CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201200234

Preparation of THP-Ester-Derived Pyridinium-Type Salts and their Reactions with Various Nucleophiles

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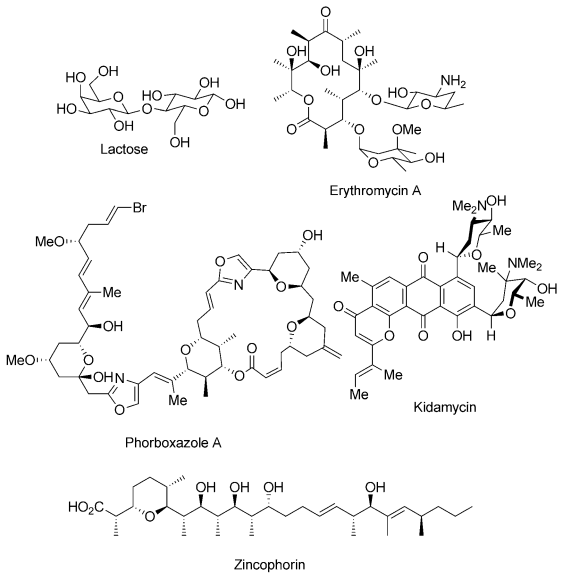
Abstract: Nucleophilic substitution at the anomeric positions of tetrahydropyranyl (THP) and related carbohydrate-derived esters that proceeded through pyridinium-type salt intermediates have been developed. Treatment of the 6-substituted α-acetoxy-tetrahydropyrans with TMSOTf (TMS = trimethylsilyl) and 2-substitutited pyridines, such as 2-*p*-tolylpyridine and 2-methoxypyridine, led to the efficient generation of *cis*-pyridinium-type salts. These salts reacted with various nucleophiles, such as alcohols, azides, and organozinc reagents, to form nucleophilic-substitution products. A characteristic feature of these processes was that they took place under mild conditions, which did not affect acid-labile protecting groups. Furthermore, the reactions that employed azides and C-nucleophiles generated 2,6-*trans* products with high degrees of stereoselectivity.

Keywords: nucleophilic substitution · protecting groups · salt effect · synthetic methods · tetrahydropyran

Introduction

Many biologically active natural products contain 2,6-disubstituted tetrahydropyranyl (THP) systems, such as dissakalaides, erythromycin A,[1a] kidamycin,[1b] phorboxazole A,[1c] and zincophorin (Scheme 1).[1d] Typical methods to construct these types of substituted frameworks use nucleophilic-substitution reactions at the anomeric position (2-position) of THP ethers or esters. For example, various O-, N-, and C-nucleophiles, including allylsilanes, silyl enol ethers, and arenes, can be introduced at the anomeric positions of THPs by using Lewis-acid-promoted reactions through the nucleophilic capture of oxocarbenium-ion intermediates (Scheme 2).[2] However, processes of this type cannot be applied to substrates that contain acid-labile groups. The same limitation applies to glycosylation reactions, in which a promoter, such as a Lewis acid, is required to promote the reaction between a glycosyl donor and acceptor.

In recent years, new glycosylation processes that rely on pre-activation strategies have garnered considerable attention (Scheme 3).[3] This general approach, which involves activation of the donor prior to the addition of the glycosyl acceptor, possesses numerous benefits, including the ability to control chemical and stereochemical selectivities. In this context, we recently developed a method to activate acetals for nucleophilic-substitution reactions that involved the treatment of these substances with TESOTf (TES = triethylsilyl) and pyridines, such as 2,4,6-collidine (Scheme 4). The overall reaction proceeded through the formation of a pyridinium-type salt intermediate, which then underwent nucleophilic-substitution reactions with heteroatom-containing nucleophiles, such as H_2O,[4] alcohols, azides, and thiols.[5] This strategy has also been applied to C–C bond-forming processes, wherein Gilman reagents were employed as C-nucle-



Scheme 1. Examples of bioactive natural products that contain 2,6-disubstituted THP groups.

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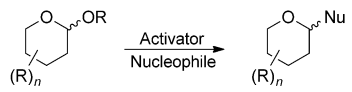
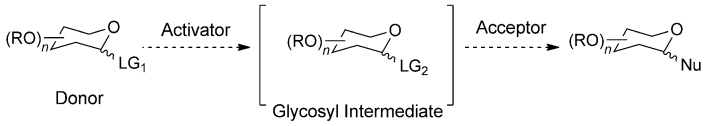
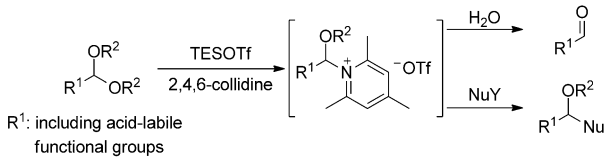
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201200234.



Scheme 2. Introduction of nucleophiles at the anomeric positions of THPs.

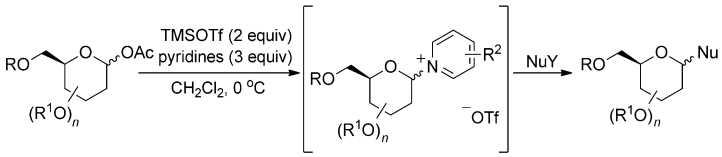


Scheme 3. Pre-activation method for the introduction of nucleophiles at the anomeric positions of THPs.



Scheme 4. Nucleophilic-substitution reactions of acetals.

ophiles in reactions with the intermediate pyridinium-type salts.[6] Moreover, this method employed almost neutral conditions and, as a result, even acid-labile functionalities, such as a trityl (Tr) group, were tolerated. In a recent investigation, we applied this strategy, which was regarded as a pre-activation strategy, for the introduction of nucleophiles, such as alcohols, azides, and C-nucleophiles, onto the anomeric centers of 6-alkoxymethyltetrahydropyranyl esters, including carbohydrate derivatives (Scheme 5).



Scheme 5. Pre-activation strategy for promoting nucleophilic-substitution reactions at the anomeric centers of 6-alkoxymethyltetrahydropyranyl esters.

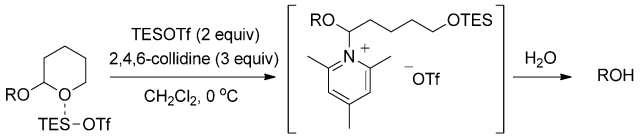
Abstract in Japanese:

THP エステル由来ピリジニウム塩中間体を経由する求核種導入反応を開発した。本反応では、基質をTMSOTf と２位置換ピリジンで処理すると系中でシス体のピリジニウム塩が選択的に生成する。その後、この塩中間体に対しアルコールなどの求核種を加えることで、アノマー位へ求核種導入できる。また、本反応は緩和な条件下進行するため、酸に不安定な基質にも適用可能である。さらに、求核種にアジドや有機亜鉛試薬を用いた場合、トランス選択的に求核種が導入できることも見出した。

Results and Discussion

Preparation of THP Pyridinium-type Salts

Initially, we investigated the conditions required to prepare THP pyridinium-type salts from the reactions of THP ethers with TESOTf and pyridines. A major issue in these processes concerned the selectivity of the reactions that involved two different ether oxygen centers in THP ethers. Importantly, the selective coordination of silyltriflate to the exocyclic oxygen was required to form THP pyridinium-type salts that would participate as intermediates in anomeric-substitution reactions. However, our previous investigation of the deprotection of THP ethers suggested that the endocyclic oxygen center in these substances was more reactive. Specifically, we observed the selective coordination of TESOTf to the less-hindered endocyclic oxygen of THP-protected alcohols, followed by displacement with 2,4,6-collidine to form the ring-opened pyridinium-type salt, which subsequently reacted with H_2O to give the deprotected alcohol (Scheme 6).[7]

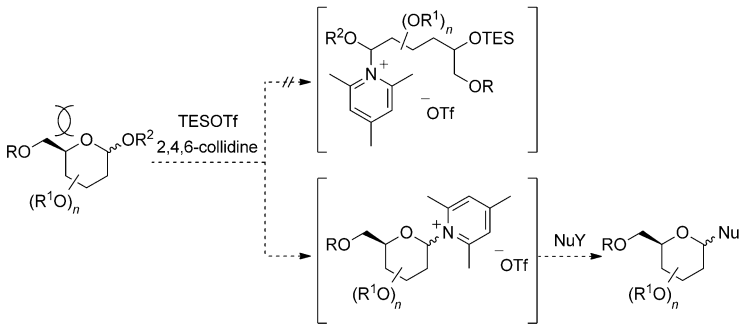


Scheme 6. Deprotection of THP ethers by using a combination of TESOTf and 2,4,6-collidine.

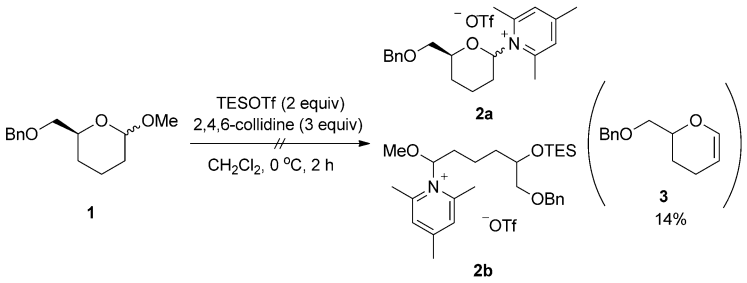
In contrast, we anticipated that, when this procedure was applied to 6-alkoxymethyl-substituted tetrahydropyran derivatives, TESOTf coordination would occur selectively at the less-sterically encumbered exocyclic oxygen and, as a result, that pyridinium-salt formation and subsequent nucleophilic displacement would take place at the THP anomeric center (Scheme 7).

To explore this proposal, we investigated the reaction of 6-benzyloxymethyl-substituted THP methyl ether **1** with TESOTf and 2,4,6-collidine (Scheme 8). We observed that collidinium salts **2a** and **2b** were not generated in this process but instead a small quantity of enol ether **3** was obtained. Based on the thought that the failure of this process might be a consequence of the poor leaving ability of the methoxy group, we probed the reaction of 2-acetoxy derivative **4** with TESOTf and 2,4,6-collidine, followed by the addition of EtOH. However, again, the reaction led to the formation of enol ether **3** as the major product along with small amounts of THP ethyl ether **5a**. Although the use of TMSOTf instead of TESOTf led to a slightly improved yield of compound **5a**, the major product was still enol ether **3** (Scheme 9).

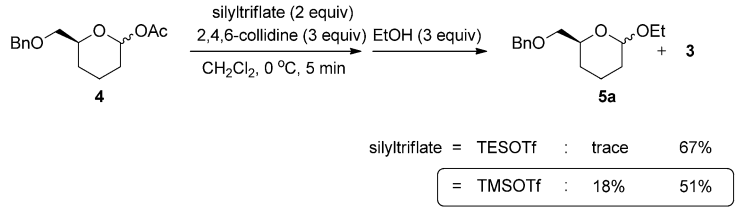
The low yield of substitution product **5a** compared to enol ether **3** in the reaction of THP ester **4** suggested that the nucleophilic-substitution reaction of the silyltriflate complex was slower than β-elimination, owing to the high basicity and low nucleophilicity of 2,4,6-collidine. To investigate



Scheme 7. Selective nucleophilic substitution of 6-alkoxymethyltetrahydropyranyl ethers at their anomeric positions.



Scheme 8. Reaction of THP ether **1** with TESOTf and 2,4,6-collidine.



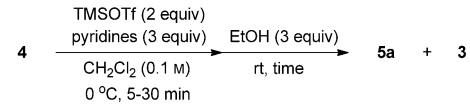
Scheme 9. Reaction of THP ester **4** with silyltriflate and 2,4,6-collidine, followed by the addition of EtOH.

this issue further, we performed the reactions of compound **4** with TMSOTf and other pyridines (Table 1). These results showed that the use of 2,6-lutidine was not effective (Table 1, entry 2) but that, when the less-bulky 2-picoline was used, the pyridinium-type salt was efficiently formed and reacted with EtOH to produce compound **5a** in 73% yield, although a long reaction time was required (Table 1, entry 3). However, the reaction with 2,2′-bipyridyl, which is known to be an efficient base for the transformations of methoxymethyl (MOM) ethers into alcohols[8] and methylene acetals into 1,2- or 1,3-diols,[9] gave compound **5a** in almost the same high yield but in a much shorter reaction time (Table 1, entry 4). The use of other 2-substituted pyridines, including 2-phenylpyridine and 2-*p*-tolylpyridine, also led to minimization of the contribution of β-elimination and efficiently generated compound **5a** as the main product (Table 1, entries 5 and 6). Finally, a highly stable pyridinium salt was formed when pyridine was used and a long reaction time was required for its conversion into compound **5a** (Table 1, entry 7).

The formation of pyridinium-type salt intermediates in the substitution-reaction pathway was demonstrated by using HRMS (FAB; Scheme 10). MS (FAB+) analysis of the mixture from the reaction of compound **4** with TMSOTf (2 equiv) and 2-*p*-tolylpyridine (3 equiv) in CH_2Cl_2 (0.1 M) showed a $[M]^+$ peak at *m*/*z* 374.2115 with a molecular formula of $C_{25}H_{28}NO_2$, which corresponded to 2-*p*-tolylpyridinium salt **6**. Importantly, a $[M]^+$ peak owing to 2-*p*-tolylpyridinium salt **7**, which would have been produced from a reaction initiated by complexation of the endocyclic oxygen, was not observed. In addition, a $[M]^+$ peak that was associated with the glycosyl triflate **8** was not found.

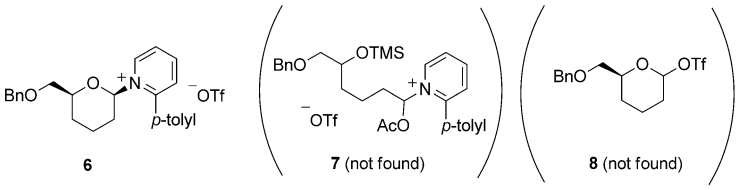
Analysis of the ^{1}H NMR spectra of starting THP ester **4** (*cis*/*trans* = 1:1.5) and the mixture that was formed by the reaction of this THP ester with TMSOTf and 2-*p*-tolylpyridine in CD_2Cl_2 (Figure 1, also see the Supporting Information) demonstrated that complete conversion of the substrate took place to form the pyridinium-type salt intermediate. Furthermore, the presence of a doublet-of-doublets (J = 10.0

Table 1. The use of various pyridines in the TMSOTf-promoted reactions of THP ester **4** with EtOH.



Entry	Pyridines	t	Yield [%] of **5a** (*trans*/*cis*)[a]	Yield [%] of **3**
1	2,4,6-collidine	2 h	18 (64:36)	51
2	2,6-lutidine	5 min	trace	65
3	2-picoline	27 h	73 (63:37)	9
4	2,2′-bipyridyl	15 min	71 (71:29)	16
5	2-phenylpyridine	30 min	83 (68:32)	trace
6	2-*p*-tolylpyridine	30 min	86 (67:33)	trace
7	pyridine	4 d[b]	30 (65:35)	trace

[a] Stereoisomeric ratios were determined by using ^{1}H NMR spectroscopy; [b] unreacted pyridinium salt remained.



Scheme 10. Possible intermediates in the reaction of compound **4** with TMSOTf and 2-*p*-tolylpyridine.

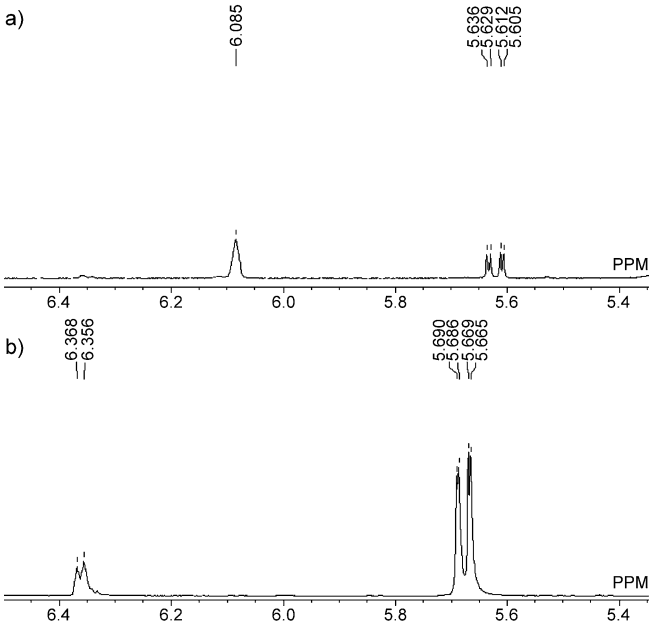
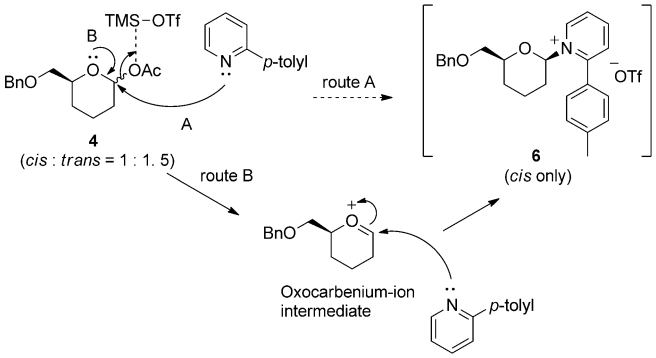
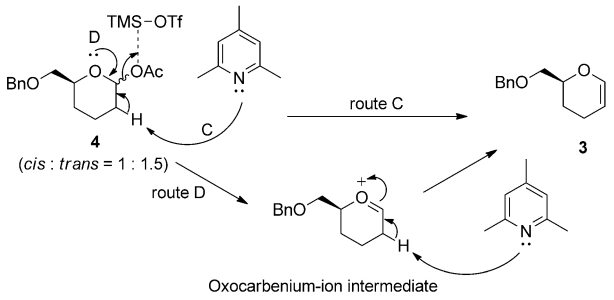


Figure 1. ^{1}H NMR spectra of: a) THP ester **4**, b) the mixture produced by its reaction with TMSOTf and 2-*p*-tolylpyridine.



Scheme 11. A plausible mechanism for formation of pyridinium-type salts in the TMSOTf-promoted reactions of THP ester **4**.



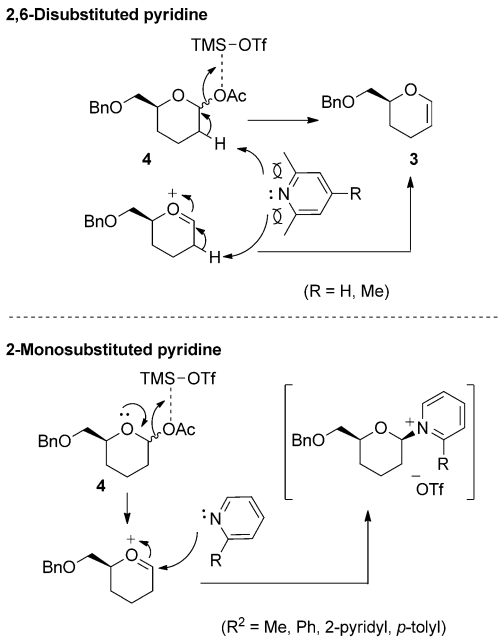
Scheme 12. Plausible mechanisms for formation of enol ether **3** in the TMSOTf-promoted reactions of THP ester **4**.

and 2.0 Hz) at $\delta = 5.68$ ppm demonstrated that the anomeric proton was axial. The signal at $\delta = 6.34$ ppm did not correspond to an equatorial 2-proton in the pyridinium-type salt intermediate but rather the α-proton of enol ether **3**, which was formed during the acquisition of the NMR spectra at room temperature, owing to the instability of the pyridinium-type salt to generate enol ether **3** above 0 °C. These results showed that the 2-*p*-tolylpyridine group in the salt adopted an equatorial orientation and that the salt possessed 2,6-*cis* stereochemistry. It has been previously reported that equatorial THP 2-pyridinium-type salts are favored.[10]

Based on these observations, we proposed a mechanism (Scheme 11) for the formation of the salt intermediate in the TMSOTf-promoted reaction of THP ester **4**. Because a *cis*/*trans* ratio of 1:1.5 of compound **4** was not reflected in pyridinium-type salt **6** (*cis* only), salt-formation did not appear to occur via route A, which involved the S_N2-type concerted nucleophilic addition of 2-*p*-tolylpyridine and the elimination of acetate. Instead, a pathway (route B) in which the reaction proceeded through the formation of, and pyridine addition to, an oxocarbenium-ion intermediate was more likely. Enol ether **3** was generated in this process by either E_2 elimination (route C) or pyridine-induced deprotonation of the oxocarbenium-ion intermediate (route D; Scheme 12). Independent of which pathway was involved in the enol-ether formation, the steric bulk of the pyridine derivative would be a governing factor in determining the yield of the substitution product. In the case of 2,6-disubstituted pyridines, such as 2,4,6-collidine and 2,6-lutidine, enol ether **3** was produced by one of the elimination pathways, whereas the reactions that used less-hindered 2-monosubstituted pyridines, such as 2-*p*-tolylpyridine, afforded the desired substitution products (Scheme 13).

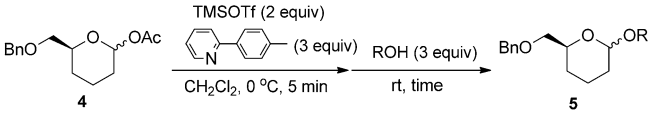
Use of Alcohol Nucleophiles

Having established optimized conditions (TMSOTf-2-*p*-tolylpyridine) for the substitution reaction of THP ester **4**, the scope of this substitution process was investigated with a variety of alcohols (Table 2). Alcohols other than EtOH (Table 2, entry 1), including benzyl and secondary alcohols (Table 2, entries 2 and 3), participated in this reaction to form their corresponding THP ethers in high yields. When the less-nucleophilic phenol was used, the desired product (**5d**) was generated in moderate yield (Table 2, entry 4). Moreover, when propargyl alcohol was the nucleophile, the reaction proceeded with high efficiency (Table 2, entry 5). In all cases, 2,6-*trans* products were formed in higher yields than their corresponding 2,6-*cis* isomers.[11]



Scheme 13. Effects of the steric bulk of the pyridine derivative on TMSOTf-promoted reactions of THP ester **4**.

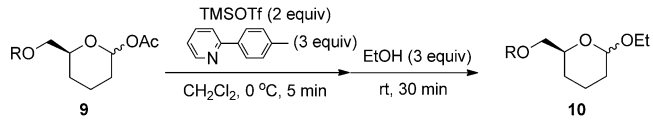
Table 2. Reaction of **4** with various alcohols.



Entry	R	*t*	**5**	Yield [%]	*trans*/*cis*[a]
1	Et	30 min	**5a**	86	67:33
2	Bn	1 h	**5b**	88	79:21
3	*i*Pr	30 min	**5c**	80	71:29
4	Ph	1 h	**5d**	43	77:23
5	propargyl	30 min	**5e**	83	85:15

[a] Stereoisomeric ratios were determined by using ^{1}H NMR spectroscopy.

Table 3. Reactions of compound **9** with EtOH.

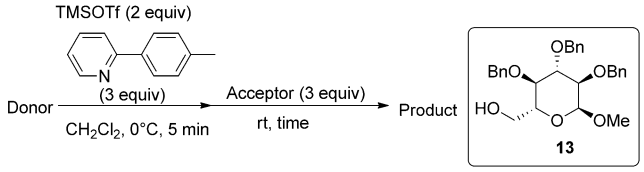


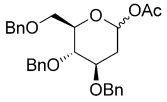
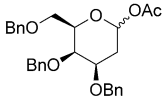
Entry	R	**9** (*trans*/*cis*)	**10**	Yield [%]	*trans*/*cis*[a]
1	TBS	**9a** (37:63)	**10a**	80	73:27
2	Tr	**9b** (34:66)	**10b**	76	74:26

[a] Stereoisomer ratios were determined by using ^{1}H NMR spectroscopy.

Further studies of this process found that acid-labile groups, such as TBS and trityl ethers, were stable under the reaction conditions (Table 3, entries 1 and 2). Because the previously reported methods for promoting these types of substitution reactions employed acidic conditions that did not tolerate the presence of acid-labile groups,[12] this result demonstrated the power of this procedure.

Table 4. Reaction of sugar derivatives.



Entry	Donor	Acceptor	*t* [h]	Product	Yield [%] (α/β)[a]
1		EtOH	3	**14a**	73 (45:55)
2	**11** (α:β =83:17)	**13**	3	**14b**	57 (62:38)
3		EtOH	2	**15a**	88 (63:37)
4	**12** (α:β =50:50)	**13**	3	**15b**	65 (85:15)

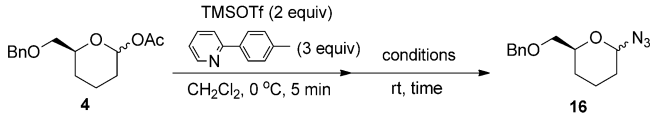
[a] Stereoisomeric ratios were determined by using ^{1}H NMR spectroscopy.

The reactions of 2-deoxysugar derivatives were also examined (Table 4).[13] 2-Deoxyglucose derivative **11** and 2-deoxygalactose derivative **12** reacted smoothly with EtOH to form their respective glycosidic ethers (Table 4, entries 1 and 3). Glucose derivative **13**, which possessed a free primary alcohol group, also served as a nucleophile in this process (Table 4, entries 2 and 4). These findings showed that this method could be applied to the synthesis of disaccharides.

Use of Azide as a Nucleophile

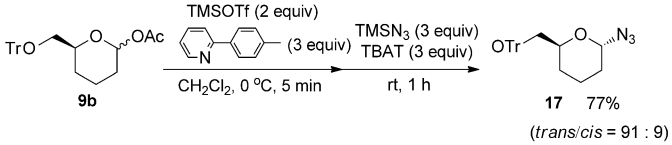
The use of this method for the formation of glycosyl azide was also probed. Under the optimized conditions, which have previously been shown to be applicable to the formation of *N*,*O*-acetal,[5] THP ester **4** reacted with NaN_3 in the presence of [18]crown-6 to form their corresponding azide (**16**) in excellent yield (Table 5, entry 1). Moreover, by using a combination of $TMSN_3$ and tetrabutylammonium difluorotriphenylsilicate (TBAT) to promote this process, the formation of the desired product (**16**) occurred in excellent yield with high *trans* selectivity (Table 5, entry 4).

Table 5. Reaction conditions.



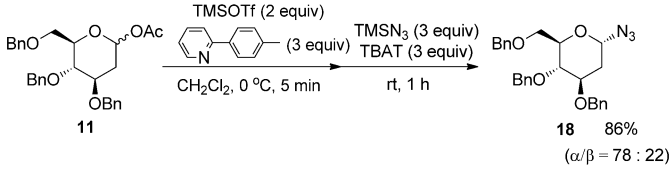
Entry	Conditions	*t* [min]	Yield [%]	*trans*/*cis*[a]
1	NaN_3, [18]crown-6	60	88	65:35
2	$TMSN_3$	–	N.R.	–
3	$TMSN_3$, TBAF	30	60	>95:5
4	$TMSN_3$, TBAT	5	88	>95:5

[a] Stereoisomeric ratios were determined by using ^{1}H NMR spectroscopy. N.R. = no reaction.



Scheme 14. Reaction of THP ester **9b** with $TMSN_3$ and TBAT.

Next, this azidation process was applied to THP ester **9b**, which contained a trityl group (Scheme 14). The desired product (**17**) was formed without the loss of the acid-labile trityl group in moderate yield with high diastereoselectivity. The reaction of a pyridinium-type salt that was derived from 2-deoxyglucose derivative **11** with $TMSN_3$ and TBAT also proceeded efficiently to form the desired azide product but with only moderate diastereoselectivity (Scheme 15). These



Scheme 15. Reaction of glycosyl ester **11** with $TMSN_3$ and TBAT.

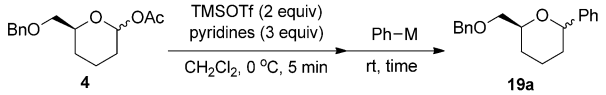
findings showed that this mild and high-yielding method can be used to prepare glycosyl azides, which are potentially useful substrates in click chemistry[14] and Staudinger ligation[15] approaches for the generation of glycoarrays[16] and glycoconjugates.[17]

Use of C-Nucleophiles

Finally, we considered the use of C-nucleophiles in substitution reactions with pyridinium-type salts that were derived from THP and other related esters.[18–21] The 2-*p*-tolylpyridinium salt of compound **4** did not react with the Gilman reagent (Ph_2CuLi), which was previously observed to participate in similar alkylation reactions of acetals (Table 6, entry 1).[6] Phenyl lithium and phenyl magnesium bromide also did not react to yield substitution products (Table 6, entries 2 and 3). On the other hand, the reaction of diphenylzinc (Ph_2Zn) with the pyridinium-type salt of THP ester **4** produced the desired product (**19a**) in 40% yield (Table 6, entry 4). Importantly, the 2,6-*trans*/*cis* diastereomeric ratio of the product was >95:5. Thus, the nature and level of the stereoselectivity were similar to those by using Lewis-acid-promoted methods.[18a] Exploration of the addition of diphenylzinc to several pyridinium-type salts showed that the reaction of the one salt that was derived from 2-methoxypyridine and compound **4** was optimal (Table 6, entry 5).

With the optimized conditions in hand, the scope of the substitution reaction was explored by using several types of organozinc (R_2Zn) reagents (Table 7). The reactions of aromatic zinc reagents produced the desired products in excellent yields with high levels of *trans* selectivity (Table 7, entries 2–4). Electron-deficient nucleophiles participated in this reaction (Table 7, entries 3 and 4) and 2-methoxyphenyl-, 2-naphthyl-, and heteroaromatic zinc reagents were also good substrates for the substitution reaction (Table 7, entries 5–7). Dimethylzinc and diethylzinc, as well as divinylzinc, di(phenylalkynyl)zinc, and di(trimethylsilylalkynyl)zinc, reacted with the salt that was derived from 2-methoxypyridine and compound **4** to form their corresponding products in good yields and stereoselectivities (Table 7, entries 8–12).

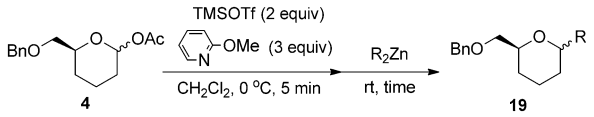
Table 6. Nucleophilic-substitution reactions of various pyridinium-type salts and C-nucleophiles.

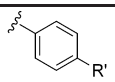
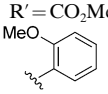
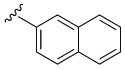


Entry	Pyridine	Ph–M	*t* [h]	Yield [%][a]	*trans*/*cis*[b]
1	2-*p*-tolylpyridine	Ph_2CuLi	–	trace	–
2	2-*p*-tolylpyridine	PhLi	–	dec.	–
3	2-*p*-tolylpyridine	PhMgBr	–	dec.	–
4	2-*p*-tolylpyridine	Ph_2Zn	7	40	>95:5
5	2-methoxypyridine	Ph_2Zn	2	95	>95:5

[a] Yield of isolated product; [b] stereoisomeric ratios were determined by using ^1H NMR spectroscopy. dec. = decomposed.

Table 7. Reactions of salts that were derived from compound **4** and 2-methoxypyridine with various organozinc reagents.



Entry	R	*t* [h]	**19**	Yield [%][b] (*trans*/*cis*)[c]
				
1	R′ = H	2	**19a**	95 (>95:5)
2	R′ = Me	7	**19b**	89 (>95:5)
3	R′ = F	8	**19c**	87 (>95:5)
4	R′ = CO_2Me	4	**19d**	70 (>95:5)
5		5	**19e**	89 (>95:5)
6		5	**19f**	83 (>95:5)
7[a]		8	**19g**	86 (>95:5)
8	Me	4	**19h**	76 (91:9)
9	Et	7	**19i**	70 (>95:5)
10[a]	vinyl	3	**19j**	81 (>95:5)
11[a]	≡—Ph	3	**19k**	80 (89:11)
12[a]	≡—TMS	5	**19l**	77 (>95:5)

[a] The C-nucleophilic-substitution process was performed at 0°C; [b] yield of isolated product; [c] stereoisomeric ratios were determined by using ^1H NMR spectroscopy.

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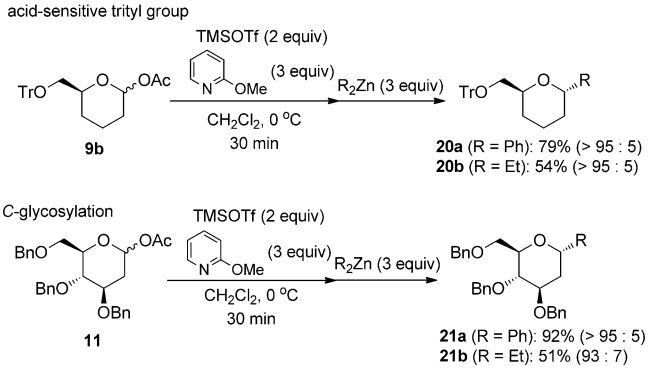
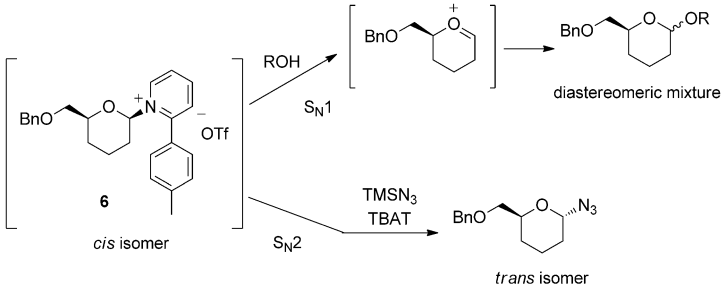


Scheme 16. Reactions of THP and related esters in the presence of Et_2Zn or Ph_2Zn; the C-nucleophilic-substitution reactions were carried out at 40 °C in 1,2-dichloroethane (DCE).



Scheme 17. Plausible reaction mechanisms for the substitution reactions with heteronucleophiles.

The attractive features of this C-nucleophile-substitution process were exemplified by the processes (Scheme 16) in which THP ester **9b**, which contained a trityl group, was used as the reactant. The reactions of a salt that was derived from compound **9b** with diphenyl- and diethyl zinc occurred under mild conditions to produce their respective products, which retained the acid-sensitive trityl group. In addition, the salt that arose from 2-deoxyglucose-derived glycosidic ester **11** also participated in reactions with organozinc reagents to generate C-glycosides (Scheme 16).

Mechanism of the Nucleophilic-Substitution Process

The reactions of 2-*p*-tolylpyridinium salts with heteronucleophiles suggested that the mechanisms shown in Scheme 17 were plausible. The observation that the reactions of 2,6-*cis*-substituted pyridinium-type salts with alcohols proceeded with low levels of diastereoselectivity suggested that the process likely proceeded in an S_N1 fashion via an oxocarbenium-ion intermediate. On the other hand, when the more-nucleophilic $TMSN_3$ participated in the reaction, an S_N2 pathway was more likely followed, based on the observation that 2,6-*cis*-substituted pyridinium-type salts yielded predominantly 2,6-*trans* products.

The mechanism for the reactions of C-nucleophiles is shown in Scheme 18. MS (FAB+) and ^1H NMR spectroscopy demonstrated that these reactions took place through initially formed 2,6-*cis*-pyridinium-type salt intermediates (e.g., **22**).[21] The formation of substitution products **19** from these intermediates could occur through concerted (route A) or non-concerted pathways (route B).[18a]

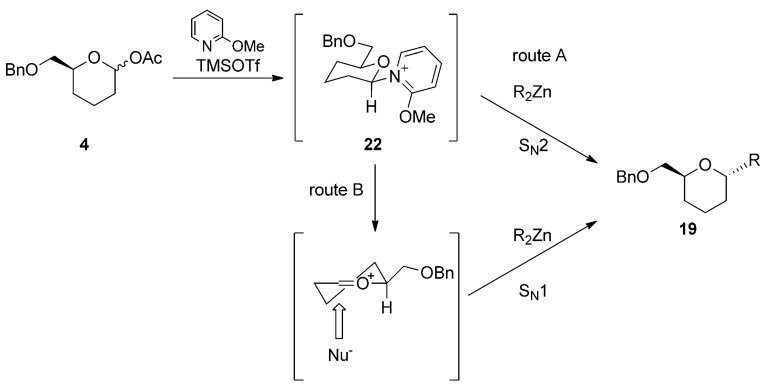
Conclusions

We have developed a nucleophilic-substitution reaction at the anomeric position of THP esters. The process, which employs a pre-activation strategy, relies on the initial formation of a pyridinium-type salt intermediate that acted as an oxocarbenium-ion equivalent. Alcohols, azides, and C-nucleophiles were introduced onto the anomeric centers of both THP and the carbohydrate substrates. Furthermore, this method afforded 2,6-*trans* products with high levels of stereoselectivity in reactions that generated azide and C-nucleophile adducts. Moreover, the process proceeded under mild conditions and, as a result, it was applicable to the reactions of THP and related esters that contained acid-labile functional groups. We believe that this method will be a useful tool for the synthesis of carbohydrates and biologically active THP-containing natural products.

Experimental Section

General Procedure for the Introduction of an Alcohol

2-*p*-Tolylpyridine (3 equiv) and TMSOTf (2 equiv) were added to a solution of starting THP ester (1 equiv) in CH_2Cl_2 (0.1 M) at 0 °C under a N_2 atmosphere. The mixture was stirred at 0 °C until the disappearance of the starting material was confirmed by TLC analysis. Next, the alcohol (3 equiv) was added and the resulting mixture was stirred vigorously. Following disappearance of the polar 2-*p*-tolylpyridinium salt intermediate



Scheme 18. Plausible reaction mechanisms for C-nucleophilic-substitution reactions.

by TLC analysis, the mixture was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a residue that was subjected to column chromatography on silica gel to give the product.

General Procedure for the Introduction of an Azide

2-*p*-Tolylpyridine (3 equiv) and TMSOTf (2 equiv) were added to a solution of starting THP ester (1 equiv) in CH_2Cl_2 (0.1 M) at 0 °C under a N_2 atmosphere. The mixture was stirred at 0 °C until the disappearance of starting material had been confirmed by TLC analysis. Next, $TMSN_3$ (3 equiv) and TBAT (3 equiv) were added and the resulting mixture was stirred vigorously. Following disappearance of the polar 2-*p*-tolylpyridinium salt intermediate by TLC analysis, the mixture was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a residue that was subjected to column chromatography on silica gel to give the product.

General Procedure for the Introduction of a C-Nucleophile

2-Methoxypyridine (3 equiv) and TMSOTf (2 equiv) were added to a solution of starting THP ester (1 equiv) in CH_2Cl_2 (0.1 M) at 0 °C under a N_2 atmosphere. The mixture was stirred at 0 °C until the disappearance of the starting material was confirmed by TLC analysis. Next, a solution of R_2Zn in THF (3 equiv) was added and the resulting mixture was stirred vigorously. Following disappearance of the polar 2-methoxypyridinium salt intermediate by TLC analysis, the mixture was quenched with aqueous 3.5% HCl and stirred for more than 10 min at 0 °C and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a residue that was subjected to column chromatography on silica gel to give the product.

Acknowledgements

This work was financially supported by the Hoansha Foundation, the Uehara Memorial Foundation, and by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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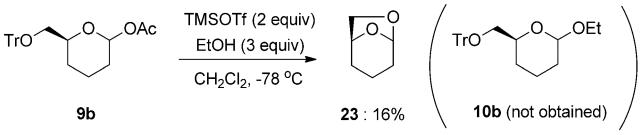
[11] The configuration of the major product was determined by the *J* value of the anomeric proton in the ^1H NMR spectrum, NOE DIFF experiments, or literature data.

[12] The reaction of compound **9b** with EtOH under Lewis acidic conditions did not give compound **10b** but instead afforded compound **23**.



9b **23** : 16% **10b** (not obtained)

[13] Unfortunately, 3-*O*-substituted THP 2-Ac-esters, such as glucopyranose 2,3,4,6-tetrakis-*O*-Bn-1-OAc, did not afford the pyridinium-type salt intermediate.

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[22] MS (FAB+) of the mixture that was obtained from the reaction of TMSOTf (2 equiv) and 2-methoxypyridine (3 equiv) in CH_2Cl_2 (0.1 M) showed a $[M]^+$ peak of 2-methoxypyridinium salt **22** at *m*/*z* 314.1772, with a formula of $C_{19}H_{24}NO_3$. Furthermore, the ^{1}H NMR spectrum of the reaction mixture in CD_2Cl_2 showed that the 2-methoxypyridine was oriented equatorially in a highly stereoselective manner and that 2-methoxypyridinium salt **22** was 2,6-*cis*. ^{1}H NMR spectra of the reaction mixture are shown in Supporting Information.

Received: March 14, 2012
Published online: ■■ ▮▮, 0000

Synthetic Methods

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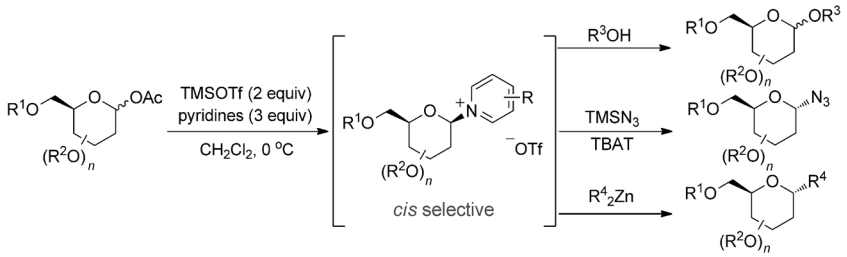
Kenichi Murai ———— ▮▮▮▮–▮▮▮▮

Preparation of THP-Ester-Derived Pyridinium-Type Salts and their Reactions with Various Nucleophiles



Salty but sweet: Nucleophilic substitution at the anomeric position of tetrahydropyranyl esters via pyridinium-type salt intermediates proceeded without affecting acid-labile protecting groups owing to the use of mild reaction conditions (see scheme).

