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p-tert-Butyl Groups Improve the Utility of Aromatic Protecting Groups in Carbohydrate Synthesis

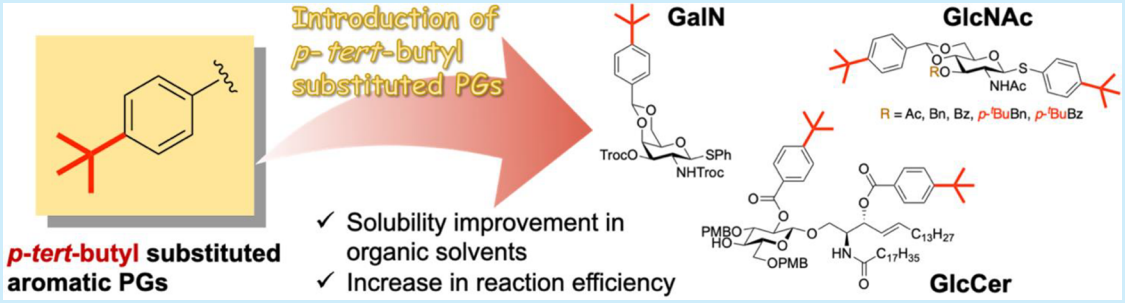
Sachi Asano,[‡,§] Hide-Nori Tanaka,[†,‡] Akihiro Imamura,[‡,§] Hideharu Ishida,[†,‡,§] and Hiromune Ando*[,†,‡]

[†]Center for Highly Advanced Integration of Nano and Life Sciences (G-CHAIN), Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

[‡]The United Graduate School of Agricultural Science, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

[§]Department of Applied Bioorganic Chemistry, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

Supporting Information



ABSTRACT: Aromatic protective groups are widely used in carbohydrate synthesis owing to their numerous merits. However, they unpredictably make certain compounds insoluble in organic solvents owing to their π-stacking abilities. It was found that introducing a *tert*-butyl group onto the aryl moiety improves the solubility of highly insoluble carbohydrate derivatives, such as those of *N*-acetylglucosamine. In this study, *tert*-butyl-substituted aromatic protecting groups are demonstrated to work as well as the original unsubstituted form, while improving the efficiency of glycosylations.

In organic synthesis, protective groups (PGs) serve to distinguish intended reaction sites from other comparably reactive moieties.[1] The methods for the introduction and removal of PGs need to be compatible with other functional groups in the synthetic unit, and the installed PGs must be unaffected during the entire process of molecular assembly and transformation. Therefore, feasible syntheses of highly functionalized molecules largely depend on the use of well-chosen PG combinations. PGs for carbohydrate synthesis are particularly important because the chemical properties of the PGs used can have profound effects on the reactivities of glycosylation substrates and the stereoselectivities of glycosylation reactions.[2−4]

More importantly, PGs are indispensable for converting hydrophilic saccharides into hydrophobic forms. In practice, the synthesis of carbohydrates is often complicated by the poor solubilities of saccharide units in organic solvents, which hinder transformation reactions and product purification. Empirically, the installation of fixed aromatic substituents, such as benzylidene acetals, phenyl (thio)ethers, benzoyl esters, and phthalimides, can dramatically decrease the solubilities of saccharides in organic solvents. This is often due to enhanced $\pi-\pi$ (or CH$-\pi$) stacking aggregation. Accordingly, this issue limits the choices of PGs and glycosylation methods, thereby restricting the scope of carbohydrate synthesis. Despite these drawbacks, aromatic PGs are widely employed in carbohydrate synthesis because of their otherwise excellent utility.

Benzyl and phenyl ether groups are chemically stable, and most are selectively removable. Benzylidene acetals are the PGs of choice for protecting the two hydroxyl groups in 1,3-diols simultaneously, and they can be removed easily under acidic conditions. Furthermore, they are convertible into the corresponding benzoyl esters or benzyl ethers via oxidative or reductive opening reactions, respectively, to regioselectively give just one free hydroxyl group.

The benzoyl (Bz) group is the most widely used acyl group in PGs. This is largely because the moderately bulky phenyl moiety adjacent to the carbonyl of the Bz group facilitates its kinetically controlled regioselective installation onto one of several hydroxyl groups in a sugar compound. More importantly, the neighboring effects of Bz groups are frequently exploited for 1,2-*trans*-selective glycosylations because the bulkiness of the phenyl moiety suppresses *ortho*-ester formation from the acyloxonium cation intermediate. Furthermore, the UV absorptivity of aromatic PGs facilitates reaction monitoring and product purification.

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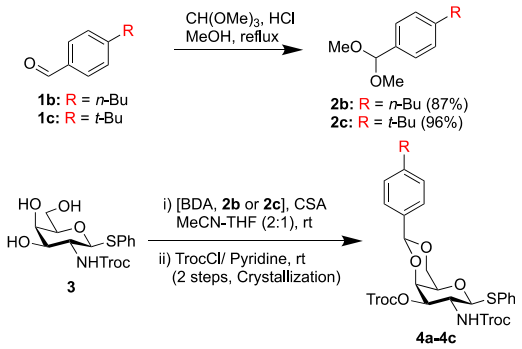
In this Letter, we present a solution to the aforementioned solubility issues associated with aromatic protecting groups in carbohydrate synthesis. Our strategy involves the use of *p-tert*-butyl-substituted aromatic PGs, and its utility is demonstrated through glycan synthesis.

As a means to improve the utility of aromatic PGs, we envisioned that simply introducing an alkyl substituent at the aromatic ring of the PG would prevent self-aggregation of aromatic PG-loaded compounds via $\pi-\pi$ or CH$-\pi$ interactions. We assumed that *p*-substitution would be most appropriate, as it would minimize the steric influence of the alkyl group on the reaction site during the introduction and removal of the PG.

To evaluate the efficacy of our strategy, we chose the benzylidene (Bzld)-protected galactosamine (GalN) derivative **4a**[5] as a poorly soluble standard, which was then compared with *p-n*-butyl- and *p-tert*-butyl-substituted derivatives (**4b** and **4c**, respectively) in terms of solubility in EtOH. To synthesize **4a**–**4c**, GalN derivative **3** underwent 4,6-acetalization with benzaldehyde dimethylacetal, **2b**, and **2c**, and introduction of Troc group at O-3 position (Scheme 1).

Scheme 1. Synthesis of GalN Derivatives 4a–4c[a]



[a]BDA = benzaldehyde dimethylacetal. CSA = (±)-10-camphorsulfonic acid. Troc = 2,2,2-trichloroethoxycarbonyl.

Solubility in EtOH was determined by following a previously reported procedure.[6] An excess amount of each derivative was suspended in EtOH (>1 mL) at 40 °C. The suspension was then cooled to room temperature and filtered to provide a saturated solution. Solubility (mg/mL) in EtOH was then obtained from the mass of the residue obtained upon evaporating 1 mL of the saturated solution.

As shown in Table 1, the solubility of Bzld-protected **4a** is dramatically improved by the introduction of a *p-tert*-butyl group. Accordingly, **4c** exhibits excellent solubility.

The particle size (diameter) of the solute in EtOH was measured using dynamic light scattering (DLS).[7] This revealed

Table 1. Solubilities, Particle Sizes, and mps of Bzld-Protected Galactosamine Derivatives in This Study[a]

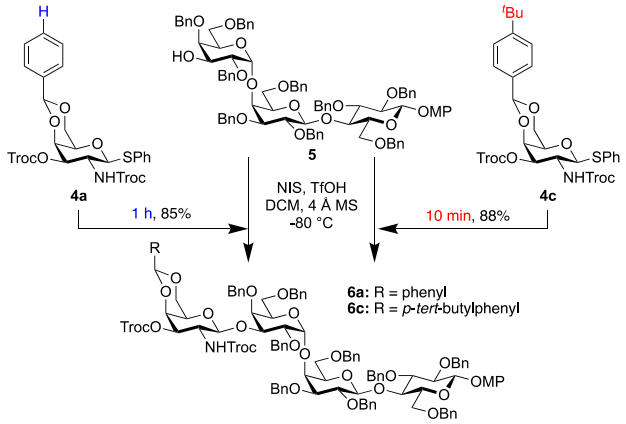
compound	solubility[b] (mg/mL)	particle size[c] (nm)	mp (°C)
4a (R = H)	22.1	199.8	189–194
4b (R = *n*-Bu)	30.8	243.3	183–188
4c (R = *t*-Bu)	149.2	1.0	141–147

[a]All data were obtained by single measurement. [b]Solubility in EtOH. [c]5 mg/mL in EtOH. Measured by a Zetasizer Nano ZS (Malvern Instruments, Ltd., UK).

that the solubility of compound **4c** is increased by a factor of 6.9 compared to that of **4a**. Particle size measurement also revealed the distinctly different solubilities of the compounds. In line with these results, the melting point (mp) of **4c** is significantly lower than those of **4a** and **4b**, further indicating that the bulky structure of the *p-tert*-butyl group disrupts its crystal packing.[8]

Given the high solubility of **4c**, we next examined the efficacy of **4c** as a glycosyl donor in comparison with **4a** (Scheme 2). Trisaccharide **5** was coupled with each donor in

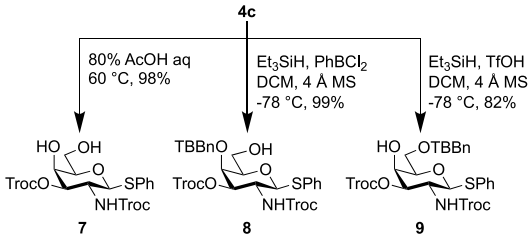
Scheme 2. Glycosylation of Trisaccharide 5



CH_2Cl_2 at −80 °C in the presence of *N*-iodosuccinimide (NIS)-TfOH. Despite its poor solubility (soluble in CH_2Cl_2 at 25 °C but partially precipitated at −80 °C), **4a** reacted with **5** to give tetrasaccharide **6a** in 85% yield after 1 h. In contrast, **4c** reacted much more rapidly, completing the reaction in 10 min with a similar glycosidation yield. Thus, **4c** serves as a highly effective glycosyl donor due to its high solubility in the reaction medium.

Next, we investigated the cleavage and transformation of the *p-tert*-butyl-substituted benzylidene acetal (Scheme 3) employ-

Scheme 3. Manipulation of the TBBzld Group



ing procedures commonly used for benzylidene groups. The protecting group on **4c** was almost quantitatively hydrolyzed in 80% aqueous acetic acid at 60 °C to give its 4,6-diol derivative **7**. Regioselective reductive ring opening was also successfully performed to afford the *p-tert*-butylbenzyl (TBBn)-protected derivative. Treatment of **4c** with $Et_3SiH/PhBCl_2$[9] afforded 4-*O*-TBBn derivative **8** in 99%, while 6-*O*-TBBn isomer **9** was generated upon treatment with $Et_3SiH/TfOH$.[10] These results indicate that *p-tert*-butyl substitution of the 4,6-*O*-benzylidene group improves the solubilities of the corresponding carbohydrate derivatives in organic solvents while retaining the properties of the benzylidene group.

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Inspired by these results, we examined the efficacy of *tert*-butyl substitution for other aromatic PGs such as Bn, Bz, and phenyl thioether. We used *N*-acetylglucosamine (GlcNAc) as a model monosaccharide as it is known for its exceptionally poor solubility, which is due to its extensive intermolecular hydrogen bonding and CH−π interactions.[11]

We used the phenylthioglycoside of 4,6-benzylidenated GlcNAc (**10a**), which is insoluble in EtOH, as the benchmark. Sixteen GlcNAc derivatives (**10a**−**13d**) were prepared (Figure 1), and their solubilities, mps, and particle sizes were

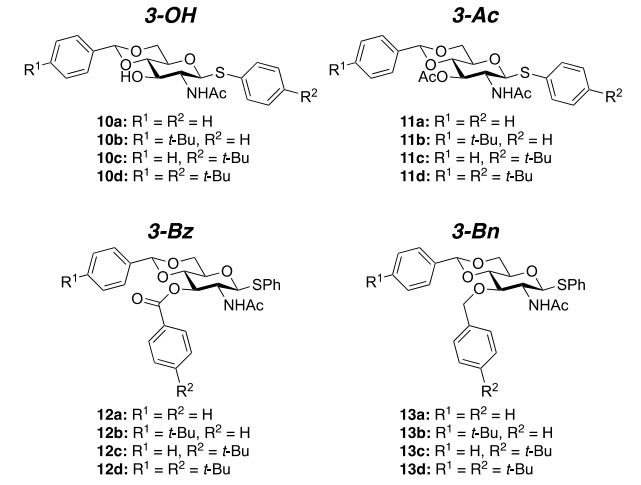


Figure 1. GlcNAc derivatives used in this study.

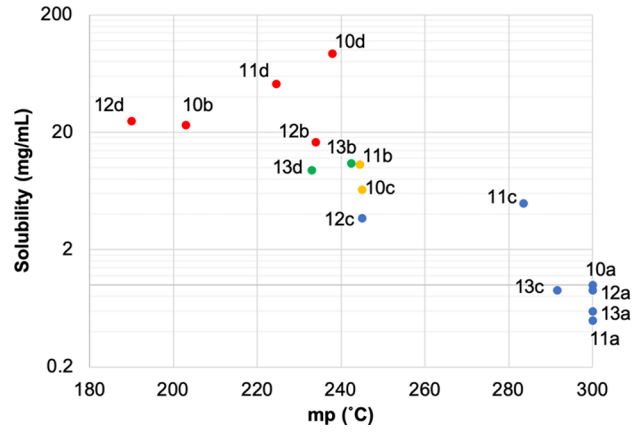
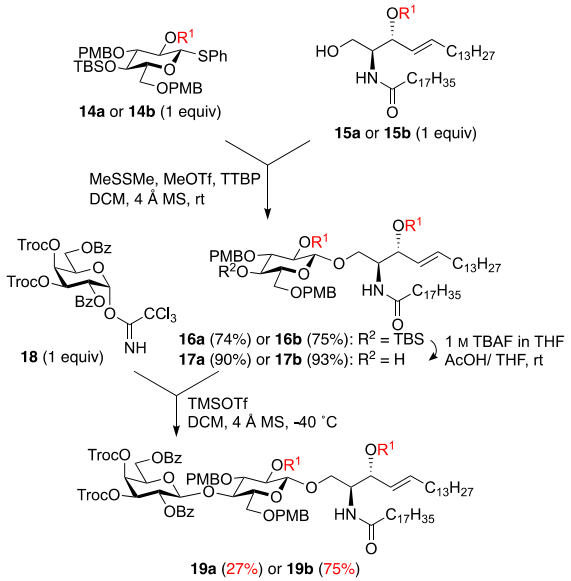


Figure 2. Relationships between mp, solubility, and particle size of GlcNAc derivatives. The colors of the data points indicate their particle diameters (∼1.0 nm (red), ∼300 nm (yellow), ∼1000 nm (green), and N.D. (blue)).

measured. The scatter diagram in Figure 2 indicates the considerable correlation among these parameters. Again, TBBzld introduction (**10b**, **11b**, **12b**, and **13b**) improves the solubility of the corresponding Bzld-protected derivatives to a large extent. These results are in contrast to *p*-nitrophenyl *O*-glycoside of GlcNAc.[11b] While *p*-*tert*-butyl-substituted phenylsulfenyl (**10c** and **11c**), Bz (**12c**), and Bn (**13c**) groups exert weak effects, their incorporation in combination with the TBBzld group was found to be significantly effective. Comparison between compounds **12c**−**12d** and **13c**−**13d** revealed the higher efficiency of the *p*-*tert*-butyl Bz (TBBz) group than that of the *p*-*tert*-butyl Bn group. Thus, these results indicate that not only TBBzld groups but also other *p*-*tert*-butyl substituted aromatic PGs are effective for improving the solubility of carbohydrate derivatives in organic solvents. The drastic decrease in the particle diameters implies that supramers[12] would be less likely to form in the solutions of **12b** and **10d**−**12d** due to the bulkiness of the *tert*-butyl group.

Further inspired by the potential of the TBBz group, we employed TBBz groups for the synthesis of the extensively hydrophobic molecule lactosyl ceramide (LacCer) (Scheme 4). For the construction of the β-glycoside from Glc and Cer,

Scheme 4. Glycosylation of a Glc-Cer Acceptor[a]



[a]**14a**−**17a**, **19a**: R^1 = Bz. **14b**−**17b**, **19b**: R^1 = TBBz. TTBP = 2,4,6-tri-*tert*-butylpyrimidine.

TBBz group was utilized in the Glc donor **14b** as a neighboring group to impart β-selectivity. The glycosidation of **14b**, which was promoted by dimethyl(methylthio)sulfonium trifluoromethanesulfonate generated in situ,[13] produced β-glucosyl ceramide **16b** in a comparable yield to that obtained with the 2-*O*-Bz Glc donor without producing the stereoisomer or the orthoester. Compound **16b** was then converted into Glc-Cer acceptor **17b** having two TBBz groups.

As expected, the solubility of **17b** is significantly improved compared with that of the known GlcCer acceptor **17a**[5] protected with two Bz groups, and thereby **17b** undergoes glycosylation with the galactosyl donor **18** in CH_2Cl_2 at −40 °C, yielding LacCer derivative **19b** in high yield. In contrast, the low solubility of **17a** (soluble in CH_2Cl_2 at 25 °C but largely precipitated at −40 °C) depresses the glycosylation yield at the same temperature.

These results demonstrate that the TBBz group is a promising alternative to the Bz group widely used in carbohydrate chemistry, not only for improving the solubility of glycosylation units but also for directing 1,2-*trans*-glycosidation. The high solubility at low temperature endowed by TBBz groups as well as other *tert*-butyl-substituted aromatic PGs may enable solvent effects (e.g., nitrile solvent effect, ethereal solvent effect) to be exploited during glycosylation reactions and help to suppress side-reactions during chemical transformations.

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In summary, we have found *p-tert*-butyl substitution of aromatic PGs effective as a strategy to improve the solubility of carbohydrate derivatives in organic solvents. This methodology would be useful for various oligosaccharide syntheses, especially for impeding the intra- and intermolecular hydrophobic interactions of protected oligosaccharides composed of repeating sugar residues. *tert*-Butyl-substituted aromatic PG could be employed as the equivalents of parent aromatic PGs, which are thus highly compatible with established strategies of carbohydrate synthesis. The concept described in this Letter may be extendable to the syntheses of polar or aggregate compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01372.

Additional experimental details and characterization data for all new compounds with their ^{1}H and ^{13}C spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hando@gifu-u.ac.jp.

ORCID

Hide-Nori Tanaka: 0000-0001-5307-4909

Hiromune Ando: 0000-0002-0551-0830

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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