ORGANIC LETTERS

2001
Vol. 3, No. 13
2045−2048

Enamide–Olefin Ring-Closing Metathesis

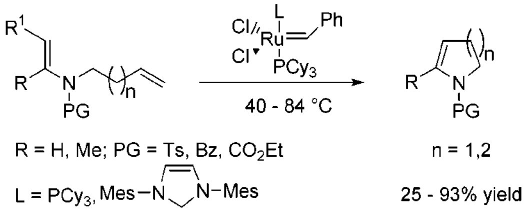
Sape S. Kinderman,[†] Jan H. van Maarseveen,[†] Hans E. Schoemaker,[†,‡]
Henk Hiemstra,[†] and Floris P. J. T. Rutjes*[,†,§]

Institute of Molecular Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands, DSM Research,
Life Science Products, P.O. Box 18, 6160 MD Geleen, The Netherlands, and
Department of Organic Chemistry, University of Nijmegen, Toernooiveld 1,
6525 ED Nijmegen, The Netherlands

rutjes@sci.kun.nl

Received April 20, 2001

ABSTRACT



The first examples of ring-closing metathesis reactions of olefin-containing enamides using ruthenium-based catalysts have been demonstrated. A preliminary investigation into the scope and limitations, leading to protected five- and six-membered cyclic enamides, will be presented.

The use of ring-closing olefin metathesis in organic synthesis has seen explosive growth over the past decade.[1] This is not only expressed by the large number of articles appearing on this subject but also by the rapid emergence of new improved catalysts with a higher stability under more forcing conditions and a wider functional group tolerance.[2]

The importance of ring-closing and related ring-opening metathesis strategies is further underlined by an impressive number of total syntheses of natural products.[1a] In the majority of these syntheses, the first- and second-generation olefin metathesis catalysts **1**, **2** and **3**, **4**, respectively (Figure 1), have been employed to give high yields of the metathesis products. Ring-closing metathesis is routinely applied to construct cyclic olefins of virtually all ring sizes containing ether, ester, amide, and/or amine functionalities.[1]

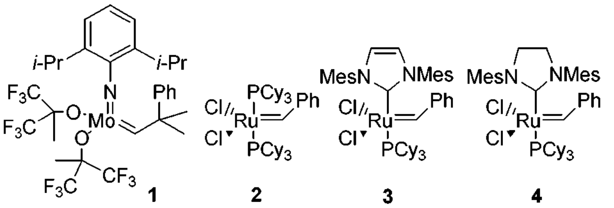


Figure 1. First- and second-generation olefin metathesis catalysts.

The synthesis of sulfur-[3] and phosphorus-containing heterocycles[4] via ring-closing metathesis has also been reported.

Considering the numerous examples, it becomes apparent that ring-closing metathesis of olefins connected directly to

---

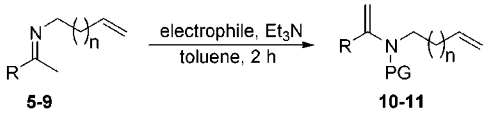
[†] University of Amsterdam.
[‡] DSM Research.
[§] University of Nijmegen.
(1) For review articles, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (e) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (f) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer: Berlin, 1998.
(2) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (d) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251. (e) Wheaterhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828.

10.1021/ol016013e CCC: $20.00 © 2001 American Chemical Society
Published on Web 06/02/2001

a heteroatom are significantly less abundant. For example, ring-closing metathesis of enol ethers is more difficult to achieve than that of regular olefinic ethers.[5] In addition, successful metathesis cyclizations of olefins substituted with a phosphorus atom (viz. vinylphosphonates and vinylphosphonamides) have recently been carried out.[6] In contrast, to the best of our knowledge, ring-closing metathesis of enamines or enamides so far has not been reported in the literature.[7]

In this paper, we wish to present the first examples of ring-closing metathesis of olefinic enamides, to obtain the corresponding cyclic enamides. These enamides are versatile structural moieties, which are amenable to further functionalization.[8] Most of the enamide RCM precursors were synthesized using the procedure of Breederveld, see Table 1.[9] The yields of the precursors **10** and **14** (entries 1 and 5) were low, probably due to the instability of both the starting aldimines and the products. The yields of the other precursors **11**−**13** and **15**−**20** were comparable to the yields reported in the literature for Breederveld conditions on similar compounds.

Table 1. Synthesis of the RCM Precursors

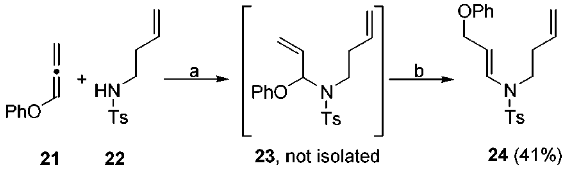


entry	imine	*n*	R	electrophile	product (PG)	yield (%)[a]
1	**5**	1	H	Ts$_2$O	**10** (Ts)	14
2	**6**	1	Me	Ts$_2$O	**11** (Ts)	37
3	**6**	1	Me	BzCl	**12** (Bz)	40
4	**6**	1	Me	$(EtO_2C)_2O$	**13** (CO_2Et)	30
5	**7**	2	H	Ts$_2$O	**14** (Ts)	5
6	**8**	2	Me	Ts$_2$O	**15** (Ts)	52
7	**8**	2	Me	BzCl	**16** (Bz)	44
8	**8**	2	Me	$(EtO_2C)_2O$	**17** (CO_2Et)	41
9	**9**	3	Me	Ts$_2$O	**18** (Ts)	48
10	**9**	3	Me	BzCl	**19** (Bz)	63
11	**9**	3	Me	$(EtO_2C)_2O$	**20** (CO_2Et)	68

[a] Isolated yield after column chromatography.

In addition to the unsubstituted and 1-substituted enamides shown in Table 1, we prepared similar 2-substituted enamides. This proceeded via a reaction that was accidentally encountered during the palladium-catalyzed *N*,*O*-acetal formation of tosylamide **22**.[10] Reaction of tosylamide **22** with phenyl propadienyl ether (**21**) in the presence of Pd(OAc)$_2$ led to the initial formation of the *N*,*O*-acetal **23**. This acetal spontaneously isomerized during the aqueous workup, leading to the thermodynamically more stable enamide **24** in 41% yield after column chromatography (Scheme 1).

Scheme 1. Synthesis of Enamide **24** via the Palladium-Catalyzed *N*,*O*-Acetal Formation with Phenyl Propadienyl Ether[a]



[a] Conditions: (a) Pd(OAc)$_2$, dppp, Et$_3$N, MeCN, room temperature, 16 h; (b) aqueous workup.

With these precursors in hand, we commenced the ring-closing metathesis experiments (Table 2). We were very pleased to find that the five-membered ring precursors (entries 1−6) readily underwent ring closure at temperatures between 20 and 40 °C using Grubbs catalyst **2** (the reaction was monitored by TLC and ^{1}H NMR). Silica gel column chromatography was used to remove the catalyst, yielding the pure cyclic enamides **25**−**28** in isolated yields around 60% and higher.

With a methyl substituent on the 1-position of the precursor (entry 2), the yield dropped slightly when the same catalyst was used. Gratifyingly, the yield increased again to 86% by subjecting the tosyl-protected precursor **26** to the more stable catalyst **3** at 84 °C (entry 3). Experiments with a benzoyl or ethoxycarbonyl protecting group partly led to degradation of starting materials and products at elevated temperatures. Therefore, the yield of **27** could not be

---

(3) For RCM examples to sulfur-containing heterocycles, see: (a) Shon, Y.; Lee, T. R. *Tetrahedron Lett.* **1997**, *38*, 1283. (b) Armstrong, S. K.; Christie, B. A. *Tetrahedron Lett.* **1996**, *37*, 9373. (c) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761. (d) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126. (e) Long, D. D.; Termin, A. P. *Tetrahedron Lett.* **2000**, *41*, 6743. (f) Dougherty, J. M.; Hanson, P. R.; Klein, T. A.; Moore, J. D.; Probst, D. A. Robinson, R. E.; Snelgrove, K. A. *Tetrahedron* **2000**, *56*, 9781. (h) Lane, C.; Snieckus, V. *Synlett* **2000**, 1294.

(4) For RCM examples to phosphorus-containing heterocycles, see: (a) Hetherington, L.; Greedy, B.; Gouverneur, V. *Tetrahedron* **2000**, *56*, 2053. (b) Leconte, M.; Jourdan, I.; Pagano, S.; Lefebvre, F.; Basset, J.-M. *J. Chem. Soc., Chem. Commun.* **1995**, 857. (c) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998**, *39*, 3939. (d) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119. (e) Trevitt, M.; Gouverneur, V. *Tetrahedron Lett.* **1999**, *40*, 7333. (f) Schuman, M.; Trevitt, M.; Redd, A.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 2491. (g) Sørensen, A. M.; Nielsen, P. *Org. Lett.* **2000**, *2*, 4217. (h) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2000**, 1031. (i) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Synthesis* **2001**, 612.

(5) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061. (c) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123, 127. (d) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623. An efficient approach was recently published: Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179.

(6) (a) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G.; van Boom, J. H. *Tetrahedron Lett.* **2000**, *41*, 8635. (b) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1999**, *40*, 3297. (c) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2000**, *2*, 1769.

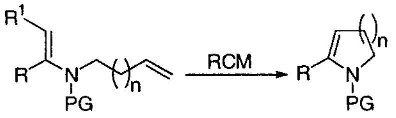
(7) For an attempt, see: Agami, C.; Couty, R.; Rabasso, N. *Tetrahedron Lett.* **2000**, *41*, 4113.

(8) (a) For *N*-acyliminium ion chemistry on enamides, see: Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1047. (b) For a recent example of an asymmetric Heck reaction on cyclic enamides, see: Tietze, L. F.; Thede, K. *Synlett* **2000**, 1470.

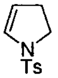
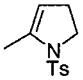
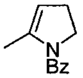
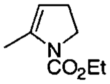
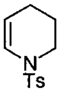
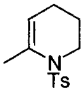
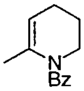
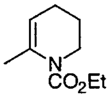
(9) (a) Breederveld, H. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 401. (b) Bach, T.; Schröder, J. *J. Org. Chem.* **1999**, *64*, 1205.

(10) Tjen, K. C. M. F.; Kinderman, S. S.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Chem. Commun.* **2000**, 699.

Table 2. Ring-Closing Metathesis of the Olefinic Enamides



10-17, 24 **25-32**

entry	enamide	conditions[a]	product	yield (%)[b]
1	**10**	**2**, 20 °C, 16 h	 **25**	84
2	**11**	**2**, 40 °C, 2 h	 **26**	59
3	**11**	**3**, 84 °C, 2 h	**26**	86
4	**12**	**2**, 40 °C, 6 h	 **27**	63
5	**12**	**3**, 84 °C, 4 h	**27**	60
6	**13**	**2**, 40 °C, 4 h	 **28**	62
7	**14**	**2**, 40 °C, 2 h	 **29**	80
8	**15**	**2**, 40 °C, 24 h	 **30**	26
9[c]	**15**	**3**, 80 °C,[c] 6 h	**30**	75
10	**16**	**3**, 84 °C, 16 h	 **31**	93
11	**17**	**3**, 84 °C, 6 h	 **32**	57
12	**24**	**2**, 20 °C, 16 h	**25**	42
13[c]	**24**	**3**, 80 °C,[c] 16 h	**25**	75

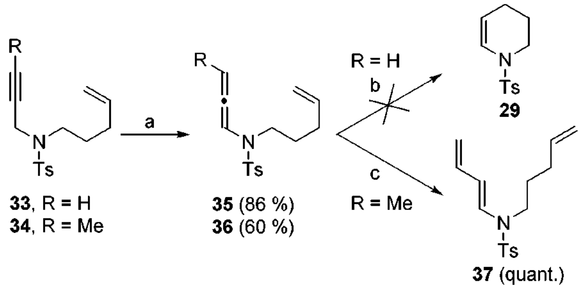
[a] 17.5 μM substrate concentration; 1−5 mol % of catalyst. Catalyst **2** was used in dichloromethane; catalyst **3** was used in ethylene dichloride unless otherwise stated. [b] Isolated yield after column chromatography. [c] In toluene.

increased (entry 5). To obtain the five-membered cyclic enamide **28**, the use of catalyst **2** at 40 °C (entry 6) gave an optimal result. In the case of the six-membered rings, the same trend was observed. The 2-unsubstituted enamide **14** closed in a good yield of 80% at 40 °C in 2 h (entry 7). In contrast, with the same catalyst it took 24 h to ring-close the methyl-substituted analogue in the somewhat disappointing yield of 26% (entry 8). Use of the Ru−imidazoline catalyst **3** also led to an improved yield of 75% for **30** at 80 °C in toluene at a reasonable rate (entry 9). With the benzoyl protecting group, the isolated yield exceeded 90% when the same catalyst was used at 84 °C with 1,2-dichloroethane (EDC) as the solvent (entry 10). The isolated yield of the carbamate-protected precursor **17** dropped to 57% under the same conditions (entry 11). Precursor **24**, bearing a substituent on the 2-position of the enamide part, gave the ring-closed product **25** in only a moderate yield using catalyst **2**. However, with catalyst **3** at higher temperature this precursor showed full conversion on both TLC and ^{1}H NMR, leading to an isolated yield of 75% of **25** after column chromatography (entries 12 and 13).

Inspired by the successful enamide ring-closures and the recently reported examples of allene cross-metathesis,[11] we set out to explore ring-closing metathesis of olefin-containing allenamides.

We anticipated that due to the impossibility of forming cyclic six-membered allenes, the corresponding cyclic enamides would be formed. The advantage of this approach is the better accessibility of the precursors. Therefore, precursors **35** and **36** were synthesized using a base-induced isomerization of the corresponding alkynyl precursors **33** and **34** (Scheme 2),[12] which were obtained in good yields (86 and 60%, respectively) from the tosylamides. Allenamide **35** was subjected to ruthenium catalyst **2** at 40 °C and to catalyst **3** at 84 °C, but in both cases no cyclic products were observed and only starting material was recovered. We reasoned that this might be due to the fact that the ruthenium catalyst has a greater affinity for the allene fragment of the molecule. Once the initial metathesis takes place at this end, it will not react further with the double bond, since further reaction would require incorporation of the allene fragment in the ring.

Scheme 2. Synthesis and Attempted RCM of the Olefinic Allenamides **35** and **36**[a]



[a] Conditions: (a) *t*-BuOK, THF, room temperature; (b) **2**, CH_2Cl_2, 40 °C or **3**, EDC, 84 °C, no reaction; (c) **3**, EDC, 84 °C.

Next, a comparison was made with precursor **36** containing a methyl substituent on the allene side, thus preventing initial metathesis at that side. Instead of cyclization, an interesting and unprecedented ruthenium-catalyzed isomerization to dienamide **37** was observed.

A remarkable phenomenon was encountered in attempts to create seven-membered cyclic enamides through ring-

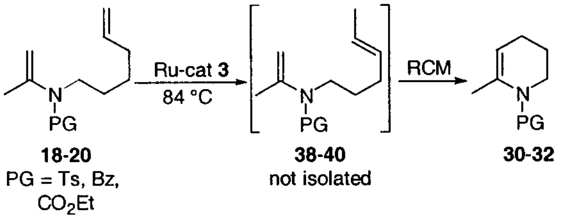
---

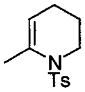
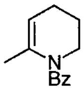
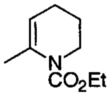
(11) Ahmend, M.; Arnauld, T.; Barrett, A. G. M.; Braddock, D. C.; Flack, K.; Procopiou, P. A. *Org. Lett.* **2000**, *2*, 551.

(12) For a recent example, see: Wei, L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkansah, N. T. *Org. Lett.* **1999**, *1*, 2145.

closing metathesis. Subjection of precursors **18**−**20** to the metathesis conditions (Ru catalyst **3**, 84 °C, EDC, entries 1−3, Table 3) surprisingly led to six- rather than seven-membered rings. Probably, ruthenium-catalyzed isomerization to the more stable olefins **38**−**40** took place, followed by ring closure of the isomerized intermediates to the six-membered enamides **30**−**32**.

Table 3. Seven-Membered Ring Precursors **18**−**20** Leading to Six-Membered Ring Products **30**−**32**



entry	enamide	conditions[a]	product		yield (%)[b]
1[c]	**18**	**3**, 80 °C,[c] 16 h		**30**	62
2[c]	**19**	**3**, 80 °C,[c] 24 h		**31**	24
3	**20**	**3**, 84 °C, 48 h		**32**	34[d]

[a] 17.5 μM substrate concentration; 1−5 mol % of catalyst. Catalyst **3** was used in ethylene dichloride unless otherwise stated. [b] Isolated yield after column chromatography. [c] In toluene. [d] Determined by ^{1}H NMR. An inseparable mixture of isomerized and ring-closed products was formed.

In conclusion, the first successful examples of ring-closing metathesis of olefin-containing enamides are described. We demonstrated the possibility of constructing five- and six-membered cyclic enamides in good yields using this pathway. Because of a remarkable isomerization of the seven-membered ring precursors, a challenge lies ahead for the construction of medium-sized enamide rings. An interesting problem was encountered in the case of the allenamides, where the catalyst has to discriminate between the allene moiety and the olefin part. Thus far, there are no such examples, but investigations to successfully carry out these types of olefin−allenamide metathesis reactions are currently underway.

Acknowledgment. This research has been financially supported by the Council for Chemical Sciences of The Netherlands Organization for Scientific Research (CW-NWO).

Supporting Information Available: Representative experimental procedures and spectroscopic data of the compounds **10**−**20**, **24**−**32**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016013E