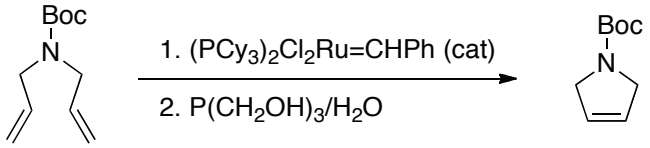
DOI:10.15227/orgsyn.089.0170

Discussion Addendum for: Ring-closing Metathesis Synthesis of *N*-Boc-3-pyrroline



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Original article: O'Leary, D. J.; Ferguson, M. L.; Grubbs, R. H. *Org. Synth.* **2003**, *80*, 85.

The olefin metathesis reaction has emerged as a widely used transformation in organic chemistry and materials science.[4] In keeping with the theme of our original article, this discussion addendum provides an overview of current large-scale ring-closing metathesis (RCM) applications of the Ru-based family of metathesis catalysts, the structures of which are shown in Figure 1.[5]

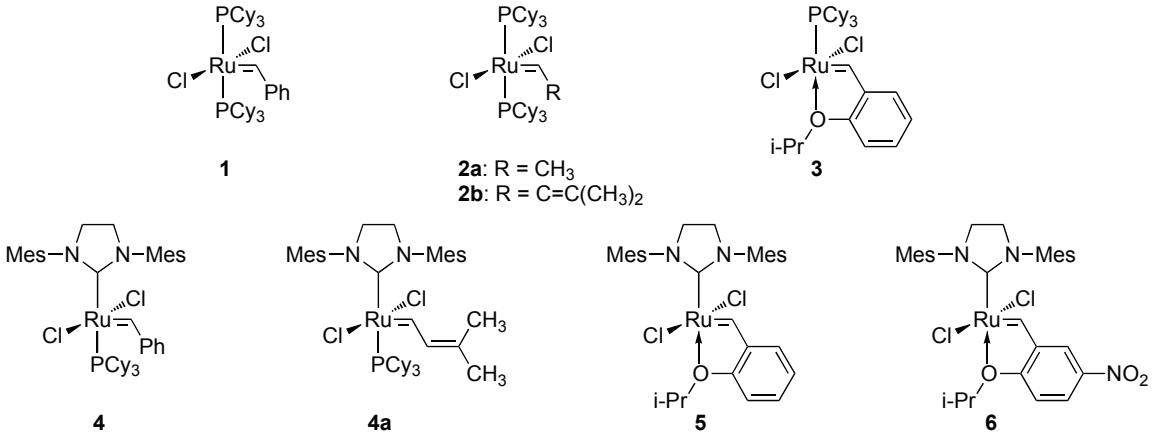

Figure 1. Commonly Used Olefin Metathesis Catalysts.

In our 2003 report for the preparation of *N*-Boc-3-pyrroline, we utilized 0.5 mol% of catalyst **1** in a refluxing (2.5 h) 0.4 M solution of *N*-Boc-diallylamine in CH_2Cl_2. The report also described an extractive method for removing Ru-derived catalytic species/impurities using the water-soluble

Org. Synth. **2012**, *89*, 170-182
Published on the Web 10/18/2011

$P(CH_2OH)_3$, readily prepared from a commercially available fire-retardant aqueous formulation of $P(CH_2OH)_4Cl$. Following Kugelrohr distillation, this method reliably provided ca. 30 g of crystalline *N*-Boc-3-pyrroline in 90-94% isolated yield. Concurrent with the development of our procedure, Helmchen reported[6] a 100 g preparation of Boc-3-pyrroline using 0.1 mol% of ethylidene **2a** in a room-temperature (15 h) 0.57 M CH_2Cl_2 solution of *N*-Boc-diallylamine. Catalyst deactivation or removal procedures were not taken and the product was isolated in 98% yield after vacuum distillation. This transformation has also been reported to proceed in 87% yield when run neat and with catalyst **5** loading as low as 500 ppm.[7]

Since the time of our report, however, RCM has rapidly matured and has been used to prepare kilogram quantities of structurally complex macrocyclic synthetic intermediates within the pharmaceutical industry. Optimizing a large-scale RCM process requires that several conditions be studied, namely, substrate type and functional group compatibility, catalyst selection, and solvent/temperature/time requirements. In many applications, removal of residual ruthenium is also a concern. In this Discussion Addendum, large-scale industrial RCM processes will be used to frame the relevant issues. These examples include Boehringer-Ingelheim's Hepatitis C protease inhibitor BILN-2061, GlaxoSmithKline's cathepsin K inhibitor SB-462795, and RCM-tethered macrocyclic peptides. The discussion will conclude with an overview of developments in the area of ruthenium removal.

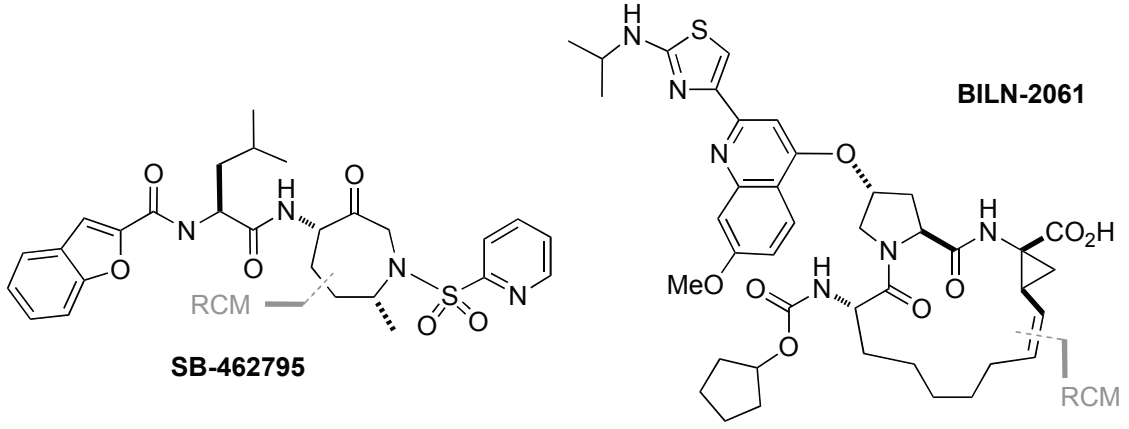

Figure 2. SB-462795 and BILN-2061 and their RCM disconnections.

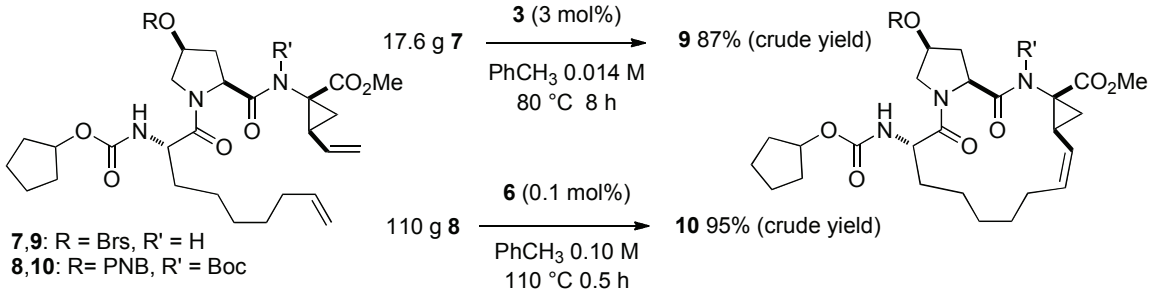

Figure 3. Comparison of the 2006 and 2009 RCM processes for construction of the BILN-2061 peptide macrocycle.

Boehringer-Ingelheim's 2006 disclosure[8-13] of a large-scale RCM approach to the hepatitis C viral protease inhibitor BILN-2061 provides an interesting case study for those contemplating a large-scale metathesis process. The BILN-2061 metathesis substrate is an unnatural tripeptide-derived diene, which closes to a (*Z*)-olefin-containing 15-membered ring. Two of the conformation-restraining amide bonds are endocyclic, and two additional macrocyclic torsional degrees of freedom are fixed by the presence of the five-membered proline ring and an endocyclic *trans*-cyclopropane. The optimized 2006 RCM process (Figure 3) was scaled up to produce >400 kg of cyclized product.[10] Three years later, the BI group reported a higher-yielding and order-of-magnitude greener procedure, one which dramatically reduced the amount of time, solvent, and catalyst loading.[13]

The first efforts to construct the BILN-2061 macrocycle used catalyst **1**.[9] These trials were met with problematic epimerization at the β-carbon of the vinylcyclopropyl amino acid residue (Figure 4). When a mono-phosphine catalyst such as **3** was used, the epimerization reaction was not observed. Analysis of model systems revealed that the rearrangement was facile when the bis-phosphine catalyst **1** was used. The rearrangement could also be promoted by adding one equivalent of phosphine to a mixture of catalyst **3** and the model system (Figure 4). The origin of this rearrangement was suggested to occur via the intermediacy of bis-phosphino or amino phosphino ruthenacyclopentene intermediates.[9,11] Further studies revealed that the site of catalyst initiation in the macrocycle precursor depended upon the substitution of the aminocylopropylcarboxylic acid nitrogen atom: acyl-type substituents such as *N*-Boc shifted the initiation to the rearrangement-stable nonenoic residue (Figure 4).[12] Before this detail was known, the reasonably efficient 2006 process using diene **7** and catalyst **3** was plagued

by problematic batch inconsistencies. Traces of morpholine (<20 ppm) in the toluene solvent were shown to be responsible for substrate isomerization and catalyst inhibition, with the former arising from bis-ligated Ru species of the type discussed earlier. These problems were alleviated by acid-washing the solvent prior to the metathesis reaction.

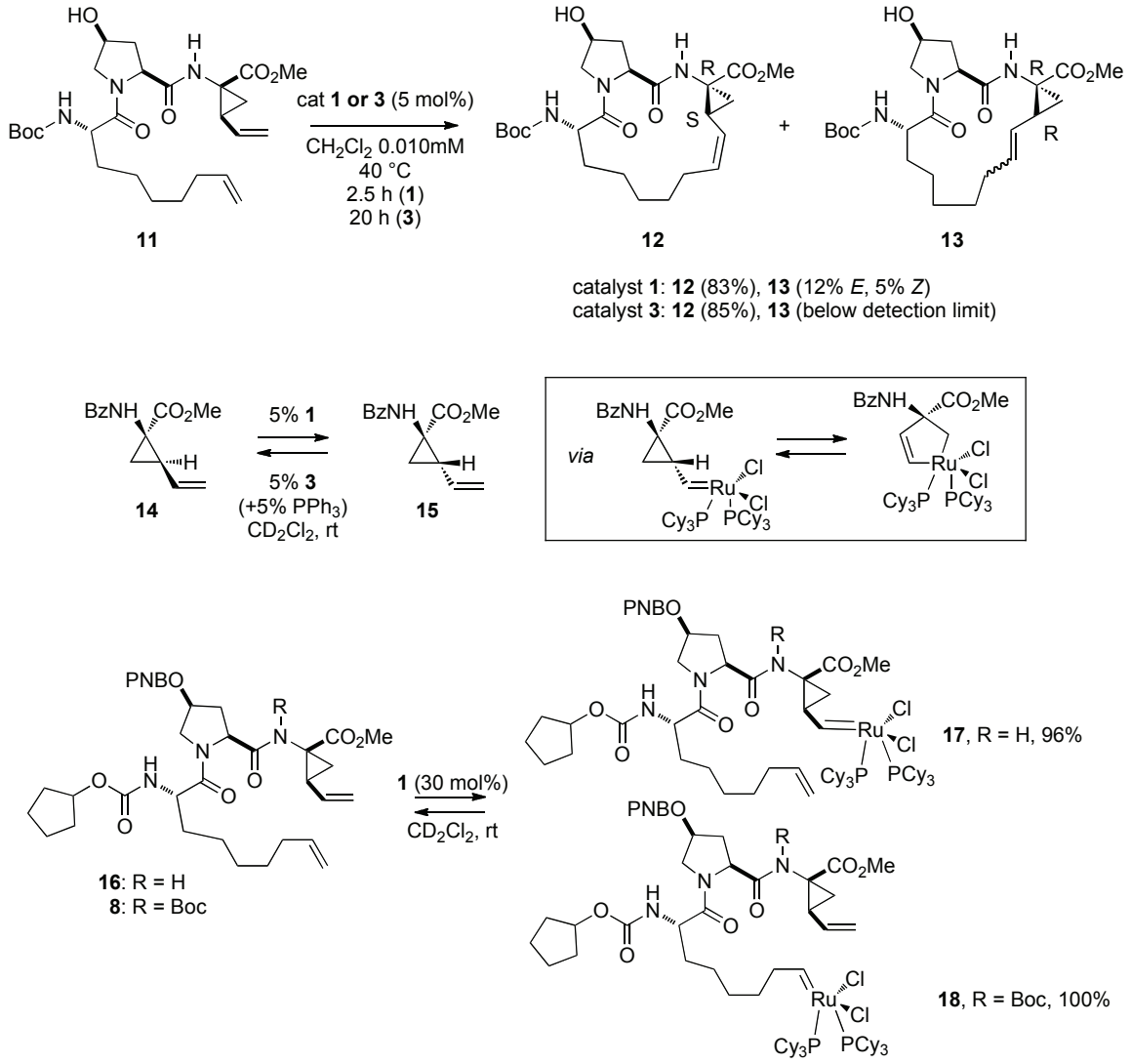

Figure 4. Catalyst-specific epimerization observed in RCM reactions of BILN-2061 substrates, suggested ruthenacyclopentene intermediates, and the effect of *N*-Boc substitution on site of catalyst initiation.

The aminocyclopropyl metathesis rearrangement encountered by the BI group was unexpected and highly substrate-specific. The most common side reactions in metathesis processes are alkene isomerization reactions.[14] Because of the reversible nature of olefin metathesis, isomerization can alter unreacted starting material or products. It can be problematic in reactions

where the catalyst is stressed by temperature or time or in some product purifications involving direct distillation from Ru-containing pot residues.[15] For example, ring closure of diallyl ether **19** to **20** with catalyst **4** (Figure 5) is a rapid reaction, but significant product isomerization to vinyl ether **21** can occur at extended reaction times. Rearrangement is thought to arise from Ru-H species; it can be suppressed by solvent selection[16,17] or by additives such as tricyclohexylphosphine oxide,[18] acetic acid or 1,4-benzoquinones,[19] phenylphosphoric acid,[20] chlorocatechol borane,[21] or Cy_2BCl.[22]

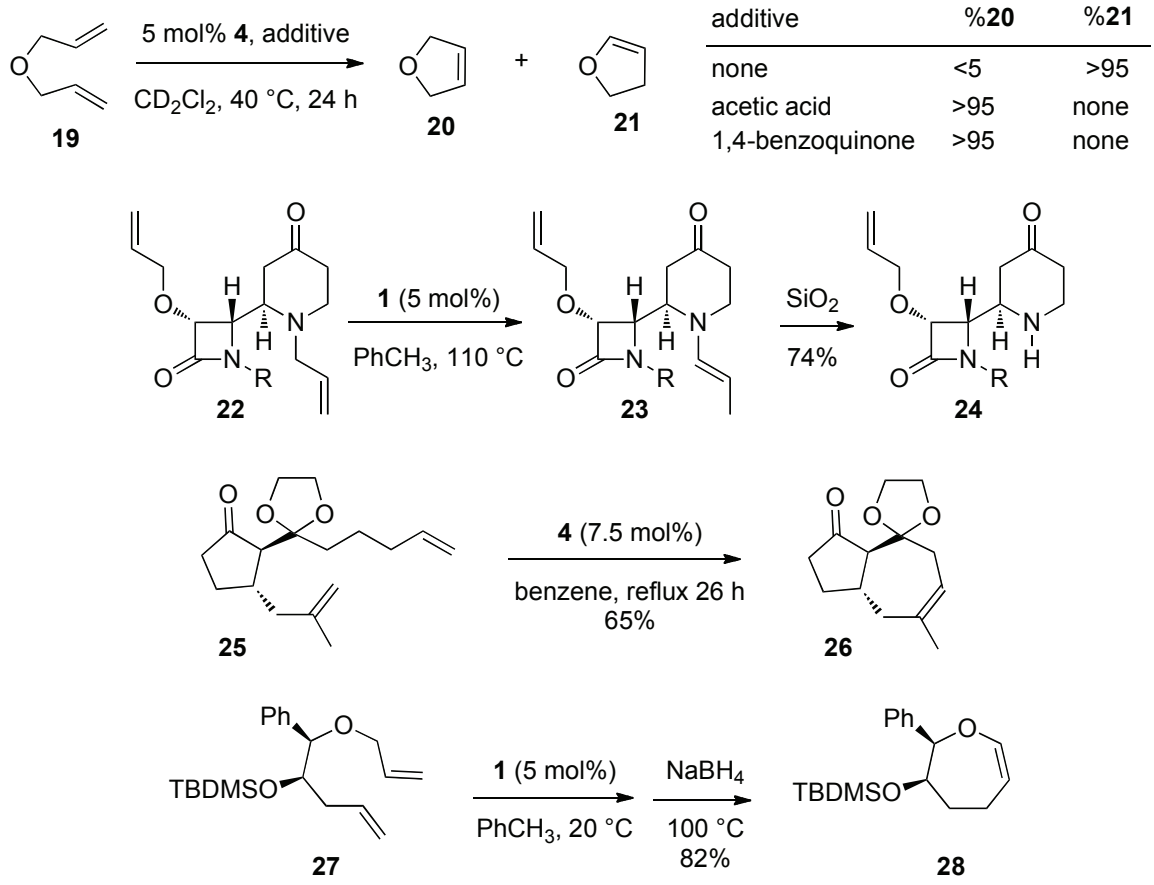

Figure 5. Select rearrangements observed in Ru-catalyzed metathesis reactions.

Rearrangement chemistry is the desired outcome in some applications. For example, Ru-catalyzed rearrangements are used for selective *O*-allyl[23] and *N*-allyl[24] deprotections. The latter, an allylamine to enamine transformation, was observed in lactam-piperidone **22** when treated with catalyst **1** in refluxing toluene (Figure 5). Olefin migration can also occur in hydrocarbon chains. For example, attempts to ring-close cyclopentanone-derived diene **25** with catalyst **4** did not return the [9.5.0] ring system.[25] Instead, the monosubstituted double bond was found to migrate at a rate

faster than 9- or 8-membered ring closure, leading to exclusive generation of the [7.5.0] product **26**. Another strategy purposefully adds a hydride source to promote rearrangement after ring closure. For example, enol ether **28** is formed in 82% yield by first performing an RCM reaction on diene **27** to form the seven-membered ring product, which is then isomerized in a second step involving addition of $NaBH_4$ to the Ru-containing reaction mixture.[26]

Non-metathesis side reactions have also been reported in the context of Ru-promoted metathesis reactions. Hoye and Zhao have reported fragmentation reactions in RCM substrates containing secondary allylic alcohols; in sluggish metathesis reactions these systems can fragment to the methyl ketone.[27] Kharasch additions of $CHCl_3$ to olefins, as catalyzed by **1** at 65 °C, are also known.[28]

Although the problem of isomerization was largely solved and the RCM reaction was utilized at kg scale, the 2006 BILN-2061 process suffered from several other drawbacks. The first of these was the dilute substrate concentration (0.014 M), which required excessive solvent consumption. A study of the macrocyclization behavior of different acyclic dienes and dimeric intermediates revealed a 27-fold improvement in the effective molarity (EM) of cyclization, which translated to a 0.2 M RCM process.[12] A significant shortening of the reaction time was also realized. As mentioned earlier, an *N*-Boc group at the vinylcyclopropane amide residue was found to productively shift the site of catalyst initiation and led to a more facile and robust ring-closing reaction. While adding protection-deprotection steps, the improved 2009 process could therefore be run at higher concentrations and temperatures and with lower catalyst loadings (0.1 mol% **6** vs. 3 mol% **3**). Each of these factors contributed in a positive manner to the EM of cyclization. Although the details will not be considered here, one of the principle steps in optimizing the BILN-2061 macrocyclization was defining conditions which (i) minimized formation of dimeric compounds arising from acyclic diene metathesis (ADMET) processes,[29,30] and (ii) one in which these oligomers could be equilibrated to product.

The BILN-2061 RCM reaction optimization is best viewed in terms of green chemistry considerations. The 2009 process[13] represented a significant savings in terms of time, energy, and material. The RCM step was reduced to minutes instead of hours. Scrupulous degassing and solvent purification was necessary for the 2006 process, whereas the new process

only required a brief degassing boil-out. The 2006 RCM process required as much as 150,000 L solvent per metric ton of diene, whereas the 2009 process reduced this amount to 7,500 L/MT. Because catalyst loading was greatly reduced in the 2009 process, Ru removal was likewise less resource-intensive. The 2006 process used excess 2-mercaptonicotinic acid (2 kg/1 kg diene) and aqueous bicarbonate to remove a portion of the soluble ruthenium, with subsequent silica gel and charcoal filtrations necessary to reduce Ru levels to 10 ppm in the active pharmaceutical ingredient (API). In contrast, the 2009 process used 50-fold less 2-mercaptonicotinic acid and did not utilize silica or charcoal filtrations. The Sheldon *E*-factor,[31] which is the ratio of waste mass to product mass, improved to 52 (computed for the 2009 Boc protection/RCM/Boc deprotection process) from 370 (computed for the 2006 RCM process).

Large-scale RCM was also used in GlaxoSmithKline's 2009 synthesis of the seven-membered azapane ring in cathepsin K inhibitor SB-462795 (Figure 6).[32] The metathesis step in this synthesis also required multiple optimization attempts. Initial efforts using diene **29** and catalyst **5** were stymied by the need for high catalyst loadings (5-10 mol%). Substrate-catalyst coordination was suspected to be the source of the problem, but reactions using $Ti(O\text{-}iPr)_4$ as a chelation inhibitor[33,34] were not successful due to substrate/product decomposition. Additionally, large residual Ru levels were deemed a safety hazard with downstream steps involving H_2O_2 (for chiral auxiliary removal) and an acyl azide (for nitrogen insertion via Curtius rearrangement). To complicate matters, the β-hydroxy ketone RCM product **30** decomposed via a retro-aldol reaction when the basic $P(CH_2OH)_3$/NaOH ruthenium removal procedure was employed. These setbacks led to the design of *N*/*O*-protected RCM precursor **31**. This substrate closed with lower catalyst loadings (1-2 mol%) but gave capricious levels of olefin migration when attempted with crude product coming out of a Curtius rearrangement employing hydrazine and *t*-butyl nitrite/HCl (Figure 6). Solvent swaps or isomerization inhibitors (acetic acid, styrene, or Cy_3PO) did not suppress the isomerization. The RCM process was made tractable by purifying precursor diene **31** as the HCl salt. When converted to the free base, it reliably provided **32** as a crystalline product in 90% yield using 1-2 mol% of catalyst **5**. A basic cysteine wash was used to remove Ru; this thiol-based approach was utilized after it was discovered that (i) formaldehyde, generated during *in situ* generation of $P(CH_2OH)_3$, added to

the carbamate nitrogen of product **32** to form hydroxymethylated **35**, and (ii) residual P reagents proved problematic for subsequent olefin hydrogenation.

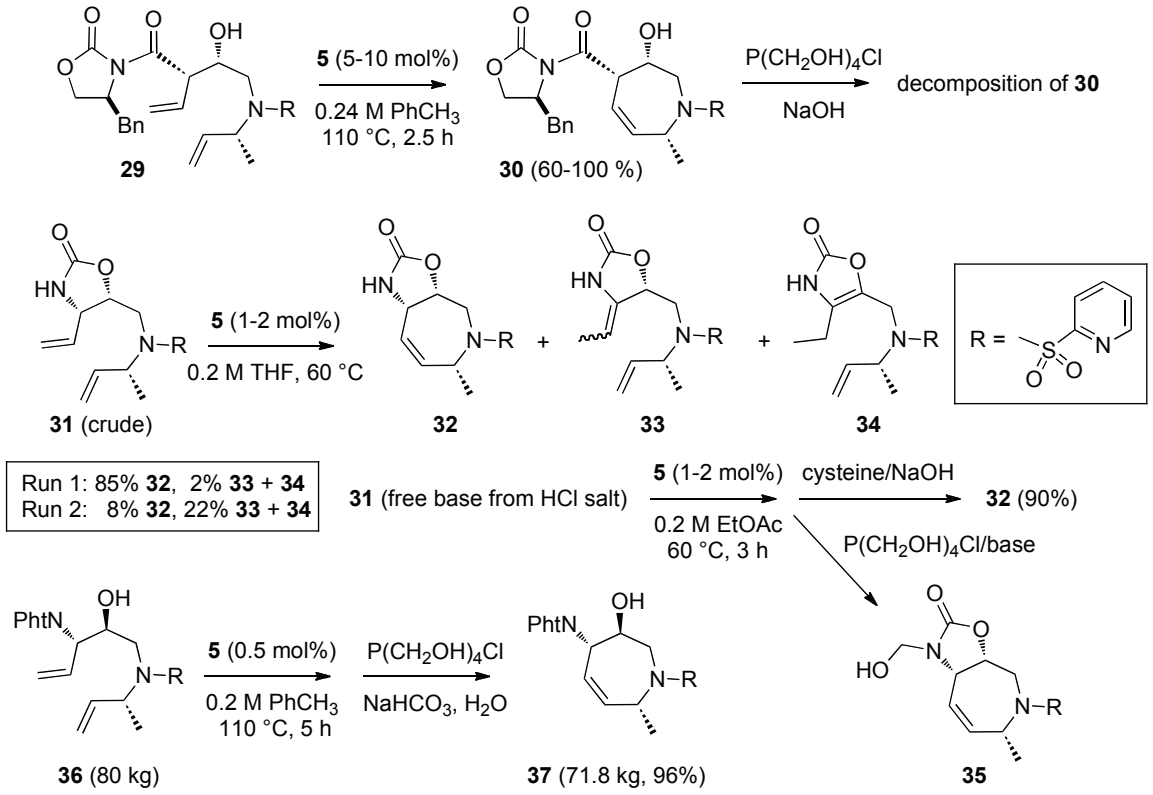

Figure 6. Selected RCM reactions used in the synthesis of SB-462795.

An alternative route to SB-462795 employed RCM precursor **36** containing a phthalimide-protected *trans*-1,2-aminoalcohol moiety. In comparison with diene **31**, this substrate offered a significant improvement in the RCM process, although here again significant optimization efforts were directed at identifying and minimizing trace impurity catalyst inhibitors.[35] Highly purified material could be closed in quantitative yields with as little as 0.25-0.5 mol% catalyst **5**. Olefin migration was not observed, even in reactions using crude material. When conducted in toluene, the product readily crystallized and provided material with low residual Ru content after the slurry was washed with $P(CH_2OH)_3/NaHCO_3$.[36] According to the published account, both approaches were amenable to large-scale manufacturing and the *trans*-1,2-aminoalcohol route was used to provide over 200 kg of SB-462795.

Other publicly disclosed pharmaceutical applications of RCM involve its use to conformationally constrain[37,38,39] and alter the metabolic profile of helical peptides by forming peptide macrocycles.[40] Scale-up aspects of this

chemistry remain proprietary, but much of the exploratory work has been on solid support,[41] with microwave-assisted RCM macrocyclizations.[42,43] Many examples undergo efficient RCM reactions, and in a solution-phase study of minimal RCM constraints in 3_{10}-helical peptides, it was found that high *E*-selectivity could be realized in an unoptimized 18-membered macrocyclization (**38**→**39**, Figure 7) catalyzed by 5-7 mol% **4** in refluxing dichloromethane.[44]

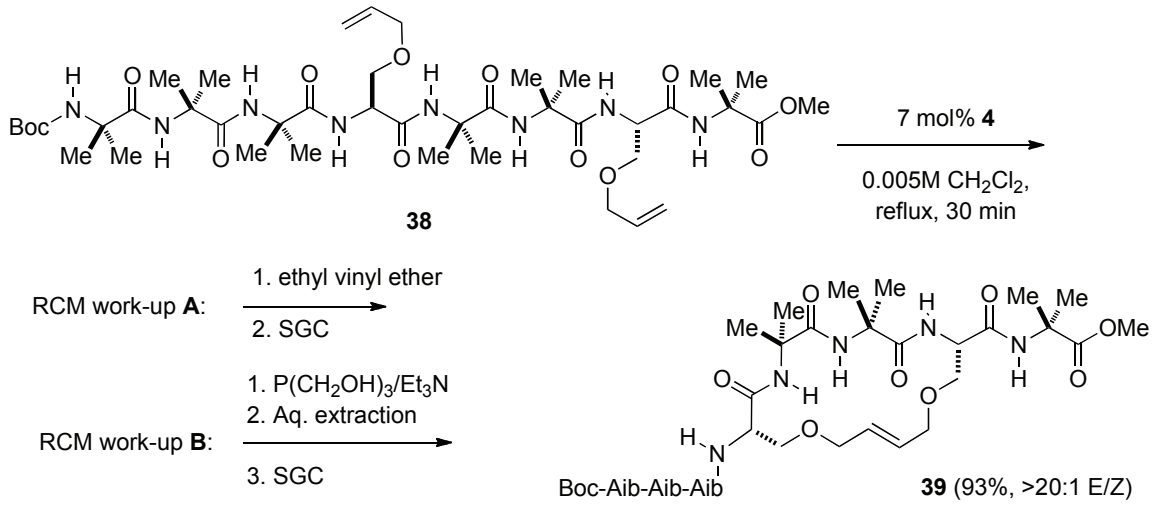

Figure 7. Representative helical peptide macrocyclization and work-up procedures.

The reactions shown in Figure 7 highlight two additional methods for post-RCM reaction processing: (i) the use of ethyl vinyl ether as a Ru catalyst poison (by formation of the stable Fischer carbene) prior to evaporation and silica gel chromatography (SGC), and (ii) a Ru removal procedure utilizing the commercially available, albeit expensive, tris(hydroxymethyl)-phosphine.[15,45]

The BI and GSK investigations show that large-scale RCM reactions can require significant optimization. It is expected that these paths will shorten as more applications are reported. These two examples reveal that at-scale process applications can utilize as little as 0.1-0.5 mol % Ru catalyst, which minimizes the waste stream and is in accord with sustainable green chemistry practice. Sustainable concepts in olefin metathesis have been reviewed elsewhere.[46] Pharmaceutical applications require that the API contain <10 ppm metal, and the two industrial examples discussed here utilized water-solubilizing procedures using 2-mercaptonicotinic acid,[13] cysteine,[32] or tris(hydroxy-methyl)phosphine.[36] Downstream processes such

as hydrogenation over charcoal-based catalysts can also be used to reduce Ru levels to <1 ppm.[35] Other approaches to remove Ru include amine-functionalized mesoporous silicates,[47] polar isocyanides,[48] lead tetraacetate,[49] activated carbon/silica gel,[50] and DMSO or triphenylphosphine oxide treatment of crude reaction mixtures.[51] DMSO/DMF mixtures have been used to remove colored Ru impurities in solid-phase RCM applications.[52] A recent report describes the use of 15% aqueous hydrogen peroxide as an efficient Ru removal agent; this process also oxidizes residual phosphine and carbene ligands to more polar entities, thus easing purification in some cases.[53]

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Richard L. Pederson was born in Albert Lea, Minnesota in November 1962. In 1990 he earned his Ph.D (with Chi-Huey Wong) from Texas A&M University and later that year joined Bend Research Inc, Bend OR, where in 1997 he and Professor Grubbs patented the production of insect pheromones using ruthenium metathesis. In January 2000, he joined Materia Inc., Pasadena CA, to start up the Fine Chemicals group and currently is the VP of R&D. His research interests include using metathesis to develop new products from renewable seed oils and the synthesis of insect pheromones. He is an inventor on 34 patents and patent applications.

Robert H. Grubbs was born in rural Kentucky on 27 February 1942. He earned his B.S. and M.S. degrees in chemistry in 1963 and 1965 from the University of Florida (working with Merle Battiste) and his Ph.D. (with Ron Breslow) from Columbia University in 1968. Following an NIH post-doctoral fellowship (with Jim Collman) at Stanford University, he joined the faculty at Michigan State University in 1969 and moved to the California Institute of Technology in 1978, where he is presently Victor and Elizabeth Atkins Professor of Chemistry. His research interests include mechanisms of metal-catalyzed reactions, polymer synthesis, and catalysis in organic synthesis.