Industrial Olefin Metathesis

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Olefin Metathesis at the Dawn of Implementation in Pharmaceutical and Specialty-Chemicals Manufacturing

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industrial chemistry · large-scale synthesis · olefin metathesis · pharmaceutical chemistry · renewable feedstocks

The recent uptake of molecular metathesis catalysts in specialty-chemicals and pharmaceutical manufacturing is reviewed.

1. Introduction

The uptake of olefin metathesis in pharmaceutical and specialty-chemicals manufacturing, anticipated for decades, is a recent reality. Metathesis has been a key industrial process since the 1950s, but applications to functional-group-rich targets were long precluded by catalyst sensitivity. The advent of readily handled, comparatively robust ruthenium catalysts, coupled with the discovery of the synthetic potential of ring-closing metathesis (RCM), brought metathesis methodologies to the attention of organic chemists. Applications to the synthesis of complex, biologically active organic molecules exploded.[1] Cross metathesis (CM) benefited in parallel, particularly as the capacity to transform unsaturated seed oils into specialty chemicals gained impetus from new markets for sustainable products.[2,3] Given these advances, it is perhaps surprising the first industrial processes are only now emerging. Examined in this Minireview are some of the challenges involved, and an overview of recent industrial advances beyond the discovery stage that illustrate both the breadth of opportunities, and issues in implementation.

1.1. Molecular Metathesis Catalysts: The Research Context

Hundreds of metathesis catalysts have now been developed, of which more than 60 are now commercially available.[4] Particularly prominent are examples based on ruthenium and the Group 6 metals molybdenum and tungsten. While the majority have been explored almost solely in the research context, Figure 1 highlights ruthenium catalysts known to have been adopted in industrial processes or scale-up campaigns (see Sections 2 and 3). Most of the catalysts in confirmed use are second-generation derivatives containing an N-heterocyclic carbene (NHC) ligand, which significantly expanded catalyst scope and performance.

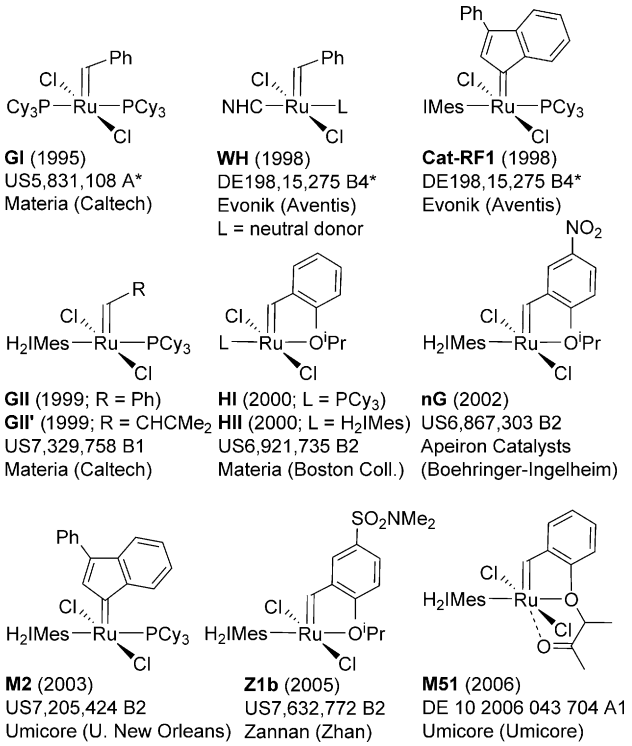

Figure 1. Commercially available ruthenium metathesis catalysts, highlighting examples used in recently disclosed industrial processes or scale-up, and the parent Grubbs' catalyst **GI**. Shown are the priority year and the corresponding patent number, with the primary licensee and intellectual property (IP) owner as of the time of writing. See: https://www.epo.org and https://www.uspto.gov. *An EP patent embodying some of these claims was recently revoked. Cy = cyclohexyl, IMes = *N*,*N*′-bis(mesityl)imidazol-2-ylidene, H_2IMes = *N*,*N*′-bis(mesityl)-4,5-dihydroimidazol-2-ylidene.

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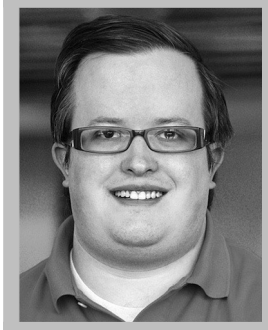
As noted above, the greater ease of handling of the Ru systems led to their widespread adoption for target-directed synthesis. Nevertheless, the Group 6 catalysts (Figure 2) stand out for their high, tunable reactivity and potential selectivity.[1e] In particular, tempered-activity monoalkoxide–pyrrolide (MAP) catalysts have enabled spectacular advances in *Z*-selective metathesis.[5] Strategies developed to improve the ease of handling, range from the use of masked, air-stable precursors, such as **Mo-P** (Figure 2), to formulation of the active Mo catalysts into wax pills for convenient dosing of reactions.[6] No industrial processes utilizing these catalysts have yet been disclosed, however, although intriguing advances have been hinted by press releases[7,8] (see Section 3.2).

1.2. Catalyst Choice in the Industrial Context

Catalyst choice in process development is governed by business considerations. Notwithstanding the importance of catalyst performance, primary issues are cost, freedom to operate, and security of supply on scale. Figure 1 shows the original patent number and priority year for the catalysts used in the processes discussed, the corporate entity that holds primary licensing rights, and the intellectual property (IP) owner.

Because the catalyst composition patents are still in force, the IP situation is complex, and concerns about freedom to operate have slowed commercial uptake of metathesis technologies. The concerns are illustrated by long-running litigation between Materia (exclusive licensee of the extensive Grubbs patent portfolio), and Evonik, which now holds the rights to Herrmann/Aventis patents claiming priority to Ru-NHC catalysts based on the generic structure **WH**. Elevance Renewable Sciences, the dominant company involved in plant-oil metathesis (Section 3), recently opted to license a subset of the Evonik patents as well as Materia's, to secure unambiguous rights to practice, and avert legal costs and implementation delays.[9,10]

Carolyn Higman is a final-year doctoral candidate in the Fogg group at the University of Ottawa (Canada). Her research focuses on isomerization in olefin metathesis, and new opportunities in nanoparticle catalysis.



Justin Lummiss received his Ph.D. in 2015 from the University of Ottawa, for work with Deryn Fogg on mechanistic organometallic chemistry in olefin metathesis. He is presently an NSERC postdoctoral fellow with Timothy Jamison at MIT.

Deryn Fogg, Professor and University Research Chair at the University of Ottawa, is a Fellow of the Royal Society of Canada. She carried out Ph.D. studies on imine hydrogenation with Brian James (University of British Columbia), and postdoctoral research with Richard Schrock (MIT) on polymer–quantum dot composites. Her research interests include issues of mechanism and design in olefin metathesis and tandem catalysis.

A limited number of companies supply metathesis catalysts, according to business models that have varied widely. Now increasingly common is bulk catalyst pricing that includes the associated IP, although uncertainties concerning freedom to operate remain incompletely resolved, as noted

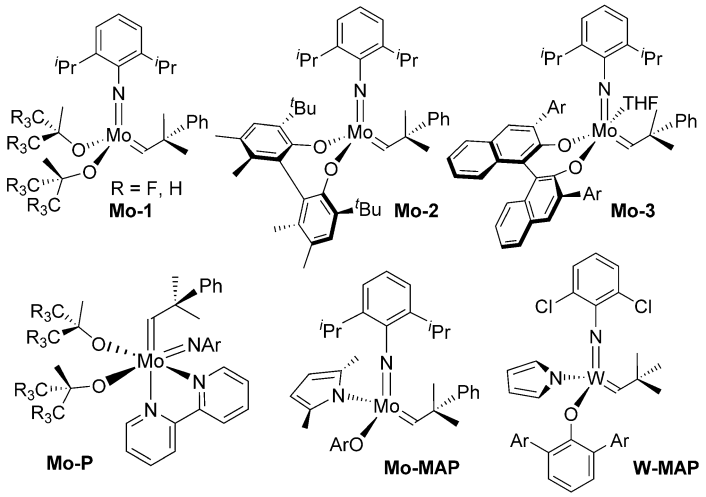


Figure 2. Leading Group 6 metathesis catalysts or (**Mo-P**) catalyst precursors.

above. A further issue is security of supply on the ton scale required for large-scale industrial applications (termed by a reviewer a "chicken or egg" problem). Nevertheless, the developments outlined in Sections 2 and 3 demonstrate satisfactory resolution of these challenges in a growing number of cases.

1.3. Impact of Impurities

Robust, reliable catalyst performance is the cornerstone of plant-scale production. The issue is particularly acute in the manufacturing of active pharmaceutical ingredients (APIs), where a failed batch is not only very costly, but can potentially compromise both drug supply, and compliance with current Good Manufacturing Practice (cGMP) regulations. In general, metathesis catalysts are less stable than reports centered on target-directed synthesis tend to suggest. Oxidative degradation by air, reactions with solvent, and intrinsic C–H activation pathways involving neutral ancillary ligands and the metallacyclobutane all limit productivity.

Further challenges become evident when very high turnover numbers (TONs) are required from technical-grade feedstocks. Certain impurities are severely detrimental to metathesis rates and yields, and ultimately to process reproducibility.[11–15] For Ru metathesis catalysts, both Brønsted and Lewis base functionalities are now known to be problematic (Figure 3; see also Section 2.4). This becomes critical at low catalyst loadings, where the concentration of adventitious contaminants may exceed that of the catalyst. Such destructive agents commonly derive from a prior reaction step. Minor impurities in industrial-grade solvents can likewise be important, particularly at the high dilutions frequently required for RCM. Undesired epimerization, a recurring problem in the RCM step for Ciluprevir and related APIs (next section), was traced to ppm levels of morpholine in the toluene solvent.[13] Similar issues, encountered during the synthesis of Simeprevir, were eliminated by sequestering amine and phosphine residues.[15] In a leading Review from Farina and Horváth suggested that a strategic purification stage—ideally, crystallization of the diene—be considered prior to any metathesis step, to safeguard process robustness.[15]

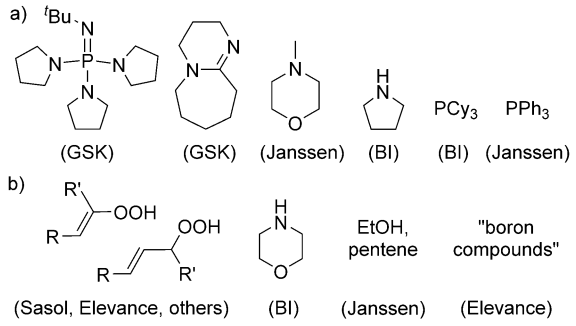


Figure 3. Examples of contaminants identified as detrimental to metathesis in industrial applications and firm reporting it. a) Residues from catalyst or prior step. b) Contaminants in solvent or feedstock.

Plant-oil feedstocks contain impurities that vary widely in distribution and proportion. Beyond the usual problems posed by Lewis bases, peroxides formed by autoxidation of unsaturated triglycerides are detrimental to catalyst productivity. Water and protic compounds also present difficulties, in part due to competing hydrolysis during the transesterification step used to liberate the desired unsaturated esters (Section 3). The patent literature describes pre-treatment methods aimed at conserving catalyst productivity.[16,17] These range from simply heating under N_2 to decompose peroxides, to treating with alumina, magnesol (magnesium silicates), silica gel, or other inorganic absorbents and desiccants to remove water, and treating with these agents, or with activated carbon, to remove polar compounds. Acetic anhydride treatment is suggested as a potential means of removing alcohols and hydroperoxides.[16] While purification can protect the catalyst from poisons, and hence improve productivity, this adds to process and materials costs. Given the lower profit margins in the specialty chemicals sector, gains in catalyst productivity must be balanced against the cost of pretreatment.

2. Pharmaceutical Applications

RCM is the most important application of metathesis in the production of APIs. To our knowledge, CM is not yet deployed in the pharmaceutical manufacturing sector on process scale. Summarized in Table 1 (see also the Supporting Information) are recently disclosed examples for which RCM reactions have advanced into clinical trials and/or production. The majority of targets are macrocyclic peptidomimetics, which afford opportunities to address protein–protein interactions impervious to small molecules, while maintaining cell permeability and oral bioavailability. Synthetic details, including disconnection strategies and the viability of alternative, non-metathetical routes, have been knowledgeably reviewed elsewhere.[15,18] The discussion below focuses on challenges in the RCM step once the site of C=C bond formation has been set, and on issues relevant to scale-up, where details have been disclosed.

2.1. Operational Challenges in Large-Scale RCM Macrocyclization

Arguably the single biggest challenge in RCM macrocyclization is the large volume of solvent normally required. Even at standard concentrations of around 0.2 M, solvent consumption is a major cost driver in pharmaceutical manufacturing,[34] and the high dilutions required to minimize metathesis oligomerization[35] exert considerable pressure on process economics. Even more critical, from a strategic perspective, is the impact on space–time yields: that is, the tradeoff between inefficient batchwise throughput, versus the capital investment for reactors of sufficient volume. The problem is illustrated by the original production run for Ciluprevir at 0.01 M (see next Section), in which 47 000 L of toluene was required to produce 400 kg of the API.[13] Batch

Table 1: Ring-closing metathesis (RCM) beyond the discovery stage, as used in synthesis of active pharmaceutical ingredients (APIs) for production and/or clinical trials.

API name (research code, license holder)	Ring size	Catalyst (max. reported scale, concentration)	Ref.	Regulatory Status[a]
HCV inhibitors				
Ciluprevir (BILN 2061; BI)	15	**nG** (400 kg; 20 kg batches, 0.2 M)	[13]	Halted in Phase 2 (2002)
Simeprevir (TMC435; Janssen)	14	**M2** (kg, 0.05 M, slow diene addition)	[19]	Approved (US, Canada, Japan, Russia, EU; 2013-14)
Paritaprevir (ABT-450; AbbVie)	15	ND[b] (1.2 g, ND)	[20]	Approved (US, Canada, EU; 2014-15)
Vaniprevir (MK-7009; Merck)	20	**HII** (200 g; 0.13 M, slow diene addition)	[21]	Approved (Japan; 2014)
MK-6325 (Merck)	15	**Z1b** ("multi-kg", 0.06 M)	[22]	Completed Phase 1 (2012)
IDX320 (Idenix)	14	**Z1b** (1 kg, 0.0024 M)	[23]	Halted in Phase 1 (2010)
Danoprevir (ITMN-191, R7227, ASC08; Roche)	15	Ru-NHC (13 g, 0.013 M)	[24,25]	Completed Phase 2 (2015)
Kinase inhibitors				
Pacritinib (SB1518; CTI BioPharma, Baxter)	18	**HII**, **Z1b** (50 g, ND)	[26,27]	In Phase 3 (2012)
TG02 (SB1317; Tragara Pharma)	18	**GII** (20 g, ND)	[26,27]	In Phase 1 (2012)
SB1578 (S*Bio)	18	**GII** (50 g, ND)	[26]	Completed Phase 1 (2011)
Cathepsin K inhibitor				
Relacatib (SB-462795; GSK)	7	**HII** (200 kg; 80 kg batches, 0.2 M)	[28]	Halted in Phase 1 trials (2009)
Stapled peptides				
ALRN-6924 (Aileron)	ND	ND	[29]	In Phase 1 (2015)
ALRN-5281 (Aileron)	ND	ND	[30]	Completed Phase 1 (2013)

[a] See https://clinicaltrials.gov. [b] ND = not disclosed. Earlier examples not detailed herein include KOS-1584 and other epothilones prepared via RCM, but discontinued following Phase 2 trials.[31] Also instructive are examples in which metathesis routes were ultimately excluded on the basis of poor RCM yields, and scale-up was not undertaken (e.g. Norgine's ulimorelin; originally TZP-101,[32] and Merck's MK-5172).[33]

scales were limited to 20 kg by the 3000 L capacity of the available stirred-tank reactors.

Associated challenges are the cumulative impact of impurities in such large volumes of industrial-grade solvent (Section 1.3), the bottleneck of solvent evaporation,[23] and poor mass transfer with respect to removal of ethylene from solution. In the original Ciluprevir campaign, ethylene removal proved inefficient even when sparging with N_2 at 1000 L h^{-1} during RCM.[13] Retention of ethylene has multiple negative consequences, including regeneration of diene, unproductive cycling of the catalyst, and catalyst deactivation.

2.2. Macrocyclic HCVP Inhibitors via RCM at more than 0.1 M

Abundant activity has centered on the RCM assembly of macrocycles that function as competitive inhibitors of proteases,[36] particularly the Hepatitis C virus protease (HCVP) NS3/4A. The first such drugs very recently reached the market. Simeprevir (Johnson & Johnson) was launched in December 2013, and rapidly achieved blockbuster status. Multiple therapeutic options are desirable to counter the emergence of drug-resistant strains arising from rapid virus mutation, and Simeprevir was followed in late 2014 by Vaniprevir (Merck) and Paritaprevir (AbbVie; Figure 4). Common features include a macrocyclic linker connecting peptide side-chains, and an endocyclic proline or proline mimic, elements also evident in Ciluprevir, the first such API to have been reported.[13,15,18] While Ciluprevir failed in clinical trials, it remains important for the insights its scale-up afforded into commercially viable RCM macrocyclization, and the influence of these advances on subsequent synthetic campaigns.

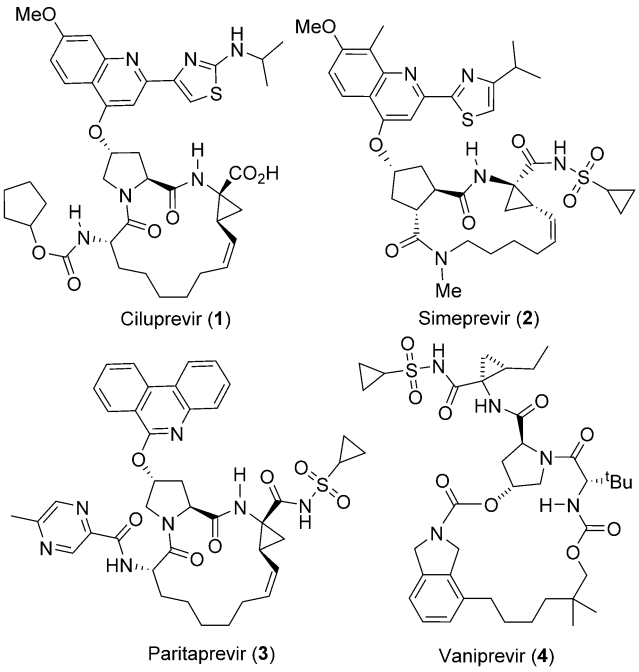


Figure 4. First-in class HCV drug candidate Ciluprevir, and currently approved HCV drugs prepared via RCM.

2.2.1. Ciluprevir (1, 0.2 M)

Boehringer–Ingelheim's 2005 report of the large-scale synthesis of Ciluprevir was a milestone: not only a first-in-class HCV protease inhibitor, but the first pilot-scale implementation of RCM.[13,37] The original scale-up (Figure 5a) was carried out at dilutions of 0.01 M; consequent challenges were

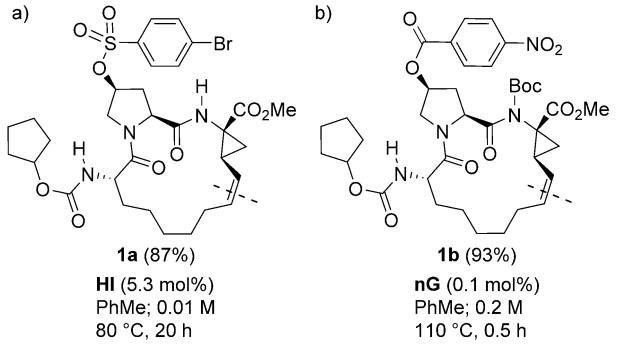


Figure 5. RCM scale-up conditions in production of Ciluprevir. a) Original conditions. b) Second-generation process. For API structure, see Figure 4.

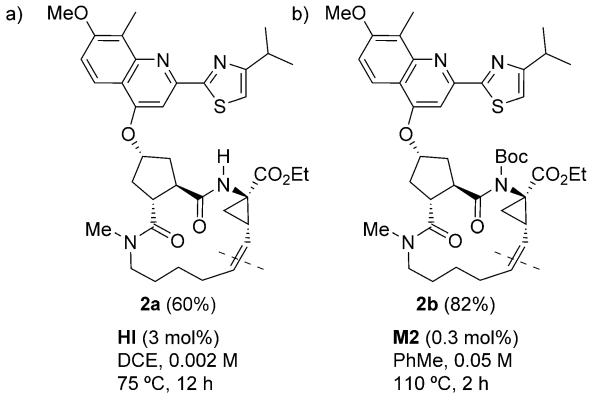


Figure 6. RCM step in the synthesis of Simeprevir. a) Discovery stage. b) Reported process conditions, with slow addition of diene and catalyst.[19] For API structure, see Figure 4. DCE = 1,2-dichloroethane.

noted in Section 2.1. Key to a more economical process was the discovery that acyl-protection of the endocyclic secondary amide significantly reduced ring strain, hence raising the effective molarity (EM) of the diene. The kinetic EM value, EM_k, corresponds to the concentration at which $k_{intra}/k_{inter} = 1$ (where k_{intra} and k_{inter} are the rate constants for the intramolecular and intermolecular reactions, respectively). Likewise, the thermodyamic EM value, EM_K, corresponds to the concentration at which $K_{intra}/K_{inter} = 1$.[35] Higher EM values are thus important in permitting ring-closing at higher concentrations. In the case of **1b**, use of a Boc protecting group (Figure 5b) limited oligomerization even at concentrations 10–20 times higher than those required for **1a**. Solvent requirements were thereby reduced from 150000 L to 7500 L per tonne of diene, enabling production in standard 2000 or 4000 L reactors, and eliminating the need for specialized rapid-evaporation equipment.[38] As an added, unanticipated advantage, N-protection favored initiation at the sterically unencumbered olefin, rather than the vinylcyclopropane site. This adaptation suppressed epimerization, and prevented catalyst degradation by the unprotected amide.

A switch to fast-initiating **nG** (Figure 1) as catalyst, and to reaction in refluxing toluene, greatly improved space–time yields. The timescale for metathesis was compressed from days to minutes, such that the RCM step was no longer a bottleneck in operations. A 50–100-fold increase in catalyst productivity also facilitated catalyst quenching and removal, an issue described in more detail in Section 2.7. More recently, the synthetic strategies optimized for Ciluprevir were applied to the assembly of a closely related API still in pre-clinical study (BI201302; see Supporting Information).[39]

2.2.2. Simeprevir (2; 0.05 M, slow diene addition)

The Medivir/Tibotec team recently reported process details for the synthesis of Simeprevir, the first RCM-enabled drug to come to market (Janssen Pharma).[19,40a] The low effective molarity of the unprotected diene was again a challenge in the discovery route, resulting in partial oligomerization even at dilutions of 0.01 M (Figure 6a). Epimerization was also an issue, but was circumvented by neutralizing residual bases present. Working concentrations were raised to 0.05 M by Boc-protection, as for Ciluprevir, and by adding diene slowly to limit intermolecular reaction (an approximation of the classic Ziegler "infinite-dilution" approach; Figure 6b).[19] To retard catalyst deactivation in refluxing toluene, catalyst **M2** was also added slowly. The catalyst loading was thereby reduced from 2.5 mol% to 0.3 mol%. No epimerization was observed for **M2** or other Ru-NHC catalysts, although such problems were encountered with catalyst **HI**.

Despite the fact that Boc was originally chosen for its ease of installation and removal, recent Janssen patents note that deprotection required drastic conditions, which led to product decomposition.[41] Halogenated acyl groups proved more satisfactory, although dilutions of 0.02 M were required on the maximum scale reported (51 g).

2.2.3. Paritaprevir (3)

Paritaprevir (formerly ABT-450), developed by Enanta and marketed by AbbVie, is now approved for treatment of genotype 1 chronic HCV in the US and Canada, and for genotypes 1 and 4 in Europe.[40b,42] Although neither process details nor the structure of the RCM precursor have been described, the macrocyclic core is identical to that in Ciluprevir (see Figure 4 above), and similar issues, such as dilution, epimerization, are therefore probable. A 2009 patent describes use of a range of catalysts (**GI**, **GII**, **HII**, and variants), with reaction times of up to 12 h in refluxing CH_2Cl_2.[20] A subsequent update described RCM via **Z1b** in toluene, with post-metathesis quenching by imidazole (Im; Section 2.7).[43]

2.2.4. Vaniprevir (4; 0.13 M, slow diene addition)

Approved in December 2014 in Japan, Vaniprevir contains the largest (20-membered) macrocyclic core of the HCV drug candidates openly pursued to date. A degree of conformational constraint in the tripeptide-isoindoline diene **4a** is implied by the limited oligomerization (ca. 5%) observed even at 0.086 M diene, without Boc protection. Slow

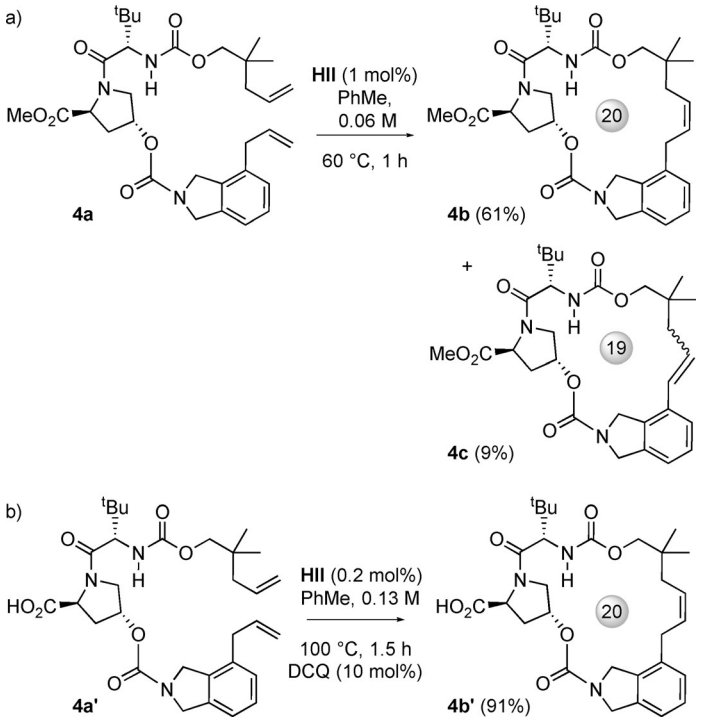


Figure 7. RCM step en route to Vaniprevir. a) Competing isomerization. b) Process route from the free acid. For API structure, see Figure 4. Note: Numbers shown in gray circles in the RCM products indicate the ring size.

diene addition enabled further reductions in the solvent volume, to 0.13 M (Figure 7).[21]

Initial challenges were posed by competing isomerization of the allylbenzene group, which resulted in contamination of the desired **4b** with about 10% of the ring-contracted product **4c**. This side-reaction was limited to under 2% by adding the catalyst slowly, sparging with N_2 to remove ethylene, and adding 2,6-dichloroquinone (DCQ). The importance of the first two factors tends to point toward catalyst decomposition as the cause of isomerization. In particular, the robustness of the process route was reinforced by pre-purifying the diene as free acid **4a**′, via conversion into the potassium salt, crystallizing, and acidifying prior to RCM.

2.3. Candidate HCVP Inhibitors via RCM at High Dilution

Use of an N-Boc group to amplify effective molarity proved less successful for two active pharmaceutical ingredients (APIs) described in this Section, MK6325 and Danoprevir.[22,25] This emphasizes the point that N-protection is a substrate-specific solution, which relies on the sensitivity of ring strain to the protectable site. In the examples below, high dilutions were essential to favor cyclization over intermolecular reaction.

2.3.1 MK6325 (5, 0.06 M)

Merck recently reported the multi-kilogram synthesis of this bicyclic drug candidate, in which one of the two macrocycles is formed by RCM.[22] Attempts to close the second ring by the same method gave low yields even at high catalyst loadings, and Suzuki–Miyaura methods ultimately proved more successful. RCM cyclization to afford **5a** was effected at 0.06 M (Figure 8a). The most successful implementation involved slow addition of catalyst **Z1b** (0.45 mol%) to toluene at 80 °C, in the presence of benzoquinone (BQ) to inhibit isomerization.

2.3.2. Danoprevir (6, 0.013 M)

In 2014, Array BioPharma and InterMune reported the synthesis of Danoprevir, an HCV protease inhibitor containing a 15-membered macrocycle, which shows potency across multiple HCV genotypes.[24] Hangzhou-based Ascletis licensed China rights from Roche in 2013, and is seeking approval for clinical trials under a fast-track regulatory pathway for domestic companies. Synthetic details are limited: only gram-scale RCM has been described, with a range of Ru-NHC catalysts, generally of the Hoveyda class.[24] The largest-scale RCM process described in the relevant patents (13 g) notes that even with N-protection and high dilutions (0.013 M), oligomerization limited yields to around 80%, with a dimer being formed as a byproduct (Figure 8b).[25] Polymeric (oligomeric) impurities were removed via a silica plug, followed by crystallization of the macrocycle directly from the filtrate. No further improvements to the RCM step have been disclosed.

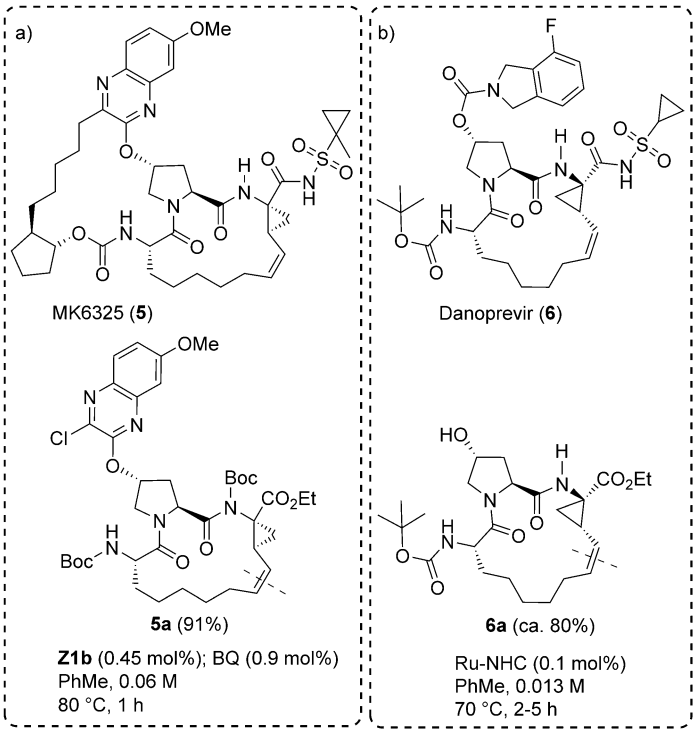


Figure 8. Candidate HCVP inhibitors accessed via RCM at diene concentrations below 0.1 M, showing API structures (top) and RCM step (bottom). a) MK6325. b) Danoprevir.

2.3.3. IDX320 (7, 0.0024 M)

Synthesis of IDX320 (**7**) was based on a route developed for IDX316, a prior clinical candidate containing an identical 14-membered macrocyclic core (Figure 9). While IDX316 did not proceed into clinical trials, development work in its synthesis revealed the impact of hydroxy substitution on RCM yields.[23] Thus, oligomerization was limited by installing the exocyclic quinolinyl group **Q** prior to RCM. Yields were raised from around 40% for **8a** to nearly 90% for **8b**, albeit at a maximum concentration of 0.008 M.

Under the same conditions, however, formation of **7** was severely hampered by cyclodimerization. Yields were improved to 66% by diluting to 0.0024 M, but further dilution afforded no improvement, implying that decomposition of the catalyst **Z1b** begins to compete. RCM was scaled to 1.5 kg in EtOAc (ca. 3 mM), which is preferred to the original chlorinated solvent for its lower toxicity. This reaction delivered 1 kg of IDX320 in 98% purity.

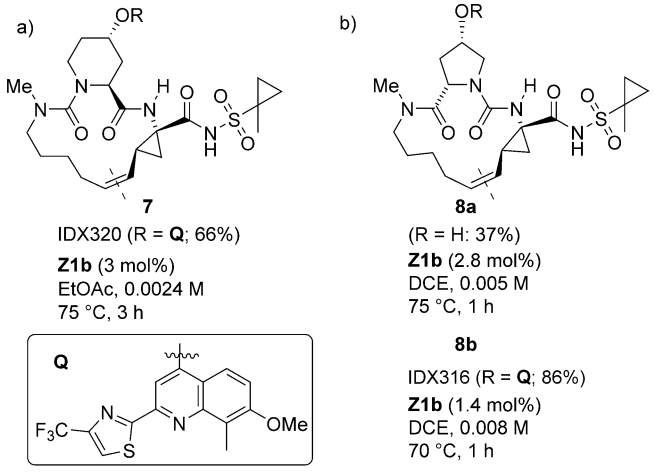


Figure 9. a) RCM step in the synthesis of IDX320 (**7**). b) Impact of peripheral bulk on RCM yields in the synthesis of IDX316 (**8b**).

2.4. Macrocyclic Kinase Inhibitors

Singapore-based S*Bio has developed routes to macrocyclic kinase inhibitors via RCM, of which the antineoplastic Pacritinib (**9**) is furthest advanced (Figure 10).[26] Initial

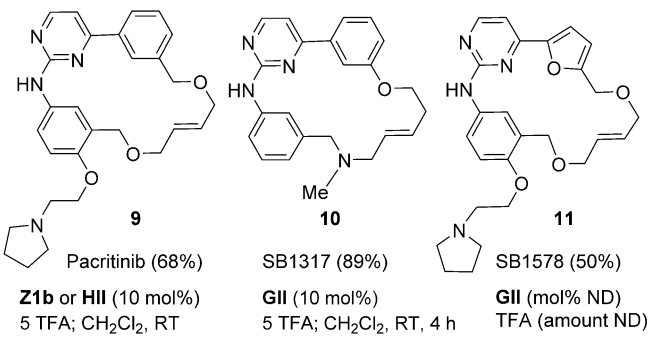


Figure 10. RCM conditions and yields in synthesis of kinase inhibitors **9**–**11**. Conditions shown are for the maximum scale reported (see Table 1).

efforts focused on **GII** as catalyst, with later reports utilizing **Z1b**. RCM could be carried out only in the presence of acid. Lewis and Brønsted bases are now known to trigger decomposition of the key methylidene and metallacyclobutane intermediates.[44] Acid treatment is thus important in quenching the basicity of the nitrogen functionalities present (as well as the basicity of free PCy_3, in cases where a phosphine-containing catalyst, such as **GII**, is used). Neither concentrations nor reaction times were specified for the largest-scale preparations of **9**–**11** reported (50 or 20 g; Table 1). However, a report of the bench-scale synthesis of SB1317 (**10**) described the need for dilutions of 0.0025 M.

2.5. Cathepsin Inhibitors

The second example of large-scale RCM was reported by the process chemistry team at GSK, en route to cathepsin K inhibitor Relacatib (**12**), a candidate for the treatment of osteoporosis and osteoarthritis.[28] RCM of **12a** was carried out in 80 kg batches to generate 200 kg of the API for clinical studies (Figure 11a,b).[28] Seven-membered azacycles normal-

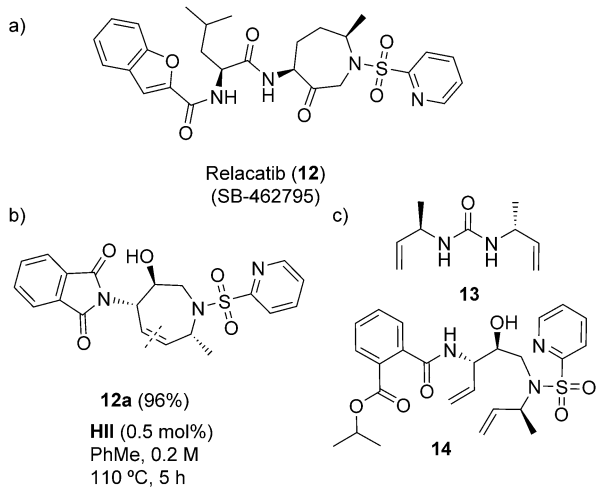


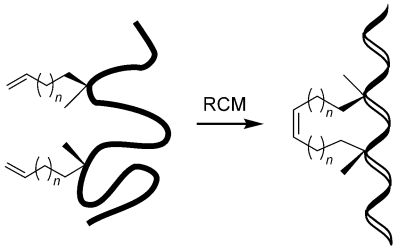
Figure 11. a) Structural formula of Relacatib (**12**; SB-462795). b) RCM product and scale-up conditions. c) Key impurities identified as detrimental to RCM.[28]

ly exhibit little ring strain, and diene concentrations of 0.2 M were tolerated without oligomerization.[28] Process robustness was a greater challenge. A phosphine-free catalyst (**HII**) was found to be essential at the discovery stage. On scale-up, however, the catalyst loadings required for complete conversion varied dramatically from batch to batch. Catalyst deactivation by contaminants from prior synthetic steps was inferred. Considered as potential culprits were DBU and phosphazene base (Figure 3), and a range of basic side-products containing a secondary amine or urea functionality.[14]

An impurity profile analysis (spiking with potential poisons, accompanied by multivariate analysis), revealed that **13** and **14** (Figure 11c) were principally responsible. Urea **13** is a byproduct of sulfonamide installation; amide **14** forms during aqueous workup prior to RCM. Both compete with **12a** as substrates, and can thereby sequester the catalyst by chelation.[1e] Reproducible operation at 0.5 mol% **HII** was achieved by eliminating aqueous work-up of the diene, and modifying the solvent system to enable crystallization prior to RCM. The RCM product crystallized as it formed, facilitating separation from Ru by-products, and delivering the tetrahydroazepine in 96% yield.[28]

2.6. Stapled Peptides

Stapled peptides, a further class of constrained peptides accessed by RCM, have garnered much attention. These compounds contain an RCM-introduced hydrocarbon link designed to constrain specific active conformations (Scheme 1). Control over peptide shape was proposed by



Scheme 1. RCM-constrained assembly of stapled peptides.

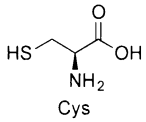
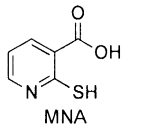
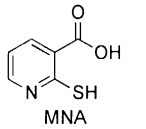
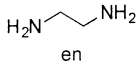
Aileron Therapeutics as a potential means of improving target binding affinities and cell permeability. The first such drug candidate, ALRN-5281, was aimed at treating rare endocrine disorders. It has completed Phase 1 clinical trials, but has not yet moved into further trials.[30] Major current efforts focus on the potential anticancer activity of ALRN-6924, and its capacity to reactivate tumour suppressor gene p53.[29,45] Neither the structures nor details of the RCM step have been disclosed.

2.7. Catalyst Quenching and Ruthenium Removal

Quenching of the metathesis catalyst before workup is essential to prevent re-opening of the RCM products. Also important is the capacity of the quenching agents to facilitate ruthenium removal, and hence to decrease heavy-metal levels in the API below FDA maxima for platinoid residues (parenteral: 0.5 ppm; oral: 5 ppm).[46] Concerns about high levels of residual Ru have led to reservations about synthetic sequences in which the RCM step is close to the API,[47] although such concerns diminish as catalyst loadings decrease. GSK scientists have pointed out additional safety concerns, particularly the potential for negative interactions between the heavy metal and downstream reagents or intermediates (oxidants, acyl azides).[28]

A comprehensive survey of methods for Ru removal appeared in 2012.[48] Table 2 summarizes methods described

Table 2: Reagents and procedures used to terminate metathesis and facilitate ruthenium removal during API synthesis.[a]

Entry	Reagent	Representative treatment	API	Cat. [mol%]	Residual Ru [ppm]	Ref.
1	 Cys	1) Cys (50 equiv vs. Ru), NaOH (2 equiv); 60 °C, overnight 2) Wash with NaOH (aq) 3) Extract with heptane	Relacatib	**HII** (1%)	148	[28]
2	 MNA	Original route 1) MNA (20 equiv vs. Ru), NEt_3 (20 equiv); 30 °C, 0.5 h; 55 °C, 6 h 2) Washed with $NaHCO_3$ (aq) 3) Stir with activated charcoal, 35 °C, 15 h; filter	Ciluprevir IDX316	**HI** (5%) **Z1b** (1.4%)	<30 14	[37] [23]
3	 MNA	Updated route 1) MNA (50 equiv vs. Ru); 60 °C, 2 h 2) Wash with $NaHCO_3$ (aq)	Ciluprevir MK6325	**nG** (0.1%) **Z1b** (0.4%)	<50 ND	[38] [22]
4	 Im	1) Im (200 equiv vs. Ru), 80 °C, 1.5 h 2) Wash with HCl (aq)	Paritaprevir BI201302	cat. ND **nG** (1%)	ND ND	[43] [39]
5	 en	1) en (20-70 equiv vs. Ru) 2) Wash with HCl (aq)	Danoprevir	Ru-NHC	ND	[25]

[a] ND = not disclosed.

in the pharmaceutical campaigns discussed in the Sections above, to the extent that details are available. Reagents used include 2-mercaptonicotinic acid (MNA), imidazole (Im), ethylene diamine (en), and basic cysteine (Cys). Treatment with the quenching agent is typically followed by aqueous workup, to maximize ruthenium extraction.

Some of the most detailed procedures were described in the production of Relacatib and Ciluprevir. The Relacatib work cited a number of methods that proved unsatisfactory on the industrial scale.[28] Importantly, some classic ruthenium scavengers, including $P(CH_2OH)_4Cl$, were found to cause product decomposition. Adsorptive methods (silica gel or alumina) removed less than 50% of the residual ruthenium. Best of the reagents explored was basic cysteine (Table 2, Entry 1). The approximately 150 ppm level of Ru remaining was deemed sufficiently low to proceed with the ensuing synthetic steps. Following catalytic hydrogenation and base hydrolysis, the Ru content dropped to 14 ppm.

The importance of catalyst quenching prior to distilling off the solvent became evident even in the first scale-ups of RCM processes.[13,37] Ring-opening of the macrocyclic product otherwise occurred during evaporation, consistent with the concentration-dependence of the ring-chain equilibrium.[35] Isomerization (probably by decomposed catalyst) was likewise problematic. 2-Mercaptonicotinic acid (MNA) treatment during the RCM workup stage (Entry 2) proved an effective solution, and enabled Ru removal to under 30 ppm, or below 10 ppm in the final API. However, large amounts of MNA were required (a later analysis put the total amount required at 2 $kg\,kg^{-1}$ diene),[38] accompanied by extensive bicarbonate extraction, silica filtration, and treatment with activated carbon in ensuing steps. The lower catalyst loading in the 2009 process greatly simplified workup: significantly less MNA was required, without the silica/carbon treatment (Entry 3).[38] An MNA treatment was likewise adopted in the production of MK6325 and IDX320, although less detail was provided.

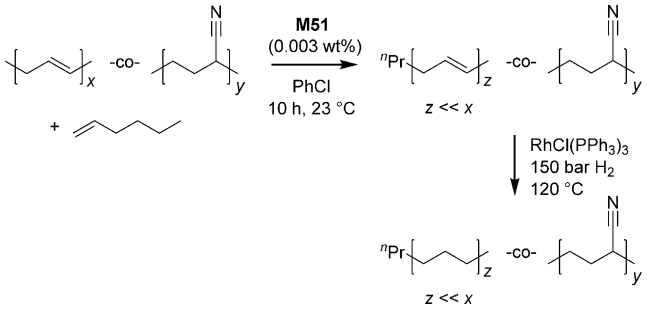
Other quenching and Ru-removal agents (specifically, Im and the chelating diamine en; Entries 4 and 5) were described in the syntheses of Paritaprevir, BI201302, and Danoprevir. Intriguingly, the firm BI replaced the reagent MNA with Im in a 2013 report in which BI201302 was prepared on 2 kg scale.[39]

3. Specialty Chemicals

Cross-metathesis (CM) predominates in the applications of metathesis to specialty chemicals manufacturing. The narrower profit margins in this sector translate into greater challenges in establishing profitability, particularly given the issues discussed in Section 1.2. Nevertheless, the patent literature indicates significant interest from many Top 50 chemical companies in metathesis-derived products with novel performance properties, as well as newer firms. In contrast to the situation in the pharmaceutical industry, however, detailed reports analyzing the technical challenges are sparse.

3.1. High-Performance Rubbers

Longest developed of the specialty materials accessible via metathesis are high-performance grades of hydrogenated nitrile butadiene rubber (HNBR), marketed by Lanxess as Therban AT. HNBR itself shows improved resistance to degradation and chemical attack in aggressive environments, relative to standard grades of NBR. Key to the enhanced performance of the metathesized material is the reduced viscosity achieved by partial metathesis depolymerization of



Scheme 2. Preparation of high-performance hydrogenated nitrile butadiene rubber (HNBR) via metathesis depolymerization of NBR, followed by hydrogenation without intervening workup.

the unsaturated NBR, prior to hydrogenation.[49] Such a process is illustrated with 1-hexene in Scheme 2. Reduced viscosity improves blending with additives: it also enables faster throughput in injection molding. Recent patent applications disclose that phosphine-free catalysts, such as **M51**, offer access to lower molecular-weight nitrile rubbers than those attainable using **GII**.[49]

3.2. Specialty Chemicals from Renewable Feedstocks

3.2.1. The Biorefinery

Metathesis "cracking" of unsaturated plant oils has long been recognized as a potential route to olefin building blocks from renewable resources.[2,3] Palm, soy, and canola oil are the major focus, given their high global production (137 million tonnes in 2014)[50] and the high proportion of unsaturates; see Figure 12a.[51] Major advances followed the 2013 commissioning of a manufacturing facility by Elevance Renewable Sciences (founded by Cargill and Materia) and Wilmar International, the largest global processor of palm oil. A detailed analysis of the metathesis process at this facility, sited in Gresik, Indonesia, appeared in a 2012 Review.[2] Shipping of palm-oil metathesis products began in mid-2013. The reported capacity of the Gresik operation is 180000 MT. Elevance announcements describe plans for added US capacity (280000 MT), based on canola and soybean oil, pending adaptation of an existing biodiesel plant in Natchez, Mississippi.[52] A third prospective facility in Lahad Datu, Malaysia, is planned as a collaborative venture between Elevance and Malaysia-based Genting Plantations Berhad.[53]

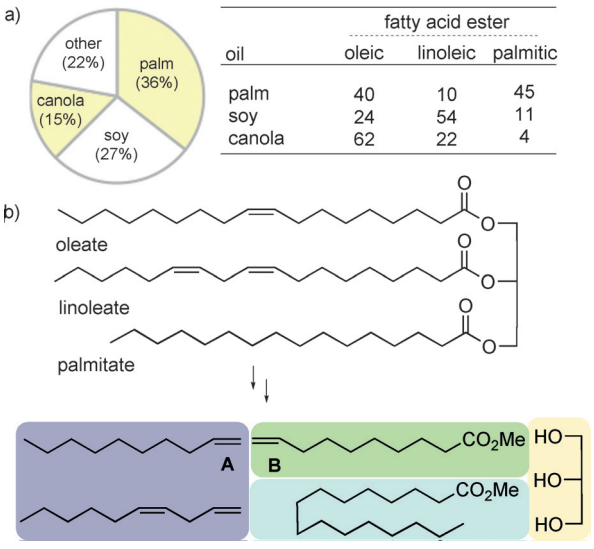


Figure 12. a) Global share of plant oil production (2014), and major constituents of palm, soy, and canola oil.[50] b) A model triglyceride, and key products obtained by metathesis and transesterification: monounsaturated α-olefins (**A**; upper structure in purple block), specialty difunctional chemicals (**B**; light green), and other oleochemicals (light blue); glycerol is shown in yellow. For additional products obtained by self-metathesis, see Figure 14 and Scheme 3.

Key products announced from the Gresik site include C_{10} α-olefins **A** (Figure 12b), the corresponding difunctional compounds **B**, which represent novel specialty chemicals, and long-chain saturated esters (oleochemicals; Figure 12b). Also relevant are self-metathesis products, particularly dimers of **B** and oligomerized triglycerides (see below).

3.2.2. Plant Oils to Olefins

Sequential processes of ethenolysis and transesterification offer, in principle, the simplest route to the desired α-olefin products of type **A** and **B** from plant-oil triglycerides (Figure 12b). The low solubility of ethylene in the feedstock oil limits process efficiency, however.[54] As well, metathesis productivity is lowered in the presence of ethylene, as recognized since early work on methyl oleate ethenolysis by Dow researchers.[55] Catalyst decomposition is detrimental not only to turnover numbers (TON), but also to selectivity, as the decomposed catalyst promotes double-bond isomerization. "Alkenolysis", or cross-metathesis with an olefin other than ethylene, is thus preferred.[54]

Figure 13 depicts a schematic of the biorefinery operation described in Elevance patents.[17,56] Technical-grade palm oil is subjected to pre-treatment to remove peroxides and other impurities that limit catalyst productivity (see Section 1.3). The unsaturated triglycerides are then cleaved at the olefinic site by alkenolysis with 1-butene. 1-Butene is attractive for its low cost and the volatility of its hydrocarbon products, which facilitates their separation from higher boiling unsaturated triglycerides by distillation. The hydrocarbon products include 1-decene **A**, the γ-olefinic co-product 3-dodecene **A′** (formation of which is due to the unsymmetrical nature of the 1-butene coupling partner), and 9-octadecene, the $\mathbf{A}_2$ dimer formed by self-metathesis.

3.2.3. α-Olefin Triglycerides and Esters

The chain-shortened triglycerides can themselves be converted into waxes described as paraffin replacements and components of personal-care products, as indicated below. Exxon patents also describe hydroisomerization of these materials to obtain lubricant base stocks.[57] Alternatively, base-catalyzed transesterification with methanol can be used to liberate the α,ω-unsaturated esters, as well as long-chain esters derived from saturated fatty acids, from the glycerol backbone. The principal oleate-derived products are

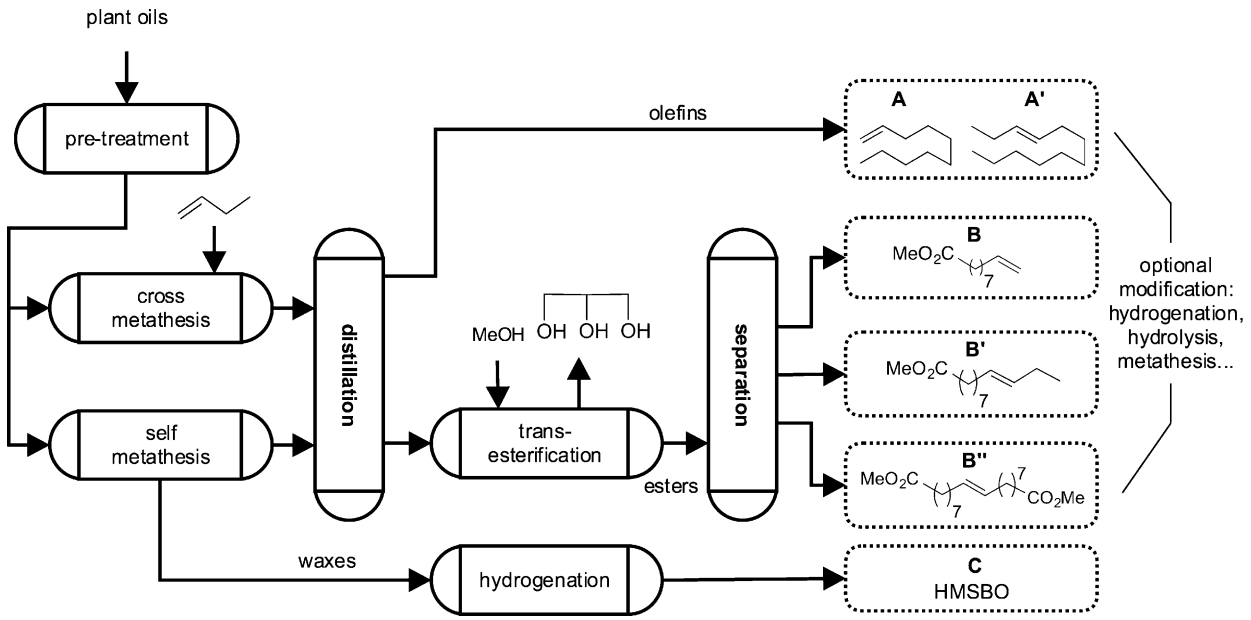


Figure 13. The Elevance "biorefinery": transformation of plant oils into key products (illustrated for oleates). Adapted from Ref. [2].

the methyl esters of 9-decenoic and 9-dodecenoic acid (**B**, **B′**; Figure 13), formed in approximately equal proportions. These compounds are marketed by Elevance as Inherent C10 and C12 methyl esters; Figure 14. Also accessible is the self-metathesis product **B″**, which on hydrogenation and hydrolysis affords the long-chain saturated diacid, marketed as Inherent C18 diacid.

Additional hydrocarbon and ester products arise from other fatty acids present, including those with zero or multiple sites of unsaturation (e.g. the esters of palmitic acid or linoleic and linolenic acid, respectively).

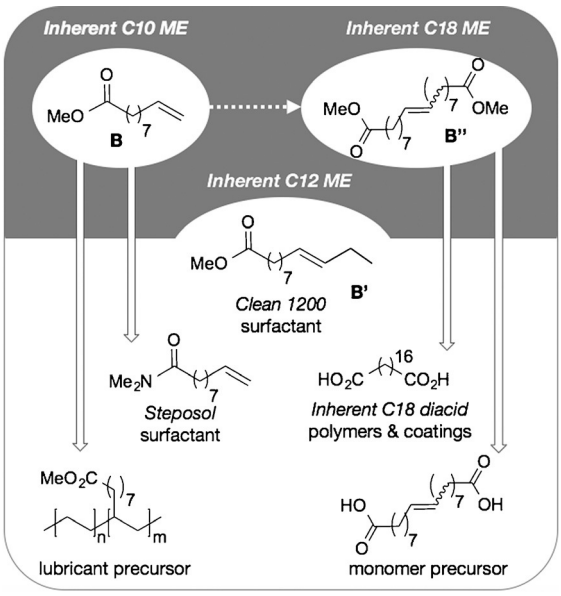


Figure 14. Typical products accessible from 9-decenoic methyl ester **B**, and reported commercial applications.

3.2.4. Applications of Mono- and Difunctional Products

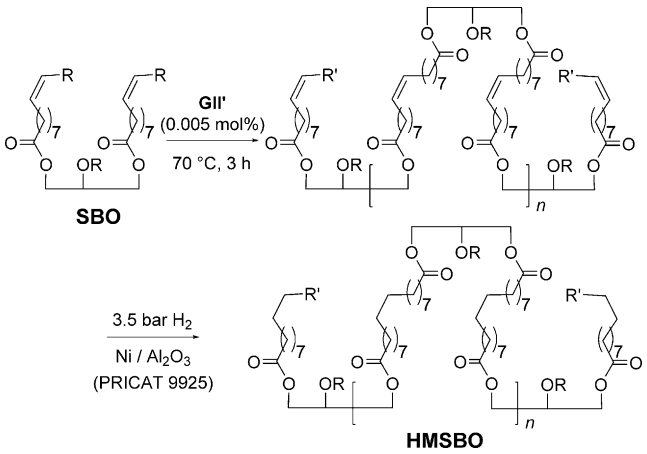
Oligomerization of the unsaturated olefin stream (**A** and its homologues) gives access to materials marketed as lubricants, while hydrogenation affords predominantly C8–C18 linear alkanes relevant to use as diesel and jet fuels. Alternatively, polymerization of 1-decene (**A**) with a proportion of **B** produces compounds suitable for use as synthetic oils.[58] The presence of the ester groups is thought to improve the solubility of polar additives. Additional specialty chemicals accessible from difunctional **B** range from surfactants and lubricants to polymer resins (Figure 14).

Among the first commercialized products was Stepan's *N*,*N*-dimethyl-9-decenamide surfactant (Steposol MET-10U), marketed as a non-ionic, water-soluble alternative to ethanolamine and volatile organic solvents in cleaning product formulations.[59] Methyl-9-dodecenoate **B′** is marketed as an industrial degreaser ("Clean 1200") in heavy manufacturing and transportation maintenance. Finally, the diacid Inherent C18 derived from **B″** is a difunctional building block for which polymer, adhesive, and coating applications are described.[58] Incorporation of the diacid in powder coatings reportedly improves toughness and impact resistance, owing to the increased flexibility associated with the C_{18} chain.

3.2.5. Plant Oils to Metathesized Triglyceride Products

Self-metathesis of soybean oil (SBO) represents the largest-scale biorefinery process for which details have been disclosed to date.[60] The process utilized 8.3 tonnes of purified oil, which was deoxygenated by sparging with N_2 prior to adding catalyst (Scheme 3). Following metathesis, hydrogenation was carried out to afford hydrogenated metathesized soybean oil (HMSBO).

HMSBO is marketed as a silicone-free emollient and thickening agent for personal care products, including sham-



Scheme 3. Oligomeric products by self-metathesis of soybean oil (SBO; Cargill RBD grade; a simplified triglyceride is shown), followed by hydrogenation.

poos, skin lotions, and cosmetics (some in partnership with Dow Corning). Applications in vegetable-oil based candles, and technical uses as lubricants, sealants, and fuels are also cited.[61,62] The polar ester functionalities appear to improve blending properties (with, e.g., pigments and fragrance additives) relative to paraffin-based materials. The relatively low melting-point range of HMSBO (48–60 °C) is suitable for candle wax and some cosmetic applications. A 2012 Elevance patent application describes methods for increasing melting points (as required for lipsticks, pomades, and sunscreens, or hot melt adhesives), by crosslinking with difunctional amines such as ethylenediamine.[61]

3.2.6. Catalyst Scope

Metathesis of plant oils is widely regarded as being restricted to Ru catalysts, owing to the oxidative and hydrolytic sensitivity of Group 6 catalysts. In ethenolysis of purified methyl oleate, however, the molybdenum catalyst **Mo-MAP** (Figure 2, Figure 15) was shown to enable TONs comparable to Ru catalysts, reaching values of 4750 over 15 h,[63] versus 2800 for **GII**, or 5470 over 4 h for **HII-u**.[64] Elevance has licensed such Group 6 catalysts from XiMo, and announced in 2012 that the Mo-catalyzed metathesis of fatty acid esters had reached commercially competitive levels.[7] No details have yet been released.

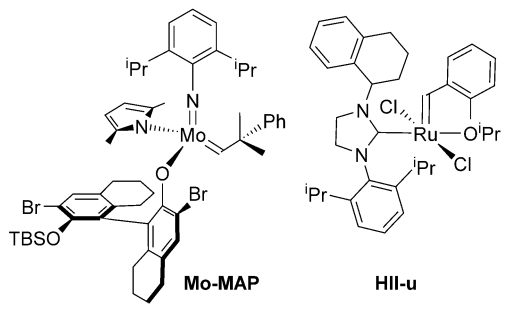
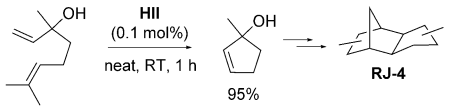


Figure 15. Advanced Group 6 and Group 8 catalysts used for ethenolysis of methyl oleate.

3.3. High-Density Aviation Fuels

A final example expands further into the strategically important realm of bio-based fuels. Linear α-olefins and hydrocarbons (C_{10+}) relevant to fuel applications were shown in Figure 13. The high-density fuel **RJ-4** (tetrahydromethyldicyclopentadiene dimer; Scheme 4) is an involatile liquid rocket propellant used in missile propulsion, and a component of the jet fuel JP-9. U.S. Navy researchers have developed an efficient RCM route to **RJ-4** from renewable sources.[65] Rapid, quantitative RCM of the freshly distilled terpene linalool at room temperature was reported under solvent-free conditions, using 0.1 mol % of catalyst **HII**.



Scheme 4. RCM of linalool en route to high-density jet fuels.

These products, as well as those obtained by hydrogenation of the linear olefin stream in Figure 13, represent potential "drop-in", bio-based fuels that could seamlessly augment or replace petrochemicals without major changes to current infrastructure. Active exploration is under way by biofuels companies, such as LS9 and Solazyme. The US military-sponsored collaboration between Elevance and Bioprocess Algae[66] targets production of drop-in jet and diesel fuels from algae oil.

4. Conclusions

The past two years have witnessed ground-breaking advances in the industrial deployment of olefin metathesis. While metathesis methodologies have been an integral part of the chemical manufacturing landscape for 60 years, implementation in pharmaceutical and specialty-chemicals manufacturing represents a new frontier. In pharmaceutical manufacturing, RCM enables rapid expansion of molecular complexity, while streamlining synthetic sequences. Outlined above are major advances, particularly within the emerging field of macrocyclic therapeutics. High-profile successes in plant-scale implementation of RCM processes will undoubtedly catalyze further development in large-scale manufacturing of active pharmaceutical ingredients (API), and indeed other contexts. New technologies, and expanded commercial opportunities, are anticipated to emerge from areas of major current activity (including *Z*- and *E*-selectivity, and metathesis of hindered olefins, among others).

The need for greener, more cost-effective manufacturing processes is anticipated to spur improvements in sustainable synthesis. In particular, creative new technologies are essential to meet the challenges associated with high dilution. Likewise essential—particularly so long as ruthenium-based processes remain central to the field—are advances in catalyst productivity, ideally in forms that withstand relaxed purifica-

tion strategies. Higher productivity offers additional advantages, diminishing the burden of heavy-metal removal and recycling. Such improvements in manufacturing efficiency will be critical to expanding uptake in narrower-margin markets.

Much attention has justifiably focused on the recent implementation of metathesis in specialty-chemicals manufacturing. Achieving commercial viability in the transformation of unsaturated plant oils into performance chemicals is particularly impressive, given the challenges of product selectivity and catalyst productivity. While the increasing demand for products based on renewable resources is an important driver, constraints are imposed by the need to ensure prices and performance competitive with petroleum-derived products. Only a portion of the plant output enters existing markets as drop-in replacements, however. Of keen interest is the stimulus provided by newly accessible difunctional feedstocks to the development of novel performance chemicals, new applications, and new markets. The advances of the past few years represent the beginning of a new era for metathesis methodologies in chemical manufacturing. Pressures and opportunities in these contexts will drive further evolution, bringing new frontiers within reach.

Acknowledgements

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