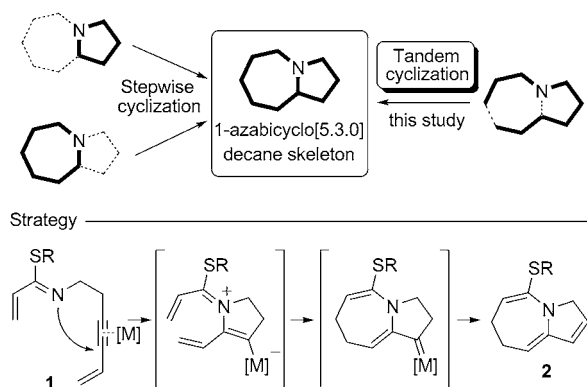


Chromium(0)-Catalyzed Tandem Cyclization of α,β -Unsaturated Thioimides Containing an Enyne Moiety**

Yusuke Karibe, Hiroyuki Kusama, and Nobuharu Iwasawa*

1-Azabicyclo[$n.3.0$] ring systems have been attracting much attention of organic chemists as a variety of important bioactive molecules contain these azabicyclic skeletons.^[1] In contrast to the abundant approaches to the construction of 1-azabicyclo[3.3.0]octane and 1-azabicyclo[4.3.0]nonane systems, the construction of the 1-azabicyclo[5.3.0]decane skeleton has not been extensively developed, although this ring system constitutes the basic core skeleton of the stemona alkaloids, some of which showed promising insecticide and antitussive activities.^[2] The central 1-azabicyclo[5.3.0]decane nucleus was formed by 7-membered-ring formation of pyrrolidine derivatives or 5-membered-ring formation of azepine derivatives in most of the previous synthetic strategies,^[3] and there were only a few reports^[4] on the one-step, stereoselective synthesis of these compounds by tandem cyclization of acyclic precursors (Scheme 1).



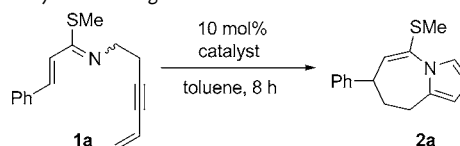
Scheme 1. Synthetic strategies toward the 1-azabicyclo[5.3.0]decane skeleton.

We have become interested in developing a new method for the stereoselective construction of the 1-azabicyclo[5.3.0]decane skeleton by using tandem cyclization of easily available compounds. Our basic strategy is shown at the bottom of Scheme 1. By treatment of α,β -unsaturated thio-

imides^[5] containing an enyne moiety **1** with an electrophilic transition-metal catalyst, zwitterionic complexes would be generated by 5-*endo* nucleophilic addition of the nitrogen atom to the electrophilically activated alkyne,^[6] followed by ring closure to give 1-azabicyclo[5.3.0]decane derivatives **2**, the core skeleton of stemona alkaloids. Herein we describe successful realization of this type of reaction.

We first examined the reaction of α,β -unsaturated thioimide **1a** containing an enyne moiety^[7] with $[\text{W}(\text{CO})_6]$ (10 mol %) under photoirradiation (250 W super high-pressure Hg lamp; Table 1, entry 1). The reaction proceeded as

Table 1: Catalyst screening.



Entry	Catalyst	Condition	Yield [%]
1	$[\text{W}(\text{CO})_6]$	$h\nu$	54
2	AuCl	80 °C	67
3	AuCl_3	80 °C	10
4	$[\text{AuCl}(\text{PPh}_3)]\text{-AgSbF}_6$	RT	trace
5	$[\text{PtCl}_2(\text{CH}_2\text{CH}_3)]^{[a]}$	80 °C	43
6	$[\text{ReCl}(\text{CO})_5]$	$h\nu$	19
7	$[\text{Mo}(\text{CO})_6]$	$h\nu$	74
8	$[\text{Cr}(\text{CO})_6]$	$h\nu$	86
9	$[\text{Cr}(\text{CO})_6]$	$h\nu^{[b]}$	92
10	$[\text{Cr}(\text{CO})_6]^{[a]}$	$h\nu^{[b]}$	15

[a] 5 mol % of catalyst was used. [b] THF was used as solvent.

expected, and 1-azabicyclo[5.3.0]decane product, pyrrole **2a**, was obtained in 54 % yield after double-bond migration. We further examined various electrophilic transition-metal catalysts to carry out the reaction more efficiently. AuCl , AuCl_3 , $[\text{PtCl}_2(\text{C}_2\text{H}_4)]$, and $[\text{ReCl}(\text{CO})_5]$ also showed moderate catalytic activity for this transformation (Table 1, entries 2, 3, 5, 6), but a cationic gold(I) complex, which was widely used as a powerful catalyst for the electrophilic activation of alkynes,^[8] failed to promote this reaction (entry 4). Among the group VI metal catalysts, $[\text{Cr}(\text{CO})_6]$ was found to show the highest activity (Table 1, entries 7, 8), and use of THF as solvent gave the best result (entry 9). Further reduction of the catalyst loading to 5 mol % lowered the yield of the product considerably (Table 1, entry 10).

As the deactivation of the catalyst was thought to be due to the coordination of the metal to the sulfur atom of **1a** and/or **2a**,^[9] we then expected that the use of thioimides containing a bulky substituent on the sulfur atom would

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inhibit the coordination of the catalyst to the sulfur atom, thereby resulting in acceleration of the reaction (Table 2). Although the benzyl group was not suitable for this reaction (Table 2, entry 2), the reaction with the (trimethylsilyl)-methyl-substituted substrate was found to be very efficient (entry 3). The reaction proceeded even with 2 mol % of $[\text{Cr}(\text{CO})_6]$ to give the cyclized product in 92 % yield (Table 2, entry 4).

Table 2: Effect of the sulfur substituent.

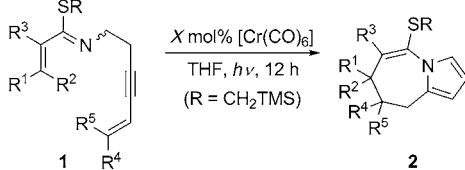
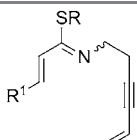
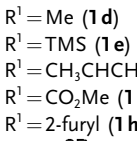
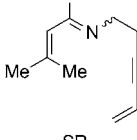
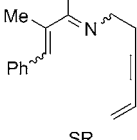
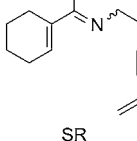
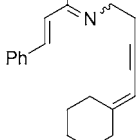
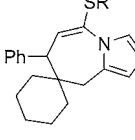
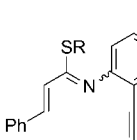
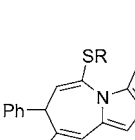
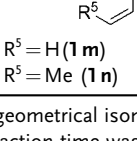
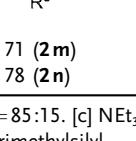
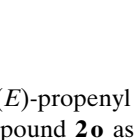
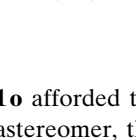
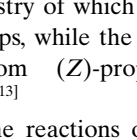
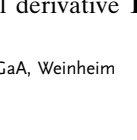
Entry	R	Yield [%]
1	CH_3 (1a)	38
2	Bn (1b)	16
3	Me_3SiCH_2 (1c)	80
4 ^[a]	Me_3SiCH_2 (1c)	92

[a] 2 mol % of catalyst was used. Reaction time was 12 h.

After having established that complexes of the composition $\text{Cr}(\text{CO})_5(\text{L})$ efficiently catalyzed the seven-membered-ring formation, the reaction was examined by employing several types of substrates with the results being summarized in Table 3. Monosubstituted α,β -unsaturated thioimides having a methyl, trimethylsilyl, propenyl, methoxycarbonyl, 2-furyl group (**1d**, **1e**, **1f**, **1g**, **1h**) also underwent seven-membered-ring formation smoothly in good yields. Even the reactions of disubstituted α,β -unsaturated thioimides (**1i**, **1j**) proceeded to afford the corresponding products in moderate to good yields. We next applied this reaction to a concise synthesis of tricyclic compounds possessing a seven-membered ring moiety. The reaction of thioimide **1k** having a cyclohexenyl group with a catalytic amount of $[\text{Cr}(\text{CO})_6]$ gave the tricyclic compound **2k** in good yield. Furthermore, the reaction of cyclohexylidene derivative **1l** also underwent seven-membered-ring formation smoothly to give spiro compound **2l** in good yield. Finally, the reaction of aniline derivatives **1m**, **1n** was examined. In these cases, formation of indole derivatives **2m**, **2n**, which contain a seven-membered ring, was found to proceed smoothly through deprotonation–protonation of an α,β -unsaturated carbene complex intermediate in the presence of NEt_3 .^[10]

Concerning the seven-membered-ring formation of this tandem cyclization, we initially assumed that the reaction proceeded through Cope rearrangement of the divinylaziridine intermediate **C**^[11] (see Scheme 3) as in the previously investigated tandem cyclization of 3-siloxy-1,3,9-trien-7-yne **3** catalyzed by complexes of the composition $\text{W}(\text{CO})_5(\text{L})$ (Scheme 2).^[12] However, it was a big surprise that comparison of the reactions of (*E*)-propenyl derivative **1o** and (*Z*)-propenyl derivative **1p** with those of the corresponding carbon analogues clearly indicated the opposite stereospecificity of the seven-membered-ring formation (Scheme 2). The

Table 3: Generality of the reaction.

			
Entry	X	Substrate	Yield [%] (product)
1	2		94 (2d)
2	5		74 (2e)
3	5		94 (2f) ^[b]
4	5		80 (2g)
5	5		88 (2h)
6	5	 (1i)	 90 (2i)
7	5	 (1j) ^[a]	 95 (2j)
8	5	 (1k)	 75 (2k)
9	5	 (1l)	 71 (2l)
10 ^[c]	10		71 (2m)
11 ^[c]	10		78 (2n)

[a] Mixture of geometrical isomers. [b] *E/Z* = 85:15. [c] NEt_3 (10 mol %) was added. Reaction time was 8 h. TMS = trimethylsilyl.

reaction of (*E*)-propenyl derivative **1o** afforded the desired bicyclic compound **2o** as a single diastereomer, the relative stereochemistry of which was *trans* between the phenyl and methyl groups, while the stereochemistry of the product **2p** derived from (*Z*)-propenyl derivative **1p** was *cis* (Scheme 2).^[13]

When the reactions of (*E*)-propenyl derivative **1o** and (*Z*)-propenyl derivative **1p** were carried out under thermal

which contain an enyne moiety; the cyclization proceeded through 1,7-electrocyclization of the zwitterionic intermediates. This reaction provides a new method for the diastereoselective synthesis of highly useful functionalized 1-azabicyclo[5.3.0]decane derivatives **2**, which constitute the basic skeleton of stemona alkaloids.

Experimental Section

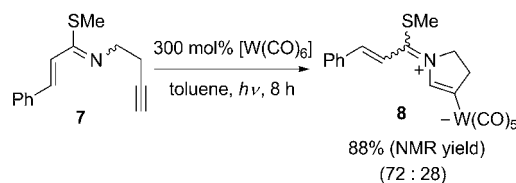
General procedure: A mixture of α,β -unsaturated thioimide **1** (0.1 mmol) and $[\text{Cr}(\text{CO})_6]$ (0.002–0.01 mmol) in THF (1 mL) was stirred for 8–12 h under photoirradiation (250 W super high-pressure Hg lamp). The reaction mixture was concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (PTLC; hexane/AcOEt = 19:1) to give the product **2**.

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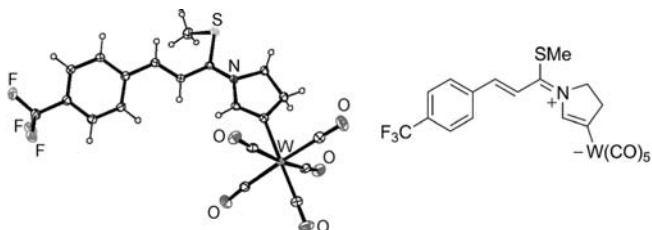
Keywords: alkaloids · chromium · homogeneous catalysis · synthetic methods · tandem cyclizations

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We have succeeded in obtaining a single crystal that was suitable for X-ray analysis for the CF_3 -substituted complex by recrystallization.



lization from pentane/CH₂Cl₂ in a nitrogen atmosphere. For details, see the Supporting Information (8).

Crystal data: monoclinic, $P2_1/n$, $a = 11.4793(4)$, $b = 16.9217(6)$, $c = 11.5189(4)$ Å, $\alpha = 90.00^\circ$, $\beta = 106.2280(10)$, $\gamma = 90.00^\circ$, R-factor = 3.37 (%).



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[18] The relative configuration of **5 n** was determined by observation of NOE spectra. For details, see the Supporting Information (6.3).