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# Toward catalyst economy: A programmed approach to the synthesis of bicyclic lactones and lactams

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Dedicated to Professors Chauvin, Grubbs and Schrock who managed to turn lead into gold.

**Abstract**

The development of sequential ring closing metathesis (RCM)–Kharasch sequences which utilize a single precatalyst is described. In these sequences the catalysts acts in a multiple role promoting two different carbon–carbon bond-forming reactions in a sequential manner.


*Keywords:* Grubbs; Metathesis; Kharasch, Cyclization; Tandem; ATRC; RCM; Radical; Ruthenium; Carbene

Ever since the 8th century alchemist Abu Musa Jabir ibn Hayyan (“Geber”) promulgated the belief that *al-iksir* (elixir) was able to transmutate one metal into another (al)chemists have searched for substances which seemingly possess magical properties such as claimed for *philosophi lapis* (the philosopher’s stone). It could be argued that a contemporary manifestation of this quest is embodied in the notion of catalysis (Gr. *katalusis*), a concept which was known to 14th century alchemists such as Al Alfani [1a]:

> *Xerion, elixir, noble stone, magisterium, that cured the disease and transformed basic metals into gold, without it underwent the smaller modification.*

Catalysis was put onto a more secure scientific footing by Berzelius [1b] in 1835 and it is his definition, which has remained largely unchanged, that can still be found in most undergraduate textbooks on chemistry:

> *The catalytic force actually appears to consist in the ability of substances to arouse the affinities dormant at this temperature by their mere presence and not by their affinity and so as a result in a compound substance the elements become arranged in another way such that a greater electrochemical neutralization is brought about.*

The synthesis of organic molecules is still largely accomplished by the stepwise formation of carbon-bonds and is heavily reliant upon the use of polarized functional groups (carbonyl groups, etc.) to provide the driving force for bond formation. The lack of functional group discrimination often observed in such reactions has spawned a whole sub-set of the discipline concerned with the development of

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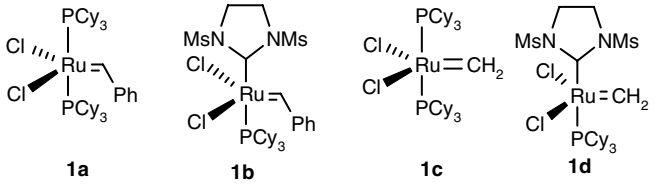
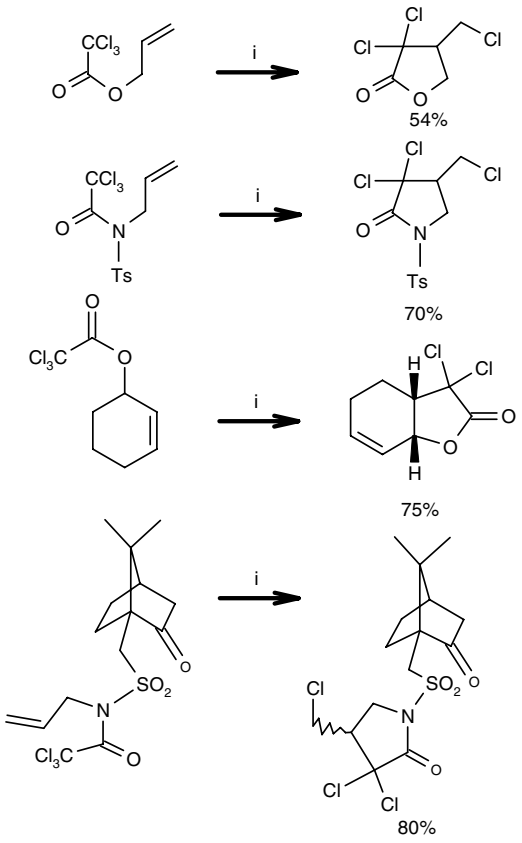
new protecting groups for the limitless number of synthetic transformations employed during a given synthetic sequence. High up on the (al)chemists wish list therefore is a general, direct, procedure for the transformation of an unpolarized functional group, such as an alkene or alkyne, into its homologue without recourse to the use of polar reagents. Although such reactions had been noted as early as 1956 [2] the development of readily accessible catalysts which enable this seemingly magical transformation – olefin metathesis – together with an understanding of their mode of action represents one of the landmark discoveries of 20th century chemistry and most deservedly resulted in the award of the 2005 Nobel Prize in Chemistry [3] to Chauvin, Grubbs and Schrock. The fact that catalysts such as **1a** and **1b** are now commercially available reflects the extent to which this rapidly developing methodology has been embraced by the synthetic community as a whole.




Our own interest in this field results from a chance observation resulting from a poorly conceived experiment. During the course of a program of research [4] concerned with the optimization of copper catalysts for use in atom transfer radical polymerisation (ATRP) and ATRC reactions we noted Snapper's paper [5] on the use of the Grubbs 1st generation catalyst, **1a**, in intermolecular Kharasch reactions. We were able to demonstrate [6] that **1a** acts as an efficient catalyst in the related atom transfer radical cyclization (ATRC) reactions affording, in certain cases, higher yields of products with much lower catalyst loading than observed with the more conventional copper-based catalyst systems (such as CuCl, 1,4-dHbipy[1]), Scheme 1.




Scheme 1. Use of catalyst **1a** in ATRC reactions. Reagents and conditions: **1a**, 5 mol%; toluene; 3.5 h; 110 °C.

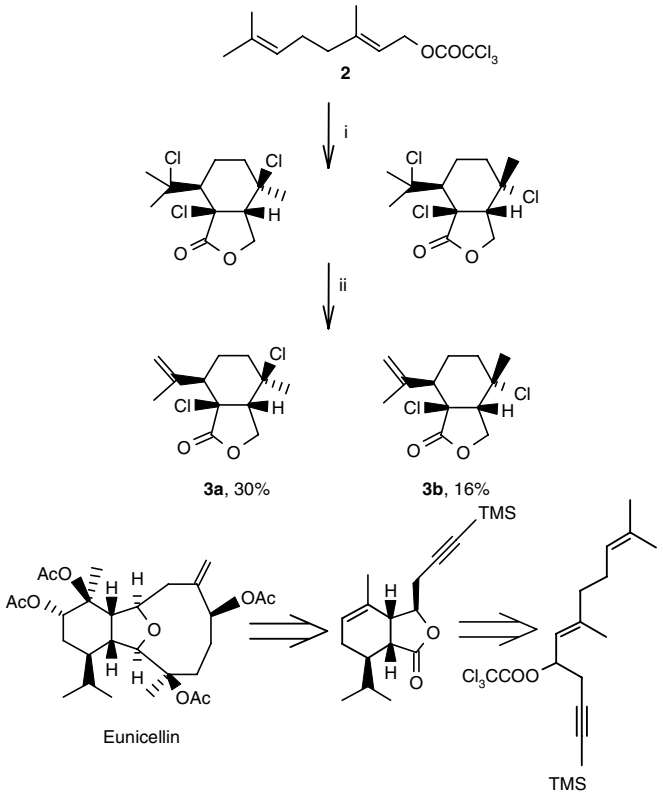
We have subsequently shown that **1a** also promotes bifurcate, tandem ATRC reactions [7] affording the functionalized bicyclic lactone **3** from the simple acyclic precursor **2** in a single operational step. Current investigations in this area are now concerned with the utilization of this methodology in target-orientated synthesis, specifically in an approach to eunicellin, Scheme 2.

While conducting these methodological studies we noted that **1a** not only catalyzed metathesis and ATRC reactions but also, under certain circumstances, effects C–C double bond migration [8]. Allylic alcohols are isomerized to aldehydes when exposed to **1a** toluene at reflux, a process which bears more than a passing resemblance to the chemistry described by Sasson and Blum some years ago [9]. Our initial mechanistic studies [8] suggested that, in case of the catalyst **1a** at least, these isomerization reactions were associated with the decomposition of the initial catalyst, or the intermediate methylidene complex **1c**, to a new ruthenium complex which is presumably responsible for the isomerization reaction. Monitoring these reactions by $^1$H NMR spectroscopy in toluene-$d_8$ indicated that the carbene complex **1a** ($^1$H NMR: Ru = C*H*Ph $\delta$ 20.4 ppm) was rapidly converted into a hydrido-ruthenium complex [$^1$H NMR: Ru–*H* $\delta$ −24 ppm, (tr $J = 17$ Hz)] during the initial stages of the reaction. We tentatively suggest, on the bases of this data, that this decomposition product is in fact the known [10] complex **4**. We now invoke that reversible addition [11] of this species to the substrate ultimately leads to enol formation and hence to the tautomeric carbonyl compound [8], Scheme 3.

We were curious at this stage as to the isolation [6] of the isomerized lactone **8** from the ATRC reaction of **5** (Scheme 4).

Further investigations could not reconcile this result with the metal-hydride mechanism described above. Naïvely, we initially thought that cyclization of **5**, ostensibly catalyzed by **1a**, initially formed **6** which suffered elimination of HCl to the unsaturated lactone **7**. We assumed that lactone **7** then participated in a reversible ruthenium hydride-mediated double bond isomerization reaction [11]

[1] dHbipy = 4,4′-di-*n*-heptyl-2,2′-bipyridine

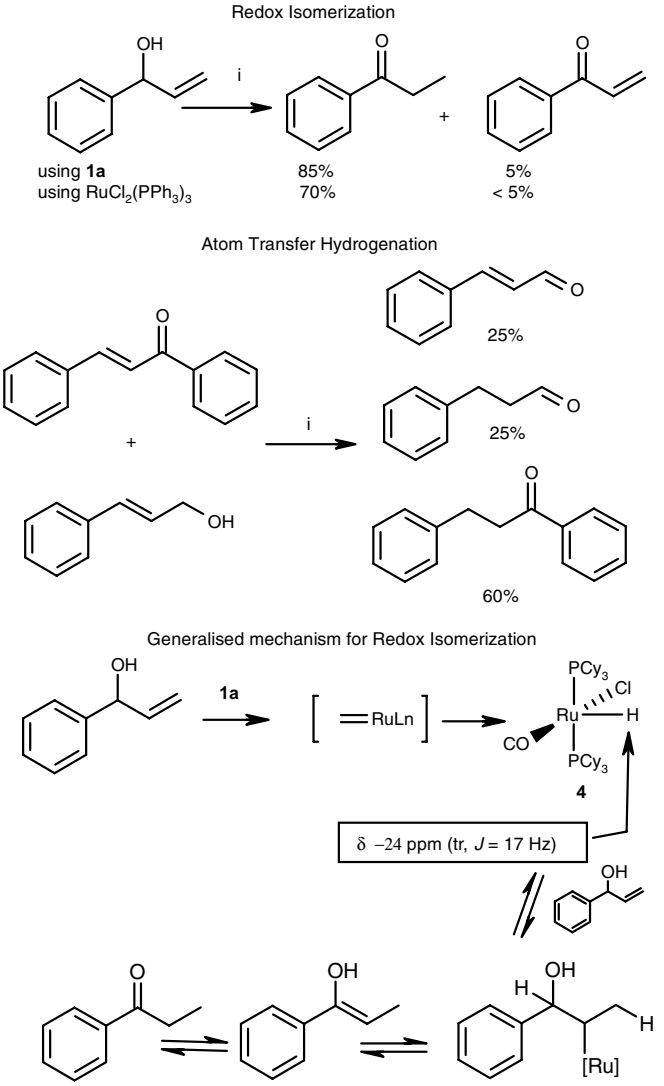



Scheme 2. Bifurcate tandem ATRC reactions catalysed by **1a**. Reagents and conditions: (i) **1a**, 5 mol%; $ClCH_2CH_2Cl$; 3.5 h; 80 °C; (ii) $SiO_2$, $CH_2Cl_2$.

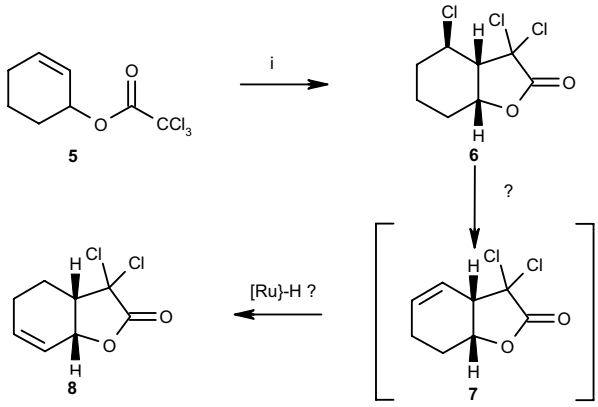
in which **8** represents the thermodynamic product of the reaction sequence, Scheme 4.

Unfortunately, we were unable to convert an authentic sample of lactone **7** to its supposedly more stable isomer **8**, furthermore the tri-chlorolactone **6** also appeared to be resistant towards dehydrochlorination under the reaction conditions employed during the ATRC reaction. Even more perplexing was the result of deuterium labeling experiments which showed that the isomerization reaction was highly regioselective in terms of the scrambling of the deuterium label, Scheme 5.

This observation in particular was inconsistent with a metal-hydride mechanism which, *a priori*, would have been expected to result in more extensive distribution of the deuterium label around the cyclohexane ring. It is however consistent with a pathway which involves competing rearrangement of the substrate **9a** to its isomer **9b** followed by elimination of tri-chloroacetic acid affording the dienes **10a**,**b**. Intermolecular Kharasch reaction of tri-chloroacetic acid with **10a**,**b** would afford the allyl chlorides **11** which on intramolecular displacement of halide would ultimately generate the lactones **12** with the observed deuterium scrambling pattern [12]. Corroborating evidence for the formation of the dienes **10a**,**b** comes from the fact that the Diels–Alder adducts **13a**,**b** were isolated in high yield (92%) from otherwise identical reactions conducted in the presence of maleic anhydride, Scheme 5.

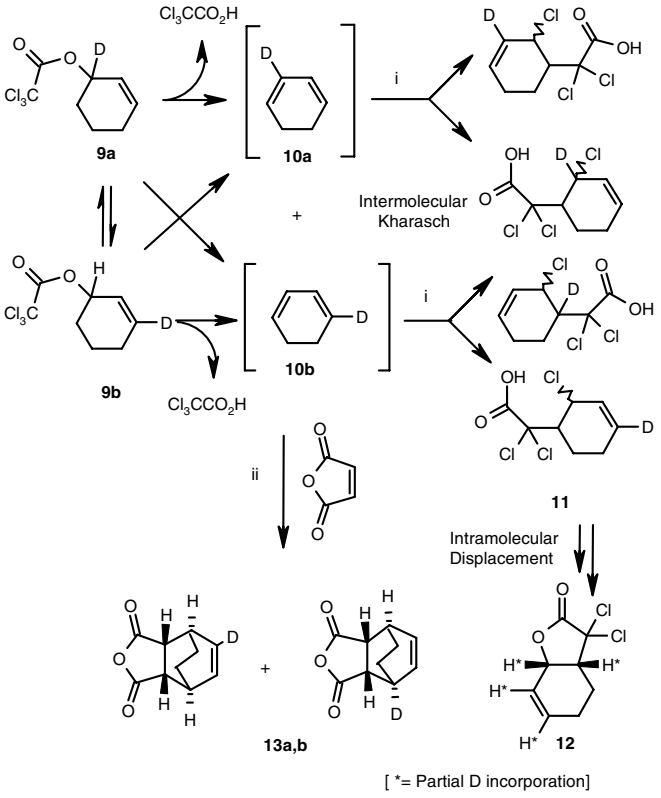



Scheme 3. Isomerization reactions catalyzed by **1a**. Reagents and conditions: (i) **1a**, 5 mol%; toluene, 110 °C; 3 h.

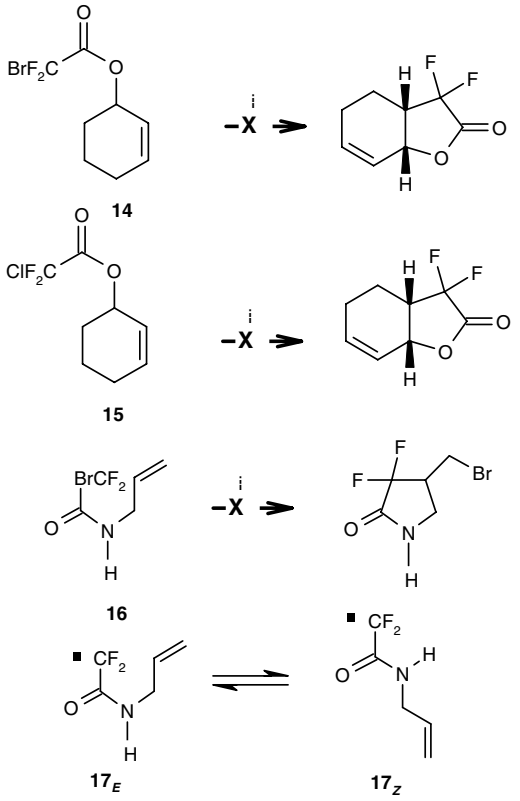



Scheme 4. Proposed route for the conversion of **5** into **8**. Reagents and conditions: (i) **1a**, 5 mol%; toluene; 3.5 h; 110 °C.

Having gained some experience in the use of **1a** as an ATRC catalyst we wished to investigate whether it would serve as a catalyst for the ATRC of the fluorinated




Scheme 5. ATRC reactions: deuterium labeling studies. Reagents and conditions: (i) **1a**, 5 mol%; toluene; 110 °C; 12 h; 80%; (ii) **1a**, 5 mol%; maleic anhydride, 1.0 eq.; $CDCl_3$; reflux; 92%.

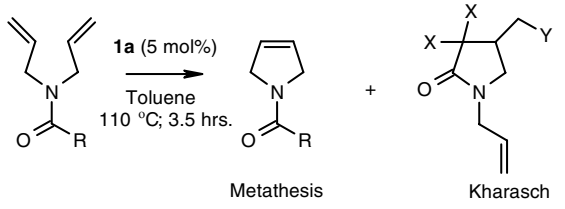



Scheme 6. Failed ATRC reactions. Reagents and conditions: (i) **1a**, 5 mol%, toluene; 110 °C.

substrates **14**–**16**, which are deemed to be unreactive in such reactions. As the ATRC reactions of **14**–**16** using **1a** met with failure, presumably due to adverse stereoelectronic/electronic effects (e.g. unfavourable equilibrium for $\mathbf{17}_Z \leftrightarrow \mathbf{17}_E$, Scheme 6) we decided to investigate the ATRC reactions of the di-allyl amide **18**. We reasoned that interception of any radical intermediate derived from **18** would be more efficient in this particular case. In retrospect this analysis was a classic example of a goal-orientated misconception, and it was not surprising therefore that exposure of **18** to the catalyst **1a** (**1a**, 5 mol%; toluene; 110 °C) afforded [13] the pyrroline **19** in excellent yield (88%) rather than our "desired" ATRC product **20**.

Similarly, other substrates such as **21** and **24**, which could cyclize either *via* an RCM or ATRC pathway underwent clean metathesis in excellent isolated yields, Scheme 7. Significantly, we were unable to detect the formation of the alternate, "Kharasch", products **20**, **23** and **26** from these cyclization reactions.

Control experiments in fact showed that RCM of substrates such as **24** was particularly rapid, going to completion in a matter of minutes at ambient temperature in solvents such as toluene or dichloromethane, and certainly with much shorter reaction times required for the related ATRC reactions leading to γ-butyrolactams. In fact the ATRC chemistry associated with catalyst **1a** appears only to be significant at temperatures in excess [14] of 80 °C a




**18**, R = $CF_2Br$
**21**, R = $CF_2Cl$
**24**, R = $CCl_3$

**19**, R = $CF_2Br$ (88%)
**22**, R = $CF_2Cl$ (89%)
**25**, R = $CCl_3$ (98%)

**20**, X = Y = Br (<1%)
**23**, X = F; Y = Cl (<1%)
**26**, X = Cl (<1%)

Scheme 7. Intramolecular competition between RCM and ATRC reactions.

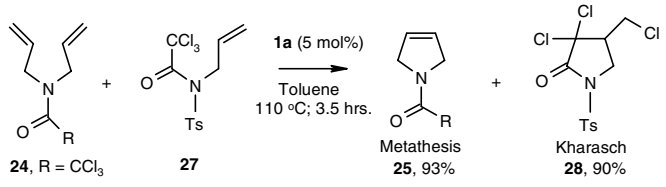
fact we ascribe to catalyst decomposition [15], presumably due to the labile nature of the methylidene complex **1c**. The rate difference between RCM and ATRC is clearly apparent from the fact that trichloroamide **24** preferred to undergo RCM to **25** (98%) rather than ATRC to **26** (<1%) under our standard reaction conditions. This reactivity difference was further underscored when we observed that exposure of a 1:1 mixture of **24** (RCM or Kharasch) and **27** (Kharasch only) to the same reaction conditions cleanly afforded pyrroline **25** and lactam **28** in excellent isolated yields (93% and 90%, respectively). Clearly, catalyst **1a** is able to promote both RCM and Kharasch reactions with a high degree of chemoselectivity and that RCM reac-

tion of **24** must be much faster than the Kharasch reaction of either **24** or **27**.

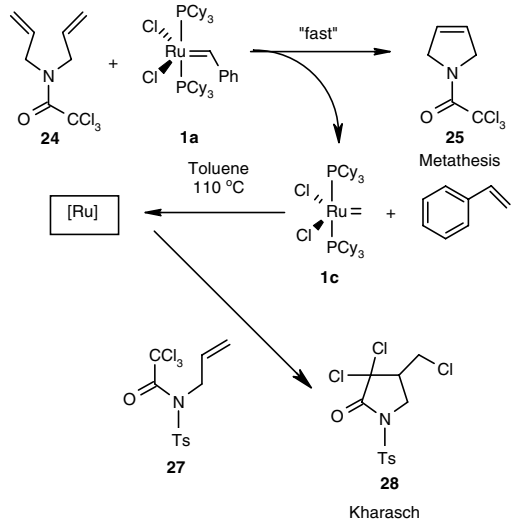
Significantly, prior denaturation of the catalyst **1a** by reaction with octa-1,8-diene also generated a catalyst which was devoid of metathetical activity but retained Kharasch activity. This circumstantial evidence again pointed to the fact that, in the case of the Grubbs catalyst **1a** at least, Kharasch activity was in fact due to a decomposition product of the initial catalyst (Scheme 8).

The potential for catalyst transmutation during a reaction sequence is a process which does not sit well with Berzelius's original paradigm but from the synthetic chemist's standpoint raises many possibilities. Not the least it opens up the possibility of *catalyst economy*, where a catalyst or pre-catalyst is used in more than one guise during a given synthetic sequence [16], Scheme 9.

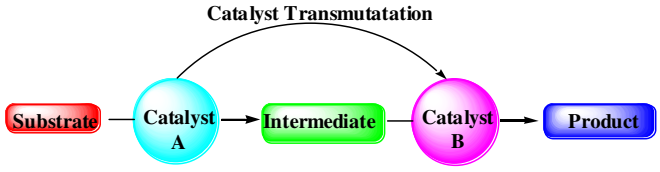
Given that the differential between the rates of the initial metathesis reactions and subsequent catalyst decomposition/Kharasch reactions were substantially different [13] we wondered if it would be possible to use the Grubbs catalysts catalyst to perform sequential cross metathesis-ATRC or RCM–ATRC reactions. Fortuitously, Grubbs had just published [17] the ground rules for cross metathesis reactions and we chose to investigate the viability of the simplest option, namely that of a cross metathesis-ATRC sequence. In an initial experiment we were delighted to find therefore that exposure of a (1:4) mixture the amide **29** and the alkenes **30a–d** to the catalyst **1a** (5 mol%) in toluene,




Metathesis-ATRC sequences: Mechanism?




Scheme 8. Intermolecular competition: metathesis versus Kharasch reactivity.

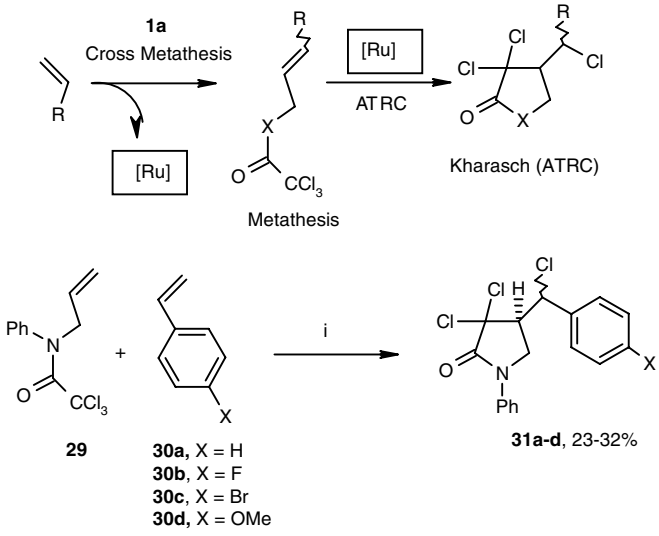



Scheme 9. "Catalyst economy": basic concept.

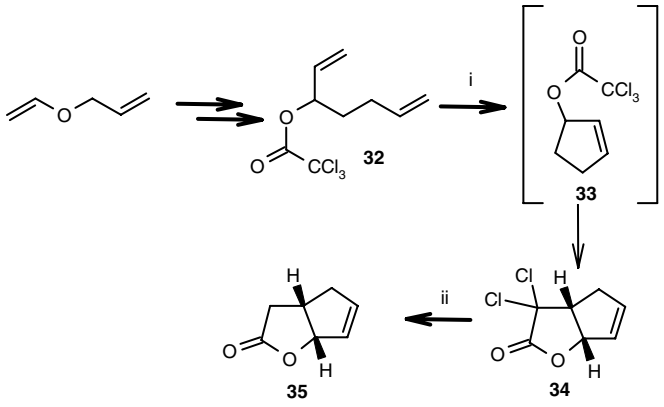
first at 40 °C and then at reflux, afforded the lactams **31a–d** in moderate overall yields (23–32%), Scheme 10.

Complications of this particular set of reactions appeared to be associated with the self-metathesis of the starting alkenes **28** and isomerization of the allyl amide **27**. Although the overall yields of the lactams produced in this sequence were modest (ca. 30%) this result did however provide proof of principle, a fact which encouraged us to investigate substrates which would be better behaved in the metathesis component of the metathesis (CM)-ATRC sequence. An obvious extension to our initial CM–ATRC cascade was an RCM–ATRC sequence in which it was thought that the relatively rapid formation of 5/6-membered rings using a **RCM** reaction would minimize self-metathesis and would therefore lead to a cleaner overall reaction profile.

The viability of this new approach to the synthesis of bicyclic systems was readily confirmed using trichloroacetate **32** as a test case. In this particular example we found that the RCM reaction of **32** leading to cyclopentene **34** proceeded cleanly over two hours at 20 °C in $CHCl_3$ using a bi-metallic catalysts system (**1b**, 5 mol%; CuCl, 5 mol%; dHbipy, 5 mol%;). The ATRC component of the reaction was then initiated by mild thermolysis (80 °C) of the crude reaction mixture, affording the unsaturated lactone **34** in 95% overall yield, Scheme 11. Finally, dechlorination of **32** (Zn, $AcOH_{(aq)}$) afforded the unsaturated lactone **35**, a




Scheme 10. Tandem cross metathesis–Kharasch sequences. Regents and conditions: (i) a: **1a**, 5 mol%; toluene; 3 h; 40 °C; b: 110 °C; 16 h.



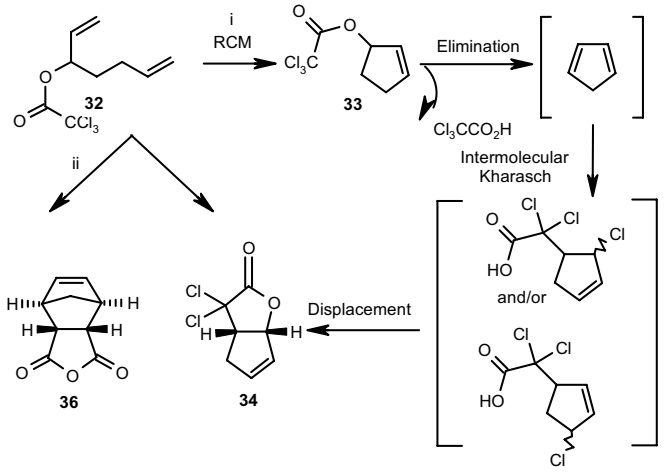
Scheme 11. Reagents and conditions: (i) **1b,** 5 mol%; CuCl, 5 mol%; dHbipy, 5 mol%; $CHCl_3$, 2 h at 20 °C and then 3 h at reflux; 95%; (ii) Zn, 10 equiv.; 1:3 AcOH–$H_2O$; 100 °C; 69%.

useful synthetic intermediate, in 69% isolated yield, Scheme 11.

We suspect that, as in the case of the conversion of ester **5** into lactone **8**, this reaction proceeds via the intermediacy of cyclopentadiene, a suspicion which again has been validated by the isolation of the Diels–Alder adduct **36** from those reactions conducted in the presence of maleic anhydride, Scheme 12. As of yet we are not able to determine whether the ruthenium assists in the elimination of trichloroacetic acid from cyclopentenyl ester **33** and is a possibility which is currently under investigation.

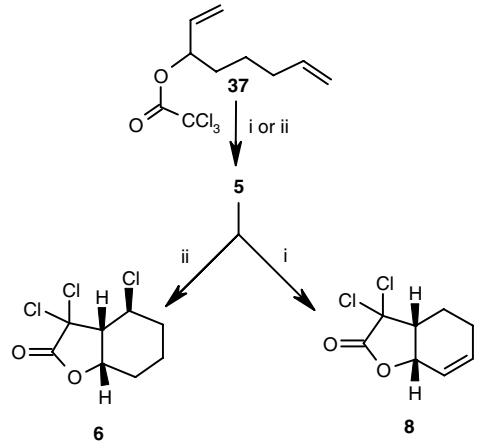
In a similar vein we have also established that exposure of **34** to the 1st generation Grubbs catalyst **1a** (5 mol% in degassed toluene) first at ambient temperature for 3 h then under conditions of mild thermolysis (110 °C; 16 h) afforded, directly, the unsaturated lactone **8** in 64% isolated yield together with trace quantities (<5%) of the trichlorolactone **6**.

Alternatively repeating this reaction, this time with the 2nd generation catalyst **1b**, resulted in the isolation of trichlorolactone **6** as the major product (in 62% yield) together with a minor amount of the unsaturated lactone **8** (*ca.* 5% by $^1$H NMR analysis of the crude reaction mixture), Scheme 13.

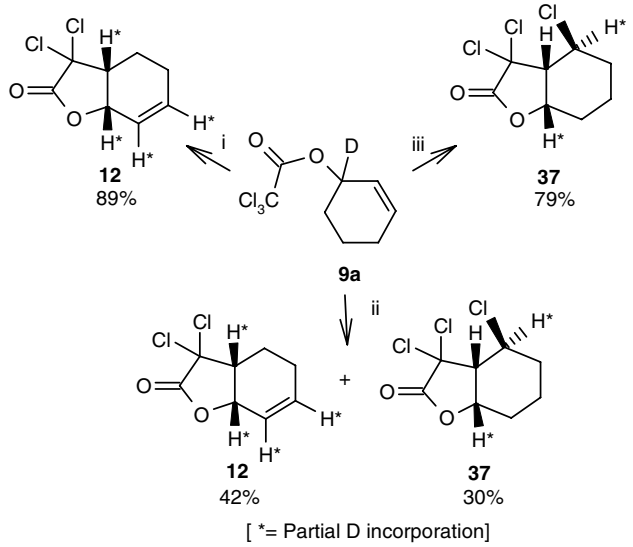


Scheme 12. Reagents and conditions: (i) a: **1b**, 5 mol%; CuCl 5 mol%; dHbipy 5 mol%; $CHCl_3$; 2 h; 20 °C; b: reflux; 3 h; 95%; (ii) as in (i) but with the addition of maleic anhydride (1 equiv.) as co-reactant; 92%.

The intermediate ester **5** in this instance appeared to be more robust than the cyclopentenyl ester **33** and did not require the addition of a copper co-catalyst in order to facilitate clean conversion to product. The fact that the product distribution from this particular cyclization sequence was dependent upon the catalyst system employed (Scheme 13) inevitably led us to reinvestigate deuterium labeling studies in this series of reactions, Scheme 14. Cyclization of the deuterated substrate **9a** using the second generation Grubbs catalysts **1b** or our standard



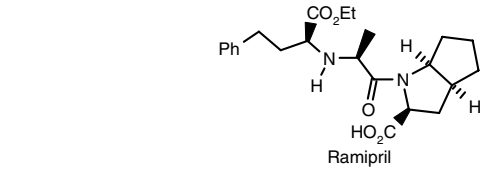
Scheme 13. Tandem RCM–ATRC reactions – catalyst dependency. Reagents and conditions: (i) a: **1a**, 5 mol%; toluene; 3 h; 20 °C; b: 110 °C; 16 h; 64%; (ii) a: **1b**, 5 mol%; toluene; 3 h; 20 °C; b: 110 °C; 16 h; 62%.



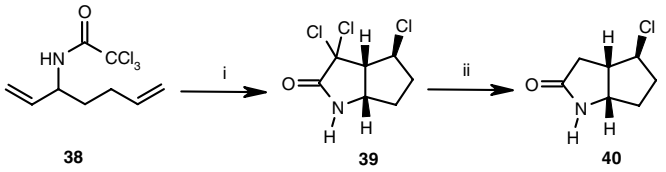
Scheme 14. Reagents and conditions: (i) **1a**, 5 mol%; toluene; 3.5 h; 110 °C; (ii) **1b**, 5 mol%; toluene; 12 h; 110 °C (iii) CuCl, 5 mol%; dHbipy, 5 mol%; $ClCH_2CH_2Cl$; 80 °C or CuCl, 5 mol%; dHbipy, 5 mol%; **1a**, 5 mol%; $ClCH_2CH_2Cl$; 80 °C.

Cu(I) system both resulted in the formation of the trichlorolactone **37** in which the deuterium label was equally distributed between C4 and C7a. In the case of catalyst **1b** the formation of unsaturated lactone **12** was also observed, where the deuterium label was scrambled in an identical manner to that previously observed for the cyclization of **9a** using **1a**. In contrast to the use of **1a** alone, exposure of **9a** to a 1:1 mixture of a catalyst system comprising of Cu(I)–dHbipy and **1a** in toluene at reflux afforded the trichloroalactone **37** (79% isolated yield) and the unsaturated lactone **12** (10% isolated yield). These results infer that cyclization of **9a** using either a copper(I) catalyst or the more robust carbene catalyst **1b** proceeds via a Kharasch reaction which is slower than the competing [3,3]-sigmatropic rearrangement of the substrate and results in the scrambling the deuterium label between C4 and C7a. In the case of catalyst **1a**, not only do we observe the background [3,3]-sigmatropic rearrangement chemistry of the substrate **9a** but this is accompanied by (the thermal?) decomposition of the substrate to the dienes **10a**,**b**. Dienes **10a**,**b** can subsequently undergo intermolecular Kharasch reactions ultimately leading to unsaturated lactone **12** in which more extensive scrambling of the deuterium label is observed, Scheme 5. Taken together these results suggest that, in the case of **1b**, the Grubbs catalyst may responsible for both the metathesis and ATRC components of the reaction sequence. However, in those cases, where the rate of the ATRC reaction of **9a** is slow compared to either the rate of decomposition of substrate or catalyst then competing cyclization processes intervene, as in the case of catalyst **1a**. The exclusive formation of unsaturated lactone **8** from the combined RCM–ATRC sequence (Scheme 13) in the presence of carbene catalyst **1a** compared to the ATRC product in the case of **1b** is, we suggest, defined by the greater instability of the intermediate methylidene complex **1c** as compared to **1d** formed during the initial RCM phase of the reaction sequence. What is not clear however at this point is why the exact product distribution of the cyclization reactions catalyzed by **1b** appears to be dependent upon the starting point in the cycle (i.e. differing outcome observed when starting from either **37** compared to **5**).

Finally, a number biologically significant compounds possess either the 2-azabicyclo[3,3,0]octane or 2-azabicyclo[4,3,0]nonane ring systems (e.g. Ramipril™). We envisaged that these heterocycles should be readily available using a modification of the tandem RCM–ATRC reactions described above. To this end thermolysis of a solution of the readily available amide **38** in xylenes containing the catalyst **1b** (5 mol%) afforded the lactam **39** as a single diastereoisomer in 91% isolated yield. Dechlorination (Zn–$HOAc_{(aq)}$) of **39** proved to be highly selective affording the mono-chlorolactam **40** in 73% yield, Scheme 15. Given that Overman [18] has shown that substrates related to **38** can be prepared with high levels of enantiomeric purity, we envisage that our RCM–ATRC methodology could be applied to the asymmetric synthesis of bicyclic nitrogen-containing systems.



Ramipril



38 39 40

Scheme 15. (i) **1b**, 5 mol%; xylenes; 20 °C, 3 h then 2 days at 120 °C; 82–91%; (ii) Zn, 10 eq.; 1:3 AcOH–$H_2O$; 100 °C; 73%.

In conclusion, we have demonstrated that the Grubbs metathesis catalysts are able to promote a variety of synthetically useful reactions including metathesis, ATRC, redox isomerization and atom transfer hydrogenations. Furthermore by judicious choice of substrate and reaction conditions it is possible to telescope a number of these reactions together in a single, ''one-pot'', operation providing access to useful synthetic intermediates from very simple starting materials. The multiple use of organometallic catalysts [19] in this manner (''catalyst economy'') complements the, now well established, concept ''atom economy'' and hopefully will have substantial applications in organic synthesis. Validation of this general concept is currently in progress.

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