Towards Sustainable Catalysis – Highly Efficient Olefin Metathesis in Protic Media Using Phase Labelled Cyclic Alkyl Amino Carbene (CAAC) Ruthenium Catalysts

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New generations of Hoveyda and bis-carbene type of ruthenium-based olefin metathesis catalysts (10 and 12), containing cationic cyclic alkyl amino carbene (CAAC) ligands, have been synthesized. The catalysts show exceptional stability and activity in environmentally benign, protic media. Various olefin metatheses reactions of OH functionalized feedstock (e.g. RCM, ROMP CM) can be carried out at as low as 0.05 mol% catalyst loading in methanol, isopropanol, water or methanol/water solvent mixture, accomplishing the lowest applied catalyst loading reported so far in these media. The facile olefin metathesis of renewable feedstocks including phospholipids (23) and vegetable oils (20) in protic media has also been demonstrated.

Nowadays catalysis is indispensable in the chemical industry both for economic and environmental reasons. It is estimated that 90% of commercially-produced chemicals are synthesized via catalytic processes.[15] The aspects of sustainability and green chemistry, i.e. the use of highly active catalyst systems at low catalyst loadings under mild reaction conditions in environ-

mental benign media, became also essential. Olefin metathesis is one of the fundamental catalytic reactions that initiated new industrial technology avenues.[2,3] The most frequently used olefin metathesis catalysts utilize Re, W, Mo and Ru compounds with the latter being the most preferable metal in homogeneous systems showing exceptional activity in chlorinated solvents and toluene (Scheme 1).[5–9] Ample effort has already been made to extend the Ru-based catalyst for applications in environmentally benign, protic,[10,11] or aprotic solvents[12,13] by introducing appropriate phase tags to the parent complexes.[14] Yet, the presently known arsenal of such Ru olefin metathesis catalysts, including numerous quaternary amino derivatives,[10–11,14–20] is far from industrial practicability as too high, 2–5 mol% catalyst loadings are required to achieve reasonable substrate conversions.[16] A possible reason for this is that typically not the most advanced and stable ligands and/or the wrong, leaving arylidene groups (or analogs)[16–18] were tagged for the purpose. It has recently been reported that Ru cyclic alkyl amino carbenes (CAAC), complexes exhibit superior olefin metathesis catalytic activity up to 315000 TON (Scheme 1).[21–25]

We have envisioned that by the introduction of a highly polar functional group to the N-aryl groups of CAAC ligands like those of complexes 1 and 2 could provide analogs, which are soluble in environmentally benign protic media meanwhile retaining their high catalytic activity and stability.

In general, two main approaches are applied in the synthesis of aqueous catalyst systems[26–28] (1) grafting the catalyst to water soluble polymers[29–31] and (2) synthesis of catalysts containing highly polar, small tags such as cationic quaternary ammonium salts[32,33] or anionic sulfonyl groups.[34,35]
In order to achieve reasonable solubility in protic solvents and water, the introduction of \( p \)-trimethylammonium groups to the N-aryl groups of Ru-CAAC has been targeted.\textsuperscript{[21–23,34]} The ligand precursor containing the \( p \)-dimethylaminoaryl moiety was synthetized via a five-step route in 19% overall yield (Scheme 2). The key step of the reaction is the synthesis of compound 5 via the nitration of 3\textsuperscript{[35]} followed by Bechamp reduction.\textsuperscript{[36]} Ligand precursor 8 was obtained then analogous to the literature procedure.\textsuperscript{[23]} The new CAAC ligands were \textit{in situ} generated by adding LiHMDS in THF solution, which were subsequently reacted either with 1\textsuperscript{st} generation Hoveyda-Grubbs (HG1) or Grubbs catalysts (G1) (Scheme 3). Complexes 9 and 11 were isolated in good yields (70% and 60%, respectively). The reaction of complexes 9 and 11 with methyl triflate (MeOTf) in cold dichloromethane gave the target complexes 10 and 12 in reasonable yields (70% and 48%). The dissociation of the carbene ligands of 9 and 11 is negligible at -30°C, which was confirmed by NMR spectroscopy.

Interestingly, the stereochemistry of the Ru-complexes by using this family of CAAC ligands (Scheme 1) and its consequences have not been treated in depth so far.\textsuperscript{[37]} As shown in Scheme 2, a chiral carbon atom (\( \text{star} \)) is brought in by using a racemic aldehyde in the synthesis step of compound 6, which will remain in the formed carbene ligand and its complexes. Consequently, the use of HG1 as precursor renders two enantiomers of 9 and 10. However, solution NMR shows two different sets of broad signals for 9 and a single broad signal for 10 at room temperature (RT) indicating exchange processes. Slowing down the exchanges by cooling to the appropriate temperature,\textsuperscript{[38]} thorough analysis of various 2D NMR spectra indicate that two species participate in both exchanges and the exchanging Ph, N-aryl groups and benzylidene protons have very different environments. Accordingly, the observed species can firmly be assigned to the two rotamers of the enantiomer pair, marked green, \( b=\text{PrO group backward} \) and blue, \( f=\text{PrO group forward} \) in Scheme 3. The ratio of the exchanging isomers is 60 to 40 and 93 to 7 in the solutions of 9 and 10, respectively, which reflects their \( \Delta \text{G} \). In solutions of 10, the major species seems analogous to that of 9, both apparently representing the \textit{green} rotamer.

As compounds with two asymmetry centers in general, complexes containing two chiral ligands with one asymmetry center each render two different pairs of enantiomers (two diastereomers). A prochiral stereogenic element is also present in G1 (the precursor to 11 and 12) complex due to the two different positions of the aryl groups at the benzylidene double bond.\textsuperscript{[39]} The latter is only relevant when the G1 analogs contain chiral ligands, which is the case for 11 and 12. The created

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\[ \text{Scheme 2. Synthesis of tagged CAAC ligand precursor, 8.} \]

\[ \text{Scheme 3. Synthesis and the stereoisomers of 9–11 Ru-CAAC complexes.} \]

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stereogenic phenyl groups of the benzylidene double the number of diastereomers in the complex from 2 to 4. Thus, complexes with the Ph-groups positioned left (l) or right (r) will be different from the plane of Cl–Ru–Cl bonds with the double bounds in the rear (Scheme 3). Compiling the conformers with their mirror images (marked in different colors) reveals the 4 enantiomer pairs, in the favorable trans-constellation of bulky N-aryl groups. However, in the bis-CAAC complexes both carbones could rotate, retaining the chirality, but providing three different constellations instead of two shown for 9 and 10. Thus, the number of rotamers could theoretically be tripled from 8 to 24 in 11 and 12 by eventual hindered rotations. Guiding principles in the determination of the most abundant species are the steric demands by space-filling and stabilizations by both the C(H)2–H–π interactions and the parallel displaced π-stacking of aromatic rings.[40] Unlike 12, complex 11 shows very little fluxionality at RT by solution NMR spectroscopy. Curiously, NMR spectra of 11 indicate only the presence of the four diastereomers of the trans-rotamer (Scheme 3), which emphasizes the importance of above mentioned π-interactions in the determination of favorable rotamers. The major species of 11 represents 64% of the content. The cationic 12 show exchanges of only three species at RT, including also one dominant (82%) species, which seems to be the product of the major species of 11.

Despite the presence of the isomers, which are especially characteristic at the benzylidene carbons around 295 ppm and protons between 16–19 ppm, diffusion-ordered spectroscopy (DOSY) shows a single peak for each new complex at RT. Also, other regions in the 1H, 1H–1H correlation and HSQC spectra, furthermore HRMS studies clearly indicate the presence of isomers with the same molecular weight (See Supporting Information).

X-ray study of complex 9 shows that it crystallizes in the monoclinic P21/n space group (#14) (Z’ = 1). The arrangement of the CAAC ligand and the o-isoproxyphenylmethylene organic ligands is presented in Figure 1 (top), representing the green R-b enantiomer in Scheme 3. However, the centrosymmetric crystal is racemic containing both enantiomers.

Compound 11 crystallizes in the monoclinic P21/c space group (#14) (Z’ = 1). The arrangement of the CAAC ligands and the benzylidene group around the Ru center is shown in Figure 1 (bottom). The absolute configurations of the two carbones are different within a complex molecule and the centrosymmetric crystal contains both S,R and R,S configurations in the centrosymmetric crystal. Both the presence of strong π–π and C(H)2–H–π interligand interactions as stabilizing forces are evident in the molecule. The X-ray structure of 11 shown in Figure 1 (bottom) represents the diastereomer, which was marked red in Scheme 3. (See Supporting Information).

Repeated kinetic investigations of the ring-closing metathesis (RCM) of diallyl malonate (13, Figure 2) indicate similar activities for 9 and 10, albeit with some initiation time using 10.

Scheme 4. Synthesis and the stereoisomers of 9–11 Ru-CAAC complexes.

Figure 1. Molecular structure and atom labelling of 9 (top) and 11 (bottom). Displacement parameters are drawn at 50% probability level. Hydrogen atoms are omitted for clarity.
Nevertheless, 90 % yield could be obtained with both 9 and 10 after 30 minutes. The HG2 showed slightly lower activity (80 % yield after 30 min). All of the new complexes show exceptional stability compared to older generation ruthenium-based metathesis catalysts. For example, complexes 9–12 could even be filtered and handled on air. Furthermore, no detectable degradation was observed by monitoring a solution of 12 in non-degassed acetone containing 20 equivalents of water at RT in the presence of an internal standard with kinetic 1H NMR for 10 hours. This together with the obtained catalytic robustness in MeOH below indicate that catalysts 10 and 12 are not particularly sensitive for degradation, neither by Ru–H nor by dimer formation.41

The catalytic activity of the complexes 10–12 in protic solvents including MeOH, MeOH/water mixture and isopropanol (IPA) or in neat (Scheme 4, Table 1) were further investigated (9 was not tested as it was insoluble in MeOH at RT). The RCM reaction of 13 with 0.05 mol % catalyst loading revealed 29 % yield at RT using catalyst 10. There was no reaction at RT using catalyst 12. However, raising the temperature to 65 °C, 64 % yield could be achieved. The isomerization of cis-butenediol (15) was carried out with catalyst 10 in methanol and isopropanol (IPA) solutions. When IPA was used, significantly higher yield (56 % vs. 36 %) was observed (Table 1, Entry 3 and 4). The ring-opening metathesis polymerization (ROMP) of 17 in methanol solution gave the target biopolymer (18) in high yields and TONs. Polymer 18 could also be synthesized via acyclic diene metathesis polymerization (ADMET) of 19, albeit only with a high, 0.5 mol % catalyst loading (Table 1, Entry 11 and 12). The lower activity could be explained by the fast decomposition of highly sensitive Ru=CH2 intermediate. The cross-metathesis (CM) of methyl oleate (20) in methanol was found straightforward using catalyst 12 at 0.05 mol % loading level at 65 °C reaction temperature. Using the non-quaternized catalyst 11 in neat, 99 % yield was achieved.

Low value added algae phospholipids containing a wide range of unsaturated fatty acids with comparable chain length have incredible potential as green and sustainable materials and energy sources.46,47

The cross-metathesis of DOPC (23) as model compound with 0.5 mol % loading of catalyst 10 gave a reasonable yield (57 %) to the target compound (22) in methanol. Interestingly, catalyst 11 was inactive for the reaction. However, 12 was also very effective with 80 % yield, although at a high catalyst loading of 4.2 mol %. In summary, new ruthenium-CAAC olefin metathesis catalysts have been synthesized, which are soluble in protic solvents showing exceptional stability and catalytic activity. It has been demonstrated that catalytic reactions of OH functionalized feedstock (RCM, ROMP, CM and isomerization) can be carried out at as low as 0.05 mol % catalyst loading in methanol, isopropanol, water or methanol/water solvent mixture. It has also been shown that the cross-metathesis of renewable feedstocks, such as methyl linolate can be carried out in

![Figure 2. Reaction kinetic investigation of the formation of 14 using catalyst HG2 (blue), 9 (red) and 10 (green). ([13] = 0.12 M; [Cat] = 6 x 10⁻⁵ M; 30 °C, acetone-d₆).](image-url)

Table 1. Results of olefin metathesis reactions.

| Entry | Solv. | S | P | C | Mol [ % ] | T [ °C ] | t [ h ] | Y [ % ] | TON |
|-------|-------|---|---|---|-----------|---------|--------|--------|-----|
| 1     | M     | 13| 14| 10| 0.05      | RT      | 3      | 29     | 580 |
| 2     | M     | 13| 14| 12| 0.05      | 65      | 3      | 64     | 1280|
| 3     | M     | 15| 16| 10| 0.05      | RT      | 3      | 36     | 780 |
| 4     | IPA   | 15| 16| 10| 0.05      | RT      | 3      | 56     | 1140|
| 5     | M     | 15| 16| 12| 0.05      | 65      | 3      | 30     | -  |
| 6     | M     | 17| 18| 10| 0.05      | RT      | 3      | 65     | 1300|
| 7     | M     | 17| 18| 10| 0.05      | RT      | 24     | 79     | 1580|
| 8     | W     | 17| 18| 10| 0.05      | RT      | 24     | 32     | 640 |
| 9     | neat  | 17| 18| 11| 0.05      | 65      | 3      | 33     | 660 |
| 10    | W     | 17| 18| 10| < 0.50    | RT      | 24     | 99     | > 200|
| 11    | neat  | 17| 18| 12| 0.05      | 65      | 3      | 50     | 1000|
| 12    | M     | 19| 18| 10| 0.50      | RT      | 3      | 39     | 78  |
| 13    | M     | 19| 18| 12| 0.50      | 65      | 3      | 50     | 1000|
| 14    | M     | 20| 22| 10| 0.05      | RT      | 24     | NR     | NR  |
| 15    | neat  | 20| 22| 11| 0.05      | 65      | 3      | 99     | 1980|
| 16    | M     | 20| 22| 12| 0.05      | 65      | 3      | 41     | 820 |
| 17    | M     | 23| 22| 10| 0.50      | RT      | 24     | 57     | 114 |
| 18    | M     | 23| 22| 11| 4.2       | 65      | 3      | NR     | NR  |
| 19    | M     | 23| 22| 12| 4.2       | 65      | 3      | 80     | 19  |

[a] mass formed; [b] mixture of 17 and 18; Solvents: (M) methanol, (IPA) isopropyl alcohol, (W) water. (Y): reaction yield, NR: no reaction.
environmental benign protic media at low catalyst loading. Further research is underway to determine the exact structures in solutions and the thermodynamic parameters of the rotamers and/or diastereomers.

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