

Grubbs Catalyst[®] Portfolio

Metathesis Catalysts

Offering the best of metathesis catalysts

First established in the 1960s, alkene metathesis is considered to be the best method to synthesize long complex alkenes through the use of highly efficient and selective catalytic reactions.

Employing a ruthenium metal complex, metathesis enables the simple synthesis of carbon-carbon double bonds. These reactions provide efficient routes to product synthesis by ensuring minimal waste due to the formation of less toxic by-products, high activity and high stereoselectivity.

Following decades of research and development in the field of metathesis, Umicore provides a comprehensive portfolio of catalysts. In early 2018, we expanded our offerings to include the world-class Grubbs Catalysts® intellectual property, following Umicore's acquisition of Materia's proprietary metathesis technologies. These catalysts, developed by the late Nobel laureate Prof. Robert H. Grubbs and his team, deliver the best-in-class conversion, enabling robust alkene conversions.

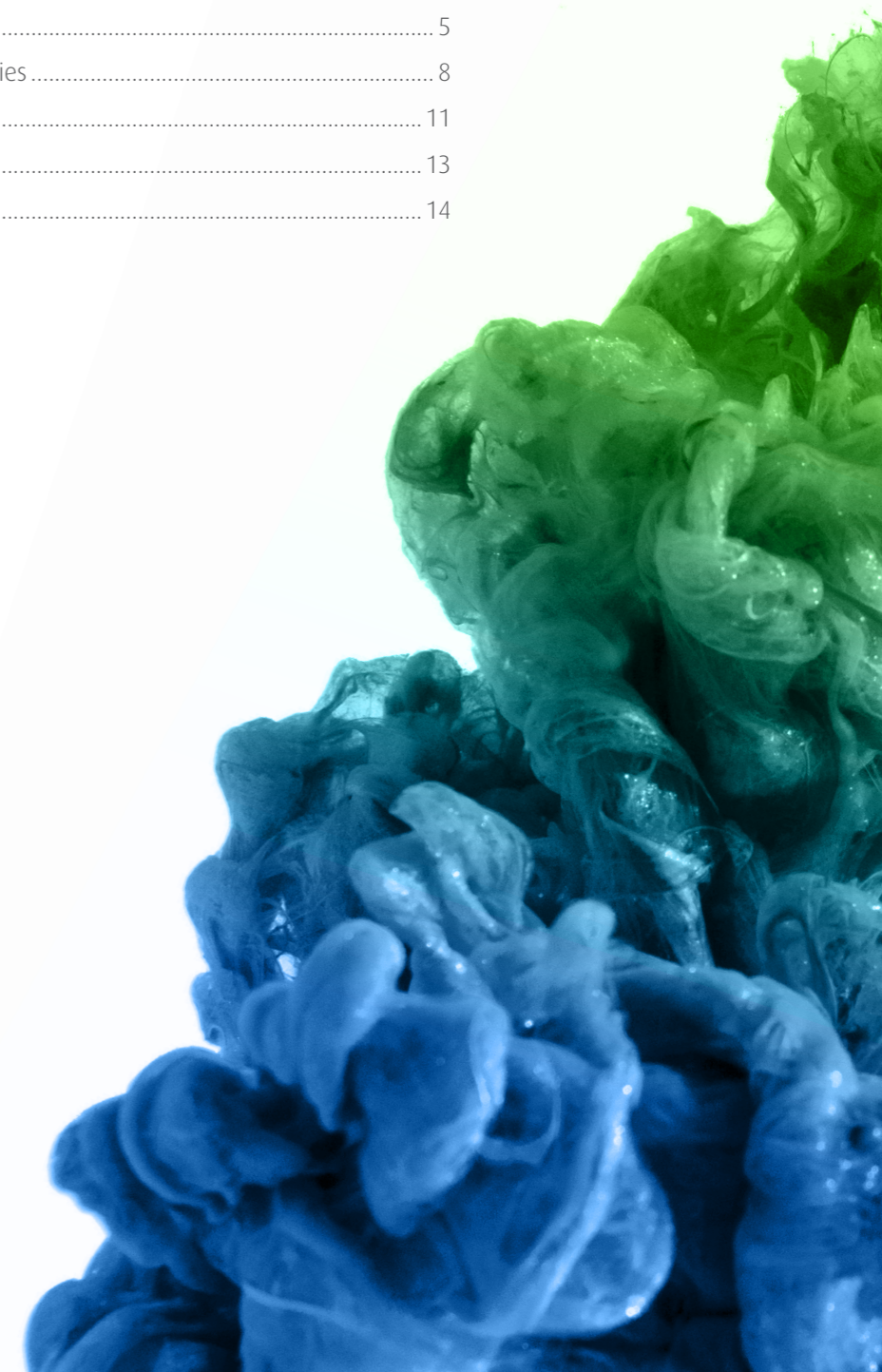
Umicore PMC has now leveraged the strong global operating and industrial scale manufacturing expertise that it has established over its decades of experience in the industry to support a broad range of commercial-scale applications of olefin metathesis. These range from polymerization and monomer modification in the materials science space to a multitude of clinical and commercial API manufacturing processes in the pharmaceutical field. Umicore's range of services are tailored to meet your specific metathesis needs. Our experts can help support development processes; from scaling a reaction or devising new reaction routes, to screening the appropriate catalyst to maximize your product formation.

Working together with Umicore means unparalleled access to Grubbs Catalyst® technologies and our development expertise; together we can work to develop your specific metathesis reaction.

“Working together with Umicore means unparalleled access to Grubbs Catalyst® technologies”

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Metathesis: the key features

Due to its versatility, metathesis can be used to synthesize a range of useful products across multiple markets. The key features of metathesis include:

Functional group tolerance: Modern active pharmaceutical ingredients are among the most complex molecules synthesized on commercial scale. Ruthenium-based metathesis catalysts succeed in forming key bonds in even the most challenging substrates, such as the macrocyclic peptide core of HCV NS3 protease inhibitors like ciluprevir, simeprevir, and related compounds used to treat hepatitis C infections.

Stereoselectivity: Recent advances in ruthenium-based metathesis catalysts offer opportunities for stereoselective metathesis reactions. In particular, Z-selective and stereoretentive catalysts offer new routes for chemists to control the E:Z ratio of newly formed alkenes. While this feature is potentially useful in almost any application, it is particularly advantageous to the production of insect pheromones, which must be prepared in the correct ratio of olefin isomers to be effective as natural pest deterrents for crop protection.

Activity and catalyst longevity: For chemical applications driven by aggressive cost targets, ruthenium-based metathesis catalysts have demonstrated unparalleled activity under rugged conditions. Renewable feedstocks such as soybean oil can be converted into specialty chemical products with turnover numbers in the hundreds of thousands. Thus, even in high-volume, low-margin products, metathesis can deliver significant cost advantages.

Grubbs Catalyst® Technology Drivers



Pharma

Need for new chemical therapeutics

Increasingly 3D molecular structures are correlated with better clinical success rates



Agrochemical

Increasing pressure to protect growing food needs

Concerns over pesticide use



Renewable Chemicals

Desire for non petrochemical-based green solutions

Cannot compromise on cost and performance



Advanced Materials

Tough materials for wind turbines

3D-printed high-performance thermosets

Choose your application

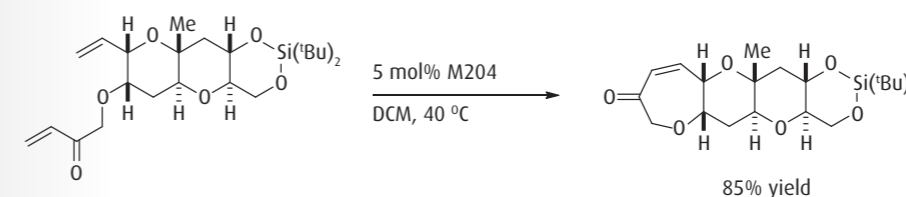
With many versatile reactions to choose from, identifying the right catalyst for your reaction also relies on identifying the right metathesis reaction. Be it ring-closing metathesis, which can be used to synthesize complex polycyclic molecules, or cross metathesis, involving the intermolecular reaction of two unconnected alkenes, we have the on-hand expertise to discuss the best routes to your product, ensuring project success.

Ring-closing metathesis

Ring-closing metathesis is a common metathesis reaction for any scientist needing to synthesize mid- and macro-sized rings, as well as offering an efficient route to synthesize strained or sterically hindered rings. Proceeding via an intermolecular process, this reaction can be made almost irreversible following appropriate reaction optimization.

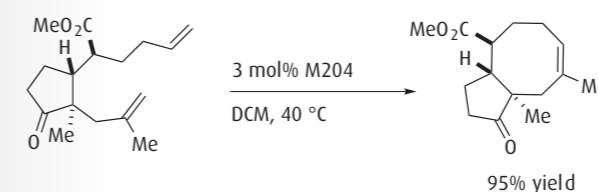
Mid-sized ring-closing metathesis

Preferred Catalysts	Optimal Catalyst Loading	Conditions
Grubbs Catalyst® M202, M204 Hoveyda Grubbs Catalyst® M720, M721, M730	3-5 mol%	Concentration: Depending on ring size: 1.0 M (5-membered ring), 0.5 M (6-membered ring) Temperature: 40-100 °C



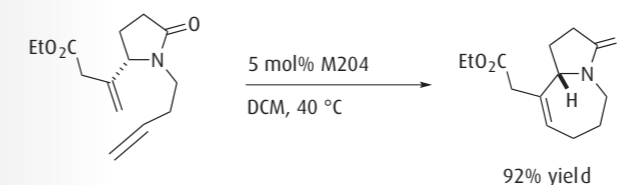
Ring-closing metathesis to form an oxepane ring embedded in (-)-gambieric acid with applications in the pharmaceutical industry.

Ref: *Organic Letters* 2015, 17, 4694



Ring-closing metathesis to yield the synthesis of an 8-membered ring structure of serpendione.

Ref: *Tetrahedron Letters*, 2005, 46, 1149

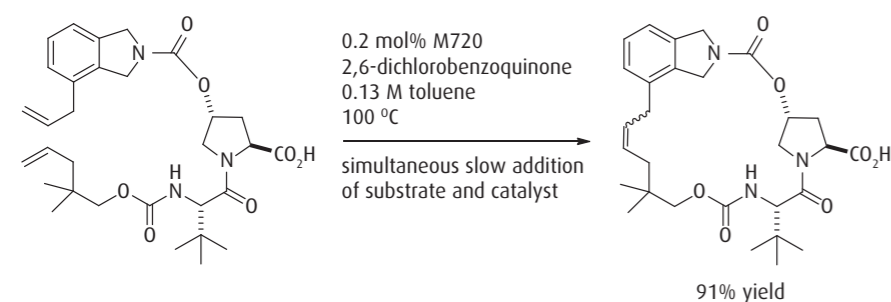


Ring-closing metathesis in the synthesis of (-)-stemoamide, a root extract used in Chinese and Japanese folk medicine.

Ref: *Journal of Organic Chemistry*, 2007, 72, 4246

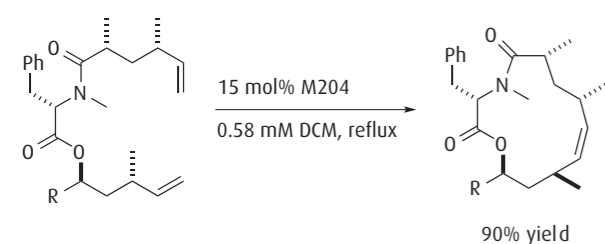
Macrocyclic ring-closing metathesis

Preferred Catalysts	Optimal Catalyst Loading	Conditions
Grubbs Catalyst® M202, M204 Hoveyda Grubbs Catalyst® M720, M730	3-10 mol%	Concentration: 0.1 - 0.05 M Temperature: 40-100 °C



Ring-closing metathesis to form a 20-membered macrocycle used as a protease inhibitor in the pharmaceutical industry.

Ref: *Journal of Organic Chemistry*, 2012, 77, 3820



Formation of a key intermediate in the preparation of the cytotoxic marine natural product (-)-spongidepsin.

Ref: *Organic Letters*, 2010, 12, 4392

Sterically demanding ring-closing metathesis

Preferred Catalysts	Optimal Catalyst Loading	Conditions
Hoveyda Grubbs Catalyst® M721	3-10 mol%	Concentration: Depending on ring size: 1.0 M (5-membered ring), 0.5 M (6-membered ring) Temperature: 40-100 °C



Formation of a trisubstituted alkene scaffold used for SAR exploration.

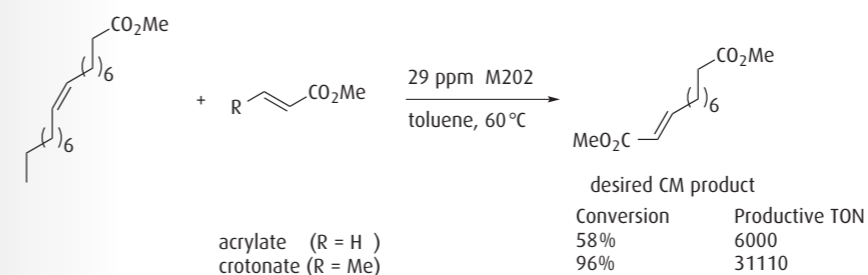
Ref: *Bioorganic Medicinal Chemistry*, 2013, 21, 5707

Cross metathesis

Bringing together two unconnected alkenes in an intermolecular reaction, cross metathesis is an extremely useful reaction that can result in the efficient synthesis of complex and long carbon-carbon chains.

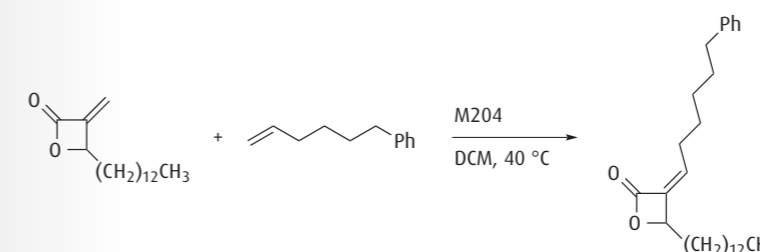
Cross metathesis of electron-deficient alkenes

Preferred Catalysts	Optimal Catalyst Loading	Conditions
Grubbs Catalyst® M202, M207 Hoveyda Grubbs Catalyst® M720, M730, M731	1-5 mol%	Concentration: 1 M or greater Temperature: 40-60 °C



Biscarbocyclic acid formation used as precursors to multiple fine chemical products.

Ref: *ChemSusChem*, 2014, 8, 1143

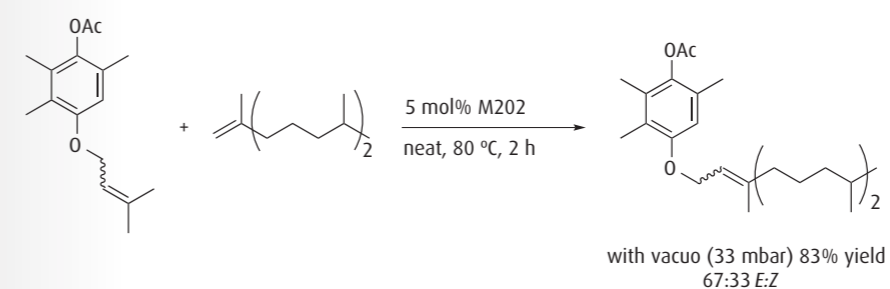


Synthesis of β -lactone structures bearing a variety of alkyl chains at the 3-position.

Ref: *Bioorganic & Medicinal Chemistry Letters*, 2015, 25, 317

Synthesis of trisubstituted linear alkenes

Preferred Catalysts	Optimal Catalyst Loading	Conditions
Grubbs Catalyst® M202, M207 Hoveyda Grubbs Catalyst® M720, M722, M730	1-5 mol%	Concentration: 1 M or greater Temperature: 40-60 °C



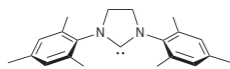
The preparation of vitamin E intermediates by cross-metathesis of trisubstituted and disubstituted alkenes.

Ref: *Helvetica Chimica Acta*, 2006, 89, 797

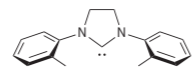
A selection of Grubbs Catalyst® Technologies

Legend

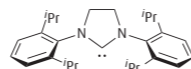
SiMes



SI(o-Tol)



SIPr



M100 series Grubbs Catalyst® 1st Generation

M101 & M110	Ligand L	Trade Name	Chemical Formula	CAS Number
	PCy ₃	Grubbs Catalyst® M101	Ru(PCy ₃) ₂ (Ind)Cl ₂	250220-36-1
	PCy ₃	Grubbs Catalyst® M102	Ru(PCy ₃) ₂ (benzylidene)Cl ₂	172222-30-9
	PCy ₃	Grubbs Catalyst® M103	Ru(PCy ₃) ₂ (butenylidene)Cl ₂	194659-03-5
	PCy ₃	Grubbs Catalyst® M104	Ru(PCy ₃) ₂ (2-thienylmethylene)Cl ₂	1190427-44-1
	ⁱ Bu-phobane	Grubbs Catalyst® M110	Ru(ⁱ Bu-phobane) ₂ (Ind)Cl ₂	894423-99-5

M200 series Grubbs Catalyst® 2nd Generation

M204 + M206	NHC	Ligand L1	Ligand L2	Trade Name	Chemical Formula	CAS Number
	SiMes	PPh ₃	Cl	Grubbs Catalyst® M200	(SiMes)Ru(PPh ₃)(Ind)Cl ₂	340810-50-6
	SIPr	PPh ₃	Cl	Grubbs Catalyst® M201	(SIPr)Ru(PPh ₃)(Ind)Cl ₂	1307233-23-3
	SiMes	PCy ₃	Cl	Grubbs Catalyst® M202	(SiMes)Ru(PCy ₃)(Ind)Cl ₂	536724-67-1
	IMes	PCy ₃	Cl	Grubbs Catalyst® M203	(IMes)Ru(PCy ₃)(Ind)Cl ₂	254972-49-1
	SiMes	PCy ₃	-	Grubbs Catalyst® M204	(SiMes)Ru(PCy ₃)(benzylidene)Cl ₂	246047-72-3
	SIPr	PCy ₃	-	Grubbs Catalyst® M206	(SIPr)Ru(PCy ₃)(benzylidene)Cl ₂	373640-75-6
	SiMes	PCy ₃	-	Grubbs Catalyst® M207	(SiMes)Ru(PCy ₃)(butenylidene)Cl ₂	253688-91-4
	IMes	Cl	PCy ₃	Grubbs Catalyst® M208	[(Me)2-IMes]Ru(PCy ₃)(2-thienylmethylene)Cl ₂	1190427-50-9
	IMes	Cl	PCy ₃	Grubbs Catalyst® M209	(IMes)Ru(PCy ₃)(2-thienylmethylene)Cl ₂	1190427-49-6
	SiMes	Cl	P(O ⁱ Pr) ₃	Grubbs Catalyst® M220	(SiMes)Ru(P(O ⁱ Pr) ₃)(Ind)Cl ₂	1255536-61-8

M300 series Grubbs Catalyst® Fast-initiating

M310	NHC	Ligand L1	Ligand L2	Trade Name	Chemical Formula	CAS Number
	SiMes	py	-	Grubbs Catalyst® M310	(SiMes)Ru(py)(Ind)Cl ₂	1031262-76-6

M700 series Grubbs Catalyst® Hoveyda-type

M700	NHC	R	Ligand L	Trade Name	CAS Number
	-	-	PCy ₃	Hoveyda Grubbs Catalyst® M700	203714-71-0
	SiMes	NH(CO)CF ₄	-	Hoveyda Grubbs Catalyst® M710	1025728-56-6
	SIPr	NH(CO)CF ₃	-	Hoveyda Grubbs Catalyst® M711	1212008-99-5
	SiMes	H	-	Hoveyda Grubbs Catalyst® M720	301224-40-8
	SI(o-Tol)	H	-	Hoveyda Grubbs Catalyst® M721	927429-61-6
	SIPr	H	-	Hoveyda Grubbs Catalyst® M722	635679-24-2
	SiMes	NH(CO)OBu	-	Hoveyda Grubbs Catalyst® M730	1025728-57-7
	SIPr	NH(CO)OBu	-	Hoveyda Grubbs Catalyst® M731	1212009-05-6

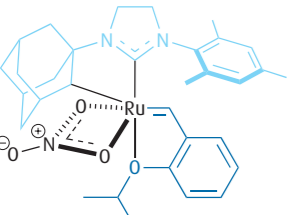
M800 series
 Grubbs Catalyst® Latent

M800	NHC	Trade Name	Chemical Formula	CAS Number
	SIMes	Grubbs Catalyst® M800	(SIMes) ₂ Ru(Ind)Cl ₂	1383684-54-5

M1000 series
 Grubbs Catalyst® CAAC-Coordinated

M1001	Trade Name	Chemical Formula	CAS Number
	Grubbs Catalyst® M1001	C ₃₂ H ₃₉ Cl ₂ NORu	1632041-02-1

M2000 series
 Hoveyda Grubbs Catalyst® Z-selective

M2001	Trade Name	CAS Number
	Hoveyda Grubbs Catalyst® M2001	1352916-84-7

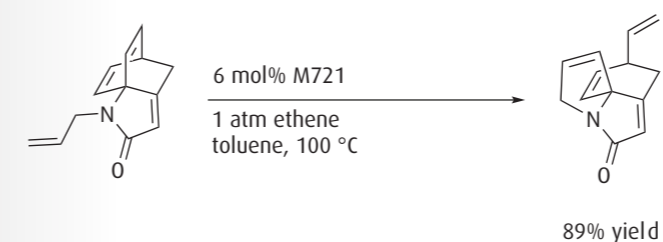
General reaction procedure

Metathesis reactions are versatile reactions that can be performed in most situations without the need for extensive optimization. But in those difficult synthetic situations, our team of industrial experts will tailor each reaction to the specific requirements for the project, ensuring precise and selective product formation.

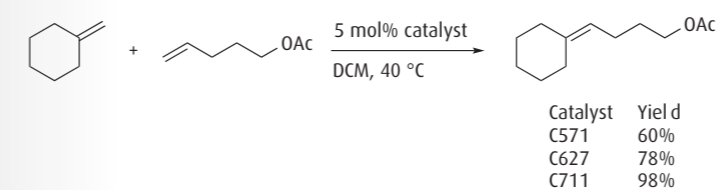
Optimizing the catalyst

For general metathesis reactions, Hoveyda Grubbs Catalyst® M720 and the Hoveyda Grubbs Catalyst® M730 series are recommended. These catalysts initiate at room temperature and are highly stable, enabling simple storage and handling.

In metathesis reactions involving sterically hindered alkenes, it may be necessary to use a more specialized catalyst. For instance, the Hoveyda Grubbs Catalyst® M721 can be used to perform sterically hindered ring rearrangement reactions owing to the decreased steric bulk of the protruding ligands.



Alternatively, if your substituents are bulky, substituted alkenes, the Hoveyda Grubbs Catalyst® M722 could result in a higher yield.



If the reaction conditions are prone to ethylene generation, a catalyst bearing cyclic alkyl amino carbene (CAAC) ligand such as M1001 or M1002 might be more suitable. Additionally, these catalysts can give different selectivity for oligomerization versus ring closure in macrocyclization reactions.

Choosing the right conditions

Choosing the right operating conditions for your industrial reaction relies on careful optimization. Finding the right temperature is vital for catalyst initiation, with low temperatures being advantageous from an environmental perspective. Umicore catalysts typically initiate at low temperatures, between room temperature and 40 °C. Furthermore, the exact concentrations of reagents vary according to the specific metathesis reaction: cross metathesis requires concentrated solutions, macrocyclizations require dilute solutions and other ring-closing metathesis reactions require intermediate concentrations.

Likewise, choosing the appropriate solvent to mediate metathesis reactions relies on understanding the various

properties of the solvents. Preferred solvents include non-polar, hydrocarbon-based solvents, chlorinated solvents and peroxide-resistant ethers, due to their weak binding affinity to the catalyst complex.

Finally, ensuring the catalytic reaction is devoid of catalyst poisons is also vital. Peroxides oxidize the metal-carbene bond, rendering the catalyst inactive. Furthermore, ethene should also be removed as its presence could also result in catalyst decomposition. In addition, all of the Hoveyda Grubbs Catalyst® products are air and moisture stable as solids, but in solution are vulnerable to oxygen. Therefore, reactions need to be run in the presence of argon or nitrogen gases to ensure the exclusion of oxygen.

Preferred solvents	Usable in certain conditions	Not recommended for use
Toluene, xylenes, mesitylene	MeOH, EtOH, nBuOH	DMSO, DMF, NMP
Heptanes, hexanes	THF, ether	MeCN
DCM DCE, chlorobenzene	Water (neutral/acidic)	Pyridine and other amines
EtOAc, ^t PrOAc		Water (basic)
TBME, Me-THF		

Optimizing the reaction procedure

Beyond conditions, there are multiple aspects of the synthetic procedure that must be considered for the successful completion of any reaction. Strongly coordinating functional groups must be masked so as to not disrupt the catalyst activity; the concentration of the various substrates must be optimized to prevent substrate polymerization, but encourage the desired format of metathesis.

Furthermore, to prevent unwanted side-effects of metathesis reactions such as the isomerization of alkenes, it is sometimes necessary to use additives to suppress the unwanted reactions. For instance, mild acids such as acetic acid can be added to reactions to prevent hydride formation, as illustrated in the following diagram.



no additive:	<5%	95%
with 10 mol% 1,4-benzoquinone:	>95%	none
with 10 mol% AcOH:	>95%	none

Metathesis reactions that bring together two terminal alkenes produce ethene as a by-product. Although ethene is a gas, it is soluble in organic solvents and can remain in the reaction mixture. Ensuring that ethene or any other gaseous by-product is efficiently removed will drive the reaction equilibrium toward completion. This can be accomplished by bubbling an inert gas through the reaction mixture over the course of the reaction. On scale, this technique is used frequently to help maximize catalyst lifetime.

For the selective formation of *cis*- or *Z*-alkenes, one can use the Hoveyda Grubbs Catalyst® M2001 and Hoveyda Grubbs Catalyst® M2002, which provide selectivity in both ring-closing or cross metathesis reactions.

Supportive services

As leading experts in catalyst research and development, Umicore has decades of experience developing ground-breaking chemistry. We offer a range of supplementary services to help scale your chemical reaction, regardless of your reactants, products and market. We work across your development pipeline to devise strategies to deliver solutions to solve any optimization challenges faced along the process; from research to product launch and beyond.

We will work with you to define the best route to your synthetic target or optimize the production to maximize yield or selectivity. This could be through identifying new reaction routes by devising alternative retrosynthesis, which are then screened as potential reactions at all scales of the industry.

Understanding the best route to your product comes down to understanding the complex chemistry driving your reaction. We work across all phases of a project's pipeline, from the initial investigations into the viability of catalytic reactions, to optimizing processes for large-scale production. Our understanding and experience in the manufacturing and

development process means we know what expertise needs to be deployed at each stage of a project.

At Umicore, we have the expertise in global manufacture and development to ensure the successful and reliable supply of reagents, as well as the technical expertise to identify the best catalyst and conditions for your reaction. Our solutions are tailored to each of our customer's reactions and each catalyst loading is optimized to the requirements of each project.

Let's work together to accelerate your product synthesis.



About Umicore Precious Metals Chemistry

Umicore Precious Metals Chemistry is part of the Umicore group, a global materials and technology company with locations around the world. With over 50 years' experience working with customers across the globe, Umicore has helped to develop innovative metals and materials technology to help solve the most challenging chemistry problems.

Taking a collaborative and simple approach to its business practice, Umicore PMC operates in many of the key markets that are vital to developing the solutions to real-world problems. This includes: pharmaceutical development, fine chemicals, automotive and electronics. Within these markets, Umicore PMC offers many competitive technologies that develop and deliver ground-breaking innovations.

With a comprehensive portfolio of catalysts including the Grubbs metathesis, cross coupling and hydrogenation catalysts, Umicore PMC offers an extensive portfolio of chemical technologies to the market.

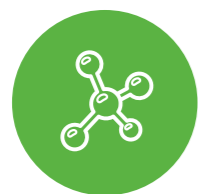
In addition to Umicore PMC's chemical and engineering expertise, sustainability lies at the heart of the Umicore PMC business and the wider Umicore group. Sustainability is materialized through Umicore PMC's drive towards developing efficient methods of recycling precious metals and discovering new more long-term sustainable chemical reactions.

Collaboration is at the center of success and innovation. By working together in multiple aspects of R&D, process development and industrial manufacturing, we can create innovative and cost-effective industrial synthesis for your project.

We understand the rapidly changing needs of our clients throughout the world, & provide:



Innovative,
metal-based
chemistry



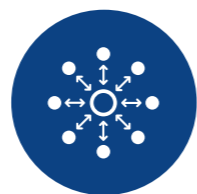
Collaborative
R&D



Process
development
and scale up



Commercial-scale
manufacturing



Supply chain
expertise

Let's work together to create ground-breaking chemistry



For inquiries and additional information please contact

Umicore AG & Co. KG
Rodenbacher Chaussee 4
63457 Hanau-Wolfgang
Germany

Tel.: +49 (6181) 59 2471
Fax: +49 (6181) 59 2970
chemistry@umicore.com
www.pmc.umicore.com

www.umicore.com


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