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Reaction of Acetals with Various Carbon Nucleophiles under Non-Acidic Conditions: C–C Bond Formation via a Pyridinium-Type Salt

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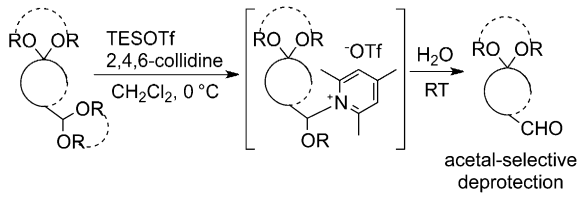
Abstract: Mild substitution reactions of acetals with carbon nucleophiles via the pyridinium-type salts generated by the treatment of acetals with TESOTf-2,4,6-collidine or 2,2′-bipyridyl have been developed. Various carbon nucleophiles, such as organocuprates, silyl enol ethers, enamines, etc., reacted with the pyridinium-type salts to give the corresponding substituted products in good yields. The reactions proceeded under very mild conditions (non-acidic conditions) and thus acid-sensitive functional groups can be tolerated during the reaction. In addition, only an acetal can form the pyridinium-type salt and react with nucleophiles in the presence of a ketal. This unusual selectivity is in contrast to general methods conducted under acidic conditions.

Keywords: acetals · carbon nucleophiles · cations · C–C bond formation · pyridinium-type salts

Introduction

The carbon–carbon bond formation is a fundamental process in organic synthesis and numerous methods have been developed for achieving it. One of the most powerful methods is the reaction of the carbonyl groups with a variety of carbon nucleophiles. Acetals are a typical carbonyl protecting group as well as a synthetic equivalent of the carbonyl group. In general, acetals are stable under strongly basic to neutral conditions and do not react with nucleophilic reagents, for example, organolithium reagents and Grignard reagents, under these conditions. However, acetals act as strong electrophiles toward various nucleophiles under acidic conditions owing to the generation of an oxonium ion intermediate. Since Mukaiyama and Murakami reported the first aldol-type reaction of acetals with silyl enol ethers using a stoichiometric amount of $TiCl_4$, a number of acid-mediated C–C bond-forming reactions of acetals have been reported.[1] To generate oxonium ions from acetals, strong Lewis acids, such as trimethylsilyl trifluoromethanesulfonate (TMSOTf), $TiCl_4$, $SnCl_4$, and $BF_3{\cdot}Et_2O$, are usually used. Typically, these reactions should be conducted at −78 °C[1a,c] because the oxonium ion intermediates generated under acidic conditions are unstable. A variety of carbon nucleophiles can react with the oxonium ion intermediates, such as silyl enol ethers, enamines, cyanides, allyl trimethylsilane, etc. On the other hand, the use of organometallic reagents as nucleophiles is not very common. Some acetals, such as α,β-unsaturated acetals, can react with these reagents to give substituted products[2–5] or the Lewis-acid-activated organocuprates can react with the acetals.[6] Therefore, nucleophiles for C–C bond formations are rather limited. In addition, these reactions have to be conducted under acidic conditions.

We recently reported the deprotection of acetals in the presence of ketals using a combination of triethylsilyl trifluoromethanesulfonate (TESOTf) and 2,4,6-collidine (Scheme 1).[7] The key to the reaction is the formation of the corresponding collidinium salts, which are rather stable even at 0 °C, in contrast to the oxonium ion intermediates.



Scheme 1. The unprecedented acetal-selective deprotection in the presence of ketals via the formation of collidinium salts in combination with TESOTf-2,4,6-collidine.

However, these salts are reactive toward nucleophiles. For instance, hydrolysis of the collidinium salts proceeds readily to give aldehydes via hemiacetal intermediates. The collidinium salts are reactive towards not only water, but also other heteroatom nucleophiles, oxygen-, sulfur-, and nitrogen nucleophiles (i.e., alcohols, thiols, azides, etc.) and the corresponding mixed *O*,*O*-acetals, *O*,*S*-acetals, and *N*,*O*-acetals were obtained in good-to-high yields (Scheme 2).[8] In

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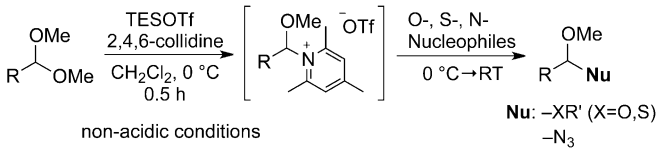
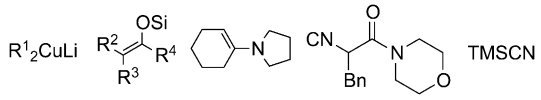


Scheme 2. The substitution reactions of acetals with various heteroatom nucleophiles via the generation of collidinium salts from acetals in combination with TESOTf-2,4,6-collidine.

addition, acid-sensitive functional groups are tolerable without any loss of them because our reactions proceeded under weakly basic conditions (a slight excess of 2,4,6-collidine over TESOTf was used). It is very significant that the selective formation of the collidinium salts from acetals led to the chemoselective deprotection of the acetals, even in the presence of ketals by distinguishing their steric environments.

We have also studied the reaction of the collidinium-salt intermediates with Gilman reagents as carbon nucleophiles.[9] Herein, we report the scope of the reactivity of the collidinium-salt intermediates to various carbon nucleophiles, including not only Gilman reagents, but also silyl enol ethers, enamines, isocyanides, and cyanides (Scheme 3).



Scheme 3. Carbon nucleophiles used in this work.

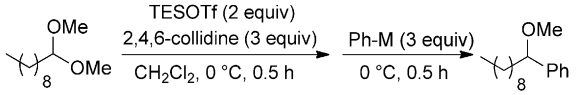
Results and Discussion

Reactions with Organocuprates

To reveal the reactivity and usefulness of the collidinium salts generated from acetals and 2,4,6-collidine, we investigated several organometallic reagents (Grignard reagents, organocuprates, and organolithium reagents). Acetals are known to be intrinsically inert to organometallic reagents. Only a limited number of examples of reactions with organometallic reagents have been reported and substitution of one of the alkoxy groups proceeded to give the corresponding products.[2] The reactions with Grignard reagents required either the use of a special acetal moiety or activation by Lewis acids. For example, mixed acetals consisting of 2,4-dichlorophenol are reactive toward the Grignard reagents because 2,4-dichlorophenol acts as a good leaving group.[3] We have previously reported the reaction of methoxyethoxy acetals with Grignard reagents, and a substitution reaction occurred by chelation of the magnesium ion with the methoxyethoxy group.[4] α,β-Unsaturated acetals could react with Grignard reagents alone or in the presence of a Lewis acid.[5] Organocuprates activated by BF_3·Et_2O could also react with acetals[6] via oxonium ion intermediates.[6g] Therefore, these reactions were usually conducted at low temperature. Accordingly, the mild substitution reaction of an acetal with organometallic reagents is difficult but interesting, especially under non-acidic conditions.

In our method, the electrophilic collidinium salts could be generated under mild reaction conditions. We then applied this method to the substitution reactions with organometallic reagents. The reactions of the collidinium salt, generated from acetal **1a** under TESOTf-2,4,6-collidine conditions, with various organometallic reagents were examined (Table 1). Although phenyllithium did not give any desired

Table 1. Reaction of organometallic reagents and acetal **1a** under TESOTf-2,4,6-collidine conditions.



1a **2a**

Entry	Ph–M	Yield [%]
1	PhLi	trace
2	PhMgBr	33
3	PhMgBr+CuI	90
4	$Ph_2Cu(CN)Li_2$	65
5[a]	Ph_2CuLi (**3a**)	93

[a] When 2,6-lutidine was used instead of 2,4,6-collidine, **2a** was obtained in 72% yield.

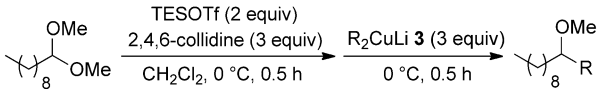
product, phenylmagnesium bromide afforded the product **2a** in 33% yield (Table 1, entries 1 and 2). The combination of CuI and phenylmagnesium bromide successfully reacted with the salt to give compound **2a** in 90% yield at 0°C (Table 1, entry 3). The use of a higher-order cuprate resulted in a decreased yield (65%) (Table 1, entry 4), but the Gilman reagent **3a** afforded the best result (93%) among the organometallic reagents (Table 1, entry 5).

Gilman reagents (**3**) bearing diverse alkyl groups reacted with **1a** via the collidinium salt; mostly afforded the substituted products (**2**) in good yields (Table 2). All the reactions were completed within 0.5 hours. Only tBu_2CuLi did not afford the corresponding product (Table 2, entry 4).

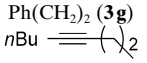
A variety of acetals are applicable for this reaction. Diethyl acetal **1b**, cyclic acetal **1c**, and substituted dimethyl acetal **1d** were converted into their corresponding collidinium salts and treated with Ph_2CuLi (**3a**) to give the substituted products **2i–k** in good yields (Table 3, entries 1–3). It should be noted that other functional groups, including acid-sensitive *tert*-butyldimethylsilyl (TBS) and trityl (Tr) groups can be

Abstract in Japanese:
緩和な条件下でのアセタールへの炭素求核種導入反応に成功した。本反応は非酸性条件下、ピリジニウム塩中間体を経由して反応が進行し、有機銅試薬やシリルエノールエーテル、エナミンなどが導入可能である。また、通常の酸性条件下での反応では適用困難な酸に不安定な官能基を損なうことなく反応が進行する。さらにこれまでに例のないケタール存在下でのアセタール選択的な炭素求核種導入にも成功した。

Table 2. Reaction with acetal **1a** with various Gilman reagents under TESOTf-2,4,6-collidine conditions.

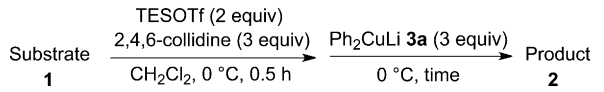


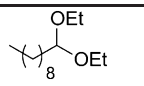
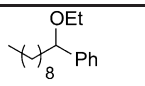
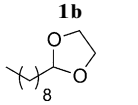
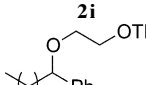
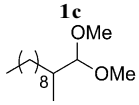
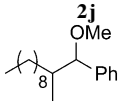
1a **2**

Entry	R	Product	Yield [%]
1	Me (**3b**)	**2b**	91
2	*n*Bu (**3c**)	**2c**	90
3	*s*Bu (**3d**)	**2d**	73
4	*t*Bu (**3e**)	**2e**	0[a]
5	$TMSCH_2$ (**3f**)	**2f**	96
6	$Ph(CH_2)_2$ (**3g**)	**2g**	87
7	 (**3f**)	**2h**	86

[a] Unknown products were obtained.

Table 3. Reaction of acetals **1** with Ph_2CuLi **3a** under TESOTf-2,4,6-collidine conditions.



Entry	Substrate	Product	*t* [h]	Yield [%]
1	 **1b**	 **2i**	1.0	80
2	 **1c**	 **2j**	1.0	86
3	 **1d**	 **2k**	1.3	90
4	R = Me (**1e**)	**2l**	0.5	84
5	R = Ac (**1f**)	**2m**	0.5	69
6	R = TBS (**1g**)	**2n**	0.5	73
7	R = Tr (**1h**)	**2o**	0.5	76

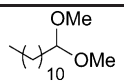
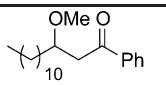
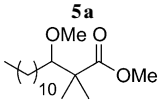
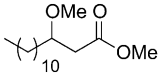
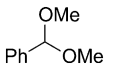
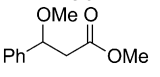
tolerated under the stated conditions, thereby indicating that the reaction conditions are non-acidic in contrast to other previously reported methods; the desired products **2l–o** were obtained in moderate to good yields (Table 3, entries 4–7).

Reactions with Silyl Enol Ethers and Silyl Ketene Acetals

Next, we examined the reactions of the collidinium salts with a silyl enol ether and silyl ketene acetals. A number of aldol-type reactions of acetals with silyl enol ethers and silyl ketene acetals under acidic conditions have been reported.[1] However, those reactions were limited to simple substrates owing to the acidic conditions being necessary for the generation of the oxonium ion intermediates.

The reactions of *n*-dodecanal dimethylacetal **1i** with silyl enol ether **4a** (3 equiv) and silyl ketene acetals **4b** and **4c** (3 and 5 equiv, respectively) at room temperature proceeded successfully under our reaction conditions. After the formation of the collidinium salt from **1i**, the addition of **4a**, **4b**, and **4c** gave the corresponding ketone **5a** and esters **5b** and **5c** in good yields, respectively (Table 4, entries 1–3). In these reactions, the silyl ketene acetals afforded higher yields than the silyl enol ether. We then chose silyl ketene acetal **4c** and investigated the scope of the acetal substrate. The reaction of the aromatic acetal **1j** and **4c** afforded the corresponding ester **5d** in moderate yield (Table 4, entry 4). Acetals **1g**, **1h**, and **1k–n**, which contain other functional groups including alcohol-protecting groups, underwent the substitution reaction to afford the corresponding products **5e–j** in good to high yields (Table 4, entries 5–10). Acid-labile groups, which cannot tolerate the Lewis-acid-mediated substitution reaction conditions, were successfully incorporated into the substitution products (Table 4, entries 5 and 6). The free hydroxy group did not affect the reaction and the silylated product **5i** was obtained in good yield (Table 4, entry 9).

Table 4. Reaction of acetals (**1**) with silyl enol ether and silyl ketene acetals (**4**) under TESOTf-2,4,6-collidine conditions.

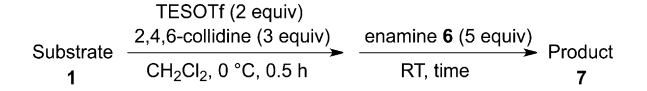
Entry	Substrate	Silicon nucleophile	Product	*t* [h]	Yield [%]
1[a]	 **1i**	 **4a**	 **5a**	2	77
2	**1i**	 **4b**	 **5b**	2	96
3[a]	**1i**	 **4c**	 **5c**	2	89
4[a]	 **1j**	**4c**	 **5d**	3.5	68
5	R = OTBS (**1g**)	**4c**	**5e**	2	92
6	R = OTr (**1h**)	**4c**	**5f**	3	75
7	R = OBn (**1k**)	**4c**	**5g**	2	80
8	R = OBz (**1l**)	**4c**	**5h**	2	85
9[b]	R = OH (**1m**)	**4c**	R = OTES (**5i**)	1	87
10	R = Br (**1n**)	**4c**	**5j**	1	94

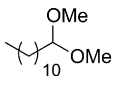
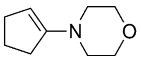
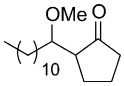
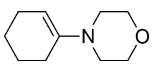
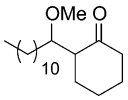
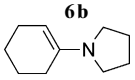
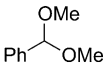
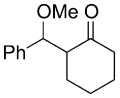
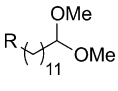
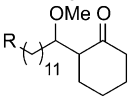
[a] 3 equiv nucleophile was used. [b] 3 equiv TESOTf and 4 equiv 2,4,6-collidine were used.

Reactions with Enamines

Enamines **6** also worked as good carbon nucleophiles for the substitution reactions of acetals in our system (Table 5). The reactions of enamines derived from morpholines **6a** and **6b** with the collidinium salt, generated from acetal **1i**, proceeded to give the substituted products **7a** and **7b** in good yields (Table 5, entries 1 and 2). Enamine **6c**, prepared from pyrrolidine, could be used to afford the corresponding carbonyl compound **7b** in good yield (Table 5, entry 3), whereas it was not effective in the acid-catalyzed substitution reaction.[10] The presence of other functional groups was also tolerated under the stated conditions (Table 5, entries 5–10).

Table 5. Reaction of acetals (**1**) with enamines (**6**) under TESOTf-2,4,6-collidine conditions.



Entry	Substrate	Enamine	Product	*t* [h]	Yield [%][a]
1	 **1i**	 **6a**	 **7a**	3	84
2	**1i**	 **6b**	 **7b**	5.5	80
3	**1i**	 **6c**	**7b**	5	89
4	 **1j**	**6c**	 **7c**	9.5	99
5	 R = OTBS (**1g**)	**6c**	 **7d**	4	88
6	R = OTr (**1h**)	**6c**	**7e**	3.5	78
7	R = OBn (**1k**)	**6c**	**7f**	2	95
8	R = OBz (**1l**)	**6c**	**7g**	5.5	78
9[b]	R = OH (**1m**)	**6c**	R = OTES (**7h**)	3.5	74
10	R = Br (**1n**)	**6c**	**7i**	4	89

[a] All products were obtained as a *threo*/*erythro* mixture. [b] 3 equiv TESOTf and 4 equiv 2,4,6-collidine were used.

Reactions with Isocyanides

We next focused on isocyanides (**8**) as carbon nucleophiles. Isocyanides can react with acetals under acidic conditions via oxonium ion intermediates, and the isocyanide adducts underwent further transformation leading to final products such as cyanides, amides, etc.[11] We chose isocyanoacetoamide **8a** as a carbon nucleophile because the isocyano moiety is known to react with aldehydes and subsequent reactions with the carbonyl groups on the amide afford oxazoles in one-pot.[12] We used isocyanoacetoamide **8a** as a nucleophile and conducted the reaction under TESOTf-2,4,6-collidine conditions (Table 6). After formation of the collidinium salts from acetals **1g–n**, the addition of 1.5 equivalents of **8a** gave the desired oxazoles **9a–h** in high yields and all reactions were completed within 0.5 hours (Table 6, entries 1–8). This result is the first example of the reaction of acetals and isocyanoacetoamide. No significant effects on the co-existing functional groups were observed, even the acid-sensitive ones (Table 6, entries 3–8). The simple isocyanide **8b** also reacted effectively in this system and the isocyanide adducts were reduced in situ with $LiBH_4$ to afford the corresponding amines **10a–c** in moderate yields (Table 6, entries 9–11).

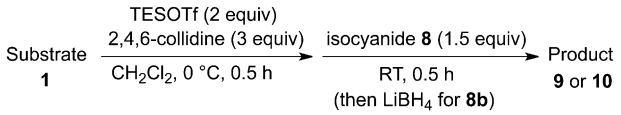
Reactions with TMSCN

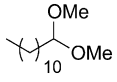
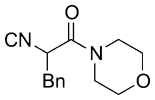
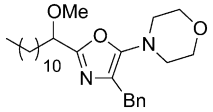
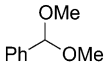
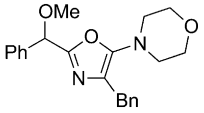
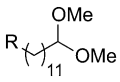
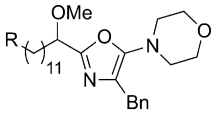
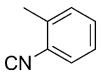
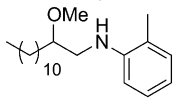
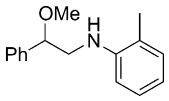
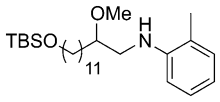
Finally, we examined the substitution reaction of acetals with cyanide. The introduction of cyanide under acidic conditions in the presence of a catalytic amount of Lewis acid has been reported previously.[13] When the reaction was performed under our reaction conditions using acetal **1i** and TMSCN, the yield of the product **11a** was moderate (71%; Table 7, entry 1). The decrease in the yield seemed to be due to the lack of the leaving ability of 2,4,6-collidine. We have already revealed that the structure of the pyridines is very important and affects the reactivity of the pyridinium-type salts in our reaction system.[7b] We have also reported the mild deprotection of the acetal-type protecting groups of alcohols (methoxymethyl-, β-methoxyethoxymethyl-, benzyloxymethyl, and 2-[(trimethylsilyl)ethoxy]methyl ethers and methylene acetal) using our reaction system. In their cases, the use of 2,2′-bipyridyl was effective for the hydrolysis of the corresponding pyridinium-type salts whereas the hydrolysis of the collidinium salts did not proceed at all.[14] We then employed 2,2′-bipyridyl in the place of 2,4,6-collidine for this cyanation reaction. As expected, the substitution occurred successfully during the reaction of the 2,2′-bipyridylium salt formed from **1i** and TMSCN to give cyanide **11a** in good yield (83%; Table 7, entry 2). The optimized conditions were applicable to the cyanation of other substrates without affecting the acid-labile functional groups (Table 7, entries 3–9).

Chemoselective Transformations of Acetals with Carbon Nucleophiles in the Presence of Ketals

Ketals are known to undergo deprotection more-readily than acetals under acidic conditions because the oxonium ion intermediates from ketals are more stable than those from acetals. On the other hand, preferential acetal depro-

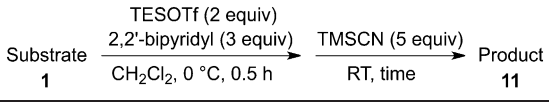
Table 6. Reaction of acetals (**1**) with isocyanides (**8**) under TESOTf-2,4,6-collidine conditions.

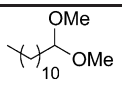
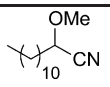
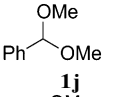
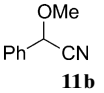


Entry	Substrate	Isocyanide	Product	Yield [%]
1	 **1i**	 **8a**	 **9a**	93
2	 **1j**	**8a**	 **9b**	84
3	 R = OTBS (**1g**)	**8a**	 **9c**	81
4	R = OTr (**1h**)	**8a**	**9d**	82
5	R = OBn (**1k**)	**8a**	**9e**	89
6	R = OBz (**1l**)	**8a**	**9f**	86
7[a]	R = OH (**1m**)	**8a**	R = OTES (**9g**)	82
8	R = Br (**1n**)	**8a**	**9h**	92
9[b]	**1i**	 **8b**	 **10a**	67
10[b]	**1j**	**8b**	 **10b**	72
11[b]	**1g**	**8b**	 **10c**	61

[a] 3 equiv TESOTf and 4 equiv 2,4,6-collidine were used. [b] 1.5 equiv **8b** was used for this reaction. Isocyanide adduct was converted into amine **10** by reduction with $LiBH_4$.

Table 7. Reaction of acetals (**1**) with cyanide under TESOTf-2,2′-bipyridyl conditions.



Entry	Substrate	Product	*t* [h]	Yield [%]
1[a]	 **1i**	 **11a**	3	71
2	**1i**	**11a**	3	83
3	 **1j**	 **11b**	5	98
4	R = OTBS (**1g**)	**11c**	4	87
5	R = OTr (**1h**)	**11d**	3	82
6	R = OBn (**1k**)	**11e**	3	86
7	R = OBz (**1l**)	**11f**	4	85
8[b]	R = OH (**1m**)	R = OTMS (**11g**)	4	80
9	R = Br (**1n**)	**11h**	4.5	93

[a] 2,4,6-Collidine was used instead of 2,2′-bipyridyl; [b] 3 equiv TMSOTf and 4 equiv 2,2′-bipyridyl were used.

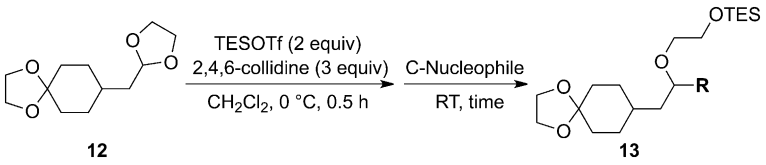
tection in the presence of ketals has been achieved using our method.[7] This is because TESOTf can distinguish between the steric environments of acetals and ketals and selectively coordinate to the acetal oxygen. Successive attack of the pyridines then leads to the chemoselective formation of pyridinium-type salts from acetals. We have also accomplished the chemoselective substitution reactions of acetals with heteroatom nucleophiles in the presence of ketals.[8a] We presumed that the chemoselective substitution of acetals with carbon nucleophiles would be feasible and then studied the reaction of an acetal with diverse carbon nucleophiles in the presence of a ketal (Table 8). The chemoselective substitution of **12** with Gilman reagent **3b** proceeded to give compound **13a** and no ketal-substituted product was obtained (Table 8, entry 1).[9] Silyl ketene acetal **4c** also reacted with **12**, affording only the acetal-substituted product **13b** in 72% yield (Table 8, entry 2). Interestingly, the acid-catalyzed substitution reaction (TESOTf and **4c** in CH_2Cl_2 at −78 °C) afforded only the ketal-deprotected product (**14**) as the sole product,[15] which indicated that the formation of a collidinium-salt intermediate is essential for this type of substitution reaction and the reaction conditions are not acidic. The reaction using other carbon nucleophiles, **6c** and **8a**, also afforded the corresponding acetal-substituted products **13c** and **13d**, respectively, in good yields under our reaction conditions (Table 8, entries 3 and 4), whereas the reaction with TMSCN resulted in a low yield (Table 8, entry 5).

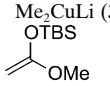
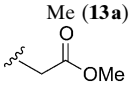
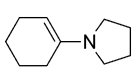
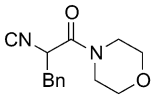
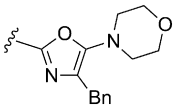
Conclusions

In summary, we have developed a new C–C bond-forming reaction of acetals with a variety of carbon nucleophiles under non-acidic conditions (Scheme 4).

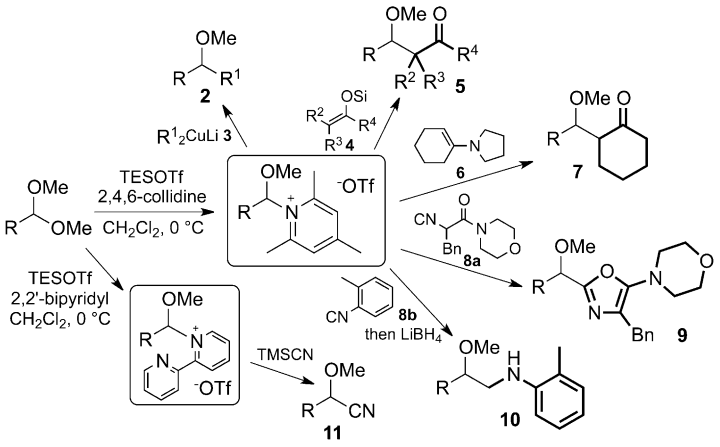
Thus, the reactions of the collidinium salts with cuprates (**3**) gave substituted products **2**, and their reaction with silyl enol ether or silyl ketene acetals (**4**) or enamines (**6**) afforded the carbonyl compounds **5** or **7**. Their reactions with isocyanoamide **8a** initially formed substituted products and successive intramolecular cyclization of the amide carbonyl group led to oxazoles (**9**) in one pot. Simple isocyanide **8b** reacted with the salts to give the substituted products, which were then converted into their corresponding amines (**10**)

Table 8. Chemoselective substitution with various carbon nucleophiles using TESOTf-2,4,6-collidine conditions.



Entry	C-nucleophile	R (product)	*t* [h]	Yield [%]
1	Me_2CuLi (**3b**)	Me (**13a**)	4.5	70
2	 **4c**	 **13b**	2.5	72
3	 **6c**	 **13c**	8	74
4	 **8a**	 **13d**	3	76
5[a]	TMSCN	CN (**13e**)	3	31

[a] 2,2′-Bipyridyl was used instead of 2,4,6-collidine.



Scheme 4. The substitution reactions of acetals with various carbon nucleophiles via the pyridinium-type salts generated from acetals under mild conditions.

by subsequent reduction with $LiBH_4$. Substitution of the collidinium salts with TMSCN was less efficient. The use of 2,2'-bipyridyl in place of 2,4,6-collidine then improved the reactivity and afforded **11** in good to high yields. A wide range of functional groups were tolerable, under the TESOTf-2,4,6-collidine conditions, including acid-sensitive groups. The reactions can be conducted at 0 °C to room temperature whereas the previous methods were usually performed at −78 °C, because the reactions proceeded via stable cationic pyridinium-type salt intermediates, rather than via the unstable oxonium ion intermediates. The unprecedented chemoselective C–C bond formation of an acetal with various carbon nucleophiles in the presence of a ketal has also been achieved.

Experimental Section

*General Procedure for the Reaction of Acetal **1** with Carbon Nucleophiles via a Pyridinium-Type Salt*

TESOTf (2.0 equiv) was added dropwise at 0 °C under a N_2 atmosphere to a solution of acetal **1** (1.0 equiv) and 2,4,6-collidine (3.0 equiv) in CH_2Cl_2 (0.2 M) and the reaction mixture was stirred for 30 min at 0 °C. After the complete consumption of **1** as confirmed by TLC (high polar component was appeared on TLC), a nucleophile (5.0 equiv) was added to the reaction mixture and the solution was warmed to RT. After the high-polarity spot had disappeared, sat. $NaHCO_3$ (aq.) was added to the reaction mixture and the solution was extracted with CH_2Cl_2. The combined organic layer was dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give the substituted product. (For the reaction with TMSCN, 2,2′-bipyridyl was used in place of 2,4,6-collidine.)

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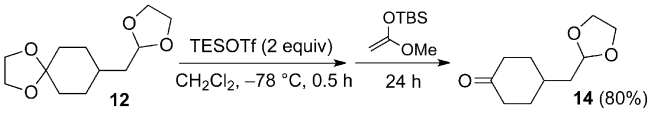
[15] Ketone **14** was obtained in 80% yield, with the acetal group remaining intact.



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