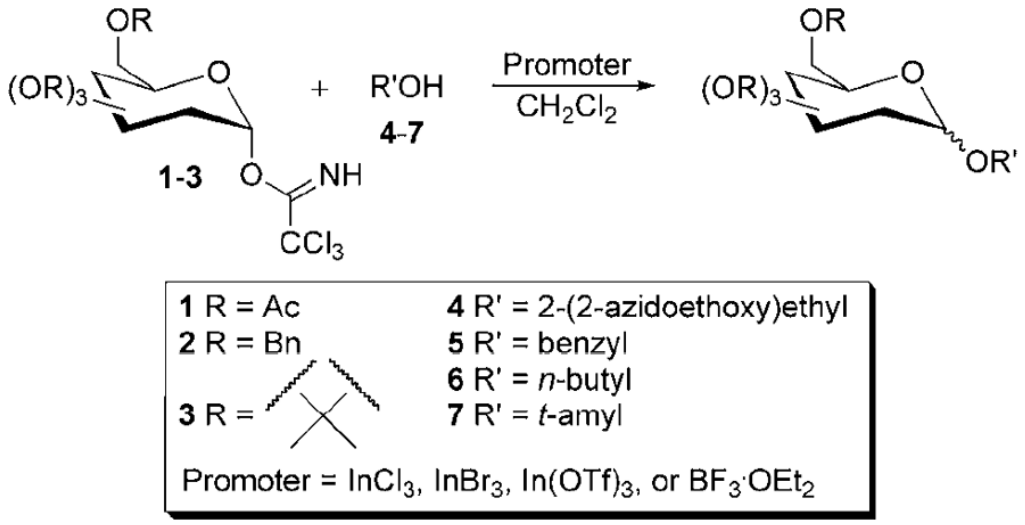
Research Highlights

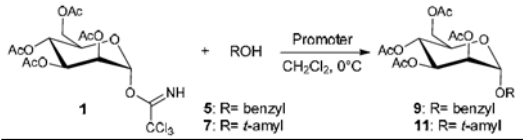
- $In(OTf)_3$ and $InBr_3$ are convenient catalytic promoters of glycosylation.
- $InCl_3$ is a convenient non-catalytic promoter of glycosylation.
- In(III) was used effectively with trichloroacetimidate donors bearing acetyl, benzyl, and acetonide protecting groups.
- Disaccharide formation using In(III) promoters was demonstrated.



Scheme 1.
In(III)-promoted glycosylation.

Table 1

Optimization of reaction conditions using **1** and **5** or **7**.



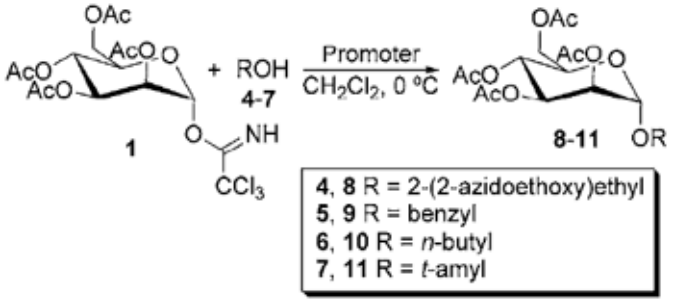
Alcohol	Promoter	Time (min)[a]	Yield (%)[b]
7	$InBr_3$ (0.9 equiv.)	20	63
7	$InBr_3$ (0.2 equiv.)	20	59
7	$InBr_3$ (0.1 equiv.)	30	75
7	$InBr_3$ (0.06 equiv.)	10	68
5	$InCl_3$ (0.5 equiv.)	20	72
5	$InCl_3$ (0.25 equiv.)	50	59
7	$In(OTf)_3$ (1.0 equiv.)	10	37
7	$In(OTf)_3$ (0.2 equiv.)	10	37
7	$In(OTf)_3$ (0.1 equiv.)	10	52
7	$In(OTf)_3$ (0.06 equiv.)	15	54
7	$In(OTf)_3$ (trace)	20	54
7	none	60	0

[a] Time to reaction completion.

[b] Yields determined by ^1H NMR spiked with a mesitylene standard.

Table 2

Glycosylation results using peracetylated trichloroacetimidate **1**.



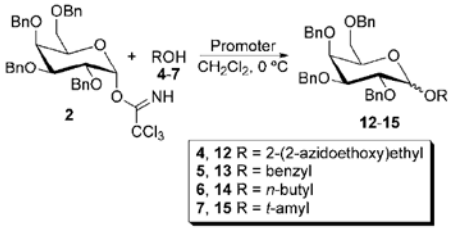
Product	Promoter (equiv.)	Time[a] (min.)	Yield (%)
8	$InBr_3$ (0.1)	30	42
8	$InCl_3$ (0.5)	20	45
8	$In(OTf)_3$ (0.05)	15	6[b]
8	$BF_3•OEt_2$ (0.2)	30	59
9	$InBr_3$ (0.1)	30	53
9	$InCl_3$ (0.5)	20	72
9	$In(OTf)_3$ (0.05)	15	31
9	$BF_3•OEt_2$ (0.2)	30	59
10	$InBr_3$ (0.1)	30	81
10	$InCl_3$ (0.5)	20	42
10	$In(OTf)_3$ (0.05)	15	33
10	$BF_3•OEt_2$ (0.2)	30	40
11	$InBr_3$ (0.1)	30	60
11	$InCl_3$ (0.5)	20	52
11	$In(OTf)_3$ (0.05)	15	57
11	$BF_3•OEt_2$ (0.2)	30	43

[a] Time to reaction completion.

[b] Yields determined by ^1H NMR spiked with a mesitylene standard.

Table 3

Glycosylation results using perbenzylated trichloroacetimidate **2**.



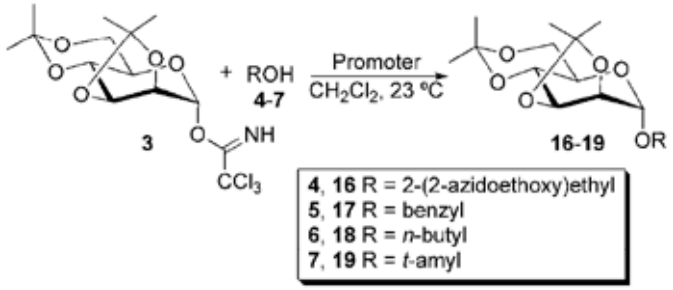
Product	Promoter (equiv.)	Time[a] (min.)	Yield[b] (%)	α:β ratio[b]
12	$InBr_3$ (0.1)	30	57	1:10
12	$InCl_3$ (0.5)	20	48	1:30
12	$In(OTf)_3$ (0.05)	20	72	0:1
12	BF_3•OEt_2 (0.2)	30	65	0:1
13	$InBr_3$ (0.1)	30	61	0:1
13	$InCl_3$ (0.5)	20	53	0:1
13	$In(OTf)_3$ (0.05)	20	68	0:1
13	BF_3•OEt_2 (0.2)	30	60	0:1
14	$InBr_3$ (0.1)	30	57	0:1
14	$InCl_3$ (0.5)	20	53	0:1
14	$In(OTf)_3$ (0.05)	20	63	0:1
14	BF_3•OEt_2 (0.2)	30	61	0:1
15	$InBr_3$ (0.1)	30	30	1:3
15	$InCl_3$ (0.5)	20	33	2:7
15	$In(OTf)_3$ (0.05)	20	52	1:1
15	BF_3•OEt_2 (0.2)	30	24	2:7

[a] Time to reaction completion.

[b] Ratios determined by ^{1}H NMR after column purification.

Table 4

Glycosylation results using acetonide-protected trichloroacetimidate **3**.

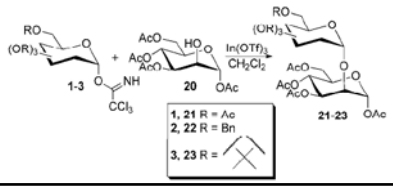


Product	Promoter (equiv.)	Time[a] (min.)	Yield (%)
16	$InBr_3$ (0.1)	25	29
16	$InCl_3$ (0.25)	45	35
16	$In(OTf)_3$ (trace)	30	92
16	$BF_3{\bullet}OEt_2$ (0.2)	30	12
17	$InBr_3$ (0.1)	25	37
17	$InCl_3$ (0.25)	45	23
17	$In(OTf)_3$ (trace)	25	90
17	$BF_3{\bullet}OEt_2$ (0.2)	30	20
18	$InBr_3$ (0.1)	25	12
18	$InCl_3$ (0.25)	45	0
18	$In(OTf)_3$ (trace)	25	78
18	$BF_3{\bullet}OEt_2$ (0.2)	30	4
19	$InBr_3$ (0.1)	25	3
19	$InCl_3$ (0.25)	60	9
19	$In(OTf)_3$ (trace)	25	83
19	$BF_3{\bullet}OEt_2$ (0.2)	30	6

[a]Time to reaction completion.

Table 5

$In(OTf)_3$ promoted disaccharide formations.



Product	Promoter (equiv.)	Temp (°C)	Time[a] (min.)	Yield (%)
21	$In(OTf)_3$ (0.05)	0	20	78
22	$In(OTf)_3$ (0.05)	0	30	27[b]
23	$In(OTf)_3$ (trace)	23	25	94

[a] Time to reaction completion.

[b] Yield is for α-linked product only.