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Synthetic Methods

Gallium Trihalide Catalyzed Sequential Addition of Two Different Carbon Nucleophiles to Esters by Using Silyl Cyanide and Ketene Silyl Acetals

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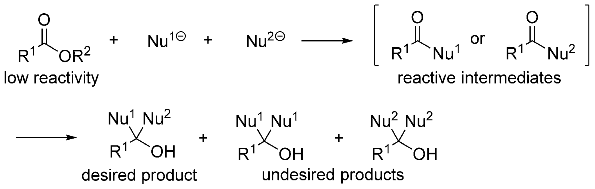
Abstract: A sequential addition of silyl cyanide and ketene silyl acetals to esters was achieved by a gallium trihalide catalyst to produce β-cyano-β-siloxy esters. This is the first example of the sequential addition of two different carbon nucleophiles to esters. The employment of lactones provided α,α-disubstituted cyclic ethers with a cyano group and an ester moiety. A variety of esters and lactones are applicable to this reaction system.

The addition of nucleophiles to carbonyl compounds is one of the most important tools in organic chemistry.[1] In this context, esters have a potential advantage because they can receive two nucleophiles to produce multi-functionalized alcohols, while ketones or aldehydes can receive only one carbon nucleophile. However, the introduction of two different carbon nucleophiles into esters is difficult, because the intermediate produced by the first addition is more reactive than the starting ester to give undesired products that possess the same substituents (Scheme 1). Therefore, a multi-step process is generally required for such a transformation.[2] In this regard, the sequential addition of two different carbon nucleophiles to esters via a single-stage treatment has been rare, though a hydride and carbon nucleophiles have been introduced by using DIBALH,[3] $LiBH_4$,[4] and hydrosilane.[5] Herein, we report the gallium trihalide-catalyzed sequential addition of two different carbon nucleophiles to esters using ketene silyl acetals and silyl cyanide.

We recently reported that the indium(III)-catalyzed reductive functionalization of esters, amides, and carboxylic acids has been achieved via the single-stage treatment of hydrosilanes and organosilicon nucleophiles such as ketene silyl acetals and silyl cyanide.[5,6] On the basis of these previous studies, we examined the successive introduction of two different carbon nucleophiles into methyl benzoate **1a** by employing trimethylsilyl cyanide **2** and dimethylketene methyl trimethylsilyl acetal **3a** (Table 1). As to indium(III) trihalides, even the use of InI_3, which showed efficient transformation in the reductive functionalization of esters, gave a low yield of β-cyano-β-siloxy ester **4aa** (Table 1, entries 1–3). A variety of Lewis acid catalysts such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $TiCl_4$, $FeBr_3$, $CuBr_2$, and $ZnBr_2$ were also found to be ineffective (Table 1, entries 4–9). To our delight, the application of $GaBr_3$ and GaI_3 successfully gave **4aa** in high yields along with a small amount of β-keto ester **5aa**, in which the successive reaction of **1a** with **2** and **3a** proceeded via single-stage treatment (Table 1, entries 11 and 12).[7] It is noteworthy that a double addition of the same nucleophiles would not proceed—neither **2** nor **3a** to **1a**. The employment of either $Ga(OTf)_3$ or $GaCl_3$ resulted in the recovery of **1a** (Table 1, entries 10 and 13). The solvent-free conditions led to an excellent yield of **4aa** (Table 1, entry 14).[8] Finally, the treatment in entry 15 using GaI_3 was determined to be the best conditions.

To discuss the reaction path, we investigated the reactions between ester **1a** with either silyl cyanide **2** or ketene silyl acetal **3a**. No cyanation took place, perhaps because of its low nucleophilicity, and **1a** was recovered [Eq. (1)]. On the other hand, the reaction of ester **1a** with ketene silyl acetal **3a** gave β-keto ester **5aa** in 94% yield [Eq. (2)]. This is the first case of a Lewis acid catalyzed cross-Claisen condensation between an ester and a ketene silyl acetal, which is an important factor in the present reaction.[9] It is noteworthy that no further reaction of the obtained **5aa** with **3a** was observed even though an excess amount of **3a** was used. The use of InI_3 in the same reaction resulted in low yields.[10] A Lewis acidity of GaX_3 that is higher than that of InX_3 effectively accelerated the cross-Claisen condensation. β-Keto ester **5aa** reacted with silyl cyanide **2** in the presence of GaI_3 catalyst to produce the corresponding product **4aa** quantitatively [Eq. (3)]. In the absence of GaI_3, neither the reaction of Equation (2) nor that of Equation (3) proceeded.



Scheme 1. Double nucleophilic addition to esters.

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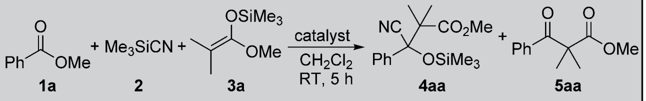
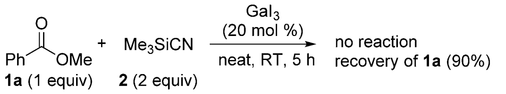
Table 1. Screening of catalysts.[a]

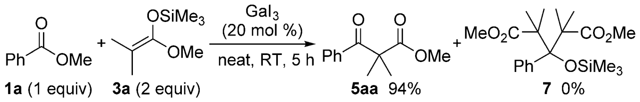


Entry	Catalyst	Yield of **4aa** [%][b]	Yield of **5aa** [%][b]
1	$InCl_3$	0	0
2	$InBr_3$	6	8
3	InI_3	15	9
4	$BF_3{\cdot}OEt_2$	2	5
5	$AlCl_3$	0	0
6	$TiCl_4$	0	2
7	$FeBr_3$	0	0
8	$CuBr_2$	0	0
9	$ZnBr_2$	0	0
10	$GaCl_3$	2	1
11	$GaBr_3$	85	1
12	GaI_3	69	1
13	$Ga(OTf)_3$	0	0
14[c]	$GaBr_3$	92	3
15[c]	GaI_3	95 (94)[d]	2

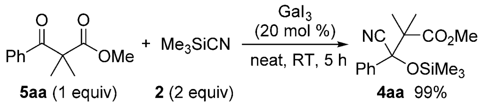
[a] **1a** (1 equiv), **2** (2 equiv), **3a** (2 equiv), catalyst (20 mol %), CH_2Cl_2 (1 м), rt, 0.5 mmol scale. [b] GC yield. [c] No solvent was used. [d] Isolated yield.



(1)



(2)

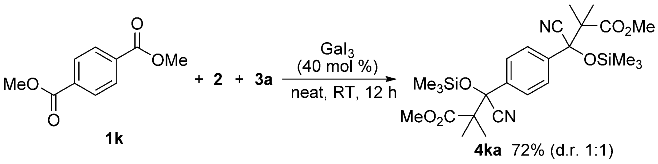


(3)

A proposed reaction mechanism that is based on the results of Equations (1)–(3) is illustrated in Scheme 2. First, the carbonyl group of the ester coordinates to GaI_3 to increase its positive charge. The nucleophilic addition of ketene silyl acetal **3** to ester **1** predominantly takes place to afford acetal intermediate **8**. An alkoxy (R^2O) group of acetal **8** selectively coordinates to GaI_3, affording Me_3SiOR^2 and β-keto ester intermediate **5**. Next, GaI_3 accelerates the nucleophilic addition of Me_3SiCN **2** to β-keto ester **5**, giving product **4** selectively. In the first addition reaction, ketene silyl acetal **3** exclusively reacts with esters due to the high nucleophilicity. And, in the second addition reaction, β-keto ester **5** does not react with **3** because of the steric repulsion between the substituents of **5** and **3**. Therefore, the addition of **2** to **5** takes place selectively.

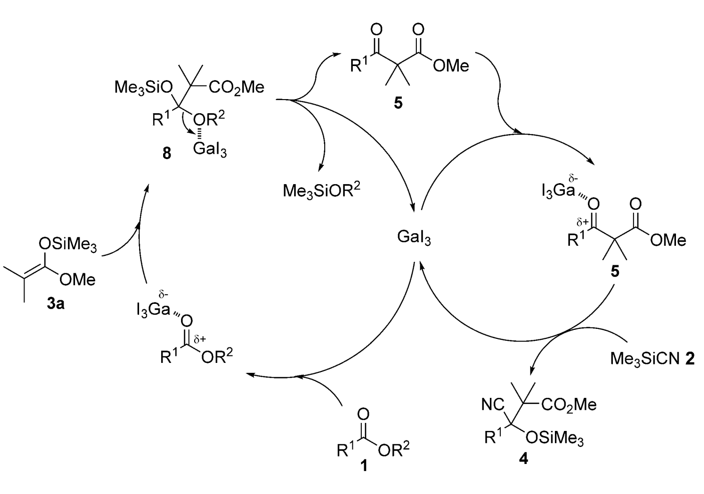
The scope and limitations of ester **1** and ketene silyl acetal **3** are shown in Table 2. Aromatic esters **1b** and **1c** bearing an electron-donating group gave high yields of **4ba** and **4ca**, respectively, whereas an electron-withdrawing group slightly decreased the yield of desired product **4da** (Table 2, entries 1–3). Ethyl ester **1e** was also applicable to afford product **4eb** in 65 % yield along with a small amount of ethyl ether product (Table 2, entry 4).[11] Disubstituted ketene silyl acetal **3c** also gave product **4ac** in 80 % yield (Table 2, entry 5). When monosubstituted ketene silyl acetal **3d** was used, 12 % yield of **7ad** accepting two equivalents of **3d** was detected along with 66 % yield of the desired product **4ad** (Table 2, entry 6). The generation of **7ad** could be explained by the low steric hindrance of β-keto ester intermediate **5ad** produced by the reaction of **1a** with **3d**.[12] Aliphatic ester **1f** and methyl acetate **1g** were also applicable to this reaction system to provide **4fa** and **4ga** in moderate to good yields (Table 2, entries 7 and 8).

Moreover, methyl fluoroacetate **1h** produced fluorinated product **4ha** in 82 % yield (Table 2, entry 9). Methyl cyclohexanecarboxylate **1i** barely gave product **4ia** because of its steric hindrance (Table 2, entry 10). Fortunately, the sequential addition reaction of formic acid ester **1j** smoothly proceeded to afford the corresponding product **4ja** in high yield despite the very low steric hindrance of **1j** (Table 2, entry 11). It is noted that β-cyano-β-siloxy ester **4ja** could not be synthesized by a stepwise approach selectively.[13] Industrial material was also applied to this system. For example, dimethyl terephthalate **1k** afforded the corresponding product **4ka** [Eq. (4)].



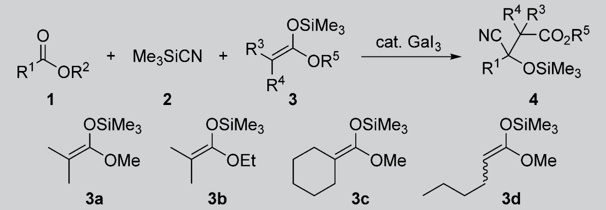
(4)

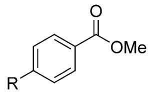
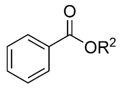
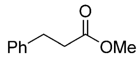
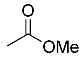
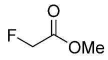
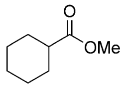
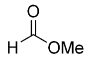
Next, we applied lactones to this reaction system (Table 3). Mukaiyama et al. previously reported the catalytic reaction of lactones with a ketene silyl acetal and other organosilicon nu-



Scheme 2. Proposed reaction mechanism for esters.

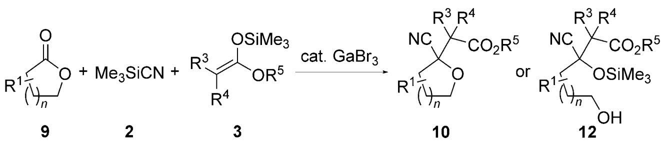
Table 2. Scope and limitation of esters and ketene silyl acetals.[a]



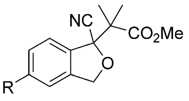
Ent.	Ester **1**		**3**	Time (h)	**4**	Yield [%][b]
1		R=Me; **1b**	**3a**	5	**4ba**	97
2		R=OMe; **1c**	**3a**	5	**4ca**	93
3		R=Cl; **1d**	**3a**	12	**4da**	73
4[c]		R^2=Et; **1e**	**3b**	9	**4eb**	65
5		R^2=Me; **1a**	**3c**	12	**4ac**	80
6[d]		R^2=Me; **1a**	**3d**	5	**4ad**	66[e]
7		**1f**	**3a**	12	**4fa**	76
8[f]		**1g**	**3a**	5	**4ga**	53
9[f]		**1h**	**3a**	5	**4ha**	82
10		**1i**	**3a**	24	**4ia**	5
11[g]		**1j**	**3a**	2	**4ja**	90

[a] **1** (1 equiv), **2** (2 equiv), **3a** (2 equiv), GaI_3 (20 mol%), neat, RT, 0.5 mmol scale. [b] Isolated yield. [c] $GaBr_3$ (20 mol%). [d] **2** (3 equiv). [e] 1:1 d.r. was determined by ^1H NMR spectroscopy. [f] CH_2Cl_2 (2 M), 2 mmol scale. [g] **2** (1.5 equiv), **3a** (1.5 equiv), GaI_3 (5 mol%), CH_2Cl_2 (1 M). Reaction was carried out from 0 °C to RT. 2 mmol scale.

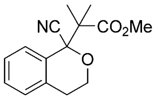
Table 3. Scope and limitation of esters and ketene silyl acetals.[a]



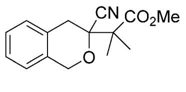
3a: $R^3 = R^4 = R^5 = Me$ **3e**: $R^3 = R^4 = R^5 = Et$
3d: $R^3 = H$, $R^4 = n\text{Bu}$, $R^5 = Me$



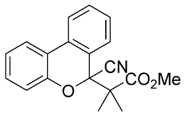
R = H; **10aa** 95%, 2 h
Me; **10ba** 88%, 2 h
Br; **10ca** 68%, 12 h
CO_2Me; **10da** 48%, 12 h



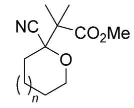
10ea 81%, 5 h



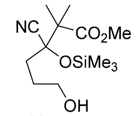
10fa 60%, 12 h



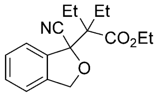
10ga[b] 73%, 12 h



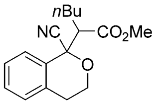
n = 1: **10ha** 67%, 2 h
2: **10ia** 64%, 2 h



12ja[c] 78%, 2 h



10ae 61%, 5 h

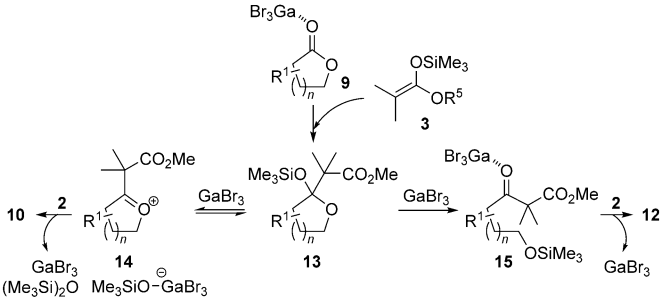


10ed[d] 59%, 2 h

[a] **9** (1 equiv), **2** (1.5 equiv), **3** (1.5 equiv), $GaBr_3$ (5 mol%), CH_2Cl_2 (1 M), RT, 2-12 h. Isolated yield. [b] $GaBr_3$ (20 mol%), 60 °C. [c] Cyclic ether **10ja** was obtained in 8% yield. [d] 1:1 d.r. was determined by ^1H NMR spectroscopy.

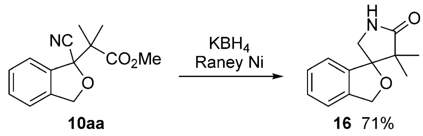
cleophiles to provide α,α-disubstituted cyclic ethers.[14] In the reported reaction, however, only one type of unsubstituted ketene silyl acetal was utilized, and temperature-controlled conditions were required. The reaction among phthalide **9a**, silyl cyanide **2**, and ketene silyl acetal **3a** in the presence of 5 mol% of $GaBr_3$ provided α,α-disubstituted cyclic ether **10aa** in 95% yield, in which bulky disubstituted ketene silyl acetal was applicable in contrast to Mukaiyama's system.[15] The use of phthalide derivatives **9b–d** also gave the corresponding products **10ba–10da**, respectively, although **9c** and **9d** had an electron-withdrawing group and required a longer reaction time. It was noteworthy that the chemoselective transformation of the lactone moiety of **9d** took place prior to the conversion of an intramolecular aromatic ester group.[16] Six-membered cyclic aromatic lactones were converted to **10ea** and **10fa**, respectively. Benzocoumarin also gave product **10ga** in 73% yield under heating conditions. The use of δ-valero- and ε-caprolactones afforded cyclic ethers **10ha** and **10ia**, respectively. On the other hand, when the reaction of γ-butyrolactone was carried out, acyclic product **12ja** was predominantly obtained. Dialkylketene silyl acetals **3e** produced product **10ae** in 61% yield. Monosubstituted ketene silyl acetal **3d** was also applicable to this reaction system to afford cyclic ether **10ed**. An unsubstituted ketene silyl acetal gave no product, because it is unstable and tends to decompose under these reaction conditions.

The reaction mechanism of lactone **9** with silyl cyanide **2** and ketene silyl acetal **3** is illustrated in Scheme 3. First, $GaBr_3$ accelerates the reaction of **3** with **9** to give cyclic acetal **13**. Next, a siloxy group in advance of the alkoxy group is eliminated by $GaBr_3$ due to the entropy gain, affording oxocarbenium ion **14**. Then, the nucleophilic attack of silyl cyanide **2** to **14** produces cyclic ether **10**. An electron-withdrawing group of phthalide derivatives destabilizes oxocarbenium ion **14** to decrease the yield of **10** (Table 3). The use of γ-butyrolactone **9j** gave acyclic product **12ja** because the corresponding acetal intermediate **13ja** has a large ring strain (Table 3).[17]



Scheme 3. Ring-maintained and ring-opening mechanism for cyclic acetals.

The preparation of a spirocyclic compound, which is a useful building block in biological chemistry,[18] from a cyclic ether was carried out (Scheme 4). The selective reduction of a cyano group in **10 aa** by the combination of a Raney nickel and KBH_4 gave spiro oxacyclic γ-lactam **16** in 71 % yield.[19,20]



Scheme 4. Synthesis of spiro oxacyclic γ-lactam **16**.

In summary, we have accomplished a gallium trihalide-catalyzed sequential addition of two different carbon nucleophiles to esters using silyl cyanide and ketene silyl acetals. The reaction of methyl esters predominantly gave β-cyano-β-siloxy esters. Aromatic, aliphatic, and formic acid esters gave the corresponding products. The transformation of lactones produced α,α-disubstituted cyclic ethers containing a cyano group and an ester moiety. The functional group transformation of the obtained cyclic ether gave spiro oxacyclic γ-lactam. Further expansion of this system is now ongoing.

Experimental Section

Typical procedure (Table 2): Ketene silyl acetal (1 mmol) was added to a suspension of catalyst (0.1 mmol), ester (0.5 mmol), and trimethylsilyl cyanide (1 mmol). The mixture was stirred at room temperature for 5 h. And then, the resulting mixture was quenched by aqueous NaOH solution. The mixture was extracted with Et_2O (3×10 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product.

Acknowledgements

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Keywords: esters · gallium · lactones · silicon · synthetic methods

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[7] For review, see the following: a) M. K. Gupta, T. P. O'Sullivan, *RSC Adv.* **2013**, *3*, 25498–25522; b) M. Yamaguchi, Y. Nishimura, *Chem. Commun.* **2008**, 35–48.

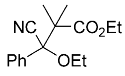
[8] See the Supporting Information for the further optimization of the reaction conditions.

[9] To the best of our knowledge, Lewis acid-catalyzed cross-Claisen condensations between simple esters and ketene silyl acetals were not developed so far. The reactions of esters or lactones with ketene silyl acetals in the presence of catalytic amount of acid were reported, but these reactions did not give cross-Claisen condensation product. See the following: a) M. Onaka, T. Mimura, R. Ohno, Y. Izumi, *Tetrahedron Lett.* **1989**, *30*, 6341–6344; b) S. Iwata, T. Hamura, T. Matsumoto, K. Suzuki, *Chem. Lett.* **2007**, *36*, 538–539; For the reaction of lactone with ketene silyl acetal, see the following: c) K. Homma, T. Mukaiyama, *Chem. Lett.* **1990**, *19*, 161–164; d) R. Csuk, M. Shaade, *Tetrahedron Lett.* **1993**, *34*, 7907–7910; e) H. Yanai, T. Taguchi, *Chem. Commun.* **2012**, *48*, 8967–8969; f) H. Yanai, N. Ishii, T. Matsumoto, T. Taguchi, *Asian J. Org. Chem.* **2013**, *2*, 989–996; We developed a Lewis acid-catalyzed cross-Claisen condensation from carboxylic acid, see: g) Y. Nishimoto, A. Okita, M. Yasuda, A. Baba, *Angew. Chem.* **2011**, *123*, 8782–8784; *Angew. Chem. Int. Ed.* **2011**, *50*, 8623–8625.

[10] Indium triiodide catalyzed cross-Claisen condensation between ester **1 a** and ketene silyl acetal gave β-keto ester **5 aa** in 41 %.

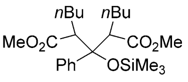
[11] Following compound **6 eb** was observed in 6 % yield.

[12] Illustrated compound **7 ad** was detected in 12 % yield by monosubstiuted ketene silyl acetal **3 d**, which was afforded by the reaction of ester **1 a** with two equivalent of **3 d**. And, intermediate **5 ad** was represented below.

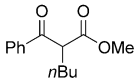


6eb

[13] In the reaction of formic acid ester **1 j** with ketene silyl acetal **3 a**, the product, which was afforded by the addition of two equivalent of **3 a** to **1 j**, was obtained mainly.



7ad



5ad

[14] a) T. Mukaiyama, K. Homma, H. Takenoshita, *Chem. Lett.* **1988**, *17*, 1725–1728; b) K. Homma, T. Mukaiyama, *Chem. Lett.* **1989**, *18*, 893–894; c) K. Homma, H. Takenoshita, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1898–1915.

[15] The use of $GaBr_3$ catalyst are slightly effective compared with the use of GaI_3 catalyst. See the Supporting Information for the optimization of reaction conditions for lactones.

[16] Aromatic ester group of **9 d** was converted in 7 % yield.

[17] Please see the Supporting Information for investigation of reaction mechanism for lactones **9**.

[18] For a review of natural products containing spiro γ-lactam heterocycles, see the following: J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munroa, M. R. Prinsep, *Nat. Prod. Rep.* **2012**, *29*, 144–222.

[19] Reduction of cyano group by Raney Ni/KBH_4 was reported, see the following: B. Wu, J. Zhang, M. Yang, Y. Yue, L.-J. Ma, X.-Q. Yu, *Arkivoc* **2006**, *xii*, 35–46.

[20] For the selected examples of synthesis of spiro γ-lactams from α,α-disubstituted compounds, see the following: a) Y. Nakao, Y. Hirata, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 7420–7421; b) C. Beemelmanns, D. Lentz, H.-U. Reissig, *Chem. Eur. J.* **2011**, *17*, 9720–9730; c) K. Nagata, Y. Kuga, A. Higashi, A. Kinoshita, T. Kanemitsu, M. Miyazaki, T. Itoh, *J. Org. Chem.* **2013**, *78*, 7131–7136.

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