

Unexpected Dramatic Substituent Effect for Tuning the Selectivity in the Double Ring-Closing Metathesis Reaction of N-Containing Tetraenes. An Efficient Synthesis of Bicyclic Izidine Alkaloid Skeletons

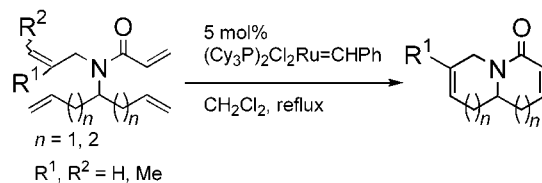
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ABSTRACT



A double ring-closing metathesis reaction for the efficient construction of the fused bicyclic izidine alkaloid skeleton was developed. In this reaction, high selectivity was realized by tuning of electronic and steric effects of substituents in the N-containing tetraenes. It was observed that the reactivity of electron-rich carbon–carbon double bonds is higher than that of electron-deficient ones. A brief mechanistic study is also discussed.

Recently, we have demonstrated that a protocol of bicyclic carbopalladation can be efficiently applied to the synthesis of fused bicyclic compounds.¹ In principle, this paradigm can be realized with any reaction, provided that a good selectivity can be realized. Here, we wish to report our recent results on the double ring-closing metathesis for the efficient construction of bicyclic izidine alkaloid skeletons, in which the selectivity was tuned by the electronic and steric effects of the substituents of the N-containing tetraenes.

Bicyclic izidine alkaloid skeletons are structural units commonly observed in many important compounds.^{2,3} These

compounds can usually be synthesized via a sequential ring formation approach^{4–6} (Scheme 1).

We envisioned that it would be possible to construct both rings via a double RCM protocol in just “one shot” (Scheme 1).^{6–8} Here, the key point would be the control of the RCM mode (*ab/cd* mode vs *ac/bd* mode, Scheme 2).

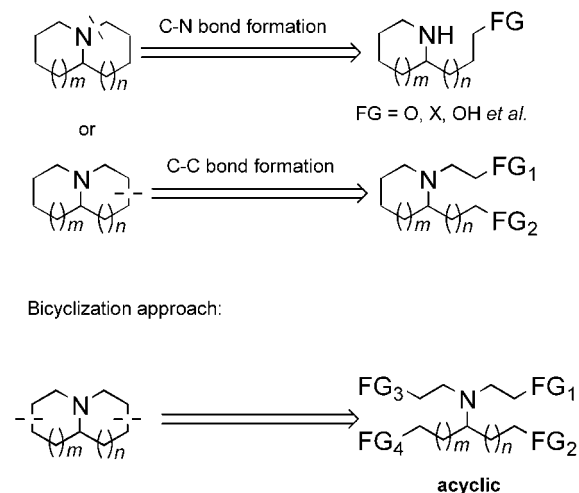
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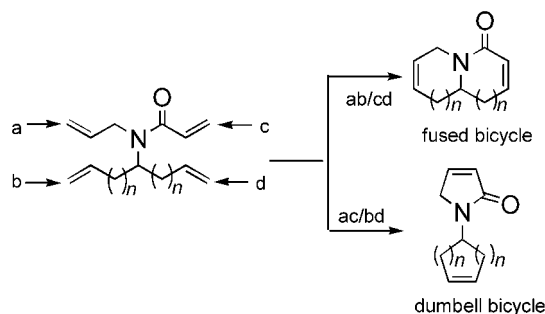
(1) Ma, S.; Xu, B. *J. Org. Chem.* **1998**, *63*, 9156–9157. (b) Ma, S.; Xu, B.; Ni, B. *J. Org. Chem.* **2000**, *65*, 8532–8543.

Scheme 1



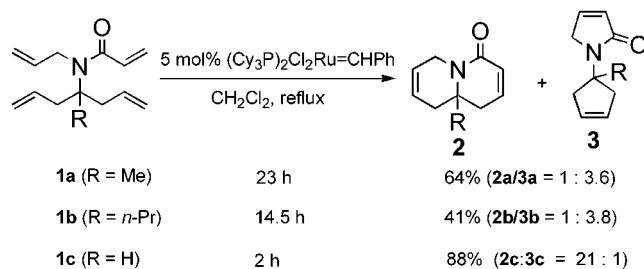
As expected, the reaction of **1a** and **1b** did afford a mixture of ab/cd-mode and ac/bd-mode products with the dumbbell-type products **3** as the major products (Scheme 3).

Scheme 2. Double RCM Strategy for N-Containing Bicycles



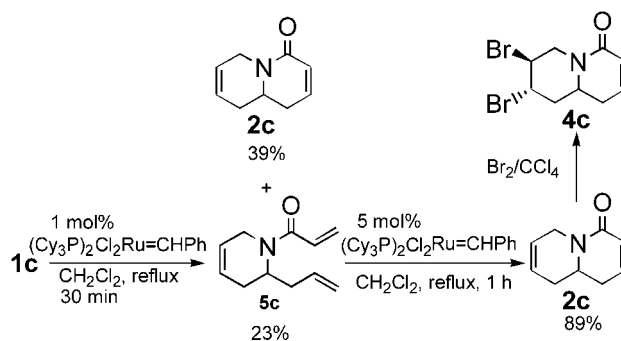
To our surprise, the reaction of **1c**⁹ afforded the corresponding products with a ratio of fused bicyclic compound **2c** to dumbbell-type bicyclic compound **3c** as high as 21:1 in a combined yield of 88% (Scheme 3). The structure of **2c** was unambiguously determined by its conversion to the *trans* dibromide **4c**, which was characterized by an X-ray diffraction study.¹⁰ When we followed this reaction carefully, it

Scheme 3



was observed that the monocyclic intermediate **5c** was formed highly selectively, suggesting that the *ab*-mode RCM reaction may be much faster than those of *ac*, *bd*, and *cd* modes, which may account for the highly selective formation of fused bicyclic product **2c**. Upon treating of **5c** with 5 mol % of $(\text{C}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh}$, **2c** was formed exclusively in 89% yield (Scheme 4).

Scheme 4



To investigate the possibility of fast conversion of the in situ formed dumbbell-type product **3c** to **2c**, *N*-(4-(1,6-heptadienyl)propenamido)propanamide **6c**, precursor to **1c**, was synthesized.⁹ The reaction of **6c** afforded monocyclic products **7c** and **8c** in 79% and 10% yields, respectively. Here, the RCM reaction of the *bd* mode is much faster than that of the *cd* mode. Monocyclic product **7c** can be further converted to **9c**, which upon treatment with 5 mol % of $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ afforded **3c** and **2c** in 62% and 13% yields, respectively (Scheme 5). Treatment of isolated pure dumbbell-type product **3c** under the catalysis of $(\text{C}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh}$ in CH_2Cl_2 did not afford the fused bicyclic product **2c**, indicating that **2c** was formed directly via the double RCM reaction of **1c** (Scheme 5).

Furthermore, it is interesting to note that by starting from **1d** (a methyl group was introduced into the terminal position

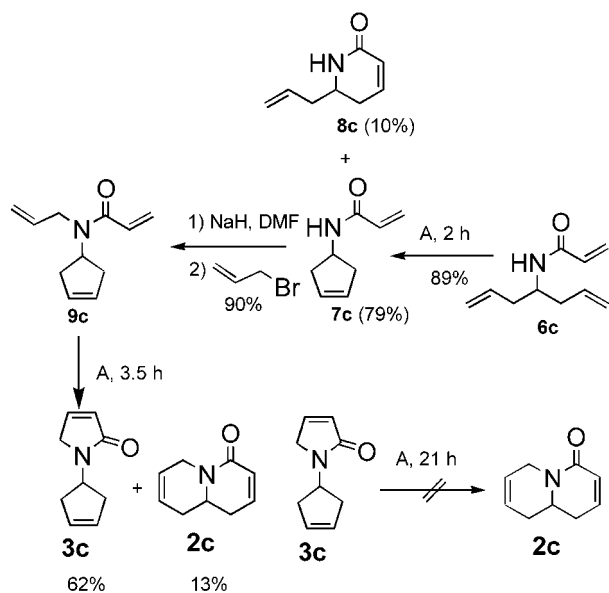
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(6) For reports on the synthesis of izidine alkaloid skeletons through the ring by ring approach via a RCM reaction, see: (a) Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415–1417. (b) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179–1180. (c) Barrett, A. G. M.; Baugh, S. P. D.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A. *J. Chem. Soc., Chem. Commun.* **1997**, 155–156.

(7) For the formation of spirocyclic compounds via double or triple RCM, see: (a) Baylon, C.; Heck, M. P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354–3360. (b) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247–3250; (c) Wallace, D. J.; Cowden, C. J.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U. H. *Tetrahedron Lett.* **2000**, *41*, 2027–2029. (d) Heck, M. P.; Baylon, C.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2001**, *3*, 1989–1991.

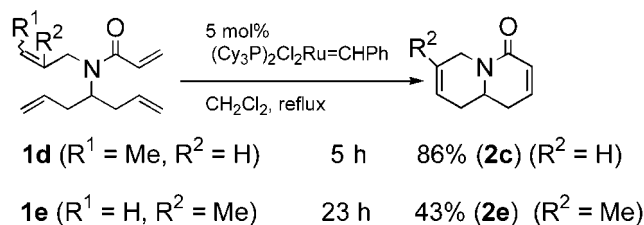
Scheme 5



A = 5 mol% $(\text{Cy}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh}$, CH_2Cl_2 , reflux

of the C=C bond a in **1c** (Scheme 2)), **2c** was formed as the only product in 86% yield, indicating an interesting substituent effect on the selectivity of the cyclization. This reaction can be extended to the synthesis of substituted 6,6-bicyclic lactam **2e** (Scheme 6).

Scheme 6

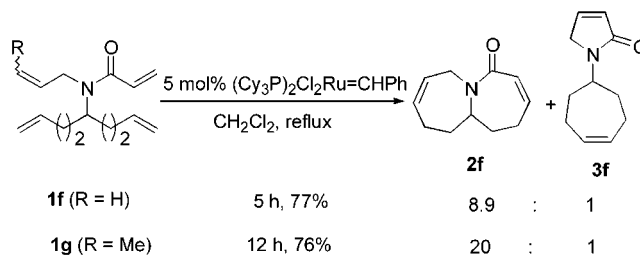


For the synthesis of 7,7-bicyclic lactam **2f**, the introduction of a methyl group at the terminal position of the C=C bond increased the selectivity of **2f/3f** increased from 8.9:1 to 20:1 (Scheme 7)!

In conclusion, we have observed interesting steric and electronic effects of substituents in tetraenes **1** for tuning

(8) For the formation of fused carbobicyclic or polycyclic compounds via double RCM reaction, see: (a) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129–131. (b) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372–374.

Scheme 7



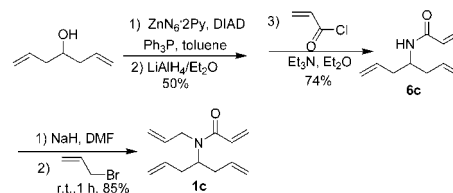
the selectivity of the double RCM reaction leading to a highly selective synthesis of izidine alkaloid skeleton:¹¹ (1) Introduction of a substituent at the C=C bond increases the ab/cd vs ac/bd selectivity (Scheme 2). (2) Introduction of an alkyl group to the secondary carbon center next to the nitrogen atom may make the C=C bonds b and d relatively closer, which increases the possibility of the bd-mode RCM reaction leading to the dumbbell-type product **3**. Further studies on this reaction including the scope and the synthetic application are being carried out in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) As a typical example, **1c** was prepared according to the following scheme:



(10) Crystal Data for **4c**: $\text{C}_9\text{H}_{11}\text{NOBr}$, MW = 309.01, triclinic, space group *P*-1, Mo K α , final R indices [$I > 2\sigma(I)$], $R_1 = 0.0571$, $wR_2 = 0.1570$, $a = 7.7149(10)$ Å, $b = 8.1119(10)$ Å, $c = 8.6994(11)$ Å, $\alpha = 94.146(2)^\circ$, $\beta = 103.579(2)^\circ$, $\gamma = 95.786(2)^\circ$, $V = 523.92(11)$ Å³, $T = 293$ K, $Z = 2$, reflections collected/unique: 5210/1945 ($R_{\text{int}} = 0.1721$), no observation [$I > 2\sigma(I)$] 1658, parameters 163.

(11) For a study on the relative reaction rate of olefin substrates with Ru carbenes see: Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484–2489.