

Tandem RCM–Isomerization–  
Cyclopropanation Reactions

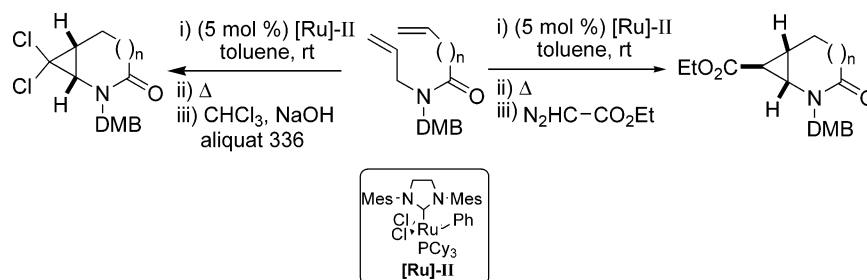
Álvaro Mallagaray, Gema Domínguez, Ana Gradillas, and Javier Pérez-Castells\*

*Facultad de Farmacia, Dpto. Química, Universidad San Pablo CEU, Urb.  
Montepríncipe, ctra. Boadilla km 5,300 Boadilla del Monte, 28668 Madrid, Spain*

jpercas@ceu.es

Received December 3, 2007

## ABSTRACT



A new triple tandem process has been discovered in which simple acyclic substrates can be transformed into bicyclic compounds via RCM–double bond isomerization–cyclopropanation. This process is catalyzed by second generation Grubbs' catalyst without the requirement of other reagents or additives. In addition, a *one-pot* RCM–isomerization reaction followed by cyclopropanation with CHCl<sub>3</sub>/NaOH allows the synthesis of products related to iNOS (nitric oxide synthase) inhibitors, which are currently under clinical evaluation.

Ruthenium alkylidene catalysts have triggered the utility of metathesis reactions in synthesis.<sup>1</sup> Many groups have observed non-metathetic transformations as side reactions during their studies using these complexes.<sup>2</sup> If these alternative reactions are combined with metathesis, the synthetic potential of ruthenium catalysts is enhanced. The ability of one species to mediate or catalyze sequentially several transformations adopts several names although the term concurrent tandem transformation expresses conveniently this concept.<sup>3</sup>

Recently, Snapper's group has made interesting contributions in tandem transformations involving ruthenium alkylidene compounds. In particular, they have described an enyne metathesis–cyclopropanation sequence leading to alkenyl

cyclopropanes using first generation Grubbs' catalysts [Ru]-I.<sup>4</sup> This group and others have accounted for the ability of second generation complex [Ru]-II to isomerize emerging with double bonds after a RCM. Heteroatoms which are suitably located within the substrate facilitate the isomerization process. Thus, Fustero has described the synthesis of unsaturated lactams via RCM–double bond shift, a process in which the presence of fluoro atoms improves the results of the isomerization step.<sup>5</sup>

Synthesis of highly functionalized cyclopropanes is a challenge as there are many biologically active compounds containing this motif.<sup>6</sup> In addition, many cyclopropane-containing non-natural products have been prepared to study enzyme mechanism or inhibition.<sup>7</sup> Transition metal-catalyzed decomposition of diazocompounds is a convenient procedure to synthesize cyclopropanes. The use of ruthenium carbenes to catalyze cyclopropanations via decomposition of diazocompounds would increase their use, particularly if the reaction is combined with a metathesis. In particular, a new

(1) For reviews on olefin metathesis, see: (a) Katz, T. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3010–3019. (b) Schrock, R. R. *J. Mol. Catal. A: Chem.* **2004**, *213*, 21–30. (c) Hoveyda, A. H.; Schrock, R. R. *Compr. Asymmetric Catal.* **2004**, *1*, 207–233. (d) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (e) Grubbs, R. H.; Trnka, T. M. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 6.

(2) Reviews on non-metathetic behavior of Ru catalysts: (a) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865–1880. (b) Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, *9*, 1258–1262.

(3) Wasilke, J. C.; Obrey, S. J.; Baker, T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1022.

(4) Kim, B. G.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 52–53.

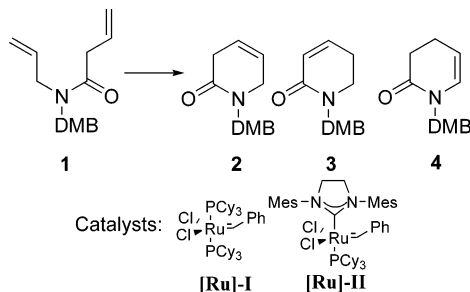
(5) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706–2714. See also: Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391.

(6) Recent review: Donalson, W. A. *Tetrahedron* **2001**, *57*, 8589–8627.

one-step entry to  $[n.1.0]$  systems can be envisioned. We discuss herein a new approach to the formation of bicyclic compounds using a novel RCM–isomerization–cyclopropanation reaction catalyzed by [Ru]-II.

Our initial aim was the synthesis of compound **4** via RCM and subsequent double bond isomerization (Scheme 1). This

**Scheme 1.** RCM–Isomerization of Compound **1**



strategy is advisable as a simple RCM reaction on enamides would imply their synthesis, which is not trivial, and the possibility that non-metathetic competitive reactions would take place as described previously.<sup>2</sup> Thus, substrate **1** was reacted with ruthenium complexes [Ru]-I or [Ru]-II under different conditions summarized in Table 1. After completion

**Table 1.**

entry	catalyst (5 mol %)	solvent	temp (°C)	time (h)	yield		
					2 <sup>a</sup>	3 <sup>a</sup>	4 <sup>a</sup>
1	[Ru]-I	toluene	rt/Δ	3–22	80	n.d.	n.d.
2	[Ru]-II	CHCl <sub>3</sub>	rt/Δ	3–12	95	n.d.	n.d.
3	[Ru]-II	toluene	rt/70	3–12	90	n.d.	n.d.
4	[Ru]-II	toluene	rt/Δ	3–12	11	21	57
5	[Ru]-II	<i>p</i> -cymene	rt/Δ	3–12	16	27	50
6	[Ru]-II	toluene	rt/200 <sup>b</sup>	3–12	15	22	48
7	[Ru]-II	CHCl <sub>3</sub>	rt/140 <sup>b</sup>	3–12	17	36	13
8	[Ru]-II	toluene	Δ	12	10	17	64

<sup>a</sup> Percent of pure product. <sup>b</sup> In a sealed tube.

of the RCM reaction, the mixture was heated to favor the double bond shift. [Ru]-I was unable to isomerize the double bond (entry 1). With [Ru]-II, no isomerization was observed in chloroform (entry 2), whereas in refluxing toluene the reaction reached acceptable results, yielding **4** as the major product (entry 4). However, at rt or 70 °C this solvent only produced **2**, and no double bond shift products such as **3** or **4** were observed (entry 3). This observation prompted us to carry out the reaction in *p*-cymene (entry 5) and in sealed tubes (entries 6 and 7). These conditions allowed the formation of **4** in chloroform but with low yields. Finally the best results were achieved by performing the reaction in refluxing toluene for the RCM and the isomerization steps (entry 8), which gave a 64% yield of the desired compound, **4**.

(7) (a) Salaün, J. *Top. Curr. Chem.* **2000**, 207, 1–67. (b) Faust, R. *Angew. Chem., Int. Ed.* **2001**, 40, 2251–2253.

Next, we combined this tandem process with a cyclopropanation reaction with dichlorocarbene. This reaction was achieved by adding a 50% solution of NaOH in water, CHCl<sub>3</sub>, and Aliquat 336 to the reaction mixture once the RCM–isomerization reaction had been completed. The overall yield of compound **5** was 21% from **1**. This result was improved by applying sonication to the cyclopropanation step, reaching a yield of 55% (Scheme 2). A different attempt

**Scheme 2.** RCM–Isomerization–Cyclopropanation of **1** with Dichlorocarbene



involved using catalysts [Ru]-I for the RCM reaction and adding NaH to perform the isomerization following Schmidt's conditions.<sup>8</sup> The cyclopropanation was effected by subsequent addition of CHCl<sub>3</sub> and gave **5** with a yield of only 11%. Compound **5** is structurally related to a recently disclosed selective inhibitor of the human inducible isoform of nitric oxide synthase (iNOS).<sup>9</sup>

To tune up a triple tandem process involving a cyclopropanation step with a diazo compound, we first checked the ability of catalyst [Ru]-II to cyclopropanate with ethyl diazoacetate (EDA). Thus, addition of EDA to compound **4** afforded bicyclic compounds **6** (mixture of *cis*:*trans* isomers) along with insertion product **7** (Scheme 3). As indicated in

**Scheme 3.** RCM–Isomerization–Cyclopropanation of **1**

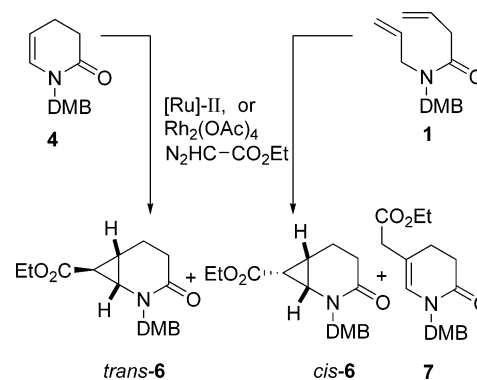


Table 2 the results are similar in terms of yields as for classical cyclopropanation methods (with rhodium acetate, entry 3). The reaction in chloroform or at room temperature did not take place. Results are similar at 70 °C (entry 2) and

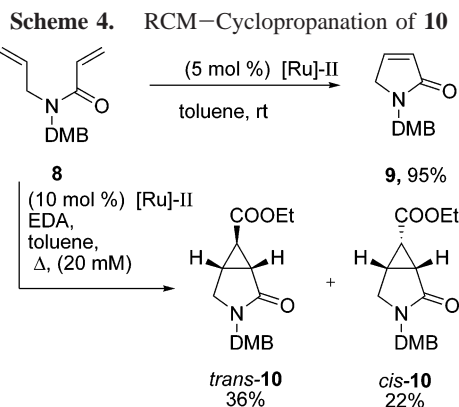
(8) Schmidt, B. J. *Org. Chem.* **2004**, 69, 7672–7687.

(9) (a) Kawanaka, Y.; Kobayashi, K.; Kusuda, S.; Tatsumi, T.; Murota, M.; Nishiyama, T.; Hisaichi, K.; Fujii, A.; Hirai, K.; Naka, M.; Komeno, M.; Odagaki, Y.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2003**, 11, 1723–1743. (b) Kawanaka, Y.; Kobayashi, K.; Kusuda, S.; Tatsumi, T.; Murota, M.; Nishiyama, T.; Hisaichi, K.; Fujii, A.; Hirai, K.; Naka, M.; Komeno, M.; Nakai, H.; Toda, M. *Eur. J. Med. Chem.* **2003**, 38, 277–288.

Table 2.

entry	starting compd	(mol %) cat.	temp (°C)	time (h)	yield		
					<i>trans</i> - <b>6</b> <sup>a</sup>	<i>cis</i> - <b>6</b> <sup>a</sup>	<b>7</b> <sup>a</sup>
1	<b>4</b>	(10) [Ru]- <b>II</b>	Δ	8 <sup>b</sup>	36	25	17
2	<b>4</b>	(10) [Ru]- <b>II</b>	70	8 <sup>b</sup> + 48	40	21	10
3	<b>4</b>	(5) Rh(OAc) <sub>2</sub>	rt	8 <sup>b</sup>	40	10	5
4	<b>1</b>	(15) [Ru]- <b>II</b>	Δ	12 + 8 <sup>b</sup>	25	15	<5
5	<b>1</b>	(15) [Ru]- <b>II</b>	Δ	8 <sup>b</sup>	34	18	<5
6	<b>4</b>	(10) [Ru]- <b>II</b> <sup>c</sup>	70	8 <sup>b</sup>	19	10	<5

<sup>a</sup> Percent of pure product. <sup>b</sup> EDA was added over 8 h with a pump syringe. <sup>c</sup> Thermally modified prior to reaction.



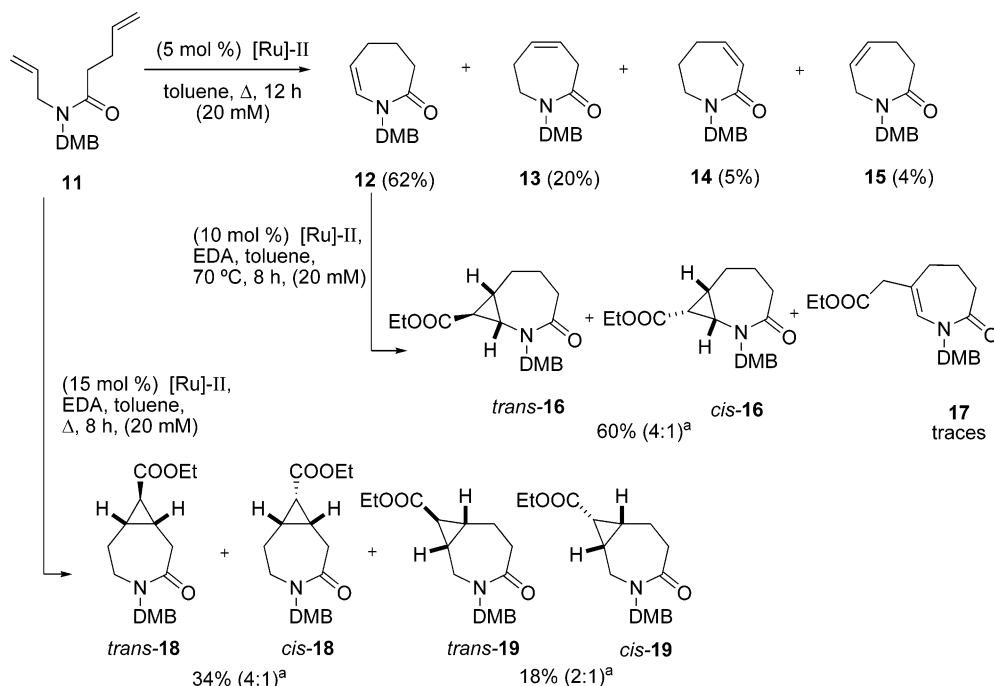
in refluxing toluene (entry 1), although the first reaction needed a supplementary time for completion. Next, we performed the three reactions from **1** in a *one-pot* fashion. Thus, after verifying the completion of the RCM–isomer-

ization (12 h), EDA was slowly added over 8 h to the reaction mixture and yielded 40% of the two isomeric cyclopropanes **6** (entry 4). A 52% yield of both cyclopropanes was obtained from the initial ethyl diazoacetate (EDA) addition over 8 h (entry 5).

From the results shown in Table 1, a thermal modification of the ruthenium complex seems to be essential for the isomerization process.<sup>10</sup> Fustero has explained the mechanism of the double bond shift by the formation of a ruthenium hydride from catalyst [Ru]-**II**, without the aid of any reactive. This hydride would add to the double bond and then eliminate to form the isomeric unsaturated lactam. The regioselectivity of the process would be due to stabilization of a positive charge by the electron lone pair of the nitrogen in its contiguous position. If the ruthenium complex is transformed into a hydride the question would be the identity of the catalyst in the cyclopropanation step. We have shown that Grubbs' catalyst [Ru]-**II** is able to cyclopropanate substrate **4** at temperatures where isomerization does not take place, i.e., Ru–H species are not formed (entry 2, Table 2).<sup>11</sup>

The methodology was extended to other starting materials, precursors of cycles of 5 and 7 members. Thus, diene **8** was reacted with EDA in refluxing toluene in the presence of [Ru]-**II**, giving **10** as a mixture of isomers in 58% combined yield (Scheme 4). The RCM alone gave conjugated enone **9** (95%), which did not isomerize in any of the previously used conditions.

When applied to substrate **11**, the RCM–isomerization phase gave a mixture of all the possible regioisomers of the seven-membered lactam although the desired compound **12** was isolated in 62% yield (Scheme 5). The other three isomers, **13**–**15**, could be characterized. This result was

Scheme 5. RCM, Isomerization, Cyclopropanation, and Tandem Reactions from **11**

<sup>a</sup> Obtained as a mixture of isomers. A small amount of major compounds *trans*-**16**, *trans*-**18**, and *trans*-**19** was isolated for characterization.

achieved by performing the RCM at rt and heating to reflux temperature after completion. The reaction in a sealed tube gave better selectivity for compound **12** but overall yield was lower (58%). Compound **12** was cyclopropanated at 70 °C, giving products **16** (60%) as a 4:1 mixture of diastereoisomers. The major isomer (*trans*-**16**) was separated and characterized whereas we were unable to obtain the minor isomer pure. Insertion product **17** was detected in the crude mixture. Interestingly, when performing the tandem process, starting from **11** (conditions from Table 2, entry 5), we obtained a mixture of cyclopropanes **18** and **19** with good global yield. In each mixture, the diastereomers could not be separated by MPLC. Major compounds *trans*-**18** and *trans*-**19** were characterized. This latter result shows that after the isomerization step there is equilibrium between the isomers **12**–**15** and the composition of the mixture may change with subtle variation of the conditions. For an

unknown reason, compounds **13** and **15** react better than **12** under these conditions. This result shows that [Ru]-**II** is able to catalyze the cyclopropanation of non-activated olefins like **13** or **15**. The identity of cyclopropanes **18** and **19** was checked by performing two independent cyclopropanation reactions from **13** and **15** using catalyst [Ru]-**II** at 70 °C.

In conclusion, we have described a new concurrent tandem catalyzed triple process including RCM–isomerization and cyclopropanation. The second generation Grubb's catalyst was able to catalyze the three processes without requiring other reagents. The identity of the catalytic species and the mechanism of this transformation needs further study, but we presume that the complex mediating in the isomerization step is a ruthenium hydride formed by thermal modification of the initial carbene. RCM–isomerizations can be combined with classical cyclopropanations with dichlorocarbenes giving products related to bioactive compounds.

**Acknowledgment.** Funding of this project by the Spanish MEC (No. CTQ2006-00601/BQU) is acknowledged. A.M. thanks FUSP-CEU for a predoctoral fellowship.

**Supporting Information Available:** Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL702766H

(10) (a) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415. (b) Hong, S. H.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1955–1957. (c) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161. (d) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.

(11) In addition, it is known that Grubbs' catalysts activate diazo compounds, maintaining their metathesis activity. See: (a) Hodgson, D. M.; Angrish, D. *Chem. Commun.* **2005**, 4902–4904. (b) Hodgson, D. M.; Angrish, D. *Adv. Synth. Catal.* **2006**, *348*, 2509–2514. (c) Hodgson, D. M.; Angrish, D. *Chem. Eur. J.* **2007**, *13*, 3470–3479. (d) Hodgson, D. M.; Angrish, D.; Labande, A. H. *Chem. Commun.* **2006**, 627–628.