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Synthesis of Carbapenam Skeletons Using a Ruthenium-Catalyzed Cyclization

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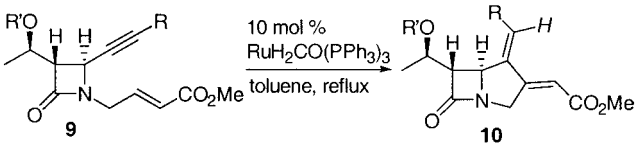
ABSTRACT



Carbapenam is a very important skeleton of β-lactam antibiotics, and it has a highly strained structure. When enynes 9 were treated with $RuH_2CO(PPh_3)_3$ (10 mol %) in toluene upon heating, carbapenams 10 were obtained in good yields.

Carbapenam is a very important skeleton of β-lactam antibiotics, and it has a highly strained structure. It is thought that the development of a novel method for synthesizing carbapenams would lead to the production of new β-lactam antibiotics. There are several reports on the synthesis of carbapenam skeletons using organometallic reagents.[1] Our plan for the synthesis of a carbapenam skeleton is shown in Scheme 1. For the construction of carbapenam skeleton III using organometallic reagent, we thought a method using reductive elimination from six-membered metalacycle I or II might be effective. Recently, Murai and Trost reported a ruthenium-catalyzed C−C bond formation via C−H activation (eq 1).[2,3] When compound IV was reacted with olefin in the presence of a ruthenium catalyst, compound VI was obtained. In this reaction the intermediary ruthenium complex is V, and insertion of olefin into the Ru−H bond of V gives VII and then reductive elimination from VII affords VI.[3] This method is very attractive for our purpose, because if compound VIII is treated in a similar manner, the reaction would proceed intramolecularly, and six-membered ruthenacycle Ia would be formed. From Ia, it should be possible to obtain carbapenam IIIa by reductive elimination (eq 2).

Initially, we tried to cyclize enyne **2** having an electron-withdrawing group on the alkene using $RuH_2CO(PPh_3)_3$.[4]

When a toluene solution of enyne **2a** and $RuH_2CO(PPh_3)_3$

(1) (a) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc*. **1980**, *102*, 6161. (b) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett*. **1980**, *21*, 31. (c) Berryhill, S. R.; Rosenblum, M. *J. Org. Chem*. **1980**, *45*, 1984. (d) Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053. (e) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc*. **1986**, *108*, 6328. (f) Williams, M. A.; Hsiao, C.-N.; Miller, M. J. *J. Org. Chem*. **1991**, *56*, 2688. (g) Kume, M.; Kubota, T.; Iso, Y. *Tetrahedron Lett*. **1995**, *36*, 8043. (h) Roland, S.; Durand, J. O.; Savignac, M.; Genêt, J. P. *Tetrahedron Lett*. **1995**, *36*, 3007. (i) For a review of the synthesis of β-lactams using organometallic reagents, see: Barrett, A. G. M.; Sturgess, M. A. *Tetrahedron* **1988**, *44*, 5615.

(2) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kametani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b). Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett*. **1995**, 681. (c) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kametani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 62. (d) Kakiuchi, F.; Sato, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett*. **1999**, 19. (e) Kakiuchi, F.; Sonoda, M.; Tsujimoto, T.; Chatani, N.; Murai, S. *Chem Lett*. **1999**, 1083, and references therein. Examples of vinylic C−H bond activation have been reported by the same group, see: (f) Kakiuchi, F.; Tanaka, Y.; Sato, T. Chatani, N.; Murai, S. *Chem. Lett*. **1995**, 679. (g) Fujii, N.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett*. **1996**, 939. (h) Sato, T.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett*. **1998**, 893. (i) Chatani, N. Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **1998**, *63*, 5129.

(3) Trost, B. M.; Imi, K.; Davies, I. M. *J. Am. Chem. Soc*. **1995**, *117*, 5371. For other related reports on the addition of a C−H bond to a multiple bond, see Jun etal. (Jun, C.-H.; Hwang, D.-C.; Na, S.-J. *Chem. Commun*. **1998**, 1405) for ruthenium-catalyzed addition of a benzylic C−H bond to alkene and see Lim et al. (Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *Chem. Commun*. **1996**, 585, and references therein) for rhodium-catalyzed addition of an aromatic or vinylic C−H bond to alkene.

(4) Levinson, J. J.; Rovinson, S. D. *J. Chem. Soc. A* **1970**, 2947.

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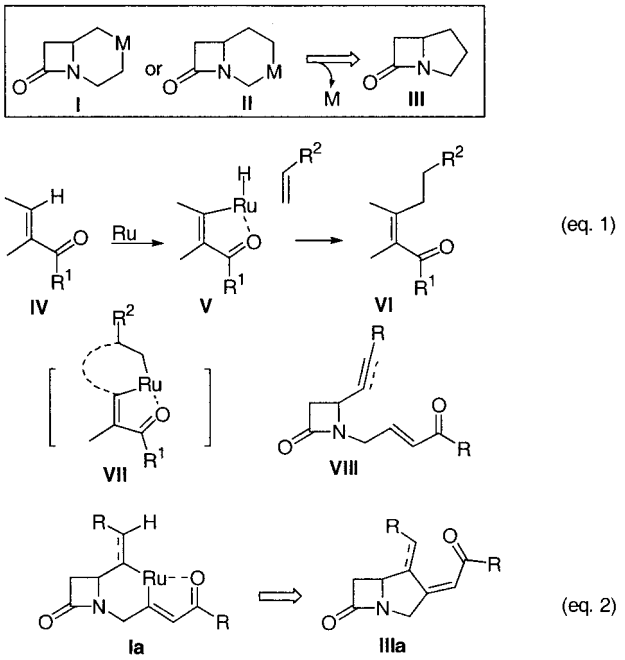
Scheme 1. Our Plan for the Synthesis of Bicyclic β-Lactams



(**1**, 5 mol %) was refluxed for 18 h, cyclized product **3a** was obtained in 77% yield. The results of an NOE experiment showed the stereochemistries of the double bonds in **3a** to be *E* and *E*. It was thought that isomerization of the double bond occurred via IXa[5] or IXb to avoid steric hindrance (Figure 1).

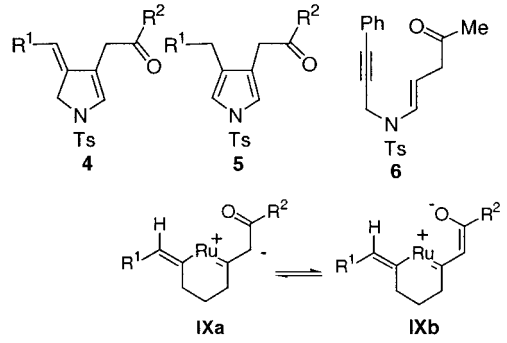
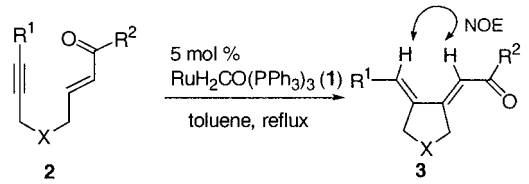


Figure 1.

Enyne **2b** having a methyl group on the alkyne afforded the desired compound **3b** (Table 1, run 2). For the synthesis of heterocycles, compounds **2c** and **2d** were treated in a similar manner, and the cyclized products **3c** and **3d** were obtained in good yields (runs 3 and 4). As a substituent on the alkene, a keto-carbonyl group could not be used for this reaction (run 5), and in this case isomerization of the double bond of **2e** occurred to give **6** in 56% yield. On the other hand, amides **2f** or **2g** gave the cyclized products **3f** and **4f** or **4g** and **5g** in good yields (runs 6 and 7).

Subsequently, to synthesize bicyclic heterocycles, when a toluene solution of pyrrolidine derivative **7** was refluxed in the presence of $RuH_2CO(PPh_3)_3$ for 7 h, pyrrolizidine derivative **8** was obtained in 53% yield (Scheme 2).

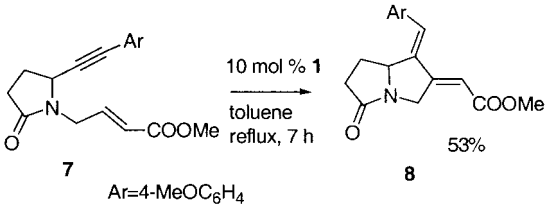
Table 1. Reaction of **1** with **2**



run	X	R^1	R^2		time (h)	yield (%)
1	CH_2	4-$MeOC_6H_4$	OEt	**2a**	18	77
2	CH_2	Me	$O(CH_2)_3Ph$	**2b**	18	55
3	NTs	Ph	OEt	**2c**	18	83
4	NTs	4-MeC_6H_4	OEt	**2d**	18	50
5	NTs	Ph	Me	**2e**	8	0[a,b]
6	NTs	Ph	NEt_2	**2f**	6	76[a,c]
7	NTs	Ph	NHEt	**2g**	6	58[a,d]

[a] 10 mol % of $RuH_2CO(PPh_3)_3$ was used. [b] **6**; 56%. [c] **3f**:**4f** = 4:1. [d] **4g**:**5g** = 1:1.5

Scheme 2. Synthesis of Bicyclic Heterocycles

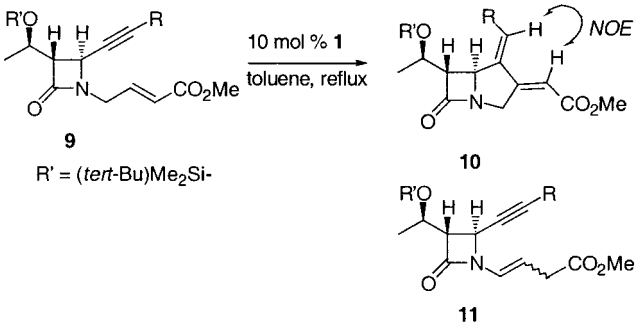


Using this procedure, we tried to synthesize bicyclic β-lactams. When a toluene solution of β-lactam **9a** was refluxed in the presence of $RuH_2CO(PPh_3)_3$ for 12 h, we were very pleased to find that bicyclic β-lactam **10a** was obtained in 44% yield along with the isomerization product **11a** (Table 2, run 1). The results of an NOE experiment showed the stereochemistries of the double bonds to be *E* and *E*. Various bicyclic β-lactams **10** were synthesized from the corresponding β-lactams **9**. In the case of a silyloxymethyl group on the alkyne, the yield decreased to 22% and the starting material was recovered in 31% yield (run 4).

Subsequently, compounds **12a** and **12b** were synthesized and separated, but the stereochemistry of each isomer could not be determined. Each isomer was treated in a similar manner, and **13a** was obtained in 23% yield along with the starting material in 44% yield from the more-polar compound **12a** on TLC (Scheme 3). The results of an NOE experiment showed that the stereochemistries of the double bonds in **13a** are *E* and *E* and that the ring-junction proton and methyl

(5) (a) Blackmore, T.; Bruce, M. I.; Stone, F. G. A. *J. Chem. Soc., Dalton Trans.* **1974**, 106. (b) Hart, D. W. Schwartz, J. *J. Organomet. Chem.* **1975**, *87*, C11.

Table 2. Synthesis of Carbapenam **10**



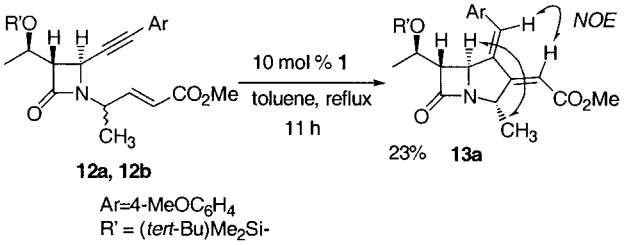
run	R	substrate	time (h)	yield (%) of **10**	yield (%) of **11**
1	Ph	**9a**	12	44	17
2	4-MeOC$_6$H$_4$	**9b**	6	63	10
3	4-MeC$_6$H$_4$	**9c**	12	45	18
4	Et$_3$SiOCH$_2$	**9d**	8	22	10[a]

[a] Recovered starting material; 31%

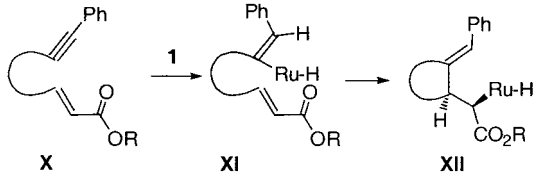
group on the five-membered ring is *cis*. However, the other isomer **12b** did not afford the desired product, and the starting material was recovered in 75% yield.

Our plan for the construction of a carbapenam skeleton is a method using the formation of six-membered ruthenacycle and then reductive elimination from it. However, several methods for cyclization using various ruthenium complexes have recently been reported.[6,7] In these cases, various reaction mechanisms for cyclization were proposed; for example, hydroruthenation to the alkyne by $RuH_2CO(PPh_3)_3$ followed by insertion of a double bond into the C−Ru bond gives XII via XI and then β-hydride elimination affords the desired product (Scheme 4).[7]

Scheme 3



Scheme 4. Another Possible Reaction Course



At present, it is not clear whether this reaction proceeds via C−H activation, hydroruthenation, or another mechanism.

Further investigation of the reaction mechanism is now in progress.

Supporting Information Available: Experimental procedures and spectral data for the cyclization of substrates **2c** and **9a**; spectral data for compound **2a**−**g**, **3a**−**g**, **7**, **9a**−**d**, **10a**−**d**, **12a**,**b**, and **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) (a) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049. (b) Yamamoto, Y.; Ohkoshi, N.; Kameda, M.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 2178. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 9728. (d) Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, 122, 5877. (e) Fernández-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221. (f) Morisaki, Y.; Kondo, T.; Mitsudo, T.-A. *Org. Lett.* **2000**, *2*, 949. (g) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Itoh, K. *J. Org. Chem.* **1998**, *63*, 9610. (h) Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319. (i) Chatani, N.; Fukumoto, Y.; Ida, T.; Murai, S. *J. Am. Chem. Soc.* **1993**, *115*, 11614. (j) Mitsudo, T.-A.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580. (k) Kikuchi, H.; Uno, M.; Takahashi, S. *Chem. Lett.* **1997**, 1273. (l) Nishida, M.; Adachi, N.; Onozuka, K.; Matsumura, H.; Mori, M. *J. Org. Chem.* **1998**, *63*, 9158.

(7) We have already reported on a novel cyclization using $RuClH(CO)(PPh_3)_3$. In this reaction, we proposed this hydroruthenation mechanism.[6l] Thus, when a toluene solution of **9b** was refluxed in the presence of $RuClH(CO)(PPh_3)_3$ overnight, no cyclized product was obtained.