

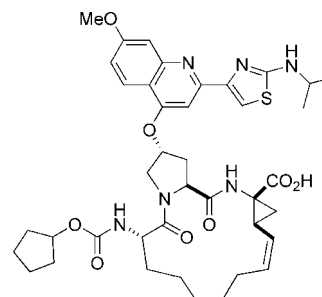
Second-Generation Process for the HCV Protease Inhibitor BILN 2061: A Greener Approach to Ru-Catalyzed Ring-Closing Metathesis†

Vittorio Farina,*§ Chutian Shu,* Xingzhong Zeng, Xudong Wei, Zhengxu Han, Nathan K. Yee, and Chris H. Senanayake*

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, U.S.A.

Abstract:

The ring-closing metathesis (RCM) step, a key reaction in our process to BILN 2061, was dramatically improved from the first-generation process by the selection of a more appropriate substrate as well as the use of a more effective catalyst. The two RCM reactions are compared in detail using criteria that are of high significance to the process chemist.



BILN 2061 (1)

Introduction

The ring-closing metathesis (RCM) reaction has recently emerged as an important tool in organic synthesis.¹ We have described an application of this reaction to the synthesis of HCV protease inhibitor BILN 2061, a 15-membered macrocyclic compound containing a (Z)-olefin (Figure 1).²

This first-generation RCM (Scheme 1) was scaled to produce > 100 kg of the active pharmaceutical ingredient (API).³ In this contribution we describe the optimization of the initial RCM, leading to a second-generation process which dramatically improves throughput and reaction efficiency, as measured by a variety of parameters.

In an effort to design a more effective second-generation process to this and related chemical targets, the high dilution of the RCM reaction (10 mM) had to be overcome; this problem is typical of macrocyclizations, including all RCM macrocyclizations known to date. In fact, a high-concentration RCM macrocyclization was unprecedented in the literature at the outset of our work, and our first-generation process was actually already at the high end of the concentration range used in the published RCM macrocyclizations.⁴

The reasons for this problem are easily understood: at higher concentration, intermolecular processes start competing with ring closure, thus lowering the yield of the desired cyclization product. In practice, one is then forced to compromise between high yield and high throughput. This can be expressed quan-

Figure 1. Structure of BILN 2061.

titatively using the concept of effective molarity (EM), which is convenient in order to formulate the above competition with one quantifiable parameter.⁵

In order to place the problem in our initial reaction on quantitative grounds, we carried out a rough calculation of EM ($= k_{\text{intra}}/k_{\text{inter}}$) for the process employing the first-generation Hoveyda catalyst **4**⁶ (Figure 2), which operates under kinetic conditions.⁷

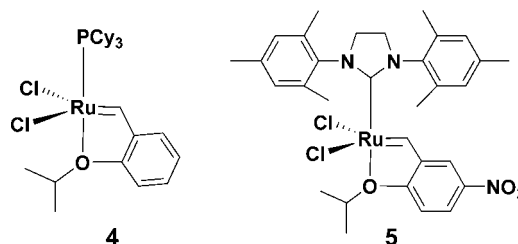


Figure 2. Catalysts discussed in this study.

We made several simplifications. We assumed that the several cyclic dimers (identified by LC/MS analysis)⁸ accounted for the missing mass balance of the reaction and that all dimers were formed at the same rate (an average rate), given that the intermolecular step of the dimerization is likely to be the same or similar. We then carried out the RCM at different diene concentrations, and estimated the starting material and product yield by a quantitative HPLC assay. We used the “product ratio” approach described by Percy et al. to estimate the kinetic EM

† Dedicated to the memory of Chris Schmidt, a friend and esteemed colleague.

* To whom correspondence should be addressed. Telephone: 203-778-7876. Fax: 203-791-6130. E-mail: chutian.shu@boehringer-ingelheim.com.

§ Current address: Johnson & Johnson Pharmaceutical Research and Development, Turnhoutseweg 30, B-2340 Beerse, Belgium.

(1) (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003. (b) Astruc, D. *New J. Chem.* **2005**, 29, 42.

(2) Yee, N. K.; Farina, V.; Houpi, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F. R.; Wang, X.-j.; Wei, X.; Simpson, R. D.; Feng, X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, L.; Xu, J.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Donsbach, K.; Nicola, T.; Brenner, M.; Winter, E.; Kreye, P.; Samstag, W. *J. Org. Chem.* **2006**, 71, 7133.

(3) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Process Res. Dev.* **2005**, 9, 513.

(4) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, 45, 6086.

(5) (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, 14, 95. (b) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117.

(6) Kingsbury, J. S.; Harry, J. P.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, 121, 791.

(7) We have shown that **3** does not re-open to **2** under the reaction conditions nor does it produce dimer, even under an ethylene atmosphere or in the presence of an analogous RCM reaction in the same pot; the main cyclic dimer does not equilibrate to **3** when treated with catalytic **4**.

Scheme 1. First-generation RCM

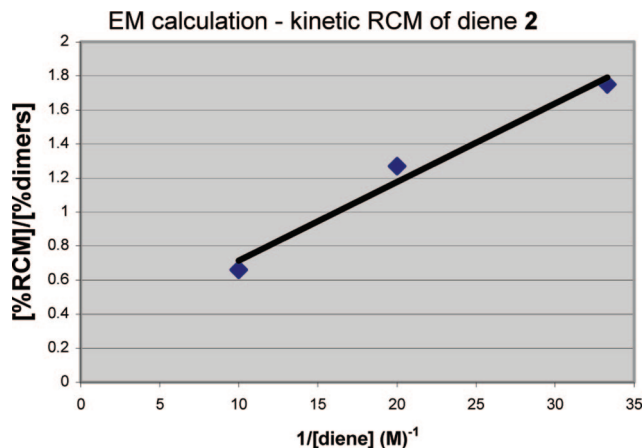
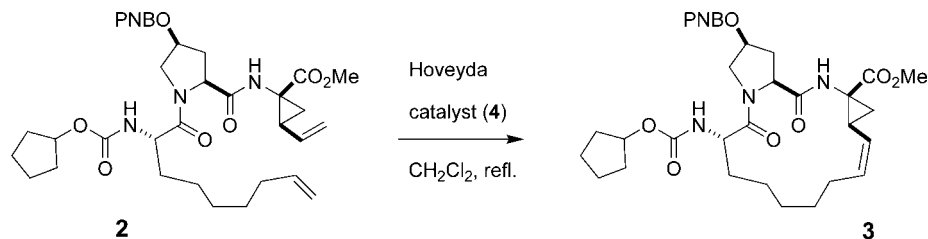


Figure 3. Calculation of EM(kin) for reaction in Scheme 1.

(EM(kin)).⁹ Expressing the rate equations and replacing the ratio of the kinetic constants of the two competing processes with EM, one obtains eq 1. Use of this equations leads to the plot in Figure 3, and to a EM(kin) value of 0.046 M.

$$(\% \text{ RCM})/(\% \text{ dimers}) = \text{EM}/[\text{diene}] \quad (1)$$

This EM represents the initial concentration of diene that will yield a ca.1:1 mixture of the RCM product and dimers. This, in practical terms, means that the RCM reaction must be run well below the EM value in order to obtain quantitative yields (>90%) of the product resulting from the intramolecular process. These concentrations are extremely impractical in a plant setting, especially if the production target for the new API is in the metric ton (MT) range. In addition, they generate enormous volumes of spent solvents which must be eventually incinerated. A “greener” process was therefore needed.

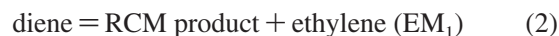
A second problem with the first-generation process was the high catalyst load. In the early runs, 5–7 mol % of the expensive catalyst **4** was routinely used. On a pilot-plant scale, once the starting diene **2** was obtained in high purity, it was possible to reduce this load to about 3 mol % and still obtain high yields of **3**. This limitation is due to the intrinsically low stability and low efficiency of catalyst **4**. On a commercial scale, this is impractical, due not only to the high cost but also to the extreme difficulty of removing the high levels of Ru metal from the API. Therefore, a better catalyst was absolutely required.

A third problem was constituted by the long reaction times, often in excess of 24 h and reaching, in some cases, 40 h. In a

highly streamlined commercial process, where all downstream manipulations have been optimized, this step will be the bottleneck, and therefore further reduce the already meager throughput.

A fourth problem we have encountered from time to time is the epimerization reaction at the vinyl-bearing cyclopropane (P1) carbon atom, due to trace impurities of amines or phosphines in the reaction medium. Although we have clarified some of the mechanistic details of the epimerization,¹⁰ this troublesome side reaction requires the most scrupulous quality control in the RCM solvent as well as in the starting diene, thus introducing extensive analytical work. Although this can be done, ideally we would prefer an RCM reaction that could be made robust under a more permissive range of conditions, thus improving ease of operation.

Although second-generation catalysts like Grela's **5** (Figure 2) address rather successfully the second and third problems, due to their better turnover numbers (TON) and turnover frequencies (TOF), they operate under thermodynamic conditions instead of kinetic ones,² producing more products of intermolecular metathesis.¹¹ This makes it difficult to compare the efficiency of catalysts **4** and **5** quantitatively. On the other hand, we wanted to express the concentration sensitivity of the RCM reaction with catalyst **5** using a single parameter, which would make comparison with other substrates easy. The problem of expressing the thermodynamic effective molarity under conditions where both cyclic and acyclic oligomers can be formed has been tackled, for the most general case, by Ercolani et al.¹² The thermodynamic EM for cyclization is expressed as the ratio of two equilibrium constants: one for the cyclization reaction, the other for a corresponding intermolecular reaction (e.g., the dimerization event). In order to simplify the problem, we have only taken into consideration the cyclizations of the monomer (starting diene) and its main dimer (eqs 2 and 3):



This, following Ercolani, leads to eq 4:

$$[\text{RCM product}]^2/[\text{dimer}] = (\text{EM}_1)^2/\text{EM}_2 \quad (4)$$

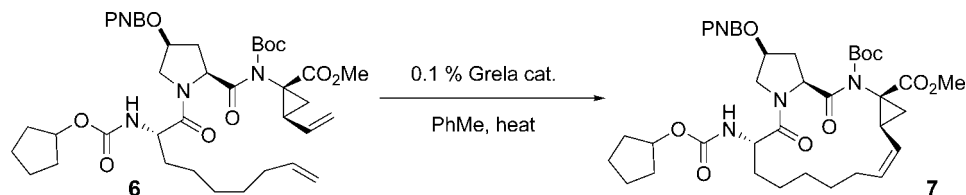
Thus, the ratio $[\text{RCM product}]^2/[\text{dimer}]$ should be constant for any concentration of starting diene. This ratio is basically

(8) For the isolation and identification of the most abundant dimer, see the Supporting Information of Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303.

(9) Mitchell, L.; Parkinson, J. A.; Percy, J. M.; Singh, K. *J. Org. Chem.* **2008**, *73*, 2389.

(10) Zeng, X.; Wei, X.; Farina, V.; Napolitano, E.; Xu, Y.; Zhang, L.; Haddad, N.; Yee, N. K.; Grinberg, N.; Shen, S.; Senanayake, C. H. *J. Org. Chem.* **2006**, *71*, 8864.

Scheme 2. Second-generation RCM process



the equilibrium constant for the disproportionation of the RCM product to a cyclic dimer (eq 5).

$$2 \text{ RCM product} = \text{dimer} \quad (5)$$

We can estimate the latter concentration, as we have done above, assuming [eq 6]:

$$[\text{diene}]_0 = [\text{RCM product}] + 2[\text{dimer}] \quad (6)$$

This leads to the plot in Figure 4; the resulting $\text{EM}_1^2/\text{EM}_2$ (a K_{eq}) represents a *Modified Effective Molarity* and has a value 0.096 M ($R^2 = 0.998$). Note that this modified thermodynamic EM was obtained under slightly different conditions than the kinetic one (PhMe at 60 °C instead of CH_2Cl_2 at 40 °C), and the two parameters cannot, at any rate, be meaningfully compared.

Table 1 summarizes our results with the two representative first- and second-generation catalysts. We had also briefly considered, as potential solutions, polymer-supported catalysts¹³

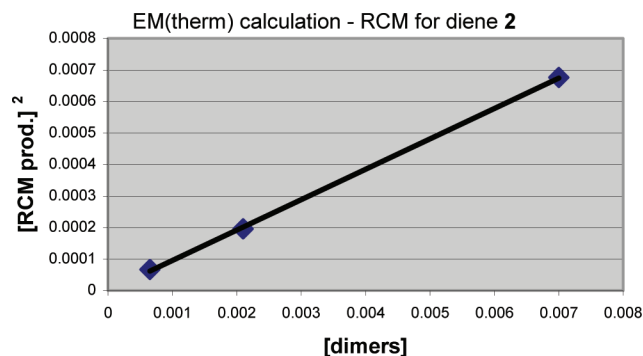


Figure 4. Calculation of modified EM(therm) for the reaction in Scheme 1.

or pseudo-high dilution conditions,¹⁴ but these initial attempts did not hold promise and are not discussed in detail here. As Table 1 shows, a higher TON and TOF were achieved with

catalyst **5**, but at the cost of product yield, and this was not acceptable, especially because removal of the dimers required multiple recrystallizations, with the associated losses.

The table also lists our goals for a second-generation metathesis process. The robust and readily initiating Grela catalyst,¹⁵ which in preliminary experiments could successfully operate at 0.3–0.4 mol % load, seemed ideally suited. Although we desired to maintain the higher performance of the Grela catalyst, we needed to increase the EM(therm). We felt that a 10-fold improvement would allow us to operate in normal process equipment and lead to a much greener process.

After considering various derivatization schemes for diene **2**, we settled on diene **6** as the new substrate (Scheme 2). The new diene **6** features a Boc group bound to the P1–P2 amide nitrogen. The selection process and an interpretation of the data have been communicated separately.¹⁶

We ran the RCM reaction of Scheme 2 under several initial diene concentrations. Calculation of $(\text{EM}_1)^2/\text{EM}_2$ for this process (Figure 5) yielded 1.85 M ($R^2 = 0.990$), which represents a 19-fold improvement over the analogous modified EM(therm) for diene **2** under the same conditions. A further improvement could be realized by running the RCM reaction at 110 °C: the $(\text{EM}_1)^2/\text{EM}_2$ in this case was 2.56 M ($R^2 = 0.955$; plot not shown).

The effect of the temperature is qualitatively understood by taking into account the entropic change in the two processes; whereas the RCM process produces two olefinic products for

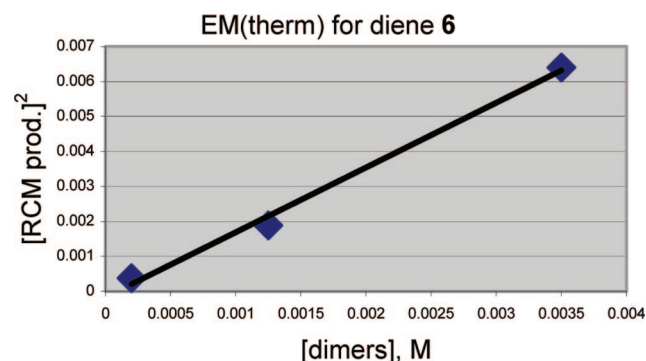


Figure 5. Modified EM(therm) calculation for N-Boc substrate **6**.

each diene molecule, the dimerization process leads to one and a half. Higher temperatures will tend to favor the RCM process

- (11) (a) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108. (b) Conrad, J. C.; Ellman, M. D.; Duarte Silva, J. A.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024.
- (12) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901.
- (13) (a) Deshmukh, P. H.; Blechert, S. *Dalton Trans.* **2007**, 2479. (b) Clavier, H.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 8029. (c) Clavier, H.; Grela, K.; Kirschning, A.; Mauduit, M.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6786. Polymer-supported catalysts are problematic for several reasons. First, many supported catalysts are used in large molar amounts and are not sufficiently challenged with a high enough number of recycles. Indeed, in publications of supported catalysts there is seldom (if ever) a direct comparison between the maximum TON obtained under homogeneous conditions and the maximum TON obtained after all possible recycles of the supported catalyst. This, on the other hand, is the decisive parameter that would establish the utility of a supported catalyst.

- (14) The problem of low EM can sometimes be alleviated by running the reaction by adding the substrate slowly to the catalyst. In practice, this was unsuccessful using catalyst **4** due to its poor thermal stability, whereas the Grela catalyst **5** operates in the thermodynamic regime, and this approach cannot be used.
- (15) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318.
- (16) Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303.

Table 1. Current RCM process vs target

	process with Hoveyda catalyst 4	process with Grela catalyst 5	desired process
catalyst load	3–5 mol %	0.3–0.4 mol %	≤0.3 mol %
reaction time	24–40 h	≤1 h	≤1 h
initial diene concentration	0.01 M	0.01 M	≥ 0.1 M
RCM yield (in situ, HPLC quant.)	92%	85%	90%

Table 2. Current RCM process vs results of second-generation process

	process with Hoveyda catalyst 4	process with Grela catalyst 5	desired process	second-generation process
catalyst load	3–5 mol %	0.3–0.4 mol %	≤0.3 mol %	0.05–0.1 mol %
reaction time	24–40 h	≤1 h	≤1 h	30 min
initial diene concentration	0.01 M	0.01 M	≥0.1 M	0.2 M
RCM yield (HPLC assay)	92%	85%	≥90%	93%

under thermodynamic conditions. Overall, a 27-fold improvement in “modified” *EM(therm)* was recorded in our new RCM vs the old one, resulting in a much more concentrated reaction. Given that the second-generation process is also a batch process, like the first, the relative efficiencies of the two approaches can be compared directly. Of course, the need to add and remove an N-Boc group needs to be factored in when comparing the two processes in terms of efficiency.

Table 2 compares the efficiencies of the first-generation process (using either catalyst) vs the new process after reoptimization (vide infra). Although the Grela catalyst (**5**) improves TON and TOF, it leads to large amounts of dimers, and this results in a modest isolated yield (ca. 75% after two recrystallizations, representing a further 10% yield loss), and therefore, its use per se does not result in a practical process improvement. The use of catalyst **5** in conjunction with modified substrate **6**, on the other hand, leads to a major improvement in all areas and exceeds our original goals when we listed the attributes of an ideally efficient, green process. The following considerations hold regarding the new RCM process shown in Scheme 2, in comparison with our first-generation manufacturing process.

Catalyst efficiency (TON and TOF). Second-generation catalysts react, in the process shown in Scheme 1, about 3 orders of magnitude more rapidly than first-generation ones like **4**.¹⁷ In addition, metathesis of **6** is about 3 times faster than that of **2** under typical conditions.¹⁸ This allows reaction completion in a manner of minutes instead of days (original process). The RCM step of the new process is no longer a bottleneck operation. The much higher TOF is complemented by a TON for **5** which is 50–100 times higher than that of **4** under identical conditions. This introduces major savings in catalyst use. We have also observed that the reaction in Scheme 1 requires scrupulous degassing for optimum results, whereas the one in Scheme 2 requires only a brief boil-out before adding the catalyst. The much higher robustness of the Grela catalyst **5** vs **4** has allowed us to dispense with oxygen sensors and oxygen specifications in the system, rendering the RCM much easier to execute on scale.

Epimerization Reaction at P1. Although the epimerization reaction in the RCM shown in Scheme 1 can be avoided by ensuring that all solvents used in the RCM are acid-washed, the new RCM (Scheme 2) requires no special precautions in

this sense. The reasons were discussed in our communication¹⁶ and can be summarized as follows: the resting state of the Ru catalyst is not at the vinylcyclopropane moiety, but at the nonenoic acid moiety, and there is no chance of epimerization even in the presence of amines or phosphines, which cause extensive epimerization in the reaction of Scheme 1. This feature allows us to simplify our manipulations, our QC of solvents and intermediates, and makes the RCM reaction much more robust and easier to execute.

Solvent Consumption. Whereas our old process utilized as much as 150,000 L solvent to process 1 MT of diene **2**, the same amount of diene **6** can now be processed with only 7500 L using the new process. This has important repercussions on the type of equipment used to carry out the reaction (simple 2000 L or 4000 L vessels are now adequate for production). Also importantly, the new process does not require the installation of equipment for rapid evaporation of organic solvents (such as wiped-film evaporators).

Ruthenium Removal. In the original process,² quenching of the catalyst and extractions required excess 2-mercaptopyridine (2 kg for 1 kg diene) and large volumes of bicarbonate to remove some of the solubilized Ru. One silica filtration was then employed in order to further reduce the Ru level, right after the RCM reaction, to 100–200 ppm. Subsequent chemical steps had to be coupled with charcoal filtrations in order to reduce the Ru levels in the API to below 10 ppm. These heroic efforts could be spared using the new RCM reaction: given the much lower catalyst load, the amount of MNA used was 50-fold lower. No silica pad or charcoal filtrations were necessary, and the Ru content of the RCM product was typically <50 ppm, yielding an API with <5 ppm Ru without further specific removal steps.

Overall Reaction Efficiency. Of all parameters that have been proposed to evaluate the efficiency of a reaction, the *E*-factor, introduced by Sheldon, is the easiest to use.¹⁹ This parameter refers to the amount of waste (e.g. in kilograms) for each unit (e.g. 1 kg) of useful product obtained, and includes all reagents and solvents. We have calculated the *E*-factors for both processes in Schemes 1 and 2. The one in Scheme 2 includes the introduction and the removal of the Boc group. The first-generation RCM is accompanied by an *E*-factor of 370, whereas the one in Scheme 2 has an *E*-factor of 52. No solvent recycle has been considered. The latter would, of course,

(17) Simpson, R. D., unpublished observations.

(18) Shu, C., unpublished observations.

(19) Sheldon, R. *Green Chem.* **2007**, 9, 1273.

improve the picture for both processes. We have not yet evaluated the suitability and efficiency of such recycles. In conclusion, the second-generation RCM process improves the greenness of the process by about 1 order of magnitude.

Conclusions

We have demonstrated elsewhere¹⁶ that the RCM macrocyclization reaction can be made more practical when the *EM(therm)* is optimized with respect to diene perimeter substitution, which affects the ring strain of the product. In this contribution, we have presented the practical outcomes of such optimization. The main benefits are increased throughput and decreased solvent consumption, thus making the RCM reaction much greener and operative under normal plant conditions in a convenient batch mode at low catalyst loads. We further suggest that parameters such as *kinetic* and *thermodynamic effective molarities* (*EM(kin)* and *EM(therm)*, respectively) are extremely useful concepts in analyzing intramolecular processes and should be calculated and reported more systematically, in order for the reader to evaluate the efficiency of a given cyclization. We hope that these concepts can be extended to other RCM macrocyclizations.

Experimental Section

Materials and Methods. All reactions were performed in vacuum-dried jacketed reactors, unless otherwise indicated. All reagents and solvents were purchased from commercial sources and used as received, unless otherwise indicated. Compound **2** was synthesized according to a literature procedure. Conversion was determined by HPLC using UV area % values. All quantifications were performed by HPLC assay using a predetermined calibration line of absorption/concentration vs an external reference standard. All compounds disclosed here have been previously described.²⁰

Synthesis of Diene 6. To a reactor containing **2** (100 g, 150 mmol, 1.0 equiv), DMAP (5.50 g, 45 mmol, 0.3 equiv), and ethyl acetate (600 mL) at 0 °C was added Boc₂O (45.6 g, 210

mmol, 1.4 equiv) slowly over 30 min. The reaction was allowed to reach rt over 1 h and stirred at rt for another 2 h. HPLC showed complete reaction (>99% conversion). The reaction mixture was washed with 0.1 M HCl (200 mL) and H₂O (200 mL), concentrated to minimum volume, diluted with toluene, and distilled under reduced pressure (total reaction volume = 1.42 L). An HPLC quantitative assay showed formation of 110 g of **6** (yield of 95%, concentration of 0.10 M).

Metathesis of 6. The toluene solution of diene **6** from the previous step was refluxed at 110 °C under air for 30 min to remove the oxygen, and then treated with a toluene (5 mL) solution of **5** (100 mg, 0.15 mmol, 0.001 equiv) slowly over 30 min at 110 °C. The conversion and yield were determined by quantitative HPLC with predetermined absorption/concentration curves vs a reference standard. After the reaction was complete (>99.9%; typically <30 min), the vessel was cooled to 60 °C, and 2-mercaptosuccinic acid (1.16 g, 7.5 mmol, 0.05 equiv) was added. The suspension was stirred at 60 °C for 2 h. The mixture was cooled to rt and extracted with 5% NaHCO₃ (200 mL) and water (200 mL) to afford a toluene solution of **7**. HPLC quantitative assay of the organic phase showed 100 g of **7** (95%).

RCM Product 3. To the toluene solution of **7** obtained above (1.4 L, 100 g by quantitative HPLC assay, 0.135 mol, 1.0 equiv) was added benzenesulfonic acid (42.8 g, 0.27 mol, 2.0 equiv). The mixture was heated to 75 °C. After 2 h, HPLC showed complete reaction (>99.5%). The solution was washed with saturated NaHCO₃ (300 mL) followed by H₂O (300 mL) to afford a toluene solution of **3**.

HPLC quantitative assay showed 82 g of **3** (yield of 95%).

This material was further processed as previously described.²

Acknowledgment

We thank Scott Denmark, Erick Carreira, and Peter Wipf, for useful discussions on the problem of low EM, and Donna Blackmond, for valuable mechanistic suggestions.

Received for review September 11, 2008.

OP800225F

(20) See Experimental Section in ref 2 and Supporting Information in ref 16.