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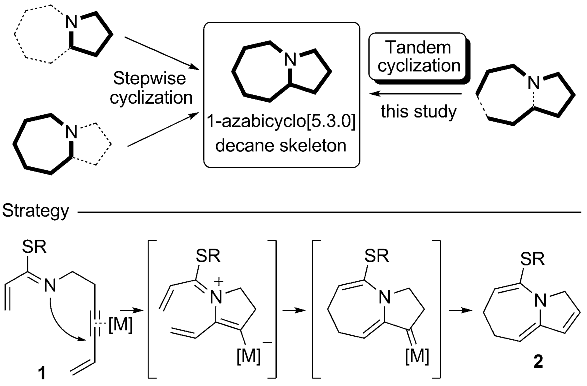
Chromium(0)-Catalyzed Tandem Cyclization of α,β-Unsaturated Thioimidates Containing an Enyne Moiety**

*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).

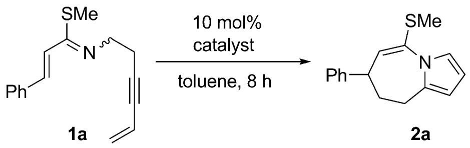


Scheme 1. Synthetic strategies toward the 1-azabicyclo[5.3.0]decane skeleton.

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 thioimidates[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 thioimidate **1a** containing an enyne moiety[7] with $[W(CO)_6]$ (10 mol%) under photoirradiation (250 W super high-pressure Hg lamp; Table 1, entry 1). The reaction proceeded as 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, $AuCl_3$, $[PtCl_2(C_2H_4)]$, and $[ReCl(CO)_5]$ 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, $[Cr(CO)_6]$ 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).

Table 1: Catalyst screening.



Entry	Catalyst	Condition	Yield [%]
1	$[W(CO)_6]$	*hν*	54
2	AuCl	80 °C	67
3	$AuCl_3$	80 °C	10
4	$[AuCl(PPh_3)]$-$AgSbF_6$	RT	trace
5	$[PtCl_2(CH_2CH_2)]$[a]	80 °C	43
6	$[ReCl(CO)_5]$	*hν*	19
7	$[Mo(CO)_6]$	*hν*	74
8	$[Cr(CO)_6]$	*hν*	86
9	$[Cr(CO)_6]$	*hν*[b]	92
10	$[Cr(CO)_6]$[a]	*hν*[b]	15

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

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 thioimidates containing a bulky substituent on the sulfur atom would

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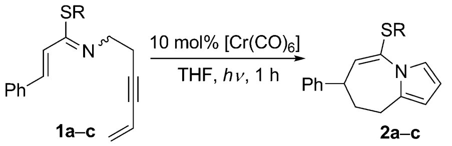
inhibit the coordination of the catalyst to the sulfur atom, thereby resulting in acceleration of the reaction (Table 2). Although the benzyl group was not suitable for this reaction (Table 2, entry 2), the reaction with the (trimethylsilyl)-methyl-substituted substrate was found to be very efficient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

Table 2: Effect of the sulfur substituent.



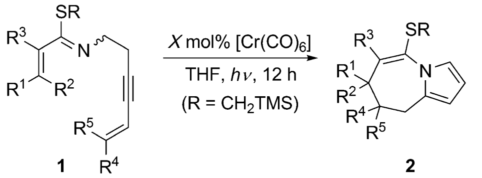
1a–c **2a–c**

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

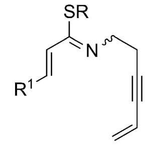
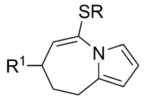
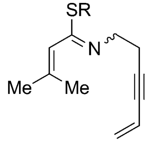
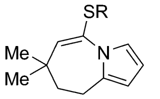
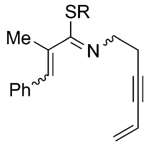
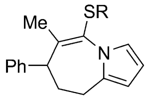
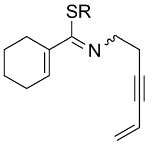
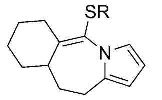
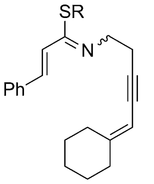
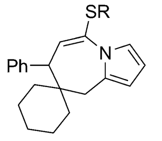
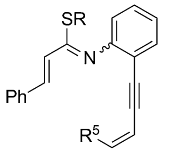
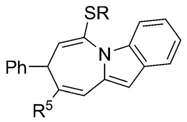
[a] 2 mol% of catalyst was used. Reaction time was 12 h.

After having established that complexes of the composition $Cr(CO)_5(L)$ 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 thioimidates 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 thioimidates (**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 thioimidate **1k** having a cyclohexenyl group with a catalytic amount of $[Cr(CO)_6]$ 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]

Table 3: Generality of the reaction.



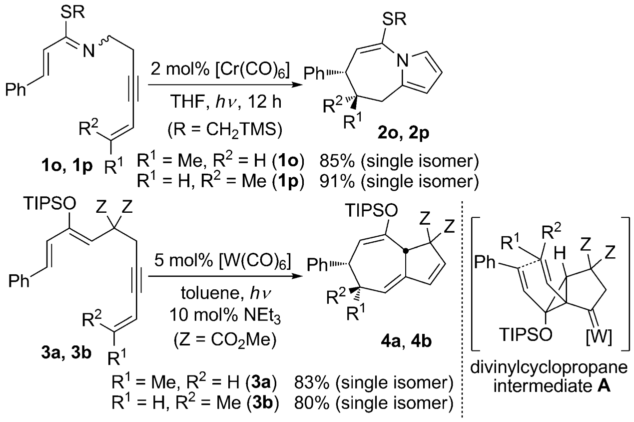
1 **2**

Entry	X	Substrate	Yield [%] (product)
			
1	2	R^1 = Me (**1d**)	94 (**2d**)
2	5	R^1 = TMS (**1e**)	74 (**2e**)
3	5	R^1 = CH_3CHCH (**1f**)[a]	94 (**2f**)[b]
4	5	R^1 = CO_2Me (**1g**)	80 (**2g**)
5	5	R^1 = 2-furyl (**1h**)	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	R^5 = H (**1m**)	71 (**2m**)
11[c]	10	R^5 = Me (**1n**)	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.

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-ynes **3** catalyzed by complexes of the composition $W(CO)_5(L)$ (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 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]

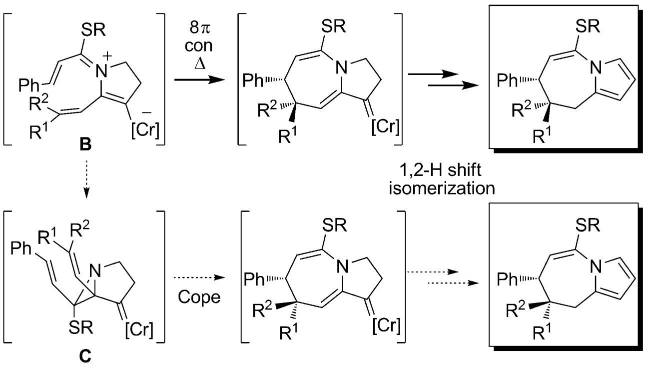
When the reactions of (*E*)-propenyl derivative **1o** and (*Z*)-propenyl derivative **1p** were carried out under thermal



Scheme 2. Stereoselectivity of the tandem cyclization. TIPS = triisopropylsilyl.

conditions (THF, reflux) using $[\mathrm{Cr(CO)_5(thf)}]$ as a catalyst, the same stereoselectivity as under photoirradiation conditions was observed. Thus, photoirradiation did not affect the stereoselectivity of the seven-membered-ring formation.[14]

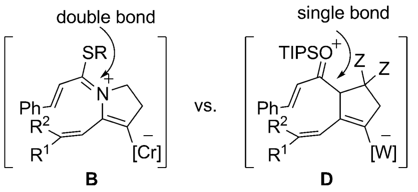
We currently believe that the product **2** was produced not through the divinylaziridine intermediate **C** but through 1,7-electrocyclization[15] (conrotatory under thermal conditions) of zwitterionic intermediate **B** based on the stereochemistry of the product (Scheme 3).



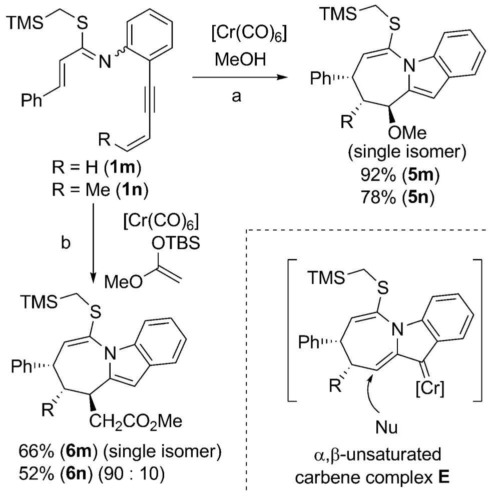
Scheme 3. Proposed mechanism.

It is likely that the present reaction could not give the divinylaziridine intermediate **C**, because the zwitterionic intermediates **B** have the planar structure between the alkenyl metal moiety and the thioiminium moiety in contrast to the carbon analogues, where no double-bond character existed at the C–C bond that is derived from the silyl enol ether moiety in the zwitterionic intermediate **D** (Scheme 4). On the contrary, in the case of the present reaction, electrocyclization was possible because of the presence of the C=N double-bond character of the thioimidate moiety of the zwitterionic intermediate **B** (Scheme 4).[16]

Interestingly, when the reaction of aniline derivative **1m** was carried out in the presence of MeOH, stereoselective 1,4-addition of MeOH to α,β-unsaturated carbene complex intermediate **E**[17] occurred to give the methoxylated tricyclic indole **5m** as a single diastereomer (Scheme 5). The stereoselectivity of the reaction could be explained by the selective attack of MeOH from the opposite face of the phenyl substituent. This method was applicable to stereoselective construction of three contiguous chiral centers. The reaction of aniline derivative **1n** containing a (*Z*)-propenyl moiety afforded the methoxylated tricyclic indole **5n** as a single diastereomer.[18] An α,β-unsaturated carbene complex intermediate, the relative stereochemistry of which was *cis* between the phenyl and methyl groups, was generated by 1,7-electrocyclization (conrotatory) and the selective 1,4-addition of MeOH from the opposite face of the phenyl and methyl substituents. Furthermore, a carbon nucleophile could also be employed in this reaction. By carrying out the reaction of **1m** and **1n** with *O*-methyl-*O*-(*tert*-butyldimethylsilyl)ketene acetal using $[\mathrm{Cr(CO)_6}]$ (30 mol%) under photoirradiation in the presence of MeOH as a proton source, tricyclic indoles **6m** and **6n** were obtained with high stereoselectivity.



Scheme 4. Structural difference between zwitterions of the thioimidate and the carbon analogues.



Scheme 5. 1,4-Addition of nucleophiles to α,β-unsaturated carbene complex intermediate. Conditions: a) $[\mathrm{Cr(CO)_6}]$ (30 mol%), MeOH (50 equiv), toluene, *hν*, 8 h; b) $[\mathrm{Cr(CO)_6}]$ (30 mol%), $\mathrm{CH_2{=}C(OTBS)OMe}$ (10 equiv), MeOH (3 equiv), toluene, *hν*, 8 h. The ratio given for **6n** is the stereoselectivity concerning the $\mathrm{-CH_2CO_2Me}$ group with the major isomer shown here. TBS = *tert*-butyldimethylsilyl.

In summary, we have developed the chromium(0)-catalyzed tandem cyclization of α,β-unsaturated thioimidates **1**, 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 thioimidate **1** (0.1 mmol) and [Cr(CO)$_6$] (0.002–0.01 mmol) in THF (1 mL) was stirred for 8–12 h under photoirradiation (250W 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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[5] Thioimidates were chosen as substrates because of their higher stability compared to imidates and higher nucleophilicity compared to imines.

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[7] The reactions of **1a–1j**, **1m**, **1n** were examined using a mixture of *Z* and *E* isomers concerning the thioimidate moiety. It was confirmed that isomerization of the zwitterionic intermediates occurred easily and there seemed to be no difference in reactivity between *Z* and *E* isomer. See the Supporting Information (8).

[8] For recent reviews on gold-mediated homogeneous catalysis, see: a) H. Huang, Y. Zhou, H. Liu, *Beilstein J. Org. Chem.* **2011**, *7*, 897–936; b) F. López, J. L. Mascareñas, *Beilstein J. Org. Chem.* **2011**, *7*, 1075–1094.

[9] When the reaction of thioimidate **1a** was carried out with [Cr(CO)$_6$] (10 mol%) in the presence of **2a** or 1,4-diphenyl-2-methylthio-1-azabuta-1,3-diene, the rate of conversion of **1a** became lower. Furthermore, in the reaction of **2a** with [Cr(CO)$_6$] under photoirradiation, the complex that was formed by the coordination of chromium to the sulfur atom was observed. For details, see the Supporting Information (7.1, 7.2).

[10] We reported one example of a similar reaction of imines, where the reaction proceeded without the thio substituent owing to the facile ring closure of the rigidity of the aromatic substrate, see: a) H. Kusama, Y. Suzuki, J. Takaya, N. Iwasawa, *Org. Lett.* **2006**, *8*, 895–897. See also; b) H. Kusama, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2002**, *124*, 11592–11593; c) J. Takaya, H. Kusama, N. Iwasawa, *Chem. Lett.* **2004**, *33*, 16–17; d) H. Kusama, Y. Miyashita, J. Takaya, N. Iwasawa, *Org. Lett.* **2006**, *8*, 289–292; e) J. Takaya, Y. Miyashita, H. Kusama, N. Iwasawa, *Tetrahedron* **2011**, *67*, 4455–4466.

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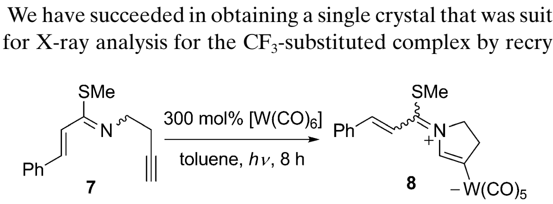
[13] The structure and relative stereochemistry of **2p** were confirmed by X-ray analysis after hydrolysis of the *N*,*S*-keteneacetal moiety. See the Supporting Information (6.1).

[14] Photoirradiation is important for facile generation of the catalytically active, coordinatively unsaturated species from [Cr(CO)$_6$] at ambient temperature. See the Supporting Information (7.3).

[15] For reviews of 1,7-electrocyclization, see: a) M. Nyerges, J. Tóth, P. W. Groundwater, *Synlett* **2008**, 1269–1278; b) T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2006**, 2873–2888; c) G. Zecchi, *Synthesis* **1991**, 181–188; for examples of the seven-membered-ring formation, see; d) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244–9245; e) J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaria, R. J. Carbajo, F. López-Ortiz, S. Garcia-Granda, P. Pertierra, *Chem. Eur. J.* **1996**, *2*, 88–97.

[16] In the reaction of ω-acetylenic thioimidate **7** with [W(CO)$_6$] (3 equiv) in toluene under photoirradiation, the zwitterionic complex **8** was obtained.

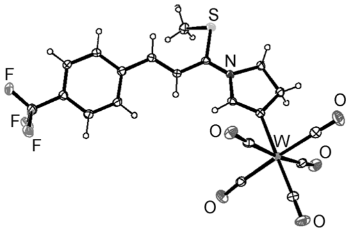
We have succeeded in obtaining a single crystal that was suitable for X-ray analysis for the CF$_3$-substituted complex by recrystal-

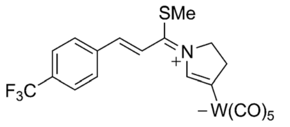


88% (NMR yield)
(72 : 28)

lization from pentane/CH_2Cl_2 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, $\alpha = 90.00$, $\beta = 106.2280(10)$, $\gamma = 90.00°$, R-factor = 3.37 (%).





[17] For an example of 1,4-addition to an α,β-unsaturated carbene complex, see: E. Nakamura, K. Tanaka, T. Fujimura, S. Aoki, P. G. Williard, *J. Am. Chem. Soc.* **1993**, *115*, 9015–9020. For reviews on catalytic generation of α,β-unsaturated carbene complex intermediates, see reference [6], see also; K. Saito, H. Sogou, T. Suga, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2011**, *133*, 689–691, and references therein.

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

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