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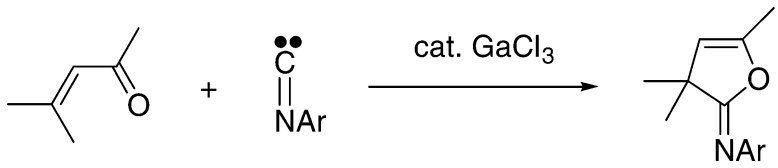

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Catalytic [4+1] Cycloaddition of α,β-Unsaturated Carbonyl Compounds with Isocyanides

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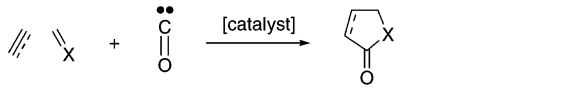
Abstract: The $GaCl_3$-catalyzed [4+1] cycloaddition reactions of α,β-unsaturated ketones with isocyanides leading to lactone derivatives are described. While some other Lewis acids also show catalytic activity, $GaCl_3$ was the most efficient catalyst. The reaction is significantly affected by the structure of both the isocyanides and the α,β-unsaturated ketones. Aromatic isocyanides, especially sterically demanding ones and those bearing an electron-withdrawing group, can be used, but aliphatic isocyanides cannot. The bulkiness of substituents at the β-position of acyclic α,β-unsaturated ketones is an important factor for the reaction to proceed efficiently. Generally, the more the bulky substituent, the higher is the yield. The reaction of α,β-unsaturated ketones bearing geminal substituents at the β-position gave the corresponding products in high yields. In monosubstituted derivatives, the yields are relatively low. However, substrates having a bulky substituent, such as a *tert*-Bu group, at the β-position give high yields. Bulkiness is also required in cyclic α,β-unsaturated ketones, but the effect is small. In alkyl vinyl ketones, the reactivity decreased with the steric bulk of the alkyl group. In aryl vinyl ketones, the presence of an electron-donating group on the aromatic ring decreases the reactivity. The success of the catalysis can be attributed to the low affinity of $GaCl_3$ toward heteroatoms, compared with usual Lewis acids.

Introduction

Cycloaddition reactions represent an important route to the production of cyclic compounds from acyclic substrates.[1] Carbon monoxide (CO) is frequently used as a one-carbon unit in cycloaddition reactions, which is recognized as carbonylative cycloaddition reaction, because of its usefulness in the construction of cyclic carbonyl frameworks. Various types of carbonylative cycloaddition reactions have been reported thus far.[2−11] A [2+2+1] cycloaddition is a useful method for the construction of five-membered cyclic carbonyl compounds, such as cyclopentenones,[2] and unsaturated γ-lactones[3] and γ-lactams,[4] or their saturated compounds[5−7] (Scheme 1).

Scheme 1. [2+2+1] Carbonylative Cycloadditions

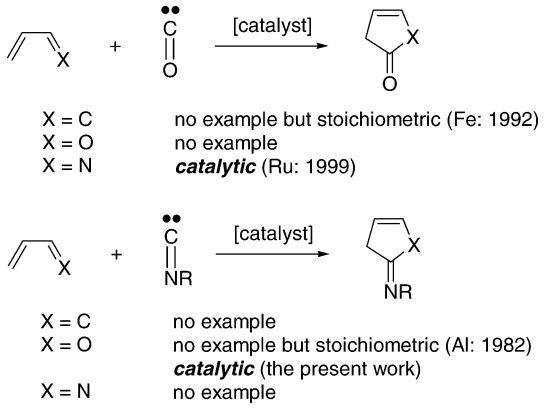


X = C Co, Ru, Rh, Ir, Ti (Pauson-Khand-type reaction)
X = O Ru, Ti
X = N Ru

A [4+1] cycloaddition of a 1,3-conjugation system with CO would be a straightforward and attractive alternate for the construction of five-membered carbonyl compounds, such as cyclopentenone, γ-butyrolactone, and γ-butyrolactam derivatives (X = C, O, and N, respectively) (Scheme 2). However, such examples are rare except for the cycloaddition of specific molecules that contain cumulated double bonds, such as vinylallenes, diallenes, allenyl ketones, and allenyl imines.[8] No

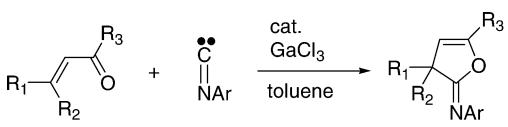
(1) For general reviews on transition-metal-promoted cycloadditions: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523.
(2) For reviews on the Pauson−Khand reaction, see Schore, N. E. *Org. React.* **1991**, *40*, 1. Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911. Blanco-Urgoiti, J.; Anorbe, L.; Pérez-Serrano, L.; Dominguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32.
(3) Chatani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335. Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1584.
(4) Chatani, N.; Morimoto, T.; Kamitani, A.; Fukumoto, Y.; Murai, S. *J. Organomet. Chem.* **1999**, *579*, 177.
(5) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4424. Mandal, S. K.; Amin, Sk. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457.
(6) Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160. Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663. Chatani, N.; Amako, K.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **2003**, *68*, 1591.
(7) Chatani, N.; Tobisu, M.; Asaumi, T.; Murai, S. *Synthesis* **2000**, 925. Göbel, A.; Imhof, W. *Chem. Commun.* **2001**, 593. Imhöf, W.; Gobel, A. *J. Mol. Catal. A* **2003**, *197*, 15.
(8) Eaton, B. E.; Rollman, B.; Kaduk, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 6245. Mandai, T.; Tsuji, J.; Tsujiguchi, Y.; Saito, S. *J. Am. Chem. Soc.* **1993**, *115*, 5865. Sigman, M. S.; Kerr, C. E.; Eaton, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 7545. Sigman, M. S.; Eaton, B. E. *J. Org. Chem.* **1994**, *59*, 7488. Murakami, M.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2691. Sigman, M. S.; Eaton, B. E.; Heise, J. D.; Kubiak, C. P. *Organometallics* **1996**, *15*, 2829. Sigman, M. S.; Eaton, B. E. *J. Am. Chem. Soc.* **1996**, *118*, 11783. Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 2950. Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4130.
(9) Morimoto, T.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 1758.
(10) Boeckman, R. K., Jr.; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 3651.
(11) Murakami, M.; Itami, K.; Ubukata, M.; Tsuji, I.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 4. Murakami, M.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3418. Suzuki, N.; Kondo, T.; Mitsudo, T. *Organometallics* **1998**, *17*, 766. Koga, Y.; Narasaka, K. *Chem. Lett.* **1999**, 705. Kamitani, A.; Chatani, N.; Morimoto, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 9230. Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876. Lee, S. I.; Park, J. H.; Chung, Y. K.; Lee, S.-G. *J. Am. Chem. Soc.* **2004**, *126*, 2714.

Scheme 2. [4+1] Carbonylative Cycloadditions



examples of a catalytic [4+1] cycloaddition of simple 1,3-butadienes or α,β-unsaturated ketones with CO have been reported.[12] On the other hand, the [4+1] cycloaddition of α,β-unsaturated imines with CO leading to γ-lactams can be accomplished using $Ru_3(CO)_{12}$ as the catalyst.[9]

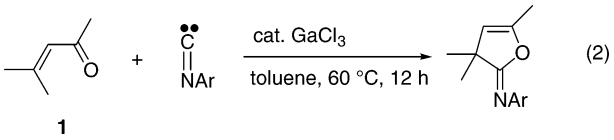
We next turned our attention to the use of isocyanides in place of CO, because isocyanides are structurally isoelectronic to CO and are easily handled in the laboratory compared with gaseous and toxic CO. Most importantly, their reactivity can be tuned electronically and sterically by simply changing the nature of the substituent on nitrogen. Our goal was to explore new catalytic transformations that cannot be accessed by the use of CO, using isocyanides as a one-carbon unit. In fact, isocyanides have often been used as a one-carbon assembling unit. Tamao[13] and Buckwald[14] reported that isocyanides could be used in place of CO in the intramolecular Pauson−Khand type transformation of enynes. Recently, Takahashi reported on the reaction of zirconacyclopentadienes with isocyanide leading to iminocyclopentadienes.[15] Ito and Saegusa reported on the Et_2AlCl-mediated reaction of α,β-unsaturated carbonyl compounds with methylisocyanide leading to unsaturated *N*-substituted iminolactones, which are readily converted to γ-butyrolactones.[16] The use of a stoichiometric amount of promoter was necessary for the reaction to proceed effectively, and the reaction was sluggish when carried out in the presence of a catalytic amount of Et_2AlCl. In a prior communication, we reported that $GaCl_3$ effectively catalyzes the [4+1] cycloaddition of α,β-unsaturated carbonyl compounds with isocyanides.[17] This paper provides a complete description of the scope of this chemistry, with particular emphasis on the effect of substituents on α,β-unsaturated carbonyl compounds and isocyanides that significantly control the efficiency of the reaction. A further focus will be on the reaction mechanism, as studied by spectroscopic measurements.



(12) The reaction of 1,3-butadiene with CO leading to cylopentenones is limited to a stoichiometric reaction by the use of η^4-butadiene-$Fe(CO)_4$ complexes. Franck-Neumann, M.; Michelotti, E. L.; Simler, R.; Vernier, J.-M. *Tetrahedron Lett.* **1992**, *33*, 7361. Franck-Neumann, M.; Vernier, J.-M. *Tetrahedron Lett.* **1992**, *33*, 7365.
(13) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286. See also Zhang, M.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 4498.
(14) Grossman, R. B.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 5803. Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8593.

Results and Discussion

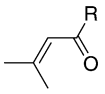
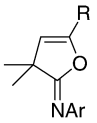
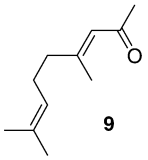
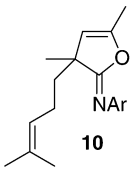
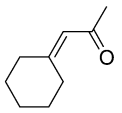
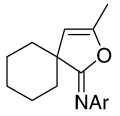
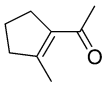
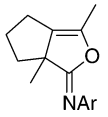
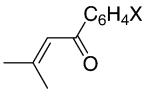
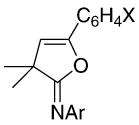
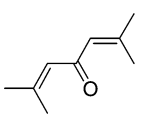
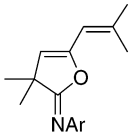
A variety of metal complexes (5 mol %) were screened for their ability to catalyze the reaction of mesityl oxide (**1**) with 2,6-$Me_2C_6H_4NC$ (1.1 equiv) in toluene at 60 °C (eq 2). We found that various Lewis acids are able to function as the catalyst for the transformation of **1** and 2,6-$Me_2C_6H_4NC$: $GaCl_3$ (94%), $ZrCl_4$ (71%), $Yb(OTf)_3$ (60%), $In(OTf)_3$ (44%), and $Y(OTf)_3$ (11%). Although Et_2AlCl is also active as a catalyst (87%) for the reaction of **1** with 2,6-$Me_2C_6H_4NC$, this appeared to be rather exceptional, since it was not effective for other enones. For example, the reaction of **15a**, **21**, and **29** using Et_2AlCl as the catalyst (5 mol %) did not give the expected products. Other Lewis acids also are not applicable to a broad range of substrates. Among the Lewis acids examined, $GaCl_3$ showed a high catalytic activity for the reaction of **1** and served as a catalyst for a broad range of substrates. We next examined the effect of isocyanide structure on the reaction. One of the characteristic features of isocyanides is the ease of tuning their reactivity by simply changing the nature of a substituent on the nitrogen. It was found that aromatic isocyanides, especially sterically demanding ones and those bearing an electron-withdrawing group, are effective, but aliphatic isocyanides were not: 2,6-$Me_2C_6H_4NC$ (94%), 2,6-^{i}-$Pr_2C_6H_3NC$ (94%), 2-MeC_6H_4NC (65%), 2,6-$(CF_3)_2C_6H_3NC$ (92%), 2-$CF_3C_6H_4NC$ (85%), $(CH_3)_3CNC$ (24%), $(C_6H_{13})NC$ (trace). Toluene and methylcyclohexane were good solvents: toluene (94%), methylcyclohexane (92%), THF (60%), and CH_2Cl_2 (60%).



The results of the reaction of acyclic α,β-unsaturated ketones bearing two β-substituents at the β-carbon with isocyanides are shown in Table 1. The efficiency of the reaction was dramatically influenced by the steric properties of the carbonyl substituent. The reactivity decreased as the alkyl group is sterically demanding (**1** > **3** > **5** > **7**). However, an increase in reaction temperature improved the yields, as in **5** and **7**. The reaction was applicable to the construction of the bicyclic lactone derivative **13**. Aryl vinyl ketones **15** are less reactive, compared with alkyl vinyl ketones. The reaction of **15a** at 60 °C gave the expected product **16a** in 52% yield. A higher reaction temperature (100 °C) improved the product yield to 81%. The use of an excess of isocyanide (1.5 equiv) at 120 °C gave **16a** in 93% yield. The presence of an electron-donating group on the benzene ring, as in **15c**, decreased the reactivity. However, the reaction proceeded efficiently irrespective of the electronic and steric nature of substituents on the aromatic ring, when the reaction was carried out at 120 °C.

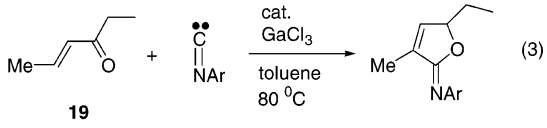
(15) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K. *Organometallics* **2001**, *20*, 4122.
(16) Ito, Y.; Kato, H.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *47*, 743.
(17) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812.

Table 1. $GaCl_3$-Catalyzed Reaction of α,β-Unsaturated Ketones Bearing Two β-Substituents at the β-Position with Isocyanide[a]

enone		product	yield[b]
			
1	R = Me	**2**	94%
3	R = Bu	**4**	81%
5	R = Pr^i	**6**	62%
			82% (80 °C, 12 h)
7	R = Bu^t	**8**	9%
			41% (100 °C, 18 h)
			91% (70 °C, 4 h)
9		**10**	
			92%
11		**12**	
			45%
13		**14**	
			
15		**16**	
X = H (**a**)			52%
			81% (100 °C, 12 h)
			93% (120 °C, 12 h)[c]
X = 4-Me (**b**)			94% (120 °C, 12 h)[c]
X = 4-OMe (**c**)			51% (100 °C, 12 h)
			86% (120 °C, 12 h)[c]
X = 3-OMe (**d**)			88% (120 °C, 12 h)[c]
X = 4-CF_3 (**e**)			79%
			95% (120 °C, 12 h)[c]
X = 2-Me (**f**)			90% (120 °C, 12 h)[c]
			71% (80 °C, 12 h)
17		**18**	

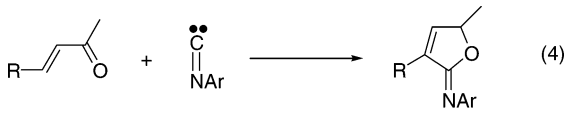
[a] The reaction conditions: α,β-unsaturated ketone (1 mmol), 2,6-xylylisocyanide (1.1 mmol), $GaCl_3$ (0.05 mmol, 1 M in methylcyclohexane) in toluene (3 mL) at 60 °C, 18 h. [b] Isolated yield. [c] 2,6-Xylylisocyanide (1.5 mmol) was used.

Bulkiness at the β-position in unsaturated ketones bearing a monosubstituent at the β-position is important for the reaction to proceed (eqs 3 and 4). The substitution of a methyl group at the β-position, as in **19**, gave a negligible amount of the expected product **20** (eq 3). However, the yields increased with increasing



19 **20** trace (3)

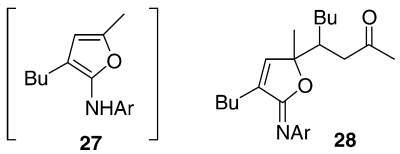
the size of the alkyl group at the β-position, as shown in eq 4. In **21**, a byproduct **28**, consisting of two molecules of the enone and one molecule of isocyanide, was isolated in 15% yield. Compound **28** could have been produced by the isomerization of **22** to **27**, which undergoes a 1,4-conjugate addition with a second molecule of **21**. In fact, **28** could be isolated from the reaction of **22** with 1 equivalent of **21** in the presence of 10 mol % of $GaCl_3$.



(4)

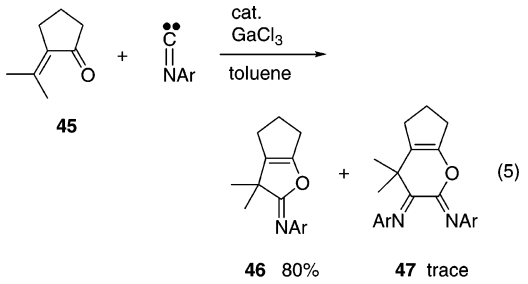
21 R = Bu
23 R = ^{i}Pr
25 R = ^{t}Bu

22 20%
24 43%
26 71%



27 **28**

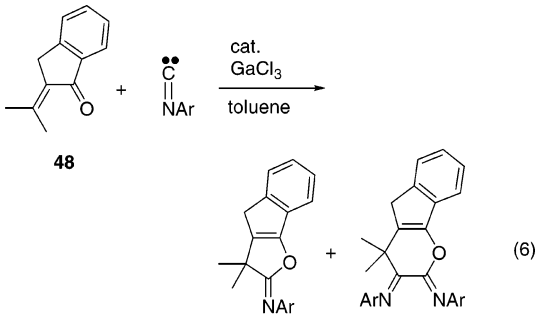
Similar to acyclic enones (shown in Table 1), cyclic enones bearing two β-substituents at the β-position or a sterically demanding substituent at the β-position gave the corresponding products in higher yields. However, bulkiness is not a critical factor in cyclic enones, in contrast to acyclic enones. The reaction of an enone bearing a methyl group at the β-position, as in **39**, gave a bicyclic lactone **40** in reasonably good yield (compare with **19** in eq 3). The bulkiness of the substitution at the β-position had no significant effect, but a slight effect on the yields of the products. The ring size also had a slight effect on the efficiency of the reaction. The reaction of seven- and eight-membered cyclic enones **41** and **43** gave the corresponding adducts in relatively low yield, compared with six-membered enones. However, satisfactory results were obtained when the reaction was carried out at a higher reaction temperature, such as 100 °C. The reaction of a five-membered enone, 2-isopropylidene-cyclopentanone (**45**), gave the expected product **46** in 89% and a negligible amount of double isocyanide insertion product **47** (detected by GCMS) was produced (eq 5).



45 **46** 80% **47** trace (5)

The formation of **47** in eq 5 prompted us to examine the reaction of various five-membered cyclic enones. Consequently,

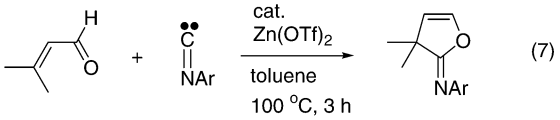
a surprising dependence of product distribution on the nature of isocyanides was observed, as shown in eq 6, when **48** was used as a substrate. The reaction of **48** with 2,6-$Me_2C_6H_3NC$ (2 equiv) gave a mixture of the expected γ-lactone product **49a** and a double-insertion product **50a**. Our attention therefore turned toward tuning the reactivity of isocyanides to allow for a more selective reaction. This might be accomplished by changing the substituent on the nitrogen of the isocyanides. Note that **49b** was obtained selectively when 2-$CF_3C_6H_4NC$ was used as the isocyanide. In contrast, the use of 2,6-$^i Pr_2C_6H_3NC$ gave the double-insertion product **50c** as the sole product. The product distribution could be precisely controlled by simply changing the structure of isocyanides.



48 (6)

Ar = 2,6-Me_2	**49a** 14%	**50a** 62%
Ar = 2-CF_3	**49b** 92%	**50b** 0%
Ar = 2,6-$^i Pr_2$	**49c** 0%	**50c** 68%

The reaction of α,β-unsaturated aldehyde **51** with 2,6-$Me_2C_6H_3NC$ in the presence of $GaCl_3$ (5 mol %) also gave the corresponding lactam derivative **52**, albeit in low yield (15% at 100 °C). By changing the catalyst to $Zn(OTf)_2$, the yield was improved to 41% (eq 7). α,β-Unsaturated aldehydes are not good substrates for the present [4+1] cycloaddition reaction, probably because isocyanides may attack the Lewis acid-activated aldehyde−carbon, as in the Passerini and Ugi reactions.[18]

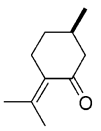
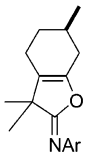
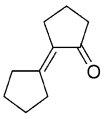
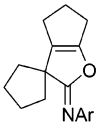
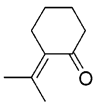
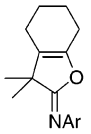
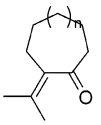
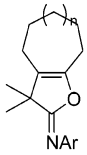


51 **52** 41% (7)

One of the possible mechanisms involves the attack of the oxygen atom of **1** to the carbon atom of the isocyanide-coordinated $GaCl_3$ complex **53** leading to **54**, which cyclizes to the final product, as shown in Scheme 3. In fact, some Lewis acid−isocyanide complexes are known.[19] We do not think that the reaction proceeds via the Lewis acid−isocyanide complexes, although we have no direct evidence.

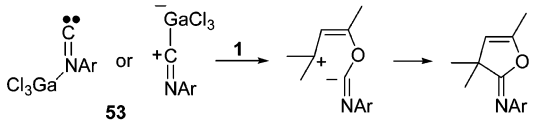
An alternate mechanism for this reaction is shown in Scheme 4. The coordination of $GaCl_3$ to the oxygen atom, as in **55**, makes the β-carbon more electrophilic. Isocyanide attacks the β-carbon to give **56**. The *Z*-isomer of **56** easily undergoes an intramolecular cyclization to give the final product. In addition, a geminal substitution effect also facilitates the cyclization. On the other hand, it is necessary for the *E*-isomer of **56** to be isomerized to a *Z*-isomer prior to the cyclization.[20] If a less bulky substituent is attached to the β-position of the α,β-unsaturated ketone, **56E** undergoes side reactions, such as reactions with other α,β-unsaturated ketone molecules or another molecule of isocyanode, prior to its isomerization to **56Z**. The presence of a bulky substituent, such as a *tert*-Bu group or two β-substituents at the β-position, prevents such intermolecular competing side reactions because of steric factors. Consequently, isomerization to the *Z*-isomer, followed by intramolecular cyclization, takes place to give lactone derivatives. In cyclic enones, such an isomerization is not necessary because the generated enolates

Table 2. $GaCl_3$-Catalyzed Reaction of Cyclic α,β-Unsaturated Ketones with Isocyanide[a]

enone	product	yield[b]
 **29**		**30** 91%
 **31**		**32** 91%
		
33 R = Bu^t		**34** 77%
35 R = Pr^i		**36** 62%
37 R = Bu		**38** 53%
39 R = Me		**40** 44%
 **41** n = 1		**42** 55% 89% (100 °C)
43 n = 1		**44** 60% 82% (100 °C)

[a] Reaction conditions: α,β-unsaturated ketone (1 mmol), 2,6-xylylisocyanide (1.1 mmol),$GaCl_3$ (0.05 mmol, 1 M in methylcyclohexane) in toluene (3 mL) at 60 °C, 18 h. [b] Isolated yield.

Scheme 3. A Proposed Reaction Mechanism

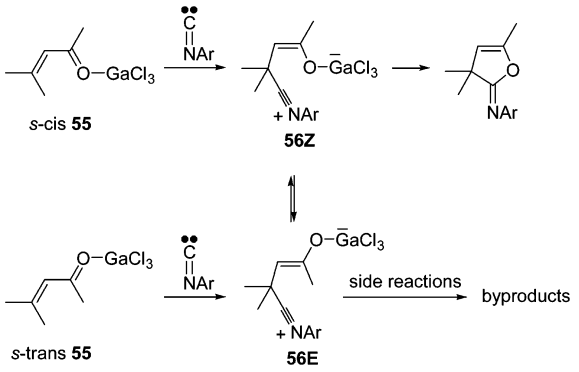


53 **54**

(18) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
(19) Brackemeyer, T.; Erker, G.; Fröhlich, R. *Organometallics* **1997**, *16*, 531. Jacobsen, H.; Berke, H.; Döring, S.; Kehr, G.; Erker, G.; Fröhlich, R.; Meyer, O. *Organometallics* **1999**, *18*, 1724.

(20) According to calculations using the B3LYP method with 6-31G* as basis sets, there is almost no energy difference between **56Z** and **56E**.

Scheme 4. A Proposed Reaction Mechanism

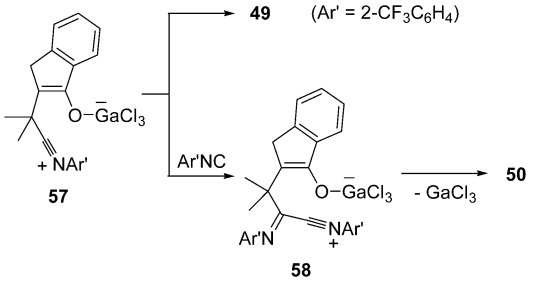


are constrained to a *Z*-geometry. This explains why cyclic enones gave the corresponding lactone derivatives in better yields compared with those in the reaction of acyclic enones, even though they have a less bulky substituent at the β-position (compare **19** and **39**). The key to successful catalysis would be the softness of $GaCl_3$ that allows all steps, facile *E*/*Z* isomerization, cyclization, and the detachment of $GaCl_3$ from the product.[21]

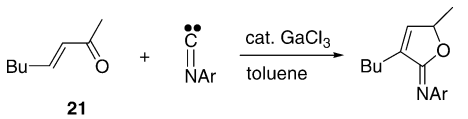
In aryl vinyl ketones **15**, the substitution of an electron-donating group on the aromatic ring retarded the reaction, as shown in Table 1. This is probably because the presence of an electron-withdrawing group makes the β carbon more electrophilic, which facilitates the attack of isocyanide to the β carbon.

The equilibrium distribution of *s*-trans and *s*-cis of enones might also be an important factor for the reaction to proceed efficiently. In mesityl oxide (**1**), the equilibrium favors the *s*-cis form because of an unfavorable methyl−methyl interaction in the *s*-trans form.[22] The attack of isocyanide to the *s*-cis form of **55** would selectively give **56Z**, which would easily undergo cyclization.

Scheme 5



In **48**, the formation of the five-membered product **49** is restricted by ring strain that led to the formation of a double-insertion product **50**. However, the use of 2-$CF_3C_6H_3NC$ facilitates the cyclization of intermediate **57** to **49** because of the higher electrophilicity of **57** as well as the reduced nucleophilicity of the isocyanide to attack **57** leading to **58** by the presence of an electron-withdrawing CF_3 group in the isocyanide. In 2,6-$^i Pr_2C_6H_3NC$, the cyclization of **57** to **49** is restricted by the ring strain and steric bulkiness around the electrophilic carbon in **57** by the diisopropylphenyl group. The dramatic effect of an electron-withdrawing group of isocyanide was also observed, as shown in eq 8. As shown in eq 4, **21** did not serve as a good substrate because it has a less bulky substituent, such as a Bu group, at the β position. However, the use of 2,6-$(CF_3)_2C_6H_3NC$ dramatically improved the product yield to 65%, even when a lower reaction temperature was used. The results shown in eqs 6 and 8 show the advantage of the use of isocyanides in cycloaddition reactions because the reactivity of isocyanides can be tuned by a simple changing of the substituent on the nitrogen.



21

Ar = 2,6-$Me_2C_6H_3$ 60 °C, 18 h **22** 20%

Ar = 2,6-$(CF_3)_2C_6H_3$ 40 °C, 12 h **59** 65%

To discuss the reaction mechanism, NMR studies were carried out with the use of mesityl oxide (**1**) and 2,6-$Me_2C_6H_4NC$. All species involved in the reaction system, such as **1**, isocyanide, and the product **2**, were found to coordinate to $GaCl_3$. Thus, upon the addition of one equivalent of $GaCl_3$ to **1** in C_6D_6 at room temperature, the signals for free **1** disappeared (5.69 ppm) and new peaks appeared (5.12 ppm).[23] The original methyl signal of 2,6-$Me_2C_6H_4NC$ at 2.06 ppm was shifted upfield to 1.55 ppm upon the treatment of $GaCl_3$ with 2,6-$Me_2C_6H_4NC$ in a 1:1 molar ratio in C_6D_6 at room temperature. The treatment of **2** with one equivalent of $GaCl_3$ gave a nearly 1:1 mixture of free **2** and a complex of $GaCl_3$ and **2**.[24] Product **2** coordinates more strongly to $GaCl_3$ than **1** or isocyanide. Treatment of **1**, **2**, and $GaCl_3$ in a 1:1:1 molar ratio resulted in no change of **1** and the formation of a complex of $GaCl_3$ and **2**. The addition of **2** to the reaction mixture of **15a** with 2,6-$Me_2C_6H_4NC$ retarded the reaction. Thus, the $GaCl_3$-catalyzed reaction of **15a** with 2,6-$Me_2C_6H_4NC$ in toluene at 60 °C in the presence of 1 equivalent of **2** gave **16a** in 7% yield, although **16a** was obtained in 52% yield in the absence of **2**, as shown in Table 1. These results indicate that **2** strongly coordinates $GaCl_3$ and, as a result, the coordination prevents $GaCl_3$ from participating in the catalytic cycle. The addition of one equivalent of 2,6-$Me_2C_6H_4$-NC to the solution of the 1:1 complex of **1** and $GaCl_3$ in C_6D_6 at room temperature gave **2** in high yield. In contrast, a catalytic reaction of **1** using 5 mol % of $GaCl_3$ at 25 °C gave **2** only in 28% yield. However, the reaction proceeded smoothly to give **2** in 94% yield when the mixture was heated to 60 °C. The heating caused the detachment of $GaCl_3$ from the product.

We next conducted some IR studies. The absorbance for an enone structure (1691 and 1620 cm^{-1}) disappeared and new absorbances appeared (1629, 1547, 1448, 1257 cm^{-1}), on the addition of 1.0 equivalent of $GaCl_3$ to **1** in C_6D_6 at room temperature. These absorbances correspond to those arising from iminolactone-coordinated $GaCl_3$. Thus, **1** was consumed immediately and **2** was simultaneously formed when 1 equivalent of $GaCl_3$ was added to a mixture of **1** (1 equiv) and 2,6-$Me_2C_6H_4NC$ (1 equiv). No intermediates were detected in the IR studies. Although direct observation of a proposed catalytic intermediate by NMR and IR does not prove it is involved in the catalytic cycle, these studies nevertheless support the proposed mechanism in Scheme 4.

(21) Morrison, D. J.; Piers, W. E. *Org. Lett.* **2003**, *5*, 2857.
(22) Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365.
(23) When the reaction was carried out in CD_2Cl_2, all peaks were downshifted.
(24) A 2:1 complex of $GaCl_3$ and **2** is proposed to form.

Conclusion

The reaction described herein represents the first example of the *catalytic* [4+1] cycloaddition of α,β-unsaturated ketones with isocyanides leading to unsaturated lactone derivatives. Although some other Lewis acids also showed catalytic activity, $GaCl_3$ was superior because of its lower oxophilicity relative to other Lewis acids, a desirable factor for all steps, such as the *E*/*Z* isomerization of the intermediate enolate, cyclization, and detachment from the products.[25] The use of α,β-unsaturated aldehydes also gave the corresponding lactones, but it is necessary to optimize the reaction conditions. A combination of isocyanides and Lewis acids represents a new reaction system that allows a new type of catalytic reaction.[26]

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

JA0450206

(25) Recently, $GaCl_3$ has been found to show a unique catalytic activity. Amemiya, R.; Nishimura, Y.; Yamaguchi, M. *Synthesis* **2004**, 1307. Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett*. **2004**, *6*, 601. Yonehara, F.; Kido, Y.; Sugimoto, H.; Morita, S.; Yamaguchi, M. *J. Org. Chem*. **2003**, *68*, 6752. Amemiya, R.; Fujii, A.; Arisawa, M.; Yamaguchi, M. *J. Organomet. Chem*. **2003**, *686*, 94. Viswanathan, G. S.; Li, C.-J. *Synlett* **2002**, 1553.

(26) Zhao recently reported that $GaCl_3$ catalyzes the double insertion of isocyanides into epoxides leading to α, β-unsaturated α-aminoiminolactones. Bez, G.; Zhao, C.-G. *Org. Lett*. **2003**, *5*, 4991.