Organic LETTERS
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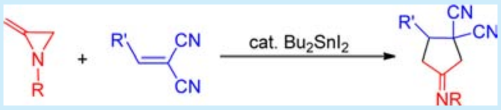
Catalytic Cycloaddition of 2-Methyleneaziridines with 1,1-Dicyanoalkenes

Hiroki Takahashi, Seiji Yasui, Shinji Tsunoi, and Ikuya Shibata*

Research Center for Environmental Preservation, Osaka University, 2-4 Yamadaoka, Suita, Osaka 565-0871, Japan

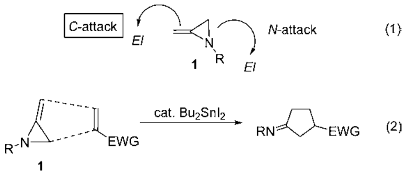
Supporting Information

ABSTRACT: 2-Methyleneaziridine are a good substrate for the catalytic synthesis of cyclopentylidenamines via a [3 + 2] cycloaddition of 1,1-dicyanoalkenes using Bu_2SnI_2 as an effective catalyst. A C-attack from 2-methyleneaziridine yielded the desired products.



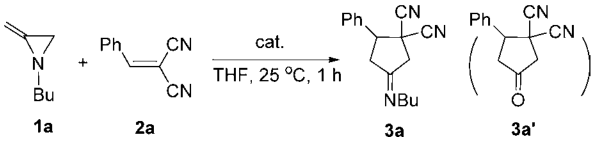
2-Methyleneaziridines **1** are easy to handle in spite of their ring strain, and the preparation procedures have been reported so far.[1,2] This compound has been used as a versatile substrate for synthesis.[2,3] The regioselective ring-opening of **1** at C-3 by a Grignard reagent and the subsequent reaction of the resultant metalloenamine with an electrophile is a representative reaction.[2b] Lewis acid-promoted intramolecular cycloadditions have been developed.[4] Almost conventional procedures are stoichiometric reactions with metallic reagents. For the catalytic reaction using **1**, transition-metal-catalyzed reactions have been reported,[5,6] in which the initial addition of a metal species to a C═C double bond is a key reaction.[6] As main group metal catalysts, organotin iodides were used in cycloaddition of epoxides in the preparation of cyclic compounds.[7] In the cycloaddition, the ring-opening of an epoxide by tin iodide is a key step.[8] However, the ring-opening of aziridines are difficult because of the diminished electronegativity of nitrogen.[9] In contrast, 2-methyleneaziridine **1** seems to cleave easily because of ring strain,[10] which makes it a good candidate for the substrate of cycloaddition reactions. Also, 2-methyleneaziridine **1** possesses two nucleophilic sites similar to that of amines (*N*-attack) and enamine (*C*-attack) (Scheme 1, eq 1). We recently reported the *N*-attack of **1** in a tin iodide-catalyzed [3 + 2] cycloaddition with isocyanates leading to nitrogen-heterocycles.[11] In view of these backgrounds, we present here the novel type of [3 + 2] cycloaddition of **1** with activated alkenes (Scheme 1, eq 2). This reaction could be a catalytic reaction involving a *C*-attack from **1** where systems employing catalytic tin have been established.

Scheme 1. [3 + 2] Cycloaddition of 2-Methyleneaziridine 1



Initially, as shown in Table 1, we performed the cycloaddition of **1a** with benzalmalononitrile (**2a**). Without a catalyst, no reaction proceeded at 25 °C for 1 h (entry 1). By using 0.1 equiv of Bu_2SnI_2 as a catalyst, the cyclic product **3a** was obtained in an 89% yield (entry 2). The initially formed product **3a** was an imine type of adduct that was detected in the reaction mixture by ^1H NMR. However, cyclopentanone **3a′** was isolated as a stable product because the hydrolysis of **3a** occurred easily during the purification process (Table 1, eq parentheses). The product **3a** was derived from the attack of the enamine carbon of **1a** to the C═C bond of **2a**. We examined other metal salts as catalysts (entries 3−9). Using LiI also gave **3a** in a 76% yield (entry 3). Bu_2SnBr_2 and LiBr catalysts did not cause the desired reaction (entries 4 and 5). Using KI as a catalyst also gave no products (entry 6). Using MgI_2 and ZnI_2 resulted in low yields (entries 7 and 8). InI_3 showed moderate activity (entry 9). Bu_2SnI_2 has thus far been the catalyst that afforded the highest yield.

Table 1. Cycloaddition of 1a with 2a



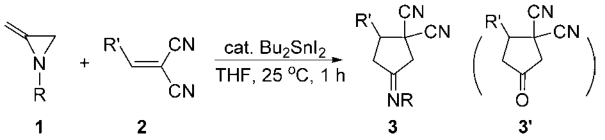
entry[a]	catalyst	yield of **3a**[b] (%)
1	none	trace
2	Bu_2SnI_2	89
3	LiI	76
4	Bu_2SnBr_2	trace
5	LiBr	trace
6	KI	trace
7	MgI_2	38
8	ZnI_2	27
9	InI_3	53

[a] **1a** (0.8 mmol), **2a** (0.5 mmol), THF (1 mL), cat (0.05 mmol). [b] Determined by ^1H NMR based on **2a**.

Table 2 shows the results of the reactions of 2-methyleneaziridines **1** with several 1,1-dicyanoalkenes **2** catalyzed by Bu_2SnI_2 under the optimized conditions. The

Received: January 8, 2014
Published: February 5, 2014

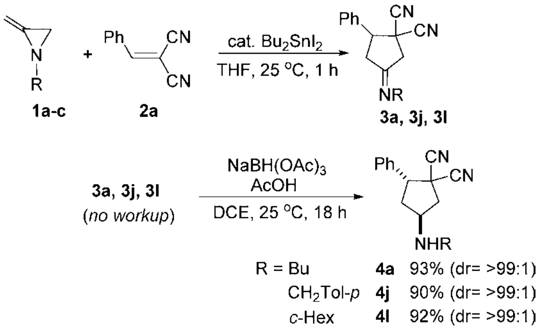
Table 2. Cycloaddition of 1 with 1,1-Dicyanoalkenes 2



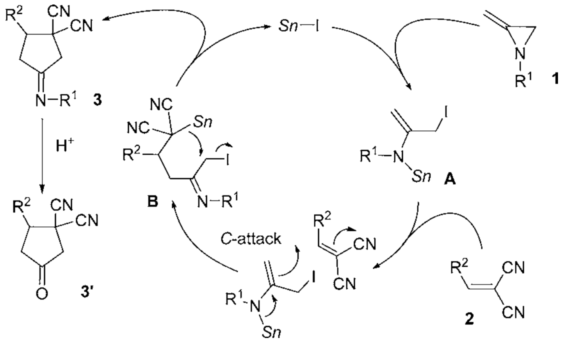
entry[a]	R	R′	product 3 or (3′)	yield of 3[b] (%)	yield of 3[c] (%)
1	*n*-Bu (**1a**)	Ph (**2a**)	**a**	89	80
2		*p*-$\mathrm{NO_2C_6H_4}$ (**2b**)	**b**	79	75
3		*p*-$\mathrm{ClC_6H_4}$ (**2c**)	**c**	93	84
4		*p*-$\mathrm{FC_6H_4}$ (**2d**)	**d**	71 (3 h)	65
5		*p*-$\mathrm{CH_3C_6H_4}$ (**2e**)	**e**	52 (3 h)	47
6		PMP (**2f**)	**f**	53	48
7		Nphth (**2g**)	**g**	50 (3 h)	48
8		furyl (**2h**)	**h**	73	66
9		$\mathrm{PhCH_2CH_2}$ (**2i**)	**i**	46 (24 h)	40
10	$\mathrm{CH_2}$tol-*p* (**1b**)	Ph (**2a**)	**3j** (**3a′**)	66 (24 h)	62
11		*p*-$\mathrm{ClC_6H_4}$ (**2c**)	**3k** (**3c′**)	58 (24 h)	50
12	*c*-Hex (**1c**)	Ph (**2a**)	**3l** (**3a′**)	76 (3 h)	73

[a] **1** (0.8 mmol), **2** (0.5 mmol), THF (1 mL), $\mathrm{Bu_2SnI_2}$ (0.05 mmol). [b] Determined by ^{1}H NMR based on **2**. [c] Isolated yield.

Scheme 2. Reduction of Imino Group of 3



Scheme 3. Plausible Catalytic Cycle



reactions of **1a** with **2a**−**2i** proceeded well at 25 °C, and cyclic products **3a**−**3i** were formed (entries 1−9). In these cases, various functionalities could be introduced on the aromatic rings of **2** (entries 1−6). Naphthyl substituted alkene **2g** gave **3g** (entry 7). Furyl-substituted alkene **2h** was also useful and gave **3h** (entry 8). Besides aromatic alkenes, aliphatic **2i** was reactive and gave **3i** (entry 9). In a similar manner, a reaction using *N*-arylmethyl-substituted substrate **1b** underwent the desired reactions (entries 10 and 11). Even the use of bulky cyclohexyl-substituted **1c** underwent the reaction well (entry 12).

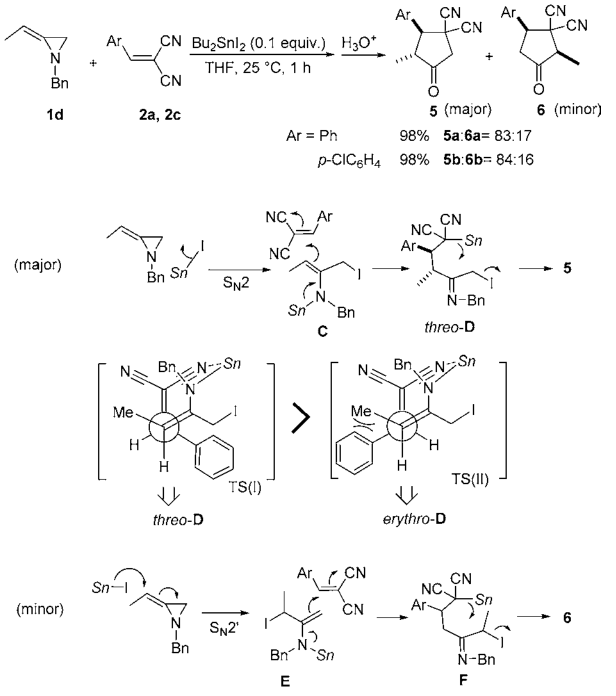
As shown in Tables 1 and 2, although the desired reactions proceeded well, products **3** had imine groups and were easily hydrolyzed during the treatment by column chromatography. Hence, cyclopentanone derivatives **3′** were obtained as pure products. In the examples shown in Table 2, entries 10 and 11, the initially obtained **3j** and **3k** were hydrolyzed to **3a′** and **3c′**, respectively. These isolated products corresponded to entries 1 and 3. In the case of entry 12, the product **3l** was also converted to **3a′**. So nitrogen functionalities were lost from the cycloadducts **3**. For the fixation of nitrogen functionalities, we tried a reduction of the imino groups of **3** (Scheme 2). Without workup, the resultant reaction mixtures that included **3a**, **3j**, and **3l** were allowed to react with a reductant NaBH(OAc)$_3$[12] at rt for 18 h. As a result, amines, **4a**, **4j**, and **4l**, respectively, were obtained as nitrogen-containing products with high diastereoselectivities.[13]

Scheme 3 shows a plausible catalytic cycle for the tin-catalyzed reaction of **1** with **2**. Initially, tin enamine **A** is formed by the attack of Sn−I toward 2-methyleneaziridine **1**.[14] Because of the ring strain of **1**, the ring-opening proceeds effectively. Next, the Michael addition of **A** to **2** takes place to give adduct **B** (*C*-attack). For the Michael addition, using highly electrophilic C=C bonds like 1,1-dicyano alkenes **2** was essential. Other alkenes such as monocyanoalkenes, unsaturated esters, and enones were unreactive because of the lack of electrophilic nature and were recovered quantitatively. The nucleophilicity of tin enamine **A** was insufficient because of electron-withdrawing ability of the halogen substituent in **A**. $\mathrm{Bu_2SnBr_2}$ or LiBr catalyst showed no catalytic activity (Table 1 entries 4 and 5). Thus the electron-withdrawing property of bromide substituent decreases the nucleophilicity of **A**. Finally, the resultant nucleophilic Sn−C bond of **B** causes *C*-alkylation to afford 4-cyclopentan-2-imine **3**, regenerating the tin iodide catalyst.

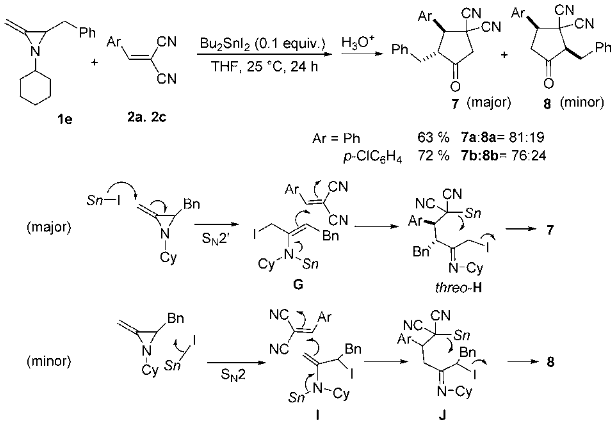
We next attempted the use 2-alkylidene aziridine **1d** including an internal (*Z*)-alkene (Scheme 4). The reactions with 1,1-dicyanoalkenes, **2a** and **2c**, proceeded well, and *α*-methyl-substituted cyclopentanones **5a** and **5b** were isolated as major products, accompanying the minor ones, **6a** and **6b**. The major products of **5** were obtained through the tin enamine **C** that was derived from the S_N2 attack of the Sn−I bond toward the aziridine ring. On the other hand, the minor products of **6** were formed through the enamine **E** that was derived from the S_N2' attack of the Sn−I bond toward the C=C bond. The S_N2' attack is known to be a minor process in the ring-opening of a simple 2-methyleneaziridine.[15] It is worth noting that major products **5a** and **5b** were obtained as single *trans*-isomers, the stereochemistry of which was determined by NOE study. Thus, in the reaction of (*Z*)-enamine **C** with **2**, passage of the sterically less-hindered 8-membered cyclic transition state TS(I) was favored over that of TS(II).[16,17] As a result, *threo*-adduct **D** was formed selectively and underwent cyclization to give **5**. Minor products, regioisomers **6a** and **6b**, were single *cis*-isomers, the stereochemistry of which was determined by NOE study.[18]

Scheme 5 shows the reaction using C3-substituted 2-methyleneaziridine **1e**. The reactions with 1,1-dicyanoalkenes **2a** and **2c** proceeded well to give major products **7a** and **7b** accompanying minor products **8a** and **8b**. Contrary to the above case using **1d**, the S_N2' attack of the Sn−I bond toward

Scheme 4. Cycloaddition of 1d with 2a or 2c



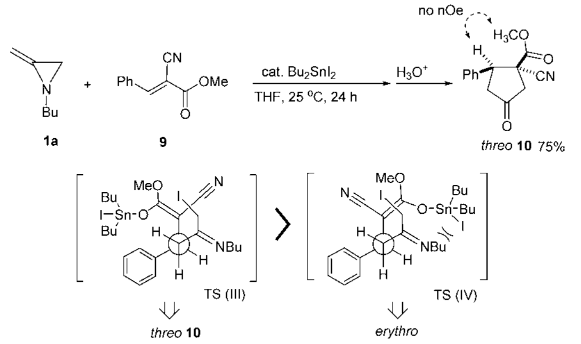
Scheme 5. Cycloaddition of 1e with 2a, 2c



the C═C bond was a major process. Thus, the products of **7** were obtained through tin enamine **G**. However, the minor products of **8** were obtained through the enamine **I** that was derived from the S_N2 attack of the Sn−I bond toward the aziridine ring. The disadvantage of S_N2 attack giving **I** was caused by the difficulty of a direct ring-opening for *vis*-disubstituted rings.[19] Major products **7a** and **7b** were obtained as single *trans*-isomers.[20] The stereoselectivity in **7** can be explained in a similar manner giving **5** as illustrated in Scheme 4, because tin enamine **G** is very similar to **C**.[18]

When an unsymmetrical alkene **9** was used as an electrophile, the desired adduct **10** was obtained in 75% yield (Scheme 6). The reaction was diastereoselective to give a *threo* isomer. The diastereoselectivity is supposed to be determinded at the step of cyclization. Namely, after the C−C bond formation, cyclization proceeds via TS(III), giving *threo*-isomer **10** rather than TS(IV) to an *erythro* isomer. Thus, the repulsion between NBu and the stannoxy group would be responsible for the observed stereochemistry.

Scheme 6. Cycloaddition of 1a with Unsymmetric Alkene 9



In conclusion, we demonstrated the catalytic conversion of 2-methyleneaziridines **1** to cyclic products **3**, **4**, **5**, **7**, and **10** via a novel type of [3 + 2] cycloaddition. Bu_2SnI_2 was employed as an effective catalyst. A C-attack from tin enamines was a key step in the reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General procedures and characterization data of new compounds, CIF file for **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shibata@epc.osaka-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture and the Naito Foundation.

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(13) We could determine the stereochemistry of products as 1,3-*trans* by NOE study for **4j**.

(14) In an equimolar mixture of **1a** with Bu_2SnI_2 the measurement of ^{1}H NMR resulted in a complex mixture, perhaps because of the fact that intermediate **A** was too labile to detect.

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(17) Acyclic antiperiplanar transition states are inconsiderable. See Supporting Information.

(18) The reason for the diastereoselective formation of minor products **6**, **8** is discussed in the Supporting Information.

(19) Organotin iodide catalyzed the cycloaddition of epoxides with isocyanates could not applied to the case using *vic*-disubstituted rings because of difficulty of ring opening.[7]

(20) The stereochemistry of **7b** is determined by X-ray crystal analysis (CCDC 972461).