XiMo the innovation catalyst

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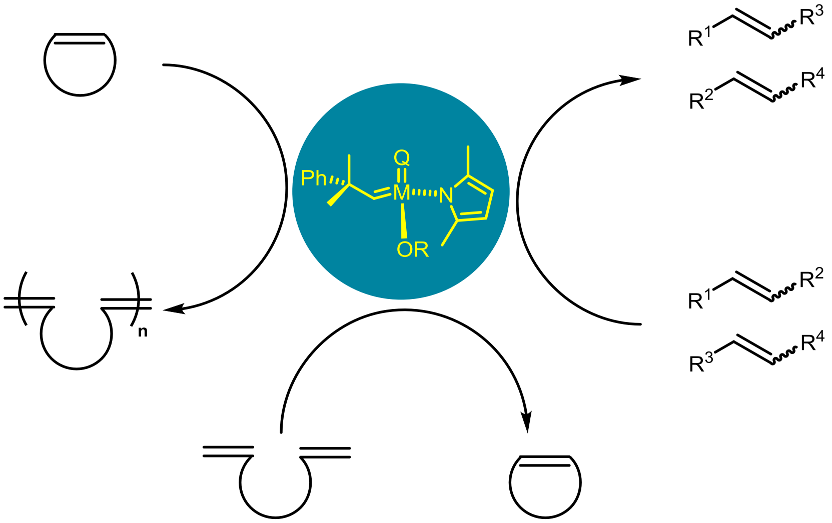
Application guide to XiMoPac-Mo001 and 003, XiMo’s Mo-based proprietary metathesis catalysts formulated in paraffin

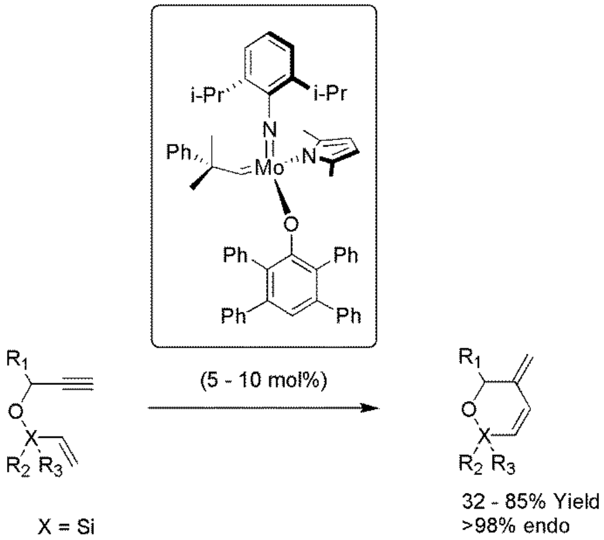


First reported in 1955 by Anderson *et al*. with a Ti(II) catalyst,[1] the metathesis reaction gained interest and popularity over the years. Further investigations in the mechanism of the transformation by Chauvin sparked the development of novel metathesis catalysts.[2] This breakthrough in olefin metathesis was rewarded in 2005 by a Nobel Prize to Chauvin, Grubbs and Schrock for their contributions. The development of this technology over the years brought to the forefront the use of Molybdenum (Mo), Ruthenium (Ru) and Tungsten (W) as metal for metathesis catalysts.[3, 4]

Early development and design of these catalysts highlighted 2 main systems, a Mo/W-based one and a Ru-based one.[3, 4] The Mo/W-system, mainly developed by Schrock, Hoveyda and their coworkers, is highly active to a broad range of substrates but has limited tolerance to certain functional groups and has high air and moisture sensitivity, making its use more limited. The Ru-system, mainly developed by Grubbs and his group, is less reactive than the Mo/W-system but is more tolerant to a variety of functional groups and is less air sensitive.[5]

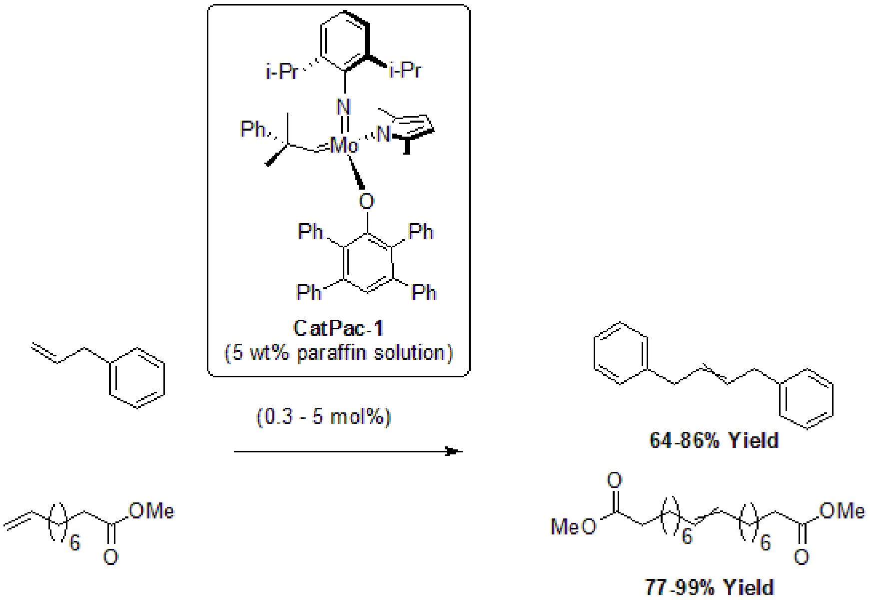
To remedy the air sensitivity of the Mo/W-based complexes, XiMo developed a process to protect these sensitive metathesis catalysts against moisture and air by formulating them in macrocrystalline wax. This formulation of catalysts allows the setup for metathesis reaction under average laboratory conditions. As a proof of concept, the team of researchers at XiMo ran several cross metathesis and ring closing metathesis reactions using basic Schlenk techniques.

The first 2 catalysts offered are XiMoPac-Mo001 and XiMoPac-Mo003, two Molybdenum based aryl-oxide catalysts. XiMoPac-Mo001 has showed great results in cross metathesis and ring closing metathesis. Recently, Hoveyda and Schrock reported the use of this catalyst in the endo-selective enyne ring closing metathesis. Using up to 10 mol% of the catalyst, good to excellent yields were observed with great selectivity (>98% endo).[6]



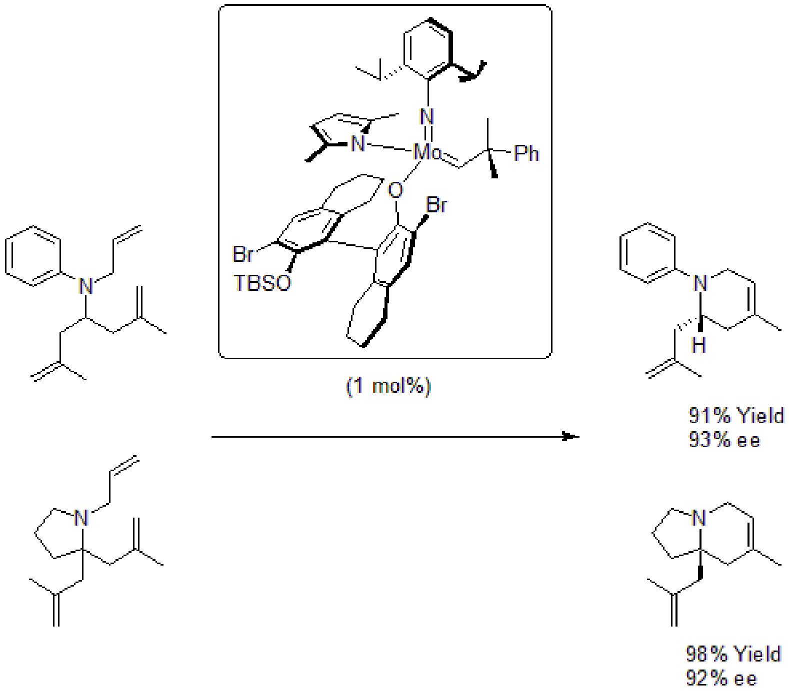
XiMoPac-Mo001 was also used in several test reactions to evaluate its activity when used outside of the glovebox. Using a simplified protocol, an oven dried Schlenk flask under a flow of Argon is used to run the reaction. The activity of XiMoPac-Mo001 was also showcased by using as little as 0.3 mol% for the homo-coupling of 9-Decenoicacid methyl ester yielding up to 84% conversion after 2 hours. When using 1 mol%, quantitative conversion was observed.

A more challenging substrate, allyl-benzene, was also tested to investigate the activity and selectivity of XiMoPac-Mo001 using a similar protocol. This substrate proves to be very challenging due to the presence of peroxide impurities that can poison the catalyst. Several procedures, described in more details below, were used to purify the substrate. Using as little as 0.3 mol% of **XiMoPac-Mo001** yielded the desired product in 64% yield. It is important to note that no isomerization of the product was observed.



The Molybdenum catalyst in XiMoPac-Mo003 was developed by Schrock and Hoveyda's group a few years ago, where they highlighted its efficiency in enantioselective alkene metathesis. Using 1 mol%

of catalyst, the researchers were able to convert a variety of alkenes to the desired ring closed product in excellent yields and enantioselectivity.[7]



XiMoPac-Mo003 was also tested in RCM using our simplified protocol, which does not require the use of a glovebox, using diethyl diallyl malonate as a substrate. Using only 1 mol% of catalyst, quantitative conversion was observed.

This newly developed technology allows researchers to use some of the most active and selective catalysts for metathesis in a more user friendly format. The wax formulation with a defined and pre-weighted catalytic amount (ca. 0.01 mmole) of catalyst, gives access to researcher tools that were previously more challenging to use due to their high air sensitivity.

These metathesis catalysts proved to be as efficient as their ruthenium counterpart and in some cases with higher activity and selectivity. Furthermore, a study of the removal of Molybdenum demonstrated the successful removal down to ppm levels. The low toxicity of molybdenum, essential in trace amounts for humans, makes these metathesis catalysts the system of choice for the synthesis of active pharmaceutical ingredients.

1. Product Identifier:

A.

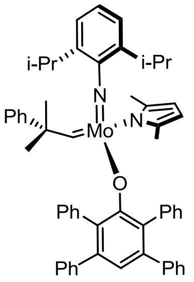
Name: **XiMoPac-Mo001**

Chemical name: Molybdenum, [2,6-bis(1-methylethyl)benzenaminato(2-)](2,5-dimethyl-1H-pyrrol-1-yl)(4',6'-diphenyl[1,1':3',1"-terphenyl]-2'-olato)(2-methyl-2-phenylpropylidene), -stereoisomers

Chemical formula: $C_{58}H_{58}MoN_2O$

Molecular weight: 895.03 g/mole

Structure:



Product composition: 200 mg, 5 wt% pellet

Melting range: 50 – 55 °C

Component	*CAS No.*	*Concentration*	*Amount*
Mo-complex	1572180-69-8	5 wt%	10 mg
Macrocrystalline wax	64742-43-4	95 wt%	190 mg

B.

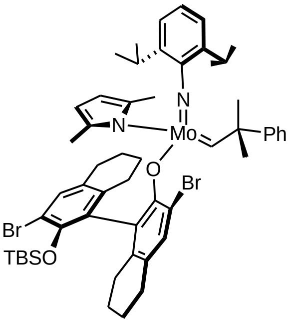
Name: **XiMoPac-Mo003**

Chemical name: Molybdenum, [2,6-bis(1-methylethyl)benzenaminato][(1*R*)-3,3’-dibromo-2’-[[(1,1-dimethylethyl)dimethlysilyl]oxy]-5-5’,6,6’,7,7’,8,8’-octahydro[1,1’-binaphtalene]-2-olato-κ*O*](2,5-diemthyl-1*H*-pyrrole-1-yl)(2-methyl-2-phenylpropylidene)-, *stereoisomer*

Chemical formula: $C_{54}H_{70}Br_2MoN_2O_2Si$

Molecular weight: 1062.98 g/mole

Structure:



Product composition: 100 mg, 10 wt% pellet

Melting range: 50 – 55 °C

Component	*CAS No.*	*Concentration*	*Amount*
Mo-complex	1101202-11-2	10 wt%	10 mg

Macrocrystalline wax	64742-43-4	90 wt%	90 mg

2. General notes:

These types of Mo- based metathesis catalysts are very sensitive to oxygen and moisture when they are handled in pure, isolated form or used in solution. Therefore it is necessary to handle these materials under inert atmosphere. This would normally require the chemist to handle them in a N_2 or Argon filled glove box where both O_2 and water content are in the low ppm range (preferably < 5 ppm).

However, catalysts in the present composition (formulated in paraffin pellets) are stable enough to be handled, weighed or even stored under air for some hours. This new formulation allows the reactions to be accomplished using ordinary Schlenk techniques.

However it is important to note that once dissolved in solvents, the catalyst becomes just as sensitive to oxygen and moisture as it was without the paraffin. Therefore the solvents and feedstock as well as the reaction environment have to be kept oxygen and moisture free. **This is absolutely essential for a successful experiment; therefore all manipulation with the solvents, substrates and reagents (once they are pretreated for the reaction) has to be accomplished under inert atmosphere.**

To fulfill the above requirements:

a) The equipment used in the experiments, especially the glassware, has to be kept in an oven at 120-140 °C for at least 4 hours in order to remove all moisture adsorbed on their surfaces and has to be cooled down under inert atmosphere.

b) Solvents, reagents and the substrates have to be free from water (preferably <10 ppm measured by coulometic KF-titration), organic hydroperoxides (determined by iodometric titration), acidic protons, alcohols, aldehydes and dissolved oxygen. Oxygen can be removed either by sonication while inert gas (N_2, Ar) is bubbled through or by distillation under inert atmosphere. Distillation at high temperature and under inert atmosphere or vacuum not only removes the dissolved oxygen but also facilitates the decomposition of organic peroxides which could be present in the olefin substrate. Once oxygen and organic peroxides are removed the next step of a proper feedstock pretreatment is the removal of water. It can be achieved by drying the feedstock over activated 3Å molecular sieves (10 wt%) or activated Al_2O_3 under inert atmosphere for at least 24h. In order to transfer substrates, solvents or stock solution, proper Schlenk technique needs to be done with a continuous flow of inert gas. Commercial alkanes (e.g. pentane, heptane) generally contain olefins as impurities which may interfere with the desired transformation, therefore these impurities have to be removed by a thorough acidic (cc. H_2SO_4 / cc. HNO_3) wash treatment followed by a careful drying and distillation from potassium metal.

c) In case of cross-metathesis of terminal olefins an equivalent amount of ethylene is formed. Therefore a gas outlet is necessary to avoid overpressure avoiding the reversibility of the reaction.

d) In general these catalysts provide high to very high TONs (turnover number) in most of the CM (cross-metathesis) and RCM (macrocyclic ring-closing metathesis) reactions at ambient temperature; however most of them can be done at 50 to 80 °C to accelerate the reaction.

<u>Storage of catalysts:</u>

Although under inert conditions these complexes are stable enough to be stored at ambient temperature for months without any detectable decomposition, to preserve their quality in the course of a long-term storage the unopened packages should be kept in a fridge at 4 °C. To prevent condensation of moisture onto the surface of pellets when packages are taken out from the fridge they should be allowed to warm back to ambient temperature prior to opening. According to our experiences they are not particularly light sensitive, but to be on the safe side it is better to protect them from direct sunlight when they are stored.

3. Reactions step-by-step:

In general, reactions are performed in dry Schlenk-tubes attached to a vacuum-argon manifold. (Below a simplified version of the procedure can also be found using only inert gas flow instead of a vacuum-argon manifold).

i. Into a Schlenk-tube which has been pre-dried at 120-140 °C for at least 4 h in an oven and allowed to cool down under Ar/N_2-atmosphere a piece of XiMoPac pellet is added.
ii. The vessel is tightly closed with a rubber septum, taken under vacuum for a few minutes before being filled back with inert Ar/N_2. This process is repeated at least 3 times before the addition of the stock solution of the substrate via cannula.
iii. For reactions in which terminal olefins are used, an equimolar of ethylene gas is generated. Therefore, the Schlenk-tube is furnished with a pressure equalizing bubbler filled with silicon oil or the same solvent used for the reaction (Paraffin oil is not suitable due to its possible olefin content! See *Figure 1*).

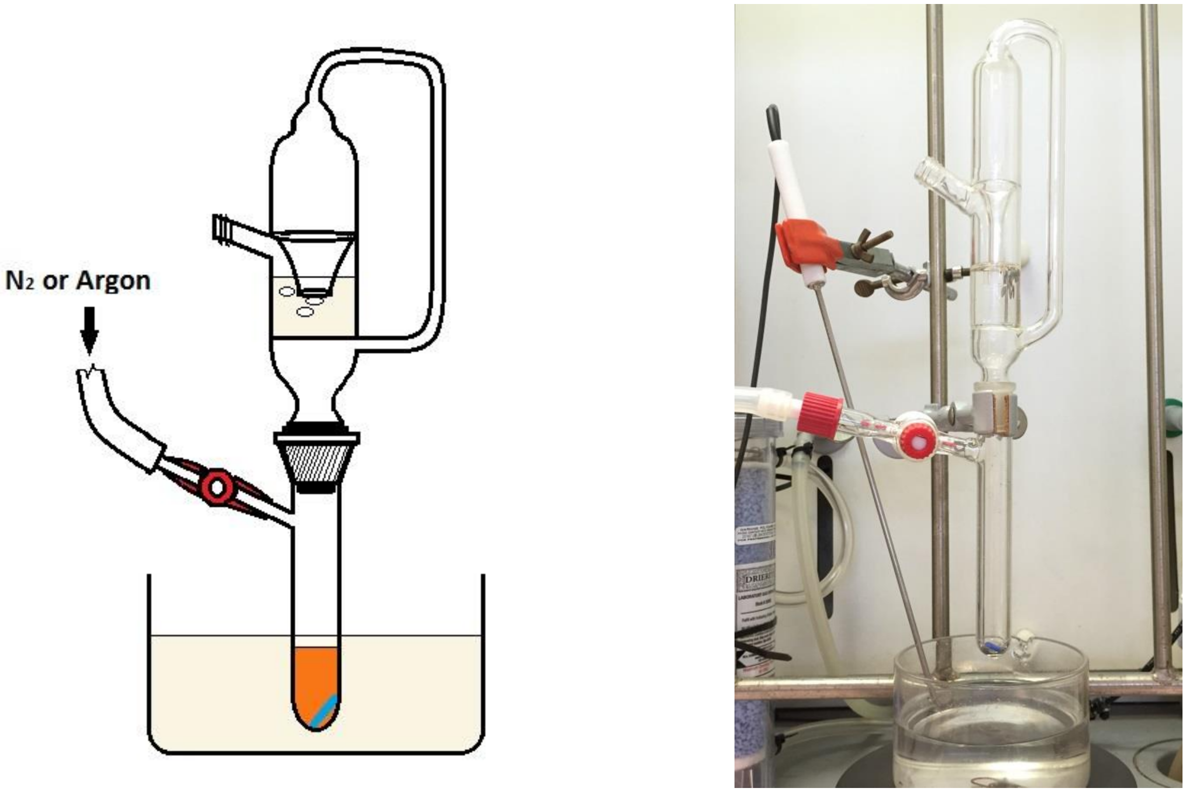


Figure 1. A typical reaction setup for olefin metathesis using XiMoPac catalyst system

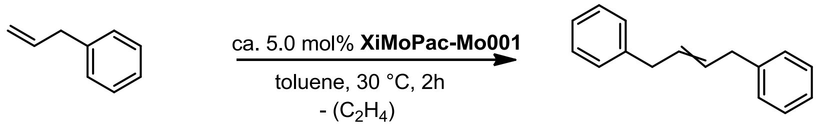
iv. Finally, under continuous purging with inert gas the reaction mixture is heated to the reaction temperature and stirred for the necessary time before it is quenched, typically with wet acetonitrile, or methanol.

4. Work-up:

The work-up procedure varies depending on the substrate. When the polarity of the product significantly differs from the paraffin, the separation is usually less problematic. However, when non-polar product is generated, the removal of paraffin can be troublesome. To overcome this problem a simple procedure was elaborated in which the paraffin is precipitated with acetonitrile followed by the filtration of the obtained slurry through a pad of SiO_2. Details of this procedure are described below.

5. Examples:

*i. Homo Cross-Metathesis (HCM) of allylbenzene (**1**) with 5.0 mol% of XiMoPac-Mo001*



1
Allylbenzene
C_9H_{10}
M.W.:118,18

2
(*E*/*Z*)-1,4-Diphenyl-but-2-ene
$C_{16}H_{16}$
M.W.:208,30

Under argon atmosphere, into a dry 10 mL Schlenk-tube one piece (200 mg) of XiMoPac-Mo001 (10 mg, 0.011 mmole X051 in 90 mg macrocrystalline wax; ca. 5.0 mol%) was added. The vessel was closed with a rubber septum and taken under vacuum for a few minutes before being filled back with argon. This step was repeated 3 times before the stock solution (deoxygenated and pre-dried according to the detailed procedure described) of allylbenzene (**1**; 29 µL, 26 mg, 0.22 mmole) in toluene (2.0 mL) was added via cannula. According to analyses the peroxide content of the stock solution was below the limit of detection and its water content was 116 ppm by weight (KF). Then the reaction mixture was heated to 30 °C and stirred for 2 h with a continuous argon flow.

<u>Work-up:</u>
After 2 h, a stock solution of 4-methylanisole, an internal standard (200 µL, c=100 mg/mL in acetonitrile), was added with wet acetonitrile (10 mL total volume). At this step the majority of the paraffin precipitated. The obtained slurry was thoroughly thoroughly stirred or shaked before it was filtered through a short silica column (2.0 mL) which was then eluted with acetonitrile (10 mL). From the homogenous combined elute 1.0 µL was injected and analyzed by GCMS-FID: column: Phenomenex Zebron-Inferno 35HT (30 m x I.D.:0.25 mm); 50 °C - 5 min, 18 °C/min ↗ 275 °C, 20 °C/min ↗ 340 °C, 6.4 min. **Conversion: 87%, Selectivity: >99%.**

When the same reaction was performed for 4 h, quantitative **conversion >99%** was obtained.

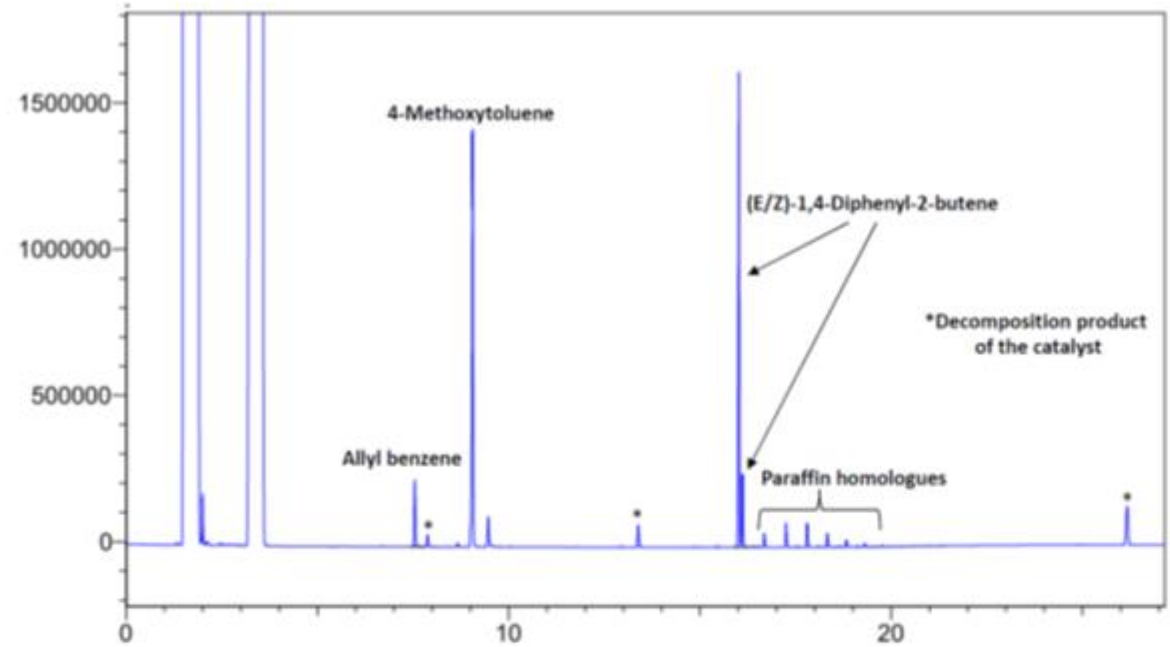
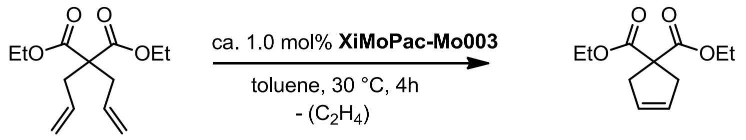


Figure 2. FID chromatogram of allylbenzene homo-cross metathesis with 5.0 mole% XiMoPac-Mo001 (Reaction time: 2 h, conversion: 87%)

ii. *Ring-Closing Metathesis (RCM) of diethyl diallylmalonate (DEDAM, **3**) with 1 mol% of XiMoPac-Mo003:*



3
Diethyl diallyl malonate
$C_{13}H_{20}O_4$
M.W.:240,30

4
4,4-Diethoxycarbonyl-1-cyclopentene
$C_{11}H_{16}O_4$
M.W.:212,24

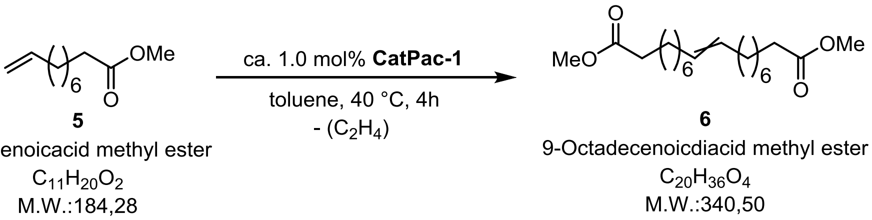
Under argon atmosphere, into a pre-dried 10 mL Schlenk-tube one piece (100 mg) of XiMoPac-Mo003 catalyst (10 mg, 0.011 mmole X051 in 90 mg macrocrystalline wax; ca. 1.0 mol%) was added. The vessel was closed with a rubber septum and taken under vacuum for a few minutes before it was filled back with argon. This step was repeated 3 times before the stock solution (deoxygenated and pre-dried according to the above detailed procedure) of DEDAM (**3**; 227 µL, 226 mg, 0.94 mmole) in toluene (2.0 mL) was added via cannula. According to analyses the peroxide content of the stock solution was below the limit of detection and its water content was 40.6 ppm by weight (KF). The reaction mixture was then heated to 30 °C and stirred for 4 h under a continuous flow of argon.

Work-up:

After 4 h, a stock solution of mesitylene, an internal standard (200 µL, c=100 mg/mL in acetonitrile) was added. The reaction mixture was diluted to 10 mL with wet acetonitrile. At that point the majority of the paraffin precipitated. The obtained slurry was thoroughly thoroughly stirred or shaked before it was filtered through a short silica column (2.0 mL) which was then eluted with acetonitrile (10 mL). From the homogenous combined elute 200 µL diluted to 1 ml with acetonitrile and 1 µL of the final solution was injected and analyzed by GC-MS-FID: column: Phenomenex Zebron-Inferno 5HT (30 m x I.D.:0.25 mm); 50 °C - 5 min, 25 °C/min ↗ 340 °C, 8.4 min.

Conversion: >99%.

iii. *HCM of methyl dec-9-enoate (9-DAME, **3**) with 1.0 mole% of XiMoPac-Mo001 – **Simplified manipulation***



5
9-Decenoicacid methyl ester
$C_{11}H_{20}O_2$
M.W.:184,28

6
9-Octadecenoicdiacid methyl ester
$C_{20}H_{36}O_4$
M.W.:340,50

Under argon atmosphere, into a pre-dried 10 mL glass vessel equipped with an oil-bubbler and an inert gas inlet (to this end typically a Schlenk-tube or a two-neck round bottle flask can be used) one piece (200 mg) of XiMoPac-Mo001 (10 mg, 0.011 mmole X051 in 190 mg macrocrystalline wax, ca. 1.0 mol%) was added while a continuous argon flow was maintained (*Note 1.*). Then 9-DAME (**5**; 235 µL 266 mg, 1.44 mmol) and anhydr. toluene (2.0 mL) were added consecutively *via automatic pipette* before the reaction mixture was heated to 40 °C and stirred for 4 h. In order to purge out the evolving ethylene the inert gas flow was kept constant in the course of the whole reaction.

Work-up:

After 4h a stock solution of ethyl palmitate (internal standard; 5 ml, c=40 mg/mL) in toluene was added. The reaction mixture was diluted to 25 mL with wet acetonitrile. At that point the majority of the paraffin precipitated. The obtained slurry was thoroughly thoroughly stirred or shaked before it was filtered through a short silica column (2.0 mL) which was then eluted with acetonitrile (15 mL). From the homogenous combined elute 200 µL diluted to 1 ml with acetonitrile and 1 µL of the final solution was injected and analyzed by GC-MS-FID: Phenomenex Zebron-Inferno 35HT (30 m x I.D.:0.25 mm); 100 °C - 5 min, 50 °C/min ↗ 250 °C, 10 min, 50 °C/min ↗ 350 °C, 5 min. **Conversion: 82%**. Selectivity: >99%

iv. ***Completion of the reaction:** working under dynamic vacuum without using solvent – neat reaction condition:*

Under argon atmosphere, into a pre-dried 10 mL glass vessel equipped with a gas inlet (a Schlenk-tube or a two-neck round bottom flask can be used) one piece (200 mg) of XiMoPac-Mo001 (10 mg, 0.011 mmole X051 in 190 mg macrocrystalline wax; ca. 1.0 mol%) was added while a continuous argon flow was maintained. Then 9-DAME (**5**; 235 µL 266 mg, 1.445 mmol) was added *via automatic pipette* before the vessel was closed with a glass stopper and the gas inlet connected to a membrane pump. Afterwards the vacuum was set to 25 mbar (*Note 2.*) and the reaction mixture was heated to 65 °C for 2 h.

Work-up:

Same as under point *iii.*
Conversion: 95% (!).

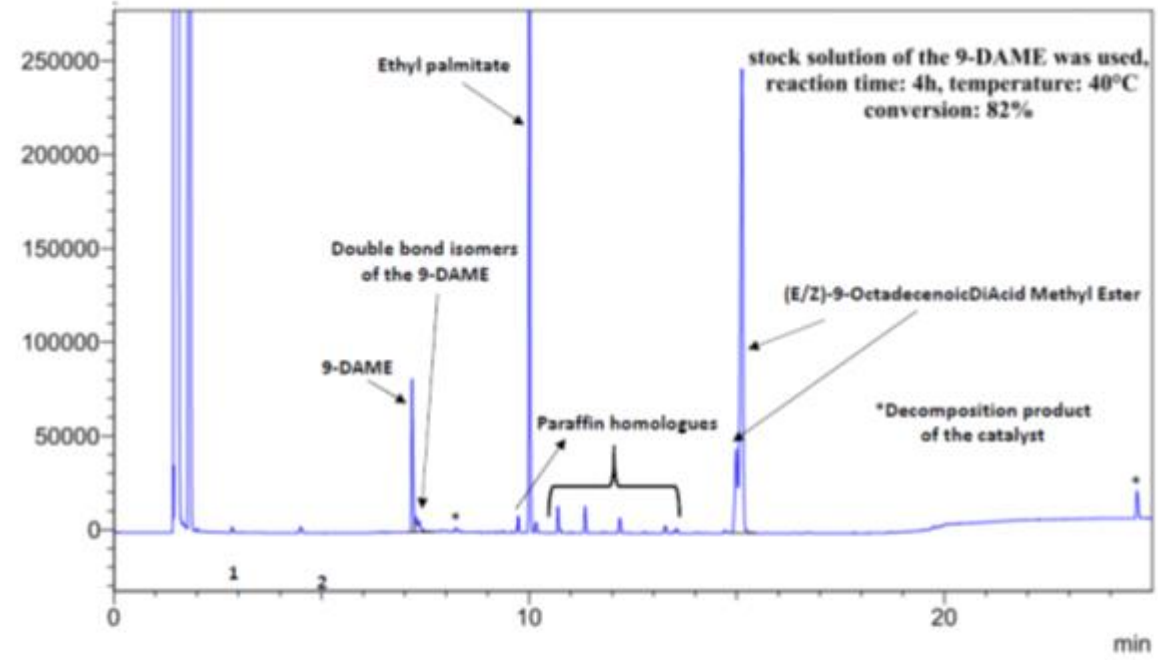


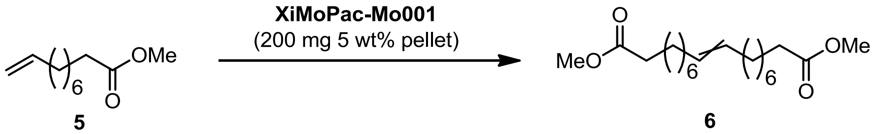
Figure 4. FID chromatogram of 9-DAME homo-cross metathesis with 1.0 mole% XiMoPac-Mo001

Notes:

1. **In these last two examples the tedious vacuum-argon cycling procedure has been avoided; instead, the hot vessel was directly connected to an argon line and let cool down in a continuous flow.**
2. **When the reaction was performed neat at 65 °C and instead of dynamic vacuum only a continuous argon flow was applied double-bond migration (isomerization) and thus formation of homologues was observed to considerable (10-15%) extent. Wherever selectivity data is disclosed it refers to the percentage of the targeted product in the reaction mixture in which various homologues derived from double-bond migratory isomerization are also present. However this type of side reaction was not noticeable when continuous dynamic vacuum was used.**

Collected results:

1. Simplification of the "Use" – Schlenk-type technique was replaced with simple argon flushing:



5
9-Decenoicacid methyl Ester
$C_{11}H_{20}O_2$
M.W.:184,28

6
9-Octadecenoicdiacid methyl ester
$C_{20}H_{36}O_4$
M.W.:340,50

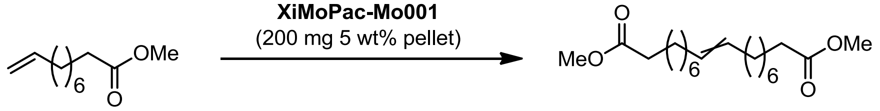
Type	Loading [mol%]	Temperature[°C]	t [h]	Conversion[a] [%]
Neat	1.0	65°C	2	98[b]
	1.0	65°C	2	98[b]
	1.0	65°C	2	99[b]
	0.3	65°C	2	77
	0.3	65°C	2	80
	0.3	65°C	2	84
Feedstock is added in toluene solution (c= 0.56 M)	1.0	40°C	4	84
	1.0	40°C	4	89

[a] The given data are based on non-calibrated GC results.

[b] Double bond shift, thus formation of homologs can be observed to considerable extent (10-14%) due to the higher temperature.

Pretreatment of the 9-DAME: distillation under inert atm., drying over 10 wt% mol. sieves; Water by *KF* = 57.6 ppmwt, peroxide content under det. limit

2. Completion of the reaction - Use of membrane pump to remove ethylene



5
9-Decenoicacid methyl Ester
$C_{11}H_{20}O_2$
M.W.:184,28

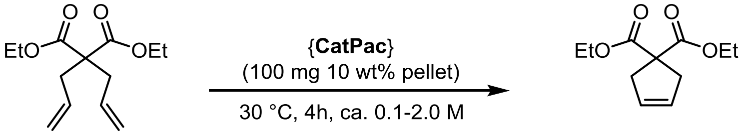
6
9-Octadecenoicdiacid methyl ester
$C_{20}H_{36}O_4$
M.W.:340,50

Type	Loading [mol%]	Temperature[°C]	t [h]	Conversion[a] [%]	Selectivity[a, b][%]
Neat	1.0	65°C	2	94	>99
	1.0	65°C	2	96	>99
	1.0	65°C	2	95	>99

[a] The given data are based on non-calibrated results.

[b] Ratio of the desired product to the undesired homologues (formed through double bond isomerization).
Pretreatment of the 9-DAME: distillation under inert atm., drying over 10 wt% mol. sieves; *KF* = 57.6 ppm, PV = <LOD.

3. RCM of DEDAM



3
Diethyl diallyl malonate
$C_{13}H_{20}O_4$
M.W.:240,30

4
4,4-Diethoxycarbonyl-1-cyclopentene
$C_{11}H_{16}O_4$
M.W.:212,24

Catalyst	Loading [mol%]	Conversion[a] [%]
XiMoPac-Mo001	5.0 [mol%]	>99 (>99) [b]
	1.0 [mol%]	86 (>99) [b]
XiMoPac-Mo003	5.0 [mol%]	>99 (>99) [b]
	1.0 [mol%]	99 (>99) [b]

[a] The given data are based on non-calibrated results. (GC peak areas).

[b] Control experiment performed in nitrogen filled glove-box.

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