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[18] Compound **14**: colorless syrup; $[\alpha]_D^{20} = -189.7$ ($c = 0.23$, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.03$ (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.20–2.50 (21H, m), 2.69 (1H, dd, $J = 18.4$, 7.8 Hz), 2.98 (1H, d, $J = 15.4$ Hz), 4.0 (1H, m), 5.10 (1H, dt, $J = 8.0$, 5.2 Hz), 5.88 (2H, m); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = -4.8$, -4.6, 14.0, 17.5, 18.0, 19.0, 22.5, 22.6, 25.5, 25.7, 31.6, 34.1, 34.9, 46.6, 54.8, 56.1, 72.2, 73.0, 79.3, 79.6, 130.4, 132.3, 172.4, 211.8; IR (neat): $\tilde{\nu} = 2955$, 2930, 2857, 1746, 1252, 1154, 1115, 964, 839, 778 cm^{-1}; MS (EI): m/z: 446 ([M^+], 1), 431 (1), 389 (33), 317 (18), 297 (8), 225 (5), 155 (5), 129 (10), 91(12), 75 (100), 55 (21); HRMS (C$_{26}$H$_{42}$O$_4$Si): m/z: 446.2850 (calcd: 446.2852); elemental analysis (%) calcd for C$_{26}$H$_{42}$O$_4$Si (446.71): C 69.91, H 9.48; found: C 70.08, H 9.42.

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[21] Compound **1**: colorless needles; mp 76.5–77.5 °C (Et$_2$O/pentane) [ref [10c] 73–76° (Et$_2$O/hexane)]; $[\alpha]_D^{20} = -185.0$ (0.15, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$): $\delta = 0.89$ (3H, t, $J = 6.8$ Hz), 1.20–2.18 (16H, m), 2.20 (1H, ddd, $J = 13.2$, 9.4, 3.3 Hz), 2.21 (1H, dd, $J = 18.9$, 9.3 Hz), 2.29 (1H, dt, $J = 13.2$, 8.8 Hz), 2.40 (1H, ddd, $J = 13.3$, 8.7, 3.2 Hz), 2.80 (1H, ddd, $J = 18.8$, 7.8, 1.2 Hz), 4.14 (1H, dt, $J = 7.9$, 9.2 Hz), 5.20 (1H, dt, $J = 8.5$, 6.0 Hz), 5.35 (1H, ddd, $J = 10.4$, 9.6, 5.5 Hz), 5.60 (1H, dt, $J = 10.5$, 5.9 Hz), 5.81 (1H, dd, $J = 15.9$, 8.7 Hz), 6.11 (1H, dd, $J = 15.8$, 6.6 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): $\delta = 14.0$, 22.5, 23.9, 25.3, 25.5, 25.6, 31.5, 34.0, 34.2, 45.5, 55.0, 57.9, 71.7, 71.8, 128.9, 129.3, 131.9, 134.7, 173.2, 213.1. IR (Kbr): $\tilde{\nu} = 3431$, 3002, 2938, 2857, 1726, 1377, 1243, 1160, 1041, 728 cm^{-1}. MS (EI): m/z: 334 ([M^+], 24), 316 (38), 298 (13), 262 (39), 208 (63), 163 (64), 151 (22), 145 (15),133 (25), 121 (28), 107 (42), 91 (78), 79 (100), 67 (83), 55 (93).

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IR-Thermographic Screening of Thermoneutral or Endothermic Transformations: The Ring-Closing Olefin Metathesis Reaction

Manfred T. Reetz,* Michael H. Becker, Monika Liebl, and Alois Fürstner

Whereas combinatorial chemistry in the area of pharmaceutical research has reached maturity,[1] the use of appropriate systems in catalysis still poses challenges.[2] Recently we reported the first cases of IR-thermographic detection and parallel screening of enantioselectivity in transition metal catalyzed and biocatalyzed organic transformations.[3] The test reactions chosen were all exothermic processes, enantioselectivity showing up as "hot spots" in the respective IR-thermographic images. IR-thermography had previously been used as a detection and/or screening system in achiral exothermic reactions mediated by heterogeneous catalysts.[4] Indeed, it was quietly assumed that only exothermic processes can be assayed by this method.[2, 4, 5] We now report that exothermicity is not a requirement in IR-thermographic screening of catalysts. Specifically, we demonstrate for the first time that in appropriate systems endothermic or even thermoneutral reactions can be successfully screened by time-

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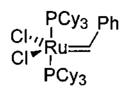
resolved detection of "cold spots" in IR-thermographic images.

We chose the well-known Ru-catalyzed ring-closing olefin metathesis (RCM)[6] as the reaction to be scrutinized IR-thermographically, not knowing at the outset whether this is actually an exo- or endothermic process. In an exploratory study using the same instrument and method as previously described,[3, 4a] the known reaction[6] of 1,7-octadiene (**5**) with formation of cyclohexene (**6**) and ethylene (**7**) was carried out at 32 °C on a 24-well microtiter plate employing the conventional Grubbs precatalysts **1** and **2** and the more recently developed complexes **3** and **4**.[7]



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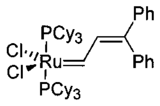

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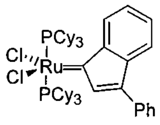

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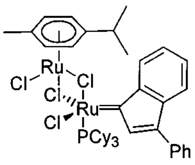

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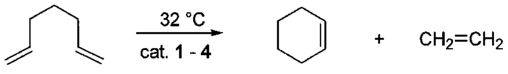


5 **6** **7**

Four wells of the microtiter plate were charged with a solution of **5** in toluene (wells 1–4), the fifth one (well C) containing octane in place of **5** as a control. Once the temperature was thermostatically set at 32 °C, 250 IR-thermographic pictures were taken within 5 s, the average of which is shown in Figure 1a.[8] The solutions in wells 1–4 were then treated with precatalysts **1**–**4**, respectively. Precatalyst **1** was also added to the control well C. After one minute, shaking was interrupted and the IR-thermographic pictures were taken (average of 250 recordings), resulting in the image shown in Figure 1b. Shaking was then resumed and the process repeated after one more minute (Figure 1c). Using the temperature/color key of the temperature window (bar on far right), several remarkable features immediately become apparent. Whereas the emissivities of wells C and 4 remain approximately constant, those of wells 1–3 clearly reveal "cold spots", implying heat uptake. This shows that the RCM of **5** leads to an endothermic effect on the microtiter plate, suggesting that the Grubbs precatalyst **1** as well as complexes **2** and **3** are considerably more active than precatalyst **4**. Close inspection of the emissivities of wells 1–3 in Figure 1c leads to the qualitative conclusion that precatalyst **2** is somewhat less active than **1** or **3**. These conjectures were tested by studying lab-scale reactions of diene **5** with precatalysts **1**–**4**. Indeed, complete correspondence was observed. Thus, it was found that under standard conditions the reactions catalyzed by **1**–**3** are essentially over within 1 min at 25 °C, whereas the reaction catalyzed by **4** requires 10 min for complete conversion under otherwise identical conditions.

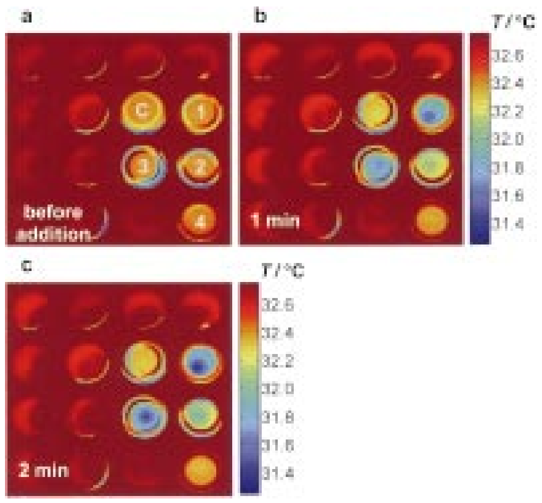
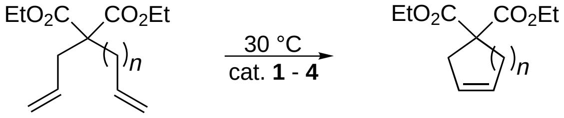


Figure 1. Time-resolved IR-thermographic imaging of the Ru-catalyzed RCM reaction of diene **5**.

Unfortunately, thermodynamic data for the reaction **5**→**6**+**7** are not available. However, application of the ASPIN program for calculating thermodynamic data predicts a heat of reaction (reaction enthalpy) of 4.8 kJ mol^{-1}, indicating that the reaction of interest should be slightly endothermic or nearly thermoneutral.[9] Thus the present data can be interpreted on the basis of slight endothermicity, differences in the IR-thermographic images being due to differences in catalyst activity. However, it is not clear how much of the liberated ethylene (**6**) actually evaporates from the solutions, a process that would also lead to "cold spots". It is likely that at least some of the effects seen in the IR-thermographic images are in fact due to the heat of vaporization of ethylene from the reaction mixture.[10] Indeed, upon gently blowing ethylene through a toluene-containing well on the microtiter plate comparable to the bubbling observed during an actual reaction, a "cold spot" immediately became visible. For the purpose of screening, the relative importance of the origins of the "cold spots" is not decisive. It is the sum of the two effects in the overall process which comprises the detection system.

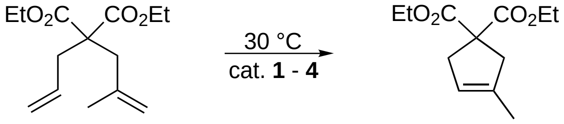
According to the mechanistic work of Grubbs et al. concerning RCM,[11] compounds **1** and **2** are precatalysts. Following initial [2+2] cycloaddition of the ruthenium–carbene complex with an olefinic function, the primary metallocyclobutane undergoes cycloreversion with formation of a new carbene complex which then adds intramolecularly to the second olefin function. The final step is cycloreversion with formation of the cyclic olefin (e.g., **6**), ethylene (**7**), and yet another carbene complex [L$_n$Ru=CH$_2$], which then mediates more than 95 % of the reaction.[11] It is therefore clear that "catalyst activity" as observed in the present IR-thermographic study or in conventional detection of lab-scale reactions reflects the ease of initiation of RCM by the carbene complexes **1**–**4**. Stated in different terms, it simply means that in the present study most or all of the precatalyst **1** or **3** has been consumed within the first two minutes, allowing the reaction of [$L_nRu{=}CH_2$] to proceed. In contrast, a considerable (or major) portion of the less reactive complexes **2** or **4** did not react at all under the same conditions.

We then proceeded to screen the reaction of other substrates **8a**–**8e** by employing the same set of precatalysts **1**–**4**. By using a modified setup,[12] the wells of a polypropylene microtiter plate were filled row by row with substrates **8a**–**8e** according to the arrangement shown in Figure 2a. After calibration the precatalysts were added simultaneously with an Eppendorf multipipette to the wells of one specific diene, starting with the least reactive substrate **8e** and ending with the most reactive substrate **8a**. All additions were completed within 90 s. Figure 2 summarizes the time-resolved IR-thermographic screening of these reactions.



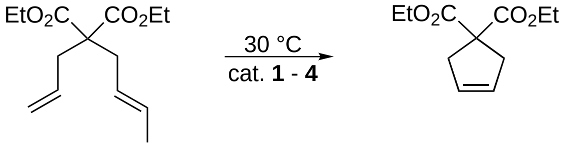
8a, *n* = 1
8b, *n* = 2
8c, *n* = 3

9a, *n* = 1
9b, *n* = 2
9c, *n* = 3



8d

9d



8e

9e

Again, several noteworthy features become visible. The substrates **8a** and **8b** are by far the most active ones yielding the five- and six-membered cyclic olefins **9a** and **9b**, respectively. As before, precatalysts **1**–**3** are considerably more active than **4**. Especially the reaction of precatalyst **1** with **8a** and **8b** is essentially complete within 2 min, which was also demonstrated in additional experiments of **1** and **3** with these substrates on a shorter time scale. Figure 2 also shows that the reaction of **8c** with precatalysts **1**–**4**, leading to the seven-membered product **9c** is considerably slower. The rate of RCM as indicated by heat uptake is lowest in the case of diene **8e** having an internal olefinic double bond. This corresponds to the results of lab-scale reactions. This also appears to be the case in the reaction of substrate **8d** which likewise contains a disubstituted olefinic function. However, since propylene rather than ethylene is liberated, direct comparison should not be made. In these experiments complex **4** seems to be the most active catalyst. However, caution must be exercised because the results suggested by the IR-thermographic images are in fact due to the delay associated with the row-wise addition of catalysts. In reality the major part of dienes **8d** and **8e** has been converted to the cyclic products **9d** and **9e** by the time the first thermographic image is taken, conversion then being in the phase of leveling off. Precatalyst **4** is actually considerably less active than complexes **1**–**3**, the system reaching maximum activity only after about 10 min (Figure 2d). At this time the reactions of substrates **8d** and **8e** catalyzed by **1**–**3** are almost over. When the order of catalyst addition to the wells on the microtiter plate was reversed starting with **8a** and ending with **8e**, heat uptake turned out to be more pronounced in reactions of substrates **8d** and **8e** catalyzed by complexes **1**–**3** (images not shown). The reactions of the more reactive substrates had proceeded to such an extent that no significant heat uptake was actually detectable at the time of recording. These observations show that two sets of experiments are necessary for correct conclusions (unless of course the precatalysts were to be added simultaneously to all wells with an appropriate multichannel pipette robot). Our conclusions concerning "catalyst activity" were fully corroborated by lab-scale kinetic studies of the reaction of diene **8e** catalyzed by complexes **1**–**4** (Figure 3). It is clear that precatalyst **4** is least active.

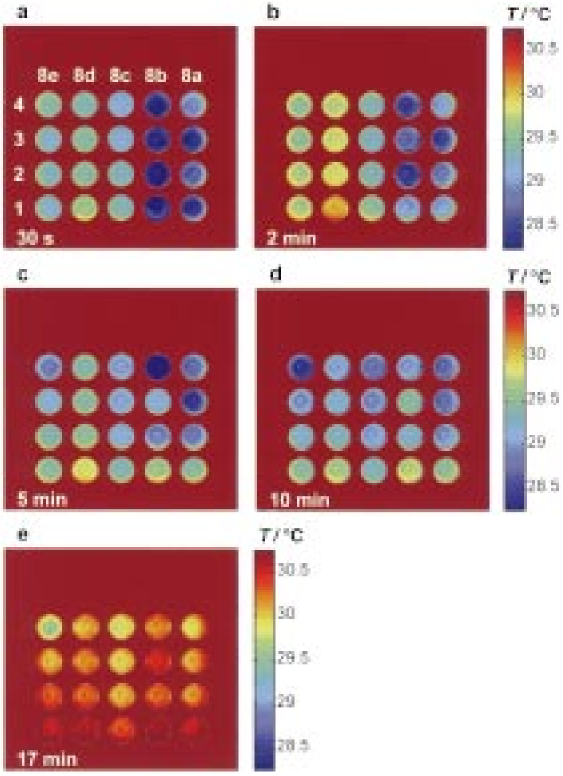


Figure 2. Time-resolved IR-thermographic imaging of the Ru-catalyzed RCM reaction of dienes **8a**–**8e** with precatalysts **1**–**4**.

We have devised an efficient screening system for catalytic reactions based on IR-thermography in which high catalyst activity is identified by heat uptake from the surroundings as monitored by the appearance of "cold spots". The heat of vaporization of one of the (gaseous) reaction products

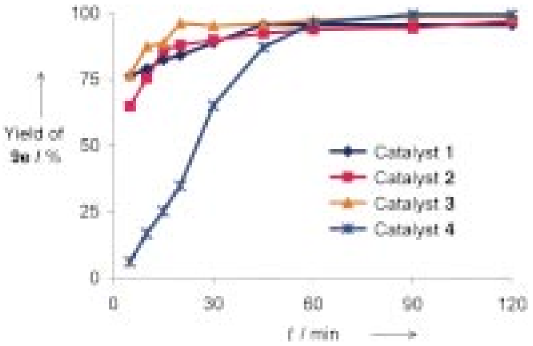


Figure 3. Kinetics of the RCM reaction of **8e** catalyzed by the Ru complexes **1**–**4**.

(ethylene or propylene) plays a pivotal role.[10] These findings add a new dimension to the evolving area of high-throughput catalyst or reagent screening based on IR-thermography.[2–4] Moreover, this study shows that IR-thermography constitutes a simple way to assess the relative rate of initiation of RCM events by different precatalysts as well as the inherent reactivity of variously substituted diene substrates towards the reaction. Therefore the method will greatly facilitate further investigations in this timely field of research.[6]

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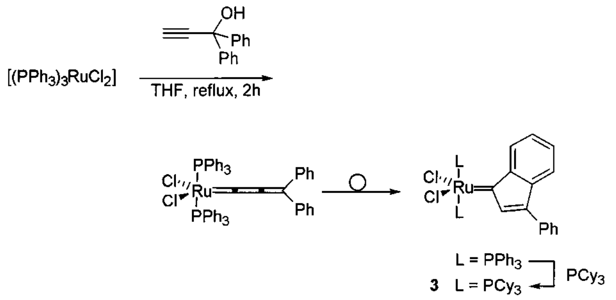
[7] a) A. Fürstner, A. F. Hill, M. Liebl, J. D. E. T. Wilton-Ely, *Chem. Commun.* **1999**, 601–602. b) Complex **3** is formed by reaction of $[(PPh_3)_3RuCl_2]$ and $HC{\equiv}CCPh_2OH$ followed by substitution of the PPh_3 ligands with PCy_3. Originally, it was believed that the complex thus formed was a ruthenium allenylidene species, cf. K. J. Harlow, A. F. Hill, J. D. E. T. Wilton-Ely, *J. Chem. Soc. Dalton Trans.* **1999**, 285–292. More detailed studies, however, have shown that the stable product formed in this reaction is the rearranged compound, that is the indenylidene ruthenium complex **3**; the same applies to the synthesis of **4**. Cf. A. F. Hill, A. Fürstner, M. Liebl, R. Mynott, B. Gabor, L. Jafarpour, S. P. Nolan, unpublished results.



[8] To prevent uncontrolled evaporation of solvent, screening was performed in a closed fume hood without ventilation.

[9] We thank Dr. P. Schwab and Dr. G. Kautz (BASF AG, Ludwigshafen) for this calculation.

[10] Strictly speaking one also has to consider various other enthalpies (i.e. enthalpy of mixing, enthalpy of solvation) which contribute to the effects seen in the thermographic images.

[11] a) E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897; b) O. M. Aagaard, R. J. Meier, F. Buda, *J. Am. Chem. Soc.* **1998**, *120*, 7174–7182.

[12] For the substrate/catalyst activity screening the substrates were placed in the wells of a 96-well polypropylene microtiter plate (100 µL substrate per well). The temperature was calibrated in the range of 25–35 °C. The reaction was initiated by the simultaneous addition of 100 µL of the four different precatalyst solutions (**1**–**4**) in toluene (0.01 M corresponding to 0.26 mol% precatalyst) at 30 °C to each substrate using a multiple pipette (the addition of the precatalyst solutions was completed within 90 s). As before, the temperature changes were detected periodically, shaking being interrupted. The detection time was 5 s, resulting in 250 recordings which were averaged.

Host within a Host: Encapsulation of Alkali Ion–Crown Ether Complexes into a $[Ga_4L_6]^{12-}$ Supramolecular Cluster[**]

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Kenneth N. Raymond[*]

We have constructed structures based on supramolecular clusters found in nature and shown that they encapsulate molecular cations.[1] The origins of supramolecular chemistry

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