

A Scalable Membrane Pervaporation Approach for Continuous Flow Olefin Metathesis

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ABSTRACT: The translation of olefin metathesis reactions from the laboratory to process scale has been challenging with traditional batch techniques. In this contribution, we describe a continuous membrane reactor design that selectively permeates the ethylene byproduct from metathetical processes, thereby overcoming the mass-transport limitations that have negatively influenced the efficiency of this transformation in batch vessels. The membrane sheet-in-frame pervaporation module yielded turnover numbers of >7500 in the case of diethyl diallylmalonate ring-closing metathesis. The preparation of more challenging, low-effective-molarity substrates, a cyclooctene and a 14-membered macrocyclic lactone, was also effective. A comparison of optimal membrane reactor conditions to a sealed tubular reactor revealed that the benefits of ethylene removal are most apparent at low reaction concentrations.

KEYWORDS: olefin metathesis, continuous flow, membrane separation, macrocyclization

INTRODUCTION

Catalytic olefin metathesis is a well-established synthetic strategy to access valuable molecular targets.¹ Ring-closing metathesis (RCM) is perhaps the most utilized transformation for the preparation of small molecules from discovery to process and is of great interest to the fragrance industry.² Despite the efficiency of olefin metathesis processes on the laboratory scale, successful implementation on the industrial scale has been challenging.^{2,3}

In 2005, a Boehringer Ingelheim team identified a set of barriers to scaling the macrocyclic RCM (mRCM) to yield the hepatits C virus protease inhibitor BILN 2061 ZW in batch.⁴ Laboratory-scale efforts proceeded smoothly, but the reaction performance suffered upon batch scaling to meet production needs. Extended reaction times and a higher catalyst loading were required to achieve the target reaction performance. The poor scaling behavior was partly attributed to inefficient mass transfer of ethylene from the reaction medium in 3000 L process vessels, where it promotes catalyst decomposition and may facilitate undesirable alkene isomerization.⁵⁻⁷ The welldocumented negative effects of persistent ethylene in metathetical processes as well as our interest in expanding the scope of continuous processing techniques prompted us to contemplate a reactor platform to address this mass-transport problem.^{8–10}

Prior work in the area of continuous olefin metathesis shows a clear dependence of the reaction outcome on the reactor design (Figure 1). Heterogeneous Grubbs—Hoveyda-type catalysts used in recirculating packed-bed reactor configurations were among the first examples.^{11–15} While effective, the preferred catalysts were not commercially available and had limited stability. Reports from Lamaty¹⁶ and Collins¹⁷ showed that flow reactions in sealed tubular reactors provide good



Figure 1. (A) Ru catalysts for homogeneous olefin metathesis. (B) Different reactor designs to achieve continuous ring-closing meta-thesis.

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throughput in RCM and mRCM reactions with homogeneous catalysts with heating and a relatively high catalyst loading. In 2010, the Fogg group leveraged flow technology in a continuously stirred tank reactor with Grubbs catalyst 4 to significantly improve the unbiased mRCM reaction of 7 compared with the batch protocol (Figure 1B).¹⁸ Notably, a large reactor headspace (~50% v/v) constantly swept with argon was required to purge ethylene. However, unfavorable surface-area-to-volume ratios in larger process vessels may challenge the scalability of this approach. In 2014, Skowerski reported that a Teflon AF-2400 tube-in-tube reactor capable of ethylene removal can be used to perform RCM, mRCM, and cross-metathesis reactions.¹⁹ However, scaling of this technology is impractical because of tubing fragility, high costs, and limited availability.

We set out to design a practical and scalable flow technology approach for RCM wherein good catalytic performance would be enabled by continuous ethylene removal in a manner that would be sufficiently robust for process intensification. To this end, we established a collaboration with Compact Membrane Systems (CMS), a team with experience in developing functional polymer membranes for selective permeation processes on process scale.²⁰ These commercially available materials are scalable by design, tolerate high pressure and temperatures, have reactor design flexibility through custom engineering solutions, and display excellent chemical compatibility. Specifically, we sought to apply this technology in creating a unique process window wherein the semipermeable membrane would facilitate continuous ethylene removal from the reaction medium, thereby driving metathesis reactions to high conversion and attenuating ethylene-mediated catalyst decomposition pathways. Herein we describe the successful development of a continuous RCM platform utilizing this membrane pervaporation technology.

RESULTS AND DISCUSSION

Before testing the continuous membrane reactor, we evaluated the influence of ethylene on the RCM reaction of diethyl diallylmalonate (11) to yield cyclopentene 12 catalyzed by the Grubbs-Hoveyda II catalyst 1 (Figure 2). A room-temperature batch reaction with 0.1 mol % 1 and a gentle sparge of N_2 resulted in rapid and complete (>99.8%) conversion of 11 to 12 within 30 min of reaction time. As expected, sealing the reaction vessel negatively impacted the conversion. Saturating the reaction medium with ethylene at ambient pressure impeded the reaction and limited the conversion to ~85%. Applying ethylene to the headspace at a pressure of 20 psi further impeded the reaction such that <50% conversion was reached. Venting and sparging after 40 min under otherwise identical conditions led to partially restored catalytic activity once ethylene was removed. Finally, a flow reaction was performed in a stainless steel tubular reactor, confirming the deleterious effect of ethylene in a continuous reactor design. These observations are consistent with Tulchinsky's findings that ethylene significantly contributes to Ru-methylidenemediated catalyst decay under continuous conditions, ultimately limiting high catalyst turnover numbers (TONs).²

For our approach to mitigate the effects of trapped ethylene, the rate of mass transport provided by the membrane would have to approach or exceed the production rate. Thus, we first sought to understand the ethylene permeation kinetics under conditions relevant to olefin metathesis. A laboratory-scale stainless steel sheet-in-frame module fitted with a membrane



Figure 2. RCM reaction conversion profiles with different modes of ethylene removal or addition. Conversion = 100% (area for 12)/(area for 11 + 12) by ¹H NMR analysis.

disk ($\emptyset = 47 \text{ mm}$) served as a test platform. The membrane is a composite material composed of a perfluorinated polymer coated on a chemically resistant microporous layer that provides structural integrity. Ethylene permeation results expressed in gas permeance units (GPU) as well as surfacearea-dependent mass flow are shown in Table 1. The ethylene

Table 1. Gas-Phase Ethylene Permeation Studies Using the Membrane Sheet-in-Frame Module

Ethylene Fe	eed — Retent (Ø = 47mm) Perme	ate	20 psi PM Ethyl Reter Ethyl Perm	lene ntate lene eate
entry ^a	temp. (°C)	permeance (GPU)	ethylene flux $(g \cdot h^{-1} \cdot m^{-2})$	²) ^b
1	25	49.6	253	
2	40	50.6	270	
3	55	63.5	354	
4	65	93.2	537	
5	80	118	710	

^{*a*}Temperatures were equilibrated for 30 min, after which the ethylene flow was started and the permeation was equilibrated for 60 min before flux measurements. ^{*b*}Averages of two trials with different membrane samples.

flux across the membrane above 65 °C suggests that useful throughputs can be achieved. For example, the 47 mm diameter membrane disk is capable of an ethylene flux of >43 mmol·h⁻¹ at 80 °C under a back pressure of 20 psi.

The same membrane sheet-in-frame module was then fitted for use as a continuous reactor. The RCM substrate and Ru catalyst are pumped through a helical-type static mixer before entering the membrane reactor. The reaction mixture then passes over the membrane, where the generated ethylene passes to the permeate chamber, which is constantly swept with N₂ metered by a mass flow controller (MFC) and flowing countercurrent to the liquid retentate stream. Constantly purging the permeate chamber provides a driving force for

Table 2. Continuous RCM of Diethyl Diallylmalonate (11) Using the Membrane Sheet-in-Frame Reactor



entry ^a	catalyst	cat. loading (mol %)	temp. (°C)	back pressure (psi)	N_2 flow rate (mL/min)	$t_{\rm R}~({\rm min})$	yield of 12 $(\%)^b$	yield of 11 (%) ^b	TON
1	1	0.100	40	20	50	19.1	74.4	24.8	744
2	1	0.100	40	40	50	19.1	72.8	25.9	728
3	1	0.100	60	20	50	19.1	95.8	4.0	958
4	1	0.100	60	20	200	19.1	95.4	4.2	954
5	1	0.050	80	20	50	20.0	95.0	4.2	1900
6	1	0.050	120	30	50	5.0	99.8	0.0	1996
7	1	0.025	120	30	50	5.1	96.1	3.2	3844
8	2	0.010	120	30	50	5.2	75.8	23.9	7580
9	2	0.050	120	30	50	1.3	98.1	1.8	1962

^{*a*}All trials were equilibrated for $3t_R$ before sampling for yield. ^{*b*}Determined by quantitative ¹H NMR analysis versus external benzyl benzoate. ^{*c*}Versus yield of 12.

diffusion by ensuring that the partial pressure of ethylene across the membrane is maximized. The retentate stream is kept under pressure through the use of an adjustable back-pressure regulator (BPR). A diagram of this reactor design is shown in Table 2.

We first tested the influence of the nitrogen sweep rate and applied back pressure (Table 2). It was initially suspected that these parameters would affect the rate of ethylene flux, thus controlling the reaction performance. A baseline experiment performed with 0.1 mol % 1, RCM substrate 11 at 0.2 M in toluene, and the membrane reactor at 40 °C resulted in a 74.4% yield of 12 in 19.1 min with unreacted 11 constituting the mass balance (entry 1). The applied back pressure was then increased from 20 to 40 psi with all of the other variables unchanged (entry 2). A similar yield of 72.8% was observed for 12, indicating that varying the transmembrane pressure does not change the reaction outcome.

Increasing the reactor temperature to 60 $^{\circ}$ C provided a 98.5% yield of 12, corresponding to a TON of 958 (entry 3). In a subsequent experiment, the permeate chamber nitrogen sweep rate was increased to 200 mL/min, which resulted in a nearly identical yield of 12 (entry 4).

Ultimately, increased temperature provided a favorable balance of short processing times and low catalyst loadings. Lowering the loading of 1 to 0.05 mol % provided a 95.0% yield of 12 after a residence time of 20 min at 80 °C (entry 5). When the reaction temperature was increased to 120 °C, a residence time of only 5.0 min was required to achieve 99.8% yield at the same catalyst loading (entry 6). Further reducing the loading of 1 to 0.025 mol % resulted in a slightly lower yield in a similar residence time, with a TON of 3844 (entry 7).

Catalyst 2 gave improved kinetics compared with 1 via electronic activation of the chelating benzylidene.^{22,23} A loading of only 0.01 mol % provided modest yield of 12 but displayed high catalytic efficiency with a TON of 7580 at elevated temperature (entry 8). In an effort to balance the catalyst efficiency with short processing times, we found that 0.05 mol % 2 provided a high yield of 12 in a residence time of just 1.3 min (entry 9).

Having established suitable conditions for the facile RCM of **11**, we next applied the system to more challenging substrates

bearing different ring sizes, alkene substitution, and heteroatom functionality (Table 3). The diene precursor of Boc-

Table 3. Substrate Scope of Continuous RCM Using the Membrane Sheet-in-Frame Reactor



^{*a*}All trials were equilibrated for $3t_R$ before collection of analytical or bulk samples. ^{*b*}Determined by quantitative ¹H NMR analysis versus benzyl benzoate as an external standard. Isolated yields are given in brackets.

protected dihydropyrrole **13** and other RCM substrates bearing sterically accessible coordinating functional groups often require higher catalyst loadings and longer processing times compared with substrates such as **11**. Nonetheless, **13** was obtained in >90% yield with 0.10 mol % **2**. Dihydropyran **14** was produced in 98.0% yield at the same catalyst loading, whereas 2.0 mol % Ru catalyst was used in previously reported batch protocols.²⁴ Dihydrobenzoxepine **15** was formed in good yield with a notably shorter processing time and lower catalyst loading compared with previous batch reports, which typically employed \geq 0.5 mol % catalyst and a reaction time of at least 8 h.^{25,26}

Lastly, we addressed the preparation of cyclooctene 16, a substrate with an effective molarity (EM) of $\leq 23 \text{ mM.}^{27} \text{ A}$ significantly lower substrate concentration and elevated catalyst loading were expected to promote the desired ring

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closing over the formation of acyclic diene metathesis (ADMET) oligomers. Indeed, substrate concentrations above 10 mM provided good conversion but low yields of 16, indicating that oligomerization was a significant competing pathway. Lowering the substrate concentration to 5 mM with 1 mol % 2 provided the desired product in good yield.

Comparing the results obtained using a sealed stainless steel tubular reactor against those obtained with the membrane reactor emphasizes the performance gains provided by ethylene removal (Figure 3). In all cases, the RCM product



Figure 3. Comparison of yields using the membrane reactor vs the stainless steel tubular reactor.

yield obtained using the membrane reactor was significantly greater than that with the sealed tubular reactor. At low substrate concentrations, the negative effects of ethylene are expected to be more acute. As anticipated, the largest observed yield difference occurred in the case of cyclooctene 16. Low-EM substrates typically face the greatest reproducibility challenges in batch reactors, so consistent performance of our membrane reactor should provide a viable option for reliable scaling.

We further explored challenging RCM substrates by performing the macrocyclic RCM reaction to yield lactone 18, a substrate with a similarly low EM and relevance to the fragrance industry (Table 4). Second-generation Grubbs

Table 4. Continuous mRCM of 17 Using the Membrane Sheet-in-Frame Reactor



^{*a*}All experiments were equilibrated for $3t_{\rm R}$ before collection of analytical samples. ^{*b*}Determined by quantitative GC-FID analysis versus external dodecane. ^{*c*}Selectivity = 100%·(% yield/% conversion).

catalyst 4 at 1 mol % loading provided an acceptable yield with a residence time of 21 min at 100 $^{\circ}$ C (entry 1). The selectivity for the desired cyclization over the formation of ADMET oligomers was also good, in agreement with results from the Fogg group.²⁷ Both higher yield and better selectivity at milder temperatures were obtained when indenylidene catalyst 5 was employed at the same loading (entry 2).

We then evaluated contemporary cyclic alkyl amino carbene (CAAC) catalyst²⁸ **6** and diiodo catalyst²⁹ **3** at the high temperature of 120 °C and an unfavorable substrate concentration of 10 mM (entries 3 and 4). Nearly 80% yield of **18** was obtained when **6** was employed at 1 mol % loading. Catalyst **3** similarly provided good selectivity and similar yield but required only 0.5 mol % loading. Increasing the catalyst **3** loading and operating at a lower concentration of **17** allowed for a shorter residence time (10.5 min) along with a higher yield and better selectivity (entry 5). Interestingly, even a high loading of **2** was not able to surpass the results obtained with catalyst **3** (entry 6), likely because of the added stability provided by the iodides.

A single membrane coupon provided robust, reproducible performance throughout this body of work. Visualization of the used membrane surface showed minor wear compared with an unused sample, but the membrane was unaffected by fouling despite extended operation under intensive conditions. The selectivity for permeation of ethylene over other volatile reaction components, such as toluene, was also unaffected over time. Measurements of retained solvent mass after passage through the membrane reactor at elevated temperature with a nitrogen sweep of the permeate chamber showed a negligible difference compared to the expected mass flow of the retentate (see the Supporting Information). It follows that further process controls that have been previously been required to manage solvent volatilization in heated, sparged batches may not be not be necessary with this reactor design. Toluene was chosen as the exclusive solvent in this work because of its general utility as a process solvent, but other industrially preferred solvents that are compatible with metathetical reactions, such as alkanes or esters, would also be suitable for use in this system. While the reactor described herein was fit for a proof-of-concept demonstration, a purpose-built reactor featuring the same functional membrane technology in a high-surface-area hollow fiber reactor design would likely afford performance gains. Intensive effort to redesign and fabricate new reactor designs to eliminate the disadvantages of the current module is beyond the scope of this demonstration.

CONCLUSION

We have demonstrated RCM enabled by selective membrane permeation of ethylene. Our reactor design takes advantage of the commercially available and inherently scalable membranes provided by Compact Membrane Systems. The stability and excellent longevity of these membranes permits an expanded thermal process window while also delivering selective and high-flux ethylene permeation. The technology was successfully applied to the RCM of small, medium, and large rings with good effect, achieving TONs of >7500 in the case of **12**. Notably, for this specific application we speculate that a smallfootprint hollow fiber reactor module could improve our reactor design. Lastly, the generality of the membrane technology discussed herein suggests opportunities in other reaction types that would benefit from the selective removal of volatile reaction components while avoiding the penalties of Teflon AF-2400 tubing.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00061.

Characterization and images of the membrane pervaporation reactor, synthetic procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Hoveyda, A. H.; Zhugralin, A. R. The remarkable metal-catalysed olefin metathesis reaction. *Nature* **2007**, *450* (7167), 243–251.

(2) Hughes, D.; Wheeler, P.; Ene, D. Olefin metathesis in drug discovery and development - examples from recent patent literature. *Org. Process Res. Dev.* **2017**, *21*, 1938–1962.

(3) Higman, C. S.; Lummiss, J. A. M.; Fogg, D. E. Olefin metathesis at the dawn of implementation in pharmaceutical and specialty-chemicals manufacturing. *Angew. Chem., Int. Ed.* **2016**, *55*, 3552–3565.

(4) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. First scale-up to production scale of a ring closing metathesis reaction forming a 15-membered macrocycle as a precursor of an active pharmaceutical ingredient. *Org. Process Res. Dev.* **2005**, *9*, 513–515.

(5) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. Decomposition of ruthenium olefin metathesis catalysts. J. Am. Chem. Soc. 2007, 129, 7961–7968.

(6) McClennan, W. L.; Rufh, S. A.; Lummiss, J. A. M.; Fogg, D. E. A general decomposition pathway for phosphine-stabilized metathesis catalysts: lewis donors accelerate methylidene abstraction. *J. Am. Chem. Soc.* **2016**, *138*, 14668–14677.

(7) Hong, S. H.; Day, M. W.; Grubbs, R. H. Decomposition of a key intermediate in ruthenium-catalyzed olefin metathesis reactions. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.

(8) Morse, P. D.; Beingessner, R. L.; Jamison, T. F. Enhanced reaction efficiency in continuous flow. *Isr. J. Chem.* 2017, *57*, 218–227.

(9) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-flow technology as a tool for the safe manufacturing of active pharmaceutical ingredients. *Angew. Chem., Int. Ed.* **2015**, *54* (23), 6688–728.

(10) Fitzpatrick, D. E.; Ley, S. V. Engineering chemistry for the future of chemical synthesis. *Tetrahedron* **2018**, *74* (25), 3087–3100. (11) Michrowska, A.; Mennecke, K.; Kunz, U.; Kirschning, A.; Grela,

K. A new concept for the noncovalent binding of a ruthenium-based olefin metathesis catalyst to polymeric phases: preparation of a catalyst on raschig rings. *J. Am. Chem. Soc.* **2006**, *128*, 13261–13267. (12) Schoeps, D.; Buhr, K.; Dijkstra, M.; Ebert, K.; Plenio, H.

Batchwise and continuous organophilic nanofiltration of grubbs-type olefin metathesis catalysts. *Chem. - Eur. J.* **2009**, *15*, 2960–2965.

(13) Duque, R.; Öchsner, E.; Clavier, H.; Caijo, F.; Nolan, S. P.; Mauduit, M.; Cole-Hamilton, D. J. Continuous flow homogeneous alkene metathesis with built-in catalyst separation. *Green Chem.* **2011**, *13*, 1187–1195.

(14) Borré, E.; Rouen, M.; Laurent, I.; Magrez, M.; Caijo, F.; Crévisy, C.; Solodenko, W.; Toupet, L.; Frankfurter, R.; Vogt, C.; Kirschning, A.; Mauduit, M. A fast-initiating ionically tagged ruthenium complex: a robust supported pre-catalyst for batch-process and continuous-flow olefin metathesis. *Chem. - Eur. J.* **2012**, *18*, 16369–16382.

(15) Autenrieth, B.; Frey, W.; Buchmeiser, M. R. A dicationic ruthenium alkylidene complex for continuous biphasic metathesis using monolith-supported ionic liquids. *Chem. - Eur. J.* **2012**, *18*, 14069–14078.

(16) Drop, M.; Bantreil, X.; Grychowska, K.; Mahoro, G. U.; Colacino, E.; Pawłowski, M.; Martinez, J.; Subra, G.; Zajdel, P.; Lamaty, F. Continuous flow ring-closing metathesis, an environmentally-friendly route to 2,5-dihydro-1*H*-pyrrole-3-carboxylates. *Green Chem.* **2017**, *19*, 1647–1652.

(17) Morin, É.; Sosoe, J.; Raymond, M.; Amorelli, B.; Boden, R. M.; Collins, S. K. Synthesis of a renewable macrocyclic musk: evaluation of batch, microwave, and continuous flow strategies. *Org. Process Res. Dev.* **2019**, *23*, 283–287.

(18) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. Getting ring-closing metathesis off the bench: reaction-reactor matching transforms metathesis efficiency in the assembly of large rings. *Chem. - Eur. J.* **2010**, *16*, 11720–11725.

(19) Skowerski, K.; Czarnocki, S. J.; Knapkiewicz, P. Tube-in-tube reactor as a useful tool for homo- and heterogeneous olefin metathesis under continuous flow mode. *ChemSusChem* **2014**, *7*, 536–542.

(20) Li, B.; Guinness, S. M.; Hoagland, S.; Fichtner, M.; Kim, H.; Li, S.; Maguire, R. J.; McWilliams, J. C.; Mustakis, J.; Raggon, J.; Campos, D.; Voss, C. R.; Sohodski, E.; Feyock, B.; Murnen, H.; Gonzalez, M.; Johnson, M.; Lu, J.; Feng, X.; Sun, X.; Zheng, S.; Wu, B. Continuous production of anhydrous tert-butyl hydroperoxide in nonane using membrane pervaporation and its application in flow oxidation of a γ -butyrolactam. *Org. Process Res. Dev.* **2018**, *22* (6), 707–720.

(21) Lysenko, Z.; Maughon, B. R.; Mokhtar-Zadeh, T.; Tulchinsky,
M. L. Stability of the first-generation Grubbs metathesis catalyst in a continuous flow reactor. *J. Organomet. Chem.* 2006, 691, 5197–5203.
(22) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. Nitro-substituted Hoveyda–Grubbs

ruthenium carbenes: enhancement of catalyst activity through electronic activation. J. Am. Chem. Soc. 2004, 126 (30), 9318–9325. (23) Vorfalt, T.; Wannowius, K.-J.; Plenio, H. Probing the mechanism of olefin metathesis in Grubbs–Hoveyda and Grela type complexes. Angew. Chem., Int. Ed. 2010, 49, 5533–5536.

(24) Schmidt, B. Ruthenium-catalyzed olefin metathesis doublebond isomerization sequence. J. Org. Chem. 2004, 69, 7672-7687.

(25) Liu, G.; Zhang, H.; Zhao, X.; Wang, J. Efficient ruthenium metathesis catalysts containing carborane ligands. *J. Organomet. Chem.* **2014**, 749, 13–17.

(26) Zhang, Y.; Shao, M.; Zhang, H.; Li, Y.; Liu, D.; Cheng, Y.; Liu, G.; Wang, J. Synthesis and reactivity of oxygen chelated ruthenium carbene metathesis catalysts. *J. Organomet. Chem.* **2014**, 756, 1–9.

(27) Conrad, J. C.; Eelman, M. D.; Silva, J. A. D.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. Oligomers as intermediates in ring-closing metathesis. *J. Am. Chem. Soc.* **2007**, *129* (5), 1024–1025.

(28) Gawin, R.; Kozakiewicz, A.; Guńka, P. A.; Dąbrowski, P.; Skowerski, K. Bis(cyclic alkyl amino carbene) ruthenium complexes: a versatile, highly efficient tool for olefin metathesis. *Angew. Chem., Int. Ed.* **2017**, *56*, 981–986.

(29) Tracz, A.; Matczak, M.; Urbaniak, K.; Skowerski, K. Nitro-Grela-type complexes containing iodides - robust and selective catalysts for olefin metathesis under challenging conditions. *Beilstein J. Org. Chem.* **2015**, *11*, 1823–1832.