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Mild and efficient direct aromatic iodination

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Abstract—Aryl iodides are important synthetic intermediates that can be transformed into tritium labelled compounds by metal-mediated hydrodehalogenation and also react in a number of important synthetic transformations. We present ICl/In(OTf)$_3$ as a new reagent combination for mild iodination, suitable for acid-sensitive substrates such as carbohydrates.

1. Introduction

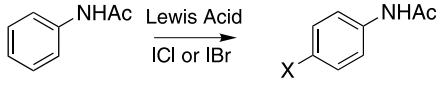
Aryl iodides can easily be transformed into tritium labelled compounds by metal-mediated hydrodehalogenation and are thus, important intermediates in medicinal chemistry.[1–3] The number of functional transformations, for example, Heck reactions as well as Stille and Negishi cross couplings, originating from aryl iodides also make these compounds valuable synthetic intermediates.[4] However, the low electrophilicity of molecular iodine, compared to that of molecular bromine and chlorine, renders direct iodination difficult, even in combination with activating Lewis acids. The direct iodination is also hampered by the formation of HI, which can cause proteolytic cleavage of sensitive compounds. To overcome these problems, iodinations are often performed under oxidative conditions where iodide ions, formed in the reaction, are reoxidized to molecular iodine. However, the oxidizing reagents can degrade sensitive groups, and are, therefore, not always feasible.

There has been a number of reports on direct aromatic iodination (i.e., by direct formation of a carbon–iodine bond from an iodonium species),[4] but few Lewis acids have been evaluated. The most common Lewis acids are silver and mercuric salts in combination with I_2. Recently a super active iodinating reagent, capable of iodinating even deactivated aromatic compounds, using ICl was reported. However, the use of strong acids (i.e., H_2SO_4) renders this and other similar methods less suitable for sensitive compounds such as carbohydrates.[5–8] In order to perform iodination under mild, yet effective, conditions we present the ICl/In(OTf)$_3$ system.

2. Optimization of aromatic iodination

The activating properties of various Lewis acids, together with either ICl or IBr, were examined using the halogenation of acetanilide as a model reaction. Acetanilide was treated with interhalogen in the presence of different Lewis acids for 15 min at room temperature. The reaction mixtures were then extracted and the crude mixtures were analyzed by NMR in order to estimate the reaction conversion of acetanilide into halogenated products. The results are summarized in Table 1.

Table 1. The halogenating properties of ICl and IBr in combination with various Lewis acids



1 **2a** X=I **2b** X=Br

Entry	Lewis acid	ICl (%) X=I[a]	IBr (%) X=I[a]	X=Br
1	HOTf	0	0	3
2	Sc(OTf)$_3$	0	0	8
3	Sn(OTf)$_2$	0	0	0
4	Al(OTf)$_3$	14	0	14
5	Yb(OTf)$_2$	16	0	14
6	—[b]	21	0	21
7	Mg(OTf)$_2$	24	0	26
8	Mn(OTf)$_2$	25	0	17
9	LiOTf	25	0	18
10	Cu(OTf)$_2$	30	0	36
11	AgOTf	43	13	32
12	Zn(OTf)$_2$	46	0	19
13	In(OTf)$_3$	79	27	11
14	Hg(OTf)$_2$	100	100	0

[a] Conversion into halogenated product. The reaction conditions are chosen for best comparison of the Lewis acids, and are by no means optimized.
[b] No Lewis acid added.

Keywords: Iodination; Lewis acids; Interhalogens; Carbohydrates.
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As expected, the most potent activator was $Hg(OTf)_2$ (entry 14, Table 1), a well known activator of iodinations,[4] but to our surprise we found that $In(OTf)_3$ (entry 13) was an even better activator than AgOTf (entry 11) in the ICl mediated iodination. In a preparative reaction using 1.5 equiv of ICl and 1.0 equiv of $In(OTf)_3$, 4-iodoacetanilide was isolated in 99% yield after 30 min reaction time.

In order to optimize the amount of $In(OTf)_3$ used, acetanilide was dissolved in CD_3CN in an NMR tube together with various equivalents of $In(OTf)_3$ (0, 0.1, 0.5, 1.0). The reactions were started by the addition of 1.0 equiv ICl and the conversion into 4-iodoacetanilide was estimated using NMR. The results, shown in Figure 1, indicate that only 0.5 equiv of $In(OTf)_3$ are necessary for efficient conversion into iodinated product.

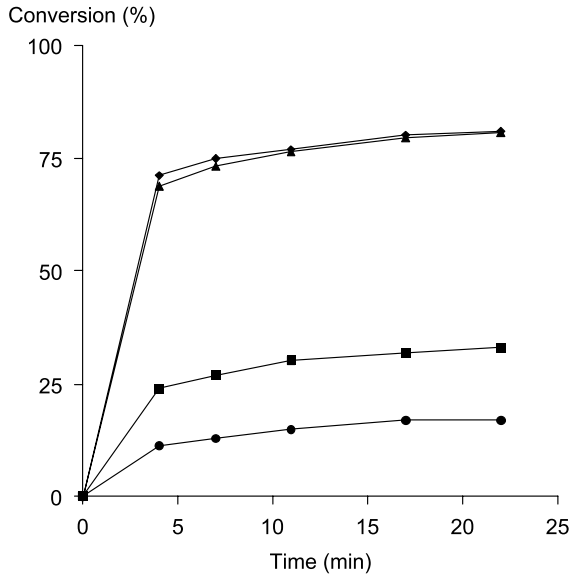
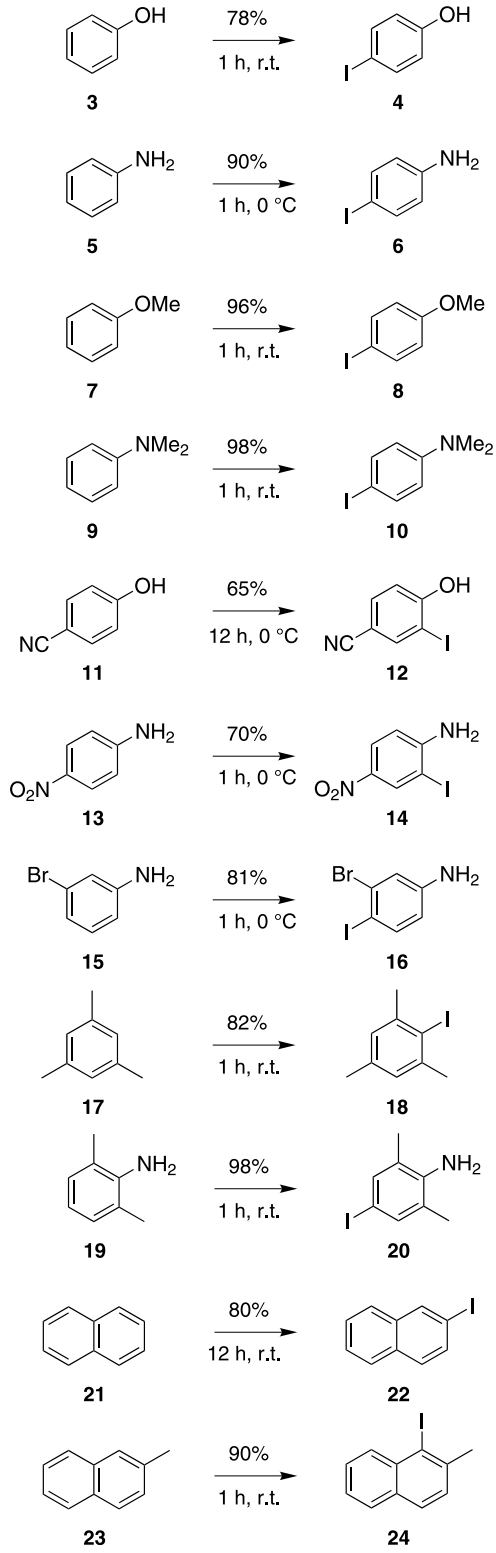


Figure 1. Iodination of acetanilide using various amounts of $In(OTf)_3$. ICl/acetanilide 1:1. ♦, 1 equiv $In(OTf)_3$; ▲, 0.5 equiv $In(OTf)_3$; ■, 0.1 equiv $In(OTf)_3$; ●, 0 equiv $In(OTf)_3$.

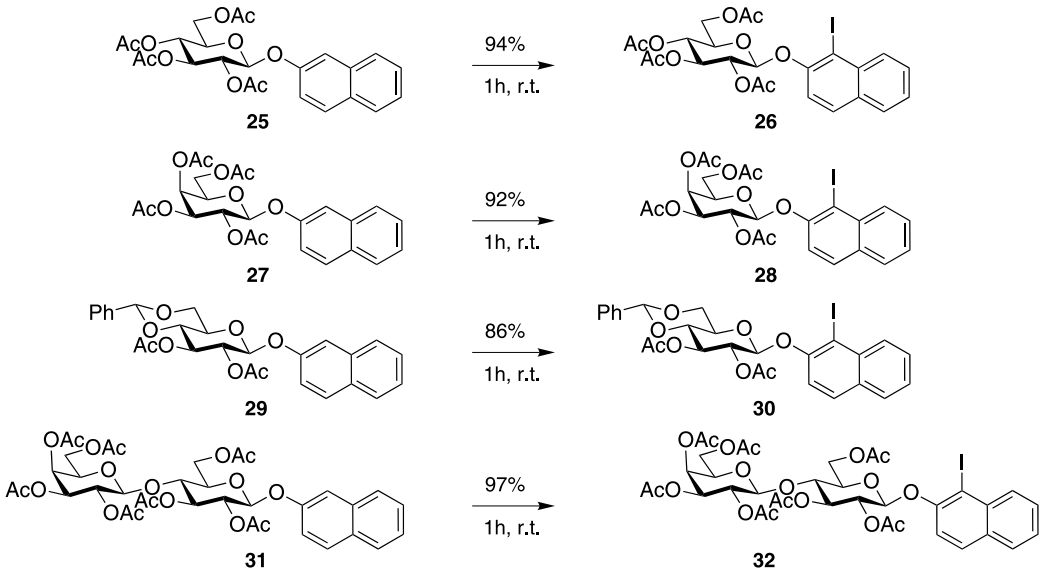
3. Application of aromatic iodination

The novel iodination reagent $ICl/In(OTf)_3$ was applied to a wide range of aromatic compounds (Scheme 1). Deactivated and weakly activated compounds, that is, nitrobenzene, acetophenone, bromobenzene, benzene and toluene were not iodinated, whereas more activated compounds were cleanly converted into the *para*-iodinated product with no *ortho*-product observed. However, by using $Hg(OTf)_2$ it was possible to iodinate toluene to give a mixture of *para*-iodinated and *ortho*- and *para*-diiodinated compounds in 30 and 23% yield. All reactions were performed at room temperature unless otherwise stated. The highly activated aniline (**5**) was *para*-iodinated (66%) as well as *ortho*- and *para*-diiodinated (13%) at room temperature but the reaction gave 90% *para*-iodinated product and only 6% diiodinated product when the temperature was lowered to 0 °C. 4-Hydroxy-benzonitrile (**11**), an easily reducible compound[9] was iodinated in 16% yield in room temperature, but prolonged reaction time at 0 °C gave 65% product. Iodination of 4-nitroaniline (**13**) at room temperature gave



Scheme 1. The halogenating properties of $ICl/In(OTf)_3$. Aryl/$In(OTf)_3$/ICl 1:0.5:1.1, MeCN.

63% yield. By adding molecular sieves, which can function as a neutral acid scavenger,[10] the yield increased to 67% while reaction with molecular sieves at 0 °C gave 70% product. Iodination of 3-bromo-aniline (**15**) gave 73% at room temperature and the yield increased to 81% at 0 °C. Naphthalene (**21**) was converted into 2-iodonaphthalene



Scheme 2. The halogenating properties of ICl/In(OTf)$_3$. Aryl/In(OTf)$_3$/ICl 1:0.5:1.1, MeCN.

(**22**) in 42% yield after 60 min, whereas prolonged reaction time increased the yield to 80%.

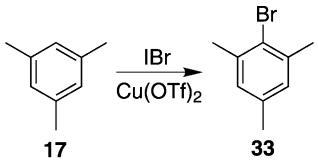
To verify the mildness of the reaction conditions, aromatic carbohydrate aglycons were iodinated in excellent yields (Scheme 2) without decomposition of the acid sensitive carbohydrate moiety. The more acid sensitive 2-naphthyl 4,6-*O*-benzylidene-2,3-di-*O*-acetyl-β-D-glucopyranoside (**29**) was iodinated in the presence of molecular sieves as a neutral acid scavenger.[10] All attempts to iodinate unprotected carbohydrates resulted in complete decomposition.

4. Aromatic bromination

The halogenations using IBr gave either bromination (through the in situ formation of molecular bromine from IBr)[11,12] or iodination, or a mixture of both, compared with ICl that gave pure iodinated product (Table 1). Apparently IBr is less suitable for aromatic iodination due to the competing bromination reaction. However, of the Lewis acids capable of activating IBr (i.e., compared to no Lewis acid added) both Cu(OTf)$_2$ (entry 10, Table 1) and Hg(OTf)$_2$ (entry 14) gave clean conversion into either brominated or iodinated product, that is, the choice of Lewis acid control whether an electrophilic bromonium or iodonium species is reacting in the aromatic halogenations using IBr.

The brominating capabilities of IBr/Cu(OTf)$_2$ was investigated using mesitylene as a model system (Fig. 2). To CD_3CN, 1.0 equiv of mesitylene and various equivalents of Cu(OTf)$_2$ were added. The reaction was initiated by addition of 1.0 equiv of IBr. The reactions were run in NMR tubes and the conversion of mesitylene into bromomesitylene was monitored. The results (Fig. 2) indicate that the bromination does not follow the stoichiometry of the reported reaction pathway, where 2 equiv of IBr are required for brominating 1 equiv of an aromatic compound.[11,12] Instead, it is shown that IBr is needed only in stoichiometric amount when in combination with Cu(OTf)$_2$.

It is known that copper(II) ions are capable of oxidizing iodide ions to molecular iodine, and this has been used in iodinations of aromatic compounds.[13] Apparently the brominating properties of IBr/Cu(OTf)$_2$ are enhanced due



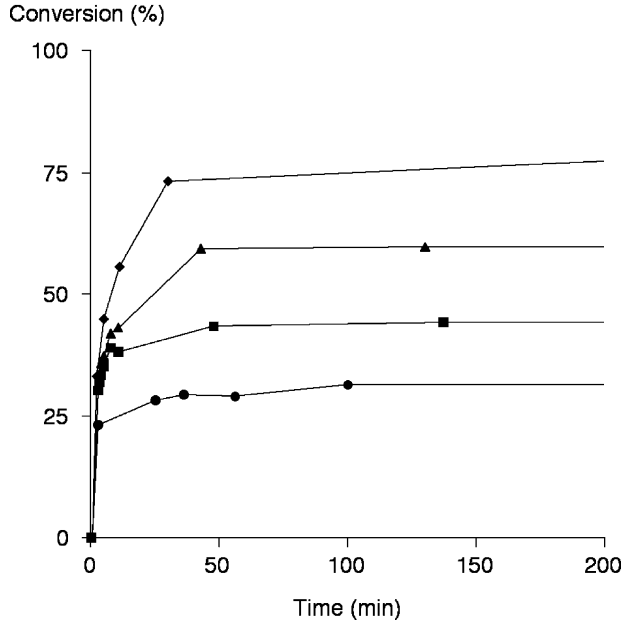


Figure 2. Bromination of mesitylene using various equivalents of Cu(OTf)$_2$. The time interval is minimized for clarity; after 8000 min the reaction promoted by 1.0 equiv Cu(OTf)$_2$ had reached 92% conversion, while the others had reached their maximum after 200 min. IBr/mesitylene 1:1 ♦, 1.0 equiv Cu(OTf)$_2$; ▲, 0.50 equiv Cu(OTf)$_2$; ■, 0.25 equiv Cu(OTf)$_2$; ●, 0 equiv Cu(OTf)$_2$.

to the regeneration of molecular bromine from bromide ions formed in the bromination reaction by the oxidation of copper(II) ions.

5. Conclusion

We have introduced ICl/$In(OTf)_3$ as a mild and effective reagent combination for aromatic iodination, suitable even for acid sensitive compounds, such as carbohydrates. We have also shown that the halogenating (i.e., bromination or iodination) properties of IBr can be controlled by the appropriate choice of Lewis acid. These results can hopefully be correlated to other reactions involving iodonium ions, for example, glycosylations.[14,15]

6. Experimental

6.1. General

General experimental conditions: NMR spectra were recorded at 300 or 400 MHz. ^1H NMR spectra were assigned using 2D-methods (COSY). Chemical shifts are given in ppm downfield from the signal for Me_4Si, with reference to residual $CHCl_3$. Reactions were monitored by TLC using alumina plates coated with silica gel and visualized using either UV light or by charring with *para*-anisaldehyde. Preparative chromatography was performed with silica gel (35–70 μm, 60 Å). MeCN used in iodination reactions was distilled from CaH_2 before use. ICl and IBr are commercially available as 1 M solutions in CH_2Cl_2. Compounds **1**–**9**, **11**, **13**–**15**, **17**–**19**, **21**, **23**, **27** and **33** are commercially available. Known and commercially available compounds were in agreement with previously published data (e.g., NMR).

Table 1. General procedure for evaluating Lewis acid mediated halogenation of acetanilide. Solution A: acetanilide (135 mg, 1 mmol) was dissolved in MeCN (10 mL). Solution B: Lewis Acid (0.2 mmol) was dissolved in MeCN (4 mL). Solution C: ICl (0.95 mL, 1.0 M in CH_2Cl_2) was dissolved in MeCN (9.05 mL). Solution B (0.74 mL) and solution A (0.37 mL) were added to an argon flushed test tube. To the stirred mixture was then added solution C (0.39 mL). After 15 min diisopropyl amine (0.10 mL, excess) and CH_2Cl_2 (5 mL) were added and the mixture was extracted twice with acidified water (2 mL, H_2SO_4, pH 2) and once with water (2 mL). The mixture was then concentrated before analysis using NMR.

Figure 1. General procedure for NMR reactions with acetanilide. To CD_3CN (0.5 mL) were added acetanilide (5.0 mg, 0.037 mmol) and $In(OTf)_3$ (0.1–1.0 equiv). The reaction was initiated by the addition of ICl (0.037 mL, 1.0 M in CH_2Cl_2).

6.1.1. 4-Iodoacetanilide (2a). Acetanilide (**1**) (68 mg, 0.50 mmol) and $In(OTf)_3$ (281 mg, 0.50 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.750 mL, 0.75 mmol) was added and the mixture was stirred for 30 min at room temperature. The solution was then diluted with CH_2Cl_2, washed with satd aq $NaHCO_3$ and $Na_2S_2O_3$, dried (Na_2SO_4), concentrated and chromatographed (SiO_2, 1:1 heptane/EtOAc) to give 4-iodoacetanilide (130 mg, 99%) as an amorphous off-white solid.

6.1.2. 4-Iodophenol (4). Phenol (**3**) (48 mg, 0.51 mmol) and $In(OTf)_3$ (140 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 2:1 heptane/EtOAc) to give 4-iodophenol (88 mg, 78%) as an amorphous off-white solid.

6.1.3. 4-Iodoaniline (6). Aniline (**5**) (0.046 mL, 0.50 mmol), and $In(OTf)_3$ (141 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 60 min at 0 °C. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 3:1 heptane/EtOAc) to give 4-iodoaniline (99 mg, 90%) as an amorphous off-white solid.

6.1.4. 4-Iodoanisole (8). Anisole (**7**) (0.055 mL, 0.51 mmol), and $In(OTf)_3$ (142 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, heptane) to give 4-iodoanisole (113 mg, 96%) as an amorphous off-white solid.

6.1.5. 4-Iodo *N*,*N*-dimethylaniline (10). *N*,*N*-dimethylaniline (**9**) (0.064 mL, 0.51 mmol) and $In(OTf)_3$ (140 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 10:1 heptane/EtOAc) to give 4-iodo *N*,*N*-dimethylaniline[16,17] (122 mg, 98%) as an amorphous off-white solid.

6.1.6. 4-Hydroxy-3-iodo-benzonitrile (12). 4-Hydroxybenzonitrile (**11**) (60 mg, 0.50 mmol) and $In(OTf)_3$ (141 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 12 h at 0 °C. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 1:0→1:1 CH_2Cl_2/acetone) to give 4-hydroxy-3-iodo-benzonitrile[18,19] (80 mg, 65%) as an amorphous white solid.

6.1.7. 2-Iodo-4-nitroaniline (14). 4-Nitroaniline (**13**) (71 mg, 0.52 mmol) $In(OTf)_3$ (141 mg, 0.25 mmol) and molecular sieves 3 Å (1 g) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 60 min at 0 °C. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and

chromatographed (SiO_2, 3:2 heptane/EtOAc + 1% triethylamine) to give 2-iodo-4-nitroaniline (95 mg, 70%) as an amorphous yellow solid.

6.1.8. 3-Bromo-4-iodoaniline (16). 3-Bromoaniline (**15**) (0.054 mL, 0.50 mmol) and $In(OTf)_3$ (140 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 60 min at 0 °C. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 3:1 heptane/EtOAc) to give 3-bromo-4-iodoaniline[20] (119 mg, 81%) as an amorphous off-white solid.

6.1.9. Iodomesitylene (18). Mesitylene (**17**) (0.070 mL, 0.50 mmol) and $In(OTf)_3$ (141 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, heptane) to give iodomesitylene (102 mg, 82%) as an amorphous off-white solid.

6.1.10. 4-Iodo-2,6-dimethylaniline (20). 2,6-Dimethylaniline (**19**) (0.062 mL, 0.50 mmol) and $In(OTf)_3$ (139 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 3:1 heptane/EtOAc) to give 4-iodo-2,6-dimethylaniline[21,22] (122 mg, 98%) as an amorphous off-white solid.

6.1.11. 2-Iodonaphthalene (22). Naphthalene (**21**) (64 mg, 0.50 mmol) and $In(OTf)_3$ (141 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 12 h at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, heptane) to give 2-iodonaphthalene[23,24] (102 mg, 80%) as an amorphous off-white solid.

6.1.12. 1-Iodo-2-methylnaphthalene (24). 2-Methylnaphthalene (**23**) (72 mg, 0.47 mmol) and $In(OTf)_3$ (141 mg, 0.25 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.550 mL, 0.55 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, heptane) to give 1-iodo-2-methylnaphthalene[25,26] (114 mg, 90%) as a yellow oil.

6.1.13. 2-(1-Iodonaphthyl) 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (26). 2-Naphthyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[27] (**25**) (83 mg, 0.175 mmol) and $In(OTf)_3$ (51 mg, 0.09 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.275 mL, 0.28 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 1:2 heptane/EtOAc) to give 2-(1-iodonaphthyl) 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (99 mg, 94%). Recrystallization from EtOAc/heptane gave an analytical sample of white crystals; mp 180.0–181.0 °C; $[\alpha]_D^{22}$ −62.6 (*c* 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.16 (d, 1H, J=8.4 Hz), 7.80 (d, 1H, J=8.9 Hz), 7.76 (d, 1H, J=8.1 Hz), 7.57 (dt, 1H, J=8.5, 1.2 Hz), 7.45 (dt, 1H, J=7.9, 0.9 Hz), 7.32 (d, 1H, J=8.9 Hz), 5.48 (dd, 1H, J=9.3, 7.9 Hz), 5.33 (dd, 1H, J=9.4, 9.3 Hz), 5.24 (dd, 1H, J=9.7, 9.5 Hz), 5.18 (d, 1H, J=7.8 Hz), 4.32 (dABq, 1H, J=12.3, 5.3 Hz), 4.23 (dABq, 1H, J=12.3, 2.5 Hz) 3.93–3.89 (m, 1H), 2.13, 2.10 (s, 3H each), 2.06 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 170.7, 170.5, 169.53, 169.47, 154.5, 135.5, 132.0, 131.1, 130.5, 128.5, 128.3, 125.7, 116.9, 100.4, 90.2, 72.9, 72.4, 71.1, 68.4, 62.1, 21.5, 20.9, 20.81, 20.77. HRMS calcd for $C_{24}H_{25}IO_{10}Na$ (M+Na) 623.0390, found 623.0356.

6.1.14. 2-(1-Iodonaphthyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (28). 2-Naphthyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**27**) (118 mg, 0.25 mmol) and $In(OTf)_3$ (73 mg, 0.13 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.275 mL, 0.28 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 1:1 heptane/EtOAc) to give 2-(1-iodonaphthyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (138 mg, 92%). Recrystallization from ether gave an analytical sample of white crystals; mp 147.0–148.0 °C; $[\alpha]_D^{21}$ −39.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.17 (d, 1H, J=8.5 Hz), 7.80 (d, 1H, J=9.0 Hz), 7.76 (d, 1H, J=8.1 Hz), 7.57 (t, 1H, J=7.8 Hz), 7.45 (t, 1H, J=7.7 Hz), 7.35 (d, 1H, J=8.9 Hz), 5.70 (dd, 1H, J=10.4, 8.0 Hz), 5.50 (d, 1H, J=3.3 Hz), 5.15 (d, 1H, J=7.8 Hz), 5.14 (dd, 1H, J=10.5, 3.4 Hz), 4.30 (dABq, 1H, J=11.2, 7.0 Hz), 4.20 (dABq, 1H, J=11.2, 6.2 Hz), 4.12 (t, 1H, J=6.4 Hz), 2.22, 2.14, 2.09, 2.04 (s, 3H each). ^{13}C NMR ($CDCl_3$): δ 170.5, 170.44, 170.35, 169.5, 154.7, 135.5, 132.0, 131.0, 130.5, 128.5, 128.3, 125.6, 116.7, 100.9, 89.8, 71.4, 71.1, 68.4, 67.0, 61.6, 21.6, 20.86, 20.85, 20.8. HRMS calcd for $C_{24}H_{25}IO_{10}Na$ (M+Na) 623.0390, found 623.0375.

6.1.15. 2-Naphthyl 4,6-*O*-benzylidene-2,3-di-*O*-acetyl-β-D-glucopyranoside (29). 2-Naphthyl β-D-glucopyranoside (363 mg, 1.19 mmol) and benzaldehyde dimethyl acetal (0.325 mL, 2.17 mmol) were suspended in MeCN (5.5 mL). *p*TSA (5 mg, 0.03 mmol) was added and the mixture was stirred for 50 min at room temperature. Triethylamine (0.5 mL) was added and the mixture was co-concentrated with toluene. The crude product was dissolved in pyridine (5 mL) and acetic anhydride (4 mL, 42.4 mmol) was added and the mixture was stirred for 3.5 h at room temperature. Co-concentration with toluene and chromatography (SiO_2, 2:1→0:1 heptane/EtOAc) gave 2-naphthyl 4,6-*O*-benzylidene-2,3-di-*O*-acetyl-β-D-glucopyranoside (523 mg, 92%). Recrystallization from EtOAc/heptane gave an analytical sample of white crystals; mp 194.0–196.0 °C; $[\alpha]_D^{21}$ −19.3 (*c* 1.1, $CHCl_3$). ^1H NMR (C_6D_6): δ 7.64–7.09 (m, 12H), 5.68–5.61 (m, 2H), 5.16 (s, 1H), 5.07 (d, 1H, J=7.5 Hz), 4.00 (dd, 1H, J=10.4, 5.0 Hz), 3.48 (t, 1H, J=9.6 Hz), 3.36 (t, 1H, J=10.3 Hz), 3.13 (m, 1H), 1.78, 1.74 (s,

3H each). ^{13}C NMR (C_6D_6): δ 169.8, 169.3, 155.3, 137.8, 134.8, 130.7, 130.1, 129.3, 128.7, 128.4, 127.6, 127.4, 127.0, 126.7, 124.9, 119.1, 112.0, 101.8, 99.7, 78.3, 72.8, 72.2, 68.5, 66.6, 20.4, 20.3. HRMS calcd for $C_{27}H_{27}O_8$ (M+H) 479.1706, found 479.1682.

6.1.16. 2-(1-Iodonaphthyl) 4,6-*O*-benzylidene-2,3-di-*O*-acetyl-β-D-glucopyranoside (30). 2-Naphthyl 4,6-*O*-benzylidene-2,3-di-*O*-acetyl-β-D-glucopyranoside (**29**) (121 mg, 0.25 mmol), $In(OTf)_3$ (70 mg, 0.12 mmol) and molecular sieves 3 Å (1 g) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.275 mL, 0.28 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 2:1 heptane/EtOAc) to give 2-(1-iodonaphthyl) 4,6-*O*-benzylidene-2,3-di-*O*-acetyl-β-D-glucopyranoside (131 mg, 86%). Recrystallization from EtOAc/heptane gave an analytical sample of white crystals; mp 223.0–225.0 °C; $[\alpha]_D^{22}$ −100.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 1H, *J*=8.6 Hz), 7.82 (d, 1H, *J*=9.0 Hz), 7.77 (d, 1H, *J*=8.0 Hz), 7.57 (dt, 1H, *J*=8.5, 1.3 Hz), 7.48–7.43 (m, 3H), 7.39–7.37 (m, 3H), 7.31 (d, 1H, *J*=8.9 Hz), 5.57 (s, 1H), 5.50–5.40 (m, 2H), 5.31 (d, 1H, *J*=7.4 Hz), 4.45 (dd, 1H, *J*=10.5, 5.0 Hz), 3.92 (t, 1H, *J*=9.6 Hz), 3.89 (t, 1H, *J*=10.4 Hz), 3.74 (dt, 1H, *J*=9.7, 4.9 Hz), 2.12, 2.10 (s, 3H each). ^{13}C NMR ($CDCl_3$): δ 170.5, 169.8, 154.6, 136.9, 132.0, 131.1, 130.7, 129.5, 128.6, 128.5, 128.4, 126.4, 125.7, 116.5, 101.9, 100.8, 90.0, 78.2, 72.2, 72.1, 68.8, 67.0, 21.5, 21.1. HRMS calcd for $C_{27}H_{25}IO_8Na$ (M+Na) 627.0492, found 627.0530.

6.1.17. 2-Naphthyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (31). Peracetylated lactose (683 mg, 1.00 mmol) and 2-naphthol (231 mg, 1.6 mmol) were dissolved in CH_2Cl_2 (10 mL, filtered through Al_2O_3). $BF_3{\cdot}OEt_2$ (0.190 mL, 1.5 mmol) was added and the mixture was stirred for 60 min at room temperature under argon. Triethylamine (1.5 mL) was added and the mixture was concentrated and chromatographed (SiO_2, 1:2 heptane/EtOAc) to give 2-naphthyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (609 mg, 79%). Recrystallization from EtOAc/heptane gave an analytical sample of white crystals; mp 169.5–170.5 °C; $[\alpha]_D^{21}$ −19.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.80–7.71 (m, 3H), 7.46 (dt, 1H, *J*=7.1, 1.0 Hz), 7.39 (dt, 1H, *J*=7.0, 1.0 Hz), 7.32 (d, 1H, *J*=2.3 Hz), 7.16 (dd, 1H, *J*=8.9, 2.4 Hz), 5.37 (d, 1H, *J*=3.0 Hz), 5.32 (t, 1H, *J*=8.3 Hz), 5.26–5.19 (m, 2H), 5.14 (dd, 1H, *J*=10.4, 7.9 Hz), 4.98 (dd, 1H, *J*=10.4, 3.4 Hz), 4.55–4.49 (m, 1H), 4.53 (d, 1H, *J*=8.0 Hz), 4.19–4.07 (m, 3H), 3.92 (t, 1H, *J*=9.9 Hz), 3.92–3.88 (m, 2H), 2.16, 2.09 (s, 3H each), 2.07 (s, 12H), 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.52, 170.48, 170.3, 170.2, 169.9, 169.8, 169.3, 154.7, 134.2, 130.2, 129.8, 127.9, 127.2, 126.8, 124.8, 118.9, 111.5, 101.3, 98.9, 76.5, 73.00, 72.97, 71.7, 71.1, 70.9, 69.2, 66.8, 62.3, 61.0, 21.0, 20.92, 20.85, 20.8, 20.7. HRMS calcd for $C_{36}H_{42}O_{18}Na$ (M+Na) 785.2269, found 785.2239.

6.1.18. 2-(1-Iodonaphthyl) 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (32). 2-Naphthyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**31**) (188 mg, 0.25 mmol) and $In(OTf)_3$ (69 mg, 0.12 mmol) were dissolved in MeCN (5 mL). ICl (1 M in CH_2Cl_2, 0.275 mL, 0.28 mmol) was added dropwise and the mixture was stirred for 60 min at room temperature. Triethylamine (1.5 mL) followed by $Na_2S_2O_3$ (1.5 g) were added and the mixture was concentrated and chromatographed (SiO_2, 2:3 heptane/EtOAc) to give 2-(1-iodonaphthyl) 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (212 mg, 97%). Recrystallization from ether gave an analytical sample of white crystals; mp 195.0–196.0 °C; $[\alpha]_D^{21}$ −50.0 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, *J*=8.4 Hz), 7.78 (d, 1H, *J*=9.0 Hz), 7.75 (d, 1H, *J*=8.2 Hz), 7.56 (dt, 1H, *J*=6.9, 1.0 Hz), 7.44 (dt, 1H, *J*=7.9, 0.7 Hz), 7.29 (d, 1H, *J*=9.0 Hz), 5.37 (t, 1H, *J*=9.0 Hz), 5.36 (d, 1H, *J*=3.5 Hz), 5.31 (t, 1H, *J*=8.8 Hz), 5.17 (d, 1H, *J*=7.2 Hz), 5.14 (dd, 1H, *J*=10.4, 7.9 Hz), 4.98 (dd, 1H, *J*=10.4, 3.4 Hz), 4.56 (dd, 1H, *J*=11.8, 2.1 Hz), 4.55 (d, 1H, *J*=7.9 Hz), 4.18 (t, 1H, *J*=5.5 Hz), 4.15–4.08 (m, 2H), 4.01 (t, 1H, *J*=8.6 Hz), 3.91 (t, 1H, *J*=6.9 Hz), 3.86–3.83 (m, 1H), 2.16, 2.12, 2.11, 2.08, 2.07, 2.06, 1.97 (s, 3H each). ^{13}C NMR ($CDCl_3$): δ 170.5, 170.4, 170.3, 170.2, 169.9, 169.7, 169.2, 154.5, 135.5, 131.9, 131.0, 130.5, 128.5, 128.3, 125.6, 116.6, 101.3, 99.8, 90.0, 76.2, 73.1, 71.4, 71.1, 70.9, 69.2, 66.8, 62.0, 61.0, 21.4, 21.0, 20.9, 20.81, 20.80, 20.78, 20.7. HRMS calcd for $C_{36}H_{41}IO_{18}Na$ (M+Na) 911.1235, found 911.1212.

Figure 2. General procedure for NMR reactions with mesitylene. To CD_3CN (0.4 mL) were added mesitylene (**17**) (0.0025 mL, 0.018 mmol) and $Cu(OTf)_2$ (0.25–1.0 equiv). The reaction was initiated by the addition of IBr (0.018 mL, 1.0 M in CH_2Cl_2). The NMR spectrum of bromomesitylene was in agreement with published data.

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