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Intramolecular metathesis versus Kharasch reactions using the Grubbs metathesis catalyst: towards catalyst economy

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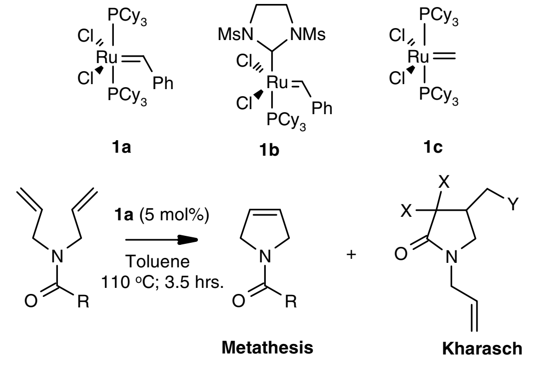
Dedicated to R. T. Brown, J. A. Joule and P. Hodge on the occasion of their ‘retirement’ from The Victoria University of Manchester

Abstract—The first generation Grubbs catalyst can promote either ring closing metathesis (RCM) or atom transfer radical cyclisation reactions (ATRC) depending upon the reaction conditions employed.

We recently reported[1] that the commercially available, air stable, Grubbs carbene complex **1a** acts as an efficient catalyst in intramolecular Kharasch reactions leading to the synthesis of γ-butyrolactones and γ-lactams and serves to compliment the most commonly recognised reactivity of **1a** as an olefin metathesis catalyst. The fact that ruthenium carbene complexes such as **1a** and **1b** prove to be exceptional in their ability to promote olefin metathesis of highly functionalised substrates[2] has been extensively exploited by polymer and synthetic organic chemists such that it now rivals the use of the Wittig reaction in many synthetic contexts. In recent years it has been recognised that catalysts such as **1a** may be implicated in a number of other synthetically useful transformations although such reactions are, as yet, at an embryonic stage of development.[3] As complex **1a** is seemingly able to catalyse two different carbon–carbon bond-forming reactions the question arose as to the relative rates of these distinctly different bond-forming processes. In this letter we present the results of our initial investigations indicating that there is in fact a synthetically useful rate difference between olefin metathesis and Kharasch reactions in substrates able to take part in both reactions. We were pleased to observe therefore that exposure of the readily available amides **2**, **3** and **4** to the Grubbs catalyst **1a** (5 mol%) in degassed toluene (110 °C; 3 h) under an atmosphere of argon afforded the Δ^2-pyrrolines[4] **5**, **6** and **7** in excellent yields (98%, 88% and 89%, respectively) after column chromatography, Scheme 1.

Significantly we were able to detect only trace amounts (<5%) of the alternate Kharasch products **8**[5] and **9**[6] in



2, R = CCl_3
3, R = CF_2Br
4, R = CF_2Cl

5, R = CCl_3 (98%)
6, R = CF_2Br (88%)
7, R = CF_2Cl (89%)

8, X = Y = Cl (<1%)
9, X = F; Y = Br (<1%)
10, X = F; Y = Cl (<1%)

Scheme 1. Initial intramolecular competition experiments.

Keywords: Grubbs; Metathesis; Kharasch; Cyclisation; Competition; Decomposition; Stability; ATRC; RCM.

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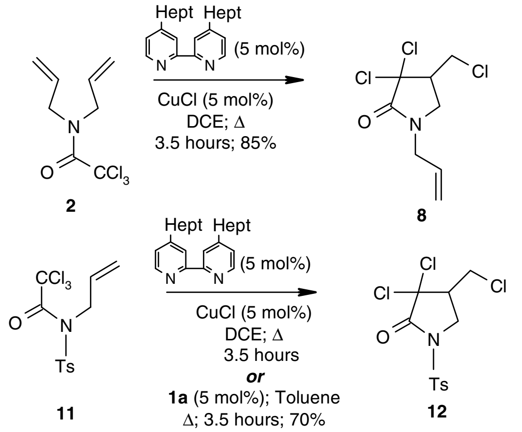
the ^{1}H NMR spectra of the respective crude reaction mixtures whilst **10** was not generated at all under these reaction conditions, Scheme 1.

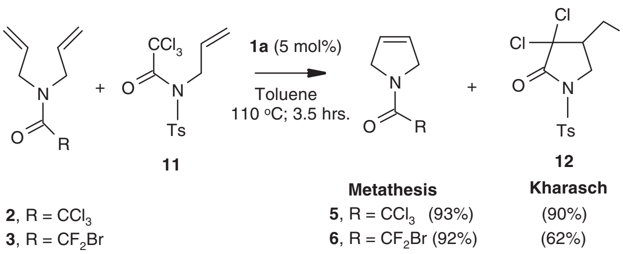
Of note is the fact that blank reactions confirmed that **2** is in fact a good substrate for the intramolecular Kharasch reaction as its exposure to a conventional CuCl-based catalyst system[7] led to the isolation of **8** in good overall yield (85%). Similarly the tosamide **11** could also be transformed to the analogous γ-lactam **12**[8] in good yield using either Cu(I) or the Grubbs catalyst **1a**, Scheme 2.

Based upon this set of observations we next turned our attention to competition experiment in which a 1:1 mixture of the amide **2** and tosamide **11** was subjected to our standard reaction conditions using **1a**. Again the Δ^2-pyrroline **5** ('metathesis') and the γ-lactam **12** ('Kharasch') products were isolated in excellent yields (93% and 90%, respectively) after chromatography. Crucially none of the alternate Kharasch product **8** could be detected in the crude product of this reaction. A similar reaction profile was also observed for the fluoro-derivative **3**, Scheme 3.

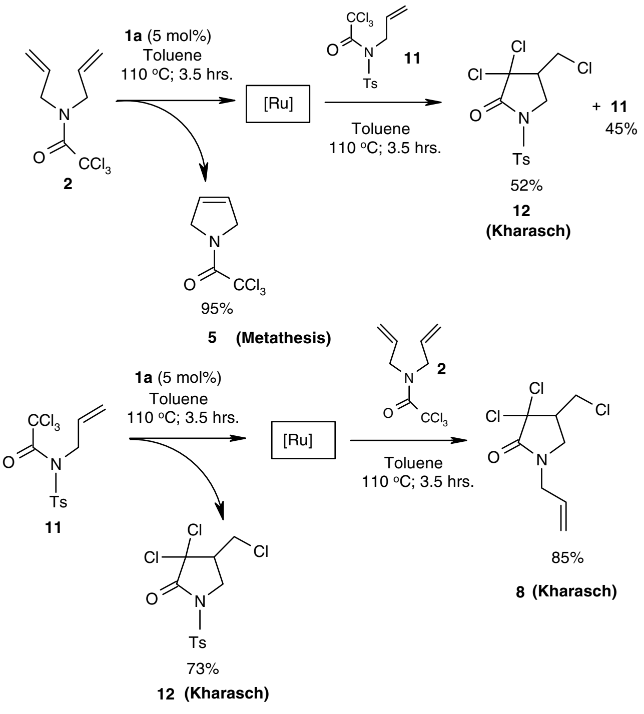
We concluded, on the basis of ^{1}H NMR studies (in benzene-d_6), that the metathesis reaction of **11** occurs very rapidly even at 20 °C ($t_{1/2} \approx 5$ min) whilst the Kharasch reaction is initiated at temperatures in excess of ca. 70 °C. In addition variable temperature ^{1}H NMR experiments conducted in toluene-d_8 also revealed that the catalyst **1a** has a half life of ca 30 min at 110 °C but is rapidly denatured ($t_{1/2} \approx 10$ min) in the presence of substrates such as **2** or **3**. These ^{1}H NMR experiments clearly confirmed that the formation of styrene occurs as soon as mixing is achieved and that this metathesis reaction proceeds with the concomitant loss of the methylidene proton of **1a** at δ 20.6 ppm. Although the parent methylidene complex **1c** (δ =CH 18.9 ppm) would also be expected to be generated in this initial metathesis reaction its concentration in solution was apparently so low as not to be observed. Presumably once formed the relatively unstable methylidene complex **1c** rapidly decomposes at these elevated reaction temperatures.[9] It is clear from these ^{1}H NMR studies however that the metathesis reactions precede the build up of the Kharasch product **12** which gradually occurs over a much longer time scale. Unfortunately we have not been able, in keeping with many others,[10] to identify the inorganic by-products of the decomposition reaction of the parent methylidene complex **1c**. Overall these results suggest that, for the substrate combination of **2** (or **3**) and **11** at least, the metathesis reaction initiates at a much faster rate than the Kharasch reaction (by a factor ≈100 at 110 °C). At this stage therefore we presumed that it was a by-product generated in the breakdown of the catalyst **1a** which was responsible for the Kharasch activity in these reactions. In order to probe this question further we varied the order in which competing substrates were added to the catalyst. Unsurprisingly sequential addition of the amide **2** followed by the tosamide **11** to a solution of the catalyst **1a** in refluxing toluene again afforded the Δ^2-pyrroline **5** ('metathesis') and the lactam **12** ('Kharasch') in 95% and 52% isolated yield, respectively. However upon reversing the order of addition of the substrates to the catalyst, that is when tosamide **11** was added first to a solution of the catalyst



Scheme 2. Blank reactions to form Kharasch products.



Scheme 3. In situ sequential metathesis–Kharasch reactions.



Scheme 4. Sequential addition of substrates to catalyst **1a**.

1a in toluene at 110 °C followed by the amide **2**, then the 'Kharasch' products **8** (85%) and **12** (73%) became the only isolable products of the reaction, with none of the alternate metathesis product **5** being generated (^{1}H NMR of crude reaction mixture), Scheme 4.

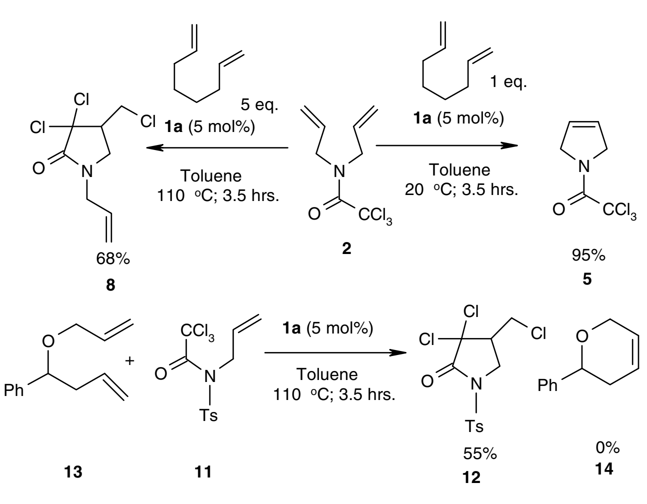
Similarly sequential addition of **3** to the catalyst **1a** in toluene at 110 °C followed by **11** afforded the metathesis product **6** (91%) and the Kharasch product **12** (89%). Clearly the initial interaction of the carbene complex **1a** with **11** at elevated temperatures in some way alters the nature of the catalyst such that it is no longer metathetically active but remains active as a radical initiator in the Kharasch reaction.

We have also briefly screened other, less valuable, sacrificial ω-dienes for the generation of the methylidene complex **1c** with the hope that its rapid decomposition would provide an operationally simple method for the in situ generation of an active Kharasch catalyst. In keeping with our hypothesis addition of a 1:1 mixture of 1,7-octadiene and **2** in toluene to a solution of **1a** in toluene at ambient temperature afforded the metathesis product **5** in 95% isolated yield, whereas addition of a 1:1 mixture of **2** and 1,7-octadiene to a solution of **1a** in toluene, pre-heated to 110 °C, led to the isolation of the Kharasch product **8** in 42% yield together with the metathesis product **5** (21%). Finally, increasing the 1,7-octadiene: **2a** ratio to 5:1 led to a near complete reversal in reaction pathway, and afforded the Kharasch product **8** in 68% isolated yield. Cyclohexene, the presumed organic by-product of this reaction, was lost in work-up due to its volatility. In addition mild thermolysis of a 1:1 mixture of **11** and **13** in the presence of **1a** (5 mol%) in toluene at 110 °C for 3.5 h afforded the γ-lactam **12** (55%) with the diene **13** remaining substantively unchanged, Scheme 5.

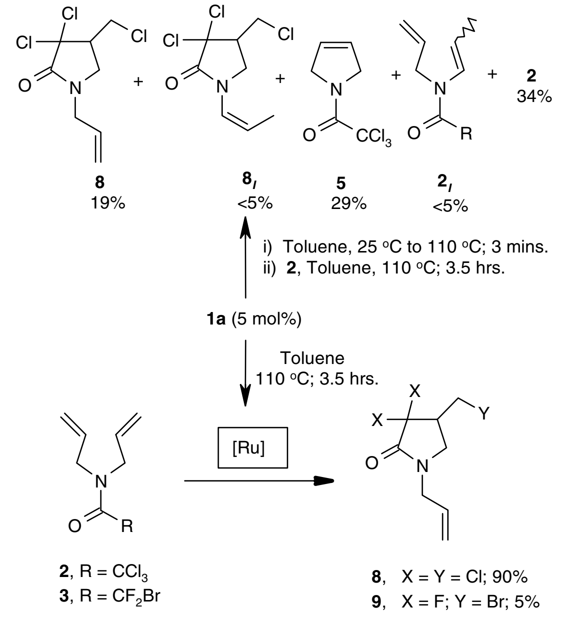
At this stage we mused whether it would be possible to generate a Kharasch catalyst from **1a** merely by thermolysis prior to the addition of substrate. This speculation seemed all the more plausible in the light of our recent observation[11] that the ability of the Grubbs catalyst **1a** to promote redox isomerisation of allyl alcohols is in fact linked to its thermal instability and most probably proceeds via the generation of hydrido ruthenium complexes. Gratifyingly we observed that warming a solution of **1a** in degassed toluene from 20 °C to 110 °C in a Schlenk tube over a period of 3 min prior to the addition of **2**, followed by further reaction at 110 °C for 3.5 h. afforded a mixture of **5** (29%), **8** (19%), starting material **2** (34%) together with minor amounts (ca. 5%) of the isomerised Kharasch product **8**$_{\mathrm{I}}$ and isomerised starting material material **2**$_{\mathrm{I}}$. In terms of a preparative procedure we found thatthermolysis of **1a** in toluene resulted (110 °C; 3.5 h) followed by the addition of the amide **2** and further thermolysis for an additional period of 3.5 h at 110 °C afforded the γ-lactam **8** in 80% isolated yield. Curiously repeating this sequence on the fluorinated substrate **3** afforded only trace amounts of the Kharasch product **9** which is in stark contrast to the reported[6] behaviour of this substrate in copper catalysed cyclisation reactions (Scheme 6).

In conclusion we have demonstrated that the Grubbs complex **1a** serves as catalyst (or precatalyst) for two distinctly different carbon–carbon bond forming reactions and our tentative explanation of these experimental results is outlined in Scheme 7. We find that the olefin metathesis of substrates such as **2** and **3**, forming Δ^2-pyrrolines, is substantially faster than the alternative Kharasch reaction, which generates γ-lactams.

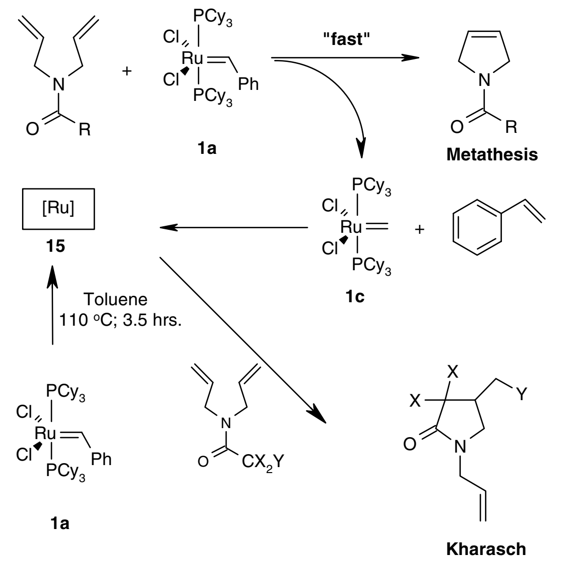
We suggest that the latter process requires either direct denaturation of complex **1a** or of **1c**, which is itself formed as a by-product of the initial metathesis cycle, and in doing so generates a new ruthenium complex (or complexes) **15**. Presumably there is a fine balance between the rate of decomposition of **1c** into **15** and its participation in subsequent metathesis reactions.[12] However once **1c** has decomposed into **15** metathetical reactivity is lost whilst 'Kharasch' activity is retained.



Scheme 5. Sacrificial olefins in Kharasch reactions.



Scheme 6. In situ thermolysis of Grubbs catalyst.



Scheme 7. Proposed reaction pathway.

Support of this hypothesis can be found in Grubbs's[9] work where it has shown that **1c** is considerably less stable than **1a** and is known to undergo thermolysis to a ruthenium complex of unknown constitution. Conversion of the metathesis catalyst **1a** into a very active Kharasch catalyst has a number of appealing synthetic aspects.[13] This simple experimental device opens up the possibility of performing sequential metathesis–Kharasch sequences[14] which are controlled merely by the temperature at which the reactions are conducted. Further studies in this area of 'catalyst economy'[15] are underway and will be reported elsewhere.

Acknowledgements

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4. All new compound were fully characterised by ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry. Typical experimental procedures are detailed below:

A: Equimolar mixture of radical substrate **11** and metathesis substrate **2** added to **1a**: A dry flask was charged with catalyst **1a** (30 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze–thaw cycle) to which was added, by syringe, a solution of **11** (0.2 g, 0.56 mmol) and **2** (0.56 mmol) in toluene (3 mL). After degassing (three times, freeze–thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen for 3.5 h. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/petrol) to afford **12** (90% yield) and **5** (93% yield).

B: Sequential addition of **3** first then **11** to **1a**: A dry flask was charged with catalyst **1a** (30 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze–thaw cycle) to which was added, by syringe, a solution of **2** (0.56 mmol) in toluene (1 mL). After degassing (three times, freeze–thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen for 3.5 h. A solution of **11** (0.2 g, 0.56 mmol) in toluene (1 mL) was then added and the reaction mixture was allowed to stir at refluxing temperature for a further 3.5 h. The toluene was then removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/petrol) to afford **12** (52% yield along with 45% recovered **11**) and **5** (95% yield).

C: Sequential addition **11** first then **3** to **1a**: A dry flask was charged with catalyst **1a** (30 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze–thaw cycle) to which was added, by syringe, a solution of **11** (0.2 g, 0.56 mmol) in toluene (1 mL). After degassing (three times, freeze–thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen for 3.5 h. A solution of **2** (0.2 g, 0.56 mmol) in toluene (1 mL) was then added and the reaction mixture was allowed to stir at refluxing temperature for a further 3.5 h. The toluene was then removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/petrol) to afford **12** (73% yield) and **8** (85% yield).

Representative spectroscopic data: **5** δ_H (300 MHz, $CDCl_3$) 4.3 (2H, br m, $-NCH_2$), 4.6 (2H, br m, $-NCH_2$), 5.8 (2H, m, olefin); δ_C (75 MHz, $CDCl_3$) 159.0, 125.3, 124.6, 91.0, 57.1, 55.1; ν_{max} (evaporated film) 2935, 1672 (s) cm^{-1} ; *m/z* (CI) 214($M^{Cl = 35}$+H+, 100%), 180 (50%), 96 (60%). HRMS $C_6H_7{}^{35}Cl_3NO$ ($M+H^+$) requires: 213.9593; found: 213.9597; **8** δ_H (300 MHz, $CDCl_3$) 3.1 (1H, m, $CHCCl_2$), 3.2 (1H, dd, $J = 10$, 8 Hz, $CHCl$), 3.6 (1H, dd, $J = 10$, 7 Hz, $CHCl$), 3.8 (1H, dd, $J = 11$, 10 Hz, CHN), 4.0 (1H, dd, $J = 11$, 4 Hz, CHN), 4.0 (2H, m, $CH_2–CH{=}CH_2$), 5.2 (2H, m, $CH_2–CH{=}CH_2$), 5.7 (1H, m, $CH_2–CH{=}CH_2$); δ_C (75 MHz, $CDCl_3$) 165.6, 130.4, 119.5, 83.6, 51.5, 47.3, 46.2, 40.9; ν_{max} (evaporated film) 2922, 1726 (s), 1645 cm^{-1}; *m/z* (CI) 242 (100%), 208 (75%), 172 (65%). HRMS $C_8H_{11}{}^{35}Cl_3NO$ ($M+H^+$) requires: 241.9906; found: 241.9912; **6**: δ_H (300 MHz, $CDCl_3$) 5.9 (2H, m, olefin) 4.52 (2H, br m, $C\mathbf{H}_2$), 4.39 (2H, br m, CH_2); δ_F (282 MHz, $CDCl_3$) −58.0 (s); ν_{max} (evaporated film) 2927; 2874, 1885, 1629 cm^{-1}; *m/z* (CI) *m/z* (CI) HRMS $C_6H_{10}{}^{80}BrF_2NO$ (M^+) requires 225.9674; found 225.9670; **7**: δ_H (300 MHz, $CDCl_3$) 5.9 (2H, m, olefin) 4.52 (2H, br m, CH_2CH), 4.39 (2H, br m, CH_2CH); δ_F (282 MHz, $CDCl_3$) −62.0 (2F, s); ν_{max} (evaporated film) 2926, 2875, 1690, 1630 cm^{-1}; *m/z* (CI) *m/z* (CI) HRMS $C_6H_{10}{}^{35}ClF_2NO$ ($M+NH_4{}^+$) requires: 199.0450; found 199.0444; **8$_I$**: δ_H (300 MHz, $CDCl_3$) 6.25 (1 H, dq, $J = 8$, 2 Hz), 5.35 (1H, dq, $J = 8$, 7 Hz), 4.05 (1H, dd, $J = 11$, 4 Hz, CHN); 3.95 (1H, dd, $J = 10$, 7 Hz, CHN), 3.80 (1H, dd, $J = 11$, 10 Hz, $CHCl$), 3.6 (1H, dd, $J = 10$, 8 Hz, $C\mathbf{H}Cl$), 3.2 (1H, m, $CHCCl_2$), 1.8

(3H, dd, $J = 8$, 2 Hz, CH_3CH); **12**: 2.5 (3H, s, *Me*Ar), 3.15 (1H, m, CHCCl$_2$), 3.6 (1H, dd, $J = 9$, 10 Hz, CHCl), 3.7 (1H, dd, $J = 11$, 10 Hz, CHCl), 3.9 (1H, dd, $J = 11$, 4 Hz, CHN), 4.2 (1H, dd, $J = 10$, 7 Hz, CHN), 7.4 (2H, d, $J = 8$ Hz, aromatic H), 7.95 (2H, d, $J = 8$ Hz, aromatic H); δ_C (75 MHz, CDCl$_3$) 167.6, 145, 139.4, 129.9, 128.2, 87.4, 52.8, 41.6, 40, 22.6;ν_{max} (Nujol) 1760 (s) cm^{-1}; *m*/*z* (EI) 356($M^{Cl=35}$+H^+, 20%), 291 (55%), 155 (100%), 91 (100%); *m*/*z* (CI) 373 $M^{Cl = 35}$+NH_4^+, 80%), 339 (100%). HRMS $C_{12}H_{13}{}^{35}Cl_3NO_3S$ ($M+H^+$) requires: 355.9682; found: 355.9682.

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