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Efficient Glycosylation Using $In(OTf)_3$ as a Lewis Acid: Activation of *N*-Phenyltrifluoroacetimidate or Thioglycosides with Halogenated Reagents or PhIO

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$In(OTf)_3$ efficiently activated *N*-phenyltrifluoroacetimidate and $In(OTf)_3$ in combination with various halogenated reagents or PhIO promoted glycosylation using thioglycoside in good yields. The combination with iodine interhalogens (e.g., ICl or IBr) effectively promoted α-sialylation.

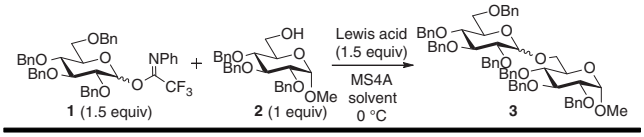
Recently, indium(III) salts have attracted much attention as Lewis acids for various organic reactions because of their mild acidity, tolerance to moisture, and stability at high temperature or over a prolonged reaction time.[1] In(III) salts have been applied to a number of carbohydrate reactions such as Ferrier-type rearrangements and glycosylation reactions.[2,3] In(III) salts have been used as Lewis acid catalysts for glycosylation with several glycosyl donors: $InCl_3$ for glycosylation with glycosyl bromides,[3a] $InBr_3$ for glycosylation with sugar peracetates,[3b] indium(III) trifluoromethanesulfonate ($In(OTf)_3$), $InCl_3$, and $InBr_3$ for glycosylation with glycosyl trichloroacetimidates,[3c] and $In(OTf)_3$ for *C*-glycosylation with glycal derivatives.[3d]

In the present study, we further investigate In(III)-promoted glycosylation using thioglycoside and *N*-phenyltrifluoroacetimidate donors. The latter is effectively activated by $In(OTf)_3$, affording the corresponding glycoside in good yield. The combination of $In(OTf)_3$ with halogenation reagents or PhIO efficiently promotes glycosylation with thioglycosides. Additionally, effective α-sialylation is achieved using $In(OTf)_3$ with iodine interhalogens as oxidants.

We initially examined glycosylation with *O*-benzylated *N*-phenyltrifluoroacetimidate[4] donor **1** and acceptor **2** in the presence of In(III) salts in dichloromethane at 0 °C (Table 1). InF_3 did not activate the donor even after a prolonged reaction time (Entry 1), whereas $InCl_3$ resulted in a low yield with an almost equal ratio of α- and β-isomers (Entry 2). The enhanced Lewis acidity of $InCl_3$ by the combined use of TMSCl[2d,5] increased the reaction rate and yield compared to $InCl_3$ or TMSCl (Entries 3 and 4). Higher yields were obtained with InI_3, $InBr_3$, and $In(OTf)_3$ (Entries 5–7). Among these, the reactions with InI_3 and $In(OTf)_3$ were completed within 10 min, with a higher β-selectivity observed in the former, but a higher yield in the latter. Larger amounts of In(III) salts were necessary to activate *N*-phenyltrifluoroacetimidate compared to trichloroacetimidates.[3c] The reactivities of the In(III) salts tested followed the order $In(OTf)_3 = InI_3 > InBr_3 > InCl_3 + TMSCl > InCl_3 > InF_3$.

Considering the reaction time and yield, glycosylation using $In(OTf)_3$ was further examined by employing other solvents [e.g., diethyl ether (Et_2O) and propionitrile (EtCN)] (Entries 8 and 9). Common solvent effects of ether and nitrile were observed.[6]

Table 1. Glycosylation with *N*-phenyltrifluoroacetimidate



Entry	Lewis acid	Solvent	Time	Result[a]
1	InF_3	CH_2Cl_2	2 h	NR
2	$InCl_3$	CH_2Cl_2	1.5 h	10% (α:β = 48:52)
3	TMSCl	CH_2Cl_2	1.5 h	29% (α:β = 62:38)
4	$InCl_3$ (1.5 equiv) + TMSCl (1.5 equiv)	CH_2Cl_2	1.5 h	53% (α:β = 44:56)
5	$InBr_3$	CH_2Cl_2	1.5 h	71% (α:β = 50:50)
6	InI_3	CH_2Cl_2	10 min	68% (α:β = 28:72)
7	$In(OTf)_3$	CH_2Cl_2	10 min	84% (α:β = 59:41)
8	$In(OTf)_3$	Et_2O	30 min	86% (α:β = 73:27)
9	$In(OTf)_3$	EtCN	30 min	60% (α:β = 15:85)

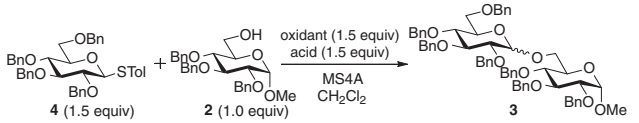
[a]Estimated by NMR.

Thioglycosides have been used in numerous synthetic works because of their stability and ease of preparation. They are commonly activated by NIS/TfOH[7] or NBS/TfOH,[8] although our previous work used NBS in combination with several strong acids (e.g., Bu_4NOTf and Ph_2IOTf) as activators.[9] We have also reported glycosylation with thioglycosides using PhIO in combination with various acids.[10] Other activation methods for thioglycosides have also been reported.[11]

The efficiency of glycosylation using In(III) with various oxidants was then investigated. Because $In(OTf)_3$ afforded the best result among the In(III) salts, its efficiency in thioglycoside activation was compared with TfOH and AgOTf in combination with NBS, NIS, ICl, IBr, or PhIO as the oxidant (Table 2).[12] $In(OTf)_3$ was as good and in some cases even better as an activator than TfOH or AgOTf. All the five tested oxidants afforded the desired disaccharide in good yields (Entries 3, 6, 9, 12, and 15). The initial reaction rates estimated by TLC were [ICl = IBr > NBS > NIS > PhIO]/$In(OTf)_3$. However, the reaction rates using ICl and IBr significantly differed during the reaction, suggesting that the active chemical species changed from ICl (or IBr) to PhSI or another species. Consequently, the reaction temperature was raised from −80 to 0 °C to complete the reaction.

To further investigate the efficiency of $In(OTf)_3$ as an activator, several armed and disarmed thioglycosides were utilized (Table 3). NBS/$In(OTf)_3$ and NIS/$In(OTf)_3$ were effective for glycosylation with both armed benzylated donor **4** and disarmed benzoylated donor **7** (Entries 1, 2, 6, 7, 11, and 12). Although ICl/$In(OTf)_3$ was a good promoter for glycosylation of both **4** and **7** with primary (1°) alcohol acceptor **2**

Table 2. Glycosylation with a thioglycoside donor using In(III) salts, halogenated reagents, and PhIO



Entry	Oxidant	Acid	Temp/°C	Time/min	Result[a]
1	NBS	TfOH	−80	10	quant (α:β = 7:93)
2	NBS	AgOTf	−80 to 0	10	97% (α:β = 27:73)
3	NBS	$In(OTf)_3$	−80 to −40	10	98% (α:β = 16:84)
4	NIS	TfOH	−80	10	91% (α:β = 14:86)
5	NIS	AgOTf	−80 to 0	10	96% (α:β = 26:74)
6	NIS	$In(OTf)_3$	−80 to 0	10	96% (α:β = 21:79)
7	ICl	TfOH	−80 to rt	30	45% (α:β = 54:46)
8	ICl	AgOTf	−80 to 0	10	33% (α:β = 44:56)
9	ICl	$In(OTf)_3$	−80 to 0	10	92% (α:β = 42:58)
10	IBr	TfOH	−80 to rt	30	39% (α:β = 71:29)
11	IBr	AgOTf	−80 to 0	10	98% (α:β = 19:81)
12	IBr	$In(OTf)_3$	−80 to 0	10	61% (α:β = 65:35)
13	PhIO	TfOH	−80 to −40	10	93% (α:β = 25:75)
14	PhIO	AgOTf	−80 to rt	30	NR
15	PhIO	$In(OTf)_3$	−80 to 0	10	86% (α:β = 60:40)

[a]Estimated by NMR.

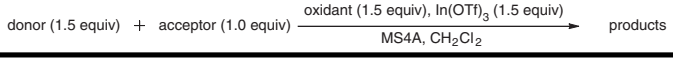
(Table 2: Entry 9, Table 3: Entry 8), the yields with secondary (2°) alcohol acceptor **5** were lower than those with NBS/$In(OTf)_3$ and NIS/$In(OTf)_3$ (Table 3: Entries 3 and 13). IBr/$In(OTf)_3$ afforded a good yield in the glycosylation of benzoylated donor **7** with **2** (Table 3: Entry 9). When less reactive acceptor **5** was used, the donors decomposed (Table 3: Entries 4 and 14). The yields with PhIO/$In(OTf)_3$ were generally moderate (Table 3, Entries 5, 10, and 15).

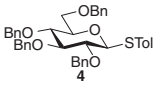
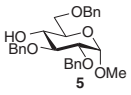
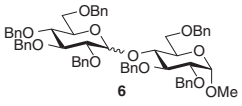
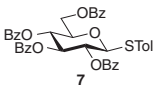
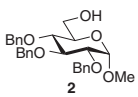
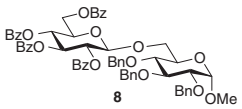
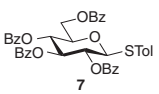
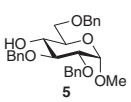
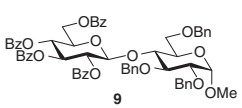
Stereoselective α-sialylation has been intensively studied to synthesize sialoglycans,[13] which have diverse biological functions in the blood, nerve, immune systems, etc.[14] The electron-withdrawing carboxylic acid at C1 and the lack of participating groups at C3 are inherent difficulties in α-sialylation. A kinetic solvent effect of nitrile for α-sialylation is well known, and low temperatures facilitate the formation of α-anomeric products.[15] We recently reported stereoselective α-sialylation using a C5-acetamido *N*-phenyltrifluoroacetimidate donor with TMSOTf.[16] A high yield and stereoselectivity require strict temperature control at −80 °C and the efficient removal of the reaction heat.

In this work, we develop practical α-sialylation using commercially available sialyl thioglycoside **10** with a similar low-temperature control (Scheme 1). Although sialylation using sialyl thioglycosides with NIS–TfOH has been widely used to synthesize various sialylated glycans, these conditions did not promote the glycosylation of **10** with galactose acceptor **11** at −85 °C. Because the combination of halogenated reagents with $In(OTf)_3$ efficiently promoted the glycosylation with thioglycoside donors **4** and **7**, we examined sialylation with NBS, NIS, ICl, and IBr with $In(OTf)_3$ in propionitrile at −85 °C. Although NBS/$In(OTf)_3$ and NIS/$In(OTf)_3$ did not activate **10** at −85 °C, ICl or IBr together with $In(OTf)_3$ promoted sialylation at the same temperature. ICl/AgOTf and IBr/AgOTf have been reported to activate thioglycoside in sialylation.[17] We observed that both ICl/AgOTf and IBr/AgOTf showed lower reactivities than the ICl/$In(OTf)_3$ system. The reproducibility of the reaction with IBr was low, likely because of the inherent instability of IBr. Thus, ICl/$In(OTf)_3$ was used as a promoter for the α-sialylation of thioglycosides **10** and **15**. In α(2,6)-sialylation, disaccharide **12** was obtained in good yield with a high selectivity. On the other hand, α(2,3)-sialylation with acceptor **13** resulted in 26% yield, albeit with perfect α-selectivity. The low yield probably attributed to the steric hindrance in the 2° alcohol acceptor. This promoter system was also applied to prepare sialyl Tn antigen (STn antigen), a disaccharide often expressed in tumors and a variety of cancers.[18] Glycosylation formed desired disaccharide **17** in good yield and selectivity after the amounts of ICl and $In(OTf)_3$ were optimized to prevent cleavage of the isopropylidene group.

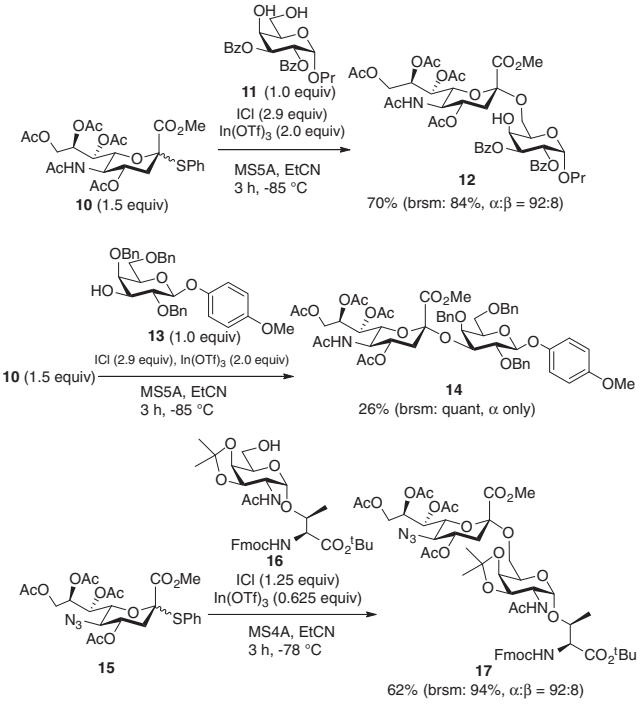
In conclusion, In(III) salts promoted glycosylation with *N*-phenyltrifluoroacetimidate. Among the salts tested, $In(OTf)_3$ afforded the best results. $In(OTf)_3$ together with various oxidants efficiently activated thioglycosides to afford the corresponding

Table 3. $In(OTf)_3$-mediated glycosylation of armed and disarmed thioglycosides



Entry	Donor	Acceptor	Product	Oxidant	Temp/°C	Time/min	Result[a]
1				NBS	−80 to −40	10	79% (α:β = 41:59)
2				NIS	−80 to 0	10	76% (α:β = 46:54)
3				ICl	−80 to rt	30	64% (α:β = 54:46)
4				IBr	−80 to rt	30	38% (α:β = 44:56)
5				PhIO	−80 to rt	10	65% (α:β = 61:39)
6				NBS	−80 to 0	10	quant
7				NIS	−80 to 0	30	quant
8				ICl	−80 to rt	10	87%
9				IBr	−80 to rt	60	97%
10				PhIO	−80 to rt	30	89%
11				NBS	−80 to rt	10	98%
12				NIS	−80 to rt	60	98%
13				ICl	−80 to rt	30	69%
14				IBr	−80 to rt	30	21%
15				PhIO	−80 to rt	60	69%

[a]Estimated by NMR.



Scheme 1. ICl/In(OTf)$_3$-promoted α-sialylation.

glycosides in similar or better yields and selectivities compared to those with TfOH or AgOTf. Because In(OTf)$_3$ was a relatively harder acid than AgOTf, but had a soft character, In(OTf)$_3$ could efficiently activate thioglycosides when combined with various oxidants, although In(OTf)$_3$ was a mild Lewis acid. In general, the combination of In(OTf)$_3$ with NBS or NIS was effective for various glycosylations of both reactive and less reactive donors and acceptors. Additionally, the ICl/In(OTf)$_3$ system was effective for α-sialylation reactions. The reactivity using ICl/In(OTf)$_3$ is higher than that using other activators such as NIS/TfOH, NIS/AgOTf, or IBr/AgOTf; only ICl/In(OTf)$_3$ system smoothly promotes the sialylation using sialyl donor **10** at very low temperature to realize excellent α-selectivity.[19]

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References and Notes

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19 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.