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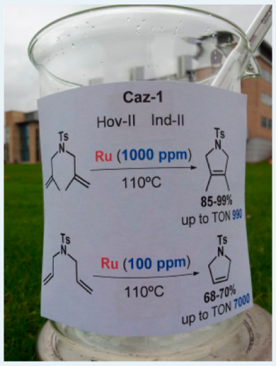
Conducting Olefin Metathesis Reactions in Air: Breaking the Paradigm

Stefano Guidone, Olivier Songis, Fady Nahra, and Catherine S. J. Cazin*

EaStCHEM School of Chemistry, University of St. Andrews, St. Andrews, KY16 9ST, United Kingdom

S Supporting Information

ABSTRACT: The first study of low catalyst loading olefin metathesis reactions in air is reported. TON values of up to 7000 were obtained using nondegassed solvents with commercially available precatalysts **Caz-1**, **Hov-II**, and **Ind-II**. The simple experimental conditions allow olefin metathesis reactions to be carried out on the benchtop using technical grade solvents in air.



KEYWORDS: *olefin metathesis, homogeneous catalysis, ruthenium, phosphite, air*

The olefin metathesis reaction represents a powerful tool for the formation of carbon−carbon bonds.[1] Development of precatalysts by modification of the original ruthenium complex reported by Grubbs and co-workers has led to more robust and active catalysts.[2] Even if ruthenium precatalysts display better tolerance toward water and oxygen than early transition metal complexes,[2b] inert atmosphere and anhydrous solvents are generally used to carry out such reactions.[2] In the past two decades, only a few studies have started to question the catalytic performance of Ru systems in the presence of air.[3] In 1991, Marciniec and Pietraszuck reported the catalytic activity of [RuCl$_2$(PPh$_3$)$_3$] in the self-metathesis of silicon-containing olefins in air with 1 mol % Ru at 150 °C. Long reaction times were necessary to obtain moderate to good yields of 1,2 bis(silyl)ethenes (E/Z [5:1]−[10:1]).[3a] Some 10 years later, Dowden and Hoveyda independently reported the use of modified Hoveyda−Grubbs-type precatalysts for ring-closing metathesis (RCM) reactions affording disubstituted olefins in air with nondegassed CH_2Cl_2 and THF using 5 mol % Ru at 22−80 °C.[3b,c] Subsequently, Blechert and co-workers described the use of commercially available **G-II** and **Hov-II** (Figure 1) in nondegassed MeOH at 22 °C, affording disubstituted olefins in high yields with 3−5 mol % of Ru.[3d] To obtain systems suitable for use in protic solvents, the Raines group isolated salycilaldimine-based benzylidene ruthenium precatalysts active in the RCM of dienes and in enyne metathesis. The precatalysts showed moderate to high conversions in nondegassed methanol-d_4 as well as benzene-d_6 in air with 5−10 mol % Ru at 55 °C.[3e]

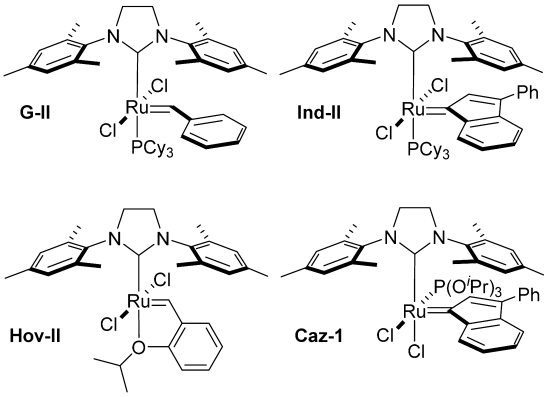


Figure 1. Commercially available ruthenium precatalysts studied in this work.

More recently, a Hoveyda-Grubbs type precatalyst immobilized on polyethylene glycol able to perform RCM in air was reported by Abell and co-workers. Di- and trisubstituted olefins were reacted with the use of nondegassed CH_2Cl_2 in air and 10 mol % Ru at reflux.[3f] Inspired by the Raines work with salycilaldimine derivatives,[3e] Verpoort and co-workers introduced a Schiff base in the phosphine-containing indenylidene ruthenium system. This system was shown active in ring-closing metathesis (RCM) and cross-metathesis (CM) of allyl benzene and *cis*-1,4-diacetoxy-2-butene in air with 1−2.5 mol % Ru at 40−80 °C.[3g] In 2010, Tew and co-workers described the ring-opening metathesis polymerization (ROMP) of a hydrophilic norbornene monomer, leading to the formation of hydrogels using the pyridine-based Grubbs precatalyst in air at room

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temperature. Despite the living polymerization nature of this specific transformation, the propagating catalyst attached to the polymer chains was found to be inactive after 1 h under these reaction conditions.[3h]

Recently, other modified Hoveyda−Grubbs type precatalysts have been reported independently by Jensen and Grela.[3i,j] Jensen and co-workers described the replacement of a chloride anion with a 2,4,6-triphenylbenzenethiolate ligand affording a highly *Z*-selective olefin metathesis catalyst. Despite the high activity under typical reaction conditions, no activity was observed when conducting the self-metathesis of 1-octene with 0.01 mol % Ru in air at 50 °C in neat substrate.[3i] In the search for ruthenium precatalysts suitable for olefin metathesis in water,[4] Grela and co-workers reported the activity of a ruthenium species containing quaternary ammonium chloride tags in nondegassed CH_2Cl_2 in air with 1 mol % Ru at reflux. The RCM of the easily reacting diethyl diallylmalonate led to high yields of the five-membered ring product, and the precatalyst could be recycled after extraction with D_2O to perform the isomerization of *cis*-2-butene-1,4-diol to the trans isomer (94% isolated yield).[3j]

In early 2014, Grela and co-workers investigated the catalytic efficiency of new mixed NHC/phosphine indenylidene precatalysts. In this report, a slightly more comprehensive study on the reactivity of ruthenium complexes in air was carried out. Moderately challenging transformations were performed using 1−5 mol % Ru.[3k] In contrast, Meier and co-workers were the first to disclose a highly efficient metathesis reaction performed in air and with low catalyst loading. Full conversion of the easily cyclized diethyl diallylmalonate was obtained with only 0.2 mol % of **Hov-II** (Figure 1).[5a] This is in marked contrast with a report from Grubbs and co-workers that concomitantly disclosed the very poor conversion (<10%) of the same substrate under similar conditions using even higher catalyst loadings and longer reaction times.[6]

More recently, reports by Skowerski and Olszewski showed that metathesis reactions could be achieved in nondegassed ACS grade green solvents (e.g., ethyl acetate, alcohols, dimethyl carbonate, cyclopentyl methyl ether and 2-MeTHF), with results comparable to those obtained with dichloromethane and toluene.[5b,c] The diverging conclusions drawn from these studies, as well as the robustness of **Caz-1**, incited us to study low catalyst loading metathesis reactions in air using the complexes shown in Figure 1.[7]

The RCM reaction profiles of the challenging substrate **1** using the commercially available precatalysts **Caz-1**, **G-II**,[8b] **Ind-II**, and **Hov-II** were first recorded in air and in nondegassed reagent-grade toluene.[8] Whereas at least 90% conversion of the challenging substrate **1** to product was observed with 0.1 mol % of **Caz-1** after 2 h at 80 °C under an atmosphere of nitrogen,[9a] only traces of product were obtained in air for all precatalysts tested at this temperature. Results seemed to be in agreement with the presumed instability of Ru species in air and in reagent-grade solvents. Surprisingly, increasing the reaction time led to the unexpected activation of the more thermally stable precatalysts **Caz-1** and **Hov-II**, allowing moderate conversions of the challenging substrate (31% and 15% after 6 h, respectively).[8] More strikingly, these catalysts were found to remain active after 20 h.[10] When the more thermally sensitive complex **G-II** and the indenylidene analogue **Ind-II** were employed, almost no conversion was observed under these conditions. The long induction period (~1 h) observed at 80 °C for **Caz-1** and **Hov-II** suggests an unexpected latent behavior displayed by Ru precatalysts under aerobic conditions. To reduce this induction period, the reactions were conducted at higher temperature (110 °C) (Figure 2). Gratifyingly, short induction periods and good to moderate conversions of the challenging substrate **1** were obtained for all thermally stable precatalysts under these conditions. As shown in Figure 2, with the phosphine-based complex **Ind-II**, more rapid catalyst activation was observed, leading to 22% conversion in less than 3 min (at 80 °C, only 4% conversion was recorded after 1 h).[8,10] When **Hov-II** was employed, an activation period of ~6 min was needed, leading to 38% conversion after 1 h (at 80 °C, an activation time of 1 h was required, with 28% conversion recorded after 27 h).[8,10] With the robust and highly active precatalyst **Caz-1**, a short activation time was also required (~3 min) leading to more than 60% conversion in less than 15 min.[8,10]

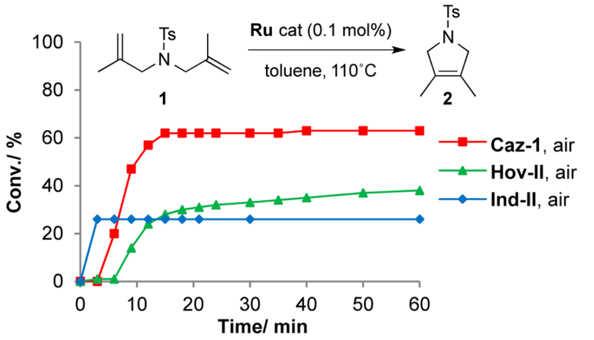


Figure 2. Comparison of commercially available Ru-based olefin metathesis active complexes in air at 110 °C (lines are visual aids and not curve fits). Reaction conditions: Ru cat (0.1 mol %), substrate **1** (0.25 mmol), reagent-grade toluene (1.5 mL), in air, 110 °C.

To gain more information about this latent behavior displayed in air, further studies taking into account the components of air separately were carried out (Figure 3).[11] Contrary to popular belief, oxygen was found to be relatively innocuous at this temperature because similar conversions of the challenging substrate **1** were observed while carrying out the reaction in parallel under nitrogen and under oxygen for all precatalysts.[12] Again, higher temperatures facilitate the activation of the precatalysts, especially in the case of **Caz-1**, for which the proposed isomerization from cis to trans configuration and the release of the active species lead to faster and more efficient reactions.[9a]

The presence of water was found to be very detrimental to the phosphorus-based precatalysts **Ind-II** and **Caz-1** because 8% and 15% conversion of the substrate were observed before catalyst degradation in the presence of water (3 and 20 min respectively, Figure 3a,b). **Hov-II** was found to be less sensitive to water, with a 36% conversion recorded after 1 h (Figure 3c). The deleterious effect of water is also reflected by the results obtained when conducting the reaction in air and in dry air. Indeed, although the latter did not affect the catalyst efficiency, reactions carried out in "wet" air led to a substantially lower catalyst activity. The relatively moderate activities observed in the presence of water suggest why high catalyst loadings are required when performing RCM reactions in water.[4] The influence of CO_2 on the reaction outcome was also investigated. For all catalysts, slightly lower catalyst efficiency was observed. Therefore, the effect (detrimental) on catalyst activity of the components of air decreases as follows: H_2O >

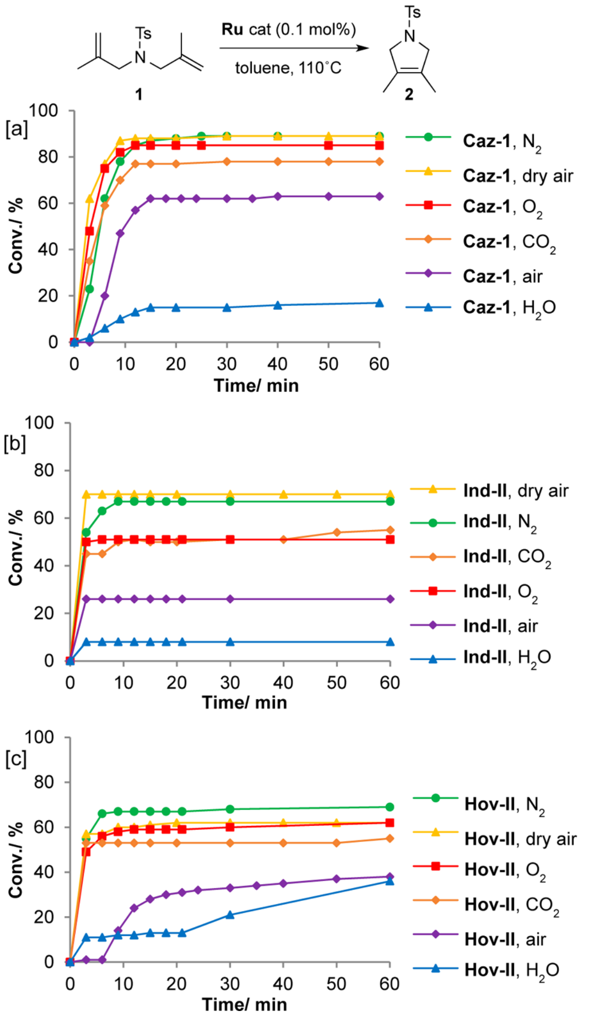


Figure 3. Reaction profiles of (a) **Caz-1**, (b) **Ind-II**, and (c) **Hov-II** under N_2, O_2, dry air, CO_2, and air and in the presence of H_2O at 110 °C (lines are visual aids and not curve fits). Reaction conditions: (in air) Ru cat (0.1 mol %), substrate **1** (0.25 mmol), reagent-grade toluene (1.5 mL), in air, 110 °C; (under O_2, CO_2, dry air) Ru cat (0.1 mol %), substrate **1** (0.25 mmol), toluene saturated with adequate gas (1.5 mL), under adequate gas, 80−110 °C; (in the presence of water) Ru cat (0.1 mol %), substrate **1** (0.25 mmol), anhydrous toluene (1.5 mL), 100 μL of freshly distilled and degassed water, under nitrogen, 110 °C.

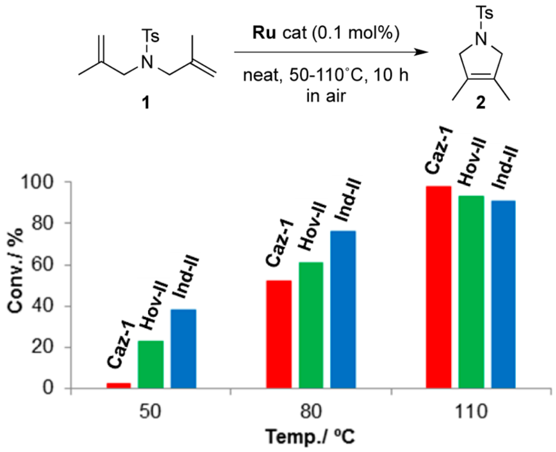


Figure 4. Catalytic properties of **Caz-1**, **Hov-II**, and **Ind-II** at different temperatures in solvent-free conditions in air.[14]

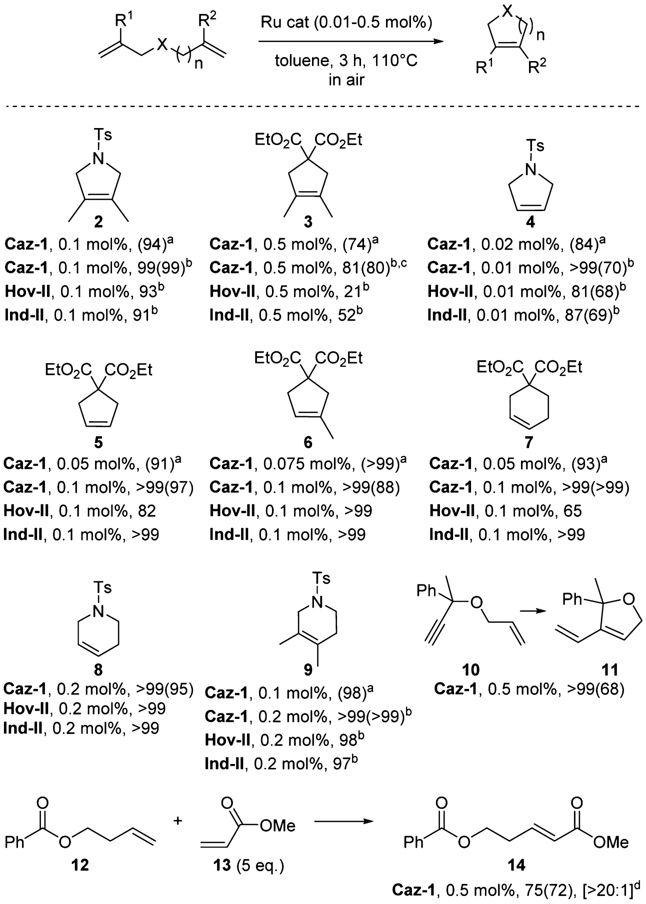
$CO_2 \geq O_2$. It is worth noting that the phosphite-based complex **Caz-1** led to the best catalyst efficiency.

As expected, although **Caz-1** was the most active at 110 °C, **Ind-II** and **Hov-II**, which are faster initiators, displayed better activity than **Caz-1** at lower temperatures (Figure 4). However, only moderate to good conversions were reached using these complexes, independently of the temperature, whereas complete conversion was reached with **Caz-1** (in air). This result is comparable to the-state-of-the-art reaction carried out under inert atmosphere (TON of 990 based on isolated yield).[9a,13]

Solvent-free conditions are preferable (when reagents are liquids) for efficient RCM in air (Figure 4) due to faster kinetics and lower water content. It should be noted that the water content relative to the substrate increases when the reaction is carried out with a nonanhydrous solvent.[14] Because toluene is a solvent of choice in RCM, we carried out studies using different sources of toluene to ascertain the effect of the latter on the catalytic system.[15] Satisfactorily, no significant difference was observed as a function of batch of reagent-grade toluene and provider. As expected, a slight increase in conversion was observed by drying the reagent-grade solvent over activated 4 Å molecular sieves or by using anhydrous degassed toluene (70% conversion of **1** using 0.1 mol % of **Caz-1** at 110 °C). This illustrates again the important effect of water on the reaction outcome.

The scope of the reaction was next examined in air with reagent-grade toluene or solvent-free conditions at 110 °C (Figure 5). As expected, complex **Caz-1** exhibited high activity in air for a wide range of substrates in ring-closing, enyne and cross-metathesis reactions. High to quantitative yields were obtained using catalyst loadings of only 0.01 to 0.5 mol %. These results are comparable or superior to what has previously been reported for **Caz-1** under inert atmosphere.[9a] More surprisingly, **Ind-II** and **Hov-II** precatalysts were able to perform the RCM of the substrates studied here under the same conditions, with yields ranging from moderate to excellent. All three catalysts performed well, except for the formation of the challenging compound **3**, for which **Caz-1** was largely superior. Of note is a TON of 7000 obtained in the RCM leading to **4**, which corresponds to a good yield using only 100 ppm of catalyst, an unprecedented high activity for RCM in air.

In conclusion, we have reported the first study of low catalyst loading olefin metathesis reactions in air using commercially available precatalysts and nondegassed reagent-grade solvents. Water rather than oxygen or carbon dioxide was found to be detrimental to the catalytic activity, suggesting the reason for high catalyst loading when reactions are carried out in aqueous media.[4] This phenomenon is still poorly understood and is currently under investigation in our group. Higher temperatures favor activation rather than degradation of the Ru species under the conditions investigated. Complete conversions of easily reacting substrates at low catalyst loading were achieved at reflux of reagent grade toluene. Challenging substrates were also converted in air with TONs comparable with the best reported in the literature under inert atmosphere and anhydrous conditions.[9a,13] Ruthenium metathesis catalysts are considered more tolerant toward water and oxygen than their Mo counterparts; nevertheless, a rapid review of the most recent studies reported in the field suggests that the community is not yet fully aware that a number of ruthenium complexes are



Reaction conditions: **Ru** cat (0.01-0.5 mol%), substrate (0.25 mmol), reagent-grade toluene (0.5 mL), 3 h, 110°C in air; average of 2 runs; conversions were determined by GC; isolated yield in parentheses; ^{a}Inert atmosphere (ref 9a); ^{b}solvent-free in air; ^{c}isolated as mixture, NMR yield; ^{d}E/Z ratio determined by ^{1}H NMR.

Figure 5. Scope of the reaction using **Caz-1**, **Hov-II**, and **Ind-II** in air at 110 °C.

air-stable tools for organic synthesis, or at least tools compatible with fully aerobic conditions. The poor activity reported for commercial Ru complexes in the course of experiments in aqueous media and the belief that low-catalyst loading reactions in air were problematic may have contributed to this way of thinking.[4,6] We hope that the present report exposes these earlier conclusions as dogma and will encourage the use of metathesis in more user-friendly conditions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00197.

Experimental details, NMR of products of catalysis, decomposition studies (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Fax: (+)44 (0) 1334 463808. E-mail: cc111@st-andrews.ac.uk.
Homepage: http://ch-www.st-andrews.ac.uk/staff/cc/group/.

Notes

The authors declare no competing financial interest.

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(7) Experiments using 0.2 mol % of **Hov-II** as described by Meier and co-worker (ref 5) were successfully reproduced in our laboratories (Supporting Information section 2.2 page S4). Experiments using 0.1 mol % of **Hov-II** as described by Grubbs and co-workers gave different results (78% conversion observed, to be compared with <10% published, ref 6)

(8) (a) See Supporting Information section 2.3 page S5. (b) Reactions with **G-II** were not carried out at 110°C because of the lack of activity/stability observed at 80°C..

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(10) See Supporting Information, section 2.4, page S6.

(11) See Supporting Information, section 2.5, page S6.

(12) See Supporting Information, section 4, page S24 for decomposition study of **Caz-1** under oxygen and section 5, page S30 for stoichiometric reaction of **Caz-1** with water.

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(14) Precatalysts added as stock solution with the solvent evaporating during the process. See Supporting Information, section 2.6, page S13.

(15) See Supporting Information, section 2.7, page S13 for Karl Fischer titration data and graphical representation of the catalytic activity of **Caz-1**.