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A RING-OPENING CROSS-METATHESIS REACTION OF *N*-TRIALKYLSILYL 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE WITH ALLYLTRIMETHYLSILANE

Minoru Ishikura,*[a] Miyako Hasunuma,[a] and Kazuo Yanada[b]

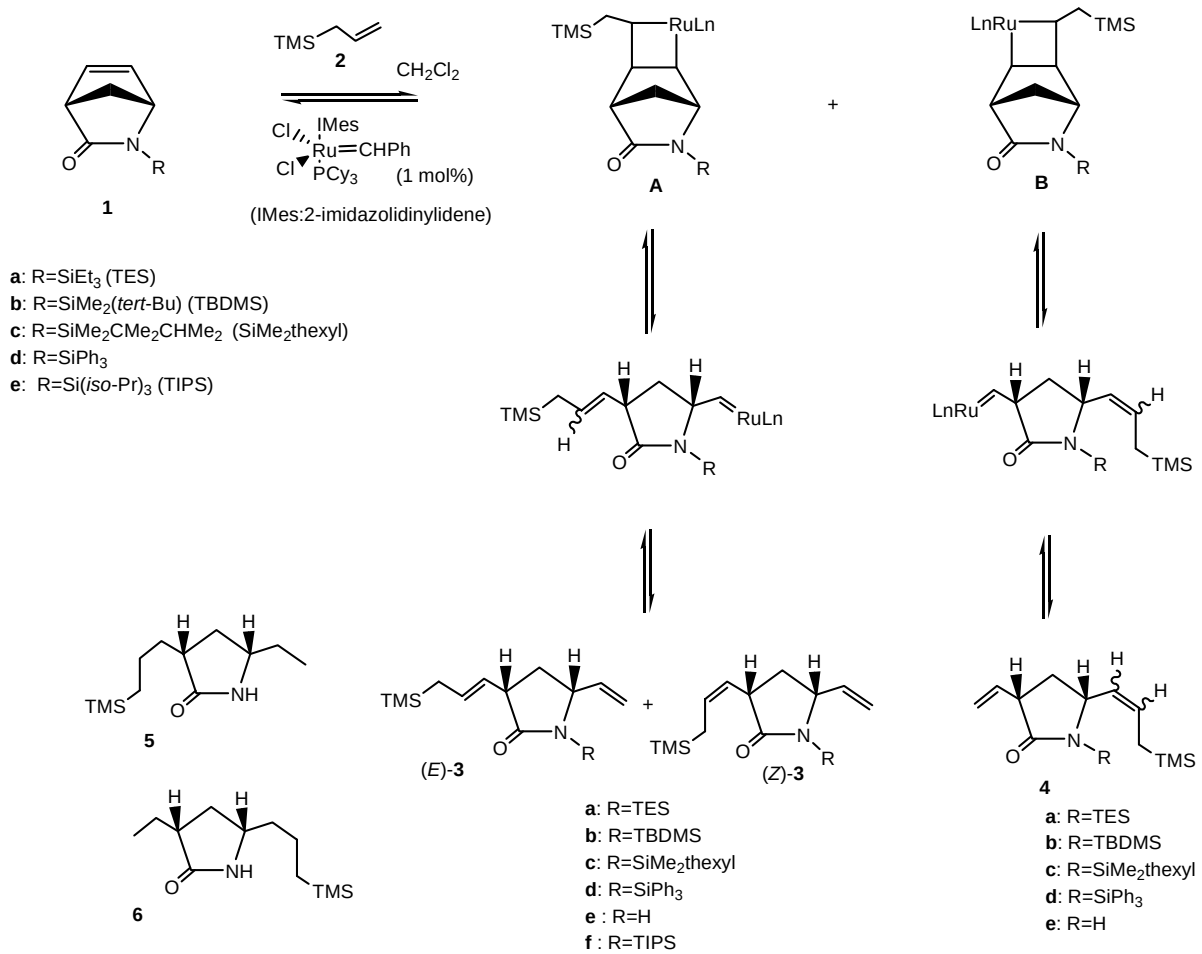
[a] Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan; e-mail: ishikura@hoku-iryo-u.ac.jp
[b] Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagatoge-Cho, Hirakata, Osaka 573-0101, Japan

Abstract – Subjection of *N*-trialkylsilyl-2-azabicyclo[2.2.1]hept-5-en-3-one (**1**) to a ring-opening cross-metathesis reaction with allyltrimethylsilane in the presence of Grubbs' catalyst was found to allow the predominate formation of pyrrolidine (**3**) over pyrrolidine (**4**).

The use of 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) (**1**;R=H) has proven to be highly successful in the preparation of a number of carbocyclic nucleosides,[1] and we have previously reported the first preparation of 2',3'-methano-, 2',3'-epimino- and 2',3'-oxirane-fused carbocyclic nucleosides based on ABH.[2] In spite of its attractive chemical lability, the development of the synthetic potential of ABH still remains challenging. Among only a few hitherto known reports of ruthenium-catalyzed metathesis reactions of ABH,[3] we have re-examined the known metathesis reaction of *N*-Boc-ABH (**1**;R=Boc) with allyltrimethylsilane (**2**) in the presence of Grubbs' catalyst in order to gain more detailed knowledge of the exemplified high regioselectivity.[3a] However, as a result, we observed insufficiency in regioselectivity in the ring-opening of ABH (**1**), leading to a pair of regioisomeric ring-opening products (through **A** and **B** to **3** and **4**, respectively), which has become a crucial issue to be overcome[4] (Scheme 1). The transannular participation of the nitrogen and carbon at the 6 position in ABH (**1**;R=H) has been recognized during bromination of **1** (R=H), leading to dibromide by way of addition-rearrangement.[5] Thus, we reasoned that this nitrogen participation would be essential to achieve regioselectivity successfully. First, therefore, we began by establishing the effects of *N*-substituents in ABH on the regioselectivity of the metathesis reaction. In our previous report, we observed low regioselectivity of the reaction of *N*-acyl ABH with **2**,[4a,b] but *N*-trialkylsilyl group in ABH (**1**) was eventually found to be

significantly effective in promoting the metathesis reaction in a regioselective manner.[4c] Encouraged by these results, we turned our attention to the isolation of metathesis products (**3**,**4**), and their conversion to pyrrolizines (**8**,**9**).

After the reaction of **1a** with **2** (1.2 equiv.) was successfully and cleanly carried out using Grubbs' second generation catalyst (1 mol%) in CH_2Cl_2 at room temperature for 2h under argon atmosphere, the reaction mixture was concentrated and directly subjected to separation by medium pressure liquid chromatography (MPLC) with hexane-AcOEt, allowing the isolation of (***Z***)-**3a** and (***E***)-**3a** as major products and a minor amount of **4a** as a *E/Z* mixture[6] (Scheme 1). Catalytic hydrogenation (4 atm of H_2, 10% Pd on C in THF) of (*E*)-**3a** and (*Z*)-**3a**, accompanied by spontaneous *N*-desilylation during the reduction, provided **5** as a sole product. Otherwise, **6** was the sole product of catalytic hydrogenation of an inseparable *E/Z* mixture of **4a**.



Scheme 1

Similarly, formation of **3b,c** predominated over **4b,c** in the reaction of *N*-trialkylsilyl ABH (**1b**,**c**) with **2**. These products (**3a-c** and **4a-c**) were somewhat less stable, accompanied by decomposition to some

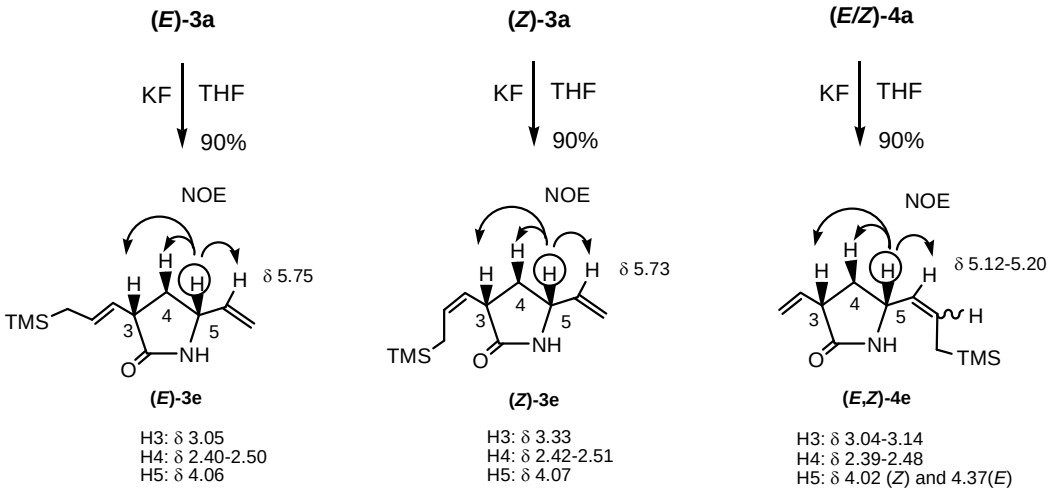
extent during the separation and handling, but enough to be isolated and characterized. However, probably due to their intrinsic instability, only (***E***)-**3f** was isolated from the reaction mixture of *N*-triisopropylsilyl ABH (**1e**) with **2** in low yield (Table 1). On the other hand, when *N*-triphenylsilyl ABH (**1d**) was exposed to the reaction with **2,** it appeared that *E/Z* mixture of **4d** was more likely to be obtained than (***Z***)-**3d** and (***E***)-**3d**.

Table 1 Isolation of **3** and **4***

1	Isolated yield (%) of **3**	Isolated yield (%) of **4**
1a	46% [(***E***)-**3a**)], 14% [(***Z***)-**3a**)]	10% (**4a**)
1b	55% [(***E***)-**3b**)], 15% [(***Z***)-**3b**)]	8% (**4b**)
1c	56% [(***E***)-**3c**)], 17% [(***Z***)-**3c**)]	8% (**4c**)
1d	20% [(***E***)-**3d**)], 5% [(***Z***)-**3d**)]	41% (**4d**)
1e	10% [(***E***)-**3f**)]	-------

*Yields (%) based on the corresponding **1**

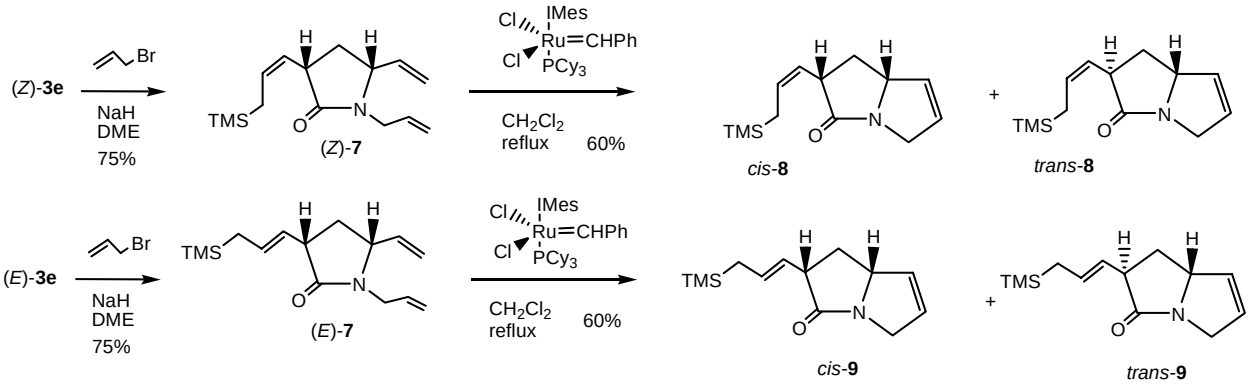
Removal of *N*-trialkylsilyl group from (***E***)-**3a**, (***Z***)-**3a**, and *E/Z* mixture of **4a** was achieved easily with KF in THF at room temperature to give (*E*)-**3e**, (*Z*)-**3e**, and *E/Z* mixture of **4e,** respectively. *cis*-Configuration at the 3- and 5-positions in **3e** and **4e** was firmly established based on NOE experiments, in which irradiation of 5-proton gave NOE enhancement at 3-proton (Scheme 2).



Scheme 2

Further conversion of **3e** to pyrrolizines (**8**,**9**) was performed as follows. *N*-Allylation of (*E*)-**3e** and (*Z*)-**3e** by treatment with NaH and allyl bromide gave (***E***)-**7** and (***Z***)-**7**, respectively. Ring-closing metathesis reaction of (***Z***)-**7** and (***E***)-**7** was successfully carried out in the presence of Grubbs' second generation catalyst in CH_2Cl_2 under reflux. Under these conditions, the ring-closing reaction accompanied the

isomerization at the C3 in (*Z*)- and (*E*)-**7**, producing **8**[7] and **9** as a pair of *cis:trans*=1:1 isomers, respectively (Scheme 3).[8]



Scheme 3

In conclusion, the regioselectivity in the ruthenium-catalyzed ring-opening cross-metathesis reaction of **1** with allyltrimethylsilane was markedly improved by the introduction of a trialkylsilyl group into the nitrogen of ABH (**1**), though the mechanistic features that control the regioselectivity are not obvious. The metathesis products (**3**,**4**) were successfully isolated by MPLC, and moreover, transformation of **3a** allowed an access to pyrrolizines (**8**,**9**). Investigations including further improvement in the regioselectivity and mechanistic insight are in progress.

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6. **(*E*)-3b:** ^{1}H-NMR ($CDCl_3$) δ; 0.00 (s, 9H), 0.20 (s, 3H), 0.24 (s, 3H), 0.93 (s, 9H), 1.45 (d, 2H, *J*=8.0 Hz), 1.69 (ddd, 1H, *J*=4.6, 6.3, 13.2 Hz), 2.47 (ddd, 1H, *J*=8.0, 9.8, 13.2 Hz), 2.96-3.03 (m, 1H), 4.07 (dt, 1H, *J*=4.6, 8.0 Hz), 5.03 (d, 1H, *J*=10.3 Hz), 5.08 (d, 1H, *J*=17.2 Hz), 5.31 (dd, 1H, *J*=6.3, 14.8 Hz), 5.54 (dtd, 1H, *J*=14.8, 8.0, 1.5 Hz), 5.82 (ddd, 1H, *J*=8.0, 10.3, 17.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: -4.2, -4.0, -1.8, 19.1, 23.0, 27.3, 36.0, 46.3, 60.8, 114.8, 126.3, 129.0, 142.8, 183.7. HR-MS *m/z*: Calcd for $C_{18}H_{35}NOSi_2$: 337.2254. Found: 337.2257. **(*Z*)-3b:** ^{1}H-NMR ($CDCl_3$) δ: 0.00 (s, 9H), 0.20 (s, 3H), 0.26 (s, 3H), 0.94 (s, 9H), 1.46 (ddd, 1H, *J*=1.5, 7.4, 13.7 Hz), 1.58 (ddd, 1H, *J*=5.1, 6.8, 13.2 Hz), 1.67 (ddd, 1H, *J*=1.1, 9.7, 13.7 Hz), 2.47 (ddd, 1H, *J*=8.0, 9.8, 13.2 Hz), 3.27 (ddd, 1H, *J*=1.1, 6.8, 9.1 Hz), 4.07-4.13 (m, 1H), 5.05 (d, 1H, *J*=10.3 Hz), 5.10 (d, 1H, *J*=17.2 Hz), 5.27 (dd, 1H, J=9.1, 10.6 Hz), 5.57 (ddt, 1H, *J*=1.1, 7.4, 10.6 Hz), 5.81 (ddd, 1H, *J*=7.5, 10.3, 17.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: -4.1, -3.9, -1.7, 19.1, 21.0, 27.3, 36.7, 41.8, 60.7, 115.0, 125.4, 129.1, 142.6, 183.9. HR-MS *m/z*: Calcd for $C_{18}H_{35}NOSi_2$: 337.2254. Found: 337.2268. **4b:** ^{1}H-NMR ($CDCl_3$) δ: 0.00 (s, 9H), 0.20 & 0.22 & 0.23 (three s, 6H), 0.93 & 0.94 (two s, 9H), 1.35 (ddd, 0.8H, *J*= 1.5, 6.3, 13.7 Hz), 1.43 (d, 1.2H, *J*=8.0 Hz), 1.61-1.75 (m, 1H), 2.44 (ddd, 0.6H, *J*=8.1, 9.8, 13.2 Hz), 2.42-2.49 (m, 0.4H), 3.01-3.09 (m, 1H), 4.05 (dt, 0.6H, *J*=5.1, 8.0 Hz), 4.36-4.42 (m, 0.4H), 5.13-5.19 (m, 2H), 5.20-5.32 (m, 1H), 5.36-5.50 (m, 1H), 5.87-5.94 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ: -4.3, -4.2, -4.1, -3.9, -1.8, -1.6, 19.0, 22.5, 25.8, 27.3, 27.4, 47.3, 54.3, 60.5, 116.5, 116.6, 126.3, 127.9, 132.2, 132.8, 136.2, 136.3, 182.6. HR-MS *m/z*: Calcd for $C_{18}H_{35}NOSi_2$: 337.2254. Found: 337.2268.

7. ***cis*-8:** IR (neat): 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:. 0.00 (s, 9H), 1.47-1.63 (m, 3H), 2.55 (ddd, 1H, *J*=13.7, 7.4, 6.3 Hz), 3.68 (dd, 1H, *J*=3.5, 15.5 Hz), 3.63-3.69 (m, 1H), 4.40 (dd, 1H, *J*=4.0, 15.5 Hz), 4.53-4.59 (m, 1H), 5.23 (dd, 1H, *J*=9.7, 10.9 Hz), 5.64 (dt, 1H, *J*=8.0, 10.9 Hz), 5.84-5.90 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: -1.8, 18.9, 38.3, 43.2, 50.0, 65.1, 123.7, 128.3, 130.2, 130.3, 178.2. HR-MS *m/z*: Calcd for $C_{13}H_{21}NOSi$: 235.1392; Found: 235.1400. ***trans*-8:** IR (neat): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.00 (s, 9H), 1.57 (ddd, 1H, *J*=1.1, 8.6, 13.7 Hz), 1.70 (ddd, 1H, *J*=1.1, 1.9, 13.7 Hz), 2.05 (dt, 1H, *J*=8.6, 12.1 Hz), 2.14 (dd, 1H, *J*=6.3, 12.1 Hz), 3.42 (dd, 1H, *J*=8.6, 9.2 Hz), 3.64 (dd, 1H, *J*=3.5, 16.0 Hz), 4.38 (dd, 1H, *J*=4.0, 16.0 Hz), 4.72-4.78 (m, 1H), 5.45 (dd, 1H, *J*=9.2, 9.7 Hz), 5.56 (q, 1H, *J*=9.7 Hz), 5.83-5.89 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: -1.7, 18.9, 36.8, 45.1, 49.9, 65.9, 123.3, 128.2, 129.5, 130.6, 179.2. HR-MS *m/z*: Calcd for $C_{13}H_{21}NOSi$: 235.1392; Found: 235.1390.

8. Although we have no clear accout, this may involve the isomerization of less stable metallacycle

intermediate (**A**) to intermediate (**B**).