Metathesis reactions with a low-cost spinning disk system

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ABSTRACT
Experimental procedures have been developed to provide at the laboratory scale an efficient and relatively inexpensive continuous flow processing system to undertake metathesis chemistry. Glass discs, coated with porous silica particles impregnated with Grubbs (I) generation or Hoveyda–Grubbs (II) generation catalysts through non-covalent interactions, have been successfully used as annular zones for in situ metathesis reactions. The supported catalysts were active for ring closing metathesis and self-metathesis reactions with a variety of substrates with nearly quantitative conversion depending on the substrate structure. Advantages of these procedures include the ability to conduct reactions efficiently at small (low mmole) scale under ambient laboratory conditions, thereby avoiding the need for high energy/thermal procedures. Multiple experiments can be undertaken during the same day if catalyst screening is required. Moreover, separation of starting materials from products can be achieved using the same unit operations, avoiding the need for additional purification steps, thereby reducing the total solvent consumption.

1. Introduction
Applications of spinning disc reactors (SDRs) for the production of chemicals, polymers and particles can be traced back to the early 1980s (1), derived from technology developed in the late 1930s (2). During the past decade, a number of differently configured spinning disk reactors (SDRs) have become available commercially for laboratory and process scale applications (3). However, the relatively high-cost of this equipment (in the range of USD100-250 K and higher) has often precluded many research or university undergraduate training laboratories from gaining access to this technology. Nevertheless, when available these systems provide an entrée into process intensification (4,5) for the synthesis of chemicals, polymers and nano-materials, offering process-responsive tools to alternative technologies, such as pumped flow or vortex micro-reactors. By taking advantage of centrifugal forces generated by the rotation of the disc, thin films (ca. 10–200 nm) of liquids/reagents flow over the rotating surface. Rapid mixing of reagents, including gases, occurs in this liquid film, permitting short reaction residence times...
(typically ca. 1–5 sec) and significantly improved mass and heat transfer.

The potential of SDR technology to achieve enhanced reaction rates and efficient control of product properties for polymerization, crystallization and precipitation processes has been confirmed (6–8). Compared to reactions carried out in the batch mode with the catalyst in the solution state, to date, the use of SDR technology with chemisorbed or immobilized catalysts has, however, been less well developed, although interest is growing. For example, Vicevic et al. (9) have described the preparation of a Zn(OTf)3-HMS24 catalyst, derived from zinc triflate supported on a mesoporous silica via wet impregnation and attachment to a SDR disk using an epoxy-based glue. With this SDR system, rearrangement of α-pinene oxide to campholenic aldehyde was achieved in a higher yield and with faster processing time than by conventional batch methods. Importantly, loss of catalyst and production of inorganic waste – problems associated with the original batch processes – were reduced with this immobilized zinc triflate catalyst, highlighting the scope of SDR technologies to operate as a greener, more efficient tool for performing catalytic reactions.

Although various applications with well-engineered SDR equipment marketed by a number of vendors, e.g. Synthetron™ (KinetiChem, Inc USA) or SpinPro (Flowid, The Netherlands), have been described (10–12), the availability of alternative, much lower cost spinning reactor systems (differentiated by cost factors that are 10–50 fold lower than the above high-end SDR systems) would greatly facilitate the more general uptake of process intensifications methods within the cash-lean environment that often exists within many undergraduate/postgraduate teaching departments in Universities and some research laboratories that undertake chemical synthesis at the low mmole laboratory scale. In this manuscript, we describe the use of one such system, based on an “in-house” modified Chromatotron™ system, although the general principles arising from this study could be applied to coated disks spun by other types of suitably adapted, intrinsically safe and explosion-proofed turntables. The potential of using such modified systems as a low cost green chemical technology to efficiently perform both catalytic reactions and separation as part of the same set of unit operations has been examined for a variety of olefin metathesis reactions at the mmole scale. For this purpose, porous silica particles, coated onto glass disks and rotated using a modified Chromatotron™ system, were in situ impregnated centrifugally with an annular zone of catalyst. It was envisaged that separation of the products from the catalyst and residual starting materials could then be concomitantly achieved in situ as part of the same unit operation by manipulating the solvent polarity and, thereby, affecting the affinities of the catalyst, starting materials and products for the silica support material.

2. Results and discussion

Olefins metathesis is a well-known, convenient and mild transformation method widely utilized in organic synthesis, whereby carbon–carbon double bonds are converted or redistributed into new products via rupture and reformation. The key step in this process is the reaction between an olefin and a transition metal alkylidene (carbene) complex in a [2 + 2] fashion to generate an unstable metallocyclobutane intermediate. This intermediate can either revert back to the starting materials or open to afford a new carbene and hence produce a new olefin. If this process is repeated then eventually an equilibrium mixture of olefins is produced. Metathesis chemistry is important in the petrochemical and oleochemical industry. Unlike petrochemicals, oleo-chemicals are, however, derived from renewable resources, and have improved biodegradability and lower sulphur contents. In terms of oleo-chemical applications, metathesis chemistry has been used (13) to transform natural fats and oils into consumable products, such as lubricants, liquid fuels, paints, surface coatings and surfactants. Metathesis chemistry is also important in the manufacture of other bulk chemicals and polymers (14,15) and has numerous applications in the synthesis of chemical and pharmaceutical lead compounds (16–18). With traditional batch approaches, overall E-factors and other measures of green chemical efficiencies at laboratory scale can, however, be high for ring closing metathesis (RCM) reactions due to the high dilution that is often required, leading to large volumes of solvent waste and related high operational cost. It was anticipated that these constraints could be offset through the scaled-up use of SDR technologies validated at the proof-of-principle stage with smaller laboratory systems.

The Chromatotron™ system was originally designed as a laboratory tool for the separation of organic molecules and has several features from green chemical perspectives that offer an efficient alternative to traditional column chromatography techniques. In a Chromatotron™ system, a centrifugal flow of solvent across a spinning glass disk coated with an adsorbent is used to affect separation of a reaction mixture. This often leads to efficient separations, requiring the use of less solvent and adsorbent than would otherwise be needed in, e.g. flash chromatography. Because silica-based materials with an inbuilt UV absorber can be employed, separation of UV active compounds can be visualized with a portable UV light and the desired fractions conveniently
identified and collected. Moreover, equipment such as the Chromatotron™ system or other suitable turntable-based systems can be readily adapted “in house” to function as lower cost versions of these more highly engineered and costlier SDR equipment.

In these investigations, several different Grubbs ruthenium catalysts (Figure 1) have been used to document the potential of this low-cost SDR system, since they are widely employed in metathesis reactions owing to their exceptional turnover numbers and high functional group tolerance compared to W- and Mo-based catalysts. Immobilization or encapsulation of ruthenium catalysts onto support materials, including silica, zeolites, polystyrene or other polymer resins, in principle, also enables facile recovery of expensive catalysts (19).

Although the work described below has concentrated on the use of the ruthenium-based metathesis catalysts (1) and (3), many other alternative types of catalysts can be contemplated for use in the described SDR system.

2.1. Ring closing metathesis (RCM)

The carbene-coordinated Grubbs (I) generation (1) and the Hoveyda–Grubbs (II) generation catalyst (3), were impregnated as an annular zone into porous silica particles that had been coated onto glass disks and mounted on a rotating “in-house” modified Chromatotron™ system. These disks were then evaluated for their ability to simultaneously act as “catalytic reaction vessels” and “purification modules” for a variety of metathesis reactions. Initially, the RCM of diethyl diallylmalonate, (4) (Figure 2), was chosen as a model system (20,21) to validate the performance of these SDR systems. The stability and activity of different ruthenium carbene catalysts, such as the Grubbs (I) generation catalyst (1), for the RCM of (4) were established for different substrate conditions in both round bottom flask (RBF) and modified SDR formats (Tables 1–3) with emphasis placed on comparative catalytic activity at room temperature. Although RCM conversions can be achieved in the RBF mode at room temperature with catalyst levels of 1.0 mol% (Table 1, entry 3), more typically in the SDR and RBF modes catalyst levels in the range 2–5 mol% are employed. Previously, it has been suggested (22) that Grubbs (I) generation catalyst (1) is prone to deactivation in the absence of an inert atmosphere. However, this process did not appear to be a significant issue in the current study since the RCM could be successfully carried out under conventional stirred flask conditions or with the chemisorbed catalysts in the modified Chromatotron™ system, even when these vessels were not sealed. To further validate these observations, studies were conducted under conventional stirred flask and SDR conditions to assess the degree of catalyst deactivation in an air environment. Entry 4 (Table 1) shows that in the presence of air, quantitative conversion of diethyl diallylmalonate (4) was still achieved. These RCM reactions were also performed under SDR conditions in the presence of naked silica (Table 1, entry 5).

Figure 1. Examples of Ru-based metathesis catalysts.

![Figure 1](image1.png)

Figure 2. RCM of diethyl diallylmalonate, (4), with Grubbs (I) generation catalyst (1).
and silica/water mixtures (e.g. Table 1, entries 6 and 7) to establish the resilience of catalyst (1) under these conditions.

From Table 1, entry 5, it is evident that in the presence of the impregnated porous silica particles, the RCM reaction proceeded with moderate to high levels of conversion. These findings confirm that significant disruption of the catalytic cycle did not occur in these systems with the Grubbs (I) generation catalyst (1), despite the fact that this catalyst was strongly adsorbed onto the silica particles. These experiments demonstrated that with short residence times that can be employed with the modified SDR system, the stability of catalyst (1)

Table 1. RCM of diethyl diallylmalonate (4) using the Grubbs Generation (I) catalyst, (1), at different mol% at room temperature.

| Entry | Atmosphere | Mol% | Solvent (mL) | Time (min) | Conversion (%) |
|-------|------------|------|--------------|------------|---------------|
| 1     | Ar         | 5.0  | CH₂Cl₂ (15)  | 120        | 100           |
| 2     | Ar         | 5.0  | CH₂Cl₂ (15)  | 30         | 100           |
| 3     | Ar         | 1.0  | CH₂Cl₂ (15)  | 30         | 92            |
| 4     | Ar         | 5.0  | CH₂Cl₂ (15)  | 30         | 100           |
| 5     | Ar         | 1.0  | CH₂Cl₂ (15)  | 120        | 75            |
| 6     | Ar         | 1.0  | CH₂Cl₂ (15)  | 120        | 63            |
| 7     | Air        | 1.0  | CH₂Cl₂ (15)  | 120        | 56            |
| 8     | Ar         | 1.0  | C₆H₁₄ (15)   | 30         | 65            |

Note: Reactions with diethyl diallyl malonate and the Grubbs Gen(I) catalyst 1 were performed (a) in the presence of 1.0 g silica gel; (b) in the presence of 1.0 g silica gel and 100 μl distilled water; (c) Calculated from 1H NMR data.

Table 2. Ring-closing metathesis reactions with various dienes in RBF format and SDR format carried out with different catalysts and under different catalyst loading conditions.

| Entry | Starting material | Product/s | RBF format | SDR format |
|-------|-------------------|-----------|------------|------------|
|       |                   |           | Catalyst/mol% | Time (h) | Yield (%) | Catalyst/mol% | Method* | Yield (%) |
| 1     | H:G-11 (3)/1      | Ts        | H:G-11 (3)/1 | 1        | 100      | d            | 98       |
| 2     | G-1 (1)/3         | (9)       | G-1 (1)/4   | 2        | 71       | e            | 41       |
| 3     | G-1 (1)/3         | (13)      | G-1 (1)/3   | 2        | 85       | E            | 10       |
| 4     | G-1 (1)/2         | (17)      | G-1 (1)/4   | 1        | 90       | E            | 37       |
| 5     | G-1 (1)/2         | (21)      | G-1 (1)/4   | 1        | 92       | d            | 62       |
| 6     | G-1 (1)/2         | (23)      | G-1 (1)/4   | 1        | 99       | e            | 100      |

Note: (a) Yields from RBF reactions are isolated yields after chromatography; (b) yields from SDR reactions are isolated yields from fractions directly collected from disc; * For Methods d and e, see Experimental Section 4.2.
was compatible with its intended use. Even lower catalyst concentrations (< 0.01 mol%) could be used for the RCM of (4), but, in general, such low catalyst concentrations may not be fully compatible with spinning disk systems when very short residence times are used.

When analogous RCM reactions with diethyl diallylmalonate (4) were carried out using hexane as the solvent rather than CH$_2$Cl$_2$ under the same operating conditions, lower yields were obtained (Table 1, entry 3 vs entry 8), presumably due to the more limited solvation of the catalyst (1). On the basis of TLC results, the use of hexane provided better in situ chromatographic resolution of the product from the catalyst compared to CH$_2$Cl$_2$. These experiments documented several pertinent advantages of using silica particles impregnated with catalysts with the modified Chromatotron$^\text{TM}$ system. For example, problems associated with diminished catalytic activity due to Ru leaching, purification difficulties or long reaction times that have previously been reported for the batch mode with bulk adsorbed or immobilized metathesis catalysts, can be avoided with this modified SDR system.

These experiments with diethyl diallylmalonate (4) confirmed that ring closing metathesis at room temperature was feasible with the modified Chromatotron$^\text{TM}$ system. Further studies were carried out using both commercially available olefinic substrates, as well as newly synthesized novel dienes containing various amide, ester and ether linkages. To provide comparative data, several of these SDR RCM reactions were also carried out under standard RBF conditions. The results of these additional room temperature RCM reactions using both the RBF format and the SDR format with the modified Chromatotron$^\text{TM}$ spinning disk system are summarized in Table 2. Thus, under standard RBF and SDR conditions, N-p-toluenesulphonyldiallylamine (6) was converted in very high yields to the corresponding five membered ring product (7) within 1 h with the catalyst (3) (Table 2, entry 1).

For all SDR experiments, the glass disks were first coated with silica gel 60 pre-mixed in water with gypsum, which acted as a binder to allow the silica particles to adhere to the disk. The reactions were carried out at the scale of 0.5–1.0 mmol. A very high conversion level was observed for substrate (6) (Table 2, entry 1) with the catalyst loaded before the substrate. Conversion of substrates (8) and (12) were moderate, 54% and 48% respectively, when the substrates were loaded before the catalyst (Table 2, entries 2 and 3). Similarly to the reaction of the ether (8) in the RBF format, the bis-cyclic compound (13) was the major product using the SDR format, although in lower yield. In contrast, the monocyclic product (14) was predominantly produced using these modified Chromatotron$^\text{TM}$ spinning disk conditions, suggesting that longer residency times are required to obtain higher levels of conversion to the bis-product in this case (Table 2, entry 3). Substrate (16) (loaded before the catalyst) gave an overall 72% conversion but again a higher level (compared to the RBF reaction) of the mono-cyclic product was formed (Table 2, entry 4). Quantitative conversion of (22) was obtained with the substrate loaded before the catalyst (Table 2, entry 5). In contrast, when the homologous substrate (20) was loaded after the catalyst, conversion was

### Table 3. Self-metathesis of methyl oleate (24) in SDR format, carried out with the Hoveyda-Grubbs Gen-(II) catalyst (3); under different catalyst loading conditions, for conversion to octadec-9-ene (25) and dimethyloctadec-9-ene-dioate (26).

| Entry | Methyl oleate (24) (Mol%) | Catalyst (3) (Mol%) | Eluting Solvents (mL) | Conversion$^{a}$ |
|-------|--------------------------|---------------------|-----------------------|------------------|
| 1     | 1                        | 4.0                 | 100% Hexane (50)      | 40               |
|       |                          |                     | 25% CH$_2$Cl$_2$/Hexane (50) |                  |
|       |                          |                     | 50% CH$_2$Cl$_2$/Hexane (100) |                  |
| 2$^{bc}$ | 1                        | 4.0                 | 100% Hexane (30)      | 9                |
|       |                          |                     | 25% CH$_2$Cl$_2$/Hexane (60) |                  |
| 3     | 1.7                      | 4.0                 | 75% CH$_2$Cl$_2$/Hexane (60) | 45               |
|       |                          |                     | 25% CH$_2$Cl$_2$/Hexane (60) |                  |
| 4     | 1.7                      | 2 x 4.0              | 75% CH$_2$Cl$_2$/Hexane (50) | 50               |
|       |                          |                     | 50% CH$_2$Cl$_2$/Hexane (40) |                  |
|       |                          |                     | 75% CH$_2$Cl$_2$/Hexane (40) |                  |
| 5$^{cd}$ | 1.7                      | 2 x 4.0              | 75% CH$_2$Cl$_2$/Hexane (40) | 12               |
|       |                          |                     | 75% CH$_2$Cl$_2$/Hexane (40) |                  |

**Note:** Unless otherwise noted, disks with a radius of 7 cm and a silica coating of 1 mm thickness were used. Substrate was added neat. (a) Conversions determined by GC. (b) Substrate added slowly as a dilute solution. (c) Disk with a radius of 5 cm and a silica coating of 2 mm thickness.
lower, i.e. 62%, concordant with catalyst separation during the reaction and consistent with the conclusion that the addition of substrate prior to the addition of low polarity catalysts is the preferred method for reactions with these spinning disk systems.

When glyoxal bis(diallylacetal) (8) was subjected to similar metathesis conditions using catalyst (1) the biscyclic product (9) was obtained in 71% yield and the mono-cyclic product (10) in 11% yield in 2 h (Table 2, entry 2). There was a clear preference for formation of the seven membered ring product (9), with its structure confirmed by X-ray diffraction studies, rather than an eight membered ring product (11) was not detected, see Figure 3. Similarly RCM of (12) and (16) led to five membered ring structures rather than the anticipated nine or ten-membered ring structures (Figure 3). Periodic TLC analyses of the RCM reaction mixtures confirmed that when two diene moieties were present as part of the substrate, i.e. compounds (8), (12) or (16), kinetically the mono-ring product formed faster, followed by slow conversion to a bis-product, suggesting that longer reaction times are required for full conversion. Substrates (20) and (22), each containing a single diallylamine moiety with protected acid group, gave very high conversion with the Grubbs (I) generation catalyst (1) in 60 mins (Table 2, entries 5 and 6).

In all cases, the overall process, including separation, was typically complete in less than 30 mins, with the substrate and products isolated directly from the Chromatotron™ spinning disk plate well separated from each other and any eluted “catalyst” material. Generally, the recovered substrate eluted first followed by mono-cyclic product then the bis-cyclic product. Such enhanced kinetic control of metathesis reactions with these spinning disk systems compared to the batch RBF reaction conditions could prove to be very useful for production of mono-cyclic products with substrates having multiple diene moieties.

2.2. Self-Metathesis of methyl oleate

Self-Metathesis (SM) is an equilibrium reaction with a net enthalpy change of zero. Upon completion of the reaction the maximum conversion that can therefore be expected is 50% of each product in equi-molar quantities. With methyl oleate (24) as substrate, the equilibrium mixture will thus consist of 50 mol% of the substrate and 25 mol% of each of octadec-9-ene (25) and dimethyl octadec-9-ene-dioate (26) (Figure 4). For practical applications, the unreacted substrate can be recycled after separation of the reaction products.

In an effort to find suitable SM conditions with catalyst impregnated silica particles with these modified Chromatotron™ SDR systems, various experimental conditions including choice of solvent and catalyst concentrations were examined in the RBF format. Reaction of methyl oleate (24) in hexane using 1 mol% of the Hoveyda–Grubbs (II) generation catalyst (3) gave only 4% conversion. Further studies led to significant improvements in the conversion, making it possible to achieve the theoretical maximum conversion of 50% using CH₂Cl₂ as solvent and a catalyst concentration of 2 mol%. For these SM experiments using the modified SDR, the substrate addition method “c” (refer to Materials and Methods) was found to be optimal when the substrate was added neat directly to the spinning disk (Table 3). Elution with solvents of increasing polarity was used to separate the products from the catalyst. GLC analysis of the directly collected fractions showed that the elution order was octadec-9-ene (25), followed by unreacted starting material (24), then green colored Ru-containing material and dimethyl octadec-9-ene-dioate (26) which co-eluted. Further analysis revealed the conversion was 40%, giving 20% each of products (25) and (26) (Table 3, entry 1).
This result also provided evidence that the Hoveyda-Grubbs (II) generation catalyst, (3), was active on the silica surface of the spinning disk for these SM reactions at room temperature. Addition of the substrate as a dilute solution (method "b"; refer to Materials and Methods) was also used for the same reaction in an effort to minimize any potential saturation of the active sites of the immobilized catalyst (Table 3, entry 2). Moreover, in an effort to speed up the separation process overall, the polarity of the solvents was also significantly increased, allowing a reduction in solvent use overall by about 20%, but the conversion was low under these conditions (9%, Table 3, entry 2).

This SM reaction was scaled-up by 1.7-fold with substrate addition method “c” (i.e. neat). The conversion was 45% (Table 3, entry 3), close to the theoretical maximum conversion of 50%, with these conditions. Figure 5 shows the purity of the fractions collected overall.
without further purification from the SM of methyl oleate (24) (Table 3, entry 3) and provides insight into the overall efficiency of the process. Octadec-9-ene (25) was eluted first from the spinning disk and isolated in fractions F1-6 with 99% purity. The starting material, methyl oleate (24) was eluted in fractions F7-13 in 95% purity but also tailed into fractions F14-21 as a mixture with the diester (26). The dimethyl octadec-9-enedioate product (26) was the final compound to elute and was isolated in fractions F22-25 with 96% purity.

Because the starting material and products are continually being separated on the surface of the impregnated silica particles on the modified Chromatotron™ spinning disk, according to the Le Chatelier Principle, it should be possible to drive the equilibrium towards product formation and achieve greater than 50% conversion. To test this hypothesis, the catalyst concentration was doubled by loading two separate aliquots of the catalyst as two concentric bands onto the silica surface of the modified SDR spinning disk. Once on the spinning silica disk both zones of the catalyst merged to form a larger continuous band of catalyst as elution of products proceeds (Table 3, entry 4). Analysis of all collected fractions by GLC showed that maximum conversion reached 50%. Similar experiments with a disk of smaller radius and thicker silica layer enabled a reduction in solvent use for separation process (Table 3, entry 5), but the conversion was also reduced, probably due to the faster rate of separation of the catalyst from the substrate with reduction in the contact time required to achieve full conversion.

Table 4. Self metathesis of methyl undec-9-enoate (27) carried out with the Hoveyda-Grubbs Gen-(II) catalyst (3) with conversion to butene (28) and dimethyl octadec-9-ene-dioate (26).

| Entry | Methyl undec-9-enoate (27) (mmol) | Catalyst (3) Mol% | Solvent/s (mL) | Time (min) | Conversion(a) % |
|-------|---------------------------------|-------------------|----------------|------------|-----------------|
| 1(b)  | 5.0                             | 5.0               | CH₂Cl₂ (50)    | 30         | 43              |
| 2(c)  | 5                               | 2 × 4.0           | 100% Hexane    | 5          | 49              |
|       |                                 |                   | 54% CH₂Cl₂/ Hexane (70) |      |
|       |                                 |                   | 50% CH₂Cl₂/ Hexane (50) |      |
|       |                                 |                   | 75% CH₂Cl₂/ Hexane (40) |      |

Note: (a) Conversions determined by GLC. (b) Reaction performed in RBF format; (c) Reaction performed in SDR format; the substrate was added neat in two portions each of 2.5 mmol whilst the elution solvents employed are as indicated.

2.3. Self metathesis of methyl undec-9-enoate

In order to further examine whether conversion yields >50% could be achieved for metathesis reactions on these spinning disks, the SM of methyl undec-9-enoate (27), which produces two products, namely butene (28) and dimethyl octadec-9-ene-dioate (26), was investigated (Figure 6). By performing this reaction as a thin film on the spinning disk, butene is efficiently removed as a gas and thus the equilibrium is shifted towards formation of (26). The SM of methyl undec-9-enoate (27) was also performed under standard RBF conditions for comparison and gave ca. 43% conversion after 30 mins at room temperature under an argon atmosphere (Table 4, entry 1). In comparison, when SM of methyl
undec-9-enoate (27) was carried out on the modified SDR disk under similar conditions. (Table 4, entry 2); the conversion was 49%. The separation efficiency with this SDR system (Figure 7) showed that fractions F1–17 contained only the starting material (27). When solvent mixtures of higher polarity were used, the diester (26) eluted in fractions F18–23 with 85% purity, and in fractions F24–27 in 95% purity (Table 4, entry 2).

3. Conclusion

In this study, the application of spinning disks coated with silica particles impregnated with carbene-coordinated ruthenium-based catalysts have been successfully employed in metathesis reactions at the low mmole laboratory scale. These disks were highly effective for both RCM and SM reactions with various substrates. The supported catalysts were well dispersed as an annulus and provided a low organic solvent environment to carry out metathesis reactions. In addition, the reaction products, including Ru-containing material, could be easily and concomitantly separated by simple in situ solvent elution methods. For example, the SM of methyl oleate (24) and methyl octadec-9-enoate (27) using this simple catalyst impregnation technique achieved high conversions, 50% and 49% respectively with catalyst (3) (Tables 3 and 4). Moreover, nearly quantitative RCM conversions were achieved for substrates (6) and (22) (Table 2).

With more polar substrates, lower conversions were realized for some SDR RCM reactions, presumably due to the separation of the lower polarity catalyst from the substrate during the passage of the polar solvent across the disk, thereby, reducing the contact time. In cases when one of the products was volatile, high conversion to a desired product was obtained for SDR SM reactions. To extend these methods with polar substrates, more polar metathesis catalysts with the capability to be chemically immobilized are currently under development in our laboratory. Achievement of both solvent-lean metathesis reactions and the separation of products to high purity in a single unit operation represent an important green chemical objective. The procedures described above with a low cost spinning disk system go some way towards satisfying this proof-of-concept goal at the low mmole scale, and are consistent with laboratory practices that replicate some of the features of continuous manufacture procedures for the synthesis of chemicals via metathesis reactions, particularly in circumstances where undergraduate/postgraduate training modules are required.
4. Materials and methods

4.1. General

Reagents and solvents were purchased from commercial sources and used without further purification. Novel dienes used in this study were synthesized in-house. TLC was performed on Merck silica gel 60F254 precoated alumina plates. The components were visualized by fluorescence under 254 nm ultraviolet irradiation or by exposure to a variety of development/charring reagents where necessary. Flash chromatography was performed on FlashMaster II using Merck silica gel 60, 0.040–0.063 mm, (230–400 mesh) for normal phase chromatography and Grace Vydac C18 silica gel (Davisil), 35–70 μm for reverse phase chromatography using automated gradient elution mode. A Chromatotron Model 7924 T system was obtained from Harrison Research (T-Squared Technology Inc, San Bruno CA, USA) and was modified “in house” with reagent addition and gas entry ports to accommodate the reagent, solvent and gas delivery via tubing from either funnels or if required with metered pumps/syringes.

NMR spectra were recorded either on a Bruker DPX-300 spectrometer (300 MHz $^1$H, 75 MHz $^{13}$C) or on a Bruker DPX-400 spectrometer (400 MHz $^1$H, 100.6 MHz $^{13}$C) running Topspin 2.1 software. The NMR spectra refer to solutions in deuterated solvents as indicated. The residual solvent peaks have been used as an internal reference, except for CDCl$_3$ where tetramethylsilane (TMS) was used as the internal standard and chemical shifts are reported in parts per million (ppm). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), septet (sept), multiplet (m), and broad (br). Low resolution electro spray ionization mass spectra (ESI) were recorded on a Micro mass Platform II API QMS Electro spray mass spectrometer with cone voltage at 25 V as solutions in MeOH unless otherwise indicated. HRMS were recorded with an Agilent 6220 Accurate Mass TOF LC/MS spectrometer in positive (ESI+) mode.

4.2. Metathesis experiments using modified Chromatotron™ system

For these experiments, disks of two silica coating diameters were employed, namely (1), silica radius: 7 cm, silica thickness: 1 mm and (2), silica radius: 5 cm, silica thickness: 2 mm. The apparatus was positioned inside a fume hood. The silica-coated disks were secured to the rotating frame inside the vessel and the lid attached. An argon (air or nitrogen) line was attached to the gas inlet port of the modified Chromatotron™ and a continuous flow established of approx. 10 bubbles/sec. Organic reagent transfer lines were then attached to the reagent inlet ports with reagents and solvents delivered using tubing from reservoir funnels. The disk was then spun at 750 rpm. When funnel(s) filled with solvent (or other reagents) were employed, the funnel(s) were positioned at a height of approx. 25 cm above the inlet of the modified Chromatotron™, and at this height, a flow from the funnel onto the spinning disk could be maintained at approx. 2.5 mL/min.

Upon application to the center of the spinning disc, hexane was visible as an annular band moving across disk surface. Once the surface of the disc was saturated with hexane, the catalyst (in CH$_2$Cl$_2$ or another solvent) was added as a concentrated solution (ca 1 mL) via a reagent inlet port to the center of the spinning disc, forming a tight annular band. After the addition of the catalyst was completed, hexane (20 mL) was introduced and allowed to flow over the spinning disk. The substrate was then added using one of the methods described below. After the substrate addition, eluting solvent mixture(s) of increasing polarity were introduced via the inlet ports to the center of the spinning disc and allowed to centrifugally migrate over the surface to affect separation. Using a portable UV lamp it was possible to visualize UV-active bands moving across the disk. Fractions were collected and analyzed by TLC, NMR, IR and MS spectroscopy to reveal the product identities. Ethyl vinyl ether was added to any fractions containing catalyst to prevent further reaction. At the end of the reaction and separation cycle, the disk was washed with polar solvent mixtures (50% EtOH/hexane, followed by 100% EtOH) to clean the disk which was then dried in an oven at 60°C to regenerate and then reused.

Substrate addition: Depending on the type of catalyst and the relative polarity of the substrate employed, one of the following substrate addition methods was used:

Method (a): Substrate added directly as a solution in a single dose via the reagent inlet port to the center of the rotating disk in the modified Chromatotron™. Method (b): Substrate added slowly as a dilute solution to the center of the rotating disk in the modified SDR via a reagent inlet port and tubing connected to a funnel.

Method (c): Substrate added without dilution, i.e. neat, directly to the center of the rotating disk in the modified SDR via a reagent inlet port using organic reagent tubing connected to a dispensing syringe.

Catalyst addition: Depending on the type of catalyst and the relative polarity of the substrate employed, one of the following catalyst addition methods was used:
Method (d): The catalyst was added before addition of the substrate (as a concentrated solution or neat) to the center of the rotating disk in the modified SDR via a reagent inlet port. The disk was then spun for 1 h with occasional addition of 5% (v/v) CH₂Cl₂/hexane (a few drops) before eluting the products with the chosen solvent combination.

Method (e): The substrate (as a concentrate solution or neat) was added before addition of the catalyst to the center of the rotating disk in the modified SDR via a reagent inlet port and tubing. The disk was then spun for up to 1 h depending on the synthetic task with the occasional addition of 5% (v/v) CH₂Cl₂/hexane (a few drops) before eluting the products with the chosen solvent combination.

### 4.3. Metathesis reactions under RBF and SDR conditions

The following procedures are representative of the protocols employed for the RBF and SDR experiments. Methyl oleate (24) (300 mg, 1.01 mmol) in dry CH₂Cl₂ (15 mL) was added to a pre-weighed round bottomed flask containing the Hoveyda–Grubbs (II) generation catalyst (3) (1–5 mol%) under argon to form a green colored solution. The resulting solution was stirred at room temperature for 30 min. The reaction mixture was then quenched by adding a solution of ethyl vinyl ether in CH₂Cl₂, concentrated and purified by column chromatography. Product analysis of the crude extract was performed by GLC using 30QC51BPX5 column (Method: 50°C for 2 min, then 10°C/min to 280°C for 5 min). Retention times for each component were: 16.2 min for (25); 19.4 min for (24); 22.1 min for (26). GC-MS (EI) was also used as a quantitative means of analysis.

For the experiments with the modified Chromatotron™ system, the protocols as stated in the Section entitled “Metathesis Experiments using the modified Chromatotron™ system” were employed. A solution of catalyst (3) (25 mg, 4 mol%) in dry CH₂Cl₂ (1 mL) was added to the disk followed by hexane (10 mL) then neat methyl oleate (24) (300 mg, 1 mmol). Products were eluted with solvents of increasing polarity as described in Table 3. When two aliquots of catalyst were used (for example Table 3, entry 4), the first catalyst solution was loaded as usual followed by 10% CH₂Cl₂/hexane (30 mL) to move the catalyst band. The second catalyst solution was then loaded, followed by a small amount of hexane to give two separate catalyst bands. Neat methyl oleate (24) was loaded and reaction products eluted as usual, with the catalyst bands merging into one band during elution.

For the reaction of methyl undec-9-enoate (27) with the modified Chromatotron™ system, two aliquots of catalyst were loaded as described above for methyl oleate (24). Methyl undec-9-enoate (27) (500 mg, 2.5 mmol) was added neat followed by hexane (30 mL), 10% CH₂Cl₂/hexane (40 mL) and 50% CH₂Cl₂/hexane (20 mL). A further amount of (27) (500 mg, 2.5 mmol) was added and elution continued with the same solvents in increasing polarity hexane (30 mL), 10% CH₂Cl₂/hexane (30 mL), 50% CH₂Cl₂/hexane (30 mL) and 75% CH₂Cl₂/hexane (40 mL).

#### 4.4. Synthesis of 2-(bis(allyloxy)methyl)-4,7-dihydro-1,3-dioxepine (10)

To a stirred solution of glyoxal bis(diallylacetal) (8) (127 mg, 0.5 mmol) in dry CH₂Cl₂ (3 mL) under N₂ was added Grubbs (I) generation catalyst (1) (12.4 mg, 3 mol%). The resulting solution was stirred at room temperature for 2 h. After complete conversion (followed by TLC), the reaction mixture was concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane, 1/4) afforded 4,4′,7,7′-tetrahydro-2,2′-bi(1,3-dioxepine) (9) as a colorless solid (70 mg, 71%) and 2-(bis(allyloxy)methyl)-4,7-dihydro-1,3-dioxepine (10) as a colorless liquid (12 mg, 11%). For (10), ¹H NMR (CDCl₃) δ 4.14–4.26 (m, 6H), 4.51–4.57 (m, 2H), 4.58 (d, J = 4.8 Hz, 1H), 4.74 (d, J = 4.8 Hz, 1H), 5.19 (dq, J = 10.4, 1.5 Hz, 2H), 5.31 (dq, J = 17.2, 1.7 Hz, 2H), 5.71 (app. t, J = 1.7 Hz, 2H), 5.94 (ddt, J = 17.1, 10.4, 5.7 Hz, 2H). ¹³C NMR (CDCl₃) δ 66.7 (CH₂O x₂), 68.4 (CH₂O x₂), 100.0, 102.7, 117.5 (x₂), 129.6 (x₂), 134.6 (x₂); HRMS (ESI): m/z [M + Na]+ calcd for C₁₂H₁₈O₄: 249.1103, found 249.1096.

#### 4.5. Synthesis of 1,3-bis(2,5-dihydro-1H-pyrrol-1-yl)propane-1,3-dione (13)

To a stirred solution of N¹,N¹,N²,N²-tetraallylmalonamide (12) (100 mg, 0.38 mmol) in dry CH₂Cl₂ (3 mL) under N₂ was added Grubbs (I) generation catalyst (1) (6.3 mg, 2 mol%). The resulting solution was stirred at room temperature for 1 h. After complete conversion (followed by TLC), the reaction mixture was concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/MeOH, 9/1) afforded 1,3-bis(2,5-dihydro-1H-pyrrol-1-yl)propane-1,3-dione (13) as a white solid (67 mg, 85%) and N,N-diallyl-3-(2,5-dihydro-1H-pyrrol-1-yl)-3-oxopropamidine (14) as a colorless liquid (12 mg, 13%). For (13), ¹H NMR (CDCl₃) δ 3.44 (s, 2H), 4.24–4.28 (m, 4H), 4.41–4.44 (m, 4H), 5.79 (app. dt, J = 8.7, 2.6 Hz, 2H), 5.86 (app. dt, J = 8.7, 2.6 Hz, 2H). ¹³C NMR (CDCl₃) δ 42.9, 53.2 (x₂), 54.2 (x₂), 125.2 (x₂), 126.1 (x₂), 165.2 (x₂);
HRMS (ESI): m/z [M + Na]^+ calcd for C_{11}H_{14}N_{2}O_{2}: 229.0953, found 229.0949.

### 4.6. Synthesis of N,N-diallyl-3-(2,5-dihydro-1H-pyrrol-1-yl)-3-oxopropanamide (14)

See Section 4.5 for synthetic procedure. ^1^H NMR (CDCl$_3$) δ 3.46 (s, 2H), 4.01 (br. d, $J$ = 5.7 Hz, 2H), 4.04–4.06 (m, 2H), 4.24–4.28 (m, 2H), 4.34–4.38 (m, 2H), 5.14–5.25 (m, 4H), 5.72–5.88 (m, 4H). ^13^C NMR (CDCl$_3$) δ 41.7, 48.2, 50.0, 53.3, 54.2, 116.8, 117.5, 125.1, 126.2, 132.8, 133.2, 165.6, 16.1. HRMS (ESI): m/z [M + H]^+ calcd for C$_{13}$H$_{18}$N$_2$O$_2$: 235.1447, found 235.1436.

### 4.7. Synthesis of 1,4-bis(2,5-dihydro-1H-pyrrol-1-yl)butane-1,4-dione (17)

To a stirred solution of N$_1$N$_1$N$_4$N$_4$-tetraallylsuccinimide (16) (105 mg, 0.38 mmol) in dry CH$_2$Cl$_2$ (3 mL) under N$_2$ was added Grubbs (I) generation catalyst (1) (6.3 mg, 2 mol%). The resulting solution was stirred at room temperature overnight. After complete conversion (followed by TLC), the reaction mixture was concentrated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane, 1/1) afforded 1,4-bis(2,5-dihydro-1H-pyrrol-1-yl)butane-1,4-dione (17) as a white solid (75 mg, 90%) and N,N-diallyl-4-(2,5-dihydro-1H-pyrrol-1-yl)-4-oxobutan-amide (18) as a white solid (8 mg, 9%). For (17), ^1^H NMR (CDCl$_3$) δ 2.67 (s, 4H), 4.22–4.26 (m, 4H), 4.31–4.35 (m, 4H), 5.81 (app. dt, $J$ = 6.5, 2.0 Hz, 2H), 5.86 (app. dt, $J$ = 6.5, 2.0 Hz, 2H). ^13^C NMR (CDCl$_3$) δ 29.1 (x2), 53.0 (x2), 53.4 (x2), 125.2 (x2), 126.3 (x2), 170.5 (x2); HRMS (ESI): m/z [M + Na]^+ calcd for C$_{12}$H$_{16}$N$_2$: 243.1109, found 243.1103.

### 4.8. Synthesis of N,N-diallyl-4-(2,5-dihydro-1H-pyrrol-1-yl)-4-oxobutanamide (18)

See Section 4.7 for synthetic procedure. ^1^H NMR (CDCl$_3$) δ 2.64 (app. t, $J$ = 6.3 Hz, 2H), 2.73 (app. t, $J$ = 6.3 Hz, 2H), 3.93–3.98 (m, 2H), 3.99 (br. d, $J$ = 5.9 Hz, 2H), 4.21–4.25 (m, 2H), 4.29–4.33 (m, 2H), 5.11–5.23 (m, 4H), 5.71–5.88 (m, 4H). ^13^C NMR (CDCl$_3$) δ 28.0, 29.6, 48.4, 49.5, 53.1, 53.5, 116.9, 117.3, 125.2, 126.4, 133.1, 133.5, 170.6, 172.3; HRMS (ESI): m/z [M + Na]^+ calcd for C$_{14}$H$_{20}$N$_2$O$_2$: 271.1422, found 271.1419.

### 4.9. Synthesis of ethyl 4-(diallylamino)-4-oxobutanoate (20)

To an oven dried 50 mL round-bottom flask with stir bar and reflux condenser, under N$_2$ atmosphere, malonic acid (6.0 g, 51 mmol) and thionyl chloride (5 mL) were added. The resulting mixture was refluxed at 60°C for 1 h before evaporated to dryness. The residue was dissolved in dry CH$_2$Cl$_2$ (15 mL) under N$_2$ atmosphere and slowly added diallylamine (5.9 g, 61 mmol). The resulting solution was stirred at rt overnight before evaporated to dryness. The residue was dissolved in dry EtOH (15 mL) under N$_2$ atmosphere and slowly added conc. HCl (0.1 mL) and stirred at rt for 2 h before evaporated to dryness. The residue was diluted with saturated NaHCO$_3$ (50 mL) and extracted with CH$_2$Cl$_2$ (3 x 25 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1/1) to afford ethyl 4-(diallylamino)-4-oxobutanoate (22) as an off colorless liquid (4.2 g, 37%) and 4-(diallylamino)-4-oxobutanoic acid (1.7 g, 17%) as white solid. For (22), ^1^H NMR (CDCl$_3$) δ 1.26 (t, $J$ = 7.1 Hz, 3H), 2.61–2.69 (m, 4H), 3.89–3.93 (m, 2H), 3.99 (br. d, $J$ = 5.9 Hz, 2H), 4.14 (q, $J$ = 7.2 Hz, 2H), 5.10–5.24 (m, 4H), 5.70–5.84 (m, 2H). ^13^C NMR (CDCl$_3$) δ 14.2, 27.8, 29.4, 48.1, 49.1, 60.5, 116.7, 117.2, 132.7, 133.2, 171.3, 173.1; HRMS (ESI): m/z [M + Na]^+ calcd for C$_{12}$H$_{19}$NO$_3$: 248.1263, found 248.1258.

### 4.10. Synthesis of ethyl 4-(2,5-dihydro-1H-pyrrol-1-yl)-4-oxobutanoate (21)

To a stirred solution of ethyl 4-(diallylamino)-4-oxobutanoate (20) (96 mg, 0.43 mmol) in dry CH$_2$Cl$_2$ (3 mL) under N$_2$ was added Grubbs (I) generation catalyst (1) (7.1 mg, 2 mol%). The resulting solution was stirred at room temperature overnight. After complete conversion (followed by TLC), the reaction mixture was concentrated in vacuo. Purification by silica gel chromatography (100% ethyl acetate) afforded ethyl 4-(2,5-dihydro-1H-pyrrol-1-yl)-4-oxobutanoate (21) as a colorless liquid (78 mg, 92%). ^1^H NMR (CDCl$_3$) δ 1.26 (t, $J$ = 7.1 Hz, 3H), 2.57 (app. dt, $J$ = 6.8 Hz, 2H), 2.70 (t, $J$ = 6.8 Hz, 2H), 4.15 (q, $J$ = 7.1 Hz, 2H), 4.22–4.30 (m, 4H), 5.80 (app. dt, $J$ = 6.5, 2.0 Hz, 1H), 5.88 (app. dt, $J$ = 6.5, 2.0 Hz, 1H). ^13^C NMR (CDCl$_3$) δ 14.2, 29.0, 29.1, 52.9, 53.3, 60.6, 124.9, 126.4, 169.7, 173.2; HRMS (ESI): m/z [M + Na]^+ calcd for C$_{10}$H$_{13}$NO$_3$: 220.0950, found 220.0944.

### 4.11. Synthesis of ethyl 3-(2,5-dihydro-1H-pyrrol-1-yl)-3-oxopropanoate (23)

To a stirred solution of ethyl 3-(diallylamino)-3-oxopropanoate (22) (106 mg, 0.5 mmol) in dry CH$_2$Cl$_2$ (3 mL) under N$_2$ was added Grubbs (I) generation catalyst (1) (8 mg, 2 mol%). The resulting solution was stirred at room temperature for 1 h. After complete conversion (followed by TLC), the reaction mixture was concentrated...
in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane, 1:4) afforded ethyl 3-(2,5-dihydro-1H-pyrrol-1-yl)-3-oxopropanoate (23) as a colorless liquid (91 mg, 99%).\(^1\) H NMR (CDCl\(_3\)) \(\delta\) 1.29 (t, \(J=7.1\) Hz, 3H), 3.40 (s, 2H), 4.22 (q, \(J=7.1\) Hz, 2H), 4.28 (br. s, 4H), 5.80 (app. dt, \(J=6.5, 1.4\) Hz, 1H), 5.89 (app. dt, \(J=6.5, 1.4\) Hz, 1H); \(^1\)\(^3\)C NMR (CDCl\(_3\)) \(\delta\) 14.3, 42.3, 53.3, 63.9, 61.6, 124.8, 126.5, 164.4, 167.5; HRMS (ESI): \(m/z\) [M + Na]\(^+\) calcd for C\(_9\)H\(_{13}\)NO\(_3\); 206.0793, found 206.0788.

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