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## BOND DISCONNECTIONS ENABLED BY OLEFIN METATHESIS

Dedicated to the memory of Prof. Robert H. Grubbs, 1942-2021

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# BEYOND MACROCYCLES: BOND DISCONNECTIONS ENABLED BY OLEFIN METATHESIS

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PEER REVIEWED

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ABSTRACT

Olefin metathesis is a powerful tool that enables unique bond disconnection strategies via carbon-carbon bonds. It has been employed in commercial scale synthesis across multiple industries and in multiple reaction types including ring-closing, cross, and ring-opening metathesis. Among these, macrocyclization by ring-closing metathesis stands out as a hallmark of the technology. However, ring-closing metathesis can also serve as a highly efficient entry to smaller rings. In this article, we highlight retrosynthetic strategies toward 5- and 6-membered nitrogen heterocycles, including in the context of a commercial drug manufacturing process.

**KEYWORDS:**
- Olefin metathesis
- Alkene metathesis
- Ring-closing metathesis
- Heterocycle synthesis
- Retrosynthesis
- Peer Reviewed

In the fifty years from its discovery to the 2005 Nobel Prize awarded to Yves Chauvin, Richard Schrock, and Robert Grubbs, olefin metathesis evolved from a curious oddity to a reliable tool for chemical synthesis and polymerization. These advances were made possible by tireless investigation of mechanism, (1) the development of well-defined catalysts, (2) and the exploration of those catalysts with a multitude of potential substrates (3).

Since 2005, this work has blossomed into new commercial applications in materials science,(4) biorenewable chemistry, (5) and pharmaceuticals (6). Now, another generation of commercial-scale applications are currently in development, from pheromones for crop protection (7) to tough materials for 3D-printing (8) to structural paints for automotive coating (9).

Ruthenium-based catalysts in particular have found wide use in organic synthesis owing to their stability and functional group tolerance (Fig. 1) (10). First generation catalysts such as Grubbs Catalyst® M102 (**Ru-1**) paved the way for further development, while the two major families of second generation catalysts, Grubbs-type (**Ru-2**) and Hoveyda-type (**Ru-3**) have become workhorses in both developmental and commercial applications.

In pharmaceutical synthesis, ring-closing metathesis (RCM) remains a mainstay for macrocyclizations of complex intermediates (11). However, olefin metathesis can offer more efficient pathways to a number of other structural motifs. For instance, RCM can be a highly efficient way to disconnect 5-, 6-, and 7-membered heterocycles such as pyrrolidines, piperidines and azapanes.

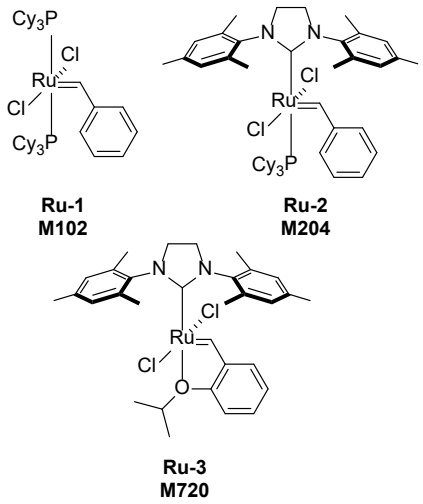
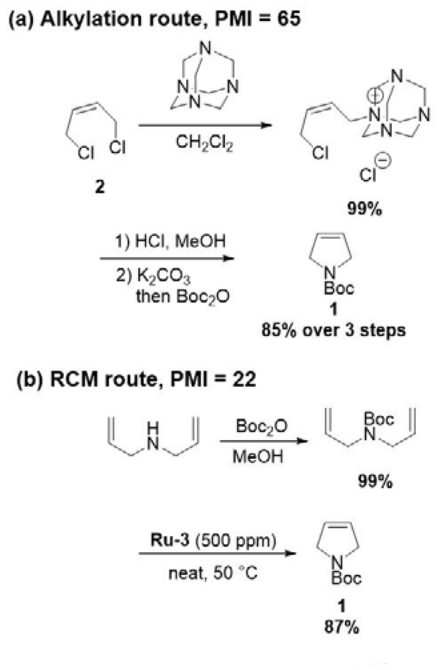



**Figure 1.** Ru-based metathesis catalysts.

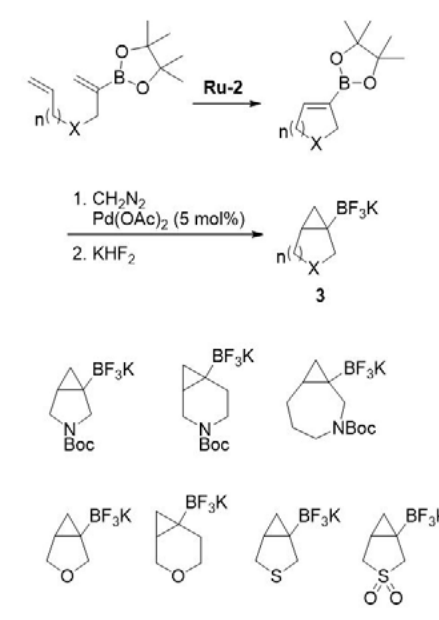
## RCM TO FORM 5-MEMBERED RINGS

In 2019, we published a case study comparing traditional versus metathesis-enabled routes to *N*-Boc-pyrroline (**1**) (12). Whereas the traditional *N*-alkylation of ammonia surrogate hexamethylene tetraamine requires 3 steps from *cis*-1,4-dichloro-2-butene (**2**) with an overall PMI of 65, Boc-protection of *N,N*-diallylamine followed by RCM proceeds in only 2 steps from with a PMI of 22 (Scheme 1). Only 0.05% loading of Grubbs Catalyst® M720 (**Ru-3**) is required for complete conversion. Thus, the target compound can be delivered more efficiently, at lower cost and reduced environmental impact by leveraging a bond disconnection at the carbon-carbon double bond.

More recently, a similar RCM approach to deliver *N*-, *O*- and *S*-heterocycles bearing vinylboronates (**3**) was reported (Scheme 2) (13). This method is based on an initial report from Renaud and Ouellet at Merck Frosst using 1st-Gen catalyst **Ru-1**. (14) Coworkers at Enamine modified these conditions by using 2nd-generation catalysts **Ru-2** and **Ru-3**. The resulting vinylboronate esters were then converted to highly complex bicyclic cyclopropane structures bearing an trifluoroborate which could serve as a $Csp^3$ coupling partner for further functionalization. Hence, the RCM strategy offers flexibility to synthesize a broad library of building blocks that can be incorporated into lead optimization studies.




**Scheme 1.** Comparative approaches to N-Boc-3-pyrroline.

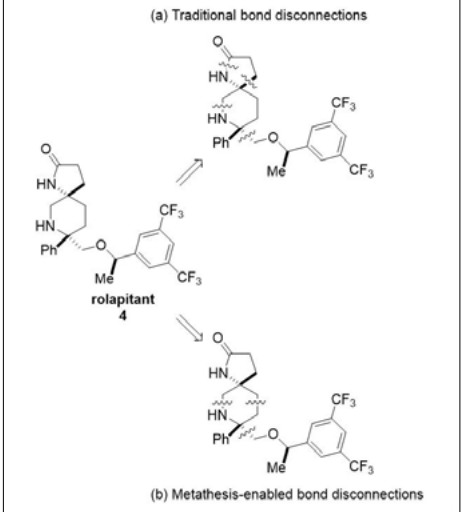



**Scheme 2.** Ring-closing metathesis of vinylboronates to form highly saturated heterocycles

**Case study in 6-membered RCM - Rolapitant**

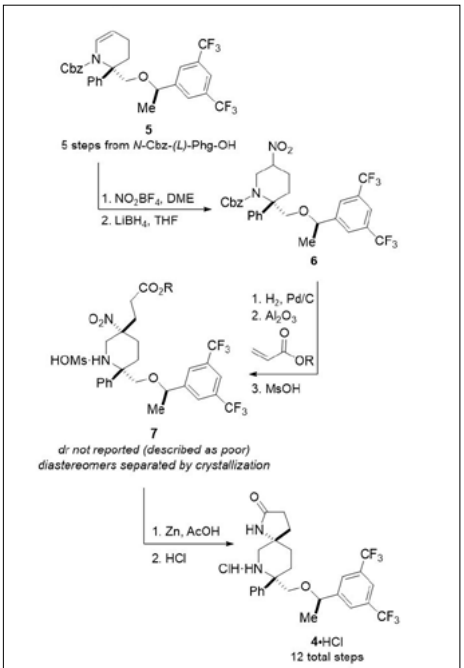
Piperidines are also excellent candidates for a potential metathesis bond disconnection. The core structure of rolapitant (**4**), an anti-emetic used to treat chemotherapy-induced nausea and vomiting, is a densely functionalized spirocycle including a piperidine ring with two tetrasubstituted stereocenters. It was first discovered and developed at Schering-Plough and later out-licensed prior to commercial launch in 2015.

Two distinct bond disconnection strategies were employed at different stages of development (Scheme 3). The first strategy (a) relied on a fairly linear sequence of steps building the piperidine ring followed by addition of the pyrrolidinone. At later stages, a more convergent strategy uniting the top and bottom fragments using a reductive amination and ring-closing metathesis sequence was adopted, leading to an improved process.




**Scheme 3.** Comparative approaches to spirocyclic API rolapitant

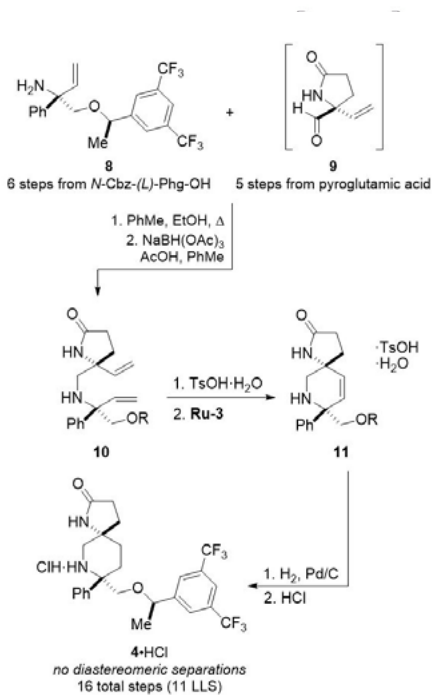
In the early development route, the piperidine ring was assembled in 5 steps from protected phenylglycine as an enantioenriched starting material (Scheme 4) (15). The enamine present in **5** was converted to nitroalkane **6** in order to activate the correct position for nucleophilic attack to an acrylate, installing the additional carbons needed to form the fused pyrrolidone. However, this conjugate addition step proceeded in poor diastereoselectivity, leading to a mixture of intermediate **7** which was purified by crystallization as the mesylate salt. Though the desired diastereomer could be obtained by this sequence, a significant hit in yield was sustained at a late stage in the synthesis. From **6**, reduction of the nitro group led to spontaneous ring closure of the pyrrolidone, and salt formation provided the API **4·HCl** in 12 steps. Though this sequence was fairly short, the poor selectivity led the team at Schering-Plough to re-examine their options.




**Scheme 4.** Early development route to rolapitant

An improved route was devised, splitting the molecule essentially in half via reductive amination and ring-closing metathesis disconnections (Scheme 3b) (16). This allowed each tetrasubstituted stereocenter to be established independently before stitching together the piperidine core, solving the selectivity issue in the previous route and giving a significant improvement in overall throughput.

In the 3rd-generation route, allylic amine **8** is prepared in 5 steps from phenylglycine, again establishing that stereocenter from a chiral pool starting material (Scheme 5). The other tetrasubstituted stereocenter is also derived from an available enantioenriched starting material, pyroglutamic acid, which is elaborated to aldehyde **9** in 5 steps.




**Scheme 5.** Metathesis-enabled 3rd-generation route to rolapitant

Though these contribute more to the total step count, the steps to form these key intermediates are performed in parallel, giving a convergent and, more importantly, selective method to form each chiral fragment. These intermediates are united under standard reductive amination conditions to form RCM precursor **10**. The unprotected secondary amine is masked as the *p*-toluenesulfonic acid salt and then treated with **Ru-3** to close the piperidine. Hydrogenation of the resultant alkene **11** followed by salt formation gives the API as the hydrochloride salt in 16 total steps.

Although there are more total steps, the RCM route is superior due to the improvement in overall yield. In the original route, a significant portion of the mid-stage intermediate **6** was consumed unproductively in a non-selective conjugate addition step. In the RCM route, each stereocenter is set independently, so there is no issue of selectivity at any stage, providing an overall more efficient process.

## CONCLUSION

Olefin metathesis continues to expand its reach into new areas, opening completely orthogonal synthetic pathways relative to traditional chemistry. This in turn enables the design of streamlined synthetic routes incorporating low-cost, and in some cases renewable raw materials. As chemists are tasked with manufacturing more and more complex and target molecules, ring-closing and cross metathesis should be considered as potential solutions, even at manufacturing scale.

In the past, some process development teams have gone to seemingly great lengths to avoid the technology. Many of the barriers that existed previously are now gone. Several key patents have expired, and those that remain are held by companies with straightforward, catalyst-price-only business models. Questions about commercial supply of the Ru-based catalysts have been answered as the catalysts are produced on metric ton scale annually.

It is up to the chemists designing new routes to determine what fits best for their target molecule, but doubts about the viability of metathesis as a commercial solution should not stand in the way. As more and more complex molecules are targeted, olefin metathesis should stand out for its potential to drastically change the overall synthetic strategy, leading to potential improvements in all relevant process metrics: yield, selectivity, PMI, and of course, overall cost efficiency.

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## ABOUT THE AUTHOR

***Philip Wheeler*** *is a native of California and earned a B. A. in chemistry at UC Santa Cruz in 2004. He worked at Amgen in Thousand Oaks as an associate in process chemistry before starting his Ph. D. studies in 2007 at Colorado State University in the laboratory of Tom Rovis. After completing his Ph. D. in 2013, Philip joined Sigma Aldrich in Milwaukee as a product manager for their catalysis portfolio. In 2015, he moved back to California to join Materia as a business development manager and joined Umicore in 2018 as part of their acquisition of Materia's Grubbs Catalyst® Portfolio. Philip is enthusiastic about catalysis and connecting clients with the best solution for their process.*