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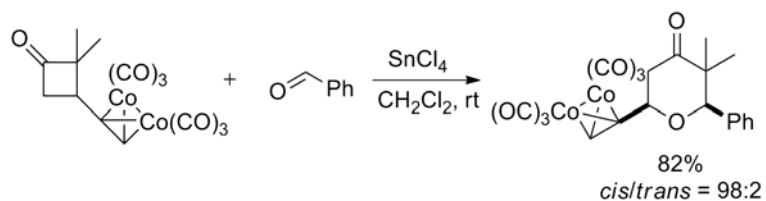
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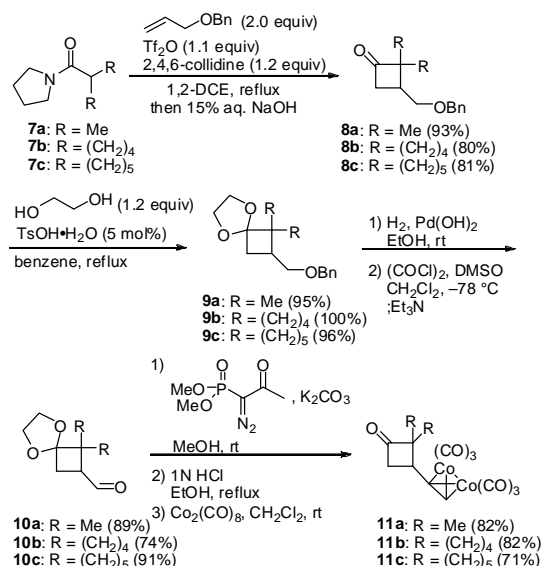
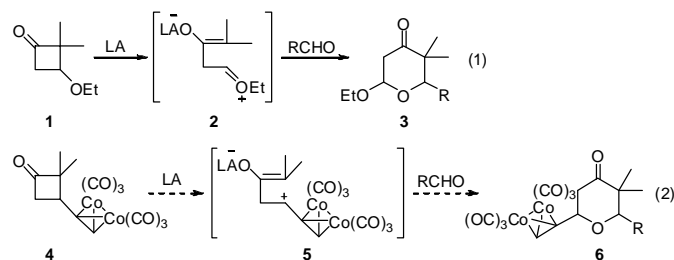
[4+2] Cycloaddition
Alkyne-cobalt complex
Cyclobutanone
Lewis acid
Tetrahydropyrone

ABSTRACT

Cyclobutanones bearing an alkyne-cobalt complex at their 3-positions reacted with aldehydes to give formal [4+2] cycloadducts by using tin(IV) chloride as a Lewis acid. Highly substituted tetrahydropyrone derivatives were stereoselectively prepared by this method.

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Cyclobutanones are important synthetic intermediates in organic synthesis.¹ We have recently reported that zwitterionic intermediate **2**, which was generated by Lewis acid-catalyzed ring cleavage of 3-ethoxycyclobutanone **1**, reacted with various aldehydes,^{2a} allylsilanes,^{2b} silyl enol ethers^{2c} and imines^{2d} to afford the corresponding formal [4+2] cycloadducts (eq 1). We have also reported diastereoselective asymmetric [4+2] cycloaddition by using 3-alkoxycyclobutanone bearing L-ethyl lactate as a chiral auxiliary.³ The generation of zwitterionic intermediate **2** was promoted by the alkoxy group at the 3-position of **1**. It was then thought that an alkyne-cobalt complex at the 3-position of cyclobutanone **4** would also promote generation of zwitterionic intermediate **5** since an alkyne-cobalt complex stabilizes the α -cation (eq 2).⁴ We report herein formal [4+2] cycloaddition of cyclobutanones bearing an alkyne-cobalt complex at their 3-positions to afford tetrahydropyrones.



Scheme 1. Preparation of Cyclobutanone **11a-c**

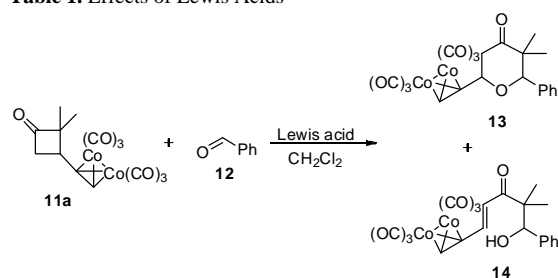
Cyclobutanones **11a-c** were prepared from amides **7a-c** by seven steps (Scheme 1). 3-Benzyloxymethylcyclobutanones **8a-c** were prepared by [2+2] cycloaddition with ketene iminium ions, which were generated from amides **7a-c** and allyl benzyl ether.⁵ Protection of the carbonyl group of **8a-c** with ethylene acetal, deprotection of the benzyl group of **9a-c**, and Swern

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oxidation⁶ of the resulting primary alcohols gave aldehydes **10a–c**. Reaction of aldehydes **10a–c** with Bestmann–Ohira reagent⁷ followed by deprotection of acetal and complexation with $\text{Co}_2(\text{CO})_8$ gave the desired cyclobutanones **11a–c**.

First, we explored a suitable Lewis acid for formal [4+2] cycloaddition between cyclobutanone **11a** and benzaldehyde **12** (Table 1). The desired product **13** was obtained in 38% yield by using boron trifluoride etherate (entry 1). Catalysis with titanium(IV) chloride gave enone **14** in 32% yield as the major product along with cycloadduct **13** (13%). Tin(IV) chloride was found to catalyze the desired [4+2] cycloaddition most effectively among Lewis acids we tested, and **13** was obtained in 82% yield with high *cis*-selectivity (*cis/trans* = 98:2) (entry 3). When ethylaluminum dichloride was employed, enone **14** was obtained in 79% yield (entry 4).

Table 1. Effects of Lewis Acids^a



entry	Lewis acid	Conditions	yield (%) ^b	
			13	14
1	$\text{BF}_3\text{-OEt}_2$	rt, 12 h	38	nd ^c
2	TiCl_4	-20 °C, 15 min	13	32
3	SnCl_4	rt, 4 h	82 ^d	trace
4	EtAlCl_2	-20 °C to 0 °C, 1 h	trace	79

^a PhCHO (**12**, 1.0 equiv), cyclobutanone **11a** (1.5 equiv) and Lewis acid (2.0 equiv) were employed.

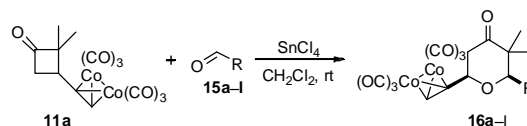
^b Isolated yield (%).

^c nd = Not detected.

^d *Cis/trans* = 98:2. The stereochemistry was determined by ¹H NMR spectra.

Next, the scope and limitations of tin(IV) chloride-catalyzed [4+2] cycloaddition of cyclobutanone **11a** were investigated by using various aldehydes **15a–l** (Table 2). 4-Methyl and 4-methoxybenzaldehydes reacted with **11a** to give the corresponding [4+2] cycloadducts in 57% and 31% yields, respectively (entries 1 and 2). The use of halogen-substituted benzaldehydes **15c–e** afforded the desired products **16c–e** in high yields (entries 3–5). These results suggest that electrophilic aldehydes reacted smoothly. In comparison with 2-naphthaldehyde **15g**, which gave cycloadduct **16g** in 45% yield (entry 7), the reaction with 1-naphthaldehyde **15f** gave the desired adduct **16f** in a lower yield (entry 6). Aliphatic aldehydes **15h–k** gave the corresponding tetrahydropyrones **16h–k** (entries 8–12). Longer reaction time was required for sterically hindered aldehydes. In all of the examples described above, cycloadducts **16a–l** were obtained with high *cis*-selectivity.

Table 2. Tin(IV) Chloride-Catalyzed Formal [4+2] Cycloaddition of Cyclobutanone **11a** to Various Aldehydes **15a–l**



entry	15 (R)	time (h)	yield (%) ^b	<i>Cis/trans</i> ^c
1	15a (4-MeC ₆ H ₄)	4	57	>99:1
2	15b (4-MeOC ₆ H ₄)	10	31	>99:1
3	15c (4-FC ₆ H ₄)	4	77	99:1
4	15d (4-ClC ₆ H ₄)	4	83	93:7
5	15e (4-BrC ₆ H ₄)	4	87	91:9
6	15f (1-naphthyl)	22	27	>99:1
7	15g (2-naphthyl)	8	45	>99:1
8	15h (PhCH ₂ CH ₂)	6	76	96:4
9	15i (<i>n</i> -heptyl)	6	68	91:9
10	15j (<i>i</i> -Bu)	9	42	94:6
11	15k (<i>i</i> -Pr)	18	61	97:3
12	15l (<i>t</i> -Bu)	12	11	98:2

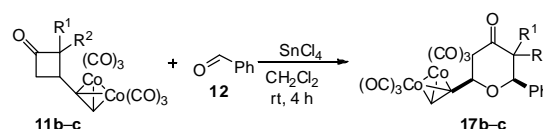
^a For reaction conditions, see Table 1.

^b Isolated yield (%).

^c The stereochemistry was determined by ¹H NMR spectra.

Reactions of spirocyclobutanones **11b** and **11c** also gave the corresponding cycloadducts **17b** and **17c** in 64% and 58% yields, respectively, as a single diastereomer (Table 3).

Table 3. Tin(IV) Chloride-Catalyzed Formal [4+2] Cycloaddition of 2,2-Dialkylcyclobutanones **11b** and **11c** to Benzaldehyde^a



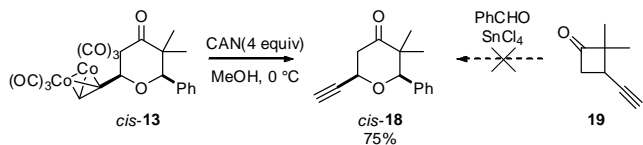
entry	cyclobutanone 11	yield (%) ^b	<i>cis/trans</i> ^c
1	R ¹ , R ² = (CH ₂) ₄ (11b)	64	>99:1
2	R ¹ , R ² = (CH ₂) ₅ (11c)	58	>99:1

^a For reaction conditions, see Table 1.

^b Isolated yield (%).

^c The stereochemistry was determined by ¹H NMR spectra.

Decomplexation of alkyne-cobalt complex **13** with cerium(IV) diammonium nitrate afforded tetrahydropyrene **18** in 75% yield (Scheme 2). Reaction of cyclobutanone **19** with benzaldehyde catalyzed by tin(IV) chloride did not proceed. Therefore, stabilization of α -cation by the alkyne-cobalt complex was important for these cycloaddition reactions.



Scheme 2. Decomplexation of Alkyne-Cobalt Complex **13**

In summary, we have developed tin(IV) chloride-mediated intermolecular [4+2] cycloaddition of cyclobutanones bearing an alkyne-cobalt complex at their 3-positions. This formal [4+2] cycloaddition showed *cis*-stereoselectivity.

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Supplementary Material

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

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