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Getting Ring-Closing Metathesis off the Bench: Reaction-Reactor Matching Transforms Metathesis Efficiency in the Assembly of Large Rings

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Dedicated to the memory of Keith Fagnou (1971–2009)

Abstract: Reported is the first study of the influence of reactor configuration on the efficiency of a challenging ring-closing metathesis (RCM) reaction. With the intention of increasing the generality of RCM scaleup and reducing its dependence on substrate modification, macrocyclization of an unmodified, low effective-molarity diene was explored using different reactor types, in conjunction with a commercial, homogeneous Grubbs catalyst. Optimized performance is compared for a conventional batch reactor (BR), a continuous plug-flow reactor (PFR), and a continuous stirred-tank reactor (CSTR). In the PFR, maximum conversion is achieved most rapidly, but product yields and selectivity are adversely affected by co-entrapment of ethylene with the catalyst, substrate, and product in the traveling "plug". Use of the CSTR, in which ethylene is efficiently swept out, affords an order-of-magnitude increase in total turnover numbers, and reduces the required catalyst loadings by 25× relative to the BR (to 0.2 mol%), while improving RCM yields and selectivity to quantitative levels. Continuous-flow methodologies that support liberation of the ethylene co-product thus show great promise for industrial uptake of RCM.

Keywords: continuous flow · industrial chemistry · macrocycles · olefin metathesis · ruthenium

Introduction

Ring-closing metathesis (RCM) has revolutionized laboratory approaches to the assembly of cyclic molecules.[1] Nearly 20 years after the breakthrough discovery of "robust" ruthenium catalysts, however,[1b] industrial uptake remains startlingly small. A major impediment is the high catalyst loading required for quantitative conversion to desired products, which imposes very high catalyst costs on production scale, exacerbated by the high costs of purification required to remove ruthenium residues. While improvements have been made in RCM of dienes such as diethyl diallylmalonates,[2,3] which are characterized by very high effective molarity (EM) values and hence a strong bias toward cyclization, synthesis of macrocyclic targets of broader industrial interest is considerably more problematic.[4] The low EM values characteristic of the diene precursors to macrocyclic rings result in a competition between intra- and intermolecular metathesis. High dilutions are required to improve selectivity for RCM, and high temperatures are then required to overcome the unfavorable effect of high dilutions on the kinetics of reaction. Both exact a severe penalty in terms of catalyst lifetimes, loading, and removal. Inefficient, wasteful,[5] uneconomical processes result.

In a few instances, achieved with much effort, these challenges have been resolved to the point that industrial-scale RCM is now beginning to become feasible for high-value targets, such as precursors to active pharmaceutical ingredients.[6] Prominent among such efforts is a major Boehringer-Ingelheim (BI) campaign directed at the synthesis of an HCV protease inhibitor, BILN 2061, in which Ru-catalyzed RCM is the key step required for assembly of the 15-membered macrocyclic core.[6a–f] Extensive catalyst optimization, accompanied by screening of a fortuitously well-sited pro-

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tecting group to maximize the diene EM, proved key to achieving high RCM yields and acceptable rates at a viable catalyst loading (93% yield; $\leq$1 h reaction time; 0.1 mol% Ru: cf. 92% yield, 40 h and 5 mol% Ru for the unoptimized process).

While a textbook case for advance through chemical ingenuity, this approach suffers from limited generality in its reliance on substrate modification. In seeking alternative, less time-intensive, and potentially more general paradigms, we asked whether catalyst efficiency in macrocyclization reactions might be artificially constrained by the reliance on conventional, batchwise RCM. Often overlooked in fundamental synthetic research is the decisive impact that reactor design can have on reaction outcome. Continuous flow (CF) reactors open new avenues: their improved control over mass and heat transfer can in turn improve reaction yields and selectivity, while reducing reaction and cycle times, catalyst loadings, and (depending on configuration) facilitating process scaleup.[7] Recent reviews describe the implementation in CF of industrially relevant reactions, including catalytic transformations such as cross-coupling, cycloaddition, and hydrogenation.[8]

We chose to explore the potentially higher efficiency of CF-RCM macrocyclization by using the two dominant continuous reactor configurations, the plug-flow reactor (PFR) and continuous stirred-tank reactor (CSTR), and comparing their performance with that in a batch reactor (BR). To press the case, and to maximize the potential for generality, we deliberately selected a standard "off-the-shelf" homogeneous catalyst, and an *unmodified* low-EM substrate (Figure 1a), the latter being the precursor to an important, macrocyclic perfumery agent.[9] Here we show that by intelligent, mechanism-based matching of the reactor design to the chemical problem, RCM macrocyclization can be made dramatically more efficient than the corresponding batch reaction,[10] thereby reducing process and environmental costs.[5] This approach offers a powerful and exceptionally facile alternative to standard paradigms based on catalyst and substrate tuning.

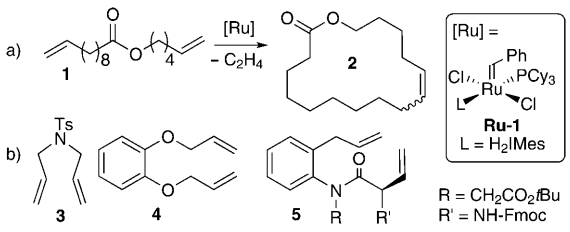

Figure 1. a) RCM reaction examined herein; b) dienes used in comparative literature studies of batch versus CF-RCM. Fmoc = 9H-fluoren-9-ylmethoxycarbonyl.

Results and Discussion

While CF studies of cross-metathesis (CM)[11] date back 40 years, CF-RCM has been less examined,[8b,12] and challenging, macrocyclic targets not at all. In a rare comparative study of the effect of reactor configuration in RCM, Kirschning, Grela and co-workers reported poorer performance in CF-RCM of **3** via a ruthenium catalyst ionically bound to Raschig rings, versus batch RCM (B-RCM) with the same catalyst.[8b,13] In contrast, the Organ group found that CF-RCM was superior to batch reaction in cyclization of the high-EM dienes **4**–**5** via the homogeneous Grubbs-class catalyst **Ru-1** with microwave heating.[14]

Prior work on B-RCM of **1** described the suitability of both supported[15] and homogeneous[4b,9a,b] Ru-NHC catalysts, quantitative RCM being achieved in as little as 5 h at a catalyst loading of 5 mol% (5 mM **1**, CH_2Cl_2, reflux).[4b] We began by assessing the efficiency of CF versus batch RCM of **1** under these optimized conditions, but using toluene as solvent, in place of methylene chloride. The latter is undesirable in industrial practice: as well, its lower boiling point limits reaction rates and the thermodynamic driving force that controls selectivity in equilibrium RCM.[4a]

Comparison of BR and PFR performance: Simplified reactor configurations are depicted in Figure 2. The batch reactor consisted of a round-bottom flask equipped with a condenser and an argon inlet. The progress of RCM was monitored by periodically removing samples and quenching with KTp (KTp = potassium tris-pyrazolyl borate)[16] prior to GC-FID analysis. The PFR consisted of two independent Teledyne ISCO syringe pumps connected to a microstructured IMM mixer, and a stainless steel coil immersed in a temperature-controlled oil bath. The syringe pumps were used to introduce equal-volume solutions of catalyst and substrate into the micromixer, and to drive the resulting reactant stream through the coil. Reactions were quenched on exit by addition to a KTp solution. Reaction times (i.e., the residence time in the coil, τ)[17] were varied by altering flow rates (0.10–96 mL min^{-1}; corresponding to 0.03–60 min). For each data point in the time profiles, the new flow rate was allowed to stabilize for 10 s, followed by purging for 3τ to flush out residues from the previous "experiment", prior to collecting samples for analysis.

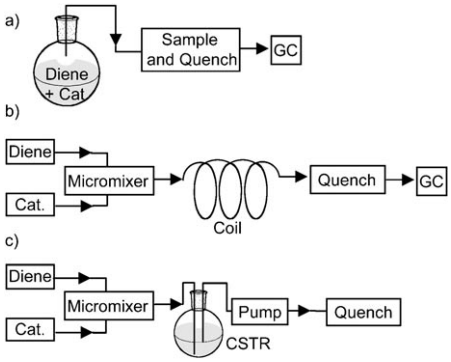

Figure 2. Simplified schematics depicting a) BR; b) PFR; c) CSTR. In a), **Ru-1** is added in one dose once the operating temperature is reached.

At 60 °C, RCM rates and conversions are consistently slightly lower in the PFR, versus the BR (Figure 3a), despite the closely comparable performance expected for these homogeneous, kinetically controlled reactions. We attribute the difference to entrapment of the ethylene co-product, the effect of which is discussed in more detail below. We deemed the agreement sufficiently good, however, to warrant deeper exploration. To extract the maximum performance from the PFR, we examined the effects of temperature, catalyst loading, and feed concentration on space-time yields and selectivity.

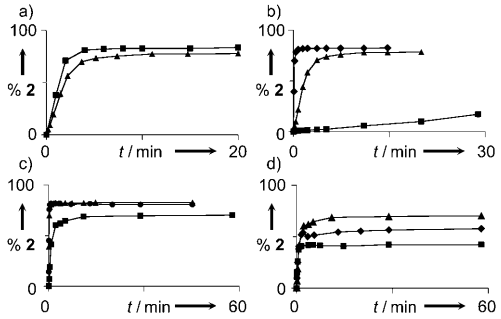

Figure 3. Yields of **2** as a function of time in RCM of **1** by **Ru-1**. a) Comparison of BR (■) versus PFR (▲) performance: 5 mol % Ru, 60 °C, 5 mM **1**, C_7H_8. All of b)–d) carried out in the PFR. b) Effect of temperature: 80 °C (◆), 60 °C (▲), 40 °C (■). c) Effect of Ru loading at 80 °C: 10 mol % (●), 5 mol % (▲), 1 mol % (■). d) Effect of diene concentration on RCM yields for reaction at 80 °C, 1 mol % Ru: 20 mM (■), 10 mM (◆), 5 mM (▲).

PFR: Temperature (Figure 3b; Table 1, entries 2–4): At 40 °C, the RCM rate is slow, reaching only 17 % after 0.5 h. The proportion of oligomers, initially high, declines over time as backbiting liberates cyclic **2**. Thus, RCM selectivity (% **2** / % conversion × 100) is 33 % at 1 min, rising to 55 % at 30 min. At 60 °C, solely **2** is observed, and reaction is much faster, though RCM yields are limited to about 80 % by competing catalyst deactivation. At 80 °C, 82 % conversion is achieved in only 1.5 min. While conversions again plateau at this value, GC analysis reveals no side-reactions potentially mediated by catalyst decomposition products. Of note, the rate of RCM relative to catalyst deactivation *increases* in the PFR at the higher temperature. Maximum conversions are essentially identical to those at 60 °C, but are achieved 10× faster, without adversely affecting selectivity. In engineering terms, transferring operations from the BR to the PFR transforms a slow, unproductive ("type C") reaction requiring hours into a highly intensified ("type B") reaction requiring minutes.[18] This dramatic improvement in space-time yields is of keen interest from a process engineering perspective in limiting reactor costs. Subsequent experiments were therefore carried out at 80 °C.

PFR: Catalyst loading (Figure 3c; Table 1, entries 4–6): Decreasing catalyst loadings from 5 to 1 mol % has an unexpectedly low impact, maximum conversions dropping by only 12 %. Catalyst lifetimes are also extended, with RCM being sustained over 11 min. Importantly, this implies that bimolecular deactivation dominates over unimolecular[19] deactivation under these process conditions. Sustained consumption of diene **1** (20 min) is also observed at 10 mol % Ru, but RCM ceases after only 1 min: that is, the product distribution is dominated by non-metathetical reactions[20] (isomerization, ring-contraction; see Supporting Information). Subsequent experiments were thus carried at ≤1 mol % Ru.

Table 1. Overview of performance for RCM of **1** via **Ru-1**.[a]

	Reactor	mol % Ru	T [°C]	[**1**] [mM]	τ_{end} [min][a]	Conv. [%] (Sel.)[b]	Yield [%]
1	BR	5	60	5	10	84 (*)	84
2	PFR	5	60	5	11	79 (*)	79
3	PFR	5	40	5	30	31 (55)	17
4	PFR	5	80	5	1.5	82 (*)	82
5	PFR	10	80	5	1	94 (86)[c]	81
6	PFR	1	80	5	11	70 (*)	70
7	PFR	1	80	10	2	72 (79)	57
8	PFR	1	80	20	1	84 (51)	43
9	CSTR	1	80	5	20	>99 (*)	>99
10	BR	1	80	5	10	82 (*)	82
11	CSTR	0.2	80	5	50[d]	>99 (*)	>99
12	CSTR	0.1	80	5	50[d]	76 (*)	76
13	CSTR	1	80	20	10	>99 (65)	65

[a] See Supporting Information for full rate data. τ_{end} indicates the reaction time required to reach maximum RCM yield (see Figure 3), except for entry 3, for which reaction was terminated at 30 min. Yields in reactions for which no starting diene was detected by GC-FID analysis indicated as >99 %. [b] Selectivity = % **2** / % Conv. × 100; ≤ ±2 (entry 5: ±3 %). (*) = no observable byproducts. [c] Isomerized and ring-contracted byproducts observed; [d] τ unoptimized.

PFR: Concentration (Figure 3d; Table 1, entries 6–8): Because RCM macrocyclization of **1** via **Ru-1** proceeds under thermodynamic control, high dilutions (5 mM **1** in batch RCM) are essential to shift the concentration-dependent ring-chain equilibrium in favor of cyclic **2**.[4] As expected, increasing the concentration of **1** above 5 mM increases rates of metathesis (see Supporting Information), but the selectivity for **2** suffers (Figure 3d). Moreover, selectivity decreases over time, presumably owing to competing re-opening and polymerization of **2**, as reported by the Fürstner[21] and Yamamoto[22] groups for other macrocylic targets.

Comparison of CSTR performance (Figure 4; Table 1, entries 9, 11–13): The CSTR differs from the PFR and BR in its characteristically broad residence time distribution (RTD), in consequence of which longer reaction times are required to reach comparable conversions. (The high rates of RCM achieved in the PFR are thus an important prerequisite for transfer of this process to the CSTR.) A compensating feature of great interest is the capacity of the CSTR to permit escape of ethylene (in contrast to the PFR, in which the ethylene is trapped along with catalyst, reactant and products in the traveling "plug"), and hence to limit non-productive metathesis and ethylene-mediated deactivation.[23] We chose a CSTR design that provided a large head-

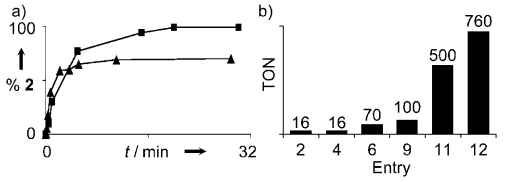

Figure 4. Performance of CSTR (■) versus PFR (▲) in RCM of **1**. a) Yield of **2** as a function of time (5 mM **1**, 80 °C, 1 mol % **Ru-1**). b) Catalyst productivity, as indicated by maximum turnover number, TON_{max} (i.e., TON at τ_{end}; see corresponding entry in Table 1) at 100 % selectivity.

space, which was continuously flushed with argon to maintain sub-millimolar concentrations of ethylene in solution.[24]

As the broad RTD of the CSTR can limit selectivity if competitive reaction pathways are accessible, inhibiting oligomerization is critical. We therefore adopted the conditions of temperature and dilution established as optimal for selectivity in the PFR study, and chose the CSTR flow rate (0.1 mL min^{-1}) to maximize conversions. That is, primarily cyclic **2** is present, accompanied by low concentrations of **1** and **Ru-1**, at all times following the initial incubation perido (10 τ). Experiments were carried out by infusing the solution of substrate and catalyst (homogenized at 20 °C using the micromixer) into a 10 mL round-bottom flask containing 5 mL of toluene at 80 °C. An "exit" pump was used to maintain a constant volume of 5 mL in the tank. The product distributions shown in Table 1 are those present at steady state (typically 10τ; confirmed by GC analysis of the KTp-quenched effluent).

Maximum RCM yields in the CSTR were significantly higher than in our optimized PFR or BR setups, with quantitative yields at 20 min when using 1 mol % **Ru-1** at 80 °C and 5 mM **1** (Figure 4a; Table 1, entry 9: cf. entries 6, 10). Even on decreasing the catalyst loading five-fold, quantitative RCM was achieved by 50 min reaction time (entry 11). At 0.1 mol % Ru, however, only 76 % **2** was obtained at the same stage (entry 12). Use of the potentially more robust styrenyl ether analogue of **Ru-1** gave similar results (72 % RCM): that is, in neither case was complete conversion effected within 1 h, which we set as a maximum tolerable duration of reaction to maintain space-time yields.

A key finding from Figure 4a is that although initial reaction is faster in the PFR (as predicted by theory; see above), it is rapidly outstripped by that in the CSTR. Moreover, RCM activity is sustained over a longer period in the CSTR. The beneficial impact of efficient removal of ethylene on catalyst lifetime and productivity has been noted in two earlier CF studies,[25,26] but this is the first delineation of its impact on the synthesis of a challenging, real-world RCM target. More unexpected is the slower deactivation in the CSTR relative to the BR implied by comparison of entries 9 and 10. Whether the simultaneous presence of fresh and "old" catalyst in the CSTR is a factor is targeted for future study.

Finally, increasing feed conversions in the CSTR reduced selectivity, as expected, albeit to a lesser extent than in the PFR. At 20 mM **1**, conversion was quantitative after 10 min using 1 mol % **Ru-1**, but RCM yields reached only 65 % (entry 13). Noteworthy, however, is the improved selectivity relative to that in the PFR under identical conditions (entry 8). Operation in the CSTR thus appears to permit a slight increase in the diene concentration that can be tolerated in RCM macrocyclization. This may reflect the long "tail" in the RTD, which allows more time for backbiting, and hence establishment of equilibrium RCM yields.

The impact of these reactor configurations on catalyst productivity is highlighted in Figure 4b, which depicts maximum turnover numbers at 100 % selectivity (TON_{max}). Values of TON_{max} in the CSTR approach 800, an order of magnitude higher than in the PFR or BR. Maximum turnover frequencies (TOF_{max} = 15.2, 8.2 and 6.4 min^{-1} for the CSTR, BR and PFR, respectively; see Table 1, entries 12, 10, and 6),[25] and hence reactor throughput, show a less dramatic improvement, owing to the RTD issue noted above. It will be noted, however, that at TOF_{max}, conversions are incomplete in all reactor configuration. Realization of quantitative RCM conversions, as well as complete selectivity, is critical to minimizing purification requirements, with their deleterious economic and environmental impacts. A more relevant metric is thus TOF_{max} at quantitative conversion and 100 % selectivity. In this respect the CSTR (with a value of 10 min^{-1}, see entry 11) stands alone: neither the PFR nor the BR permits full conversions under these optimized reaction conditions, even at 1 mol % Ru (BR) or 5 mol % (PFR). Quantitative conversions were attained in the earlier work in the BR using refluxing CH_2Cl_2,[4b] but only at a catalyst loading of 5 mol %.

Conclusion

The foregoing demonstrates that dramatic improvements can be achieved in RCM efficiency for a challenging, low-EM diene, without recourse to catalyst or substrate tuning, by the use of an appropriate continuous-flow reactor. Quantitative RCM (i.e., full conversion and complete selectivity) is achieved in the CSTR at 0.2 mol % Ru, a catalyst loading 25× lower than that required for comparable performance in batch mode. Operation in the PFR can reduce reaction times further, but at the cost of RCM yields and selectivity. Continuous-flow methodologies that permit removal of ethylene thus show great potential to facilitate uptake of RCM into industrial practice. Experiments directed at increasing the working concentration in these reactions are under way, and will be reported in due course.

Experimental Section

Material: Toluene (Fluka) was degassed by sparging with Ar for a minimum of 3 h, and stored over activated 4 Å molecular sieves (Aldrich). Decane (Fluka), potassium tris-pyrazolyl borate (KTp; Strem), argon

(Carbagas), and catalyst **Ru-1** (Aldrich) were used as received. Substrate **1** was prepared by the reported method.[27]

Analytical method: GC-FID analyses were performed on an Agilent Technologies 6850 GC-FID equipped with an Agilent 6850 Series autosampler and a Agilent DB-1701 column (60 m length, 320 μm diameter), using an inlet split ratio of 50:1, an inlet temperature of 200 °C, and helium (UHP grade) as carrier gas with a flow of 98.5 mL min^{-1}. Method parameters: an initial oven temperature of 60 °C was maintained for 2 min, after which it was ramped up at 25 °C min^{-1} until 280 °C was reached, at which temperature it was maintained for 2 min. Retention times for diene **1** (9.73 min), RCM product **2** (*E* isomer = 9.84 min; *Z* isomer = 9.93 min) and decane (3.93 min) were confirmed with samples authenticated by GC-MS and NMR analysis. The FID response was maintained between 100–2000 pA, using analyte concentrations of 5 mM. GC-FID quantification was established by constructing calibration curves of peak area versus concentration to account for the dependence on detector response for the substrate, product, and decane (internal standard in catalytic runs) in the relevant concentration regime. Yields in catalytic runs were determined from the integrated peak areas, referenced against decane, and compared to the integration ratio of **1**/decane at time zero (t_o).

Equipment for continuous-flow experiments: Two independent Teledyne ISCO D-Series pumps, one containing the catalyst solution and the other containing the diene solution, were used in parallel to drive the reactants through the system. Mixing was accomplished using a CPMM-V1.2 caterpillar mixer of internal structure R-1200 (internal volume 25 μL), manufactured by the Institute for Mikrotechnik Mainz (IMM). For PFR experiments, a stainless-steel coil (0.72 mm inner diameter, internal volume 2.87 or 11 mL) was used as the residence time module. For CSTR experiments, an Ismatec pump was used to maintain a constant volume in the tank.

Representative procedure for RCM of 1 using a batch reactor (BR): A 500 mL three-neck round-bottom flask was dried in a Salvis vacuum oven (80 °C, 25 mbar) for a minimum of 15 h before use. It was then cooled to room temperature under a stream of Ar, and charged with substrate **1** (464 mg, 1.74 mmol), decane (248 mg, 1.74 mmol), toluene (350 mL, [**1**] = 5 mM) and a stir bar, again under a flow of Ar. A 1 mL aliquot was removed and analyzed by GC-FID to establish the initial ratio of substrate to decane at t_o (0 % conversion). The remaining solution was heated in a oil bath until the temperature of the solution inside the flask stabilized at 60 °C, at which point catalyst **Ru-1** (74 mg, 0.087 mmol, 5 mol %) was added as a solid against a flow of Ar. Samples (1 mL) were removed periodically, quenched with KTp (10 μL of a 258 mM stock solution in THF; 40 equiv versus Ru; the large excess is for experimental convenience) and analyzed by GC-FID.

Representative procedure for RCM of 1 using a plug-flow reactor (PFR): Two 250 mL Schott borosilicate bottles were dried in a Salvis vacuum oven (80 °C, 25 mbar) for a minimum of 15 h before use. They were then removed from the oven, allowed to cool under a flow of Ar for 10 min, and capped. Substrate **1** (464 mg, 1.74 mmol), decane (248 mg, 0.174 mmol) and toluene (175 mL) were added to the first bottle. A 0.75 mL aliquot was removed and diluted with toluene (0.75 mL) to assess the ratio of **1**/decane before addition of catalyst by GC-FID. To the second bottle was added toluene (175 mL) and **Ru-1** (74 mg, 0.087 mmol, 0.50 mM). The substrate and catalyst solutions were introduced into a syringe pump at a fill rate of 20 mL min^{-1}, from which they were pumped into the micromixer where the solutions were homogenized. The combined solution was then sent to the residence time module immersed in a Julabo HC temperature-controlled silicon oil bath maintained at a temperature of 40, 60, or 80 °C (±0.1 °C). The effluent from the coil was sampled periodically by diverting an aliquot (1 mL) into a 4 mL vial containing a KTp solution (10 μL of a 258 mM stock solution in THF; 40 equiv vs. Ru). The quenched solution was then analyzed by GC-FID. **Note**: The ethylene formed as a co-product during RCM escapes only on exit of the reactant/product "plug" from the coil.

Construction of time profile using the PFR: Reaction times were varied by controlling the flow rates through the system: each data-point in the rate curves thus corresponds to a separate experiment. For each, a 10 s interval was allowed for the new flow rate to stabilize, followed by purging for 3τ prior to collecting samples for analysis. The minimum flow rate is 0.1 mL min^{-1} (irrespective of coil volume). At slower rates, axial diffusion and upstream mixing can limit the reproducibility of the coil residence time. For τ = 0.03–28.7 min, the 2.87 mL coil was used. To gain access to longer reaction times (τ = 30–60 min), the 11.00 mL coil was used to maintain flow rates above the 0.1 mL min^{-1} threshold. Upon exit of the effluent from the coil, a 1 mL sample was quenched with KTp as above. Of note, immediate quenching (essential to ensure that residence times are reproducible and accurate) was confirmed in control experiments in which KTp was charged along with the substrate feed. The duration of sampling ranged from < 1 s at a flow rate of 96 mL min^{-1} (reaction time 0.03 min), to 10 min for flow rates of 0.1 mL min^{-1} (reaction time 1 h). The total residence time remains constant for each sub-zone in the reacting solution: that is, it is independent of the sampling time.

Representative procedure for RCM of 1 using the continuous stirred-tank reactor (CSTR): The reaction was set up as for the PFR, up to the point of transfer from the micromixer. Following homogenization, the reactant solution was driven through a fine Teflon tube (total internal volume 247 μL; selected for fast transfer, ≤2.5 min) into the bottom of the residence time module. The tank consisted of a 10 mL round-bottom flask containing toluene (5 mL) and a magnetic stir bar, immersed in an oil bath maintained at 80 °C. A second Teflon tube (total internal volume 3 mL), connected to a piston pump and positioned at the 5 mL mark of the round-bottom flask, was used to remove any volume of solution in excess of 5 mL. The speed of the piston pump was maintained at 40 mL min^{-1}, versus a maximum of 5 mL min^{-1} for the upstream syringe pumps, to ensure a constant volume of 5 mL, and to minimize the time interval (maximum 5 s) between removal of the reactant solution from the tank, and its addition to the quenching solution. This minimizes any run-on metathesis following exit from the tank, and has the added benefit of promoting exchange of the headspace gas. The system was purged with 50 mL of the substrate and catalyst solution (i.e., 10× the residence time) before sampling. Upon exit, samples were quenched and analyzed as above.

Acknowledgements

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[1] For recent overviews, see: a) R. R. Schrock, *Angew. Chem.* **2006**, *118*, 3832–3844; *Angew. Chem. Int. Ed.* **2006**, *45*, 3748–3759; b) R. H. Grubbs, *Angew. Chem.* **2006**, *118*, 3845–3850; *Angew. Chem. Int. Ed.* **2006**, *45*, 3760–3765; c) T. J. Donohoe, L. P. Fishlock, P. A. Procopiou, *Chem. Eur. J.* **2008**, *14*, 5716–5726; d) A. Brik, *Adv. Synth. Catal.* **2008**, *350*, 1661–1675.

[2] M. B. Dinger, J. C. Mol, *Adv. Synth. Catal.* **2002**, *344*, 671–677.

[3] M. Gatti, L. Vieille-Petit, X. Luan, R. Mariz, E. Drinkel, A. Linden, R. Dorta, *J. Am. Chem. Soc.* **2009**, *131*, 9498–9499.

[4] a) S. Monfette, D. E. Fogg, *Chem. Rev.* **2009**, *109*, 3783–3816; b) J. C. Conrad, M. D. Eelman, J. A. Duarte Silva, S. Monfette, H. H. Parnas, J. L. Snelgrove, D. E. Fogg, *J. Am. Chem. Soc.* **2007**, *129*, 1024–1025; c) J. C. Conrad, D. E. Fogg, *Curr. Org. Chem.* **2006**, *10*, 185–202.

[5] a) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283; b) R. A. Sheldon, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, **2007**; c) D. J. C. Constable, C. Jimenez-Gonzalez, R. K. Henderson, *Org. Process Res. Dev.* **2007**, *11*, 133–137.

[6] No industrial RCM processes are yet on stream, although scale-up to multi-kilogram levels has been achieved in several cases. These include the BI process for BILN 2061, implemented on a maximum of 200 kg scale in one iteration: a) V. Farina, C. Shu, X. Zeng, X. Wei, Z. Han, N. K. Yee, C. H. Senanayake, *Org. Process Res. Dev.*

2009, *13*, 250–254; b) C. Shu, X. Zeng, M.-H. Hao, X. Wei, N. K. Yee, C. A. Busacca, Z. Han, V. Farina, C. H. Senanayake, *Org. Lett.* **2008**, *10*, 1303–1306; c) Y. S. Tsantrizos, J.-M. Ferland, A. McClory, M. Poirier, V. Farina, N. K. Yee, X.-J. Wang, N. Haddad, X. Wei, J. Xu, L. Zhang, *J. Organomet. Chem.* **2006**, *691*, 5163–5171; d) N. K. Yee, V. Farina, I. N. Houpis, N. Haddad, R. P. Frutos, F. Gallou, X.-J. Wang, X. Wei, R. D. Simpson, X. Feng, V. Fuchs, Y. Xu, J. Tan, L. Zhang, J. Xu, L. L. Smith-Keenan, J. Vitous, M. D. Ridges, E. M. Spinelli, M. Johnson, K. Donsbach, T. Nicola, M. Brenner, E. Winter, P. Kreye, W. Samstag, *J. Org. Chem.* **2006**, *71*, 7133–7145; e) T. Nicola, M. Brenner, K. Donsbach, P. Kreye, *Org. Process Res. Dev.* **2005**, *9*, 513–515; f) A. M. Faucher, M. D. Bailey, P. L. Beaulieu, C. Brochu, J. S. Duceppe, J. M. Ferland, E. Ghiro, V. Gorys, T. Halmos, S. H. Kawai, M. Poirier, B. Simoneau, Y. S. Tsantrizos, M. Llinas-Brunet, *Org. Lett.* **2004**, *6*, 2901–2904. In recent work, GlaxoSmithKline utilized RCM as a key step in the synthesis of SB-462795, implemented on a maximum scale of 80 kg: g) H. Wang, H. Matsuhashi, B. D. Doan, S. N. Goodman, X. Ouyang, W. M. Clark, *Tetrahedron* **2009**, *65*, 6291–6303; h) H. Wang, S. N. Goodman, Q. Dai, G. W. Stockdale, W. M. Clark, *Org. Process Res. Dev.* **2008**, *12*, 226–234. Gram-scale RCM processes are under investigation at Merck and at Johnson & Johnson: i) N. J. Liverton, M. K. Holloway, J. A. McCauley, M. T. Rudd, J. W. Butcher, S. S. Carroll, J. DiMuzio, C. Fandozzi, K. F. Gilbert, S.-S. Mao, C. J. McIntyre, K. T. Nguyen, J. J. Romano, M. Stahlhut, B.-L. Wan, D. B. Olsen, J. P. Vacca, *J. Am. Chem. Soc.* **2008**, *130*, 4607–4609; j) J. A. McCauley, M. T. Rudd, K. T. Nguyen, C. J. McIntyre, J. J. Romano, K. J. Bush, S. L. Varga, C. W. Ross III, S. S. Carroll, J. DiMuzio, M. W. Stahlhut, D. B. Olsen, T. A. Lyle, J. P. Vacca, N. J. Liverton, *Angew. Chem.* **2008**, *120*, 9244–9247; *Angew. Chem. Int. Ed.* **2008**, *47*, 9104–9107; k) L. J. Wilson, R. Malaviya, C. Yang, R. Argentieri, B. Wang, X. Chen, W. V. Murray, D. Cavender, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3333–3338.

[7] For a recent review discussing the advantages of CF processes, see: a) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318. For a discussion of the advantages of single-channel, versus parallel, CF systems in achieving required reactor throughput while maintaining satisfactory mixing, residence times, and rates of heat and mass transfer, see: b) D. M. Roberge, M. Gottsponer, M. Eyholzer, N. Kockmann, *Chim. Oggi* **2009**, *27*, 8–11.

[8] Selected reviews of CF in organic synthesis, including industrial applications; a) B. K. Singh, N. Kaval, S. Tomar, E. Van der Eycken, V. S. Parmar, *Org. Process Res. Dev.* **2008**, *12*, 468–474; b) A. Kirschning, W. Solodenko, K. Mennecke, *Chem. Eur. J.* **2006**, *12*, 5972–5990; c) K. Geyer, J. D. C. Codee, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434–8442; d) V. Hessel, P. Loeb, H. Loewe, *Curr. Org. Chem.* **2005**, *9*, 765–787; e) P. Watts, S. J. Haswell, *Chem. Soc. Rev.* **2005**, *34*, 235–246.

[9] a) L. Ackermann, A. Fürstner, T. Weskamp, F. J. Kohl, W. A. Herrmann, *Tetrahedron Lett.* **1999**, *40*, 4787–4790; b) A. Fürstner, H. Krause, L. Ackermann, C. W. Lehmann, *Chem. Commun.* **2001**, 2240–2241. The saturated lactone is marketed as Exaltolide (Firmenich), Cyclopentadecanolide (Symrise), Pentalide (Soda Aromatics), and Thibetolide (Givaudan). See: c) D. J. Rowe, *Chemistry and Technology of Flavors and Fragrances*, CRC Press, Boca Raton, Florida, **2005**.

[10] Worth noting are the targets set by the BI group for improved commercial viability for the BILN 2061 process: $>90\%$ yield, ≤ 1 h, ≤ 0.3 mol% catalyst (ref. [6a]). While the economics will necessarily be project-specific, these figures represent a useful point of comparison.

[11] Selected examples of CF-CM: a) R. Nakamura, H. Iida, E. Echigoya, *Chem. Lett.* **1972**, 273–275; b) N. Rendón, R. Berthoud, F. Blanc, D. Gajan, T. Maishal, J.-M. Basset, C. Coperet, A. Lesage, L. Emsley, S. C. Marinescu, R. Singh, R. R. Schrock, *Chem. Eur. J.* **2009**, *15*, 5083–5089; c) F. Blanc, N. Rendon, R. Berthoud, J.-M. Basset, C. Coperet, Z. J. Tonzetich, R. R. Schrock, *Dalton Trans.* **2008**, 3156–3158.

[12] Selected examples of CF-RCM by using supported ruthenium catalysts: a) M. Mayr, B. Mayr, M. R. Buchmeiser, *Angew. Chem.* **2001**, *113*, 3957–3960; *Angew. Chem. Int. Ed.* **2001**, *40*, 3839–3842; b) J. O. Krause, S. Lubbad, O. Nuyken, M. R. Buchmeiser, *Adv. Synth. Catal.* **2003**, *345*, 996–1004; c) J. O. Krause, S. H. Lubbad, O. Nuyken, M. R. Buchmeiser, *Macromol. Rapid Commun.* **2003**, *24*, 875–878. See also: reference [13] and (for a study using unsupported, homogeneous **Ru-1**), reference [14].

[13] A. Michrowska, K. Mennecke, U. Kunz, A. Kirschning, K. Grela, *J. Am. Chem. Soc.* **2006**, *128*, 13261–13267.

[14] E. Comer, M. G. Organ, *J. Am. Chem. Soc.* **2005**, *127*, 8160–8167.

[15] K. Grela, M. Tryznowski, M. Bieniek, *Tetrahedron Lett.* **2002**, *43*, 9055–9059.

[16] J. M. Blacquiere, T. Jurca, J. Weiss, D. E. Fogg, *Adv. Synth. Catal.* **2008**, *350*, 2849–2855.

[17] The reaction time (i.e., the residence time in the heated coil, τ) is determined by the coil volume divided by the flow rate.

[18] D. M. Roberge, L. Ducry, N. Bieler, P. Cretton, B. Zimmermann, *Chem. Eng. Technol.* **2005**, *28*, 318–323.

[19] M. Ulman, R. H. Grubbs, *J. Org. Chem.* **1999**, *64*, 7202–7207.

[20] B. Alcaide, P. Almendros, A. Luna, *Chem. Rev.* **2009**, *109*, 3817–3858.

[21] A. Fürstner, O. R. Thiel, L. Ackermann, *Org. Lett.* **2001**, *3*, 449–451.

[22] K. Yamamoto, K. Biswas, C. Gaul, S. J. Danishefsky, *Tetrahedron Lett.* **2003**, *44*, 3297–3299.

[23] K. A. Burdett, L. D. Harris, P. Margl, B. R. Maughon, T. Mokhtar-Zadeh, P. C. Saucier, E. P. Wasserman, *Organometallics* **2004**, *23*, 2027–2047.

[24] Representative data for the solubility of ethylene in toluene under 1 atm of C_2H_4: at 40 °C, 8 mM; above 45 °C, <1 mM. See: L.-S. Lee, H.-J. Ou, H.-L. Hsu, *Fluid Phase Equilib.* **2005**, *231*, 221–230.

[25] In an advance that appeared just prior to submission of this manuscript, Ying and co-workers reported RCM of several high-EM dienes, including diethyl diallylmalonate, using a circulating packed-bed flow reactor in which a ruthenium catalyst was immobilized on mesoporous silica (5 mol% Ru, 50 °C, 0.05 M, CH_2Cl_2). Removal of the ethylene co-product was effected in a clever modification involving circulation of the reaction solution through an on-line degasser and an open reservoir. The maximum TOF for diethyl diallylmalonate, 1.5 min^{-1}, was reported as five times higher than that attained in the corresponding batch reaction; see: J. Lim, S. S. Lee, J. Y. Ying, *Chem. Commun.* **2010**, 806–808. For comparison, the maximum TOF measured in the CSTR process of Table 1 is 15.2 min^{-1} (entry 12; a minimum figure, as τ was not optimized). The higher efficiency attainable in the CSTR is due in part to a difference in the solvent used, and hence the maximum operating temperature. The Ying group used CH_2Cl_2, rather than toluene, having observed higher conversions in the chlorinated solvent at 50 °C.

[26] Z. Lysenko, B. R. Maughon, T. Mokhtar-Zadeh, M. L. Tulchinsky, *J. Organomet. Chem.* **2006**, *691*, 5197–5203.

[27] A. Fürstner, K. Langemann, *Synthesis* **1997**, 792–803.

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