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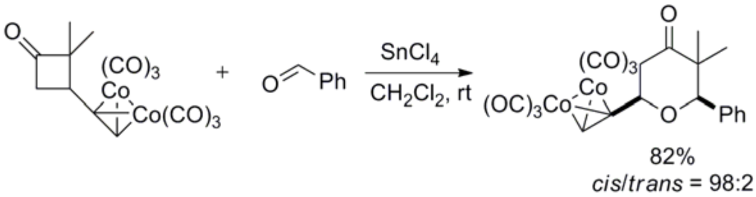


Tetrahedron Letters
journal homepage: www.elsevier.com

Formal [4+2] cylcoaddition of cyclobutanones bearing alkyne-cobalt complex at their 3-positions

Mizuki Kawano, Takaaki Kiuchi, Jun-ichi Matsuo* and Hiroyuki Ishibashi

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

ARTICLE INFO

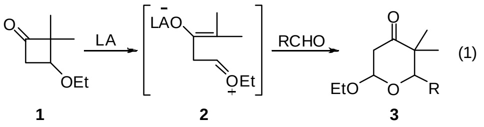
Article history:
Received
Received in revised form
Accepted
Available online

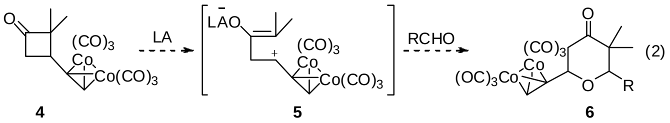
Keywords:
[4+2] Cycloaddition
Alkyne-cobalt complex
Cyclobutanone
Lewis acid
Tetrahydropyrone

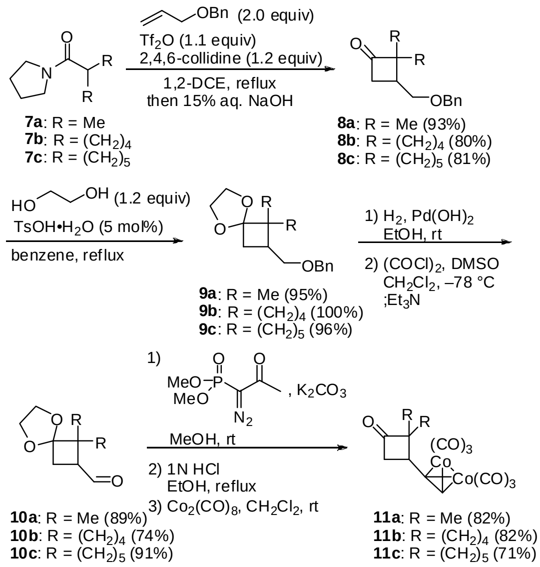
ABSTRACT

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.

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,[5] which were generated from amides **7a–c** and allyl benzyl ether. 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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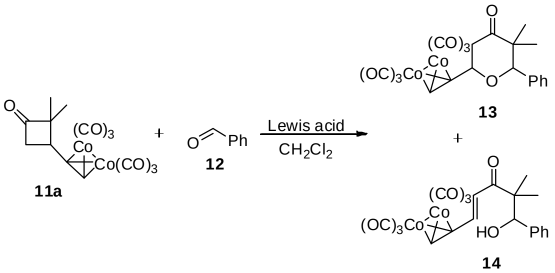
[*] Corresponding author. *E-mail address:* jimatsuo@p.kanazawa-u.ac.jp (J. Matsuo)

oxidation[6] of the resulting primary alcohols gave aldehydes **10a−c**. Reaction of aldehydes **10a−c** with Bestmann-Ohira reagent[7] followed by deprotection of acetal and complexation with $Co_2(CO)_8$ 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]

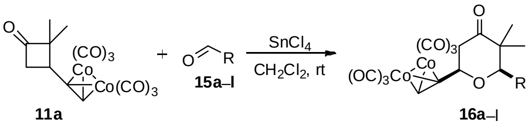


entry	Lewis acid	Conditions	yield (%)[b]	
			13	**14**
1	BF_3-OEt_2	rt, 12 h	38	nd[c]
2	$TiCl_4$	−20 °C, 15 min	13	32
3	$SnCl_4$	rt, 4 h	82[d]	trace
4	$EtAlCl_2$	−20 °C to 0 °C, 1 h	trace	79

[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-naphtaldehyde **15g**, which gave cycloadduct **16g** in 45% yield (entry 7), the reaction with 1-naphtaldehyde **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**

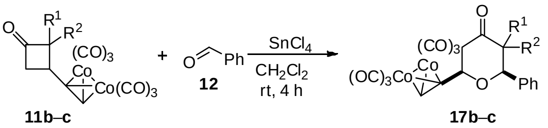


entry	**15** (R)	time (h)	yield (%)[b]	*Cis*/*trans*[c]
1	**15a** (4-MeC_6H_4)	4	57	>99:1
2	**15b** (4-$MeOC_6H_4$)	10	31	>99:1
3	**15c** (4-FC_6H_4)	4	77	99:1
4	**15d** (4-ClC_6H_4)	4	83	93:7
5	**15e** (4-BrC_6H_4)	4	87	91:9
6	**15f** (1-naphthyl)	22	27	>99:1
7	**15g** (2-naphthyl)	8	45	>99:1
8	**15h** ($PhCH_2CH_2$)	6	76	96:4
9	**15i** (*n*-heptyl)	6	68	91:9
10	**15j** (*i*-Bu)	9	42	94:6
11	**15k** (*i*-Pr)	18	61	97:3
12	**15l** (*t*-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).

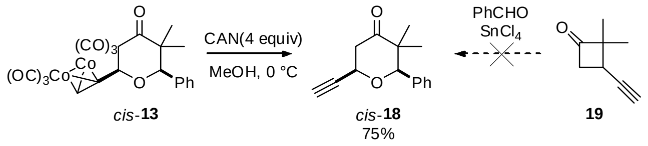
Table 3. Tin(IV) Chloride-Catalyzed Formal [4+2] Cycloaddition of 2,2-Dialkylcyclobutanones **11b** and **11c** to Benzaldehyde [a]



entry	cyclobutanone **11**	yield (%)[b]	*cis*/*trans*[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 tetrahydropyrone **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.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supplementary Material

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

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