

## GaCl<sub>3</sub>-catalyzed reactions utilizing isocyanides as a C<sub>1</sub> source\*

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*Abstract:* Two GaCl<sub>3</sub>-catalyzed reactions, which utilize isocyanides as a one-carbon unit, are described: a [4+1] cycloaddition of  $\alpha,\beta$ -unsaturated carbonyl compounds with isocyanides, and an insertion reaction of isocyanides into a C–O bond of ketals and acetals. The relatively low affinity of GaCl<sub>3</sub> toward heteroatoms enables the successful catalysis.

*Keywords:* GaCl<sub>3</sub>; isocyanide; acetals; ketals; unsaturated ketones.

### INTRODUCTION

Carbon monoxide (CO) has been recognized as an important C1 building block as exemplified by the Oxo synthesis, one of the world's largest homogeneous catalytic processes [1]. Although, to date, a variety of transition-metal-catalyzed carbonylation reactions have been reported for the synthesis of acyclic and cyclic carbonyl compounds, a number of transformations are difficult to achieve using such carbonylation reactions. A potentially effective approach for achieving such challenging carbonylation reactions is the use of isocyanides as a C1 source in place of CO. It is well known that isocyanides and CO are isoelectronic: Both contain a formally divalent carbon. In addition, the reactivity of isocyanides can be finely tuned both sterically and electronically by changing the nature of the substituents on the nitrogen atom, thus permitting a wide range of reactivities. Indeed, isocyanides are known to participate in a unique class of C–C bond-forming reactions, such as the Passerini and Ugi reactions [2], in the absence of catalysts, which is in sharp contrast to the reaction of CO, which normally requires transition-metal catalysts for its incorporation. It has also been reported that isocyanides functioned as a one-carbon unit in some Lewis acid-mediated processes, most of which require more than a stoichiometric amount of the Lewis acid. One of the most serious problems that hampers the development of Lewis acid-catalyzed reactions of isocyanides is the strong bonding between the Lewis acid and the reaction product, which typically contains a basic nitrogen atom derived from isocyanides [3]. To realize such catalytic processes, it is therefore critical to identify a Lewis acid that is sufficiently strong to accelerate the reaction and, at the same time, that is not too strong to prevent its detachment from the product. We recently discovered that GaCl<sub>3</sub> satisfies the above criteria. This article describes our progress in developing new GaCl<sub>3</sub>-catalyzed processes, which utilize isocyanides over the past few years [4].

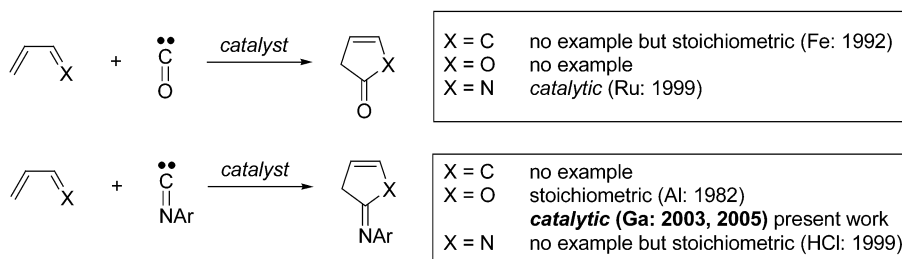
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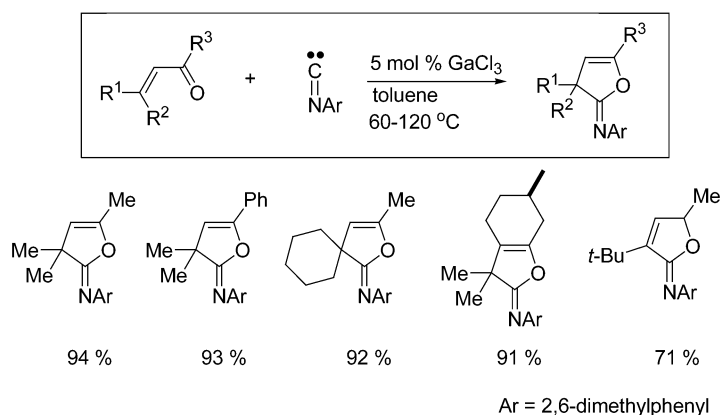
## [4+1] CYCLOADDITION OF $\alpha,\beta$ -UNSATURATED CARBONYL COMPOUNDS WITH ISOCYANIDES

Carbonylative cycloaddition represents a straightforward and atom-economical strategy for the synthesis of cyclic carbonyl compounds. Among such processes, the [2+2+1] cycloaddition of alkynes, alkenes, and CO, the Pauson–Khand-type reaction, has been the subject of intensive studies and it is now recognized as a powerful strategy for the construction of cyclopentenones [5]. In addition, applications of the [2+2+1] cycloaddition strategy to the synthesis of heterocycles, such as lactones [6] and lactams [7], have also been reported, although with limited success. In terms of five-membered ring construction, a [4+1] mode, in which 1,3-conjugated systems act as four-atom assembling units, is also an attractive alternate (Fig. 1). In contrast to the considerable progress made in the Pauson–Khand-type reaction, the catalytic [4+1] carbonylative cycloaddition of simple 1,3-conjugated systems still remains in its infancy [8]. The only successful example of this class of reactions is the ruthenium-catalyzed cyclocarbonylation of  $\alpha,\beta$ -unsaturated imines, reported by us [9] (Fig. 1). Our continuing interests in this field led us to examine isocyanides as a one-carbon unit because of its isoelectronic similarity to carbon monoxide. Prior to 2003, there were no reports of catalytic [4+1] cycloaddition of simple 1,3-conjugated system with isocyanides (Fig. 1) [10,11].



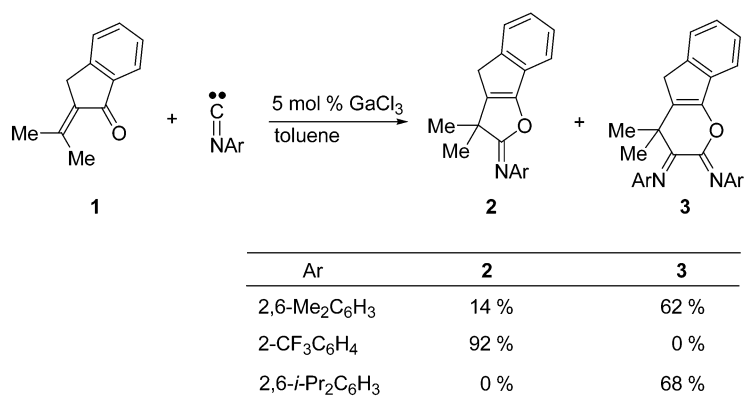
**Fig. 1** [4+1] Carbonylative cycloadditions.

After screening an array of transition-metal and Lewis acid catalysts, we discovered that  $\text{GaCl}_3$  functions as an effective catalyst for the [4+1] cycloaddition of  $\alpha,\beta$ -unsaturated carbonyl compounds [12]. Representative examples are shown in Scheme 1. It was found that  $\beta,\beta$ -di-substituted enones are excellent substrates for this cycloaddition, yielding imino lactone derivatives.  $\beta$ -Mono-substituted enones bearing a bulky substituent, such as a *tert*-butyl or an *iso*-propyl group, can also be applied, although the primary products isomerize to stable  $\alpha,\beta$ -unsaturated imino butenolides. Since the imino groups in the products can be hydrolyzed to carbonyl groups [10a], the present transformation is synthetically equivalent to the cyclocarbonylation of  $\alpha,\beta$ -unsaturated ketones, a challenging class of carbonylation reactions.



**Scheme 1** [4+1] Cycloaddition of  $\alpha,\beta$ -unsaturated ketones and isocyanides.

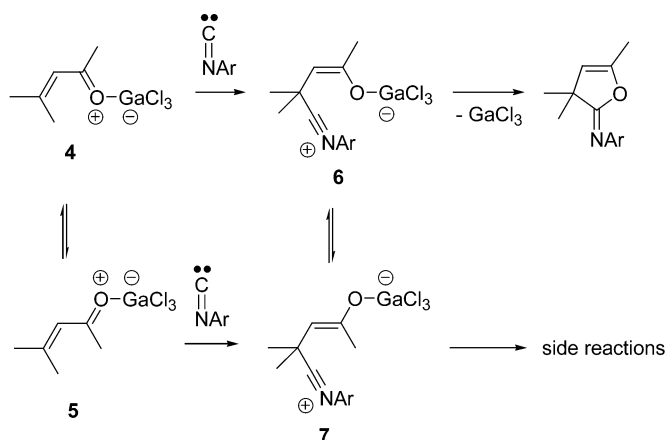
In the present GaCl<sub>3</sub>-catalyzed [4+1] cycloaddition reactions, aromatic isocyanides generally afford the corresponding imino lactones in good yields. However, an interesting substituent effect was observed when the bicyclic enone **1** was used as a substrate. The reaction of **1** with 2,6-dimethylphenylisocyanide under standard conditions led to the formation of the double-insertion product **3** as a major product, along with the expected imino lactone **2** (Scheme 2). We decided to examine the effect of substituents of isocyanides in the hope of achieving a selective synthesis of each type of the product. As a result, it was found that the mono-insertion product **2** was selectively produced when the electron-deficient isocyanide 2-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>NC was used. On the other hand, the double-insertion product **3** was selectively produced when the sterically demanding 2,6-*i*-Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NC was employed. The product distribution can be precisely controlled by simply appropriately altering the substituents on the isocyanides. This clearly demonstrates a prominent advantage of the use of isocyanides over CO.



**Scheme 2** Effect of substituents of isocyanides.

A proposed reaction pathway is illustrated in Scheme 3. The nucleophilic attack of the isocyanide on the  $\beta$ -carbon of a GaCl<sub>3</sub>-activated enone **4** affords the zwitterionic intermediate **6**. Subsequent cyclization via an intramolecular attack of the oxygen atom bound to gallium on the cationic carbon leads to the final product. We conclude that the conformation of the starting conjugated enones is an important factor in this catalytic reaction. When conjugated enones containing only one less bulky substituent at the  $\beta$ -position are used as a substrate, the dominant conformation is the *s*-trans form **5**. The zwitter-

ionic intermediate **7**, formed from **5**, requires an *E/Z* isomerization to **6** for the intramolecular cyclization. It is likely that the *E/Z* isomerization is relatively slow compared to the rates of side reactions, thus resulting in lower yields of enones when a less bulky substituent is located at the  $\beta$ -position. In contrast, the *s-cis* isomer **4** is favored for  $\beta$ -di-substituted enones [13], leading to the more facile formation of the product without requiring *E/Z* isomerization.

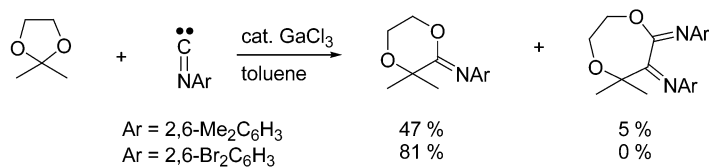


**Scheme 3** Possible reaction pathway.

An important feature of the present reaction is the fact that the reaction proceeds catalytically. NMR studies indicate that the product imino lactone is strongly coordinated to  $\text{GaCl}_3$  at room temperature even in the presence of the starting conjugated enones and isocyanides and no catalysis occurs. Further analysis revealed that  $\text{GaCl}_3$  can be detached from the product on heating, thus allowing catalyst turnover. We believe that the relatively low affinity of  $\text{GaCl}_3$  for heteroatoms enables its smooth detachment from the product.

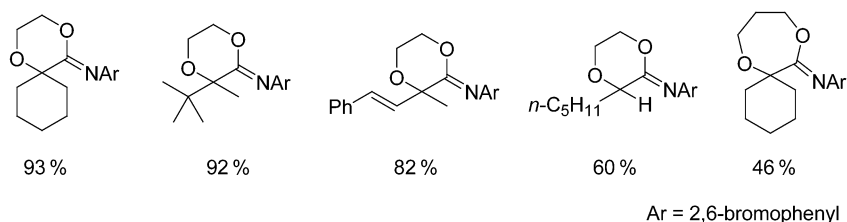
### INSERTION REACTIONS OF ISOCYANIDES INTO A C–O BOND IN CYCLIC KETALS AND ACETALS

In a search for other applications of the  $\text{GaCl}_3$ /isocyanide system, we discovered the catalytic insertion reaction of isocyanides into a C–O bond in cyclic ketals and acetals [14]. Although a stoichiometric amount of  $\text{TiCl}_4$  is known to promote this type of reaction [15], our results represent the first catalytic variant. In our  $\text{GaCl}_3$ -catalyzed reaction, the electronic property of the isocyanide has a significant effect on the efficiency of the reaction. The use of 2,6- $\text{Me}_2\text{C}_6\text{H}_3\text{NC}$  afforded the desired insertion product in modest yield, along with a small amount of the double-insertion product (5%). On the other hand, the introduction of electron-withdrawing atoms on the benzene ring of the isocyanide significantly improved the yield, and no detectable double-insertion product was produced (Scheme 4).



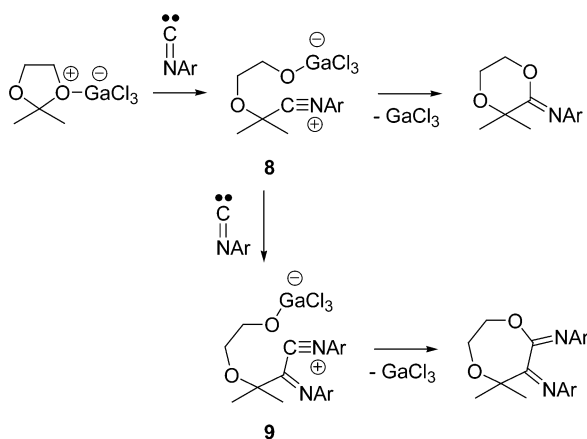
**Scheme 4** Catalytic insertion reaction of isocyanides into a C–O bond in cyclic ketals and acetals.

Representative compounds synthesized via the GaCl<sub>3</sub>-catalyzed insertion reaction are shown in Fig. 2. Again, the products can be transformed into the corresponding cyclic esters via acid hydrolysis [15], the process can be regarded as the unprecedented formal carbonylation of ketals and acetals.



**Fig. 2** Representative examples for a GaCl<sub>3</sub>-catalyzed reaction of isocyanides with ketals and acetals.

A possible reaction mechanism is shown in Scheme 5. The nucleophilic attack of the isocyanide on a GaCl<sub>3</sub>-activated ketal affords an acyclic zwitterionic intermediate **8**, which then cyclizes via intramolecular attack of the oxygen bound to the gallium on the cationic imino carbon to furnish the final product. The effect of the substituent on isocyanides can be rationalized as follows. The cyclization of **8** would be expected to be accelerated when electron-deficient isocyanides are used, since the electrophilicity of the cationic center in **8** should be increased. In addition, the decreased nucleophilicity of electron-deficient isocyanides would retard the undesired competing pathway, such as the formation of **9**, which leads to a double-insertion product. Concerning the [4+1] cycloaddition of  $\alpha,\beta$ -unsaturated enones with isocyanides, the relatively low affinity of GaCl<sub>3</sub> for heteroatoms is the key to successful catalysis.



**Scheme 5** Possible mechanism for a catalytic insertion reaction of isocyanides into a C–O bond in cyclic ketals and acetals.

## CONCLUSIONS

Two GaCl<sub>3</sub>-catalyzed reactions in which isocyanides are employed as a C1 source are described. We believe that the relatively low affinity of GaCl<sub>3</sub> for heteroatoms is the key to the successful catalysis. It should be emphasized that the transformations described herein can not be achieved when CO is used as a C1 source. The unique reactivity associated with the fine-tuning of the electronic and steric environments around the isocyanides enables these new types of reactions to proceed.

## ACKNOWLEDGMENTS

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