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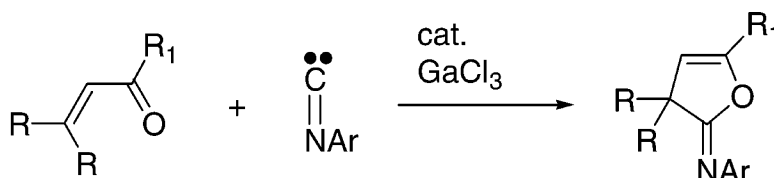
A GaCl-Catalyzed [4+1] Cycloaddition of □,β-Unsaturated Carbonyl Compounds and Isocyanides Leading to Unsaturated □-Lactone Derivatives

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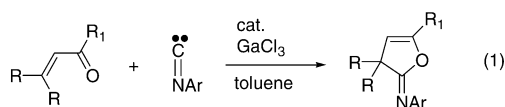
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A GaCl₃-Catalyzed [4+1] Cycloaddition of α,β-Unsaturated Carbonyl Compounds and Isocyanides Leading to Unsaturated γ-Lactone Derivatives

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Isocyanides are recognized as useful building blocks in organic synthesis[1] as well as in polymer science.[2] Among the characteristic features of isocyanide chemistry are the high acidity of the α C−H bond and a high reactivity toward cations, anions, and radicals. It should be noted that their electronic and steric properties can be finely tuned by simply changing the nature of the substituents attached to the nitrogen. Isocyanides are also often used in cycloaddition reactions in the construction of heterocyclic compounds.[3] A variety of cycloaddition reactions involving a wide spectrum of substrates, such as quinone methides,[4] thioxothiamides,[5] N-acylimines,[6] azadienes,[7] and vinyl isocyanates,[8] with isocyanides have been achieved, even in the absence of a promoter. Promoters, such as acids,[9] Lewis acids, or transtion metal complexes, were generally used with less reactive substrates. Intramolecular [2+2+1] cycloaddition reactions of enynes with isocyanides proceed when Ni and Ti complexes are used as promoters.[10] The [2+2+1] cycloaddition of alkynes and isocyanides with the aid of a wide range of transition metal complexes leading to iminocyclopentadienes has been extensively studied.[11] Ito and Saegusa reported on the Et₂AlCl-mediated reaction of α,β-unsaturated carbonyl compounds with methyl isocyanide leading to unsaturated N-substituted iminolactones, which can be easily converted to γ-butyrolactone.[12] Most of these reactions reported thus far require the use of a stoichiometric amount of promoter for the reaction to proceed effectively, partially because isocyanides and/or products strongly coordinate to the promoters, thus stopping the reaction.[13] We wish to report herein on a catalytic [4+1] cycloaddition of α,β-unsaturated carbonyl compounds and isocyanides in the presence of a catalytic amount of GaCl₃,[14] which was found to be the most effective catalyst because of its low affinity toward oxygen or nitrogen atoms (eq 1).[15]

$$R \overset{R}{\diagup} \overset{O}{\underset{R}{\diagdown}} \overset{R_1}{} + \overset{\bullet\bullet}{\underset{NAr}{C}} \xrightarrow[\text{toluene}]{\substack{\text{cat.}\\ \text{GaCl}_3}} R \overset{R_1}{\underset{\underset{NAr}{R}}{\diagup}} O \quad (1)$$

Following an extensive screening, we found that the reaction of mesityl oxide (**1**) with 2,6-Me₂C₆H₃NC proceeded to give 2,6-dimethyl-N-(3,3,5-trimethyl-2-(3H)-furanylidene)benzenamine (**2**)[16] in the presence of a catalytic amount of metal complexes. Among the complexes examined, GaCl₃ showed a high catalytic activity for the reaction of **1** at 60 °C (entry 1 in Table 1).[17] Aromatic isocyanides, especially sterically demanding ones and those bearing an electron-withdrawing group, were found to be effective, but aliphatic isocyanides were not: 2,6-Me₂C₆H₃NC (94%), 2,6-i-Pr₂C₆H₃NC (94%), 2-MeC₆H₄NC (65%), 2,6-(CF₃)₂C₆H₃NC (92%), 2-CF₃C₆H₄NC (85%), (CH₃)₃CNC (24%), (C₆H₁₃)₃NC (trace).

Some selected results are shown in Table 1. The presence of geminal substituents at the β-position, as in **3**, **5**, and **7**, led to the expected products in high yields. It appears that the substituent at the β-position must be sufficiently sterically bulky (ᵗBu versus ⁿ-

Bu) for the reaction to proceed efficiently. Enones bearing an n-butyl group at the β-position, as in **9**, did not serve as a good substrate, while t-Bu substituted enone **11** gave **12** in high yield. However, the use of 2,6-(CF₃)₂C₆H₃NC significantly improved the yield to 65%. In contrast to acyclic enones, bulkiness at the β-position, as in **17**, is not a critical factor. The use of α,β-unsaturated aldehyde **13** with isocyanide also gave the corresponding lactone **14**, but it was necessary to optimize the reaction conditions.

The reaction of **19** with 2,6-Me₂C₆H₃NC (2 equiv) gave a mixture of an expected γ-lactone product **20a** and a double-insertion product **21a**. Our attention therefore turned toward tuning isocyanides to allow for a more selective reaction. This might be accomplished by changing the isocyanides. Note that **20b** was obtained selectively when 2-CF₃C₆H₄NC was used as the isocyanide. In contrast, the use of 2,6-ⁱPr₂C₆H₃NC gave the double-insertion product **21c** as the sole product.
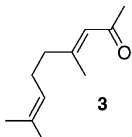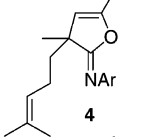
		20	21
a:	Ar = 2,6-Me₂C₆H₃	14%	62%
b:	Ar = 2-CF₃C₆H₄	92%	trace
c:	Ar = 2,6-ⁱPr₂C₆H₃	trace	68%
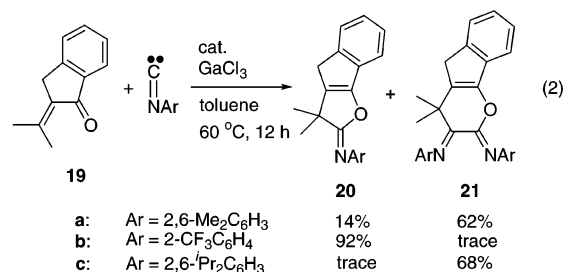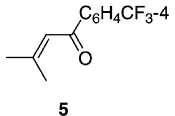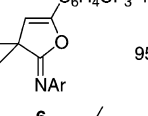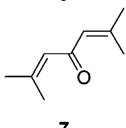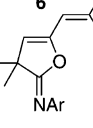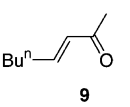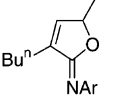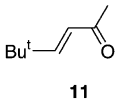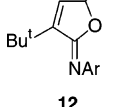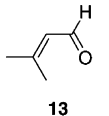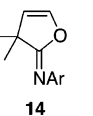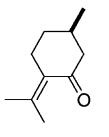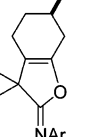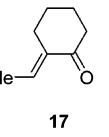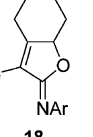
A proposed mechanism for this reaction is shown in Scheme 1. The coordination of GaCl₃ to the oxygen atom in **1** leads to a more electrophilic β-carbon.[18] Isocyanide attacks the β-carbon to give **23**. The Z-isomer of **23** easily undergoes cyclization to give the final product. On the other hand, it is necessary for the E-isomer of **23** to be isomerized to a Z-isomer prior to the cyclization. If a less bulky substituent is attached at the β-position of the α,β-unsaturated ketone, **23E** undergoes side reactions, such as reactions with other α,β-unsaturated ketone molecules.[19] The presence of a bulky substituent or disubstituents at the β-position prevents such intermolecular competing side reactions due to steric factors. Consequently, isomerization to the Z-isomer, followed by intra-

Scheme 1. A Proposed Reaction Mechanism
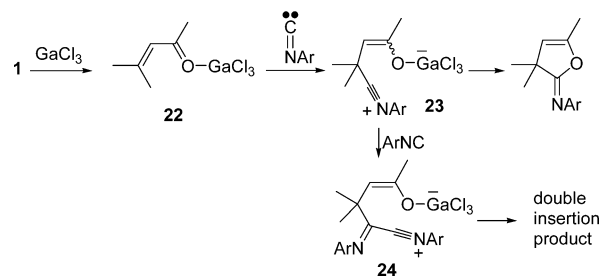
Table 1. The GaCl$_3$-Catalyzed Reaction of α,β-Unsaturated Ketones with Isocyanide[a]

enone	product	yield [b]
1	**2**	94%
3	**4**	91% (70 °C, 4 h)
5 C$_6$H$_4$CF$_3$-4	**6** C$_6$H$_4$CF$_3$-4	95% (120 °C, 12 h)[c]
7	**8**	78% (100 °C, 12 h)
9 Bu^n	**10** Bu^n	20% / 65% (40 °C, 12 h)[d]
11 Bu^t	**12** Bu^t	73%
13 H	**14**	41% (100 °C, 18 h)[e]
15	**16**	91%
17 Me	**18** Me	44%

[a] Reaction conditions: α,β-unsaturated ketone (1 mmol), 2,6-dimethylphenylisocyanide (1.1 mmol), GaCl$_3$ (0.05 mmol, 1 M in methylcyclohexane) in toluene (3 mL) at 60 °C, 18 h. [b] Isolated yield. [c] Isocyanide (1.5 mmol) was used. [d] 2,6-(CF$_3$)$_2$C$_6$H$_3$NC was used. [e] Zn(OTf)$_2$ (0.05 mmol) was used as a catalyst in place of GaCl$_3$.

molecular cyclization, takes place to give the product. In the case of cyclic enones, such an isomerization is not necessary because the generated enolates are constrained to a *Z*-geometry. The key to successful catalysis would be the softness of GaCl$_3$ that allows facile *E*/*Z* isomerization, cyclization, and the deattachment of GaCl$_3$ from the product. In the case of **19**, the formation of **20** is restricted by a ring strain that led to the formation of a double-insertion product **21**. However, the presence of an electron-withdrawing group in the isocyanide facilitates the cyclization to **20** because of a higher electrophilicity of **23** as well as less nucleophilicity of the isocyanide to attack **23**.

In summary, the reaction described here represents the first example of the catalytic reaction of α,β-unsaturated ketones with isocyanides leading to the formation of unsaturated lactone derivatives. GaCl$_3$ is an excellent catalyst due to its lower oxophilicity, which is desirable for all of the key steps, such as *E*/*Z* isomerization, cyclization, and deattachment from the products. A combination of isocyanides and soft Lewis acids would be expected to be a new reaction system that would allow new types of catalytic cycloaddition reactions. A spectroscopic study using NMR and React IR to confirm real intermediates is underway.

Supporting Information Available: Full experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) All new compounds were characterized by NMR, IR, mass spectral data, and elemental analyses or high-resolution mass spectrometry. See Supporting Information.
(17) Some other Lewis acids, such as ZrCl$_4$ (71%), Yb(OTf)$_3$ (60%), In(OTf)$_3$ (44%), and Y(OTf)$_3$ (11%), also show catalytic activity for the reaction of **1** with 2,6-Me$_2$C$_6$H$_3$NC. Although Et$_2$AlCl is also active as a catalyst (87%), this is the only case, and it was found to not be effective for other enones. For example, the reaction of **5**, **9**, and **11** using Et$_2$AlCl as the catalyst did not give the corresponding products.
(18) When **1** was treated with 1 equiv of GaCl$_3$ in C$_6$D$_6$, all of the ^{1}H NMR peaks in **1** immediately disappeared, and new peaks appeared upfield from **1**. In contrast, all new peaks appeared downfield in CD$_2$Cl$_2$. Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801.
(19) A byproduct that consists of two molecules of ketone and one molecule of isocyanide was observed by GC-MS in the reaction of **9**.

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