

RUTHENIUM-CATALYZED RING-OPENING CROSS-METATHESIS REACTION OF 2-AZABICYCLO[2.2.1]-HEPT-5-EN-3-ONE

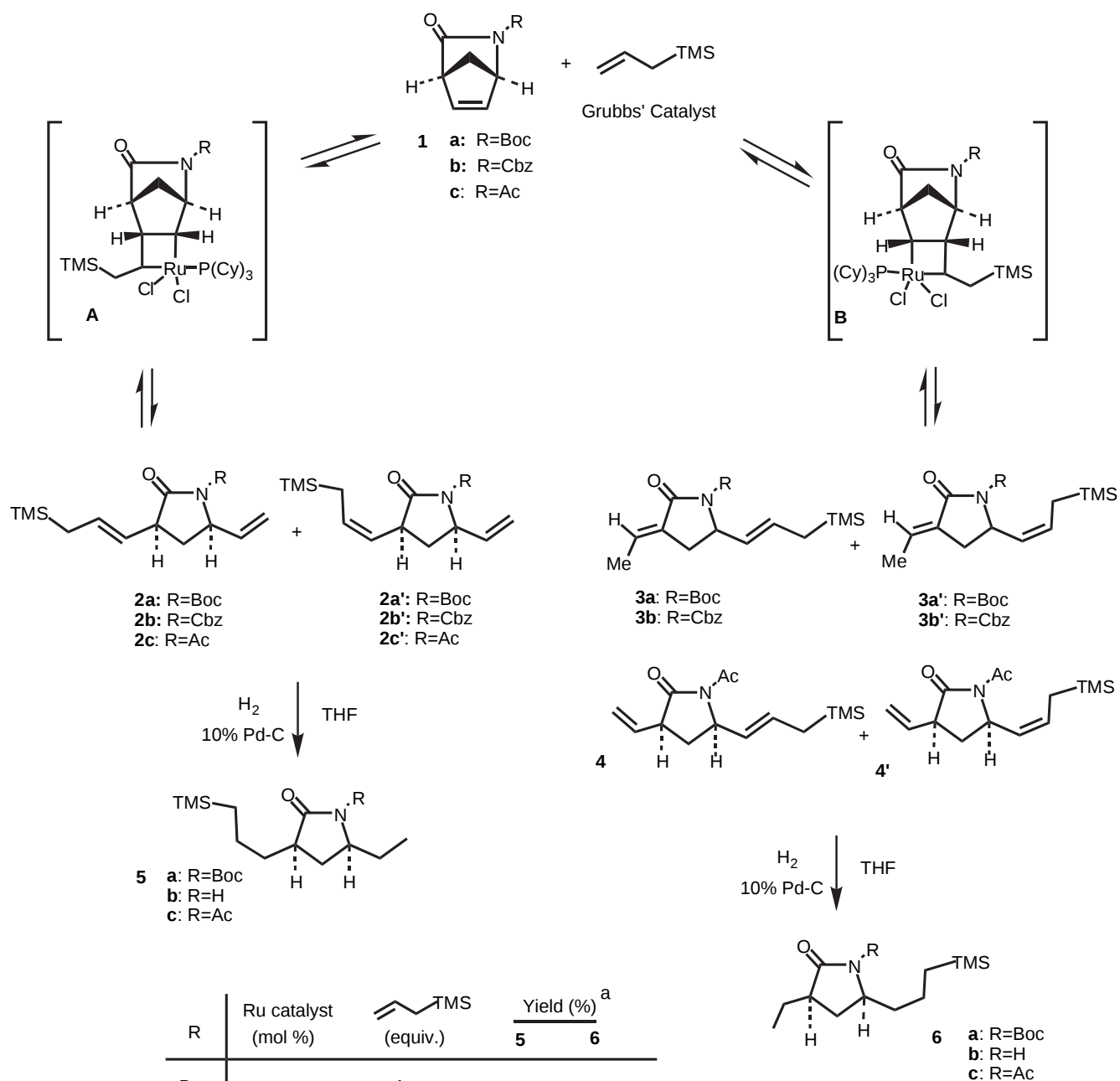
Minoru Ishikura,* Makoto Saijo, and Ayako Hino

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido,
Ishikari-Tobetsu, Hokkaido 061-0293, Japan

Abstract – An examination of the ring-opening cross-metathesis reaction of 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) (**1a**) with allyltrimethylsilane in the presence of Grubbs' catalyst showed that a pair of regioisomeric products (**2**) (R=Boc) and (**3**) (R=Boc) could be isolated instead of the known regioselective formation of **2** (R=Boc).

Among the various variants of metathesis protocols such as ring-closing, ring-opening and cross-metathesis reactions, the sequential ring-opening cross-metathesis reaction has been of special interest.¹ As a part of our recent interest in exploration of chemistry of 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) as a potential synthetic intermediate,² we have set out to apply ABH to metathesis reactions. To our knowledge, there has been only one example of a ruthenium catalyzed metathesis reaction of ABH. This report disclosed that the ring-opening cross-metathesis reaction of *N*-Boc-ABH (**1a**) with allyltrimethylsilane catalyzed by Grubbs' catalyst [RuCl₂(P(C₆H₁₁)₃)₂(CHPh)] proceeds in a completely regioselective manner to give only one regioisomer (**2**; R=Boc) as a *E/Z* mixture (**2a** and **2a'**).³ This pronounced result has kindled our interest in the development of the synthetic applicability of ABH (**1**) based on the metathesis reaction. However, on revisiting the metathesis reaction of **1a** with allyltrimethylsilane in the presence of Grubbs' catalyst, **3** and **3'**, together with the known **2** and **2'**,³ were produced. Some of our experimental results are reported in this paper.

At first, equimolar amounts of **1a** and allyltrimethylsilane were subjected to the metathesis reaction in the presence of Grubbs' catalyst (5 mol%) at room temperature for 3.5 h under an argon atmosphere according to the procedure in the literature,³ and separation of the reaction mixture by HPLC⁴ allowed the isolation of a pair of regioisomeric ring-opening products (**2**) (R=Boc)³ and (**3**)⁵ arising through intermediates (**A**) and (**B**), respectively (Scheme 1).⁶ Because of their intrinsic instability, possibly due to the presence of allylsilane group, **2** (R=Boc) and **3** decomposed to a considerable extent during the separation by HPLC. Thus, soon after the elapse of the reaction time (3.5 h), the reaction mixture was subjected to a catalytic hydrogenation on 10% Pd-C in THF, which enabled the isolation of two regioisomers (**5a**)⁵ and (**6a**)⁵ in a ratio of approximately 2.5:1, which was about the same result as when the reaction of **1a** was undertaken in the presence of a catalyst (1 mol%) and allyltrimethylsilane (1 and 1.5 equiv.).



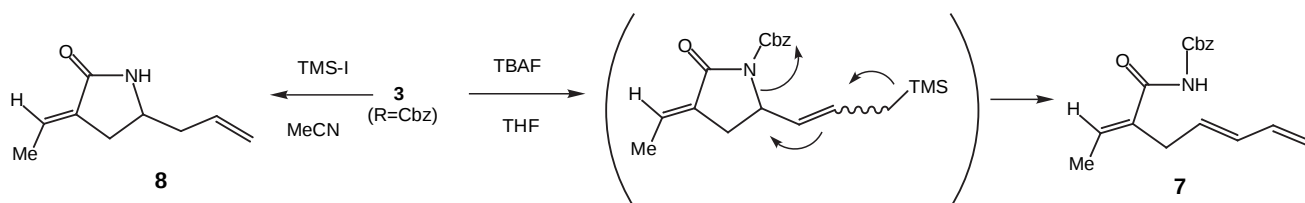
R	Ru catalyst (mol %)	TMS-CH ₂ -CH=CH ₂ (equiv.)	Yield (%) ^a	
			5	6
Boc	5	1	52	20
	5	1.5	54	21
	1	1	52	20
	1	1.5	50	20
Cbz	5	1	40	30
	5	1.5	44	31
	1	1	37	31
	1	1.5	39	32
Ac	5	1	35	23
	5	1.5	32	19
	1	1	34	22
	1	1.5	32	19

^a All yields are based on **1**.

Scheme 1

Similarly, treatment of ABH (**1b**, **c**), possessing less voluminous carbobenzyloxy (Cbz) and acetyl groups at the nitrogen, with allyltrimethylsilane in the presence of Grubbs' catalyst allowed the isolation of products (**2b**, **b'**, **3b**, **b'**) from **1b**, and **2c**, **c'**, **4** and **4'** from **1c**. Catalytic hydrogenation of the reaction mixture also afforded two regioisomers (**5b**, **c**) and (**6b**, **c**) in ratios of approximately 1.2~1.5:1, respectively.

To elucidate the structure of **3**, desilylation of **3b**, **b'** with TBAF (Bu_4NF) in THF was effected to afford diene (**7**) in 70% yield, accompanied by a ring-opening. Otherwise, treatment of **3b**, **b'** with iodo-trimethylsilane in acetonitrile at room temperature readily produced lactam (**8**) in 80% yield (Scheme 2).



Scheme 2

On re-examination of the reaction of **1** with allyltrimethylsilanes in the presence of Grubbs' catalyst, two possible ring-opening products (**2**, **3**, **4**) were isolated. The regioselectivity in the ring-opening step seems to be ascribable to the sterical interaction between the *N*-substituents of **1** and the trimethylsilyl group of allyltrimethylsilane in the intermediates (**A**) and (**B**).⁷

The development of suitable conditions for promoting the regioselective ring-opening metathesis reaction using **1** will find versatile applications in organic synthesis, and this work is now in progress.

ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in Aid for Scientific Research (No. 13672226) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

REFERENCES AND NOTES

1. A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3013; S. Blechert, *Pure Appl. Chem.*, 1999, **71**, 1393; R. H. Grubbs, S. J. Miller, and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446; A. Fürstner, Eds., *Alkene Metathesis in Organic Synthesis*, Springer-Verlag, Berlin, 1998.
2. M. Ishikura, S. Kudo, A. Hino, N. Ohnuki, and N. Katagiri, *Heterocycles*, 2000, **53**, 1499; N. Katagiri, Y. Yamatoya, and M. Ishikura, *Tetrahedron Lett.*, 1999, **40**, 9069.
3. M. F. Schneider, N. Lucas, J. Velder, and S. Blechert, *Angew. Chem. Int., Ed., Engl.*, 1997, **36**, 257.
4. According to the procedure reported in the literature,³ the reaction of **1a** with allyltrimethylsilane in the presence of Grubbs' catalyst was carried out for 3.5 h. The mixture was separated by HPLC [Mightysil Si-60 (Kanto Chemical Co. Inc.)] with hexane:AcOEt=10:1 as an eluent.
5. **3a**: IR (neat):1776, 1742, 1718 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (s, 9H), 1.45 (d, 1H, $J=7.5$ Hz), 1.50-1.55(m, 1H), 1.53 (s, 9H), 1.81 (d, 3H, $J=7.4$ Hz), 2.39 (dd, 1H, $J=1.5, 6.6$ Hz), 2.78-2.88 (m,

1H), 4.60 (dt, 1H, $J=2$, 7.8 Hz), 5.18 (dd, 1H, $J=7.8$, 15 Hz), 5.63 (ddd, 1H, $J=7.8$, 8.3, 15 Hz), 6.72-6.80 (m, 1H). ^{13}C -NMR (CDCl_3) δ : -2.0, 14.8, 22.5, 28.1, 29.5, 56.6, 82.4, 127.8, 129.3, 131.4, 133.0, 150.5, 166.6. HR-MS m/z : Calcd for $\text{C}_{17}\text{H}_{29}\text{NO}_3\text{Si}$ 323.1916. Found: 323.1925. **3a'**: IR (neat): 1776, 1736, 1720 cm^{-1} . ^1H -NMR (CDCl_3) δ : 0.00 (s, 9H), 1.38 (ddd, 1H, $J=2$, 6.8, 13.5 Hz), 1.46 (s, 9H), 1.75 (d, 3H, $J=7.3$ Hz), 1.81 (d, 1H, $J=13.5$ Hz), 2.26 (d, 1H, $J=16$ Hz), 2.75-2.82 (m, 1H), 4.83 (dt, 1H, $J=2$, 10 Hz), 5.15 (t, 1H, $J=10$ Hz), 5.47 (dt, 1H, $J=7$, 10 Hz), 6.66-6.74 (m, 1H). ^{13}C -NMR (CDCl_3) δ : -1.6, 14.9, 19.2, 28.1, 29.5, 51.6, 82.5, 127.9, 128.1, 131.3, 133.0, 150.8, 167.0. HR-MS m/z : Calcd for $\text{C}_{17}\text{H}_{29}\text{NO}_3\text{Si}$: 323.1916. Found: 323.1910. **5a**: IR (neat): 1784, 1744, 1722 cm^{-1} . ^1H -NMR (CDCl_3) δ : 0.00 (s, 9H), 0.45-0.59 (m, 2H), 0.91 (t, 3H, $J=7.8$ Hz), 1.30-1.60 (m, 5H), 1.55 (s, 9H), 1.90-2.30 (m, 2H), 2.31 (ddd, 1H, $J=7.8$, 9.8, 13 Hz), 2.43-2.53 (m, 1H), 3.85-3.95 (m, 1H). ^{13}C -NMR (CDCl_3) δ : -1.9, 8.7, 16.4, 21.8, 27.2, 27.9, 28.0, 28.9, 35.3, 42.3, 57.2, 82.5, 150.4, 176.6. HR-MS m/z : Calcd for $\text{C}_{17}\text{H}_{33}\text{NO}_3\text{Si}$: 327.2229. Found: 327.2220. **6a**: IR (neat): 1784, 1746, 1718 cm^{-1} . ^1H -NMR (CDCl_3) δ : 0.00 (s, 9H), 0.46-0.62 (m, 2H), 1.00 (t, 3H, $J=7.8$ Hz), 1.25-1.41 (m, 3H), 1.41-1.60 (m, 2H), 1.54 (s, 9H), 1.90-2.10 (m, 2H), 2.28-2.42 (m, 2H), 3.91-3.99 (m, 1H). ^{13}C -NMR (CDCl_3) δ : -1.7, 11.7, 16.6, 19.2, 24.5, 28.0, 29.0, 39.0, 44.2, 56.0, 82.6, 150.5, 176.5. HR-MS m/z : Calcd for $\text{C}_{17}\text{H}_{33}\text{NO}_3\text{Si}$: 327.2229. Found: 327.2219.

6. E. L. Dias, S. T. Nguyen, and R. H. Grubbs, *J. Am. Chem. Soc.*, 1997, **119**, 3887.
7. In the intermediate **B** ($\text{R}=\text{Boc}$), there seems to be serious steric repulsion between the *N*-Boc group and the trimethylsilyl group (Figure).

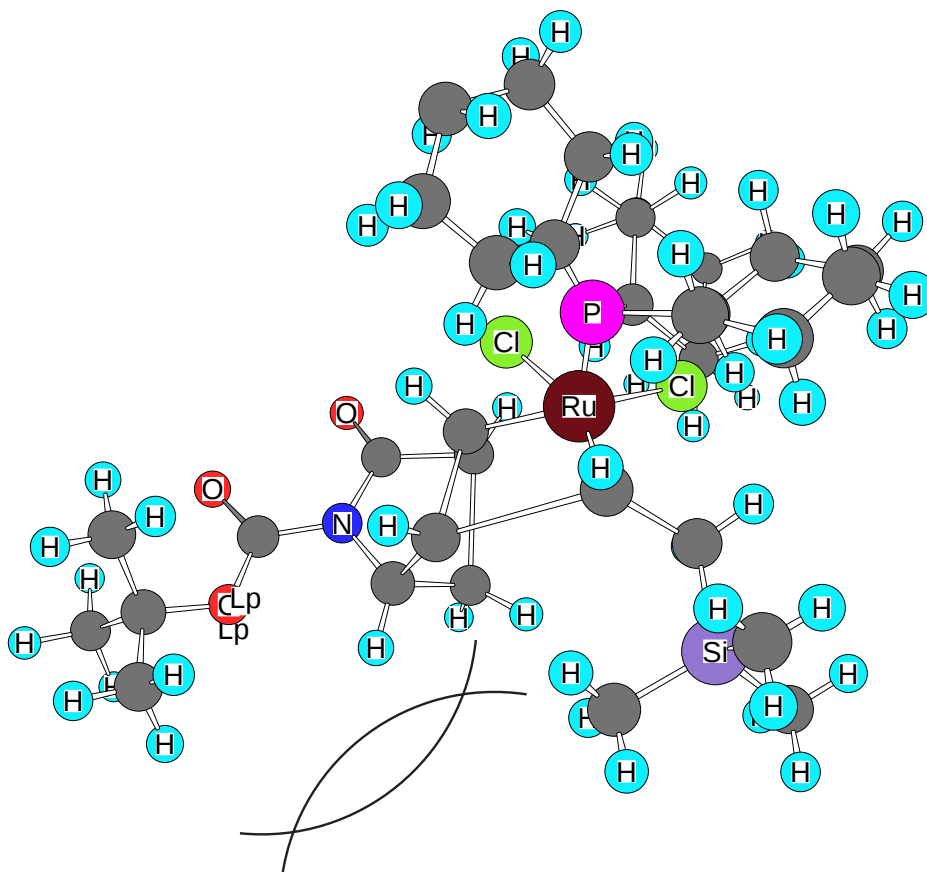


Figure Schematic representation of intermediate **(B)** ($\text{R}=\text{Boc}$)