

University of Groningen

Volume intensified dilution of a ring-closing metathesis in ethyl acetate by means of a membrane-assisted process in solvent recycle

Porto-Carrero, Wim; Cupani, Anna; Veenstra, Marieke J.; Dorbec, Matthieu; Eykens, Lies; Ormerod, Dominic

Published in:
Journal of Chemical Technology and Biotechnology

DOI:
[10.1002/jctb.6109](https://doi.org/10.1002/jctb.6109)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Porto-Carrero, W., Cupani, A., Veenstra, M. J., Dorbec, M., Eykens, L., & Ormerod, D. (2019). Volume intensified dilution of a ring-closing metathesis in ethyl acetate by means of a membrane-assisted process in solvent recycle. *Journal of Chemical Technology and Biotechnology*, 94(9), 2990-2998.
<https://doi.org/10.1002/jctb.6109>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Volume intensified dilution of a ring-closing metathesis in ethyl acetate by means of a membrane-assisted process in solvent recycle

Wim Porto-Carrero,^a Anna Cupani,^{a,b} Marieke J Veenstra,^{a,c}
Matthieu Dorbec,^a Lies Eykens^a and Dominic Ormerod^{a*} 

Abstract

BACKGROUND: Ring-closing metathesis (RCM) for the synthesis of macrocycles has been used more and more often over recent years, including some interesting applications on industrial scale. However, like all macrocyclization strategies RCM is plagued by the traditional issue of low volume efficiency. To-date this is typically addressed in a molecule specific manner with varying degrees of success. Here we report a process intensification method of metathesis macrocyclization that reduces the solvent load required for the reaction significantly.

RESULTS: Metathesis macrocyclizations were successfully carried out in a solvent volume of upto 82% lower than an equivalent batch reaction, with only minimal impact upon the reaction outcome. A switch of reaction solvent to ethyl acetate renders the process more benign and applicable to large scale.

CONCLUSION: A membrane-assisted processing method that relies upon organic solvent nanofiltration permitting an internal solvent recycling and concomitant *in situ* product removal. The method is also designed to be applicable to a wide range of metathesis cyclizations.

© 2019 Society of Chemical Industry

Keywords: organic solvent nanofiltration; membrane filtration; macrocyclization; process intensification; ring closing metathesis

INTRODUCTION

Cyclic molecules containing 12 or more atoms, known as macrocycles,¹ constitute a unique class of compounds that can be found in natural products,² drug molecules,³ metal ligands⁴ and (chiral) chromatography stationary phases⁵ to name but a few. However, the synthesis of macrocycles remains a challenge due to the competition between cyclization and oligomerization. This typically results in the requirement for high dilution techniques that consume large volumes of solvent in the production of a relatively small quantity of reaction product.

Though there is a plethora⁶ of methods to synthesize macrocycles, ring-closing metathesis (RCM) has become a popular method^{7–11} due in part to the high chemoselectivity and functional group tolerance of the catalysts that have been developed over recent decades.^{12,13} Furthermore, the inherent reversibility of olefin metathesis reactions can have important implications on the outcome of the equilibrium between RCM and cross-metathesis (CM); the latter leading to acyclic products. Indeed, Fogg and co-workers reported oligomers as intermediates¹⁴ in RCM reactions. However, despite the fact that this equilibrium ring-closing metathesis (ERCM)¹⁵ can potentially be exploited during the synthesis of macrocycles there is often still the necessity to use high dilution conditions.^{16,17}

Reducing the amount of waste from industrial chemical production is of fundamental importance both from an environmental and an economic point of view. Because 80% to 90%¹⁸ of the

reaction mass and a significant portion of energy use can be directly attributed to solvents, a reduction of the quantities used can have a significant effect on emissions,¹⁹ economics and health and safety issues related to a chemical macrocyclization process.

Recently we have developed a membrane-assisted processing method to enable reactions that require high dilution to be performed in significantly reduced solvent volumes.²⁰ This new membrane-based processing method has been demonstrated with cyclic peptide formation²¹ a type of molecule that possess conformational preorganization²² that tends to be beneficial for cyclization. Cyclization of molecules that have lower conformational preorganization where the reactive ends are less likely to be in the required conformation for cyclization are even more problematic, resulting in longer reaction times and more secondary products.

* Correspondence to: D Ormerod, VITO (Flemish Institute for Technological Research), Separation and Conversion Technology, Boeretang 200, B-2400 Mol, Belgium. E-mail: dominic.ormerod@vito.be

a VITO (Flemish Institute for Technological Research), Separation and Conversion Technology, Mol, Belgium

b Department of Chemical Engineering, Imperial College London, London, UK

c Stratingh Institute for Chemistry, University of Groningen, Groningen, The Netherlands

In this work we address the application of this membrane-assisted processing method to ruthenium catalysed RCM to yield a macrocyclic compound.²³ Organic solvent nanofiltration (OSN)²⁴ despite being a relatively new separation technique has already demonstrated its potential in sustainable industrial processing.^{25–27} Here OSN is used to effect the in-line solvent recycling. The performance of the membranes is characterized by their solute rejection and permeance.²⁴ The use of membranes in RCM reactions has already been reported in the literature^{28–36} with the emphasis being placed upon separation of catalyst from reaction products of very small molecular mass and in general in post-reaction processing situations. In contrast the focus of this work is the in-line solvent recycling with the aim of reducing the solvent volumes required for the macrocyclization. Incorporation of the membrane within the reaction is not simply a question of size exclusion to remove organometallics or other species from the reaction mixture, the presence of the membrane will have a fundamental effect on issues such as reaction yield and catalyst stability. Indeed, any release–return mechanism that may³⁷ or may not³⁸ be operating in the catalytic cycle will possibly be prevented by permeation of the catalyst released ligand through the membrane thus, effectively removing it and disrupting any return.

Comparison of the cyclization efficiency can be carried out in a number of ways such as E_{mac} ,³⁹ defined as $E_{mac} = \log_{10}(\text{yield}^3 \times \text{concentration})$ a metric that takes into account the reaction yield and concentration. Process mass intensity (PMI)⁴⁰ a mass based metric, which is defined as the total mass used (in kilograms) in a process or process step including solvents, divided by the mass of product (in kilograms). The lower the figure the more efficient the process. or a holistic approach that has recently been proposed,⁴¹ a more comprehensive approach that includes different levels that reflect the differing levels of development of particular projects. In this case the emphasis will be on PMI as this encapsulates all mass based inputs into the process. However, as this does not highlight areas of concern easily, the holistic approach has also been taken into consideration.

EXPERIMENTAL SECTION

General

The solvents used in this study were dichloromethane (DCM), toluene, ethyl acetate (EtOAc) and dimethylformamide (DMF) all were technical grade purchased from VWR (Oud-Heverlee, Belgium) and used without prior purification. 1,1-Bi-2-naphthol (Binol) and 4-bromo-1-butene were purchased from Sigma-Aldrich (Overijse, Belgium) and used as supplied. Water was reverse osmosis purified water. Metathesis catalysts dichloro(2-isopropoxy phenylmethylene) (tricyclohexylphosphine)ruthenium(II), [Cas number: 203714-71-0] (HG-1); dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](3-phenyl-1H-inden-1-ylidene)(tricyclohexylphosphine)ruthenium(II), [Cas number: 536724-67-1] (M-2) and dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] {2-(1-methylacetoxy)phenyl}methylene)ruthenium(II) [CAS number: 1031262-71-1] (M-51) were purchased from Sigma-Aldrich and used as supplied. The annotations HG-1, M-2 and M-51 refer to Hoveyda–Grubbs first generation catalyst (HG-1), and M-2 and M-51 both make reference to the Umicore M series nomenclature for these catalysts for which Umicore are the original manufacturers of the complexes.

Commercially available membranes selected for this study were Inopor[®] ceramic membranes (Inopor, Veilsdorf, Germany),

Starmem membranes (Evonik-Met Ltd, London, UK) and Solsep membranes (Solsep, Apeldoorn, The Netherlands). Membranes modified with either alkyl or aromatic groups were Inopor membranes modified in-house to have organic groups on the top layer. The ceramic membranes used in this study, both commercial and modified were asymmetric tubular titanium oxide (TiO₂) membranes; length 120 mm, outer diameter 10 mm, inner diameter 7 mm and a top layer thickness of approximately 50 nm. Polymeric membranes were flat sheet. All membrane experiments were carried out in a cross-flow filtration unit made in-house, pressurized with nitrogen gas. Filtration experiments were performed with cross-flow velocity of 2 m s⁻¹.

Proton (¹H) and carbon-13 (¹³C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV 300 spectrometer (Karlsruhe, Germany). Deuterated chloroform (CDCl₃) (Euriso-Top, Paris, France, 0.03% tetramethylsilane (TMS), 99.80% D) was used as deuterated solvent. The multiplicities of signals were abbreviated as follows: s: singlet; d: doublet; dd: doublet of doublets; dt: doublet of triplets; t: triplet; tt: triplet of triplets; ttt: triplet of triplets of triplets; q: quartet; quint: quintet; sept: septet; m: multiplet; br: broad signal. The ¹³C spectra were recorded proton decoupled unless otherwise noted.

Reactions were analysed on a Waters UPLC (Waters Corporation, Milford, Massachusetts, USA) with a UV-visible photodiode array detector, a Waters Acquity BEH C18 column with dimensions of 2.1 mm × 50 mm, 1.7 μm, and a gradient of methanol and acetonitrile, Table 1. The column temperature was 40 °C.

Analysis of ruthenium (Ru) species was carried out using inductively coupled plasma atomic emission spectroscopy (ICP-AES). After evaporation of the solvent from the sample, the residue was digested using aqua regia and diluted with deionized water to the required concentration range. The samples were then analysed for metal content.

Thin-layer chromatography (TLC) was carried out on silica gel plates (Merck F254). Spots were detected with UV light and revealed with potassium permanganate (KMnO₄) or ninhydrin solutions.

2,2'-Bis(but-3-en-1-yloxy)-1,1'-binaphthalene (1)

Synthesis was adapted from the literature procedure.⁴²

Williamson reaction

A 1 L round bottom flask was charged with Binol (35.4 g, 0.12 mol) and DMF (650 mL). Potassium carbonate (204.7 g, 1.48 mol) was added and the mixture warmed to 80 °C for 30 min. 4-Bromo-1-butene (100 g, 0.74 mol) was added dropwise and the mixture stirred at 80 °C for 12 h. After allowing to cool to 23 °C the reaction mixture was filtered and the filtrate added to water (1000 mL) and the mixture extracted four times with EtOAc. The combined organic layers were dried over magnesium sulphate (MgSO₄) and the solvent removed under reduced pressure. The crude residue was recrystallized from ethanol/2-propanol (96:4) to yield 26.4 g of an off-white solid.

Mitsunobu reaction

In a 250 mL round-bottomed flask are introduced Binol (1.99 g 7 mmol, 1 eq) and 100 mL of toluene. The flask is wrapped in aluminium foil and heated to 80 °C. Diisopropyl azodicarboxylate (DIAD) (5.5 mL, 28 mmol, 4 eq) was added to the stirred mixture, followed by triphenylphosphine (7.3187 g, 28 mmol, 4 eq). The resultant mixture was stirred for approximately 10 min before

3-buten-1-ol (2.4 mL, 28 mmol, 4 eq) was added to the mixture. The resulting mixture was stirred at 80 °C for 24 h. Solvent was removed under reduced pressure and the resulting oily mass purified by flash chromatography. Eluent: *n*-hexane/diethyl ether 98:2.

¹H-NMR (300 MHz, chloroform-*d*) δ ppm 2.10–2.18 (m, 4H), 3.97 (q, 4H, *J* = 9.04, 6.78 Hz), 4.73–4.82 (m, 4H), 5.34–5.48 (m, 2H), 7.28–7.42 (m, 10H_{ar}), 7.84–7.95 (dd, 2H_{ar}).

¹³C-NMR (75 MHz, chloroform-*d*) δ ppm 153.61, 133.27, 129.81, 128.25, 127.99, 126.75, 124.45, 122.35, 115.03, 113.10, 76.00, 68.90, 28.37, 28.22.

High-resolution mass spectrometry (HRMS) *m/z*: [MS + H]⁺ calculated for C₂₈H₂₇O₂: 395.2011. Found: 395.2001.

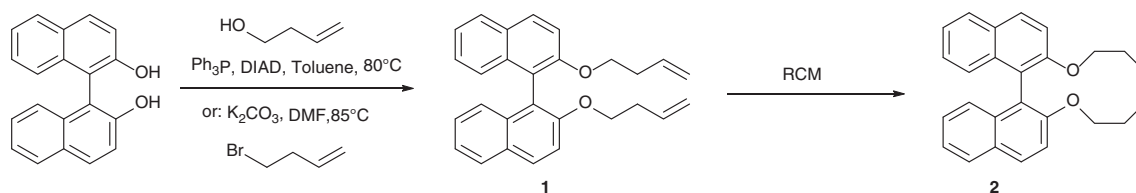
General RCM batch process [8,9,12,13-tetrahydro rodinaphtho[2,1-b:1',2'-d][1,6]dioxacyclododecine (2)]

In a 20 mL test tube are introduced (0.0166 g, 0.04 mmol) of 2,2'-bis(but-3-en-1-yloxy)-1,1'-binaphthalene (**1**) and 5 mL of solvent. From a stock solution of catalyst (HG-1 or M-2) (0.026 mol L⁻¹) in the solvent of choice was added 0.212 mL (5 mol%) via a micropipette, under continuous stirring. The reaction was carried out with stirring at 23 °C until considered complete via TLC analysis eluting with *n*-hexane/diethyl ether 98:2.

General RCM with membrane assisted processing

To a filtration apparatus fitted with a membrane, preconditioned if required (some membranes are supplied by the manufactures containing a preservative within the membrane, these preservatives need to be removed prior to use, typically with the process solvent to be used), was added 400 mL of EtOAc and circulated through the system at atmospheric pressure until the internal temperature was 23 °C. The filtration loop was brought under pressure (10 bar ceramic membranes 20 bar for polymeric membranes) and the membrane flux continually monitored. Connected to the filtration unit via a pump and set up to perform constant volume diafiltration was 200 mL stirred EtOAc at 23 °C; this is the diafiltration solution. Permeate from the membrane was added directly to the diafiltration solution. To the diafiltration solution was added via a syringe pump a solution of HG-1 in DCM (0.026 mol L⁻¹) and via a Dosimat a solution of **1** in EtOAc (1.2 mol L⁻¹). The addition speed and concentration were so that 5 mol% of catalyst was added when the substrate was added. Regular sampling of the filtration loop contents (retentate), the diafiltration solution (mix), and the membrane permeate outlet (permeate) was performed for analysis. TLC of the samples was performed in cyclohexane/acetone (98:2).

¹H-NMR (500 MHz, chloroform-*d*) δ ppm 7.92 (d, *J* = 8.9 Hz, 2H), 7.84 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.41 (d, *J* = 9.1 Hz, 2H), 7.29 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 2H), 7.20 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 2H), 7.12 (ddt, *J* = 8.5, 1.4, 0.7 Hz, 2H), 5.11–5.04 (m, 2H), 4.44 (ddd, *J* = 11.6, 4.9, 3.9 Hz, 2H), 4.05 (ddd, *J* = 11.6, 10.3, 4.4 Hz, 2H), 2.50 (ddd, *J* = 18.8, 14.7, 5.2 Hz, 2H), 2.20–2.07 (m, 2H).



Scheme 1. Synthesis of 2,2'-bis(but-3-en-1-yloxy)-1,1'-binaphthalene (**1**) and ring-closing metathesis (RCM) cyclization reaction.

Table 1. Ultra-performance liquid chromatography (UPLC) solvent gradient

Time (min)	Mobile phase composition	
	Methanol (%)	Acetonitrile (%)
0	70	30
3	0	100
10	0	100
10.1	70	30
13	70	30

Flow rate: 0.5 mL min⁻¹.

¹³C-NMR (126 MHz, CDCl₃) δ ppm 152.04, 134.64, 128.88, 128.67, 127.75, 126.11, 125.44, 123.33, 120.50, 114.91, 66.29, 46.09, 30.91.

HRMS *m/z*: [MS + H]⁺ calculated for C₂₆H₂₃O₂: 367.1698. Found: 367.1695.

RESULTS AND DISCUSSION

Reaction substrate and cyclization reaction

To demonstrate the membrane-assisted processing method, a cyclization precursor that is rapidly and easily synthesized is required. To fulfil these requirements the Binol derivative **1** was chosen, synthesis of which can be carried out either by Mitsunobu reaction of Binol with 3-buten-1-ol or via a Williamson ether synthesis with Binol and 4-bromo-1-butene. RCM on this material will yield a 12 membered macrocycle (Scheme 1).

Using the Mitsunobu route isolated yield of **1** was 85% however, chromatography was required to isolate the pure material. In contrast with the Williamson ether synthesis pure **1** was isolated via a crystallization process though in moderate unoptimized yield of 54%. Batchwise cyclization of **1** to 8,9,12,13-tetrahydro rodinaphtho[2,1-b:1',2'-d][1,6]dioxacyclododecine (**2**) under RCM conditions was initially carried out at room temperature in DCM using either Hoveyda–Grubbs first generation catalyst (HG-1) or the second generation indenylidene catalyst from the Umicore portfolio sold as the Umicore M-2. The reactions were also carried out at a number of different concentrations, with respect to cyclization precursor **1** in order to establish the optimal reaction concentration, results are shown in Fig. 1.

Clearly the Hoveyda–Grubbs type catalyst was the more performant in this reaction, the differences in cyclization efficiency resulting from differences in precatalyst initiation. Whereas, phosphine bearing precatalysts such as the M-2 generally initiate via a dissociative mechanism, thus allowing the possibility that at low concentration secondary unproductive reactions may occur, the Hoveyda–Grubbs type catalyst initiate through a mechanism with a greater degree of interchange character.⁴³ Highest reaction yields and selectivity were achieved at concentrations of 0.01 mol L⁻¹ (100 L mol⁻¹) with respect to **1**. However, though

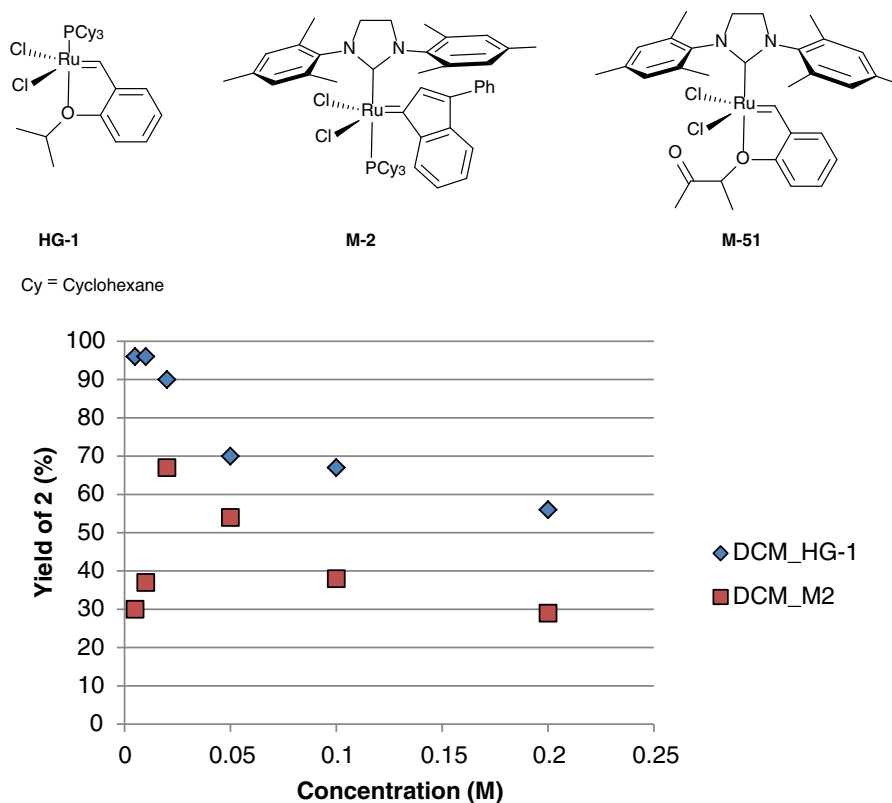


Figure 1. Ring-closing metathesis (RCM) of 2,2'-bis(but-3-en-1-yloxy)-1,1'-binaphthalene (**1**) to yield (*Z*)-8,9,12,13-tetrahydrodinhphtho[2,1-b:1',2'-d][1,6]dioxacyclododecine (**2**) with Hoveyda–Grubbs first generation catalyst (HG-1) and the second generation catalyst Umicore M-2 at varying concentration, with respect to **1**. Reaction was carried out in a Schlenk tube under an inert atmosphere at room temperature, with 2.5 mol% catalyst. Structures of catalysts used in this work are shown above figure.

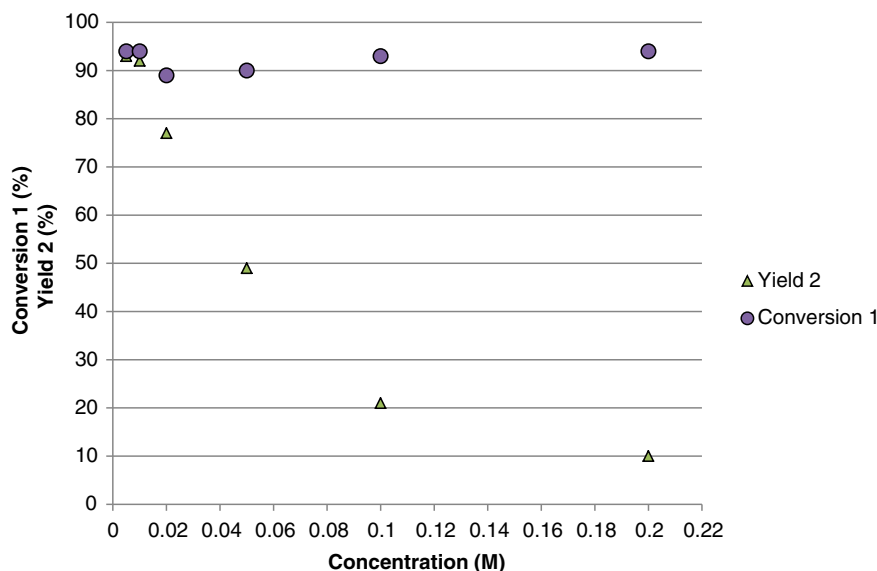


Figure 2. Comparison of conversion of starting material **1** and yield of **2** after 16 h with Hoveyda–Grubbs first generation catalyst (HG-1) at increasing initial concentrations of **1**. The reactions are tested in ethyl acetate, at room temperature, with 2.5% mol catalyst.

DCM is a solvent often used for RCM reactions, it is classed as hazardous^{44,45} and as such is likely to be problematic if scale-up is required. Recently metathesis reactions in solvents that are less hazardous has been demonstrated,⁴⁶ as such the cyclization in EtOAc at various concentrations under analogous conditions as used previously in DCM was evaluated (Fig. 2). Again high

conversion of **1** and yield of **2** can be achieved in these batchwise reactions at concentrations at or below 0.01 mol L⁻¹ (100 L mol⁻¹), with respect to **1**. Though the plot of yield versus concentration gives a qualitative notion of the required reaction concentration in order to obtain a more quantitative maximal concentration of the reaction, the effective molarity^{47,48} was estimated using the

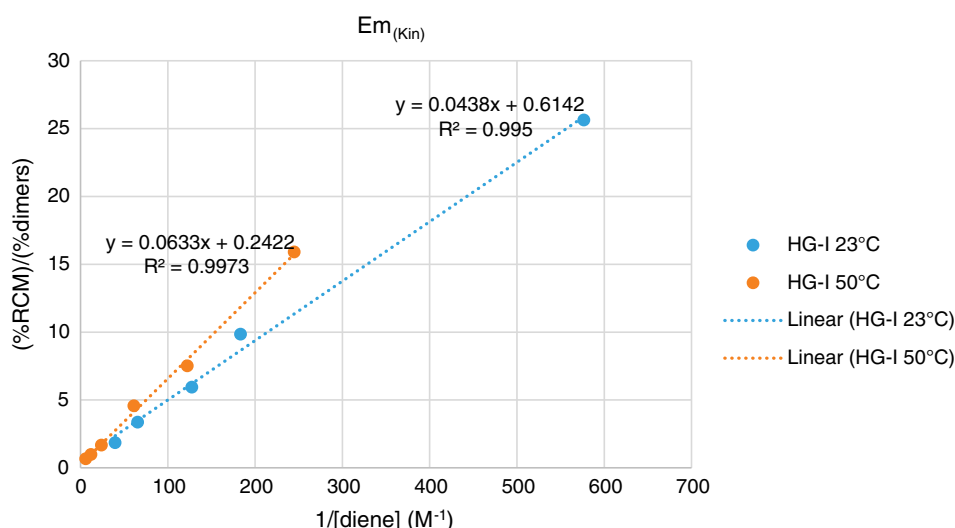


Figure 3. Plot of kinetic effective molarity [$EM_{(Kin)}$] for the cyclization of **1** to **2** using HG-1 as catalyst in ethyl acetate.

method described by Farina *et al.*⁴⁹ Treatment of **2** with up to 10 mol% of the Hoveyda–Grubbs first generation catalyst did not result in ring opening or further impurity formation thus kinetic effective molarity was used which is the ratio of the rate constant of the first-order reaction (cyclization) to the rate constant of the second-order reaction (oligomerization). The effective molarity is the concentration of **1** at which cyclization and oligomer formation are approximately equal and can be derived from the slope of the plot of $[\%RCM]/[\%oligomers]$ versus $1/[diene]$ (Fig. 3). The effective molarity was thus, estimated to be 0.044 mol L^{-1} at room temperature and 0.063 mol L^{-1} at 50°C . In practice this means the reaction needs to remain well below this concentration in order to obtain high yield of **2**.

The similarity of reaction yields achieved in EtOAc as compared to DCM, and its greater amenability to scale-up resulted in this solvent being preferred for reactions in the membrane assisted set up.

Membrane process and membrane requirements

The membranes primary role in this processing method is to allow internal solvent recycling which imposes a certain membrane performance. Key parameters to characterize the filtration properties of a membrane are flux and rejection.

The flux J is defined as the volume V of solvent (or of a solution) permeating through a membrane of area A in a defined time interval t (Eqn (1)).

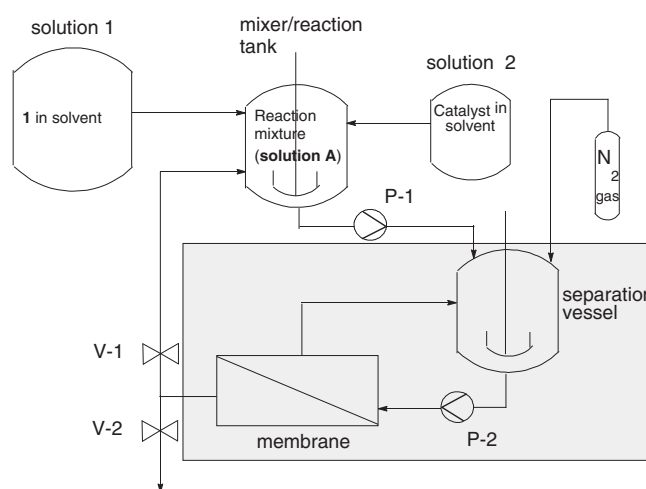
$$J = \frac{V}{At} \quad (1)$$

This value normalized for the transmembrane pressure ΔP applied is defined as permeance L (Eqn (2))

$$L = \frac{J}{\Delta P} \quad (2)$$

Given a standard set of conditions (temperature, pressure, solvent, concentration) the rejection of a given species in solution is defined as the ratio between its concentration in the permeate (C_p) and in the retentate (C_r) and it is calculated as follows (Eqn (3)):

$$\text{Rejection (\%)} = \left(1 - \frac{C_p}{C_r}\right) \times 100 \quad (3)$$



Scheme 2. Reaction set-up for macrocyclization via ring-closing metathesis (RCM) with internal solvent recycling. The area within the shaded box is under pressure during operation. P-1 is a diafiltration pump; P-2 a circulation pump. During the cyclization V-1 would be open and V-2 closed, allowing total return of the permeate.

The experimental set up for the reactions is shown in Scheme 2. Concentrated solutions of catalyst and starting material **1** are mixed, diluted and reacted within the mixer/reaction tank. Only a small volume of the reaction mixture at low concentration (0.01 mol L^{-1}) is formed in this vessel; but if the reaction is to proceed this requires continual replenishment during the process. The contents of this tank are added to the filtration system via constant volume diafiltration the rate of which is controlled by the membrane permeance (constant volume diafiltration is the addition of solvent, or in this case reaction solution, to the filtration unit at a rate equal to the rate at which solvent is removed via permeation through the membrane. thus, solvent volumes within the filtration unit remain the same). This diafiltration addition of the contents of the reactor tank occurs in a semi-continuous manner. The cyclization occurs in a significantly reduced solvent volume as compared to a standard batch reaction because during the reaction V-2 is closed and V-1 open, the solvent permeating through the membrane is therefore, recycled back into the mixer/reaction tank

Table 2. Membrane characteristics

Entry	Membrane	Type	MWCO ^a	Supplier
1	0.9 nm TiO ₂	Ceramic	450 ^b	Inopor
2	1.0 nm C ₈ TiO ₂	Ceramic	1500 ^c	Vito
3	1.0 nm phenyl TiO ₂	Ceramic	1500 ^c	Vito
4	0.9 nm C ₈ TiO ₂	Ceramic	600 ^d	Vito
5	0.9 nm phenyl TiO ₂	Ceramic	600 ^d	Vito
6	0.9 nm C ₈ H ₄ F ₁₃ TiO ₂	Ceramic	600 ^d	Vito
7	Starmem-122	Polymeric	220 ^b	Evonik
8	Solsep-10206	Polymeric	~300 ^b	Solsep
9	Solsep-10306	Polymeric	1000 ^b	Solsep

^a MWCO = molecular weight cut-off (molecular weight cut-off is defined as the molecular weight of a reference solute corresponding to a 90% rejection for a given membrane and a given solvent).

^b Information from supplier.

^c Based on the rejection of polyethylene glycols in water.

^d Based on the rejection of styrenes in acetone.

where it is used to further regenerate the low concentration reaction solution. For internal solvent recycling, the solution permeating through the membrane should be essentially solvent. Thus, high rejection of **1**, **2** and all organometallic species is required. High rejection of **2** is desirable as this will allow it to accumulate in the separation vessel away from the site of reaction, protecting it from possible further unwanted reactions. Though ideally all of **1** would have been consumed prior to the reaction mixture coming in contact with the membrane, its rejection is expected to be very similar to that of **2**. Thus if rejection of **1** and **2** are very similar, residence time of **1** in the mixer/reaction tank (Scheme 2) will also be relevant. It should also be noted that although in principle it would be possible to load the catalyst in the separation vessel so that the dilute solution of **1** only comes in contact with the catalyst within the pressurized filtration loop, shaded area Scheme 2, and thus, cyclization occurs within the filtration loop. The experiment was not carried out in this manner as this could have a significant and negative effect on the rate of cyclization. If the reaction was to be carried out within the filtration loop the RCM secondary product ethene, a catalyst poison, can only escape the system via permeation through the membrane and with the system under pressure more ethene will be dissolved in solution. The negative effect of ethene within the pressurized system has already been demonstrated.²⁸

The membranes included in this work and their characteristics are listed in Table 2 and comprise a selection of the commercial ceramic (Inopor) and polymeric (Solsep and Starmem) membranes that have previously proved to be stable in organic solvents. Also included are a series of ceramic membranes with the surface modified, in-house, with organic groups.^{50–52}

Membrane evaluation and choice

As previously stated high rejection of the organometallic species within the reaction was desired. However, screening experiments to identify a membrane capable of giving high rejection of the pre-catalyst would be of little use as the catalytic species under reaction conditions has very different structure and mass to the pre-catalyst.⁵³ Therefore, rejection of the organometallic species were established directly under the conditions of cyclization of **1** within the reaction set-up shown in Scheme 2.

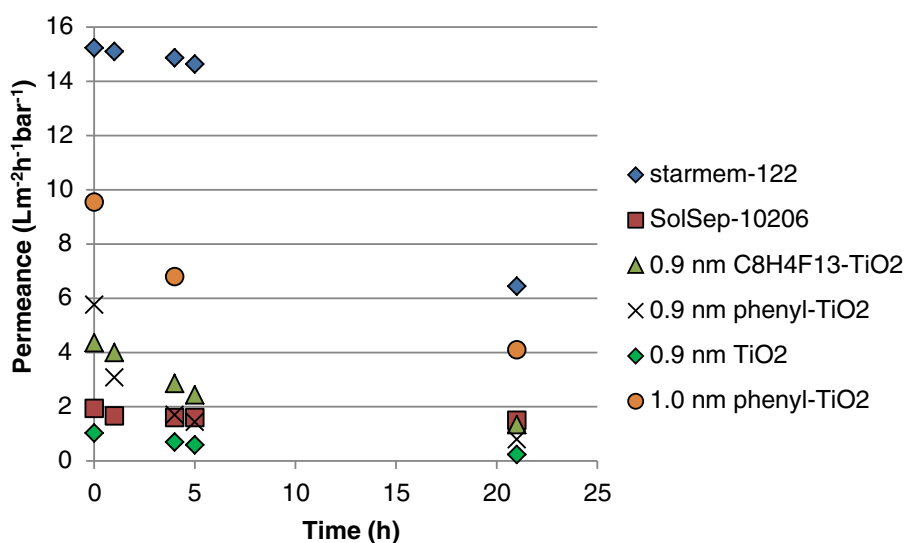
In a series of small-scale experiments the membrane performance with respect to permeance, and rejection of catalyst,

cyclization precursor **1** and cyclic product **2** was determined for a number of membranes in DCM, EtOAc and toluene as solvents (Table 3). High catalyst rejection can only be achieved in EtOAc as solvent, the most performant membranes in this solvent being the Starmem-122 and Solsep-10206, entries 8 and 13 Table 3. Both membranes have similar rejection profiles of **1**, **2** and catalyst but the Starmem membrane having significantly higher permeance. Differences in rejection of **1** and **2** were minimal and not unexpected as for there to be a notable difference in rejection of these two molecules there would have to be a significant difference in either molecular mass or solubility parameters, neither of which are present in these two molecules.

Noteworthy within these results is though the solutes remain the same on changing the solvent the rejection profile, even when using the same type of membrane, can change dramatically. This is most notable within the ceramic membranes due to compatibility issues as some of the polymeric membranes were not used in some of the solvents; ceramic membranes in contrast are typically chemically more stable than the polymeric equivalents. The changes in the rejection profiles on changing the solvent are explicable by taking Spiegler–Kedem theory into consideration. A theory that describes solute transport through a membrane as the result of two phenomena. One due to diffusion and is influenced by the solubility effects of solvent and membrane. The other convection which is related to pore size and molecular volume. The Spiegler–Kedem model can be further solved to give solute rejection and this rejection is a function of the reflection coefficient (σ), dependent on the ratio of solute size and the membrane pore size, and the ratio of the solvent flux and solute permeability by diffusion.^{54,55} If the ratio of solvent flux and solute permeability is large (≥ 10) the solute rejection approaches a limiting value equal to the reflection coefficient and thus, solute transport is dominated by convection and is due to size exclusion (i.e. the membranes action is more sieve like). Conversely, if the ratio of solvent flux and solute permeability is small then diffusion dominates solute transport and the membrane shows far more solvent like characteristics. Simply looking at catalyst rejection in Table 3, entry 2 the membranes action is solvent like, there is significant interaction between the catalyst, either in an active form or resting state, and the membrane resulting in low rejection. In contrast with the same catalyst and membrane but an alternative solvent (Table 3, entry 6) the membrane–catalyst interaction is dominated by size exclusion interactions.

Table 3. Membrane screening results

Entry	Solvent	Catalyst	Membrane	Rejection 1 (%)	Rejection 2 (%)	Rejection catalyst (%)	Av. Permeance ($\text{Lm}^{-2}\text{h}^{-1}\text{bar}^{-1}$)
1	DCM	HG-1	0.9 nm TiO_2	58	60	63	0.50
2	DCM	HG-1	1.0 nm phenyl	29	24	14	0.89
3	DCM	M-2	1.0 nm phenyl	44	63	45	0.50
4	DCM	HG-1	1.0 nm C_8	49	54	6	0.60
5	Toluene	HG-1	1.0 nm C_8	69	67	56	0.16
6	EtOAc	HG-1	1.0 nm phenyl	43	41	76	5.40
7	EtOAc	HG-1	0.9 nm TiO_2	21	16	36	0.50
8	EtOAc	HG-1	Starmem-122	88	93	97	13.3
9	EtOAc	M-51	Starmem-122	86	89	94	8.36
10	EtOAc	HG-1	0.9 nm $\text{C}_8\text{H}_4\text{F}_{13}$ TiO_2	34	37	81	3.0
11	EtOAc	HG-1	0.9 nm phenyl TiO_2	64	64	86	2.6
12	EtOAc	HG-1	0.9 nm C_8 TiO_2	68	68	82	0.69
13	EtOAc	HG-1	Solsep-10206	92	86	96	1.7
14	EtOAc	HG-1	Solsep-10306	93	72	90	2.1


Figure 4. Membrane permeance for a number of membranes on small-scale cyclization reactions in ethyl acetate with HG-1 as catalyst.

The permeance data quoted in Table 3 is the average permeance during the whole process, often permeance changes during a process, particularly so if the membrane is susceptible to compaction or fouling. A more detailed view of the permeance in EtOAc with ceramic as well as polymeric membranes is shown in Fig. 4. All membranes display a drop in permeance, with the Solsep membrane having the most stable of all. Despite reductions in permeance the Starmem membrane has a significantly higher permeance than the other membranes.

The rejection profile in EtOAc and the stable permeance of the Solsep membrane made this the preferred membrane for the further development of the reaction system.







Increasing the reaction efficiency

The principle behind this system is the reaction is carried out at the ideal (low) concentration identified in the earlier experiments, in this case 0.01 mol L^{-1} (100 L mol^{-1}). This concentration has been identified based on the yield *versus* concentration data (Fig. 2) and the effective molarity (Fig. 3). It should also be noted that although the effective molarity of the reaction is higher at 50°C than at 23°C , catalyst degradation was also faster and in

the membrane-assisted process this did not lead to increased yield of the macrocycle thus all experiments to increase process intensification were carried out at 23°C .

For reaction in this type of system only a small volume of this solution is prepared and must be continually regenerated throughout the process, this occurs in the mixer/reaction tank (Scheme 2). In the reaction set up shown in Scheme 2 the rate of addition from the reactor/mixer tank into the membrane unit is being controlled by the rate of membrane permeation. This is done via the sensors that record the membrane permeation being linked to the control unit of the diafiltration pump (P-1) and thus membrane performance will have a direct influence on residence time of the substrate **1** in the reaction vessel. Membrane performance during this scale up showed it took about 100 min for an equivalent volume of solvent to permeate the membrane as was used in the reaction/mixer vessel, this time can easily be adjusted by changes to the trans membrane pressure or membrane surface area. The batchwise reactions showed that at the reaction concentration and temperature chosen complete conversion was achieved after 300 min. However, a batch reaction is somewhat different from this reaction set-up as in a batch reaction

Table 4. Scale-up reaction performance

Solvent	Ethyl acetate	
Catalyst	HG-1	
Starting material 1 (mmol)	39.4	
Yield 2 (%)	69	
Total solvent volume (mL)	680	
Solvent volume for an equivalent batch reaction (0.01 mol L ⁻¹ , mL)	3950	
Kinetic effective molarity (mol L ⁻¹)	0.044	
System molarity (mol L ⁻¹)	0.058	
Solvent reduction compared to batch reaction (%)	82	
Process mass intensity (PMI) batch reaction	270	
PMI membrane assisted process	97	

the concentration of **1** will decrease with time and so does the reaction rate. This membrane assisted set up has similarities to a continuous stirred tank reactor (CSTR).

The cyclization was carried out in the membrane unit on a multi gram scale where the total solvent used for the whole system including all addition solutions and the solvent required in the OSN unit was equivalent to the solvent volume used if the reaction was carried out in a batch reactor at a concentration of 0.058 mol L⁻¹ (denoted later as system molarity), far above the effective molarity. Despite this the yield of cyclic product was 69%, a batch reaction at the same concentration would give less than 50% yield of cyclic product. Significant improvement in mass intensity was also noted, as was the reduction in solvent used in this system considerably lower than that of a batch reaction. The colours at the end of the rows in Table 4 are based on the holistic approach to evaluate a reaction as described by McElroy *et al.*⁴¹ As this is proof of concept it was subjected to the first pass evaluation in which parameters such as yield, conversion, selectivity, mass intensity, types of solvents used and quantities, the use of catalysts and whether critical elements are used are included. Areas of concern are the yield which ideally would be improved and whereas the use of a catalysed reaction results in a green flag for that, the fact that the catalyst is ruthenium based will result in a red flag due to ruthenium being considered a critical element. Mass intensity of an equivalent batch reaction with an initial concentration of **1** of 0.01 mol L⁻¹ and the mass intensity of the membrane-assisted process are both listed in the table to highlight the improvement.

CONCLUSIONS

Using the method described here it is possible to perform metathesis macrocyclizations in a solvent volume of up to 82% lower than an equivalent batch reaction, with only minimal impact upon the reaction outcome. A switch of reaction solvent to EtOAc renders the process more benign and applicable on a large scale. Furthermore, the membrane-assisted process described here is intended to be a solution to the need for high dilution in RCM macrocyclizations. Reactions carried out in this manner can be performed in standard reaction vessels as the equipment required to perform nanofiltrations is a stand alone apparatus that connects to reactors via standard hosing. Further investigations aimed at addressing the areas of concern as highlighted in the reaction performance evaluation are currently on-going.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Stefan Voorspoels, Mario Schroeven and Karlien Duysens of Vito for analytical support.

REFERENCES

- Yudin AK, Macrocycles: lessons from the distant past, recent developments, and future directions. *Chem Sci* **6**:30–49 (2014).
- Wessjohann LA and Ruijter E, Strategies for total and diversity-oriented synthesis of natural product (-like) macrocycles. *Topp Curr Chem* **243**:137–184 (2005).
- Driggers EM, Hale SP, Lee J and Terrett NK, The exploration of macrocycles for drug discovery – an underexploited structural class. *Nat Rev Drug Discov* **7**:608–624 (2008).
- Cottet K, Marcos PM and Cragg PJ, Fifty years of oxalix[3]arenes: a review. *Beilstein J Org Chem* **8**:201–226 (2012).
- D'Acquarica I, Gasparini F, Misiti D, Pierini M and Villani C, in *HPLC chiral stationary phases containing macrocyclic antibiotics: practical aspects and recognition mechanism*, Vol. **46**, ed. by Grushka E and Grinberg N. CRC Press, Boca Raton, FL, pp. 109–173 (2008).
- Yu X and Sun D, Macrocyclic drugs and synthetic methodologies toward macrocycles. *Molecules* **18**:6230–6268 (2013).
- Gradillas A and Pérez-Castells J, Macrocyclization by ring-closing metathesis in the total synthesis of natural products: reaction conditions and limitations. *Angew Chem Int Ed Engl* **45**:6086–6101 (2006).
- Monfette S and Fogg D, in *Ring-closing Metathesis Synthesis of Medium and Large Rings: Challenges and Implications for Sustainable Synthesis*, ed. by Dragutan V, Demonceau A, Dragutan I and Finkelshtein E. Springer, Dordrecht, pp. 129–156 (2010).
- Hughes D, Wheeler P and Ene D, Olefin metathesis in drug discovery and development – examples from recent patent literature. *Org Process Res Dev* **21**:1938–1962 (2017).
- Higman CS, Lummiss J a M and fogg DE, Olefin metathesis at the dawn of implementation in pharmaceutical and speciality-chemicals manufacturing. *Angew Chem Int Ed Engl* **55**:3552–3565 (2016).
- Morin É, Sosoe J, Raymond M, Amorelli B, Boden RM and Collins SK, Synthesis of a renewable macrocyclic musk: evaluation of batch, microwave, and continuous flow strategies. *Org Process Res Dev* **23**:283–287 (2019).
- Bieniek M, Michrowska A, Usanov DL and Grela K, In an attempt to provide a user's guide to the galaxy of benzylidene, alkoxybenzylidene, and indenylidene ruthenium olefin metathesis catalysts. *Chemistry* **14**:806–818 (2008).
- Vougioukalakis GC and Grubbs RH, Ruthenium-based heterocyclic carbene-coordinated olefin metathesis catalysts. *Chem Rev* **110**:1746–1787 (2010).
- Conrad JC, Eelman MD, Silva J a D, Monfette S, Parnas HH, Snelgrove JL *et al.*, Oligomers as intermediates in ring-closing metathesis. *J Am Chem Soc* **129**:1024–1025 (2007).
- Monfette S and Fogg DE, Equilibrium ring-closing metathesis. *Chem Rev* **109**:3783–3816 (2009).
- Higman CS, Nascimento DL, Ireland BJ, Audörsch S, Bailey GA, McDonald R *et al.*, Chelate-assisted ring-closing metathesis: a strategy for accelerating macrocyclization at ambient temperatures. *J Am Chem Soc* **140**:1604–1607 (2018).
- Gawin R, Tracz A, Chwalba M, Kozakiewicz A, Trzaskowski B and Skowerski K, Cyclic alkyl amino ruthenium complexes – efficient catalysts for macrocyclization and acrylonitrile cross metathesis. *ACS Catal* **7**:5443–5449 (2017).
- Jiménez-González C, Constable DJC and Ponder CS, Evaluating the "greenness" of chemical processes and products in the pharmaceutical industry – a green metrics primer. *Chem Soc Rev* **41**:1485–1498 (2012).
- Raymond MJ, Slater CS and Savelski MJ, LCA approach to the analysis of solvent waste issues in the pharmaceutical industry. *Green Chem* **12**:1826–1826 (2010).
- Buekenhoudt, A.; Vandezande, P.; Ormerod, D. Improved dilute chemical reaction process with membrane separation step. WO Patent 2013/156600, 2013.
- Ormerod D, Noten B, Dorbec M, Andersson L, Buekenhoudt A and Goetelen L, Cyclic peptide formation in reduced solvent volumes via in-line solvent recycling by organic solvent nanofiltration. *Org Process Res Dev* **19**:841–848 (2015).

- 22 Marti-Centelles V, Pandey MD, Burguete MI and Luis SV, Macrocyclization reactions: the importance of conformational, configurational, and template-induced preorganization. *Chem Rev* **115**:8736–8834 (2015).
- 23 Cupani A, *Synthesis of Macrocycles via Olefin Metathesis: Process Intensification using Organic Solvent Nanofiltration*. Imperial College, London (2016).
- 24 Marchetti P, Solomon MFJ, Szekeley G and Livingston AG, Molecular separation with organic solvent nanofiltration: a critical review. *Chem Rev* **114**:10735–10806 (2014).
- 25 Szekeley G, Jimenez-Solomon MF, Marchetti P, Kim JF and Livingston AG, Sustainability assessment of organic solvent nanofiltration: from fabrication to application. *Green Chem* **16**:4440–4473 (2014).
- 26 Buonomenna MG, Membrane processes for a sustainable industrial growth. *RSC Adv* **3**:5694–5740 (2013).
- 27 Drioli E, Brunetti A, Di Profio G and Barbieri G, Process intensification strategies and membrane engineering. *Green Chem* **14**:1561–1572 (2012).
- 28 Ormerod D, Bongers B, Porto-Carrero W, Giegas S, Vijt G, Lefevre N et al., Separation of metathesis catalysts and reaction products in flow reactors using organic solvent nanofiltration. *RSC Adv* **3**:21501–21510 (2013).
- 29 Nasser G, Renouard T, Shahane S, Fischmeister C, Bruneau C and Rabiller-Baudry M, Interest of the precatalyst design for olefin metathesis operating in a discontinuous nanofiltration membrane reactor. *ChemPlusChem* **7**:728–736 (2013).
- 30 Rabiller-Baudry M, Nasser G, Renouard T, Delaunay D and Camus M, Comparison of two nanofiltration membrane reactors for a model reaction of olefin metathesis achieved in toluene. *Sep Purif Technol* **116**:46–60 (2013).
- 31 Kajetanowicz A, Czaban J, Krishnan GR, Malińska M, Woźniak K, Siddique H et al., Batchwise and continuous nanofiltration of POSS-tagged Grubbs–Hoveyda-type olefin metathesis catalysts. *ChemSusChem* **6**:182–192 (2013).
- 32 Keraani A, Rabiller-Baudry M, Fischmeister C and Bruneau C, Immobilisation of an ionically tagged Hoveyda catalyst on a supported ionic liquid membrane: an innovative approach for metathesis reactions in a catalytic membrane reactor. *Catal Today* **156**:268–275 (2010).
- 33 van der Gryp P, Barnard A, Cronje J-P, de Vlieger D, Marx S and Vosloo HCM, Separation of different metathesis Grubbs-type catalysts using organic solvent nanofiltration. *J Memb Sci* **353**:70–77 (2010).
- 34 Schoeps D, Buhr K, Dijkstra M, Ebert K and Plenio H, Batchwise and continuous organophilic nanofiltration of Grubbs-type olefin metathesis catalysts. *Chem A Eur J* **15**:2960–2965 (2009).
- 35 Keraani A, Renouard T, Fischmeister C, Bruneau C and Rabiller-Baudry M, Recovery of enlarged olefin metathesis catalysts by nanofiltration in an eco-friendly solvent. *ChemSusChem* **1**:927–933 (2008).
- 36 Cseri L, Fodi T, Kupai J, Balogh GT, Garforth A and Szekeley G, Membrane-assisted catalysis in organic media. *Adv Mater Lett* **8**:1094–1124 (2017).
- 37 Bates JM, Lummiss J a M, Bailey G a and Fogg DE, Operation of the boomerang mechanism in olefin metathesis reactions promoted by the second-generation Hoveyda catalyst. *ACS Catal* **4**:2387–2394 (2014).
- 38 Vorfalt T, Wannowius KJ, Thiel V and Plenio H, How important is the release-return mechanism in olefin metathesis? *Chem A Eur J* **16**:12312–12315 (2010).
- 39 Collins JC and James K, Emac – a comparative index for the assessment of macrocyclization efficiency. *MedChemComm* **3**:1489–1495 (2012).
- 40 Jimenez-Gonzalez C, Ponder CS, Broxterman QB and Manley JB, Using the right green yardstick why process mass intensity is used in the pharmaceutical industry to drive more sustainable processes. *Org Process Res Dev* **15**:912–912, 917 (2011).
- 41 McElroy CR, Constantinou A, Jones LC, Summerton L and Clark J, Towards a holistic approach to metrics for the 21st century pharmaceutical industry. *Green Chem* **17**:3111–3121 (2015).
- 42 Ashok D, Shrivani D, Sarasija M and Sudershan K, Synthesis of Z-di/tetra/hexa/hydrodiphthal[2,1-b:1',2'-d][1,6]dioxacycloalkenes via microwave-accelerated ring closing metathesis and their antimicrobial activity. *Russ J Gen Chem* **85**:1152–1155 (2015).
- 43 Nelson DJ and Percy JM, The influence of structure on reactivity in alkene metathesis. *Adv Phys Org Chem* **48**:81–188 (2014).
- 44 Prat D, Hayler J and Wells A, A survey of solvent selection guides. *Green Chem* **16**:4546–4551 (2014).
- 45 Prat D, Wells A, Hayler J, Sneddon HF, McElroy CR, Abou-Shehadeh S et al., CHEM21 selection guide of classical – and less classical – solvents. *Green Chem* **18**:288–296 (2016).
- 46 Skowerski K, Bialecki J, Tracz A and Olszewski TK, An attempt to provide an environmentally friendly solvent selection guide for olefin metathesis. *Green Chem* **16**:1125–1130 (2014).
- 47 Illuminati G and Mandolini L, Ring closure reactions of bifunctional chain molecules. *Acc Chem Res* **14**:95–102 (1981).
- 48 Galli C and Mandolini L, The role of ring strain on the ease of ring closure of bifunctional chain molecules. *Eur J Org Chem* **2000**:3117–3125 (2000).
- 49 Farina V, Shu C, Zeng X, Wei X, Han Z, Yee NK et al., Second-generation process for the HCV protease inhibitor BILN 2061: a greener approach to Ru-catalyzed ring-closing metathesis. *Org Process Res Dev* **13**:250–254 (2009).
- 50 Van Heetvelde P, Beyers E, Wyns K, Adriaensens P, Maes B, Mullens S et al., A new method to graft titania using Grignard reagents. *Chem Commun* **49**:6998–7000 (2013).
- 51 Buekenhoudt, A.; Wyns, K.; Meynen, V.; Maes, B.; Cool, P. Surface-modified inorganic matrix and method for preparation thereof. WO Patent 2010106167 A1, 2010.
- 52 Rezaei Hosseinabadi S, Wyns K, Buekenhoudt A, Van der Bruggen B and Ormerod D, Performance of Grignard functionalized ceramic nanofiltration membranes. *Sep Purif Technol* **147**:320–328 (2015).
- 53 Nelson DJ, Manzini S, Urbina-Blanco CA and Nolan SP, Key processes in ruthenium-catalysed olefin metathesis. *Chem Commun* **50**:10355–10355, 10375 (2014).
- 54 Hosseinabadi SR, Wyns K, Meynen V, Buekenhoudt A and Van der Bruggen B, Solvent-membrane-solute interactions in organic solvent nanofiltration (OSN) for Grignard functionalised ceramic membranes: explanation via Spiegler–Kedem theory. *J Membr Sci* **513**:177–185 (2016).
- 55 Ormerod D, Buekenhoudt A, Bongers B, Baramov T and Hassfeld J, From reaction solvent to crystallization solvent, membrane assisted reaction workup and interpretation of membrane performance results by application of Spiegler–Kedem theory. *Org Process Res Dev* **21**:2060–2067 (2017).