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PAPER

Continuous flow homogeneous alkene metathesis with built-in catalyst separation†

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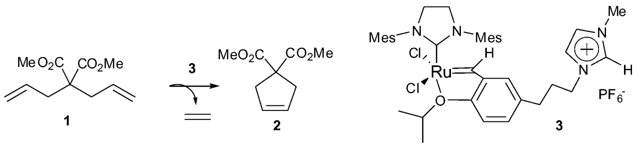
Continuous flow homogeneous alkene metathesis using a supported ionic liquid phase (SILP) catalyst with CO_2 as a transport vector allows the self-metathesis of methyl oleate with only a slight loss of activity for at least 10 h; cross-metathesis of dimethyl maleate with methyl oleate ceases after 3 h, but the catalyst remains active for methyl oleate metathesis. The reasons for this unusual behaviour are explored and a practical system for the cross-metathesis of methyl oleate with dimethyl maleate, under batch conditions, is described.

Introduction

Alkene metathesis is a reaction in which two alkenes undergo scrambling of the chains attached to the double bonds and has become very important in the construction of a wide array of unsaturated molecules.[1] Applications include the construction of cyclic compounds by ring-closing metathesis (RCM),[2] ring-opening metathesis polymerisation (ROMP),[3] allowing the formation of linear polymers from cyclic starting materials, the adjustment of alkene chain length as in the Shell higher olefins process[4] and the formation of polymer composites for use in, for example, materials fabrication. Since they are more tolerant to functional groups than molybdenum complexes, ruthenium-based catalysts have been extensively studied.[5] Nevertheless, with the exception of polymerization processes, rather few commercial applications have ensued.[6] Besides the high catalyst cost, the main reason for this industrial underdevelopment, particularly in the pharmaceutical area, may be associated with issues concerning the separation of metal waste from the product, which is time-consuming and expensive.[7]

Solutions to circumvent this problem of product/catalyst separation have been addressed,[7] in particular by carrying out reactions in an ionic liquid.[8] In this medium, ionic liquid-immobilized catalysts are soluble and importantly are not removed during product isolation by simple liquid/liquid extraction using an appropriate organic solvent, which allows for catalyst recycling at the end of the reaction. As an example, with complex **3**, used in the present study, it is possible to perform eight consecutive RCM reactions of substrate **1** with quantitative yields using a 2.5 mol% catalyst loading (Scheme 1).[9] More importantly, product contamination in ruthenium was found to be low (1–22 ppm). These latter experiments were conducted in batch mode, which is not time or energy efficient. So, for example, eight consecutive 3 h batch reactions produced a total turnover number of 386 $mol_{product}\ mol_{catalyst}^{-1}$.



Scheme 1 RCM using an ionic liquid-tagged boomerang catalyst.

Having recently developed a system permitting continuous flow catalysis,[10] we now report the first robust examples of continuous flow homogeneous olefin metathesis. For this, a supported ionic liquid phase (SILP) catalyst consisting of **3** immobilised in a thin film of imidazolium ionic liquid within the pores of silica, was used with compressed CO_2 as the flowing medium (SILP-SCF). Such systems have been used before for hydroformylation[10] and asymmetric hydrogenation,[11] and they offer advantages over systems where liquids flow through SILP catalysts[12] because the solubilities of the ionic liquid and catalyst are greatly reduced by the presence of CO_2.

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They also offer advantages over all gas phase systems using SILP catalysts[13] because the flow rate of less volatile substrates and products can be much higher. SILP-SCF systems also offer potential advantages over systems where the catalyst is immobilised by dissolving it in a bulk ionic liquid as substrates and products are transported through this solution dissolved in $scCO_2$ (SCF-IL).[14] SILP-SCF systems can be used below the critical point of the flowing medium (*i.e.* using gas expanded liquids), allowing lower pressure operation and better contact between the substrate and the catalyst. Much less ionic liquid is required in the SILP-SCF system than in the SCF-IL system.

Significant progress has been made in the preparation of metathesis catalysts covalently attached to solid supports,[15] but there are rather few examples of their use in continuous flow processing where the substrates and/or products are of relatively low volatility. Flow metathesis has been reported using a similar catalyst to ours supported on Raschig rings. Leaching and deactivation in this case are severe.[15e] A related metathesis catalyst has been immobilised within a PEEK column on a monolith prepared by the ROMP of norbornene (NBE) and $(NBE\text{-}CH_2O)_3SiCH_3$ using $[Ru({=}CHPh)Cl_2(PCy_3)_2]$ in the presence of suitable porogens. Further metathesis of the monolith, still containing the catalyst, with norborn-5-en-2-ylmethylhexafluoroglutonate gave an acid resin that was converted to its silver salt before reaction with $[Ru({=}CH(2\text{-}C_6H_4OPr^i))Cl_2(IMesH_2)]$ ($IMesH_2$ = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) to give a supported metathesis catalyst bound to the resin through a Ru-carboxylate linkage.[15f] This catalyst was used under continuous flow conditions for the RCM of diethyl 2,2-diallylmalonate (as in Scheme 1) in dichloromethane. The catalyst remained active for 140 min, although the activity dropped regularly with time (initial yield 70% dropping to < 10% at the end of the reaction). Even so, 480 turnovers were obtained within the 140 min period. Ruthenium (<0.2%) and ligand leaching were very low. Using a size expanded (through substituents on the *N*-heterocyclic carbene N atoms) catalyst, continuous flow metathesis on the same substrate has also been carried out in a membrane reactor.[15g] The conversion rose to *ca.* 35% after 100 min but then dropped steadily to < 10% after 500 min. Overall, turnover was 866, and 97.6% of the ruthenium was retained in the reactor. The drop in reactivity with time in these cases suggests that catalyst deactivation may be occurring, possibly because of a build up of ethene in the system.[15g] Perhaps the most successful flow system reported[15h] to date involves depositing a Grubbs–Hoveyda catalyst on silica by the evaporation of a toluene solution. This has been successfully used as a low leaching supported catalyst for the metathesis of a variety of alkenes and gives up to 4000 catalyst turnovers in 2 h in the continuous flow ring-opening metathesis of cyclooctene, with ruthenium leaching as low as 7 ppb. Non-polar organic solvents were used as the transport vector but the system is not really suitable for polar substrates because the catalyst is washed away.

Experimental

All manipulations were carried out using standard Schlenk techniques and oven dried glassware under a nitrogen atmosphere. CO_2 (99.9995%) was purchased from BOC gases. Diethyl diallylmalonate was purchased from Aldrich and used without further treatment. 1-Octene, 2-octene, methyl oleate, dimethyl maleate, diethyl maleate and diethyl fumarate were purchased from Aldrich, distilled and passed through a silica plug before use. Silica (Sigma-Aldrich, Merck silica gel 100, grade 10184, 70–230 mesh, 10 nm pore diameter) was purchased from Aldrich and heated to 500 °C for several hours before use.

Grubbs–Hoveyda 2nd generation catalyst was purchased from Aldrich. Catalyst **3**,[9a] $BMIM{\cdot}NTf_2$ and $OMIM{\cdot}NTf_2$[14c] were prepared by literature methods.

^1H, ^{13}C and ^{19}F NMR spectra were recorded using a Bruker 400 spectrometer. Gas chromatography was performed using a Hewlett-Packard 6890 series gas chromatograph equipped with an Agilent 6890 series injector. Analyses were performed with a Hewlett-Packard 5973 series mass selective detector and the peak areas integrated using a Hewlett-Packard Chemstation.

Compound **4** was synthesised by a method adapted from the literature.[9d]

3-(4-Isopropoxy-3-(prop-1-en-1-yl)phenyl)propan-1-ol

A Schlenk flask was charged with dry toluene (30 mL) and tetrakis(triphenylphosphine)palladium (370 mg, 0.321 mmol, 0.07 equiv.). The mixture was de-gassed and 3-(3-bromo-4-isoproxyphenyl)propan-1-ol (1.25, 4.58 mmol) diluted in dry toluene (5 mL) was added dropwise through a syringe. The resulting mixture was stirred for 15 min before adding tributylpropenylstannane (2.1 mL, 6.86 mmol, 1.5 equiv.). The flask was then heated at 110 °C overnight. After cooling to room temperature, the mixture was filtered on a plug of Celite® and the cake washed with diethylether. The solvent was evaporated under vacuum and purification by silica gel using pentane–ethyl acetate (8/2) as the eluent afforded the desired product as a colourless oil (878 mg, 3.75 mmol, 82%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.05 (m, 1H), 6.98 (ddd, J = 18.0, 8.4, 2.2 Hz, 1H), 6.82 (dd, J = 12.5, 8.4 Hz, 1H), 6.75–6.44 (m, 1H), 6.02 (ddd, J = 18.0, 12.5, 6.8 Hz, 1H), 4.48 (dd, J = 12.3, 6.2 Hz, 1H), 4.30–4.19 (m, 2H), 3.00 (d, J = 1.9 Hz, 2H), 2.69 (dd, J = 15.0, 7.6 Hz, 2H), 1.88 (dd, J = 6.9, 1.8 Hz, 3H), 1.34 (dd, J = 8.0, 6.1 Hz, 6H).

4-(3-Bromopropyl)-1-isopropoxy-2-(prop-1-en-1-yl)benzene

To a solution of 3-(4-isopropoxy-3-(prop-1-en-1-yl)phenyl)-propan-1-ol (9.817 g, 41.89 mmol) and triethylamine (8.8 mL, 62,84 mmol, 1.5 equiv.) in dry dichloromethane (200 mL) was added methanesulfonyl chloride (4.86 mL, 62.84 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was stirred for 3.5 h at room temperature before being diluted with dichloromethane. The organic phase was washed four times with a 5% citric acid solution, dried over sodium sulfate and concentrated to a yellow oil. The product was used without further purification in the following reaction.

To a crude mixture of 3-(4-isopropoxy-3-(prop-1-en-1-yl)phenyl)propyl methanesulfonate (13,09 g, 41.89 mmol) in tetrahydrofuran (200 mL) and dimethylformamide (78 mL) was added lithium bromide (7.28 g, 83.78 mmol, 2 equiv.) in one portion. The mixture was stirred overnight. After evaporation of the solvent, the residue was diluted in ethyl acetate. The organic layer was washed three times with a saturated sodium hydrogencarbonate solution, then with brine, and dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography using pentane–ethyl acetate (98/2) as the eluent afforded the desired product as a colourless oil (9.34 g, 31.42 mmol, 75% for two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, $J = 50.0, 2.2$ Hz, 1H), 7.04–6.91 (m, 1H), 6.81 (dd, $J = 13.0, 8.3$ Hz, 1H), 6.74–6.48 (m, 1H), 6.29–5.71 (m, 1H), 4.48 (dd, $J = 12.3, 6.1$ Hz, 1H), 3.41 (td, $J = 6.6, 4.5$ Hz, 2H), 2.72 (dd, $J = 15.6, 7.7$ Hz, 3H), 2.20–2.11 (m, 2H), 1.88 (ddd, $J = 21.8, 6.9, 1.8$ Hz, 3H), 1.34 (dd, $J = 8.0, 6.0$ Hz, 6H).

3-(3-(4-Isopropoxy-3-(prop-1-en-1-yl)phenyl)propyl)-1-methyl-1*H*-imidazol-3-ium hexafluorophosphate (4)

A 100 mL round-bottomed flask equipped with a condenser was charged with 4-(3-bromopropyl)-1-isopropoxy-2-(prop-1-en-1-yl)benzene (4.15 g, 13.96 mmol), methylimidazole (2.22 mL, 27.92 mmol, 2 equiv.) and dry toluene (28 mL). The mixture was stirred overnight at 100 °C and the solvent evaporated. The residue was dissolved in distilled water (200 mL) and hexafluorophosphoric acid (5.14 g, 27.92 mmol, 2 equiv.) was slowly added dropwise. After 10 min stirring, dichloromethane and brine were added. The organic phase was washed with brine until a neutral pH was reached, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography using dichloromethane/acetone (3/1) as the eluent afforded the desired product as a colourless oil (5.548 g, 12.48 mmol, 89% for two steps).

^{1}H NMR (400 MHz, MeOD) δ 8.77 (d, $J = 17.1$ Hz, 1H), 7.53 (ddt, $J = 33.0, 10.8, 1.8$ Hz, 2H), 7.13–6.94 (m, 2H), 6.87 (dd, $J = 15.1, 8.4$ Hz, 1H), 6.70–6.38 (m, 1H), 6.33–5.64 (m, 1H), 4.51 (ddd, $J = 12.1, 7.8, 5.8$ Hz, 1H), 4.32–4.08 (m, 2H), 3.32 (dt, $J = 3.3, 1.6$ Hz, 3H), 2.64 (td, $J = 7.3, 4.6$ Hz, 2H), 2.20 (ddd, $J = 15.4, 8.9, 5.3$ Hz, 2H), 1.83 (ddd, $J = 31.4, 6.8, 1.8$ Hz, 3H), 1.43–1.20 (m, 6H).

^{31}P NMR (162 MHz, MeOD) δ −144.56 (hept, $J = 708.1$ Hz).

^{19}F NMR (376 MHz, MeOD) δ −73.94 (dd, $J = 363.4, 356.0$ Hz).

^{13}C NMR (101 MHz, MeOD) δ (two isomers) 155.33, 133.65, 133.08, 131.24, 129.50, 129.16, 128.78, 128.66, 127.25, 127.12, 127.00, 126.95, 126.67, 124.87, 123.61, 115.94, 115.88, 72.10, 36.39, 32.79, 32.71, 32.43, 22.50, 22.48, 19.05, 14.99.

Catalyst preparation

A typical preparation of the SILP catalyst was performed by dissolving catalyst **3** (0.0072 g, 0.02 wt% of silica), BMIM·NTf_2 (1.276 g, 29 wt% of silica) and silica gel (4.4 g) in purified dichloromethane (20 mL). After 2 h stirring, the dichloromethane was removed at 35 °C under vacuum to recover the SILP catalyst, which, in a glove box, was charged into a 15 cm^3 tubular reactor fitted with glass wool at each end to avoid it being flushed away during the reaction. The catalyst was stored in a glove box until its use.

Continuous flow experiments

The catalytic reactions were carried out in a reactor, the design of which has previously been described,[10b] with the reactor in a vertical position and the flow being from bottom to top. The tubular reactor previously loaded with the SILP catalyst was fixed onto the rig after purging it with a flow of CO_2. The rig was pressurised to the desired pressure and the reactor heater and pre-heater raised to the desired temperature. After equilibration of the system, the substrate was pumped in with an HPLC pump, and liquid CO_2 was pumped through a Pickel pump to maintain the total pressure. The flow stream was decompressed through a decompression valve to atmospheric pressure into a collection vessel, from which the gas was passed through a flow meter, where the total gas flow was monitored at atmospheric pressure. The liquid in the collection vessel was removed periodically, weighed to check the mass balance, and analysed by GC-MS (organic products), NMR (IL leaching) and ICP-OES (Ru leaching).

Substrate ratios and flow rates are described in tables later in the article.

Batch experiments

In a typical batch reaction, methyl oleate (5 g, 16.8 mmol) was mixed with dimethyl maleate (9.7 g, 67.3 mmol) in a ratio of 1 : 4. Catalyst **3** (0.0308 g, 0.034 mmol, 0.2 mol% MO) was dissolved in OMIM·NTf_2 (5 mL) and heated at 50 °C. The substrate mixture was added to the catalyst solution. Samples were taken periodically and quenched with ethyl vinyl ether prior to GC-MS analysis.

Results and discussion

A SILP catalyst was used for the continuous flow SILP-SCF experiments. **3**, prepared as described previously,[9a] was dissolved in dichloromethane containing 1-butyl-3-methylimidazolium triflamide (BMIM·NTf_2) and silica (Sigma-Aldrich, Merck silica gel 100, grade 10184, 70–230 mesh, 10 nm pore diameter), previously heated to 500 °C to remove surface hydroxides, was added. After evaporation of the dichloromethane, the catalyst, a free-flowing pale green powder, was loaded into a tube in a glove box and fixed onto the previously described reactor[10b] under a CO_2 flow. The CO_2 was passed through the reactor while the tube was heated to the desired reaction temperature, and the substrate flow initiated once the temperature had stabilized (10 min). The effluent exiting the tube was passed through a decompression valve and the products condensed into a collection vessel. The collected material was removed from the vessel every hour and analysed by GC for organic products, by inductively coupled plasma optical emission spectroscopy (ICPOES) to determine the ruthenium content, and by ^{1}H and ^{19}F NMR spectroscopy to analyze the organic products and track possible traces of leached BMIM·NTf_2. In most cases, mass balance between substrate and product was found to be close to 100%, assuming, where relevant, that the ethene and but-2-ene were lost, as is confirmed by GC analysis.

Our initial experiments focused on the RCM of diethyl diallylmalonate (**1**; run 1, Table 1). Fig. 1 highlights the good activity of the ruthenium complex during the first hour; nevertheless, after this period, the catalyst performance decreased, possibly due to its degradation. Nonetheless, considering the low catalyst loading and the fast flow rate, high turnovers were obtained

Table 1 Conditions for continuous flow ring-closing or self-metathesis using **3** under SILP conditions[a]

Run	Substrate	$T/°C$	Catalyst[b] loading (Ru% w/w)	Substrate flow rate/cm^3 min^{-1}	Time on stream/h	Conversion after 3 h on stream (%)	TON[d]
1	**1**	50	0.18	0.1	6	7.2	242
2	**1**	23	0.048	0.2	7	2.4	564
3	**1**	50	0.022	0.2	6	0.6	550
4	1-Octene	50	0.022	0.2	6	0	28
5	2-Octene	50	0.024	0.1	5	40	3371
6	MO	50	0.020[c]	0.05	10	66.9	4247
7	MO	23	0.007[c]	0.05	9	57.2	10148

[a] BMIM·NTf$_2$ (29% w/w on silica; mass of silica = 3.4 g), CO$_2$ flow, pressure = 100 bar, total flow = 645 cm^3 min^{-1} at NTP, MO = methyl oleate. [b] g (g silica^{-1}). [c] SiO$_2$ = 4.4 g. [d] Total mol$_{\text{product}}$ mol$_{\text{catalyst}}$$^{-1}$ at the end of the reaction.

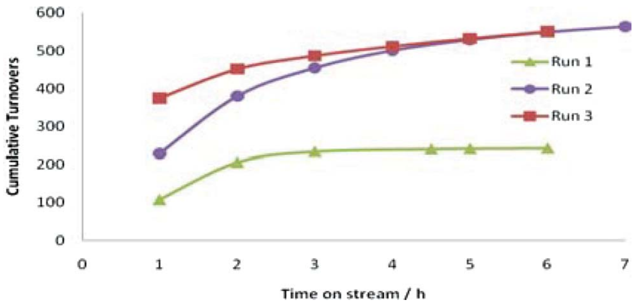


Fig. 1 Continuous flow RCM of **1** catalysed by **3** in a SILP system (for conditions, see Experimental section and Table 1).

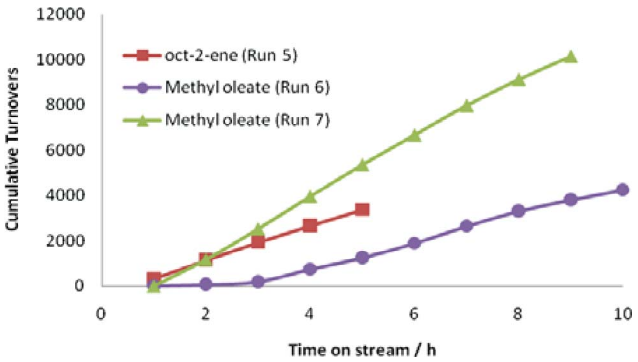


Fig. 2 Continuous flow self-metathesis of 2-octene and methyl oleate catalyzed by **3** in a SILP system (for conditions, see Table 1).

in a short time period. By reducing the catalyst loading and increasing the flow rate of the substrate (runs 2 and 3, Table 1 and Fig. 1), it was possible to obtain a turnover number of 564 in 7 h, but the conversions were found to be low and dropped significantly with time. This behaviour is similar to that in other flow metathesis systems. Although more turnover was obtained than in repetitive batch reactions in a shorter time, the instability of the catalyst makes this system unacceptable for use with this type of substrate.

It is known that ruthenium methylidenes, which represent the true active species when terminal alkenes are used as substrates, can be degraded by dimerization, and hence their stability is a crucial issue for olefin metathesis.[16] In order to test whether this was in fact the problem, we studied the metathesis of 1- and 2-octenes using the same catalytic system.

For 1-octene (run 4, Table 1), only 0.9% conversion was observed in the sample collected after 1 h, representing 28 turnovers, but subsequent samples contained no metathesis products. These observations confirm that the system is not stable for the metathesis of terminal alkenes.

We therefore turned our attention to internal alkenes and used the self-metathesis of 2-octene to 3-hexene and 2-butene as a benchmark substrate (run 5, Table 1, Scheme 2a and Fig. 2). For this transformation, catalyst **3** exhibited an enhanced stability, providing a turnover frequency of 813 h^{-1} at the end of the second hour on stream, with this only dropping to 707 h^{-1} after 5 h. The total turnover in this case was 3371 after 5 h.

The self-metathesis of oleochemicals is of considerable interest for the conversion of low value feedstocks into useful chemicals in petrochemistry and polymerization.[17] The self-metathesis of methyl oleate (Scheme 2b) yields dimethyl 1,18-octadec-9-enedioate, which may be valuable for materials applications, and 9-octadecene. We have shown that internal alkenes of this kind can be selectively methoxycarbonylated at the terminal position by a tandem isomerisation—methoxycarbonylation process (Scheme 2b).[18] The products may be important in detergents. We therefore examined the metathesis of methyl oleate in the flow system conceptualised in Fig. 3 using catalyst **3** (runs 6 and 7, Table 1 and Fig. 2). Using a flow rate of 0.05 cm^3 min^{-1} at 50 °C, up to 64% conversion was obtained over the first 6 h. At equilibrium, the conversion would be 66.7%. From the 7th hour, the conversion dropped steadily to 44% after 10 h, showing some catalyst instability. The total number of catalyst turnovers in this period was 4247. Even more impressively, on decreasing the temperature to 23 °C and the

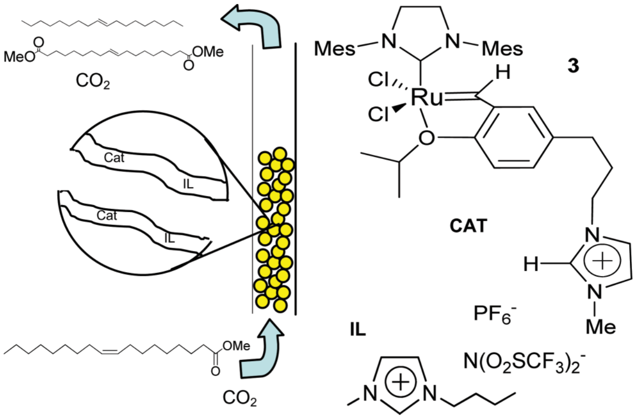
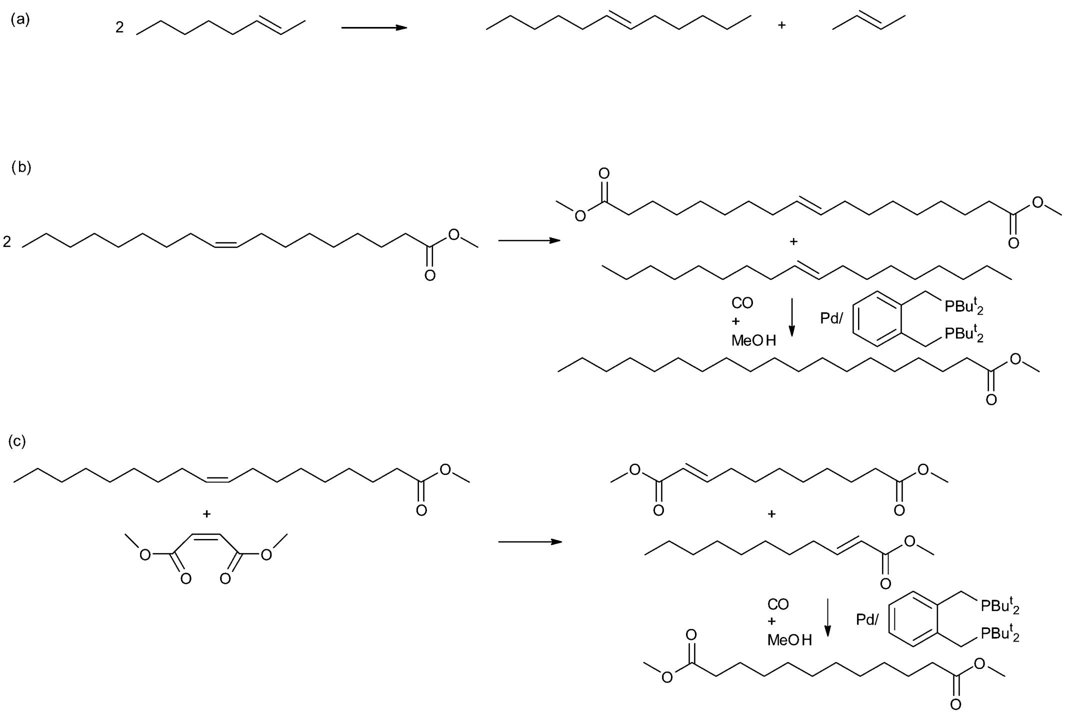


Fig. 3 Conceptual visualisation of the SILP process for the self-metathesis of methyl oleate catalysed by **3**.



Scheme 2 (a) Self-metathesis of 2-octene; (b) self-metathesis of methyl oleate, showing a possible downstream reaction of 9-nonadecene to a detergent ester; (c) cross-metathesis of methyl oleate with dimethyl maleate, showing a possible route to dimethyl 1,12-dodecanedioate and dimethyl 1,11-undecendioate.

catalyst loading to 77 ppm of Ru on SiO_2 (run 6, Table 1, and Fig. 2), high conversions were still obtained (58% at 2 h and 41% at 9 h), with a total turnover number of >10 000 after 9 h. Much higher turnover numbers (up to 470 000) have been obtained in the cross-metathesis of methyl oleate with 1-butene by using very low catalyst loadings in batch reactors, but the catalyst, albeit in small amounts, remained in the reaction products.[19] Although the catalyst in our system exhibited a relatively good stability, all the reactions presented some activity loss in time (downward curvature from linear in Fig. 2).

Because of our interest in α,ω-difunctionalised materials, we were interested in the potential of the metathesis reaction to form such compounds by cross-metathesis. Therefore, the cross-metathesis of methyl oleate with dimethyl maleate. (Scheme 2c) was investigated. This reaction should produce two C_{11} products, one an unsaturated α,ω-diester and the other an α,β-unsaturated terminal ester, which in turn might be carbonylated to dimethyl 1,12-dodecandioate using chemistry we have previously described (Fig. 2c).[20] These shorter chain products are useful as bio-derived feedstocks for applications such as the synthesis of nylon 11,11 or 12,12.[19,21] This cross-metathesis reaction between methyl oleate and dimethyl maleate has been suggested before in the literature but has not apparently been carried out.[17b] We performed catalysis using a dimethyl maleate/methyl oleate molar ratio of either 4 : 1 (run 1, Table 2 and Fig. 4) or 8 : 1 (run 2, Table 2 and ESI Fig. S1†) to favour the formation of cross-metathesis products. In both cases, the results were found to be similar. At the early stage of the reaction, cross-metathesis mainly occurred, but rapidly homo-metathesis became more competitive and then the major process. After 7 h, cross-metathesis had completely stopped, but the self-metathesis of methyl oleate continued until the reaction was stopped after 8 h, although the conversion dropped after about 6 h. The conversion of methyl oleate to self-metathesis products was still occurring with a conversion of 38% in the 8th hour.

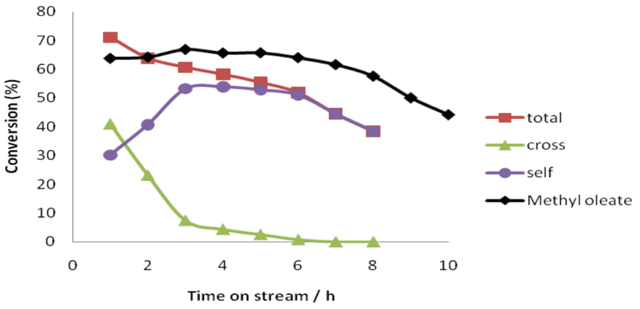


Fig. 4 Conversions in the continuous flow cross-metathesis of methyl oleate with dimethyl maleate catalysed by **3** in a SILP system (run 1, Table 2), and comparison to the self-metathesis of methyl oleate (run 6, Table 1). For conditions, see the tables.

These rather surprising results suggest that the nature of the catalysts evolve during the course of the reaction. Cross-metathesis is observed during the early part of the reaction but self-metathesis dominates later on. Turnover frequencies started at 664 $\mathrm{mol_{product}}$ $(\mathrm{mol_{catalyst}}\ \mathrm{h})^{-1}$ to a mixture of self- and cross-metathesis products but decreased during the reaction to 391 $\mathrm{h^{-1}}$ exclusively to methyl oleate self-metathesis products, giving a total turnover number of 3962 $\mathrm{mol_{product}}$ $\mathrm{mol_{catalyst}}^{-1}$ after 8 h of reaction. Leaching from both the IL and the catalyst were low, the ICP-OES analysis of the products showing a

Table 2 Methyl oleate and dimethyl maleate cross-metathesis parameters using **3** under SILP conditions[a]

Run	Dimethyl maleate : methyl oleate	Temperature (°C)	Pressure/bar	Substrate flow/mL min^{-1}	Catalyst loading (wt% Ru/SiO$_2$)[b]	Cross TON after 5 h	Total TON after 5 h[c]
1	4	50	100	0.15	0.023	502	2607
2	8	50	100	0.15	0.024	360	1409
3	8	r.t.	30	0.15	0.021	223	981
4	4	r.t.	100	0.15	0.020	56	1911
5	4	70	100	0.15	0.020	359	1641
6[d]	4	50	100	0.1	0.021	1226	1813
7[e]	4	50	100	0.1	0.022	265	1701
8[e]	8	50	100	0.1	0.019	287	1397
9[f]	8	50	100	0.15	0.019	15	1780
10[g]	4	50	100	0.1	0.020	445	1705
11[h]	8	50	100	0.15	0.019	847	1727
12[i]	8	50	100	0.15	0.018	3	1447

[a] BMIM·NTf$_2$ (29% w/w on silica; mass of silica = 4.4 g), CO$_2$ flow, pressure = 100 bar, total flow = 645 cm^3 min^{-1} at NTP. [b] g (g silica^{-1}). [c] Total mol$_{\text{product}}$ mol$_{\text{catalyst}}$$^{-1}$ after 5 h. [d] 2-Octene in place of dimethyl maleate. [e] 2-Octene in place of methyl oleate. [f] **4** (5 mol (mol **3**)$^{-1}$) added. [g] The dimethyl maleate flow was started 1 h before the methyl oleate flow. [h] Diethyl maleate in place of dimethyl maleate and OMIM·NTf$_2$ in place of BMIM·NTF$_2$. [i] Diethyl fumarate in place of dimethyl maleate and OMIM·NTf$_2$ in place of BMIM·NTF$_2$.

maximum ruthenium concentration of 8 ppm. The higher excess of dimethyl maleate (8-fold; run 2, Table 2 and ESI Fig. S1†) did not produce a higher conversion to cross-metathesis products but a lower one, the total turnover number for the cross-metathesis products being 360 mol$_{\text{product}}$ mol$_{\text{catalyst}}$$^{-1}$ as opposed to 502 mol$_{\text{product}}$ mol$_{\text{catalyst}}$$^{-1}$ after 5 h in the previous run with a 4-fold excess of dimethyl maleate. Lowering the temperature to room temperature or raising it to 70 °C (runs 4 and 5, Table 2, and ESI Fig. S2 and Fig. S3†) did not improve the conversion to cross-metathesis products. Indeed, the deactivation was faster at the higher temperature and there was almost no cross-metathesis at room temperature.

In seeking to understand the results obtained during cross-metathesis reactions, we carried out a number of additional experiments.

In order to check that there was no intrinsic problem with cross-metathesis in the flow system, a reaction was carried out between 2-octene and methyl oleate. This reaction was expected to give a large array of products from the desired cross-metathesis and from the self-metathesis of the two starting alkenes.

Of the 8 possible products, only 7 were recovered because 2-butene, which has low boiling point, was lost through venting to the atmosphere. The conversion towards cross-metathesis products was higher (over 60% of the total conversion) throughout the reaction than that towards self-metathesis products (run 6, Table 2 and Fig. 5). The conversion was constant throughout the reaction, suggesting that dimethyl maleate was in some way responsible for the catalyst deactivation towards cross-metathesis observed in the reaction between methyl oleate and dimethyl maleate. This was further confirmed by carrying out the cross-metathesis of dimethyl maleate with 2-octene. Using a 4-fold excess of dimethylmaleate over 2-octene, the reaction was reasonably stable (run 7, Table 2 and ESI Fig. S4†), but cross-metathesis only accounted for 5–11% of the products, whilst self-metathesis accounted for >40%. Using a larger excess of dimethyl maleate (8-fold; run 8, Table 2 and ESI Fig. S5†), cross-metathesis increased to 30% at the start of the reaction, but decreased gradually to zero over 6.5 h. Self-metathesis was constant at around 50% for 4 h and then dropped slowly.

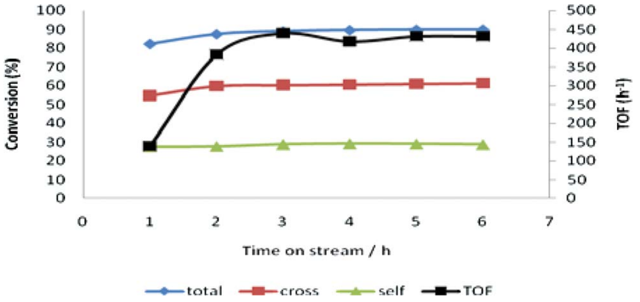
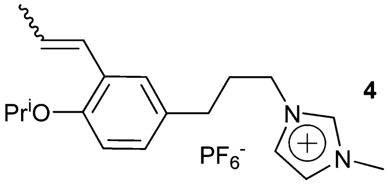


Fig. 5 Cross-metathesis of methyl oleate with 2-octene. Conditions: 50 °C, 100 bar, 0.1 mL min^{-1} substrate flow, 0.021 wt% Ru/SiO$_2$ and a 4-fold excess of 2-octene.

Because of the dramatic change in selectivity observed in the cross-metathesis of methyl oleate with dimethylmaleate, we wondered whether some change in the catalytically active species might be occurring during the reaction. Boomerang catalysts are generally believed to work by decoordination of the ether to create a site at which the alkene coordinates. The alkene then undergoes metathesis with the carbene from the boomerang ligand to introduce a carbene derived from the reacting alkene. The modified boomerang ligand is then believed to remain free in solution until the end of the reaction, when it undergoes metathesis with a metal-bound carbene (formed from a reacting alkene) and recoordinates the ether oxygen.[22] Recent studies involving fluorescence (fluorescent aryl ether) or ^{19}F NMR studies (fluorinated aryl ether) have, however, cast doubt on this interpretation.[23] We thought it possible that the boomerang ligand might be required for the activation of dimethyl maleate but not for methyl oleate. If this were the case, cross-metathesis would be observed as long as the boomerang ligand were capable of reacting back with the catalyst, but not if it diffused away from the active site. We therefore carried out a reaction in which we added excess of boomerang ligand precursor **4**.



4

Using a 5-fold excess of this compound over ruthenium and an 8-fold excess of dimethyl maleate over methyl oleate, almost no cross-metathesis products were observed, only the self-metathesis of methyl oleate at about 60% conversion dropping to 52 over 6.5 h (run 9, Table 2 and ESI Fig S6†). We also found that there was no advantage to be gained from pre-treating the catalyst with dimethyl maleate under metathesis conditions, either in the presence or absence (run 10, Table 2) of added **4**.

Since dimethyl maleate undergoes self-metathesis to give the *E* isomer, dimethyl fumarate, which is very insoluble in the reaction medium, we wondered whether dimethyl fumarate might be crystallising in the silica pores, thus lowering the accessibility of the catalyst available for the reaction. In order to prevent this, we carried out reactions using diethyl maleate (run 11, Table 2 and ESI Fig. S7†) and diethyl fumarate (run 12, Table 2 and ESI Fig. S8†), both of which are liquids, in place of dimethyl maleate. In these reactions, we also replaced BMIM·NTf$_2$ by OMIM·NTf$_2$. Diethyl maleate gave results very similar to those obtained with dimethyl maleate, whilst diethyl fumarate only gave the self-metathesis of methyl oleate (60% throughout the reaction). Interestingly, using a mixture of diethyl maleate and diethyl fumarate for the cross-metathesis with methyl oleate gave results in between those obtained using the two diesters on their own (ESI Fig. S9†), showing that the fumarate does not actually act as an inhibitor of the reaction.

Since none of these proposed solutions improved the cross-metathesis of dimethyl maleate with methyl oleate, we studied the cross-metathesis under batch conditions in the ionic liquid OMIM·NTf$_2$. Using a catalyst loading of 1 mol% and a 4-fold excess of dimethyl maleate, all the methyl oleate was converted to the desired cross-metathesis products in <10 min. We believe that this is the first time that this particular cross-metathesis reaction has been successfully carried out. Lowering the catalyst loading to 0.2 mol%, the results were as shown in Fig. 6. Initially, the only products formed were those of the self-metathesis of methyl oleate. As the products built up, they started to undergo metathesis with dimethyl maleate so that after 2 h, a full conversion to the cross-metathesis products was observed. It should be noted that significant conversion to cross-metathesis products was not observed for the first 5 min of the reaction, despite the much higher catalyst loading than in the flow system. What these results demonstrate is that the rate of self-metathesis of methyl oleate is very much faster than the rate of cross-metathesis with dimethyl maleate, despite the excess of dimethyl maleate being used and that the formation of cross-metathesis products is predominantly a secondary reaction of the methyl oleate self-metathesis products.

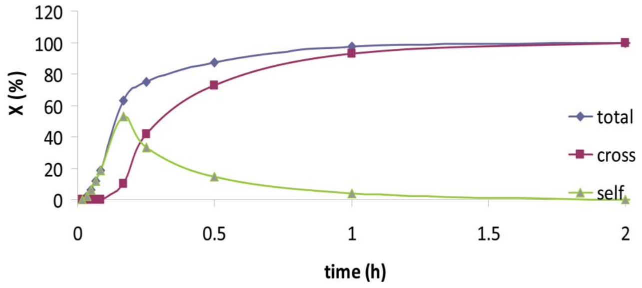


Fig. 6 Cross-metathesis of methyl oleate with dimethyl maleate in bulk OMIM MTf$_2$ (for conditions, see the Experimental section).

Given the results obtained in batch systems, it is surprising that we saw any cross-metathesis at all in the flow system, since the residence time in the reactor under our normal flow conditions was only 30–130 min and the catalyst loading was very low. However, what we should find is that cross-metathesis is increased if the residence time in the reactor is increased. We have achieved this by reducing the flow rate of the substrate.

With a flow rate of 0.05 cm^3 min^{-1} (residence time = 130 min) as opposed to 0.15 cm^3 min^{-1} (residence time = 42 min), in most reactions, the initial conversion to the cross-metathesis products was over 70% and, although the conversion dropped with time, it was still >25% after 6 h and remained higher than that to the self-metathesis products for 5 h (Fig. 7).

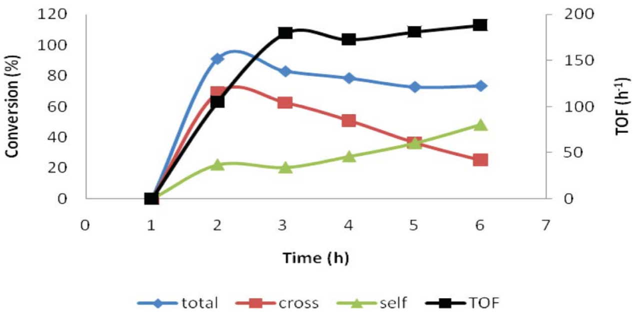


Fig. 7 Cross-metathesis of dimethyl maleate with methyl oleate at lower substrate flow.

We propose that the reason for the slightly unusual results obtained during the cross-metathesis reactions is that at the start of the reaction, all the catalyst is active and it converts the methyl oleate to self-metathesis products, which are in contact with enough catalyst and dimethyl maleate to give significant amounts of cross-metathesis products. The catalyst, which is very much more active for self-metathesis than for cross-metathesis, gradually deactivates to the point where the cross-metathesis becomes vanishingly small, but the self-metathesis still reaches an equilibrium position and so appears to be stable. The catalyst continues to degrade so that, after some time, there is insufficient active catalyst left to reach an equilibrium position in the self-metathesis reaction and so the conversion to the self-metathesis products gradually drops. The reason for the degradation of the catalyst is not clear. It does not, however, appear to be associated with the tag on the boomerang ligand, since using the unmodified Grubbs–Hoveyda catalyst gave very similar results to those obtained with **3** (ESI, Fig. S10†).

Effect of the flowing medium

Phase behaviour observations have been made on the SILP-SCF system for 1-octene hydroformylation, and have been correlated with the reaction rate and extent of IL and Rh leaching.[10b] At low pressures or in the absence of CO$_2$, the reaction rate was low and leaching was high because the reaction was carried out in the liquid phase, in which the ionic liquid has significant solubility. On increasing the pressure, the rate increased and the amount of leaching of ionic liquid and catalyst dropped as long as the reaction was carried out in an expanded liquid. Once the critical pressure was reached, *i.e.* once the flowing medium was a single phase, the rate decreased because the substrate partitioned less and less well into the ionic liquid film, where the catalyst resides. For that system, 1-octene, CO, H_2 and CO_2 at 100 °C, the critical pressure was measured to be 106 bar. For the metathesis reactions, we have typically worked at lower temperatures, sometimes below the critical temperature of CO_2 (31.1 °C) but about the same pressure (100 bar), and have used the much less volatile and soluble methyl oleate as one of the substrates. This ensures that the reactions are carried out in liquid methyl oleate expanded by CO_2. We have visually observed that a condensed phase is present under the same flow conditions as for the cross-metathesis experiments.

Phase behaviour studies have been carried out on ethyl oleate in CO_2 at 50 °C between 0 and 120 bar.[24] They show that, as the pressure of CO_2 is increased, the reaction rate and equilibrium position for ethenolysis are both increased because: a) the viscosity is reduced by the substantial mole fractions of CO_2 dissolved, and b) the products are much more soluble in the vapour phase than in the starting material, hence allowing the products selectively to be extracted and the equilibrium position to lie in favour of the products. Above 120 bar, the rate drops dramatically because the substrates are all in the supercritical phase and the catalyst remains as a solid at the bottom of the reactor.

We have analysed reaction products using ICP-OES analysis and observed only very low levels of residual Ru: 10–15 ppm in the self-metathesis of methyl oleate, 5–8 ppm in the cross-metathesis of methyl oleate with dimethyl maleate and only 0.5–0.8 ppm for 2-octene. These values for Ru loss are in the same range as those observed when catalyst **3** was used in batch mode.[9a,b] ^{19}F NMR analysis of the recovered products from reactions involving CO_2 showed only traces of fluorine (NTf_2^-), but the ionic liquid is not detectible by ^1H NMR spectroscopy (<50 mol ppm)

The apparent correlation of substrate polarity (all reactions were carried out at 50 °C and 100 bar pressure) with the loss of ruthenium and IL suggests that the catalyst is slightly soluble in the flowing medium. Confirmation that this is likely to be a problem, but one that is greatly reduced by the use of CO_2, came from a cross-metathesis reaction of methyl oleate with dimethyl maleate carried out by replacing CO_2 with N_2 at 30 bar in a classical liquid flow reaction (ESI, Fig. S11†). The solutions emanating from the reactor were highly coloured (brown, Fig. 8) and the reaction stopped after 3 h, suggesting substantial leaching of the catalyst and ionic liquid.

Conclusions

In conclusion, we have described the first catalytic system that allows continuous flow olefin metathesis using a homogeneous catalyst. It involves a boomerang catalyst with an imidazolium tag on the reactive carbene. As long as the double bonds in the alkenes are not terminal, high reactivity is observed over at least 10 h, a slight fall off in activity with time on stream suggesting some catalyst instability. Total turnover numbers >10 000 over 9 h are possible, with the products containing low ruthenium and ionic liquid contents. In the most favourable cases, 6 g of substrate per hour can be converted to an equilibrium mixture of products in a 9 cm^3 reactor. Overall, we have developed a system for alkene metathesis that allows the products to be obtained with high yields and with very low metal contamination. No solvent is present in the collected product and the only purification needed is fractional distillation of the equilibrium mixture of products.

Fig. 8 Samples recovered after 3, 4, 5 and 6 h from the cross-metathesis of methyl oleate with dimethyl maleate when using N_2 as the carrier gas (*i.e.* liquid phase flow). Conditions as for entry 2, Table 2, but with N_2 (30 bar) in place of CO_2. The two phases occur because dimethyl maleate does not mix with methyl oleate or its cross-metathesis products.

The cross-metathesis of methyl oleate with diethyl maleate can be carried out in the ionic liquid OMIM·NTf_2 with a catalyst loading of 0.2% using batch conditions, but in a flow system, an initially reasonable activity towards the cross-metathesis products drops rapidly, whilst the self-metathesis of methyl oleate continues. Studies using a variety of different conditions and substrates suggest that the problem is a low residence time within the reactor, coupled with some catalyst instability. An improved flow performance was achieved by lowering the flow rate of the substrates.

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