



# Cross metathesis with acrylates: N-heterocyclic carbene (NHC)- *versus* cyclic alkyl amino carbene (CAAC)-based ruthenium catalysts, an unanticipated influence of the carbene type on efficiency and selectivity of the reaction.

Dr. Katarzyna Kaczanowska,<sup>†</sup> Dr. Bartosz Trzaskowski,<sup>‡</sup> Aleksandra Peszczyńska,<sup>†</sup> Andrzej

Tracz,<sup>†</sup> Dr. Rafał Gawin,<sup>†</sup> Dr. Tomasz K. Olszewski\*§ and Krzysztof Skowerski<sup>\*,†</sup>

<sup>†</sup>Apeiron Synthesis SA, Duńska 9, 54-427 Wrocław, Poland

<sup>‡</sup>Centre of New Technologies, University of Warsaw, Banacha 2c, 02-097 Warszawa, Poland

§Wroclaw University of Science and Technology, Faculty of Chemistry, Wybrzeze

Wyspianskiego 29, 50-370 Wroclaw, Poland

1

ChemCatChem

10.1002/cctc.202001268

**ABSTRACT:** Olefin metathesis has been widely explored as a handle for chemical diversification, a feature critical across chemical sectors. Cross metathesis with acrylic acid derivatives is an example of important but, due to the low catalyst's efficiency, industrially non-utilized transformation. Here we report on systematic evaluation of ruthenium-based catalysts bearing *N*-heterocyclic carbene (NHC) or cyclic alkyl amino carbene (CAAC) ligands in cross metathesis (CM) with methyl acrylate. Dramatic influence of the carbene type on the reaction's efficiency and selectivity has been found. Density functional theory (DFT) calculations suggest that the kinetic selectivity is the main factor differentiating NHC- and CAAC-based ruthenium complexes. Productive turnover number (TON) of 49 900 at 10 ppm loading of nitro-substituted Hoveyda-Grubbs complex (nitro-Grela catalyst) was obtained in the studied reaction, representing the highest efficiency reported to date for this transformation. High efficiency and selectivity of nitro-Grela catalyst was then utilized in cross metathesis of *trans*-anethole with 2-ethylhexyl acrylate to efficiently produce octyl methoxycinnamate (86% yield), an antioxidant used in sunscreen formulations.

ChemCatChem

10.1002/cctc.202001268

The environmental impact and limited resources of petrochemicals drive the shift towards renewable, efficient and waste averse industrial processes. Utilization of plant oils, a natural alternative for fossil-derived chemicals remains a focus of both, the chemical industry and academia.<sup>[1]</sup> The broad availability of these raw materials, their inherent chemical functionalities along with competitive costs make them desirable in a variety of commercial applications.<sup>[2]</sup>

The enormous potential of olefin metathesis in chemical industries inspired efforts to develop efficient processes implementing this technology.<sup>[3]</sup> The requirements for economically viable processes are particularly stringent in production of commodity and specialty chemicals. As estimated by The Dow Chemical Company, turnover numbers of at least 50 000 and 35 000, respectively, are required for economical production of these materials.<sup>[4]</sup> Despite the intense research over past decades, the efficiency of metathesis catalysts remains unsatisfactory for many transformations, prohibiting its wider application.

Cross metathesis offers an efficient pathway to introduce diverse functionalities thus allowing a straightforward access to higher value, multifunctional compounds. The cross metathesis (CM) with acrylates has been widely studied in the context of depolymerization,<sup>[5]</sup> transformation of oils and their derivatives<sup>[6]</sup> as well as other natural products.<sup>[7]</sup> These type III olefins (according to Grubbs' classification)<sup>[8]</sup> are known for their low metathesis reactivity therefore cross metathesis is regarded challenging and require concerted optimization efforts that include selection of a matching metathesis catalyst. Phosphine-containing catalysts *e.g.* Grubbs 2nd generation catalyst (1, Figure 1) are considered incompatible with electron deficient metathesis partners, since phosphine ligands released into the reaction mixture upon metathesis initiation lead to undesired

3

side reactions.<sup>[9]</sup> As demonstrated by *e.g.* Fogg *et al.*<sup>[9c]</sup> and Lipshutz *et al.*<sup>[9d]</sup> efficient scavenging of phosphines during CM with acrylates resulted in dramatic improvement of performance of catalyst **1**. However, the reaction has not been optimized to the level acceptable by the industry as maximal TONs of less than 1 000 were achieved.



Figure 1. Representative olefin metathesis catalysts used in CM reaction with acrylates.

On the other hand, phosphine-free, Hoveyda type catalysts allowed for relatively efficient CM with acrylates.<sup>[10]</sup> Miao et al. investigated synthesis of polyamide precursors from renewable 10-undecenenitrile and methyl acrylate *via* olefin CM.<sup>[6d]</sup> The best productivity was obtained using continuous injection of second generation Hoveyda–Grubbs catalyst **2** (50 ppm) into the reaction mixture at 100 °C. Under these conditions 63% yield of the fatty nitrile was obtained which corresponds to TON of 12 600. Abbas and Slugovc screened a series of ruthenium catalysts in cross metathesis of 1,9-decadiene with methyl acrylate and reached full conversions with 100 ppm per double bond by using catalyst **3**.<sup>[11]</sup> In this case, however, the good efficiency came at the price of long reaction times (4 h).

In our recent work on cross metathesis of ethyl 10-undecenoate with acrylonitrile we found that substitution of the NHC ligand in the ruthenium catalyst by a properly selected cyclic alkyl amino carbene (CAAC) ligand (*e.g.* catalysts **6** and **7**, Figure 1) led to superior catalytic productivity.<sup>[12]</sup> For CAAC-based complex **6** TON of 28 500 was observed whereas catalyst **5** bearing *N*-heterocyclic carbene (NHC) ligand reached TON of only 12 000. Experimental results and DFT calculations linked improved performance of **6** with higher stability of the catalyst's active forms and the related resistance to decomposition induced by acrylonitrile. Importantly, kinetic selectivity towards cross metathesis product was similar for **5** and **6**, whereas very stable and typically efficient complex **7** performed poorly due to its low kinetic selectivity.<sup>[12]</sup>

The unexpected results of our study related to cross metathesis with acrylonitrile prompted us to investigate cross metathesis with acrylates. Two classic catalysts from NHC-based group (**4** and **5**, Figure 1) were compared to representative ruthenium catalysts from CAAC-based series (**6** and **7**, Figure 1). The goal of this exploration was to find the most efficient and selective catalyst and optimal reaction conditions for cross metathesis with methyl acrylate, as well as to understand factors which determine the catalyst's performance. Ultimately, the most favorable catalyst for this industrially important reaction should assure economically relevant efficiency expressed in high TONs.

Bulk chemical production requires careful consideration of economics in industrial processes development. In the case of commodity and specialty chemicals, well-defined ruthenium-based metathesis catalysts come at relatively high cost per kg compared to the product's price per kg, thus the catalyst loading often becomes one of the key contributors to the overall costs of the process. The most relevant parameter to estimate catalyst performance is the productive turnover number (TON). Reaction yields, although important, can be less critical, as large-scale processing

often allows recycling of unreacted substrates. Therefore, in this study, the reaction conditions were adjusted to avoid full conversions in order to register fine performance differences in the selected catalytic systems.

Table 1. Results of cross metathesis of ethyl 10-undecenoate (8) with methyl acrylate (9).



<sup>&</sup>lt;sup>a</sup>Determined by GC, for details regarding calculation of selectivity, yield, and TON, see the Supporting Information.

According to the results reported in literature methyl acrylate (9) shows no poisoning effect on Ru-based catalysts (this applies to Hoveyda-Grubbs type catalysts)<sup>[10]</sup> while its excess improves the reaction selectivity. Therefore, we ran initial experiments with 5 equivalents of this reagent using toluene as a solvent. While high conversions in all cases were observed, selectivity differences were striking. Contrary to the results observed in CM with acrylonitrile, CAAC-based catalyst **6** proved to have dramatically low selectivity (24%) towards desired CM product **10** (Table 1, entry 3). On the other hand, complex **7** showed very high, 89% selectivity, albeit to self-

metathesis product **11**, which makes it useless in CM with **9** (selectivity toward desired CM product **10** was 11%, Table 1, entry 4). However, it is also worth noting that this intriguing and unique type of selectivity could potentially be used in some specific synthesis cases where metathesis with an acryloyl group would be undesired.

Both NHC-based catalysts were much more selective than CAAC catalysts (Table 1, entries 1 and 2). Unexpectedly, the nitro substituted Hoveyda-Grubbs complex 4, commonly known as nitro-Grela catalyst,<sup>[1g]</sup> provided noticeably higher productive turnover number (TON10 34 110) (Table1, entry 1) than its bulkier derivative 5 (TON10 26 784) (Table1, entry 2). Therefore, we decided to optimize the reaction conditions for catalyst 4 with the aim to maximize TON10 (Table 2). Following the findings of Abbas and Slugovc<sup>[11]</sup> we setup the experiments without typical organic solvent (toluene). Instead, even higher excess of methyl acrylate (8 equivalents) was used to serve both as a reagent and solvent. As could be expected selectivity increased from 77% to 88%, but at the same time conversion dropped from 89% to 74%, leading to TON10 lower than that observed in the initial test (Table 2, entry 2). Very high improvement in efficiency, especially at 10 ppm catalyst loading, was gained upon temperature increase to 80 or 90 °C (Table 2, entries 4 and 5). Observed at 90°C TON10 of 49 967 at 10 ppm catalyst loading (59% yield) (Table 2, entry 5) and TON10 39 480 at 20 ppm catalyst loading (89% yield) (Table 2, entry 6) substantially outperformed results previously reported for CM with acrylates. Sharp decrease in TON10 was noted at 100 °C, which was most probably due to the fast catalyst initiation and short life time of the active species at this temperature (Table 2, entries 7 and 8). Rather surprisingly, similar

7

optimization protocol did not result in improved TON10 with bulky complex 5 (see ESI, Table

S1).

 Table 2. Efficiency of nitro-Grela catalysts (4) in cross metathesis of ethyl 10-undecenoate (8)

 with methyl acrylate (9) (8 eq.).

Entry	<i>T</i> ( <sup>o</sup> C)	[Ru] (ppm) <sup>a</sup>	Conv. (%)	Sel. (%)	Yield (%)	TON10
1	70	10	22	84	19	18 649
2	70	20	74	88	65	32 594
3	80	10	47	84	40	39 680
4	80	20	84	89	74	37 048
5	90	10	59	85	50	49 967
6	90	20	89	89	79	39 480
7	100	10	23	79	18	18 025
8	100	20	30	80	24	12 105

<sup>a</sup>Results at 10 and 20 ppm of the catalyst obtained in the same experiment in neat **8**; samples measured at 30 and 90 min reaction times respectively.

Further studies were performed in order to understand reasons for poor TON10 obtained in CM between 8 and 9 with CAAC-bearing complexes 6 and 7. First, the efficiency of examined complexes in ring closing metathesis (RCM) of diene 12 was determined (Table 3). We assumed that catalysts initiate via association of the terminal, more electron-rich double bond to the activated catalysts which, after release of the product, leads to the formation of methyl ester substituted methylidenes 14 (Table 3). No significant differences in TON were observed for complexes 4-7. This result together with high total TON's achieved by catalysts 6 and 7 in CM

between olefin 8 and acrylate 9 allowed us to conclude that the poor selectivity of CAAC based catalysts in CM with 9 is not related to the poisoning effect of acrylate.





Next, we performed theoretical studies to gain mechanistic understanding of the reaction of interest. Due to the similar selectivity represented by both NHC-based catalysts and both CAAC-based catalysts we performed calculations for the three representative structures, namely **4-6**. We used DFT calculations on the crucial intermediates in the catalytic cycle to assess their relative Gibbs free energies and use them to obtain thermodynamic ratios of the final products. The schematic representation of the most important intermediates in the initiation part of the catalytic pathways leading to the homo-metathesis products **11** and dimethylfumarate is presented in Scheme 1, while in the pathway leading to the cross-metathesis product **10** in Scheme 2. It is worth noting that using this approach we can estimate the selectivities of catalysts based on Gibbs free energies of different intermediates, e.g. taking into account only those with associated olefins (**int1, int3** ...) or only ruthenacyclobutanes (**int1\_mcb, int3\_mcb** ...). After performing all

calculations decided to base our estimates on intermediates with associated olefins, as their relative Gibbs free energies are higher than those of ruthenacyclobutanes for virtually all investigated cases. At the end of this section we also shortly consider selectivities obtained from ruthenacyclobutane intermediates for the sake of completion.



Scheme 1. A schematic representation of the most important intermediates in the catalytic cycle initiation phase and the first half of the catalytic cycle (from the precatalyst to the methylidene intermediate with the formation of the product) of the homo-metathesis of either ethyl 10-undecenoate 8 (PATH 1) or acrylate 9 (PATH 2). Numbers represent the relative Gibbs free energies of the intermediates with respect to the corresponding precatalyst (in kcal/mol).



Scheme 2. A schematic representation of the most important intermediates in the catalytic cycle initiation phase and the first half of the catalytic cycle (from the precatalyst to the methylidene intermediate with the formation of the product) of the cross-metathesis of 10-undecenoate 8 with acrylate 9. Numbers represent the relative Gibbs free energies of the intermediates with respect to the corresponding precatalyst (in kcal/mol).

The initiation of the entire catalytic cycle commences with the association of either ethyl undecenoate 8(int1) or acrylate 9(int6) to the activated precatalyst. All three examined complexes react preferentially with 8 to provide intermediate int2 in paths 1 and 3. In those pathways the association of 8 to int2 is favored over the association of 9 by approximately 0.5-1.1 kcal·mol<sup>-1</sup>

for all three catalysts and thus mostly the side product **11** is formed in this step, accompanied by the generation of ruthenium methylidenes (**int4**) which proved to be the critical catalytic species. Based on the calculated Gibbs free energies of the intermediates (Table 4) we can estimate the **10/11** ratios in the first phase of the catalytic cycle (initiation) only to be 33:67 for complex **6**, 26:74 for complex **5** and 33:67 for complex **4**, which are not in agreement with experimental data presented in Table 1 (see the ESI for the details of these calculations).

 Table 4. Differences in relative Gibbs free energies (in kcal/mol) of the crucial intermediates in

 the catalytic cycle and 10/11 ratio obtained using these computational values.

catalyst	int6-int1	int5-int3	int9-int8	int12-int11	int11-int10	10/11 ratio
4	3.1	0.5	0.6	-0.7	-0.8	77:23
5	2.2	0.8	0.2	-1.8	1.8	86:14
6	1.0	1.1	5.0	2.0	1.9	21:79



**Scheme 3.** Schematic representation of the most important intermediates in the catalytic cycle propagation phase of the investigated reaction. Numbers represent the relative Gibbs free energies of the intermediates with respect to the corresponding precatalyst (in kcal/mol).

The association of 8 to int4 leading to the formation of int11 and, in the next step, the unselective int2 is favored over association of 9 to form int12 by ca 2 kcal·mol<sup>-1</sup> for 6 (see Scheme 3 and

Table 4). For 5 and 4 the situation is the opposite, with association of 9 to form int12 being favored by ca 1-2 kcal·mol<sup>-1</sup> over the association of 8 to form int11. The energy differences are the main reason for selectivity contrast observed for both catalysts (Scheme 3). For 6, int11 is favored over int12 by 2.0 kcal·mol<sup>-1</sup> resulting in a 19:1 selectivity promoting the association of the ethyl 10undecenoate. Related to the relatively low kinetic selectivity of int2, the final computationallyestimated ratio of 10/11 is approximately 21:79, close to the experimental selectivity of 24% (24:76). On the other hand, the good selectivities of catalysts 4 and 5 stem mostly from the lower Gibbs free energy of int12 which leads to int7. The selectivity in the discussed CM reaction is calculated based on ethyl 10-undecenoate (8). From this perspective int7 offers a full selectivity towards main product even though formation of int9 and generation of dimethyl fumarate is almost equally likely as formation of **int8**.<sup>[13]</sup> Selective formation of **int6** for catalyst **5** and **4** translates to 91:9 and 77:23 selectivities towards the main product, respectively. The theoretical value for 4 is in perfect agreement with the experimental one, while for 5 it is noticeably higher that that observed experimentally (64:36).

We hypothesized that the gap between the experimental and computational results for **5** can be explained by the reuptake of 2-isopropoxy-4-nitro styrene (the so-called boomerang effect) by int4 to form int10.<sup>[14]</sup> Such event would reduce selectivity of complex **5**, and possibly also **4**, since the non-selective intermediate int2 would be formed. On the other hand for complex **6** intermediate int2 is excessively produced from int4 and thus boomerang effect is of lower importance in this case. To test this hypothesis we performed additional calculations on the thermodynamics of reuptake of 2-isopropoxy-4-nitro styrene by int4. Our calculations showed that in the case of complex **6** the boomerang effect is actually favored over propagation of the catalytic cycle by

almost 2 kcal·mol<sup>-1</sup>, resulting in an unchanged final selectivity of this catalyst of 21:79 (10:11) and in good agreement with the 24:76 experimental ratio. On the other hand, for complex **5** the association of the acrylate is favored to virtually the same extent as the boomerang effect reducing the previously mentioned selectivity of this catalyst from 91:9 to 86:14 (10:11), in qualitative agreement with experimental data (64:36). The further discrepancy can be attributed to the imperfect accuracy of the DFT methods, estimated at approximately 1 kcal/mol. Finally, the boomerang effect does not influence the ratio originally calculated for catalyst **4**. We can see that in this case the boomerang effect is predicted to have little impact on the final selectivity of examined catalysts. As a general rule, however, the importance of the boomerang effect may depend on the combination of catalysts/olefin used in the reaction and there may be certainly cases where it plays a vital role in the final ratio of obtained products. A more detailed explanation of the relationship between the structural parameters and differences in relative Gibbs free energies for **4-6** is provided in the ESI.

As mentioned above analogous calculations may be performed for ruthenacyclobutane intermediates to obtain selectivities for the studied catalysts. Based on the results presented in Schemes 1 and 2 we obtained the following values for **10:11** ratios: 6:94 for **4**, 1:99 for **5** and 89:11 for **6** (see ESI). These values are not in agreement with the experimental data suggesting, that the energetics of the ruthenacyclobutane intermediates does not play a crucial role in the final selectivities of the investigated catalysts.

It must be noted that olefin metathesis is a reversible process and the thermodynamic stability of the final products should also be taken into account. In contrast to our previous study with acrylonitrile our current calculations showed that product **10** of CM with methyl acrylate (**8**) is favored over dimeric side product **11** by only  $0.21 \text{ kcal} \cdot \text{mol}^{-1}$ . Considering the expected accuracy

of our approach of approximately 1 kcal·mol<sup>-1</sup> and lack of poisoning effect of methyl acrylate we can suggest that the kinetic selectivity is the only factor that determines the selectivity observed experimentally.<sup>[15]</sup>





In the final experiment, we attempted to extrapolate the superiority of the nitro-Grela complex (4) in cross metathesis with acrylates to the synthesis of antioxidant octyl methoxycinnamate (17), an active ingredient in sunscreen formulations with the trade name Octinoxate (Table 5). Anethol 15 could not be purified by our standard protocol probably due to the poor thermal stability. Moreover, aryl substituted internal C=C in 15 is much less reactive than terminal C=C in 8 making

the catalyst more exposed to impurities present in starting material. This was reflected in a relatively poor TON of 4 686 at 65% yield (Table 5, entry 2). Fogg et al. studies showed advantages of applying a phenol-functionalized polymer when phosphine ligands were present in the (pre)catalysts.<sup>[9c]</sup> The authors demonstrated that the beneficial effect of phenol groups arises from protonation of the enolate formed from the acrylate. Phosphine free nitro-Grela catalysts (4) bypasses this liability. On the other hand, chemists from Sasol demonstrated positive effect of phenols on efficiency of Grubbs 1st generation catalyst and negative effect on Grubbs 2nd generation catalysts.<sup>[16]</sup> In our hands, productive TON in CM between **15** and **16** was almost doubled in the presence of 1 000 ppm of butylated hydroxytoluene (BHT) (Table 5, entry 4). Further increase of BHT amount to 1 equivalent allowed full conversion of **15** and 86% yield with only 100 ppm of catalyst **4** (this result is comparable to the previously reported yields obtained with 1 000-5 000 ppm of complex **1**) (Table 5, entry 6).

In summary, DFT results suggest that the kinetic selectivity plays crucial role in CM of ethyl 10- undecenoate with methyl acrylate due to the lack of thermodynamic driving force towards CM product. Classic NHC-bearing ruthenium benzylidene catalysts are much more selective, and therefore effective in this transformation than the emerging CAAC-based catalysts. The best selectivity and overall reaction productivity were obtained with nitro-Grela catalyst (4) at 90 °C with turnover number of 49 967 for 50% yield (10 ppm of the catalyst) and 39 480 TON for 79% GC yield (20 ppm of the catalyst). Rather surprisingly, complex 4 outperformed its close, bulkier analogue 5 in terms of productive TON.

The nitro-Grela catalyst (4) catalyst was used to efficiently obtain octyl methoxycinnamate (17), an active ingredient in sunscreen formulations. The synthesis was accomplished with 86% GC

yield using only 100 ppm of **4** in the reaction between trans-anethole (**15**) with 2-ethylhexyl acrylate (**16**). Strong positive influence of a free radical scavenger (BHT) on TON in this transformation was revealed.

The challenge for the future studies is to develop a catalyst for CM with acrylates which would be more robust than standard NHC-ligated complexes (such as complex **4**) and kinetically equally or more selective towards CM product. This would allow industrially attractive, feasible processes, because efficient transformations of starting materials would be possible without their extensive purification.

#### **Experimental**

**General.** NMR spectra were acquired on Bruker spectrometer (NMR Avance III HD 500 MHz and Bruker AV II 600 MHz). High-resolution mass spectrometry was performed at the Mass Spectrometry Facility, Institute of Organic Chemistry, Polish Academy of Sciences. Gas Chromatography analyses were conducted using PerkinElmer Clarus 680 GC equipped with GL Sciences InertCap® 5MS/NP column. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization of TLC plates was performed by UV light (254 nm). The column chromatography was performed using silica gel 60 (230–400 mesh). Ethyl 10-undecenoate (Sigma-Aldrich  $\geq$  97%) was prepared according to a procedure described below. Methyl acrylate (Sigma-Aldrich 99%; contains  $\leq$ 100 ppm monomethyl ether hydroquinone as inhibitor) was treated with activated alumina overnight (2 wt%), purged with argon and stored over 4Å molecular sieves. Substrates **12**, **15** and **16** were distilled under reduced pressure and further purified by filtration through activated neutral alumina pad, degassed, purged with argon and stored over activated neutral alumina (2 wt%). All ruthenium catalysts were synthesized in house according to standard procedures. All reactions were carried out under Ar in pre-dried glassware using Schlenk techniques. All work-up and purification procedures were carried out with reagent grade solvents in air. Toluene was washed with citric acid (2.5 wt% in water) and water, filtered through activated neutral alumina, degassed by purging with argon and stored over activated 4Å molecular sieves. All other reagents were purchased from Sigma-Aldrich and used without further purification. Before GC analysis or distillation, metathesis reactions were quenched with 1,4-bis(3-isocyanopropyl)piperazine (commercial name SnatchCat, CAS: 51641-96-4).

Ethyl 10-undecenoate preparation (8). Ethyl 10-undecenoate was stirred overnight with activated alumina (0.5 wt%) and distilled under reduced pressure. Butylated hydroxytoluene (1000 ppm) was then added along with a portion of alumina (2.5 wt%) and the suspension was heated at  $200 \text{ }^{\circ}\text{C}$  for 30 min under argon. The ester was filtered through aluminum oxide pad (2.5 wt%) onto a portion of activated alumina (2.5 wt%), purged with argon and stored at 4  $^{\circ}\text{C}$ .

**Synthesis of (***E***)-12-ethyl 1-methyl dodec-2-enedioate, main isomer (10). Exemplary protocol for cross metathesis of ethyl undecanoate (8) with methyl acrylate (9) (Table 1, entry 1).** A solution of ethyl 10-undecenoate (8) (3.18 g, 15 mmol, 1 eq; contained 1000 ppm of butylated hydroxytoluene), methyl acrylate (9) (8.80 mL; 75 mmol; 5 eq), methyl stearate as an internal standard (ca. 50 mg) and toluene (7 mL, initial ethyl 10-undecenoate concentration 1 M) was equilibrated for 15 min at 70 °C under steady flow of argon through the reaction mixture. Nitro-Grela catalyst was added in 6 portions (50 uL each portion, 1 mM solution in toluene, total volume added 300 uL, 20 ppm) over 1h and the reaction mixture was stirred at 70 °C for additional 30 min (total reaction time 90 min). Two samples were analyzed by GC: at 10 ppm, 30 min and at 20 ppm,

90 min. The samples were quenched by addition of 1,4-bis(3-isocyanopropyl)piperazine (SnatchCat) prior to GC analysis.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.95 (dt, J = 15.7; 7.0 Hz, 1H), 5.83-5.77 (dt, J = 15.6; 1.6 Hz, 1H) 5.80 (dt, J = 15.6; 1.6 Hz, 1H), 4.10 (q, J = 7,2 Hz, 2H), 3.71 (s, 3H), 2,26 (t, J = 7.5 Hz, 2H), 2,17 (qd, J = 7.1; 1,6 Hz, 2H), 1.64-1.54 (m, 2H), 1.47-1.38 (m, 2H), 1.33-1.25 (m, 8H), 1,23 (t, J = 7,1 Hz, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.8, 167.1, 149.7, 120.8, 60.1, 51.3, 34.3, 32.1, 29.1, 29.1, 29.0,
29.0, 27.9, 24.9, 14.1.

HRMS-ESI calculated for C15H26O4Na [M+Na]<sup>+</sup> 293.1729; found 293.1723

Elemental Analysis calcd for C15H26O4: C, 66.64; H, 9.69; found: C, 66.57; H, 9.84

# (E)-1,1-diethyl-4-methyl but-3-ene-1,1,4-tricarboxylate, main isomer.

A solution of diethyl 2-allylmalonate (20.00 g, 100 mmol), methyl acrylate (**9**) (72.4 mL; 800 mmol; 8 eq) and toluene (142 mL) was equilibrated for 30 min at 70 °C under steady flow of argon through the reaction mixture. Nitro-Grela catalyst was added in 6 portions (6 mL, 0.05 M, 0.30 mmol, 0.3 mol%) over 1h and the reaction mixture was stirred at 70 °C for additional 30 min (total reaction time 90 min). The reaction mixture was cooled to rt, 1,4-bis(3-isocyanopropyl)piperazine (13.5 mL, 0.1 M, 1.4 mmol, 4.4 eq relative to the catalyst) was added and the mixture was stirred for additional 30 min. The product (18.32 g, 71% yield, colorless oil) was isolated by vacuum distillation (135-150 °C, 1 mbar).

<sup>1</sup>H NMR (601 MHz, CDCl<sub>3</sub>)  $\delta$  6.90 (dt, J = 15.6, 7.1 Hz, 1H), 5.91 (dt, J = 15.7, 1.6 Hz, 1H), 4.27 – 4.14 (m, 4H), 3.72 (s, 3H), 3.48 (t, J = 7.4 Hz, 1H), 2.79 (td, J = 7.3, 1.6 Hz, 2H), 1.27 (t, J = 7.1 Hz, 6H).

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 168.41, 166.52, 144.23, 123.52, 61.75, 51.66, 50.76, 31.23, 14.15.

#### (E)-4,4-diethyl 1-methyl hepta-1,6-diene-1,4,4-tricarboxylate (12), main isomer

A mixture of 1,1-diethyl-4-methyl but-3-ene-1,1,4-tricarboxylate (17.05 g, 66 mmol), allyl bromide (14.3 mL, 165 mmol, 2.5 equiv) and K<sub>2</sub>CO<sub>3</sub> (13.68 g, 99.0 mmol, 1.5 equiv) in acetonitrile (132 mL) was refluxed for 36 h. The reaction mixture was cooled to rt and filtered off. The filtrate was concentrated in vacuum, filtered through a silica pad and the product (12.80 g, 65% yield, yellow oil) was isolated by vacuum distillation (145  $^{\circ}$ C, 1 mbar).

<sup>1</sup>H NMR (601 MHz, CDC1<sub>3</sub>)  $\delta$  6.80 (dt, *J* = 15.5, 7.7 Hz, 1H), 5.87 (dt, *J* = 15.4, 1.4 Hz, 1H), 5.69 – 5.57 (m, 1H), 5.16 – 5.07 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 4H), 3.71 (s, 3H), 2.76 (dd, *J* = 7.7, 1.5 Hz, 2H), 2.64 (dt, *J* = 7.4, 1.2 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 6H).

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 170.32, 166.41, 143.03, 131.93, 124.83, 119.87, 61.73, 51.68,
37.37, 35.39, 14.23.

# Diethyl cyclopent-3-ene-1,1-dicarboxylate (13)

To a solution of 4,4-diethyl 1-methyl hepta-1,6-diene-1,4,4-tricarboxylate (**12**) (0.15 g, 0.5 mmol) in toluene (2 mL) at 70 or 90 °C under argon atmosphere nitro-Grela catalyst (total of 200 ppm, 100 uL, 1 mM in toluene) was added in two portions. The mixture was stirred for 1h. Samples

were taken at 30 min and 60 min reaction times and quenched with 1,4-bis(3-isocyanopropyl)piperazine (a drop of 0.1 M solution) prior to GC analysis.

(*E*)-2-ethylhexyl 3-(4-methoxyphenyl)acrylate (17). A solution of 1-methoxy-4-(prop-1-en-1yl)benzene (15) (0.30 g, 2 mmol, 1 eq), butylated hydroxytoluene (40 uL, 50 mM toluene solution, 0.001 eq), 2-ethylhexyl acrylate (16) (2.21 g; 12 mmol; 6 eq), methyl stearate as an internal standard (ca. 10 mg) and toluene (10 mL, final concentration 0.2 M) was equilibrated for 15 min at 70 °C under steady flow of argon through the reaction mixture. Nitro-Grela catalyst was added in 6 portions (50 uL each portion, 0.65 mM solution in toluene, total volume added 0.30 mL, 100 ppm) over 1h and the reaction mixture was stirred at 70 °C for additional 30 min (total reaction time 90 min). Two samples were analyzed by GC: at 50 ppm, 30 min and at 100 ppm, 90 min. The samples were quenched by addition of 1,4-bis(3-isocyanopropyl)piperazine (SnatchCat) prior to GC analysis.

<sup>1</sup>H NMR (601 MHz, CDCl<sub>3</sub>) δ 7.63 (d, *J* = 15.9 Hz, 1H), 7.51 – 7.44 (m, 2H), 6.94 – 6.86 (m, 2H), 6.32 (d, *J* = 15.9 Hz, 1H), 4.15 – 4.07 (m, 2H), 3.83 (s, 3H), 1.68 – 1.59 (m, 1H), 1.47 – 1.37 (m, 2H), 1.36 – 1.27 (s, 6H), 0.95 – 0.89 (m, 6H).

## **AUTHOR INFORMATION**

## **Corresponding Author**

\*E-mail for K. S.: <u>krzysztof.skowerski@apeiron-synthesis.com</u>

\*E-mail for T. K. O .: tomasz.olszewski@pwr.edu.pl

#### **Author Contributions**

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

**Supporting Information**. Synthetic procedures; NMR spectra, DFT calculation details; this information is available free of charge in the form of Electronic Supplementary Material (ESI).

KEYWORDS: carbenes, cross metathesis, cyclic alkyl amino carbene, metathesis, ruthenium.

#### REFERENCES

- [1] For recent reviews see: a) B. M. Stadler, C. Wulf, T. Werner, S. Tin, J. G. de Vries, ACS Catalysis 2019, 9, 8012-8067; b) M. Wang, J. Ma, H. Liu, N. Luo, Z. Zhao, F. Wang, ACS Catalysis 2018, 8, 2129-2165; c) A. Llevot, M. A. R. Meier, GreenChem., 2016, 18, 4800-4803; d) A. Behr, A. J. Vorholt, K. A. Ostrowski, T. Seidensticker, Green Chemistry 2014, 16, 982-1006; e) U. Biermann, U. Bornscheuer, M. A. R. Meier, J. O. Metzger, H. J. Schafer, Angew. Chem., Int. Ed. 2011, 50, 3854–3871; f) U. Biermann, W. Friedt, S. Lang, W. Lühs, G. Machmüller, J. O. Metzger, M. R. Klaas, H. J. Schäfer, M. P. Schneider, Angew. Chem. Int. Ed. 2000, 39, 2206-2224.
- [2] For example, 10-undecenoic acid and its derivatives obtained from castor oil represent a readily available renewable feedstock, which has been successfully utilized for production of polyamide (PA11) in Rilsan® process.
- [3] For recent comprehensive reviews and articles, see: a) A. C. Flick, C.A. Leverett, H. X. Ding, E. McInturff, S. J. Fink, C. I. Helal, C. I. O'Donnell, *J. Med. Chem.* 2019, 62, 7340–7382; b) G. Turczel, E. Kovaćs, G. Merza, P. Coish, P. T. Anastas, R. Tuba, *ACS*

Sustainable Chem. Eng. 2019, 7, 33–48; c) M. Yu, S. Lou, F. Gonzalez-Bobes, Org.
Process Res. Dev. 2018, 22, 918–946; d) C. S. Higman, J. A. M. Lummiss, D. E. Fogg,
Angew. Chem., Int. Ed. 2016, 55, 3552–3565; e) D. Hughes, P. Wheeler, D. Ene, Org.
Process Res. Dev. 2017, 21, 1938–1962; f) V. Farina, A. Horváth, Ring-Closing Metathesis
in the Large-Scale Synthesis of Pharmaceuticals. In Handbook of Metathesis, Vol. 2;
Grubbs, R. H.; Wenzel, A. G., Eds.; Wiley–VCH: Weinheim, Germany, 2015; pp 633–658; g) T. K. Olszewski, M. Bieniek, K. Skowerski, K. Grela, Synlett 2013, 24, 903–919;
h) T. K. Olszewski, M. Figlus, M. Bieniek, Chim. Oggi 2014, 32, 22–29; i) A. Nickel, T.
Ung, G. Mkrtumyan, J. Uy, C. W. Lee, D. Stoianova, J. Papazian, W.-H. Wei, A. Mallari,
Y. Schrodi, R. L. Pederson, Topics in Catalysis 2012, 25, 518-523.

- [4] a) 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; For recent example see: b) Pascal
  S. Engl, Alexey Tsygankov, Jordan De Jesus Silva, Jean-Paul Lange, Christophe Copéret,
  Antonio Togni, Alexey Fedorov, *Helvetica Chimica Acta* 2020, *103*, e2000035.
- [5] M. D. Schulz, R. R. Ford, K. B. Wagener, Polym. Chem. 2013, 4, 3656-3658.
- [6] a) P. Vignon, T. Vancompernolle, J. L. Couturier, J. L. Dubois, A. Mortreux, R. M. Gauvin, *ChemSusChem* 2015, 8, 1143–1146; b) M. Winkler, M. A. R. Meier, *Green Chem.* 2014, 16, 3335–3340; c) S. Chikkali, S. Mecking, *Angew. Chem., Int. Ed.* 2012, *51*, 5802–5808; d) X. Miao, C. Fischmeister, P.H. Dixneuf, C. Bruneau, J. L. Dubois, J. L. Couturier, *Green Chem.* 2012, *14*, 2179–2183; e) A. Rybak, M. A. R. Meier, *GreenChem.* 2007, *9*, 1356-1361.

- a) Y. Peng, F. Totsingan, M. A. R. Meier, M. Steinmann, F. Wurm, A. Koh, R. A. Gross, [7] Eur. J. Lipid. Technol. 2015, 117, 217-228; b) Y. Peng, J. Decatur, M. A. R. Meier, R. A. Gross, Macromolecules 2013, 46, 3293-3300; c) C. S. Higman, M. P. de Araujo, D. E. Fogg, Catal. Sci. Technol., 2016, 6, 2077-2084; d) M. Domínguez, R. Pequerul, R. Alvarez, J. Giménez-Dejoz, E. Birtac, S. Porté, R. Rühl, X. Parés, J. Farrés, A. R.de Lera, Tetrahedron, 2018, 74, 2567-2574; e) K. Vaithegi, K. R. Prasad, Tetrahedron, 2018, 74, 2627-2633; f) C. W. Plummer, C. S. Wei, C. E. Yozwiak, A. Soheili, S. O. Smithback, J. L. Leighton, J. Am. Chem. Soc. 2014, 136, 9878–9881; g) S. Chatterjee, S. Ghadigaonkar, P. Sur, A. Sharma, S. Chattopadhyay, Eur. J. Org. Chem. 2014, 79, 8067–8076; h) Q. Xiao, J. J. Jackson, A. Basak, J. M. Bowler, B. G. Miller, A. Zakarian, Nat. Chem. 2013, 5, 410-416; i) J. Willwacher, A. Furstner, Angew. Chem. Int. Ed. 2014, 53, 4217-4221; j) H. Fuwa, A. Saito, M. Sasaki, Angew. Chem., Int. Ed. 2010, 49, 3041–3044; k) L. Brewitz, J. Llaveria, A. Yada, A. Furstner, A. Chem. Eur. J. 2013, 19, 4532–4537; k) H. Bilel, N. Hamdi, F. Zagrouba, C. Fischmeister, C. Bruneau, Green Chem. 2011, 13, 1448–1452; 1) M. Xiangtao, J. B. Matson, K. J. Edgar, *Polym.Chem.*, **2014**, *5*, 7021-7033.
- [8] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, J. Am. Chem. Soc. 2003, 125, 11360-11370.
- [9] a) G. A. Bailey, D. E. Fogg, J. Am. Chem. Soc. 2015, 137, 7318-7321; b) W. L. McClennan,
  S. A. Rufh, J. A. M. Lummiss, D. E. Fogg, J. Am. Chem. Soc. 2016, 138, 14668-14677;
  For articles on phosphine scavenging see: c) A. G. Santos, G. A. Bailey, E. N. dos Santos,
  D. E. Fogg., ACS Catalysis, 2017, 7, 3181-3189; d) K. Voigtritter, S. Ghorai, B. H.
  Lipshutz, J. Org. Chem., 2011, 76, 4697–4702.

- [10] For advantages of using Hoveyda-Grubbs type complexes over Grubbs catalyst in CM with acrylates, see: a) K. Lafaye, L. Nicolas, A. Guérinot, S. Reymond, J. Cossy, Org. Lett. 2014, 16, 4972–4975; b) G. B. Djigoué, M. A. R. Meier, Appl. Catal., A 2009, 368, 158–162; c) D. Schweitzer, K. D. Snell, Org. Process Res. Dev. 2015, 19, 715–720.
- [11] M. Abbas, C. Slugovc, Tetrahedron Lett., 2011, 52, 2560-2562.
- [12] R. Gawin, A. Tracz, M. Chwalba, A. Kozakiewicz, B. Trzaskowski, K. Skowerski, ACS Catal., 2017, 7, 5443-5449.
- [13] It is worth noting, however, that the product of the acrylate coupling is thermodynamically less stable than the main product of the cross-coupling by approximately 2 kcal·mol<sup>-1</sup>, rendering its formation unfavorable with respect to the main product.
- [14] J. M. Bates, J. A. M. Lummiss, G. A. Bailey, D. E. Fogg ACS Catal. 2014, 4, 2387–2394.
- [15] For more discussion on possible origins of different selectivity of catalysts 5 and 6 see ESI.
- [16] G. S. Forman, R. P. Tooze, Olefinic metathesis in the presence of phenolic compounds. WO 2004/056728 A1, 20.12.2002.

# **Table of Contents**



We report on systematic evaluation of ruthenium-based catalysts bearing NHC carbene or cyclic CAAC ligands in CM with methyl acrylate. Dramatic influence of the carbene type on the reaction's efficiency and selectivity has been found. DFT calculations suggest that the kinetic selectivity is the main factor differentiating NHC- and CAAC-based ruthenium complexes. TON of 49 900 at 10 ppm loading of nitro-substituted Hoveyda-Grubbs complex was obtained in the studied reaction, representing the highest efficiency reported to date for this transformation.