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Communication

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Integrating Activity with Accessibility in Olefin Metathesis: An Unprecedentedly Reactive Ruthenium-Indenylidene Catalyst

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Supporting Information Placeholder

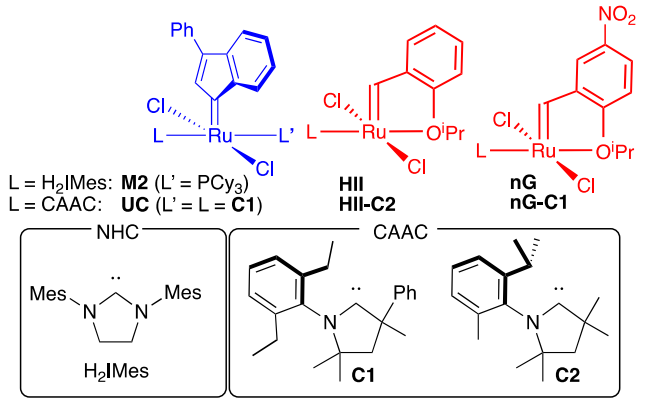
ABSTRACT: Access to leading olefin metathesis catalysts, including the Grubbs, Hoveyda, and Grela catalysts, ultimately rests on the non-scaleable transfer of a benzylidene ligand from an unstable, impure aryldiazomethane. The indenylidene ligand can be reliably installed, but to date yields much less reactive catalysts. A fast-initiating, dimeric indenylidene complex (**Ru-1**) is reported, which reconciles high activity with scaleable synthesis. Each Ru center in **Ru-1** is stabilized by a state-of-the-art cyclic alkyl amino carbene (CAAC, **C1**) and a bridging chloride donor: the lability of the latter elevates the reactivity of **Ru-1** to a level previously attainable only with benzylidene derivatives. Evaluation of initiation rate constants reveals that **Ru-1** initiates >250x faster than indenylidene catalyst **M2** ($RuCl_2(H_2IMes)(PCy_3)(Ind)$), and 65x faster than **UC** ($RuCl_2(\mathbf{C1})_2(Ind)$). The slow initiation previously regarded as characteristic of indenylidene catalysts is hence due to low ligand lability, not inherently slow cycloaddition at the Ru=CRR' site. In macrocyclization and "ethenolysis" of methyl oleate (i.e. transformation into α-olefins via cross-metathesis with C_2H_4), **Ru-1** is comparable or superior to the corresponding, breakthrough CAAC-benzylidene catalyst. In ethenolysis, **Ru-1** is 5x more robust to standard-grade (99.9%) C_2H_4 than the top-performing catalyst, probably reflecting steric protection at the quaternary CAAC carbon.

Keywords. *olefin metathesis, cyclic alkyl amino carbene, indenylidene, high activity, initiation, catalyst synthesis*

Reported herein is a ruthenium metathesis catalyst that integrates breakthrough productivity with a robust, reliably-installed indenylidene ligand. The advent of large-scale olefin metathesis processes in pharmaceutical manufacturing,[1,2] and the associated demand for catalyst supply on scale, bring to the fore long-neglected challenges in scaleable catalyst synthesis. Chief among these is the means by which the critical Ru=CRR' site is introduced.

Interest extends beyond the important N-heterocyclic carbene[3] (NHC) complexes to new cyclic alkyl amino carbene (CAAC)[4] catalysts: Chart 1. While metathesis in process chemistry[1,2] is dominated by NHC catalysts (**HII**, **nG**),[5-7] bench-scale studies report exceptional productivity for CAAC catalysts in macrocyclic ring-closing metathesis (mRCM)[8] and cross-metathesis (CM) routes to α-olefins from renewable oils.[9-12] The CAAC catalysts thus hold significant potential in the pharmaceutical and renewable-feedstock sectors.[1,12-14]

Chart 1. Literature Metathesis Catalysts Discussed.



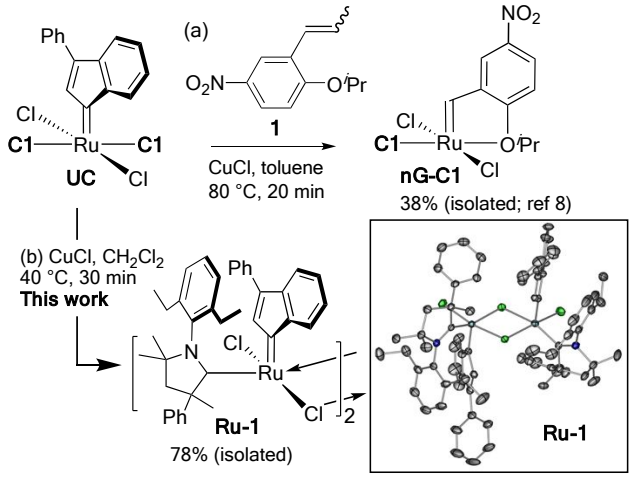
A long-standing challenge, however, is the tradeoff between metathesis activity, vs. the efficiency of catalyst synthesis. Most active are Ru-benzylidene catalysts (red; Chart 1).[8-10] Despite attempts to develop alternative synthetic methodologies,[15] optimal routes to benzylidene catalysts continue to rest on the reaction of a Ru precursor with an aryldiazomethane, typically $PhCHN_2$.[16,17] $PhCHN_2$ is toxic and unstable (indeed, potentially explosive),[18] to an extent that prevents purification. Its low purity, in turn, limits stoichiometric control over benzylidene transfer.[17,19] Significant limitations to process scaleability result.

Indenylidene catalysts (blue, Chart 1) enable straightforward, convenient, reliable installation of the Ru-carbon double bond, via the high-yield reaction of Ru precursors with propargyl alcohol.[20,21] However, study of the NHC derivatives, most extensively **M2**, reveals very inefficient initiation.[22-32] Slow loss of the stabilizing donor (PCy_3, for **M2**) impedes entry into the catalytic cycle at room temperature (RT), even for the readily-cyclized diene diethyl diallylmalonate **2**.[10,28-30] Elevated temperatures are required to elicit high activity, promoting catalyst degradation. Here we report the novel CAAC-indenylidene catalyst **Ru-1**, a labile chloride-bridged dimer, which overturns this long-accepted limitation. **Ru-1** exhibits unprecedented activity in demanding metathesis reactions (indeed, at a level comparable to the Grela-class catalyst **nG-C1**), establishing that high-performing metathesis catalysts can be accessed via simple, safe, scaleable chemistry.

It should be noted that **nG-C1** is itself accessible without recourse to diazo technology, via CM of the commercial indenylidene catalyst **UC** with the chelating *β*-methylstyrene reagent **1**, when CuCl is added to abstract the "extra" CAAC ligand (Scheme 1a).[8] Limitations, however, are the <40% yield, compounded by the multistep, low-yielding synthesis of **1**.[33,34] We queried whether *omitting* **1** might enable access to dimeric **Ru-1**, in which the precatalyst is stabilized by a dative Cl interaction. The high lability, and consequently high metathesis activity, conferred by dative chloride bonds has been recognized since Herrmann's pioneering work on bimetallic metathesis catalysts containing one [Ru]=CHR site.[35] While bimolecular elimination of the alkylidene moiety as RCH=CHR is a documented risk for dimers containing *two* [Ru]=CHR sites,[19a,36-38] this reaction is highly sensitive to alkylidene bulk.[37,39] We thus regarded the disubstituted indenylidene ligand as a potentially key asset in blocking alkylidene elimination.

Accordingly, we treated **UC** with CuCl (Scheme 1b) in the absence of additional donors. A **C1** ligand was successfully abstracted at 40 °C, enabling transformation of **UC** into dimeric **Ru-1** in ca. 80% isolated yield. The structure of **Ru-1** is supported by X-ray analysis. Consistent with the critical role of indenylidene bulk in inhibiting bimolecular decomposition, the corresponding reaction of CuCl with the second-generation Grubbs catalyst $RuCl_2(H_2IMes)(PCy_3)(=CHPh)$ led to rapid elimination of stilbene. In the absence of CuCl, this reaction requires days at 60 °C.[40]

Scheme 1. Synthesis of Ru-1.



The metathesis activity of **Ru-1** was benchmarked against key CAAC and NHC catalysts in RCM of diethyl diallylmalonate **2**. Comparison with the

state-of-the-art catalyst **nG-C1**[8] gives insight into the relative reactivity of the indenylidene and chelating *p*-nitrobenzylidene ligands. Comparison with **UC** reports on the impact of replacing a CAAC donor with a much more labile dative chloride, while comparison of **nG-C1** with its H_2IMes analogue **nG** probes the impact of the carbene. Catalyst loadings were chosen in light of prior studies of RCM of **2** via indenylidene catalyst **M2**.[10,24-32] We suspected that the reported TONs (ca. 20–2,000) might under-report catalyst productivity, given near-quantitative conversions. Initial catalyst loadings were therefore reduced to 0.005 mol% (i.e. 50 ppm Ru relative to **2**; cf. 5–0.05 mol% in the literature reports). The resulting data are summarized in Figure 1a.

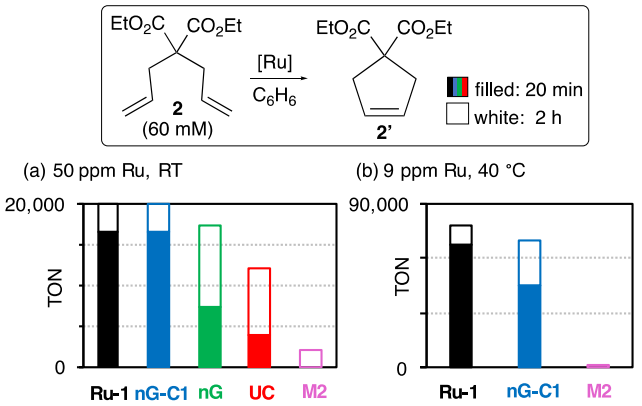


Figure 1. Turnover numbers (TON) at 2 h in RCM of **2**. For numerical values, see Table S1. Catalyst loadings are based on 2 active Ru centers in **Ru-1**.

Unexpectedly, **Ru-1** exhibited RCM activity comparable to the leading catalyst **nG-C1** at RT at this loading, and slightly *higher* activity at 9 ppm Ru and 40 °C. The basis for this difference is discussed below. **Ru-1** also outperformed **nG** and **M2**, in keeping with the trend established for H_2IMes vs. CAAC catalysts,[9,10] which may arise from faster decomposition of the H_2IMes complexes.[41]

A further inhibiting factor for **M2** is the low lability characteristic of phosphines trans to an NHC ligand,[42,43] which limits TONs to 2,000 at 50 ppm Ru. The higher RT productivity of **UC** (TON 12,000) suggests that the **C1** ligand in **UC** is more labile than the PCy_3 ligand in **M2** (confirmed below), though catalyst lifetime is almost certainly also relevant. Of note, this TON is nearly 60% of that measured for **nG** under the same conditions (17,200), despite the higher lability expected for the styrenyl ether ligand in **nG**, vs. a strongly-bound CAAC donor.[44]

As a metathesis reaction manifold of significant current interest, we next turned to macrocyclization. Substrates such as prolactone **3** (Figure 2) are challenging because the ester functionality contributes the sole conformational bias toward cyclization.[45] Oligomers are hence typically formed as the kinetic products, but can be recycled into macrocycles if catalyst activity and longevity permit.[46,47] High dilutions (5 mM, in the case of **3**) are essential to exert an entropic bias sufficient to shift the ring-chain equilibrium in favour of the macrocyclic rings.[46,48] (Carrying out mRCM of **3** at 20 mM, for example, yields ca. 40% oligomers).[8] A catalyst loading of 0.01 mol% thus corresponds to sub-micromolar concentrations of Ru. Combined with the internal, predominantly trans-substituted nature of the oligomeric olefins, this offers a stringent test of catalyst performance.

Notwithstanding these challenges, **Ru-1** enabled fast, selective mRCM at 0.01 mol% Ru, achieving TONs of ca. 9,000 within 10 min at 40 °C (Figure 2). **nG-C1** and **UC** exhibited similar, slower, performance, while the productivity of H_2IMes catalyst **nG** was ca. 30% lower, and **M2** failed to react. At RT, **Ru-1** enabled quantitative mRCM within 20 min at 0.05 mol%, where **UC** reacted much more slowly (44% yield at 2 h; Figure S2).

At 0.002 mol% and 40 °C (Figure 2b), a TON of 27,500 was measured for **Ru-1** (the highest yet reported for a Ru catalyst at dilutions compatible with selective mRCM).[49] In comparison, the record TON for NHC catalysts in this reaction is 16,000, achieved by Kadyrov at 80 °C and 8 mM **3**,[50] with rigorously purified diene and solvent, and aggressive removal of ethylene to limit catalyst decomposition.[51,52] Under standard conditions, reported TONs are ≤500.[50,52,53]

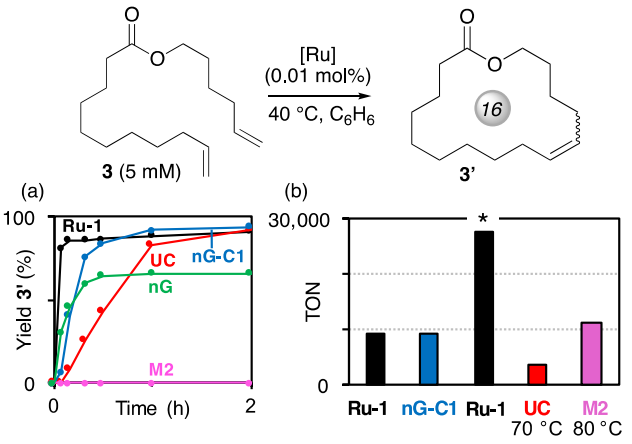


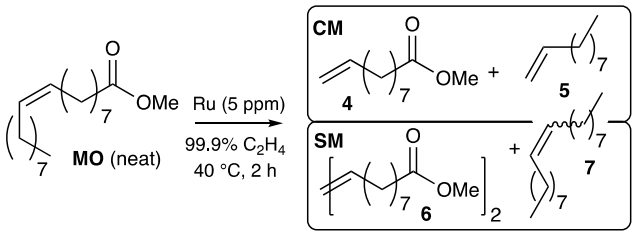
Figure 2. mRCM of **3** at 40 °C. (a) Rate profiles and (b) maximum TONs at 0.01 or (*) 0.002 mol% Ru, shown alongside the best reported TONs for **UC**[10] and **M2**.[50] For the RT plot and numerical data, see SI.

Improved stability to ethylene appears to be an important contributor to the exceptional productivity of the CAAC catalysts. This tolerance opens the door to ethenolysis of unsaturated lipids,[1,2] a reaction of keen interest for the production of α-olefins from renewable plant or algal oils.[1,12-14] Outstanding performance has been reported in ethenolysis of methyl oleate (**MO**) with CAAC catalysts,[9-11,54] particularly **HII-C2**.[9] However, **HII-C2** may be highly sensitive to impurities. Costly, very high grade (99.995%) ethylene was required for maximum productivity, and a 40–70% drop in TON was reported on using 99.95 or 99.99% C_2H_4.[9,10] We utilized affordable, technical-grade C_2H_4 (99.9%) to probe the robustness of **Ru-1** relative to this breakthrough catalyst.

Table 1 shows the impact of ethylene pressures on cross-metathesis (CM) yields at 40 °C in neat **MO**. A pressure of 200 psi proved optimal (entries 1–4), possibly indicating a trade-off between ethylene solubility and the cumulative impact of poisons. Importantly, however, **Ru-1** appears significantly more robust than **HII-C2**, as indicated by TON values of 50,000 and 10,000 (respectively) at 200 psi. Steric protection may be higher for **C1**, in which the quaternary carbon flanking the carbene site bears a methyl and a phenyl group, as compared with two methyl groups in **C2** (Chart 1).

nG-C1 delivered CM yields similar to **Ru-1**, though higher conversions of **MO**. The balance was due to 1,18-dimethyl 9-octadecenoate **6** and 9-octadecene **7**, formed via self-metathesis (SM) of **MO** or its ethenolysis products.

Table 1. Ethenolysis of Methyl Oleate: Cross-Metathesis (CM) and Self-Metathesis (SM).[a]



Entry	Catalyst	Pressure (psi)	% Conv. (% Yield)	TON
1	**Ru-1**	20	16 (3)	6,000
2	**Ru-1**	110	39 (20)	40,000
3	**Ru-1**	200	28 (25)	50,000
4	**Ru-1**	400	18 (8)	16,000
5	**nG-C1**	200	39 (23)	46,000
6	**HII-C2**	200	9 (5)	10,000

[a]5 ppm catalyst = 0.0005 mol% Ru. TON based on **4**/**5**. Quantified by ^{1}H NMR analysis (Figure S3).

The impressive activity of **Ru-1** documented above attests to the lability of the dative chloride donor, relative to the stabilizing ligands present in indenylidene catalysts such as **M2** and **UC**. It also supports the case made by Cavallo, Nolan and co-workers, on the basis of DFT analysis, that slow initiation of **M2** and related catalysts is due to slow ligand loss, not the resistance of the indenylidene moiety to cycloaddition.[30b,55,56]

To examine this key point, we measured initiation rate constants (k_1) for **Ru-1** and selected other catalysts, via the irreversible reaction with *tert*-butyl vinyl ether (tBVE; Table 2).[30b,57] The bulk of tBVE retards metathesis to experimentally convenient rates.[58]

As expected, initiation was fastest with benzylidene complex **nG-C1** (in which the inductive effect of the *p*-NO_2 substituent increases the lability of the ether donor),[7] and slowest with **UC** and **M2**. Notable is the 260x faster initiation of **Ru-1** relative to **M2**, and 65x relative to **UC**. Indeed, **nG-C1** initiates only 3.5x faster than **Ru-1**, despite the steric barrier to metathesis at the disubstituted Ru=CRR' site. Clearly, incorporating

a labile dative ligand greatly diminishes the barrier to indenylidene initiation, even relative to a classically fast-initiating[7] benzylidene ligand.

Also striking is the slightly *slower* overall rate of metathesis for **nG-C1** vs. **Ru-1** (Figs. 2a, S2), despite threefold faster initiation. As the two catalysts generate the same active species, the lower net activity of **nG-C1** suggests recapture of free 4-nitro-2-isopropoxystyrene **1′** by the active species. The rate difference is maintained even at 40 °C and sub-micromolar concentrations of Ru and **1′** (Figure 2b). While heat and high dilutions amplify engagement of **nG-C1** in metathesis, they are insufficient to inhibit re-uptake of **1′**.[59]

Table 2. Initiation rates in CM with tBVE.[a]

entry	catalyst	type	k_i (s^{-1})	k_{rel} vs. **M2**
1	**nG-C1**	Ru=CHPh	7.50×10^{-4}	903
2	**Ru-1**	Ru=CRR′	2.15×10^{-4}	259
3	**UC**	Ru=CRR′	3.33×10^{-6}	4
4	**M2**	Ru=CRR′	0.83×10^{-6}	1

[a] 30 equiv tBVE; measured in $CDCl_3$, 23 °C.

A tradeoff has long existed between the ease with which an alkylidene ligand can be installed at Ru centers, and the activity of the resulting catalysts. The need for scaleable, high-yield routes to metathesis catalysts, which obviate the unreliability and risk of diazoalkane methodologies, is becoming urgent with the increasing demand for catalyst supply on scale. The foregoing overturns the long-standing view that the synthetic accessibility of Ru-indenylidene catalysts is incompatible with high metathesis activity. Catalyst **Ru-1** exhibits a level of activity previously attainable only with benzylidene catalysts, indicating that the "fundamental" unreactivity of prior indenylidene catalysts merely reflects the low lability of the stabilizing ligands. In reconciling high metathesis activity with straightforward, reliable, safe installation of the alkylidene ligand, this advance is anticipated to create new opportunities in olefin metathesis.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

PDF file: experimental data, rate plots, crystallographic data, and NMR spectra.

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REFERENCES

(1) (a) Higman, C. S.; Lummiss, J. A. M.; Fogg, D. E. Olefin Metathesis at the Dawn of Uptake in Pharmaceutical and Specialty Chemicals Manufacturing. *Angew. Chem., Int. Ed.* **2016**, *55*, 3552–3565. (b) Grela, K., *Olefin Metathesis-Theory and Practice*. Wiley: Hoboken, NJ, 2014. (c) Grubbs, R. H.; Wenzel, A. G., *Handbook of Metathesis*. 2nd ed.; Wiley-VCH: Weinheim, 2015.

(2) For leading reviews from pharma, see: (a) Farina, V.; Horváth, A., Ring-Closing Metathesis in the Large-Scale Synthesis of Pharmaceuticals. In *Handbook of Metathesis*, Grubbs, R. H.; Wenzel, A. G., Eds. Wiley-VCH: Weinheim, 2015; Vol. 2, pp 633–658. (b) Fandrick, K. R.; Savoie, J.; Jinhua, N. Y.; Song, J. J.; Senanayake, C. H., Challenges and Opportunities for Scaling the Ring-Closing Metathesis Reaction in the Pharmaceutical Industry. In *Olefin Metathesis – Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, 2014; pp 349-366. (c) Hughes, D.; Wheeler, P.; Ene, D., Olefin Metathesis in Drug Discovery and Development: Examples from Recent Patent Literature. *Org. Process Res. Dev.* **2017**, *21*, 1938–1962.

(3) Arduengo, A. J., Looking for Stable Carbenes: The Difficulty in Starting Anew. *Acc. Chem. Res.* **1999**, *32*, 913–921.

(4) Soleilhavoup, M.; Bertrand, G., Cyclic (Alkyl)(Amino)Carbenes (CAACs): Stable Carbenes on the Rise. *Acc. Chem. Res.* **2015**, *48*, 256–266.

(5) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H., Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(6) Gessler, S.; Randl, S.; Blechert, S., Synthesis and Metathesis Reactions of a Phosphine-Free Dihydroimidazole Carbene Ruthenium Complex. *Tetrahedron Lett.* **2000**, *41*, 9973–9976.

(7) Grela, K.; Harutyunyan, S.; Michrowska, A., A Highly Efficient Ruthenium Catalyst for Metathesis Reaction. *Angew. Chem. Int. Ed.* **2002**, *41*, 4038–4040.

(8) Gawin, R.; Tracz, A.; Chwalba, M.; Kozakiewicz, A.; Trzaskowski, B.; Skowerski, K., Cyclic Alkyl Amino Ruthenium Complexes—Efficient Catalysts for Macrocyclization and Acrylonitrile Cross Metathesis. *ACS Catal.* **2017**, *7*, 5443–5449.

(9) Marx, V. M.; Sullivan, A. H.; Melaimi, M.; Virgil, S. C.; Keitz, B. K.; Weinberger, D. S.; Bertrand, G.; Grubbs, R. H., Cyclic Alkyl Amino Carbene (CAAC) Ruthenium Complexes as Remarkably Active Catalysts for Ethenolysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1919–1923.

(10) Gawin, R.; Kozakiewicz, A.; Guńka, P. A.; Dąbrowski, P.; Skowerski, K., Bis(Cyclic Alkyl Amino Carbene) Ruthenium

Complexes: A Versatile, Highly Efficient Tool for Olefin Metathesis. *Angew. Chem., Int. Ed.* **2017**, *56*, 981–986.

(11) Schrodi, Y.; Ung, T.; Vargas, A.; Mkrtumyan, G.; Lee, C. W.; Champagne, T. M.; Pederson, R. L.; Hong, S. H., Ruthenium Olefin Metathesis Catalysts for the Ethenolysis of Renewable Feedstocks. *Clean Soil, Air, Water* **2008**, *36*, 669–673.

(12) Hess, S. K.; Lepetit, B.; Kroth, P. G.; Mecking, S., Production of Chemicals from Microalgae Lipids – Status and Perspectives. *Eur. J. Lipid Sci. Technol.* **2018**, *120*, 1700152.

(13) Biermann, U.; Bornscheuer, U.; Meier, M. A. R.; Metzger, J. O.; Schafer, H. J., Oils and Fats as Renewable Raw Materials in Chemistry. *Angew. Chem., Int. Ed.* **2011**, *50*, 3854–3871.

(14) Bidange, J.; Fischmeister, C.; Bruneau, C., Ethenolysis: A Green Catalytic Tool to Cleave Carbon–Carbon Double Bonds. *Chem. – Eur. J.* **2016**, *22*, 12226–12244.

(15) For a summary of early attempts to circumvent the diazo technology, see: (a) Fogg, D. E.; Foucault, H. M., Ring-Opening Metathesis Polymerization. In *Comprehensive Organometallic Chemistry III,* Crabtree, R. H.; Mingos, D. M. P., Eds. Elsevier: Oxford, 2007; Vol. 11, pp 623–652. For a recent route to Ru thiolate-alkylidene complexes enabled by aryl vinyl sulfides, see: (b) Dahcheh, F.; Stephan, D. W., A New Route to Ruthenium Thiolate Alkylidene Complexes. *Organometallics* **2013**, *32*, 5253–5255.

(16) Schwab, P.; Grubbs, R. H.; Ziller, J. W., Synthesis and Applications of $RuCl_2(=CHR')(PR_3)_2$: The Influence of the Alkylidene Moiety on Metathesis Activity. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.

(17) More rarely, $ArCHN_2$ is used. For the reaction of $N_2CH(C_6H_4$-*o*-O^{i}Pr) with $RuCl_2(PPh_3)_3$, see: (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H., A Recyclable Ru-Based Metathesis Catalyst. *J. Am. Chem. Soc.* **1999**, *121*, 791–799. With $RuCl_2$(*p*-cymene): (b) Day, C. S.; Fogg, D. E., High-Yield Synthesis of a Long-Sought, Labile Ru-NHC Complex and Its Application to the Concise Synthesis of Second-Generation Olefin Metathesis Catalysts. *Organometallics* **2018**, *24*, 4551–4555.

(18) Sammakia, T., Phenyldiazomethane. In *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons: Hoboken, NJ, 2001.

(19) (a) Amoroso, D.; Snelgrove, J. L.; Conrad, J. C.; Drouin, S. D.; Yap, G. P. A.; Fogg, D. E., An Attractive Route to Olefin Metathesis Catalysts: Facile Synthesis of a Ruthenium Alkylidene Complex Containing Labile Phosphane Donors. *Adv. Synth. Catal.* **2002**, *344*, 757–763. Exacerbating the problem, use of the diazoalkane reagent in excess triggers alkylidene elimination as (e.g.) PhCH=CHPh. See: (b) Amoroso, D.; Fogg, D. E., Ring-Opening Metathesis Polymerization via Ruthenium Complexes of Chelating Diphosphines. *Macromolecules* **2000**, *33*, 2815–2818.

(20) Harlow, K. J.; Hill, A. F.; Wilton-Ely, J. D. E. T., The First Coordinatively Unsaturated Group 8 Allenylidene Complexes: Insights into Grubbs' vs. Dixneuf-Furstner Olefin Metathesis Catalysts. *J. Chem. Soc., Dalton Trans.* **1999**, 285–292.

(21) Boeda, F.; Clavier, H.; Nolan, S., Ruthenium–Indenylidene Complexes: Powerful Tools for Metathesis Transformations. *Chem. Commun.* **2008**, 2726–2740.

(22) Dixneuf, H. P.; Bruneau, C., Ruthenium Indenylidene Catalysts for Alkene Metathesis. In *Handbook of Metathesis*, Grubbs, R. H.; Wenzel, A. G., Eds. Wiley-VCH: Weinheim, 2015; Vol. 1, pp 389–416.

(23) Lozano-Vila, A. M.; Monsaert, S.; Bajek, A.; Verpoort, F., Ruthenium-Based Olefin Metathesis Catalysts Derived from Alkynes. *Chem. Rev.* **2010**, *110*, 4865–4909.

(24) Clavier, H.; Nolan, S. P., N-Heterocyclic Carbene and Phosphine Ruthenium Indenylidene Precatalysts: A Comparative Study in Olefin Metathesis. *Chem. – Eur. J.* **2007**, *13*, 8029–8036.

(25) Monsaert, S.; Drozdzak, R.; Dragutan, V.; Dragutan, I.; Verpoort, F., Indenylidene-Ruthenium Complexes Bearing Saturated N-Heterocyclic Carbenes: Synthesis and Catalytic Investigation in Olefin Metathesis Reactions. *Eur. J. Inorg. Chem.* **2008**, 432–440.

(26) Clavier, H.; Urbina-Blanco, C. A.; Nolan, S. P., Indenylidene Ruthenium Complex Bearing a Sterically Demanding NHC Ligand: An Efficient Catalyst for Olefin Metathesis at Room Temperature. *Organometallics* **2009**, *28*, 2848–2854.

(27) Clavier, H.; Petersen, J. L.; Nolan, S. P., A Pyridine-Containing Ruthenium–Indenylidene Complex: Synthesis and Activity in Ring-Closing Metathesis. *J. Organomet. Chem.* **2006**, *691*, 5444–5447.

(28) Jafarpour, L.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P., Indenylidene-Imidazolylidene Complexes of Ruthenium as Ring-Closing Metathesis Catalysts. *Organometallics* **1999**, *18*, 5416–5419.

(29) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K., An Attempt to Provide a User's Guide to the Galaxy of Benzylidene, Alkoxybenzylidene, and Indenylidene Ruthenium Olefin Metathesis Catalysts. *Chem. – Eur. J.* **2008**, *14*, 806–818.

(30) Pyridine- and PPh_3-stabilized indenylidene catalysts are reported to exhibit even lower room-temperature activity than **M2**. See refs 27, 28. A DFT study concluded that their slow initiation is due to reduced steric pressure in the precatalyst. See: Urbina-Blanco, C. A.; Poater, A.; Lebl, T.; Manzini, S.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P., The Activation Mechanism of Ru–Indenylidene Complexes in Olefin Metathesis. *J. Am. Chem. Soc.* **2013**, *135*, 7073–7079.

(31) Yu, B.; Li, Y.; He, X.; Hamad, F. B.; Ding, F.; Van Hecke, K.; Yusubov, M. S.; Verpoort, F., SIMes/PCy_3 Mixed Ligand-Coordinated Alkyl Group-Tagged Ruthenium Indenylidene Complexes: Synthesis, Characterization and Metathesis Activity. *Appl. Organomet, Chem.* **2018**, *32*, e4548.

(32) Smoleń, M.; Marczyk, A.; Kośnik, W.; Trzaskowski, B.; Kajetanowicz, A.; Grela, K., Ruthenium-Catalysed Olefin Metathesis in Environmentally Friendly Solvents: 2-Methyltetrahydrofuran Revisited. *Eur. J. Org. Chem.* **2019**, 640–646.

(33) Bieniek, M.; Michrowska, A.; Gulajski, L.; Grela, K., A Practical Larger Scale Preparation of Second-Generation Hoveyda-Type Catalysts. *Organometallics* **2007**, *26*, 1096–1099.

(34) Knapkiewicz, P.; Skowerski, K.; Jaskólska, D. E.; Barbasiewicz, M.; Olszewski, T. K., Nitration Under Continuous Flow Conditions: Convenient Synthesis of 2‑Isopropoxy-5-nitrobenzaldehyde, an Important Building Block in the Preparation of Nitro-Substituted Hoveyda–Grubbs Metathesis Catalyst. *Org. Process Res. Dev.* **2012**, *16*, 1430–1435.

(35) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A., Highly Active Ruthenium Catalysts for

Olefin Metathesis: The Synergy of N-Heterocyclic Carbenes and Coordinatively Labile Ligands. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416–2419.

(36) Amoroso, D.; Yap, G. P. A.; Fogg, D. E., Deactivation of Ruthenium Metathesis Catalysts via Facile Formation of Face-Bridged Dimers. *Organometallics* **2002**, *21*, 3335–3343.

(37) Bailey, G. A.; Foscato, M.; Higman, C. S.; Day, C. S.; Jensen, V. R.; Fogg, D. E., Bimolecular Coupling as a Vector for Decomposition of Fast-Initiating Olefin Metathesis Catalysts. *J. Am. Chem. Soc.* **2018**, *140*, 6931–6944.

(38) For kinetics evidence for bimolecular decomposition, see: Thiel, V.; Wannowius, K.-J.; Wolff, C.; Thiele, C. M.; Plenio, H., Ring-Closing Metathesis Reactions: Interpretation of Conversion–Time Data. *Chem. - Eur. J.* **2013**, *19*, 16403–16414.

(39) The successful deployment of chloride-bridged dimers in ring-opening metathesis polymerization (see: (a) Hansen, S. M.; Volland, M. A. O.; Rominger, F.; Eisentrager, F.; Hofmann, P., A New Class of Ruthenium Carbene Complexes: Synthesis and Structures of Highly Efficient Catalysts for Olefin Metathesis. *Angew. Chem., Int. Ed.* **1999**, *38*, 1273–1276) reflects the resistance of bulky [Ru]=CHR groups to bimolecular elimination.

(40) Higman, C. S.; Nascimento, D.; Ireland, B. J.; Audorsch, S.; Bailey, G. A.; Fogg, D. E., Chelate-Assisted Ring-Closing Metathesis: A Strategy for Accelerating Macrocyclization at Ambient Temperatures. *J. Am. Chem. Soc.* **2018**, *140*, 1604−1607.

(41) Butilkov, D.; Frenklah, A.; Rozenberg, I.; Kozuch, S.; Lemcoff, N. G., Highly Selective Olefin Metathesis with CAAC-Containing Ruthenium Benzylidenes. *ACS Catal.* **2017**, *7*, 7634–7637.

(42) Lummiss, J. A. M.; Higman, C. S.; Fyson, D. L.; McDonald, R.; Fogg, D. E., The Divergent Effects of Strong NHC Donation in Catalysis. *Chem. Sci.* **2015**, *6*, 6739–6746.

(43) Dharmasena, U. L.; Foucault, H. M.; dos Santos, E. N.; Fogg, D. E.; Nolan, S. P., N-Heterocyclic Carbenes as Activating Ligands for Hydrogenation and Isomerization of Unactivated Olefins. *Organometallics* **2005**, *24*, 1056–1058.

(44) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A., A Novel Class of Ruthenium Catalysts for Olefin Metathesis. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490–2493.

(45) Fürstner, A.; Langemann, K., Macrocycles by Ring-Closing Metathesis. *Synthesis* **1997**, 792–803.

(46) Monfette, S.; Fogg, D. E., Equilibrium Ring-Closing Metathesis. *Chem. Rev.* **2009**, *109*, 3783–3816.

(47) Such simple "olfactory lactones" were recently isolated at higher concentrations, by distilling off the cyclic product to shift the ring-chain equilbrium. See: Sytniczuk, A.; Dąbrowski, M.; Banach, Ł.; Urban, M.; Czarnocka-Śniadała, S.; Milewski, M.; Kajetanowicz, A.; Grela, K., At Long Last: Olefin Metathesis Macrocyclization at High Concentration. *J. Am. Chem. Soc.* **2018**, *40*, 8895–8901.

(48) Conrad, J. C.; Eelman, M. D.; Duarte Silva, J. A.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E., Oligomers as Intermediates in Ring-Closing Metathesis. *J. Am. Chem. Soc.* **2007**, *129*, 1024–1025.

(49) A TON of 62,000 could be achieved with **nG-C1** at higher concentrations (20 mM **3**) at 70 °C. .

(50) Kadyrov, R., Low Catalyst Loading in Ring-Closing Metathesis Reactions. *Chem. – Eur. J.* **2013**, *19*, 1002–1012.

(51) Burdett, K. A.; Harris, L. D.; Margl, P.; Maughon, B. R.; Mokhtar-Zadeh, T.; Saucier, P. C.; Wasserman, E. P., Renewable Monomer Feedstocks via Olefin Metathesis: Fundamental Mechanistic Studies of Methyl Oleate Ethenolysis with the First-Generation Grubbs Catalyst. *Organometallics* **2004**, *23*, 2027–2047.

(52) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E., Getting RCM Off the Bench: Reaction-Reactor Matching Transforms Metathesis Efficiency in the Assembly of Large Rings. *Chem. – Eur. J.* **2010**, *16*, 11720–11725.

(53) Tracz, A.; Matczak, M.; Katarzyna; Urbaniak; Skowerski, K., Nitro-Grela-Type Complexes Containing Iodides – Robust and Selective Catalysts for Olefin Metathesis Under Challenging Conditions. *Beilstein J. Org. Chem.* **2015**, *11*, 1823–1832.

(54) Zhang, J.; Song, S.; Wang, X.; Jiao, J.; Shi, M., Ruthenium-Catalyzed Olefin Metathesis Accelerated by the Steric Effect of the Backbone Substituent in Cyclic (Alkyl)(Amino) Carbenes. *Chem. Commun.* **2013**, *49*, 9491–9493.

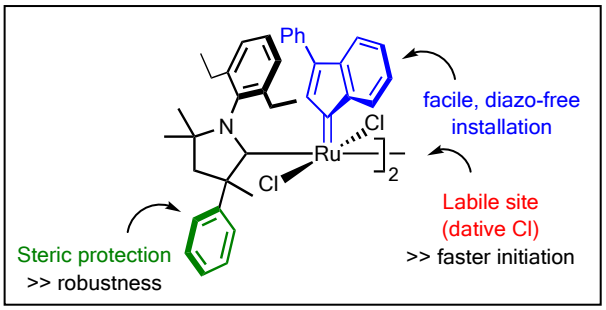
(55) Voccia, M.; Nolan, S. P.; Cavallo, L.; Poater, A., The Activity of Indenylidene Derivatives in Olefin Metathesis Catalysts. *Beilstein J. Org. Chem.* **2018**, *14*, 2956–2963.

(56) Computational studies of **M2** derivatives predict that increasing indenylidene bulk accelerates initiation by increasing steric pressure on the dissociating PCy_3 ligand. See: (a) Voccia, M.; Nolan, S. P.; Cavallo, L.; Poater, A., The Activity of Indenylidene Derivatives in Olefin Metathesis Catalysts. *Beilstein J. Org. Chem.* **2018**, *14*, 2956–2963. The rigidity of the conventional indenylidene ligand is presumed to limit such steric pressure relative to the conformationally mobile benzylidene ligand. Steric pressure exerted by the [Ru]=CHPh group has been shown to be central to the 275x faster loss of PCy_3 from **GII** vs. its methylidene analogue $RuCl_2(H_2IMes)(PCy_3)(=CH_2)$. See: (b) Lummiss, J. A. M.; Perras, F. A.; Bryce, D. L.; Fogg, D. E., Sterically-Driven Metathesis: The Impact of Alkylidene Substitution on the Reactivity of the Grubbs Catalysts. *Organometallics* **2016**, *35*, 691–698.

(57) Engle, K. M.; Lu, G.; Luo, S.-X.; Henling, L. M.; Takase, M. K.; Liu, P.; Houk, K. N.; Grubbs, R. H., Origins of Initiation Rate Differences in Ruthenium Olefin Metathesis Catalysts Containing Chelating Benzylidenes. *J. Am. Chem. Soc.* **2015**, *137*, 5782−5792.

(58) Reaction with ethyl vinyl ether was dramatically faster. For **nG-C1**, for example, reaction with 100 EVE was complete in <1 min at 23 °C.

(59) For evidence of "boomerang" recapture of 2-isopropoxystyrene, see: (a) Bates, J. M.; Lummiss, J. A. M.; Bailey, G. A.; Fogg, D. E. *ACS Catal.* **2014**, *4*, 2387−2394. (b) Griffiths, J. R.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2016**, *138*, 5380−5391. For the original proposal, see ref 5. Of note, alternative electron-deficient styrenyl ethers were reported to resist recapture in H_2IMes complexes. See: (c) Vorfalt, T.; Wannowius, K. J.; Thiel, V.; Plenio, H., How Important Is the Release–Return Mechanism in Olefin Metathesis? *Chem. – Eur. J.* **2010**, *16*, 12312–12315.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