

GaCl<sub>3</sub>-Catalyzed Insertion of Isocyanides into a C–O Bond in Cyclic Ketals and Acetals

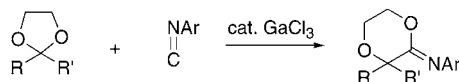
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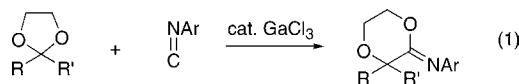
## ABSTRACT



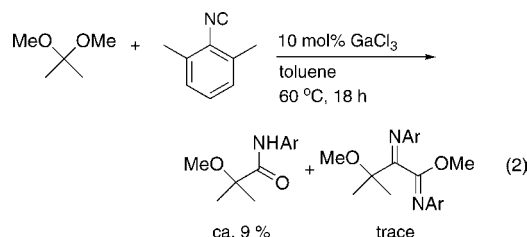
The reaction of cyclic ketals or acetals with 2,6-dibromophenylisocyanide in the presence of a catalytic amount of GaCl<sub>3</sub> results in the insertion of isocyanide into the carbon–oxygen bond of cyclic ketals and acetals.

In the course of our studies on the unique catalytic behavior of GaCl<sub>3</sub>,<sup>1–7</sup> we found that a combination of GaCl<sub>3</sub> and isocyanide is a useful system for cycloaddition reactions. A [4 + 1] cycloaddition of  $\alpha,\beta$ -unsaturated ketones and isocyanides leading to iminolactones was achieved in the presence of a catalytic amount of GaCl<sub>3</sub>.<sup>7</sup> Zhao subsequently reported on the GaCl<sub>3</sub>-catalyzed reaction of epoxides with isocyanides, in which two molecules of isocyanides are incorporated into the products.<sup>2c</sup> We believe that the key to the success of these catalyses is the appropriate Lewis acidity of GaCl<sub>3</sub> that is sufficiently strong to activate the oxygenated

substrates but is not too strong to prevent the detachment from the products, thus allowing catalyst turnover.<sup>8</sup> In this Letter, we wish to report on a new application of the GaCl<sub>3</sub>/isocyanide system to reactions of cyclic ketals and acetals in which isocyanides are inserted into the carbon–oxygen bond in ketals or acetals (eq 1).<sup>9</sup> Although a single example of a stoichiometric reaction using TiCl<sub>4</sub> has been reported previously by Ito and Saegusa,<sup>9b</sup> the present reaction represents the first catalytic version.



In an initial investigation, we observed that the reaction of 2,2-dimethoxypropane with 2,6-xylylisocyanide in the presence of a catalytic amount of GaCl<sub>3</sub> gave a complex mixture, including the  $\alpha$ -methoxy amide (eq 2).<sup>9a</sup>



We next turned our attention to the use of cyclic ketals. The reaction of 2,2-dimethyl-1,3-dioxolane (0.4 mmol, **1**)

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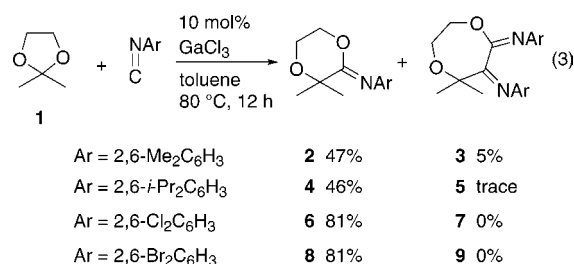
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with 2,6-xylylisocyanide (0.44 mmol) in the presence of GaCl<sub>3</sub> (0.04 mmol) in toluene (1.5 mL) at 80 °C for 12 h gave (3,3-dimethyl-1,4-dioxan-2-ylidene)-2,6-dimethylphenylamine (**2**) in 47% yield and the double insertion product **3** in 5% yield (eq 3, Ar = 2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>).<sup>10</sup> Inspired by this promising result, we next examined the impact 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 3, Ar = 2,6-*i*-Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>). 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 the yield and selectivity for the monoinsertion product (eq 3, Ar = 2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub> and 2,6-Br<sub>2</sub>C<sub>6</sub>H<sub>3</sub>). The use of *tert*-butyl isocyanide did not afford the expected product.



The effect of solvent on the GaCl<sub>3</sub>-catalyzed reaction of **1** with 2,6-dibromophenylisocyanide was next examined. Although a comparable yield was obtained when 1,2-dichloroethane (80%) was used, none of the other solvents examined were superior to toluene: CH<sub>3</sub>CN (56%), dioxane (54%), and methylcyclohexane (32%). Lewis acids other than GaCl<sub>3</sub> were also investigated for their ability to catalyze this new insertion reaction. Although AlCl<sub>3</sub> (48% yield) and InCl<sub>3</sub> (67%) also showed catalytic activity, GaCl<sub>3</sub> proved to be the most efficient under the conditions described in eq 3.

With optimized reaction conditions in hand, we explored the scope of the catalytic insertion reaction (Table 1).

The reaction proceeded effectively with 1,3-dioxolanes derived from aliphatic ketones containing cyclic (entry 2), linear (entry 3), and sterically demanding (entry 4) substituents. The yields were lowered when ketals derived from aromatic (entry 5) and  $\alpha,\beta$ -unsaturated (entry 6) ketones were employed; however, in the latter case, the use of 2 equiv of isocyanide enhanced the yield. Cyclic acetals can also be applied to the present catalytic insertion reaction, albeit in lower yields (entries 7–9). Not surprisingly, 1,3-dioxane, which requires the formation of a seven-membered ring, furnished diminished yields of the insertion product (entry 10).

A possible mechanism for the reaction is illustrated in Scheme 1. The coordination of the oxygen atom of the ketal

**Table 1.** GaCl<sub>3</sub>-Catalyzed Reaction of Ketals with 2,6-Dibromophenylisocyanide<sup>a</sup>

entry	ketal (acetal)	product <sup>b</sup>	yield <sup>c</sup>
1			<b>8</b> 81%
2			<b>10</b> 93%
3			<b>11</b> 84%
4			<b>12</b> 92%
5			<b>13</b> 51%
6			<b>14</b> 36% (82%) <sup>d</sup>
7			<b>15</b> 36% (60%) <sup>d</sup>
8			<b>16</b> 55%
9			<b>17</b> 26%
10			<b>18</b> 34% (46%) <sup>d</sup>

<sup>a</sup> Reaction conditions: ketal or acetal (0.4 mmol), 2,6-dibromophenylisocyanide (0.44 mmol), GaCl<sub>3</sub> (0.04 mmol, 1 M in methylcyclohexane) in toluene (1.5 mL) at 80 °C, 12 h. <sup>b</sup> Ar = 2,6-dibromophenyl. <sup>c</sup> Isolated yields. <sup>d</sup> 2,6-Dibromophenylisocyanide (0.8 mmol) was used.

to GaCl<sub>3</sub>, followed by nucleophilic attack by isocyanide, affords the ring-opened zwitterionic intermediate **20**. An intramolecular cyclization and the subsequent release of GaCl<sub>3</sub> leads to the monoinsertion product. When the second molecule of isocyanide adds to **20** before the intramolecular cyclization, the double insertion product is produced via intermediate **21** in a similar manner. The cyclization of **20** would be predicted to be accelerated by the presence of an electron-withdrawing group on the aryl isocyanide because of the

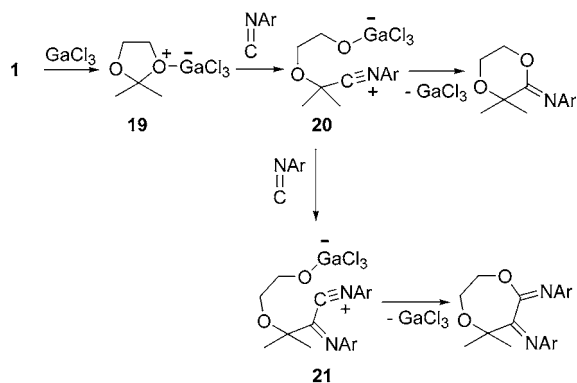
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(9) For reactions of acetals or ketals with isocyanide that lead to different types of product than that shown in eq 1: (a) Mukaiyama, T.; Watanabe, K.; Shiono, M. *Chem. Lett.* **1974**, 1457. (b) Ito, Y.; Imai, H.; Segoe, K.; Saegusa, T. *Chem. Lett.* **1984**, 937. (c) Pellissier, H.; Meou, A.; Gil, G. *Tetrahedron Lett.* **1986**, 27, 2979.

(10) Unidentified byproducts other than **3** were also observed by GC analysis of the crude reaction mixture. On isolation of the products, ca. 38% of the isocyanide was recovered.

(11) For similar discussions on substituent effects, see ref 7.

**Scheme 1.** Proposed Mechanism



increased electrophilicity of the cationic center. Moreover, the reduced nucleophilicity of the isocyanide should retard the competing undesired pathway leading to **21**.<sup>11</sup>

In summary, we reported herein on the development of a GaCl<sub>3</sub>-catalyzed insertion reaction of isocyanides into the carbon–oxygen bond of cyclic ketals and acetals, affording iminolactone derivatives.<sup>12</sup> The reaction represents the first

example of a *catalytic* variant of this type of transformation. Current efforts are focused on discovering new multicomponent transformations with isocyanides using GaCl<sub>3</sub> as a catalyst.<sup>13</sup>

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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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(12) These compounds are potentially useful for organic synthesis since hydrolysis of the imino moiety should afford 1,4-dioxane-2-one derivative. See ref 9b.

(13) Recent reviews on multicomponent transformations with isocyanides: Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133.