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IMPROVEMENT IN THE REGIOSELECTIVITY IN THE RUTHENIUM-CATALYZED METATHESIS REACTION OF 2-AZABICYCLO[2.2.1]-HEPT-5-EN-3-ONE (ABH) WITH ALLYLTRIMETHYLSILANE

Minoru Ishikura,* Miyako Hasunuma, and Makoto Saijo

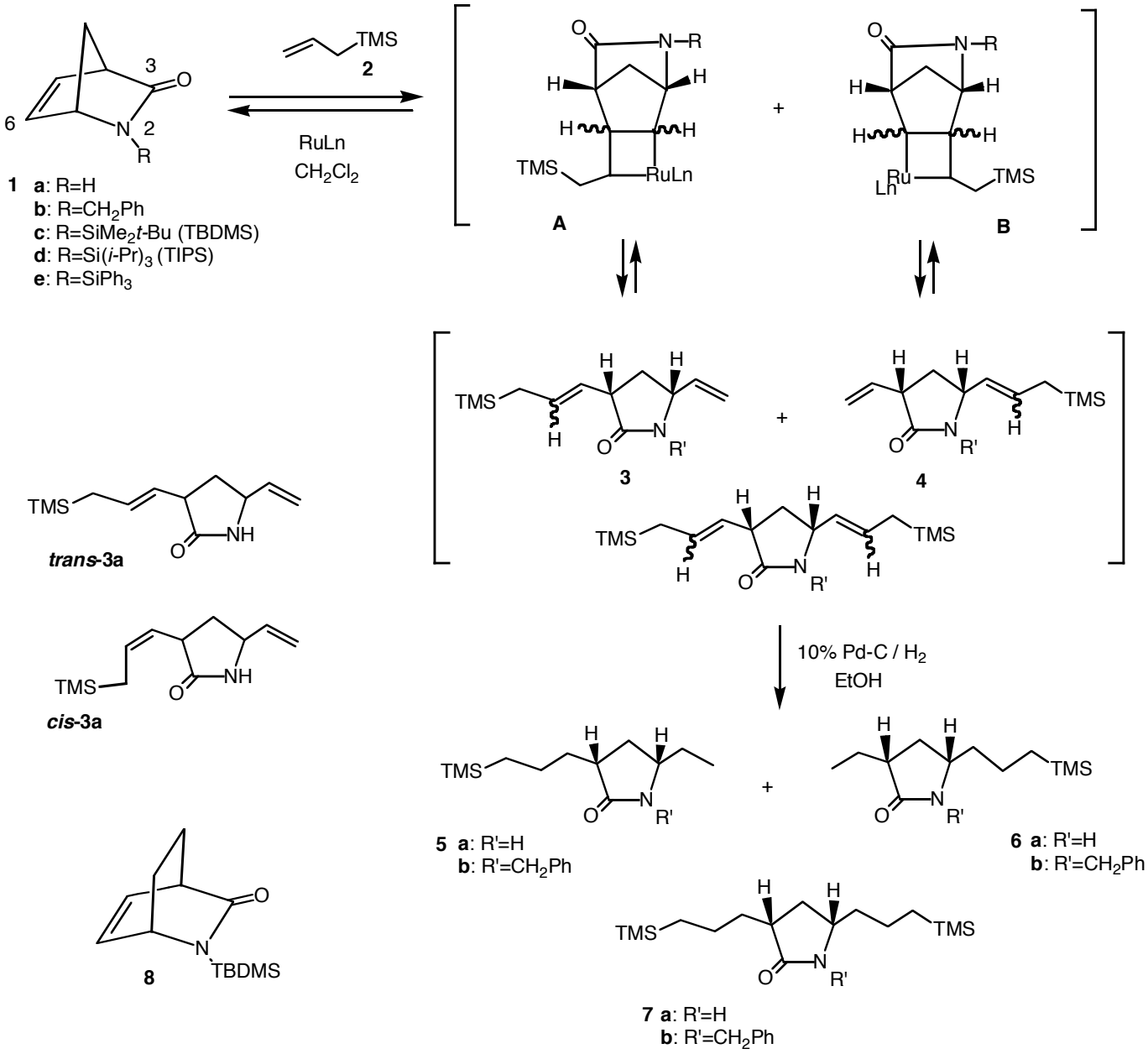
Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan. e-mail: ishikura@hoku-iryo-u.ac.jp

Abstract –2-Azabicyclo[2.2.1]hept-5-en-3-one (ABH) (**1**) with *N*-trialkylsilyl group was subjected to a ring-opening cross-metathesis reaction with allyl-trimethylsilane in the presence of a ruthenium catalyst, allowing the predominate formation of *rel*-(3*R*,5*S*)-3-(4,4,-dimethyl-4-silapentyl)-5-ethylpyrrolidin-2-one (**5**) over *rel*-(3*R*,5*S*)-5-(4,4,-dimethyl-4-silapentyl)-3-ethylpyrrolidin-2-one (**6**).

2-Azabicyclo[2.2.1]hept-5-en-3-one (ABH) (**1a**) is a versatile class of bicyclic lactam readily available from the Diels-Alder reaction of cyclopentadiene with phenylsulfonylcyanide[1] and is characteristic of bicyclo[2.2.1]heptane ring systems having greater ring strain energy. In view of its synthetic value, **1a** has been extensively used as a potential synthton for the construction of cyclopentane moieties in carbocyclic nucleosides,[2] while a ruthenium-catalyzed metathesis reaction of ABH (**1**) is limited to only a few examples.[3] In connection with our recent interest in the synthetic potential of **1a**,[4] we have previously reported the ruthenium-catalyzed ring-opening cross-metathesis reaction of *N*-acyl-ABH with allyltrialkylsilanes, which has proceeded in a clean and efficient manner.[5] However, we encountered a problem in that two isomers (**3**) and (**4**), arising from complexes **A** and **B**, were produced in a ratio of approximately ~2:1 instead of the known regioselectivity.[3a] Our previous report showed that several attempts at exposing *N*-acyl-ABH to allyltrialkylsilanes under various conditions (i.e., variations in catalyst, reaction temperature, and solvent) failed to circumvent the low selectivity.[5]

The nitrogen in **1a** is known to have the unique feature of being able to participate to the neighboring carbon at position 6, thus allowing the generation of a transannular carbonium ion.[6] We were intrigued as to whether the unique participation of the nitrogen might feasibly promote the regioselective generation of complexe **A** or **B**. Thus, **1** with *N*-electron-donating group was subjected to a metathesis

reaction with allyltrimethylsilane (**2**), and the predominate formation of **3** over **4** was eventually found. The preliminary experimental results are described in this paper.



Scheme

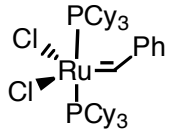
All reactions were run using **1** (1 mmol) and **2** (1.2 mmol) in the presence of a ruthenium catalyst (3 mol%) in CH_2Cl_2 at room temperature for 1 h under an argon atmosphere, followed by removal of the trialkylsilyl group with *n*-Bu_4NF (in the cases of **1c**, **1d**). The reaction mixture was immediately subjected to catalytic hydrogenation (H_2, 10% Pd-C in EtOH), and separated by flash chromatography to

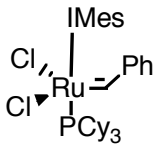
give a small amount of **7** and a mixture of **5** and **6** whose ratio was determined by gas chromatography (GC) (Scheme and Table).[7]

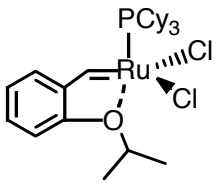
We chose **1a** as our initial metathesis partner in combination with **2**, and careful separation of the reaction mixture by flash chromatography allowed the isolation of *cis*-**3a** and *trans*-**3a**,[8] which gradually decomposed when left standing at room temperature. After the catalytic hydrogenation of the reaction

Table Rection of **1** with **2** in the presence of Ru complexes

	Catalyst[a]	CH_2Cl_2 (mL)	Yield (%) of **5** and **6**	Yield (%) of **7**	ratio of **5** : **6**
1a	A	10	68	3 (**7a**)	(**5a** : **6a** = 2 : 1)
1b	A	10	72	3 (**7b**)	(**5b** : **6b** = 3 : 1)
1c	A	10	72	3 (**7a**)	(**5a** : **6a** = 7 : 1)
1c	A	20	73	2 (**7a**)	(**5a** : **6a** = 5 : 1)
1c	A	40	72	3 (**7a**)	(**5a** : **6a** = 4 : 1)
1c	B	10	75	2 (**7a**)	(**5a** : **6a** = 13 : 1)
1c	C	10	70	3 (**7a**)	(**5a** : **6a** = 10 : 1)
1d	A	10	60	3 (**7a**)	(**5a** : **6a** = 12 : 1)
1d	B	10	67	2 (**7a**)	(**5a** : **6a** = 14 : 1)
1d	C	10	60	2 (**7a**)	(**5a** : **6a** = 8 : 1)

[a] Catalyst: A: 

B: 

C: 

IMes = 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene

mixture, a mixture of **5a** and **6a** was obtained, but in low selectivity. The same treatment of **1b** with **2** still resulted in low selectivity (**5b**:**6b**=3:1). Then, further effort was focused on the use of **1c** with *N*-*tert*-butyldimethylsilyl (TBDMS) group. We were delighted to find that reaction of **1c** improved the regioselectivity, producing **5a** in higher preference to **6a**. As seen in Table, it is highly desirable to run the reaction of **1c** with **2** in the presence of the Grubbs' second generation catalyst in CH_2Cl_2 (10 mL) for greater regioselectivity. *N*-Triisopropylsilyl-ABH (**1d**) was also effective in improving the regioselectivity, whereas the use of **1e** with *N*-triphenylsiyl group turned out to be troublesome, affording unidentified products. Subjection of 2-azabicyclo[2.2.2]oct-5-en-3-one (**8**), possessing less ring strain energy than **1c**, to the reaction under the same conditions failed to produce any metathesis products, and resulted in the recovery of **8**.

In summary, we have described the improvement in the regioselectivity in the ring-opening cross-metathesis reaction of **1** with **2** in the presence of a ruthenium catalyst, and the use of *N*-trialkylsilyl-ABH (**1c**,**d**) was found to be crucial in allowing the predominate formation of **5a** over **6a**. Whilst the detailed mechanism is not yet known, the intervention of the nitrogen participation in **1** is worthy of further consideration.

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7 GC with FID detector: column: CBP1 capillary column (25 m x 0.53 mmID x 1.5 □m thickness). Temperature: column: 150°C (2 min) – 150 to 170°C (1°C/min) – 170 to 250°C (20°C/min), injector: 150°C, detector: 150°C.

8 ***trans*-3a**: oil. IR (neat): 3432, 3204, 3076, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 0.00 (s, 9H), 1.48 (d, 2H, *J*=8.1 Hz), 1.60-1.69 (m, 1H), 2.40-2.50 (m, 1H), 3.05 (q, 1H, *J*=8.1 Hz), 4.06 (q, 1H, *J*=7.4 Hz), 5.11 (d, 1H, *J*=10.3 Hz), 5.22 (d, 1H, *J*=16.6 Hz), 5.28 (dd, 1H, *J*=15.5, 7.4 Hz), 5.55 (dtd, 1H, *J*=1.1, 8.1, 15.5 Hz), 5.75 (ddd, 1H, *J*=7.1, 10.3, 16.6 Hz), 5.87 (br s, 1H). ^{13}C-NMR ($CDCl_3$) □: -0.19, 23.1, 36.1, 45.5, 55.3, 116.3, 125.1, 130.3, 138.9, 178.8. HR-MS *m/z*: Calcd for $C_{12}H_{21}NOSi$: 223.1392. Found: 223.1418. ***cis*-3a**: oil. IR (neat): 3432, 3198, 3050, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 0.00 (s, 9H), 1.48 (dd, 1H, *J*=8.3, 13.6 Hz), 1.50-1.63 (m, 2H), 2.42-2.51 (m, 1H), 3.33 (q, 1H, *J*=9.3 Hz), 4.07 (q, 1H, *J*=7.5 Hz), 5.11 (d, 1H, *J*=10.1 Hz), 5.22 (d, 1H, *J*=17.0 Hz), 5.23-5.28 (m, 1H), 5.66 (q, 1H, *J*=10.1 Hz), 5.73 (ddd, 1H, *J*=7.1, 10.1, 17.0 Hz), 6.03 (br s, 1H). ^{13}C-NMR ($CDCl_3$) □: -1.7, 19.0, 36.8, 40.6, 55.4, 116.6, 124.1, 130.3, 138.7, 178.5. HR-MS *m/z*: Calcd for $C_{12}H_{21}NOSi$: 223.1392. Found: 223.1362.