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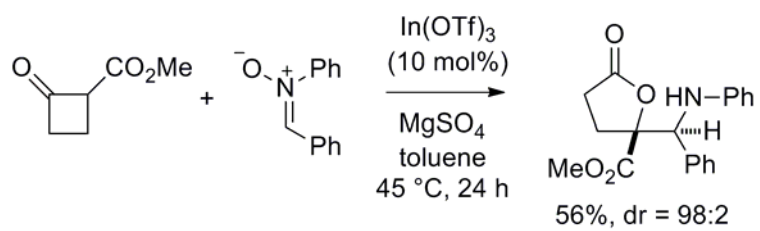
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## Graphical Abstract

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## Indium(III) triflate-catalyzed reaction of 2-carbomethoxycyclobutanone with nitrones

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### ABSTRACT

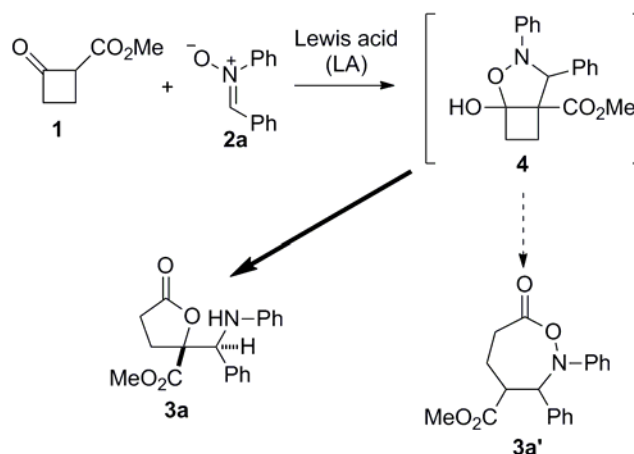
2-Carbomethoxycyclobutanone reacted with *N*-phenyl-*C*-arylnitrones to afford methyl 5-oxo-2-[aryl(phenylamino)methyl]tetrahydrofuran-2-carboxylates by the catalysis of indium(III) triflate in the presence of magnesium sulfate.

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Nitrones are useful synthetic intermediates in organic synthesis and have been used mainly in the 1,3-dipolar cycloaddition with olefins to give isoxazolidines.<sup>1</sup> In addition to olefins, nitrones reacted with donor-acceptor cyclopropanes and cyclobutanes for [3+3]<sup>2,3</sup> and [4+3]<sup>4</sup> cycloadditions, respectively. Moreover, nucleophilic additions to nitrones have been studied for carbon nucleophiles such as Grignard reagents,<sup>5</sup> cyanide ion,<sup>6</sup> and sodium salts of diethyl malonate.<sup>7</sup> We were interested in a reaction of 2-carbomethoxycyclobutanone (**1**)<sup>8</sup> with nitrones because four-membered ketoester **1** can work as a carbon nucleophile and it has a characteristic feature of facile ring cleavage.<sup>9</sup> Thus, we tried to synthesize a seven-membered ring compound **3a'** by nucleophilic addition of **1** to nitronone **2a** followed by ring cleavage of four-membered ring of **4** (Scheme 1). However, we found unexpected formation of a  $\gamma$ -butyrolactone derivative **3a** by Lewis acid-catalyzed reaction of nitronone **2a** with **1**, and we report here the results.

### Scheme 1

Formation of  $\gamma$ -butyrolactone **3a** by Lewis acid-catalyzed reaction between **1** and **2a**



First, various Lewis acids were screened in a model reaction between **1** and nitronone **2a** to afford  $\gamma$ -butyrolactone **3a** (Table 1). In the absence of a Lewis acid, cyclobutanone **1** was not react with **2a** at refluxing temperature of toluene, and even ring cleavage of **1** did not observed by TLC analysis (Entry 1). The use of catalytic amounts (10 mol%) of the typical Lewis acids  $\text{TiCl}_4$ ,  $\text{BF}_3\text{-Et}_2\text{O}$  and  $\text{Me}_3\text{SiOTf}$  gave the desired product **3a** in 16%, 34% and 27% yields, respectively (Entries 2–4), while the use of more than stoichiometric amounts (1.3 equiv) of these Lewis acids did not afford **3a** at all. Catalytic amounts (10 mol%) of several metal triflates were then tested in this reaction, and it was found that  $\text{In}(\text{OTf})_3$  promoted the reaction most efficiently (Entries 5–11). The Brønsted acid  $\text{TsOH}$  also

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catalyzed the reaction, but the reaction proceeded sluggishly (Entry 12). It should be noted that high diastereoselectivity was observed in the Lewis acid-catalyzed reaction of **1** and **2a** as shown in Table 1. We employed In(OTf)<sub>3</sub> in the following experiments since the reaction time was shorter than that for BF<sub>3</sub>-OEt<sub>2</sub> (Entries 3 and 11).<sup>10</sup>

**Table 1**

Effects of Lewis acids in a reaction of **1** and **2a** to give  $\gamma$ -butyrolactone **3a** (eq 1)<sup>a</sup>

Entry	Lewis acid	Time (h)	Isolated yield (%)	dr <sup>b</sup>
1 <sup>c</sup>	none	48	0	
2	TiCl <sub>4</sub>	48	16	99:1
3	BF <sub>3</sub> -Et <sub>2</sub> O	48	34	96:4
4	Me <sub>3</sub> SiOTf	18	27	98:2
5	AgOTf	24	29	96:4
6	Zn(OTf) <sub>2</sub>	23	18	97:3
7	Cu(OTf) <sub>2</sub>	53	1	98:2
8	Yb(OTf) <sub>3</sub>	19	12	96:4
9	La(OTf) <sub>3</sub>	29	17	98:2
10	Sc(OTf) <sub>3</sub>	19	19	96:4
11	In(OTf) <sub>3</sub>	20	32	96:4
12	TsOH-H <sub>2</sub> O	48	20	96:4

<sup>a</sup> Unless otherwise mentioned, the following reaction conditions were used: cyclobutanone **1** (1.0 equiv), nitrone **2a** (1.3 equiv), and Lewis acid (10 mol%) were reacted in toluene at 45 °C.

<sup>b</sup> Determined by <sup>1</sup>H NMR.

<sup>c</sup> Reaction conditions: 45 °C (24 h) and reflux (24 h).

Next, effects of additives in the In(OTf)<sub>3</sub>-catalyzed reaction of **1** and **2a** were investigated (Table 2). Some drying agents were employed as additives because benzaldehyde was detected by TLC analysis in the above-mentioned Lewis acid screening. The use of molecular sieves 4A and 5A was not effective and led to considerably lower yields of the desired product **3a** (Entries 2 and 3). The addition of Na<sub>2</sub>SO<sub>4</sub> did not cause any change compared with the case of no additives, whereas the use of MgSO<sub>4</sub> greatly improved the yield of **3a** to 56% (Entries 4 and 5). TLC analysis of the reaction mixture showed smooth consumption of cyclobutanone **1** in the presence of MgSO<sub>4</sub>, but benzaldehyde was still detected even in the presence of MgSO<sub>4</sub>. MgSO<sub>4</sub> did not work as a Lewis acid in this reaction because the product **3a** was detected only in a trace amount by using MgSO<sub>4</sub> in the absence of In(OTf)<sub>3</sub> (Entry 6). Therefore, at present, the role of MgSO<sub>4</sub> is not clear. The use of Mg(ClO<sub>4</sub>)<sub>2</sub> gave the desired product **3a** in 6% yield (Entry 7), and it was found that MgSO<sub>4</sub> was an appropriate additive in the present In(OTf)<sub>3</sub>-catalyzed reaction.<sup>11</sup>

**Table 2**

Effects of additives in an In(OTf)<sub>3</sub>-catalyzed reaction of **1** and **2a** to afford **3a** (eq 1)<sup>a</sup>

Entry	Additive	Time (h)	Isolated yield (%)	dr <sup>b</sup>
1	none	24	36	96:4
2	MS4A	48	0	
3	MS5A	72	5	99:1
4	Na <sub>2</sub> SO <sub>4</sub>	14	39	97:3
5	MgSO <sub>4</sub>	24	56	98:2
6 <sup>c</sup>	MgSO <sub>4</sub>	48	trace	
7	Mg(ClO <sub>4</sub> ) <sub>2</sub>	24	6	87:13

<sup>a</sup> Reaction conditions: cyclobutanone **1** (1.0 equiv), nitrone **2a** (2.0 equiv), In(OTf)<sub>3</sub> (10 mol%), and additive (300 mg/mmol of **2**) were reacted in toluene at 45 °C.

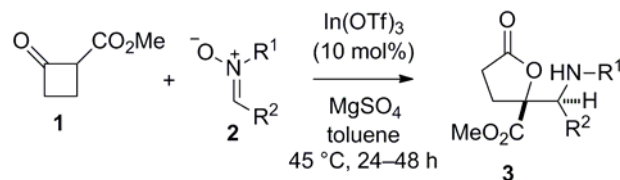
<sup>b</sup> Determined by <sup>1</sup>H NMR.

<sup>c</sup> In the absence of In(OTf)<sub>3</sub>.

The scope and limitations of the reaction of cyclobutanone **1** and nitrones were investigated by employing various nitrones **2b–g** (Table 3). *N*-Phenyl-*C*-arylnitrones **2b–d** with electron-withdrawing groups such as fluoro, chloro, and bromo groups at the *p*-position of the phenyl ring gave results comparable to those with the parent unsubstituted nitrone **2a** (Entries 1–3). Substitution with a methyl group resulted in a slightly decreased yield of **3e** (Entry 4). The use of a nitrone **2f** bearing a *C*-2-naphthyl group instead of the *C*-phenyl group lowered the yield of the corresponding  $\gamma$ -butyrolactone **3f** (entry 5). *C*-Alkyl nitrone **2g**, which was prepared in situ from 3-phenylpropanal and *N*-phenylhydroxylamine, reacted with **1** to afford **3g** in 24% yield (Entry 6) whereas *N*-methyl nitrone **2h** did not react with **1** (Entry 7). Stereochemistry of **3** was determined by X-ray crystallography of **3d**.

**Table 3**

Scope and limitations of In(OTf)<sub>3</sub>-catalyzed reaction of cyclobutanone **1** and nitrone **2b–g** to give  $\gamma$ -butyrolactone **3b–g**<sup>a</sup>



Entry	<b>2</b>	R <sup>1</sup>	R <sup>2</sup>	X	<b>3</b>	Yield (%)	dr <sup>b</sup>
1	<b>2b</b>	Ph		X = F	<b>3b</b>	51	96:4
2	<b>2c</b>	Ph		X = Cl	<b>3c</b>	46	97:3
3	<b>2d</b>	Ph		X = Br	<b>3d</b>	51	97:3
4	<b>2e</b>	Ph		X = Me	<b>3e</b>	41	98:2
5	<b>2f</b>	Ph	2-Naphthyl		<b>3f</b>	40	95:5
6	<b>2g</b>	Ph	(CH <sub>2</sub> ) <sub>2</sub> Ph		<b>3g</b>	24	93:7
7	<b>2h</b>	Me	Ph		<b>3h</b>	0	

<sup>a</sup> Reaction conditions: cyclobutanone **1** (1.0 equiv), nitrone **2** (2.0 equiv), In(OTf)<sub>3</sub> (10 mol%), and MgSO<sub>4</sub> (300 mg/mmol of **2**) were reacted in toluene at 45 °C.

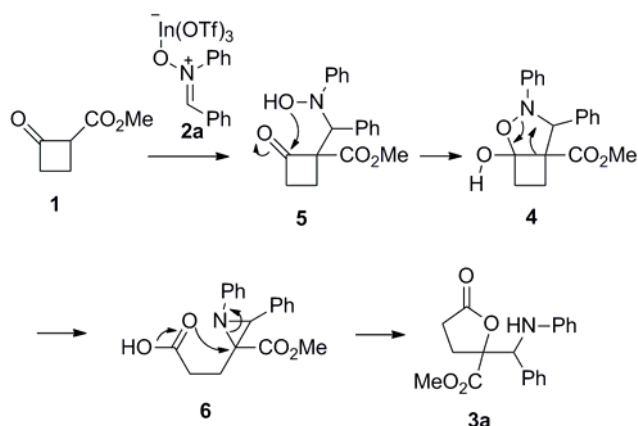
<sup>b</sup> Determined by <sup>1</sup>H NMR.

A proposed mechanism for the In(OTf)<sub>3</sub>-catalyzed reaction between cyclobutanone **1** and nitrone **2a** is shown in Scheme 2. Nucleophilic attack of cyclobutanone **1** to nitrone **2a** which is activated with In(OTf)<sub>3</sub> gives hydroxylamine **5**, in which intramolecular attack of the hydroxyl group to the carbonyl group of cyclobutanone gives isoxazolidine derivative **4**.<sup>12</sup> Valence rearrangement<sup>13</sup> of the isoxazolidine ring of **4** gives aziridin-2-yl carboxylic acid **6**. Intramolecular attack of the carboxylic acid

group to the aziridine ring gives  $\gamma$ -butyrolactone **3a**. Each step shown in Scheme 1 can be catalyzed with  $\text{In}(\text{OTf})_3$ .

### Scheme 2

A proposed mechanism for  $\text{In}(\text{OTf})_3$ -catalyzed reaction of **1** and nitrone **2a** to  $\gamma$ -butyrolactone **3a**



In conclusion, we found a new method for synthesis of functionalized  $\gamma$ -butyrolactone by a reaction of 2-carbomethoxycyclobutanone<sup>14</sup> with *N*-phenyl-*C*-arylnitrones. This reaction was effectively promoted by using a catalytic amount of  $\text{In}(\text{OTf})_3$  in the presence of  $\text{MgSO}_4$ . Valence rearrangement of an isoxazolidine intermediate followed by intramolecular attack of a carboxylate group to an aziridine ring was proposed for the formation of  $\gamma$ -butyrolactone.

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- Use of other solvents such as dichloromethane, THF, and acetonitrile gave **3a** in low yields.
- Under the reaction conditions of entry 5 (Table 1), the starting material **1** was completely consumed, and some very polar co-products were detected by TLC analysis.
- A concerted mechanism for [3+2] cycloaddition between an enol form of **1** and nitrone **2a** is also possible for generation of **4**. [3+2] Cycloaddition of nitrones and silyl enol ethers: (a) Hosomi, A.; Shoji, H.; Sakurai, H. *Chem. Lett.* **1985**, 1049; (b) Dhavale, D. D.; Trombini, C. *J. Chem. Soc., Chem. Commun.* **1992**, 1268; (c) Camiletti, C.; Dhavale, D. D.; Gentilucci, L.; Trombini, C. *J. Chem. Soc. Perkin Trans. 1* **1993**, 3157.
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- Indium(III) triflate-catalyzed reaction of nitrone **2a** with ethyl 2-oxocyclopentanecarboxylate or ethyl 2-oxocyclohexanecarboxylate did not afford the corresponding lactones

### Supplementary Material

Supplementary data associated with this article can be found in the online version.