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Brønsted Acid Catalyzed Formal Insertion of Isocyanides into a C−O Bond of Acetals

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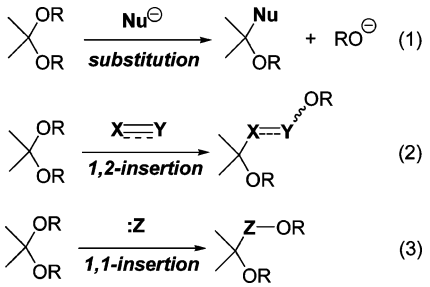
Abstract: The Brønsted acid catalyzed formal insertion of an isocyanide into a C−O bond of an acetal is described. A diverse array of acyclic and cyclic acetals can be applied to the catalytic insertion to form α-alkoxy imidates. Functional groups, such as nitro, cyano, halogen, ester, and alkoxy groups, are tolerant to the reaction conditions employed. The course of the reaction is highly dependent on the structure of the isocyanide. The use of an electron-deficient aryl isocyanide, such as **2c** and **2d**, is required to selectively obtain the monoinsertion product. When aryl isocyanides containing alkyl substituents, such as **2a** and **2b**, are employed, two molecules of the isocyanide are incorporated, and the double-insertion product is obtained. The reaction of *tert*-octyl isocyanide also induces a double incorporation, but the subsequent acid-mediated fragmentation leads to the 2-alkoxy imidoyl cyanide. The monoinsertion products, α-alkoxy imidates, can readily be hydrolyzed to α-alkoxy esters, realizing the formal carbonylation of an acetal.

Introduction

Since Mukaiyama's report on the Lewis acid mediated reaction of enol silyl ethers with acetals, the first efficient Aldol-type reaction of acetals, in 1974,[1] acetals have enjoyed widespread use as an electrophile in organic synthesis.[2] As exemplified in Mukaiyama's work, the overall process for the reactions of acetals with nucleophilic reagents is substitution, in which one of the alkoxy groups in the acetal is eliminated (eq 1). In contrast to the significant progress in the substitution processes of acetals, insertion reactions[3] into a C−O bond of an acetal remain largely unexplored despite their attractiveness as a synthetic transformation: two new bonds are formed in an atom-economical manner (eqs 2 and 3). To date, such intermolecular insertion reactions of acetals have been reported but have been restricted to two families of molecules, ketenes (1,2-insertion, eq 2)[4] and carbenes generated from diazo compounds (1,1-insertion, eq 3).[5] It has also been reported that alkynes can be inserted into a C−O bond of an acetal catalytically but only when they are tethered to an acetal substrate at a suitable position (1,2-insertion, an *intramolecular* variant of eq 2).[6,7]



To develop the 1,1-insertion reaction into a C−O bond of acetals as depicted in eq 3, isocyanides represent promising candidates as an inserting molecule, since it is known that they can be inserted into a variety of chemical bonds, including O−H,[8] N−H,[9] P−H,[10] S−H,[11] Si−H,[12] C−H,[13] C−Si,[14] Si−Si,[15] S−S,[16] and Si−B[17] bonds. As a part of our program

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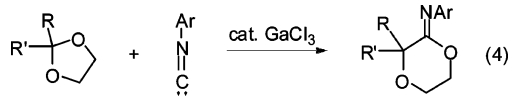
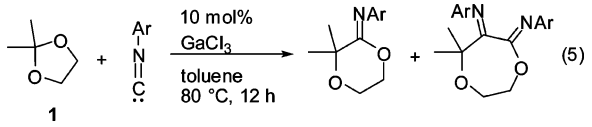
directed toward developing new Lewis acid catalyzed reactions using isocyanides as a C1 component, we found that isocyanides can indeed be inserted into a C−O bond of cyclic acetals in the presence of a catalytic amount of $GaCl_3$ (eq 4).[18]



Although such an insertion reaction has been reported by Ito and Saegusa prior to our work, the reaction, as described in their work, requires the use of a *stoichiometric* amount of $TiCl_4$, and the scope has not been investigated extensively (two examples).[19] In this paper, we disclose the full details of our work, including the discovery of a new Brønsted acid catalyst, the extension to an unprecedented insertion into *acyclic* acetals, and the control over the three different reaction pathways by the nature of N-substituents of isocyanides.

Results and Discussion

Insertion into Cyclic Acetals. Our continuing interests in the unique catalytic behavior of $GaCl_3$[18,20−26] led us to discover that a combination of $GaCl_3$ and an isocyanide is a useful system for cycloaddition reactions with α,β-unsaturated carbonyl compounds.[26] In the course of further examination of the $GaCl_3$/isocyanide system with other oxygenated compounds, we found that isocyanides can be inserted into the C−O bond in cyclic acetals (eq 5).



Ar = 2,6-$Me_2C_6H_3$ (**2a**)	**3a** 47%	**4a** 5%
Ar = 2,6-*i*-$Pr_2C_6H_3$ (**2b**)	**3b** 46%	**4b** trace
Ar = 2,6-$Cl_2C_6H_3$ (**2c**)	**3c** 81%	**4c** 0%
Ar = 2,6-$Br_2C_6H_3$ (**2d**)	**3d** 81%	**4d** 0%

Thus, the reaction of 2,2-dimethyl-1,3-dioxolane (0.4 mmol, **1**) with 2,6-xylylisocyanide (0.44 mmol, **2a**) in the presence of $GaCl_3$ (0.04 mmol) in toluene (1.5 mL) at 80 °C for 12 h gave (3,3-dimethyl-1,4-dioxan-2-ylidene)-2,6-dimethylphenylamine (**3a**) in 47% yield, along with the double insertion product **4a** in 5% yield (eq 5, Ar = 2,6-$Me_2C_6H_3$). We next examined the importance of the structure of the isocyanide on this reaction. Increasing the steric demand of the isocyanide had little effect on the efficiency of the reaction (eq 5, Ar = 2,6-*i*-$Pr_2C_6H_3$). On the other hand, the introduction of electron-withdrawing atoms, such as chlorine and bromine, on the benzene ring of the aryl isocyanide led to a marked improvement in both yield and selectivity for the monoinsertion product **3c** and **3d** (eq 5, Ar = 2,6-$Cl_2C_6H_3$ and 2,6-$Br_2C_6H_3$). The use of *tert*-butyl isocyanide did not afford the insertion product.

By employing isocyanide **2d**, we next explored the scope of the catalytic insertion reaction (Table 1). The reaction proceeded effectively with 1,3-dioxolanes derived from a range of aliphatic ketones (entries 2−4). The yields were lowered, when acetals derived from aromatic (entry 5) and α,β-unsaturated (entry 6) ketones were employed; however, in the latter case, the use of 2 equiv of isocyanide increased the yield. 1,3-Dioxolanes derived from aldehydes are significantly less reactive compared to those derived from ketones (entries 7−9). 1,3-Dioxane furnished diminished yields of the insertion product, presumably due to the requirement of the demanding seven-membered ring formation (entry 10).

Catalyst Screening for the Insertion into Acyclic Acetals. Although we established the first catalytic protocol for the insertion of an isocyanide into a C−O bond of an acetal, as mentioned above, several limitations associated with the $GaCl_3$-catalyzed reaction restricted the potential utility of the reaction. First, the applicable substrates are strictly limited to *cyclic* acetals. Moreover, within the cyclic acetals, only those derived from aliphatic ketones afforded the insertion product in good yields. Second, polar functional groups, such as nitro and cyano groups, are not compatible due to catalyst deactivation by complex formation. To overcome these drawbacks, we decided to reexamine the reaction conditions for the insertion of an isocyanide into an *acyclic* acetal. Despite the apparent similarity, cyclic and acyclic acetals pose very different synthetic challenges when applied to such reactions. The difficulty associated with acyclic acetals is not surprising considering the proposed stepwise insertion mechanism illustrated in Scheme 1. For cyclic acetals, the once cleaved alkoxy group (ROM) remains in the substrate. As a result, the recombination (**B** → **C**) proceeds via a facile intramolecular process.[18] In contrast, in the case of acyclic acetals, the recombination of the ROM competes with other undesired intermolecular processes, such as the nucleophilic attack of the second molecule of an isocyanide or contaminated water. Indeed, acyclic acetals are not applicable to insertion reactions of isocyanides reported for cyclic acetals, resulting in the formation of a substitution product rather than an insertion product.[18,27] Thus, insertion into *acyclic* acetals represents a formidable challenge in view of the lack of precedent for such a process.

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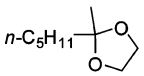
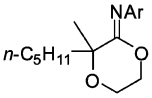
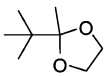
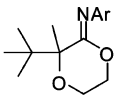
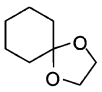
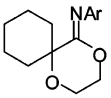
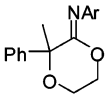
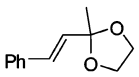
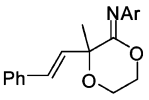
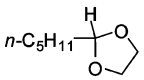
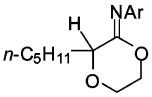
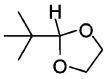
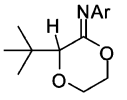
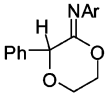
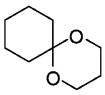
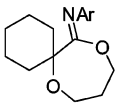
Table 1. $GaCl_3$-Catalyzed Reaction of Acetals with 2,6-Dibromophenylisocyanide (**2d**)[a]

entry	acetal	product[b]	yield[c]
1			81%
2			84%
3			92%
4			93%
5			51%
6			36% (82%)[d]
7			36% (60%)[d]
8			55%
9			26%
10			34% (46%)[d]

[a] Reaction conditions: ketal or acetal (0.4 mmol), 2,6-dibromophenylisocyanide (0.44 mmol), $GaCl_3$ (0.04 mmol, 1 M in methylcyclohexane) in toluene (1.5 mL) at 80 °C, 18 h. [b]Ar = 2,6-dibromophenyl. [c]Isolated yields. [d]2,6-Dibromophenylisocyanide (0.8 mmol) was used.

With this difficulty in mind, we initially investigated the reaction of acyclic acetal **5** with isocyanide **2c** in the presence of Lewis acid catalysts (Table 2). After screening a variety of catalysts,[28] we were pleased to find that triflate salts exhibited promising catalytic activity, furnishing the desired insertion product **6c** (entries 3−5). We next examined the catalytic activity of TfOH, a compound that could be generated in situ by the reaction of triflate salts and residual water.[29] To our delight, TfOH proved to be an excellent catalyst for this reaction, affording **6c** in 89% isolated yield at ambient temperature within 2 h (entry 6), while other Brønsted acids, such as Tf_2NH and TFA, were less effective (entries 7 and 8). It is noteworthy that only a 1:1 mixture of **5** and **2c** was needed to obtain the insertion product **6c** in a good yield, demonstrating the efficiency of the new catalytic system.

Scheme 1. Possible Mechanism for the Catalytic Insertion of Isocyanides into Acetals

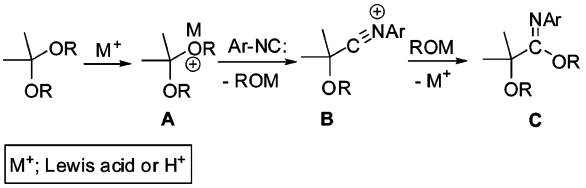
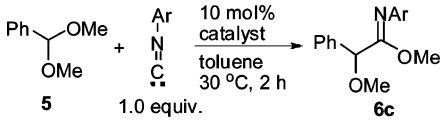


Table 2. Survey of Acid Catalysts for the Insertion of Isocyanide **2c** with Acetal **5**

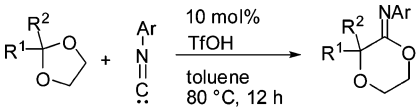


Ar = 2,6-dichlorophenyl (**2c**)

entry	catalyst	yield (%)	entry	catalyst	yield (%)
1	$GaCl_3$	<10	5	Me_3SiOTf	80
2	$InCl_3$	trace	6	**TfOH**	**89**
3	$Cu(OTf)_2$	38	7	Tf_2NH	58[a]
4	$Sc(OTf)_3$	48[a]	8	TFA	3

[a] 8−10% of the double insertion product was also obtained.

The new Brønsted acid catalyst system can also effect the insertion of an isocyanide into a cyclic acetal, affording the corresponding cyclic imidates in yields comparable to those obtained when $GaCl_3$ is used as a catalyst (eq 6).



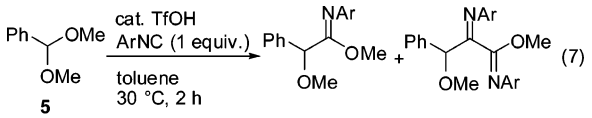
Ar = 2,6-dichlorophenyl (**2c**)

R^1 = Me, R^2 = Me	74%
R^1 = *t*-Bu, R^2 = Me	96%
R^1 = (*E*)-PhCH=CH, R^2 = Me	69%
R^1 = Ph, R^2 = H	49%

Effect of N-Substituents of Isocyanides. Having identified the catalyst for the insertion into acyclic acetals, we next investigated the effect of isocyanide structure on the TfOH-catalyzed reaction. As was observed in the $GaCl_3$-catalyzed insertion into cyclic acetals, the use of aromatic isocyanides containing alkyl substituents, such as **2a** and **2b**, afforded a mixture of mono- and double-insertion products (eq 7). Accordingly, the use of the electron-deficient isocyanide **2c** again appears to be essential for the selective formation of the mono-insertion product.

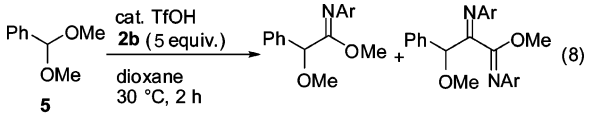
(28) Other less active catalysts that were examined: $ZrCl_4$, $HfCl_4$, $ReCl(CO)_5$, $FeCl_3$, $PtCl_2$, $AuCl_3$, MgI_2, $Zn(OTf)_2$, $Yb(OTf)_3$, $Hf(OTf)_4$, $Sn(OTf)_2$, and $B(C_6F_5)_3$.

(29) Le Roux, C.; Dubac, J. *Synlett* **2002**, 181. Dumeunier, R.; Markó, I. E. *Tetrahedron Lett.* **2004**, *45*, 825.



Ar = 2,6-$Me_2C_6H_3$ (**2a**)	**6a** 51%	**7a** 19%
Ar = 2,6-*i*-$Pr_2C_6H_3$ (**2b**)	**6b** 63%	**7b** 18%
Ar = 2,6-$Cl_2C_6H_3$ (**2c**)	**6c** 89%	**7c** 0%
Ar = 2,6-$Br_2C_6H_3$ (**2d**)	**6d** 83%	**7d** 0%

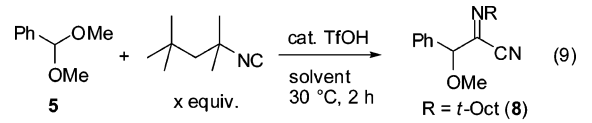
Although our prime objective was to develop a selective monoinsertion process, we briefly pursued the possibility of leading the double-insertion in a major reaction pathway. As a result, the preferential formation of the double-insertion product **7b** was observed, when acetal **5** and 2 equiv of **2b** were treated with a catalytic amount of TfOH in dioxane (eq 8).



Ar = 2,6-*i*-$Pr_2C_6H_3$ **6b** 12% **7b** 82%

The selective double-insertion of isocyanides is normally successful when the *cyclic* product is formed, since the amount of isocyanide incorporated can be controlled to lead to a favorable five- or six-membered ring formation.[21c,i,26,30a,b] Regarding the selective double-insertion of isocyanides in an *acyclic* system, we found only two reports.[16,30c] In this context, the result demonstrated in eq 8 is noteworthy.

We also examined several alkyl isocyanides for use in the TfOH-catalyzed insertion into acetals. When benzyl and cyclohexyl isocyanides were treated with acetal **5** under standard conditions, no insertion products were obtained. On the other hand, the reaction of **5** with *tert*-octyl isocyanide afforded 2-methoxy imidoyl cyanide **8** in 22% yield (eq 9).

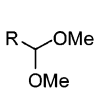
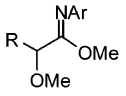
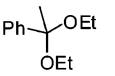
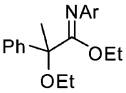
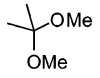
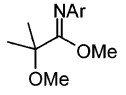
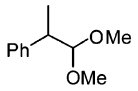
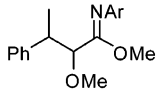
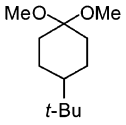
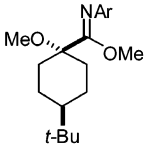
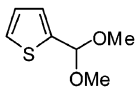
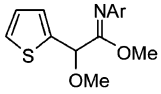
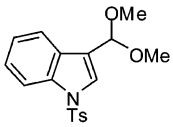
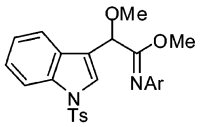


x = 1, in toluene	22%
x = 2, in toluene	42%
x = 2, in dioxane	68%
x = 3, in dioxane	78%

It is interesting to note that Ito and Saegusa previously reported that the reaction of **5** with 1 equiv of *tert*-butyl isocyanide in the presence of a stoichiometric amount of $TiCl_4$ resulted in the formation of 2-methoxy-2-phenylacetonitrile,[19] the compound which was not observed in our catalytic system. Since 2 equiv of isocyanides are incorporated into the compound **8**, we conducted the reaction using the excess amount of isocyanide, increasing the yield of **8** significantly. Optimization of the solvent further improved the yield up to 78%. Although this type of reaction has been reported to be promoted by a *stoichiometric* amount of Et_2AlCl,[27c] this represents the first catalytic variant.

(30) (a) Nair, V.; Menon, R. S.; Deepthi, A.; Devi, R.; Biju, A. T. *Tetrahedron Lett.* **2005**, *46*, 1337. (b) Masdeu, C.; Gómez, E.; Williams, N. A. O.; Lavilla, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3043. (c) Whitby, R. J.; Saluste, C. G.; Furber, M. *Org. Biomol. Chem.* **2004**, *2*, 1974.

Table 3. TfOH-Catalyzed Insertion Reaction of Isocyanide **2c** into Acetals[a]

entry	acetal	insertion product[b]	yield (%)[c]
			
1		R = Ph	89
2		(4-OMe)C_6H_4	81
3		(4-CO_2Me)C_6H_4	82
4		(4-CF_3)C_6H_4	70
5		(4-NO_2)C_6H_4	72
6		(4-CN)C_6H_4	75
7		(4-F)C_6H_4	86
8		(4-Br)C_6H_4	89
9		(2-Me)C_6H_4	91
10		1-naphthyl	86
11		2-naphthyl	86
12		$PhCH_2$	81
13		(*E*)-PrCH=CH	80
14			70
15			77
16			77[d]
17			83[e]
18			80
19			90

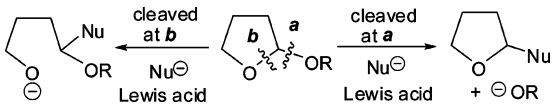
[a] Reaction conditions: acetal (1.0 mmol), 2,6-dichlorophenyl isocyanide (1.0 mmol), TfOH (0.1 mmol) in toluene (6 mL) at 30 °C, 2h. [b] Ar = 2,6-dichlorophenyl. [c] Isolated yields. [d] Stereoisomeric ratio = 1:1. [e] Stereoisomeric ratio = 20:1.

Substrate Scope. Having identified the optimal isocyanide for the selective monoinsertion process, we next explored the scope of the reaction with respect to acetals. As illustrated in Table 3, TfOH efficiently catalyzes the insertion of isocyanide **2c** into a variety of acetals. In all cases, the reaction reached completion within 2 h at ambient temperature. Unlike the $GaCl_3$-catalyzed insertion reaction, acetals derived from both aldehydes and ketones containing aliphatic and aromatic substituents all afforded the corresponding insertion products in good yields. Moreover, the large functional group compatibility is another advantage of the Brønsted acid catalysis. Functional groups, including ethers, esters, halides, nitro, and cyano groups (entries

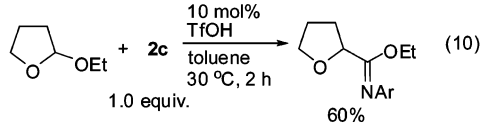
2−8), as well as heteroaromatic groups (entries 18 and 19) were tolerated under the reaction conditions employed. Interestingly, electronic properties of the aromatic ring had little impact on the yield of the insertion product in reactions of a series of *p*-substituted benzaldehyde-derived acetals (entries 1−8). An allylic rearrangement was not involved when an acetal derived from 2-hexenal was employed (entry 13). The presence of a α-stereogenic center did not regulate the stereochemical course of the reaction, affording a 1:1 diastereomeric mixture (entry 16). On the other hand, excellent stereoselectivity was observed for the reaction of 4-*tert*-butylcyclohexanone dimethyl acetal: isocyanide **2c** is selectively inserted into the axial C−O bond (entry 17). A similar stereoselectivity was previously observed in the reaction of this acetal with isocyanides and related nucleophiles.[19,31]

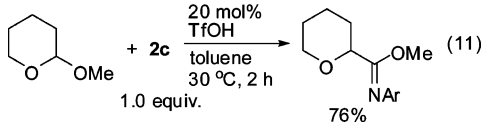
We next examined the catalytic insertion into tetrahydrofuranyl ethers, wherein two nonequivalent C−O bonds are present. As reported in the literature,[32] Lewis acid mediated substitution reactions of such compounds often afford a mixture of products via the nonselective cleavage of both C−O bonds (Scheme 2).

Scheme 2. Possible Pathways for the Substitution Reactions of Tetrahydrofuranyl Ethers



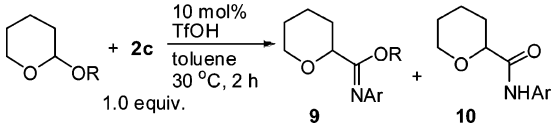
Interestingly, the reaction of 2-ethoxytetrahydrofuran with **2c** induces a selective insertion into the exocyclic C−O bond, and products derived from the cleavage of the endocyclic C−O bond were not detected at all (eq 10). The ring size of such mixed acetals sometimes affects the selectivity between the cleavage of endo- and exocyclic C−O bonds.[32] However, in our catalytic system, the insertion occurred exclusively at the exocyclic C−O bond when the six-membered analogue was applied, providing the tetrahydropyranyl imidate in good yield (eq 11).





Another factor that affects the selectivity of the reaction shown in Scheme 2 is the nature of the R group.[32] Thus, we investigated the TfOH-catalyzed reaction of tetrapyranyl ethers bearing a variety of alkoxy substituents (Table 4). Interestingly, insertion into the exocyclic C−O bond did not occur in any cases, but instead, the Passerini-type amide **10**[33] was obtained in varying yields depending on the substituents. The yield of amide **10** was increased by increasing the steric bulkiness of

Table 4. TfOH-Catalyzed Insertion Reaction of Isocyanide **2c** into Tetrapyranyl Ethers[a]

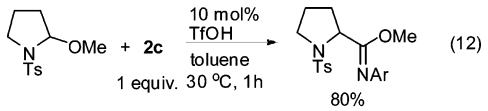


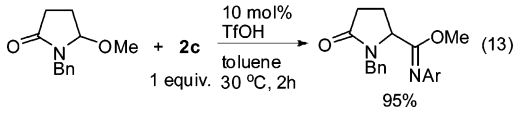
		isolated yields (%)	
entry	R	**9**	**10**
1	Me	70 (**9a**)	6
2	Et	57 (**9b**)	7
3	*i*-Pr	32 (**9c**)	14
4	*t*-Bu	0 (**9d**)	91
5	allyl	37 (**9e**)	25
6	benzyl	0 (**9f**)	94
7	Ph	75 (**9g**)	4
8	acetyl	0 (**9h**)	52

[a] Reaction conditions: acetal (1.0 mmol), 2,6-dichlorophenyl isocyanide (1.0 mmol), TfOH (0.1 mmol) in toluene (6 mL) at 30 °C, 2 h. Ar = 2,6-dichlorophenyl.

the R group, and amide **10** was formed exclusively when *tert*-butyl ether was employed (entries 1−4). A significantly larger amount of the amide product was formed with an allyl ether, compared to the primary alkyl substituents (entry 5). In the case of a benzyl ether, amide **10** was obtained in 94% yield without the formation of the insertion product **9f** (entry 6). A phenoxy group, which possesses a better leaving ability relative to an alkoxy substituent, efficiently afforded the insertion product **9g** (entry 7), whereas the use of an acetate, a much better leaving group, resulted in the exclusive formation of the amide **10** (entry 8). The mechanism for the formation of amide **10** will be discussed below.

To further expand the scope of the reaction, we examined the catalytic insertion into *N*,*O*-acetals. The reaction of 2-methoxypyrrolidine derivatives with isocyanide **2c** in the presence of a catalytic amount of TfOH cleanly furnished the insertion products into a C−O bond (eqs 12 and 13). These reactions represent a new C1 introducing method for cyclic amines, and the products should be useful precursors for amino acid derivatives.





Mechanistic Considerations. In the TfOH-catalyzed reactions of acetals with isocyanides, we observed three different products depending on the structure of the isocyanide employed. The formation of each of the products observed can be explained by assuming the formation of the common nitrilium ion intermediate **B′**, which can be generated by the reaction of the protonated acetal **A′** and isocyanides via an oxocarbenium cation or by the classical S_N2 mechanism[34] (Scheme 3). When the nitrilium cation **B′** was trapped by MeOH dissociated from acetal **A′**, the monoinsertion product **C′** was obtained. The attack by

(31) Noyori, R.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.
(32) Uchimoto, K.; Wakabayashi, Y.; Horie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967. Hojo, M.; Ushioda, N.; Hosomi, A. *Tetrahedron Lett.* **2004**, *45*, 4499.
(33) For the Passerini-type reactions of acetals that lead to α-alkoxy amide, see: Barrett, A. G. M.; Barton, D. H. R.; Falck, J. R.; Papaioannou, D.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 652. See also ref 28a.
(34) Dilman, A. D.; Ioffe, S. L. *Chem. Rev.* **2003**, *103*, 733.

Scheme 3. TfOH-Catalyzed Diverse Pathways in the Reactions of Benzaldehyde with Isocyanides

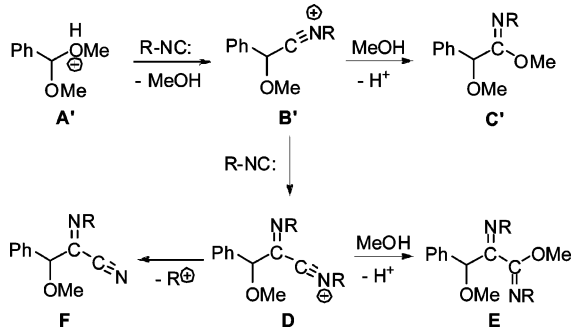


Table 5. ^{13}C NMR Chemical Shifts of the Formally Divalent Carbon Atoms of Isocyanides Used in This Study

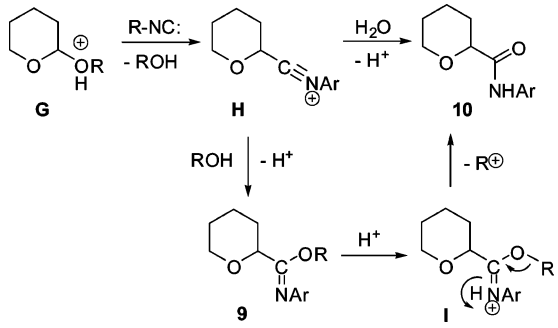
isocyanide	chemical shift (ppm)[a]
2,6-$Me_2C_6H_3NC$: (**2a**)	167.3
2,6-*i*-$Pr_2C_6H_3NC$: (**2b**)	168.3
2,6-$Cl_2C_6H_3NC$: (**2c**)	173.7
2,6-$Br_2C_6H_3NC$: (**2d**)	172.4
t-OctNC:	154.2

[a] ^{13}C NMR in $CDCl_3$. The chemical shifts of the formally divalent carbon atoms are shown.

a second molecule of isocyanide, instead of MeOH, on cation **B′** affords intermediate **D**, which is then trapped by MeOH to furnish the double-insertion product **E**. The selectivity between these two pathways (i.e., **B′** → **C′** and **B′** → **D**) is determined by the structure of isocyanides. Isocyanides containing electron-withdrawing groups, such as **2c** and **2d**, afforded monoinsertion products exclusively, while the competitive double-insertion process was observed with isocyanides containing alkyl substituents, such as **2a** and **2b**. These results indicate that the cationic intermediate **B′** reacts with a weak nucleophile MeOH more efficiently than with a second molecule of the isocyanide due to the low nucleophilicity of the electron-deficient isocyanides **2c** and **2d**. The relative nucleophilicity of isocyanides[35] can be deduced from the ^{13}C NMR chemical shifts of the nucleophilic carbon atoms (Table 5). As expected, the signals for **2c** and **2d** appeared at the lowest field among the isocyanides examined. In the reaction with *tert*-octyl isocyanide, 2-methoxy imidoyl cyanide **F** was obtained. The formation of **F** can be explained by the elimination of the *tert*-octyl cation from intermediate **D**.[27c] Since *tert*-octyl isocyanide would be expected to be highly nucleophilic from the data shown in Table 5, the second attack (**B′** → **D**) should be faster than the trapping of **B′** by MeOH or the fragmentation of **B′**,[19] therefore selectively affording **F**.

In the reactions of tetrahydropyranyl ethers with isocyanide **2c**, we observed the formation of amide **10** in addition to the monoinsertion product **9** (Table 4). Two possible pathways leading to amide **10** can be considered (Scheme 4). One is the addition of the contaminated water to the nitrilium cation **H**, in which the selectivity between **9** and **10** should depend on the relative nucleophilicity of water and the eliminated alcohol (ROH). Thus, this pathway cannot account for the observation that the benzyl ether afforded an amide as the sole product,

Scheme 4. TfOH-Catalyzed Reactions of Tetrahydropyranyl Ethers with Isocyanides



while the phenyl ether, a much better leaving group, resulted in the exclusive formation of the monoinsertion product. An alternate mechanism leading to **10** is the proton-mediated fragmentation of the monoinsertion product (**9** → **I** → **10**). In this mechanism, amide **10** would be expected to be formed more favorably when the R group contains a cation stabilizing structure, such as a tertiary alkyl or a benzyl group. This is in good agreement with the experimental results. Moreover, in the case of the reaction of a benzyl ether substrate, we observed an isomeric mixture of benzylmethylbenzenes (68% isolated yield) which is presumably formed by the Friedel−Crafts type alkylation of the solvent toluene with the postulated benzyl cation.[36]

Application to a Formal Carbonylation Process of Acetals. Carbonylation chemistry offers one of the most straightforward methodologies for introducing carbonyl functionalities into organic molecules.[37] To date, a variety of substrates have been reported to be carbonylated with the aid of transition metal catalysts. However, acetals have not been exploited in such carbonylation processes, although the insertion of carbon monoxide into a C−O bond of acetals would provide a new pathway to α-alkoxy esters, an important class of compounds[38] (eq 14). The lack of such carbonylation processes is partly due to the reluctance of acetals to oxidatively add to transition metal complexes.[39] We envisaged that this challenging class of transformation shown in eq 14 should be achieved formally by combining our catalytic isocyanide insertion and the hydrolysis of the imidates (eq 15).

To establish the two-step protocol shown in eq 15, the hydrolysis of the imidates synthesized through the TfOH-catalyzed reaction was examined. As a result, the acid hydrolysis of the insertion products proceeded smoothly as expected with the efficient recovery of 2,6-dichloroaniline, which can be recycled by converting it to isocyanide **2c** (eq 16).

To further demonstrate the utility of the catalytic insertion, we examined a one-pot protocol based on the three sequential

(35) The relative nucleophilicity of isocyanides has been estimated based on the rate constant of the reaction with benzhydrylium ions, although the data for isocyanides **2c** and **2d** are not available. Tumanov, V. V.; Tishkov, A. A.; Mayr, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3563.

(36) Benzyl alcohol did not give benzylmethylbenzenes under the reaction conditions, excluding the pathway **H** → **10**.

(37) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991. *Catalytic Carbonylation Reactions*; Beller, M., Ed.; Springer: Heidelberg, Germany, 2006.

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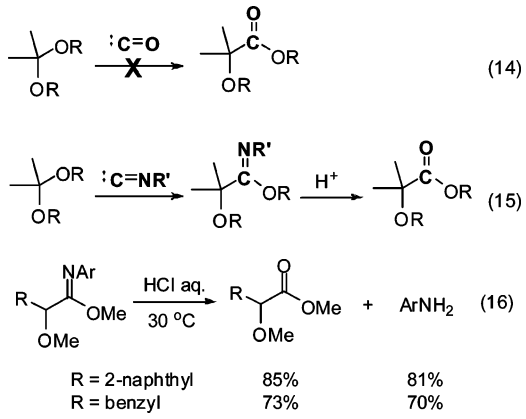
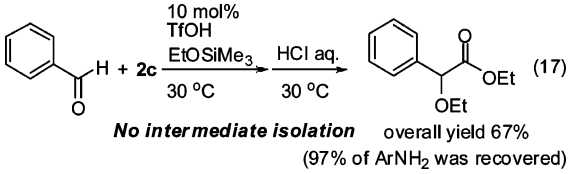


reactions, i.e., acetal formation/catalytic isocyanide insertion/hydrolysis. The treatment of a mixture of benzaldehyde, isocyanide **2c**, and ethoxytrimethylsilane[40] with a catalytic amount of TfOH followed by the acid hydrolysis furnished an α-alkoxy ester in 67% isolated yield (eq 17).[41] The aniline derived from isocyanide **2c** was recovered quantitatively.



Conclusion

In summary, we report on the development of the Brønsted acid catalyzed insertion reaction of isocyanides into a C−O bond of an acetal, leading to the production of α-alkoxy imidates. The reaction is applicable to a diverse array of cyclic and acyclic acetals that contain a wide range of functional groups, such as nitro, cyano, halogen, ester, and alkoxy groups. Particularly noteworthy is that the insertion into acyclic acetals is unprecedented. The key to success is the use of electron-deficient isocyanides **2c** and **2d**, highlighting a valuable feature of isocyanides: their reactivity can be readily controlled by the nature of the substituents on the nitrogen atom. The use of relatively nucleophilic aryl isocyanides **2a** and **2b** induced the incorporation of two molecules of isocyanide, affording the double-insertion product. The use of *tert*-octyl isocyanide resulted in the double incorporation of the isocyanide, followed by acid-mediated fragmentation with the selective formation of an imidoyl cyanide. Since the imidate functionality in the monoinsertion products can be hydrolyzed into an ester, we formally established the carbonylation reaction of acetals, a challenging transformation. Further efforts are being directed toward the application of the catalytic insertion of an isocyanide in the synthesis of more complex molecules and the development of asymmetric variants.

Experimental Procedures

General Procedure for the TfOH-Catalyzed Insertion of Isocyanides into Acetals. A 30 mL two-necked flask was heated for several minutes with a heat gun under flowing nitrogen. After cooling the flask to 30 °C, the acetal (1 mmol), isocyanide (1 mmol), and toluene (6 mL) were added under a gentle stream of nitrogen. To the stirred mixture TfOH (0.1 mmol, 8.9 uL) was added, and the mixture was stirred at 30 °C under a N_2 atmosphere. After 2 h, the mixture was quenched by the addition of Et_3N (3 mL). The product was isolated by silica gel column chromatography.

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Supporting Information Available: Detailed experimental procedures and the characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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