Catalysis Today 140 (2009) 74–83

Contents lists available at ScienceDirect

Catalysis Today

journal homepage: www.elsevier.com/locate/cattod

The chemistry of Ru cyclopropylmethylidene complexes: Mechanistic studies and synthetic implications for the ring-closing metathesis reaction

Vittorio Farina *, Xingzhong Zeng **, Xudong Wei, Yibo Xu, Li Zhang, Nizar Haddad, Nathan K. Yee, Chris H. Senanayake

Boehringer Ingelheim Pharmaceuticals, Department of Chemical Development, 900 Ridgebury Road, Ridgefield, CT 06877, USA

ARTICLE INFO

Article history:
Available online 10 September 2008

Keywords:
Ru cyclopropylmethylidene complexes
Ring-closing metathesis
Macrocyclization
Epimerization
Mechanistic study

ABSTRACT

We describe the Ru-catalyzed ring-closing metathesis (RCM) reaction of a densely functionalized diene leading to the 15-membered ring of HCV protease inhibitor BILN 2061. The evaluation of several catalysts led us to the discovery of a new epimerization reaction which plagued our initial attempts to scale-up the reaction. A mechanistic study of this side reaction is described. Factors that may contribute to render our RCM sub-optimal were identified in the low initiation rate of the best catalyst (first-generation Hoveyda), to yield what seems to be a highly stabilized and perhaps catalytically inactive intermediate. Preliminary efforts to affect the initiation site by substrate modification are also discussed.

1. Introduction

Our initial stimulus for studying the application of ring-closing metathesis [1] to macrocyclization was provided by the advancement of BILN2061, an HCV protease inhibitor, into clinical studies [2]. Faced with the challenge of producing multikilo amounts of this important product (**1**), we settled on a convergent strategy involving, as the key step, the RCM macrocyclization of dienes such as **2**, which in turn can be simply obtained by classical C–N and C–O forming reactions from a number of rather simple building blocks (**3**–**6**) [3]. Both the synthesis of the building blocks and strategies for their assembly have been described in full, and will not be discussed further (Scheme 1) [4].

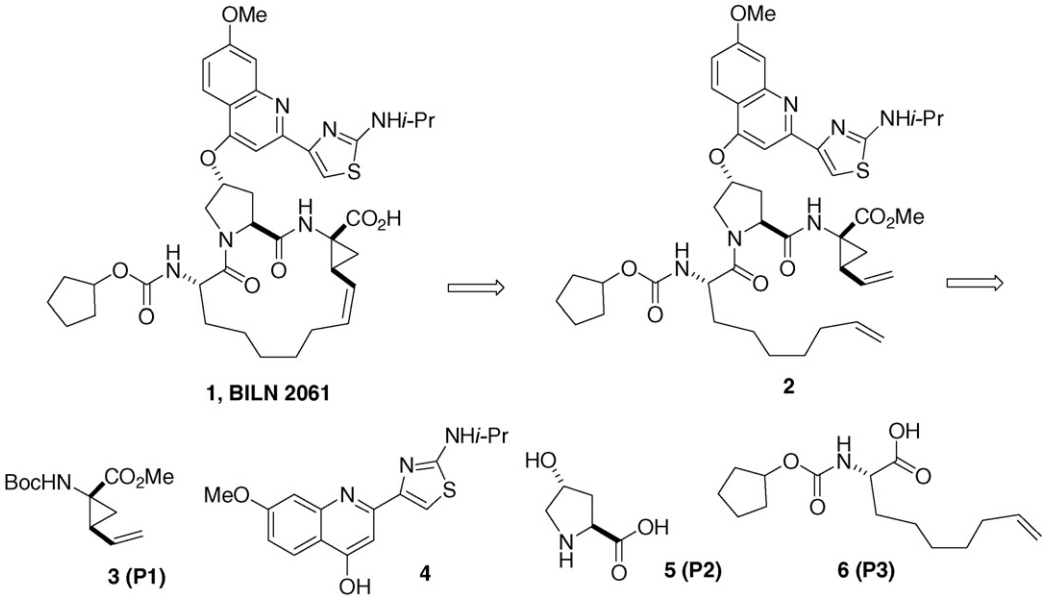
Our initial studies with this particular type of RCM showed a number of interesting features that demanded a more thorough study. We initially screened a number of well-known catalysts and substrates for this reaction (Scheme 2), and made a number of key observations.

These can be summarized as follows:

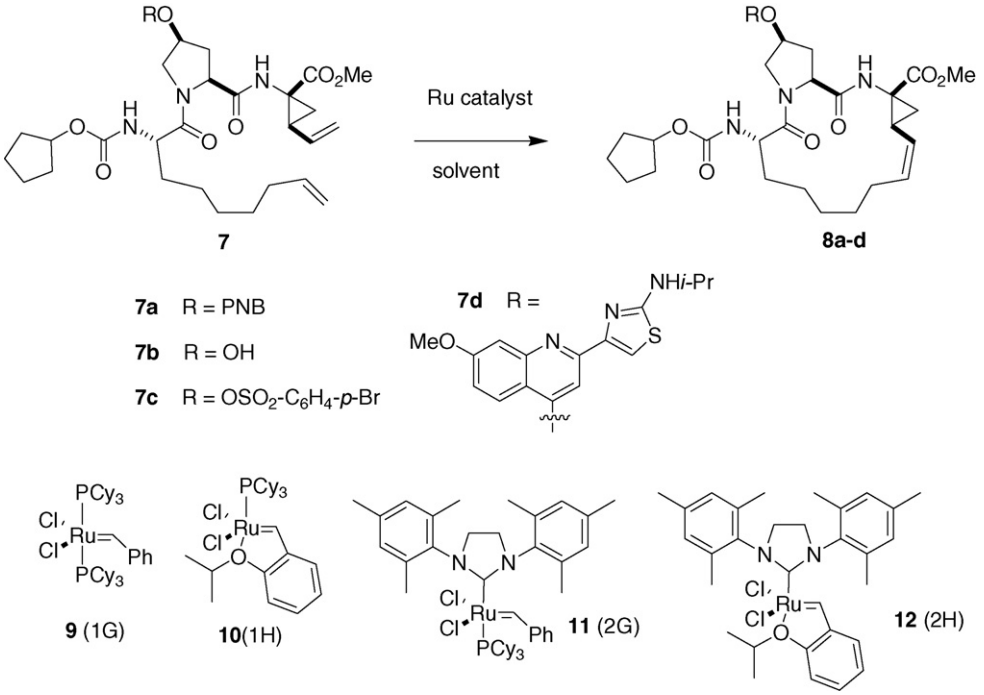
1. Use of first-generation Grubbs catalysts such as **9** (1G) led to a complex mixture due to a competing epimerization reaction, which was studied in detail (*vide infra*).
2. Use of a similar catalyst, **10** (1H), originally described by Hoveyda, led instead to almost quantitative yields of the desired product when operating in a number of solvents at rather low concentrations (up to 10 mM) over a very long reaction period (20–24 h). No epimerization was observed with this catalyst.
3. Addition of traces of amines or phosphines (at first inadvertently) to the above reaction mixture resulted in complex mixtures analogous to those obtained using the 1G catalyst.
4. Use of second-generation catalysts such as **11** and **12**, containing the imidazolium ligands, led to shortened reaction times but also to the production of up to 20% dimeric compounds (LC–MS evidence), operating at the same concentrations. The proportion of dimers and therefore the isolated yield at 10 mM concentration were markedly substrate-dependent. This was shown to be due to fast reversible re-opening of the RCM product to yield dimeric structures, whereas catalyst 1H was unable to accomplish this under "normal" conditions [3].
5. When using catalyst **9**, it could be established by NMR monitoring that initiation is fast and cyclization is rate limiting. The resting state of the catalyst could be determined and, surprisingly, initiation occurred at the more sterically encumbered P1 moiety (*vide infra*).
6. Submission of a number of vinylcyclopropanes analogous to building block P1 to typical olefin metathesis conditions led not to the expected metathesis products but to facile epimerization,

* Corresponding author. Current address: Johnson & Johnson Pharmaceutical Research and Development, Turnhoutseweg 30, 2340 Beerse, Belgium.
** Corresponding author.
E-mail addresses: vfarina@its.jnj.com (V. Farina), xingzhong.zeng@boehringer-ingelheim.com (X. Zeng).

0920-5861/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.cattod.2008.07.024



Scheme 1.



Scheme 2.

the rate of reaction and the composition of the final equilibrium depending markedly on the substrate used. We propose that the initiation site in the RCM using 1G catalysts could be predicted using these isolated P1 analogs in competition with a typical terminal olefin like 1-hexene.

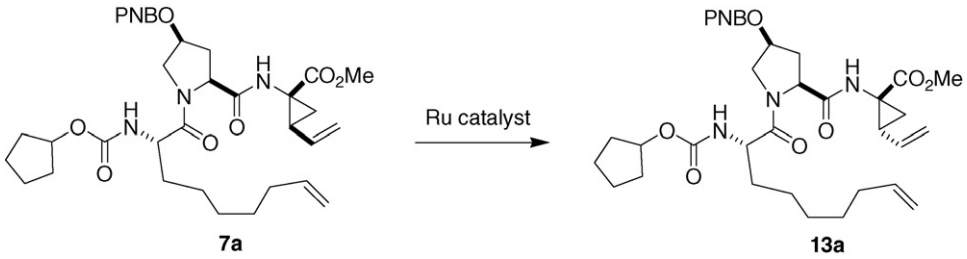
The details of these studies are discussed in the following section.

2. Discussion

By submitting **7a** to typical RCM conditions using catalyst **9**, epimerization of the substrate to diene **13a** was observed, in addition to RCM product. Diene **13a** also underwent RCM reaction, complicating product analysis (Scheme 3) [5].

This behavior was not observed when using Hoveyda's catalyst **10**. Indeed, the reaction with this catalyst led to a single product (**8a**). Initially, we did not attribute much importance to this phenomenon, and this discrepancy was pragmatically accepted as fact. Subsequently, however, when even catalyst **10** led to variable amounts of epimerization on large scale [6], we were forced to investigate the phenomenon in order to gain control of the manufacturing process.

It was quickly found that small amounts of Ru ligands such as amines and phosphines, in conjunction with catalyst **10**, promote the epimerization reaction. Among the most effective epimeriza-



Scheme 3.

tion promoters were tri(*n*-butyl)phosphine, tri(cyclohexyl)phosphine and *N*-methylpyrrolidine. Amine intermediates formed during the preceding steps of the process and not properly purged out by purification were also found to have the same effect.

In order to understand the behavior of different catalysts and the effect of added phosphines, the resting state of the catalyst was investigated by ^{1}H and ^{31}P NMR spectroscopy.

Upon admixing diene **7a** with 0.3–1.0 equiv. Grubbs catalyst **9** in CD_2Cl_2 at rt, three species were immediately visible, and they were tentatively identified as **14a**, **15a** and **16a** (Scheme 4). Only *ca.* 10% of catalyst **9** was unchanged, *i.e.* the resting state of the catalyst was a complex mixture of diene-derived Ru carbene species.

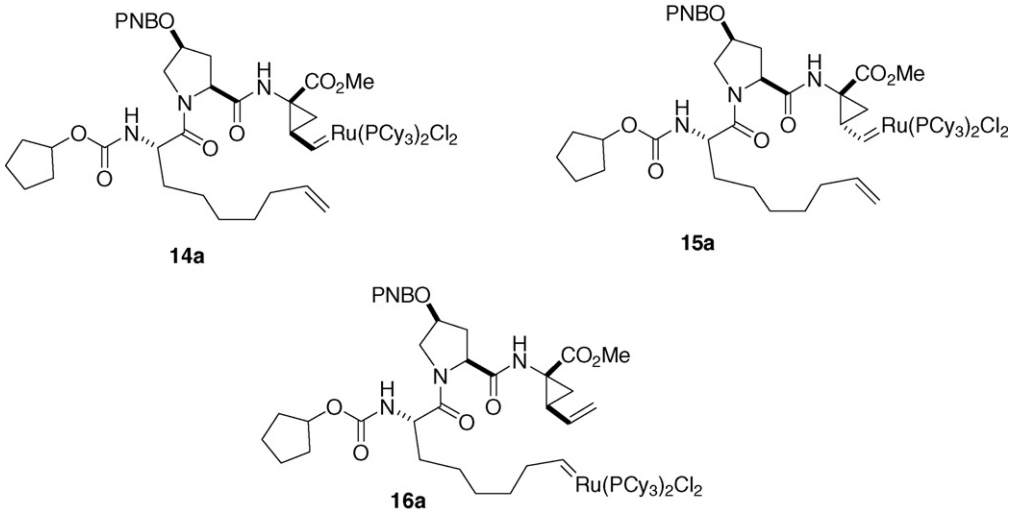
Whereas this transfer occurred instantly at rt, cyclization took many hours. Interestingly, species **14a** (identifiable in the ^{1}H NMR spectrum by the carbene methine at δ 18.49, d, J_{H-H} = 9.9 Hz) constituted at the outset *ca.* 96% of the Ru resting state, whereas the apparently less hindered species **16a** (br t at δ 19.26) formed in a proportion of only 4%. Epimerized species **15a** (δ 18.18, J = 9.9 Hz) apparently grew with time at the expense of **14a**. The sum of the two constituted 96% of the substrate-bound Ru, but their ratio grew from >99:1 to *ca.* 15:85 in a few hours, after which it stabilized. The ^{31}P NMR experiments showed two singlets at δ 37.8 and 38.9 for **14a** and **15a**, respectively, whereas the peak due to **16a** was too small for detection. The lack of H–P coupling in all these species, in analogy with catalyst **9**, demonstrates that these carbenes possess the same geometry, *i.e.* one in which the plane of the carbene is perpendicular to that of the P–Ru–P moiety. The lack of a signal for free PCy_3 suggests that all these carbene species contain two phosphine ligands each. However, the fact that in both **14a** and **15a** the two P atoms are isochronous, although they are diastereotopic, is an oddity that needs explanation. The dynamics of these Ru complexes were later investigated with the aid of variable-temperature NMR spectroscopy (*vide infra*).

When the NMR experiment was repeated with 0.3 molar equivalent Hoveyda catalyst **10**, no Ru trasfer to the substrate could be observed. Although slow turnover ensued, the only new species observable in the NMR was the corresponding Ru methylide (s at δ 19.0), which slowly built up.

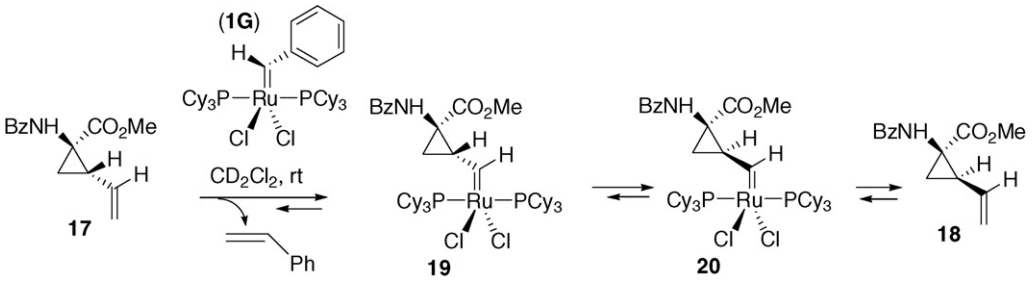
The following tentative conclusions were drawn from these experiments:

1. Epimerization of our diene substrates occurs via Ru carbene transfer from the catalyst. Given that the Ru resides, during the catalytic cycle, at the hindered P1 moiety, it has the ability to epimerize via an as yet unknown mechanism.
2. The fact that the Ru resides mostly at P1 says nothing about the direction of the metathesis. However, the fact that **14a** is much more stable than **16a**, in spite of being more sterically encumbered, suggests that it is hexacoordinated, most likely by the carbonyls present on each face of the cyclopropane ring. This extra stabilization may actually severely retard the ring-closing step and its removal may yield a much improved RCM step, in addition to eliminating the problematic epimerization.
3. The Hoveyda catalyst is characterized by a single phosphine in the coordination sphere of Ru, against the two in the Grubbs catalyst. Either the Hoveyda catalyst transfers (through an invisible steady-state species) exclusively to P3 instead of P1 or, more likely, the epimerization reaction we have witnessed requires two phosphine moieties at Ru to occur smoothly.

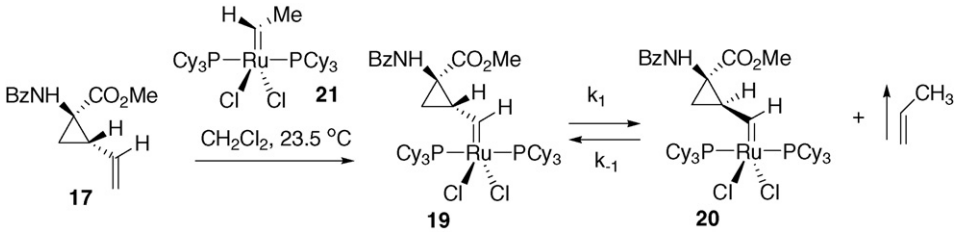
In order to probe further the above points, we decided to study the epimerization reaction on a smaller system, *i.e.* simply a P1 surrogate. Indeed, when we submitted **17** to a catalytic amount of



Scheme 4.



Scheme 5.



Scheme 6.

Grubbs catalyst **9** (or **10** plus 1 equiv. of PPh_3 or PCy_3), slow epimerization to **18** took place, presumably through Ru carbenes **19** and **20** (Scheme 5).

The apparent equilibrium constant in CD_2Cl_2 at 50 °C is *ca.* 5.3, which was obtained by carrying out the reaction in both directions. The kinetics of the reaction were equilibrium first-order, and the rate constant was derived by HPLC monitoring (toluene, 50 °C).

The kinetic constant for both forward and backward reactions increased with increased catalyst load, but not linearly. They were both inhibited by added phosphine (PCy_3) but not linearly [5]. This inhibition by free phosphine is typical of the metathesis reaction, because initial olefin complexation is a dissociative process: in our case, as discussed, amines and phosphines are promoters of the epimerization. There must be, therefore, a critical step in the mechanistic cycle that is associative. Thus, the epimerization event itself is likely to proceed through a 16e or 18e intermediate, and not a 14e intermediate like the metathesis initiation step.

NMR monitoring revealed, as expected, the intermediacy of **19** (^{1}H NMR δ 18.5, d, J = 9.9 Hz; ^{31}P NMR δ 38.37, s) and **20** (^{1}H NMR δ 18.3, d, J = 9.9 Hz; ^{31}P NMR δ 38.74, s). Their ratio reached 1:7 after several hours at rt, and this ratio could be duplicated by studying the backward reaction.

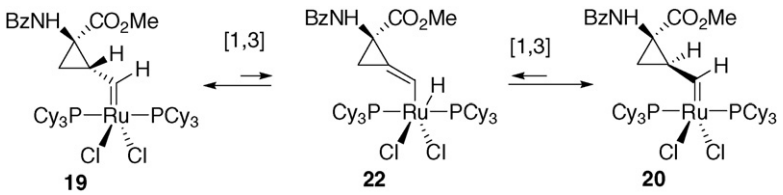
In order to prove without any doubt that species **19** spontaneously and directly converts to **20**, it was necessary to isolate **19,** remove the styrene that made the initial reaction reversible, and study its epimerization. This was carried out by using, as carbene transfer agent, ethylidene Ru species **21** (Scheme 6). The propene gas that was formed was evaporated, rendering the reaction irreversible.

The epimerization kinetics were carried out by ^{1}H NMR spectroscopy (CD_2Cl_2, 23.5 °C), and this indicated that the kinetic constant for the epimerization (1.36×10^{-2} min^{-1}) was basically identical with that of the catalytic reaction (1.27×10^{-2} min^{-1}), after correcting for the Ru used in the latter (10 mol%). Thus, spontaneous epimerization of species **19** fully accounts for the catalytic behavior observed with olefin **17**.

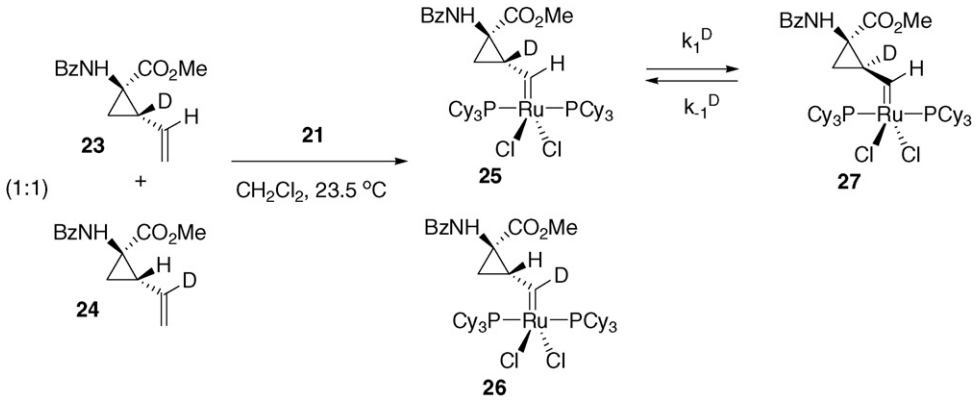
Isomerization of olefins can be catalyzed by Ru(II) species during metathesis reaction [7]. Of the mechanisms proposed for such isomerization, only one could be invoked to explain our new reaction [8]. This is shown in Scheme 7, and involves an allylic hydride shift which temporarily removes the stereogenic center at C-2 (through intermediate **22**).

An unequivocal way to test this mechanism or any other that would involve breakage of the cyclopropyl allylic proton would be to carry out a kinetic isotope effect (KIE) study. This is shown in Scheme 8.

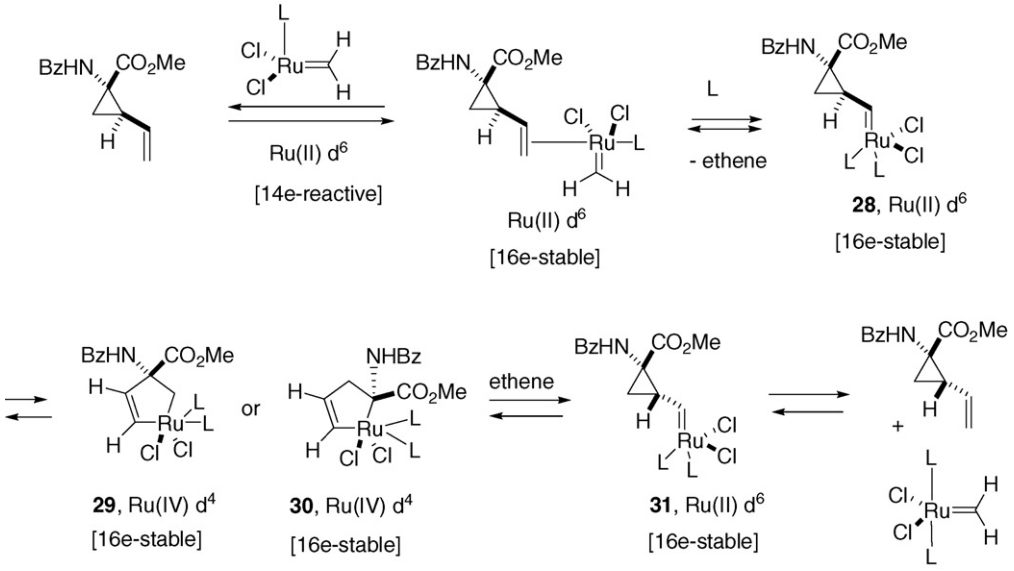
Mono-deuterated species **23** and **24** were obtained as a 1:1 mixture [5]. The NMR experiment measured the kinetics of the epimerization reaction of carbene **25**–**27** only (by integrating the low-field carbene protons), and yielded a KIE of 1.19 + 0.21, *i.e.* at most a small secondary isotope effect, but no primary one [9]. Further, this reaction is neither inhibited nor accelerated by added ligand. We must conclude that the C-2 stereocenter in species like **28** is epimerized via a 16e Ru species which incorporates two phosphine moieties in the coordination sphere of Ru and proceeds without breakage of the C(2)–H bond. Thus, we are led to invoke a brand new mechanism for such transformation. A mechanism that appears reasonable and explains all experimental facts is given in Scheme 9 and involves the intermediacy of ruthenacyclopentenes. Clearly, it is difficult to say which C–C bond is being broken, as both



Scheme 7.



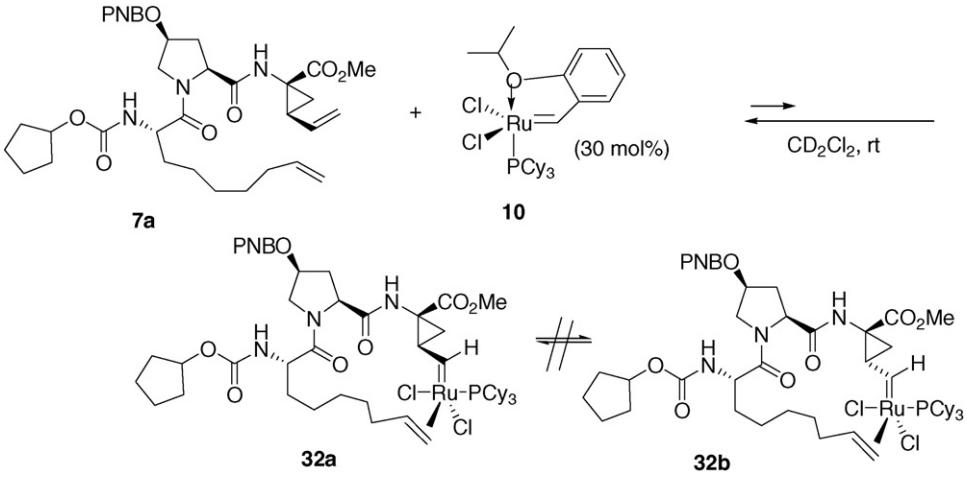
Scheme 8.



Scheme 9.

pathways can lead, through **29** or **30**, to the epimeric carbenes **28** and **31**.

After providing what we believe is a satisfactory rationalization for the epimerization process, it remained for us to explain why the Hoveyda catalyst **10** leads to no epimerization, and why it cyclizes so slowly. We believe that the RCM proceeds through a steady-state species such as **32a** (Scheme 10), where the Ru is probably further coordinated with the carbonyl of the methyl ester group and the



Scheme 10.

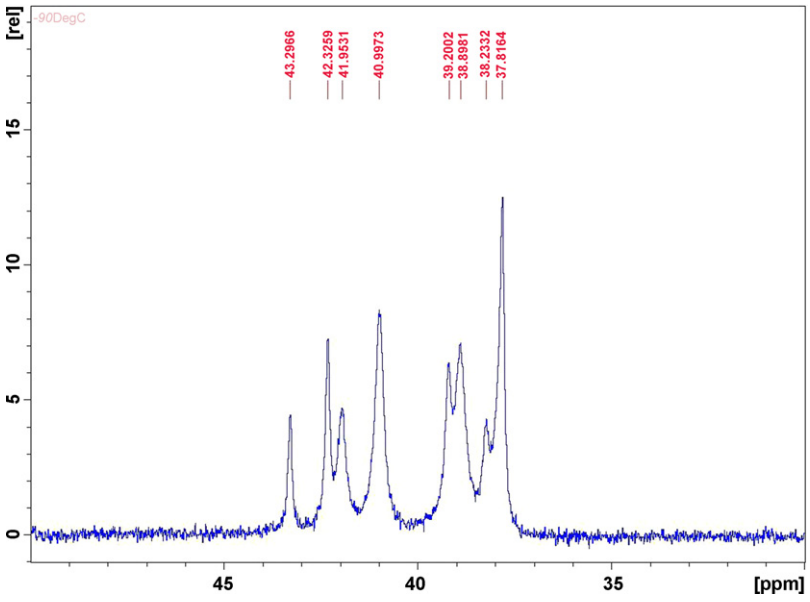
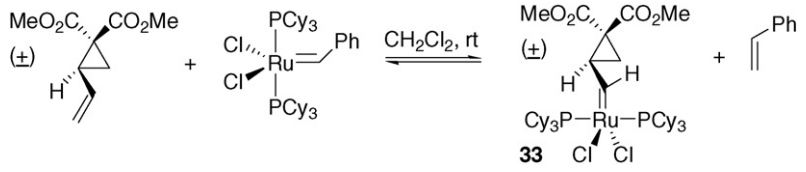


Fig. 1. ^{31}P NMR spectrum of **19** and **20** at −90 °C (peak at 37.8 is residual **9**).



Scheme 11.

olefin of the P3 moiety. This intermediate is probably incapable of epimerizing to **32b** for steric or electronic reasons, and leads only slowly to ring closure because it is stabilized by hexacoordination.

One piece of the puzzle that remained to be solved was the equivalence in the NMR spectrum of the two P atoms in species like **19** and **20**. In order to evidence the dynamic nature of the complex, we cooled a solution of **19** and **20** in CD_2Cl_2 to −90 °C, and obtained a spectrum consisting of two sets of AB quartets (J_{P-P} *ca.* 195 Hz) (Fig. 1). This is in agreement with P–P coupling constants reported for octahedral *trans*-diphosphine ruthenium metal complexes [10]. In order to study the phenomenon in a simpler system, we prepared the malonate complex **33** in quantitative yield as shown in Scheme 11.

This complex, an amorphous purple powder (^{1}H NMR δ 18.19, d, J = 10.0 Hz, ^{31}P NMR δ 38.5), exhibited the same behavior as **19** and **20**, and standard line-shape analysis [11] *vs.* temperature (from 189 to 263 K) led to the determination of the activation energy for the averaging process (9.9 kcal/mol, see Figs. 2 and 3).

This process is most likely a rotation process around the Ru=C double bond, although we lack conclusive evidence. It is consistent with the low barriers calculated for related carbene complexes [12]. Interestingly, in spite of its possible relevance to catalysis, the barrier of rotation around such double bond has never been reported in the literature for Ru carbenes that are also metathesis catalysts [13].

We were unable to obtain X ray-quality crystals of **33**, and sought to confirm the proposal of a hexacoordinated geometry for Ru by studying the catalytic properties of the new complex. When comparing the reaction rate in an RCM reaction where ring closure is fast and overall rate reflects initiation rates (Scheme 12), complex **33** gave a rate that was much faster than the one displayed by the Hoveyda catalyst **10**, but slower than that of the Grubbs catalyst **9**, qualitatively confirming our proposal of the weak extra stabilization (Fig. 4).

We are also interested in the reactivity of these cyclopropylmethylidene complexes, initially in a stoichiometric sense. We have observed that **33** engages in cyclocondensation reactions with alkynes. Indeed, when **33** was reacted with 5 equiv. of phenylacetylene in dichloromethane at rt, cyclohexadiene **34** was formed in *ca.* 50% yield, presumably through the mechanism shown (Scheme 13), which involves standard enyne metathesis

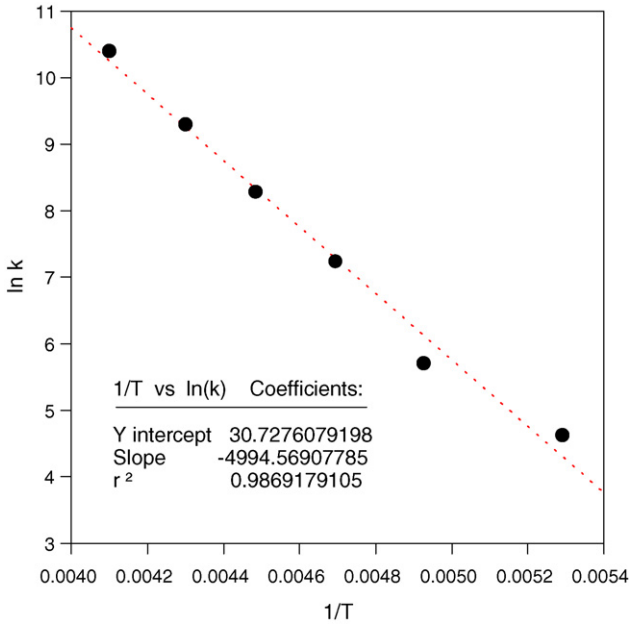


Fig. 2. Arrhenius plot for the dynamic process of **33** from ^{31}P NMR data.

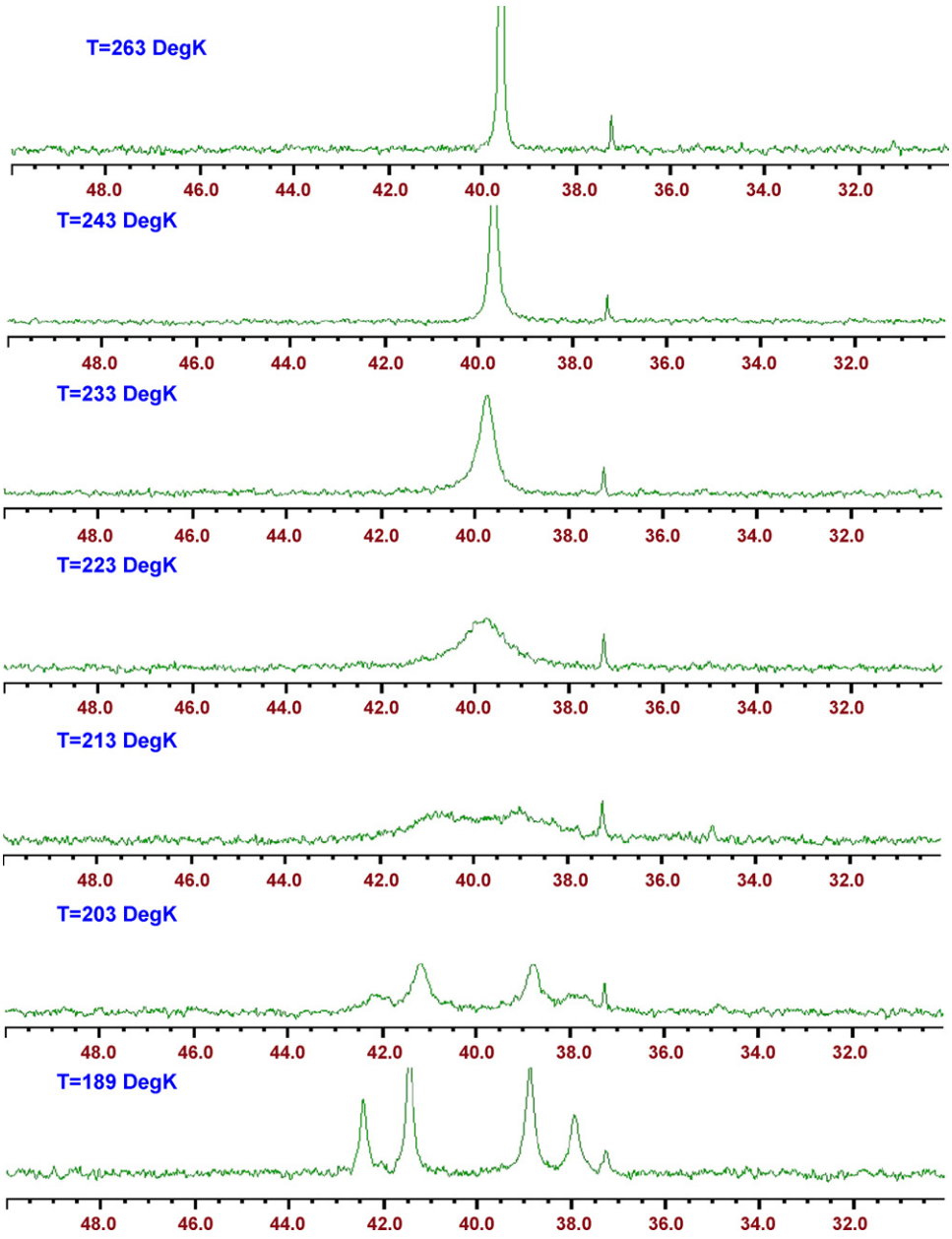
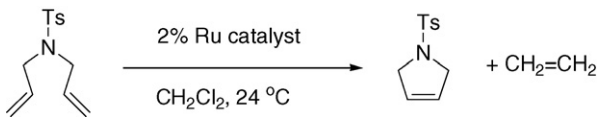


Fig. 3. ^{31}P NMR spectra of **33** at different temperatures.

steps [14]. The low yield may be due to the fact that the initial enyne metathesis is not selective in yielding the *Z* configuration at the newly formed C–C double bond, which is presumably necessary for the cyclization process. This novel reaction will be the subject of further in-depth studies.

Having been unable to prove conclusively that the initiation at P1 is due to Ru stabilization through hexacoordination, we decide to prepare a number of P1 surrogates with different Ru



Scheme 12.

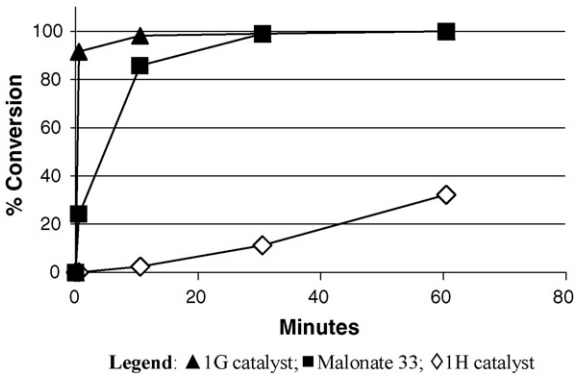
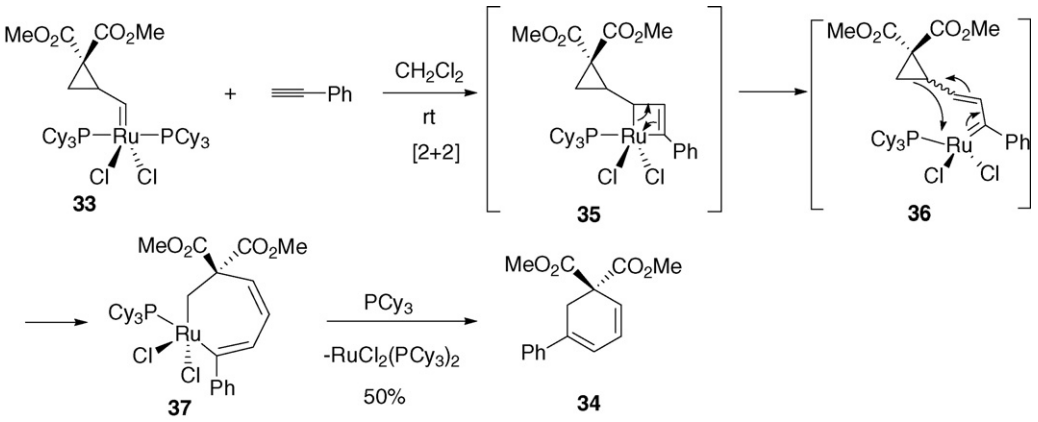
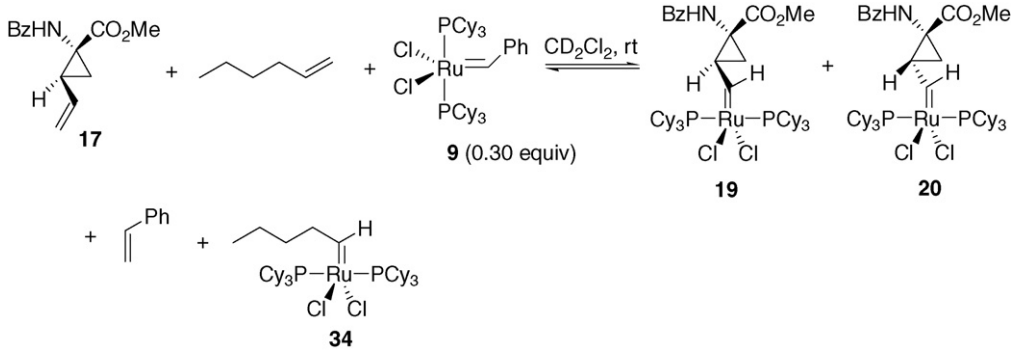


Fig. 4. RCM of diallyltosylamide with different catalysts.



Scheme 13.



Scheme 14.

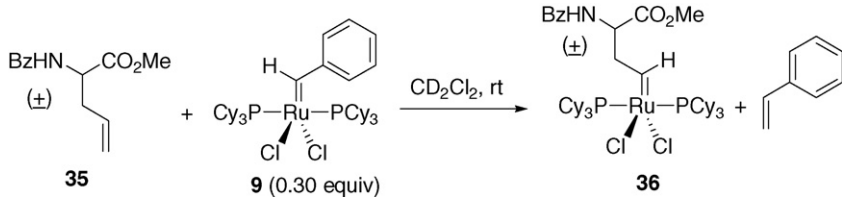
coordinating ability and geometry, and then study their ability to compete with a terminal, hindrance-free olefin for the Ru carbene transfer from **9**. This would presumably give us a reasonable estimate of the relative initiation chemoselectivity when these P1 surrogates would be inserted in typical dienes such as **7a**. To validate this model, we started with an intermolecular competition study between our P1 synthon **17** and 1-hexene (Scheme 14).

Upon reaction of **17** and an equimolar amount of 1-hexene with a substoichiometric amount of **9**, an apparent equilibrium was achieved in 2 h at rt, leading to a mixture in which the ratio P1 transfer/1-hexene transfer, *i.e.* [(**19** + **20**)/(**34**)] equaled 91:9, which is close to the P1/P3 initiation ratio observed during initiation with diene **7a** (96:4). New complex **34** was characterized by a triplet at δ 19.30 (J_{H-H} = 5.3 Hz) in the ^{1}H NMR spectrum and a singlet at δ 35.5 in the ^{31}P NMR spectrum. Again, the transfer of Ru carbene from **9** was almost complete (90%) and only 10% of **9** was still present at equilibrium. This experiment suggested that our model can be qualitatively useful.

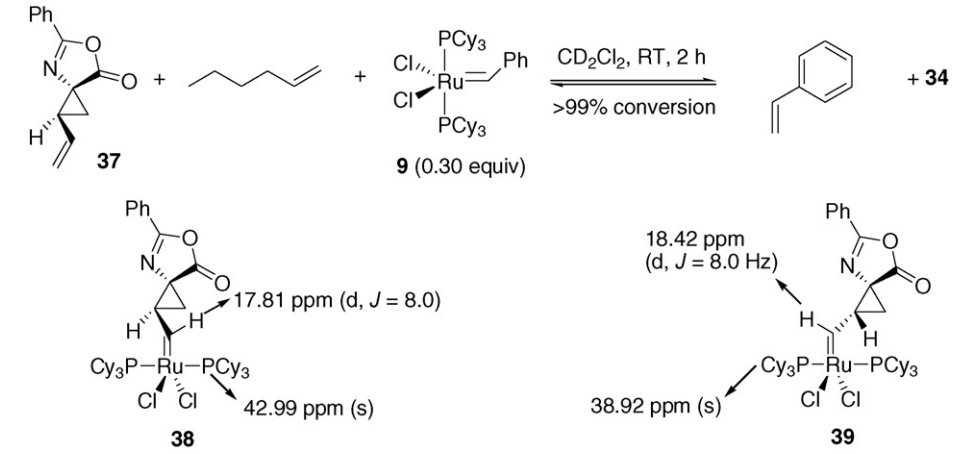
In order to probe the role of the rigidifying cyclopropane ring on the Ru transfer to P1, we used allyl glycine derivative **35** in the Ru exchange reaction. Minimal exchange (12–15%) from **9** was observed, in addition to slow metathesis, using ^{1}H NMR under standard conditions (Scheme 15). This confirms that the cyclopropane ring is most likely needed in order to enforce the coordination of the carbonyl groups to the Ru atom in **19** and **20**.

Bicyclic P1 analog **37**, containing an oxazolone ring, led to predominant formation (92:8) of **38** + **39** over the P3-type transfer product **34**, indicating once again a strong coordination, both by the carbonyl oxygen and especially the imide nitrogen. Interestingly, at equilibrium (2–3 h at rt) the epimerized species **39** largely predominates (96:4) over **38,** confirming that N coordination is stronger, at least in this particular case (Scheme 16). Salient NMR data are shown in the Scheme.

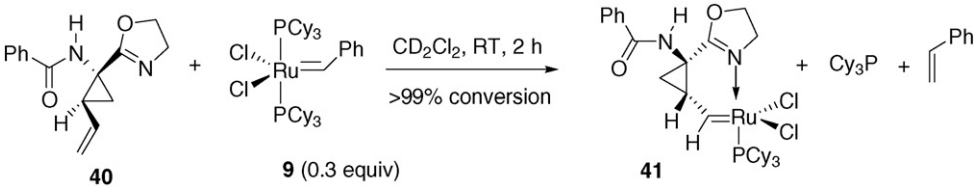
A very striking case of increased coordinative ability was provided by studying oxazoline **40**. Here, there was >99% transfer of Ru carbene from **9**, and 1-hexene could not compete at all with **40** for Ru transfer (<1% of **34**). In addition, as evidenced by the ^{31}P NMR spectrum, 1 equiv. of phosphine was displaced by the strong ligand oxazoline, producing only **41**, as shown in Scheme 17. Diagnostic are the NMR data (^{1}H NMR δ 18.97, dd, J_{H-H} = 11.3 Hz, J_{P-H} = 4.3 Hz; ^{31}P NMR δ 34.37, d, J = 4.3 Hz), in addition to the signal of free tri(cyclohexyl)phosphine (^{31}P NMR δ 10.77). No



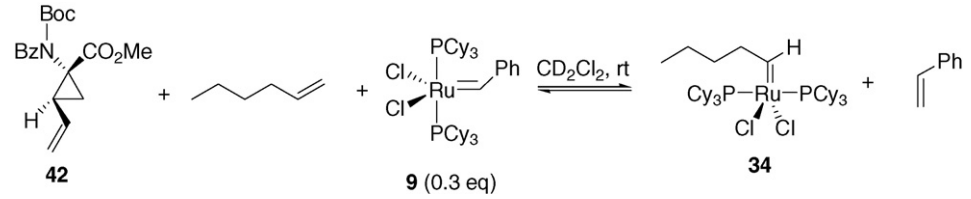
Scheme 15.



Scheme 16.



Scheme 17.



Scheme 18.

evidence of epimerization could be obtained in this case, most likely due to the strong chelating effect of the oxazoline moiety.

Finally, another P1 synthon of special interest is one in which the amide nitrogen is further functionalized. For example, P1 analog **42** was prepared [15], and it was found unable to compete with 1-hexene for Ru carbene transfer. No trace of a cyclopropylmethylidene species was observed, **34** being the only carbene transfer product (Scheme 18). We do not know whether the lack of carbene transfer to **42** is due to slow kinetics or lack of the type of stabilization encountered with **17**. If the latter is the case, it is tempting to speculate that *A* (1, 3) strain between either of the two acyl groups on the nitrogen atom and the carbomethoxy group in its coordination mode to the Ru atom may function to prevent this type of key stabilization.

We believe these divergent results are of the utmost importance in understanding the role of P1 structure on the chemoselectivity of RCM initiation. This may, in turn, help modulate the kinetics of our key RCM reaction by tuning the reactivity of our tripeptide through structural modifications. These efforts are underway.

3. Conclusion

We have described our studies aimed at elucidating the subtle factors affecting our key RCM reaction. It was found that first-generation catalysts such as **9** and **10** effect the reaction in high yield under "kinetic" conditions (*i.e.* the product does not re-open). Unfortunately, catalyst **9** catalyzes a novel epimerization reaction, whose mechanism we have studied in great detail, and cannot be used in our manufacturing process, but **10** is highly effective. Second-generation catalysts, although more active and free from the troublesome epimerization, yield thermodynamic products, which, at the same initial concentration, translates into more dimers and oligomers at equilibrium (*vs.* **10**). Leads to further improve this reaction (especially in relation to its low throughput and its extremely slow rate with **10**) were generated by modifying the P1 moiety and studying the striking effect of these modification on a model initiation study. These leads may help us develop a more practical RCM reaction. With the necessary improvements in catalyst performance and reaction throughput, we are confident that the RCM macrocyclization can be used for the multiton manufacturing of BILN 2061 or related analogs.

Acknowledgements

We thank Ioannis Houpis, Rogelio Frutos, Fabrice Gallou, Robert D. Simpson, Xuwu Feng, Victor Fuchs, Jonathan Tan, Lana L. Smith-Keenan, Jana Vitous, Michael D. Ridges, Earl Spinelli and Michael Johnson for their contributions to the BILN 2061 project. We also thank Profs. Erick Carreira, Scott Denmark, Peter Wipf and Donna Blackmond for useful suggestions.

References

[1] (a) R.H. Grubbs, Tetrahedron 60 (2004) 7117;
(b) R.H. Grubbs (Ed.), Handbook of Metathesis, 1–3, Wiley-VCH, New York, 2003;
(c) R.R. Schrock, A.H. Hoveyda, Angew. Chem. Int. Ed. 42 (2003) 4592;
(d) T.M. Trnka, R.H. Grubbs, Acc. Chem. Res. 34 (2001) 18;
(e) A. Fürstner, Angew. Chem. Int. Ed. 39 (2000) 3012.

[2] Y.S. Tsantrizos, G. Bolger, P. Bonneau, D.R. Cameron, N. Goudreau, G. Kukolj, S.R. LaPlante, M. Llinàs-Brunet, H. Nar, D. Lamarre, Angew. Chem. Int. Ed. 42 (2003) 1356.

[3] N.K. Yee, V. Farina, I. Houpis, N. Haddad, R.P. Frutos, F. Gallou, X.-j. Wang, X. Wei, R.D. Simpson, X. Feng, V. Fuchs, Y. Xu, J. Tan, L. Zhang, J. Xu, L.S. Smith-Keenan, J. Vitous, M.D. Ridges, E.M. Spinelli, M. Johnson, K. Donsbach, T. Nicola, M. Brenner, E. Winter, P. Kreye, W. Samstag, J. Org. Chem. 71 (2006) 7133.

[4] (a) P.L. Beaulieu, J. Gillard, M.D. Bailey, C. Boucher, J.-S. Duceppe, B. Simoneau, X.-j. Wang, L. Zhang, K. Grozinger, I. Houpis, V. Farina, H. Heimroth, T. Krueger, J. Schnaubelt, J. Org. Chem. 70 (2005) 5869;
(b) R.P. Frutos, N. Haddad, I. Houpis, M. Johnson, L.L. Smith-Keenan, V. Fuchs, N.K. Yee, V. Farina, A.-M. Faucher, C. Brichu, B. Haché, J.-S. Duceppe, P.L. Beaulieu, Synthesis (2006) 2563;
(c) X.-j. Wang, L. Zhang, L.L. Smith-Keenan, I. Houpis, V. Farina, Org. Process Res. Dev. 11 (2007) 60.

[5] X. Zeng, X. Wei, V. Farina, E. Napolitano, Y. Xu, L. Zhang, N. Haddad, N.K. Yee, N. Grinberg, S. Shen, C.H. Senanayake, J. Org. Chem. 71 (2006) 8864.

[6] T. Nicola, M. Brenner, K. Donsbach, P. Kreye, Org. Process Res. Dev. 9 (2005) 513.

[7] D.V. McGrath, R.H. Grubbs, Organometallics 13 (1994) 224.

[8] D. Bourgeois, A. Pancrazi, S.P. Nolan, J. Prunet, J. Organomet. Chem. 643-4 (2002) 247.

[9] Secondary isotope effects in metathesis reactions range from slightly positive to slightly negative, depending on the turnover-limiting step: (a) M. Ulman, R.H. Grubbs, Organometallics, 17 (1998) 2484. (b) C. Adlhart, C. Hinderling, H. Baumann, P. Chen, J. Am. Chem. Soc., 122 (2000) 8204.

[10] M. Pankowski, W. Chodkiewicz, M.-P. Simonnin, Inorg. Chem. 24 (1985) 533.

[11] H.A. Pople, W.G. Schneider, H.J. Bernstein, High-Resolution Nuclear Magnetic Resonance, McGraw-Hill, New York, 1967, p. 74.

[12] G.J. Spivak, J.N. Coalter, M. Olivan, O. Eisenstein, K.G. Caulton, Organometallics 17 (1998) 999.

[13] The same conclusion was reached by Grubbs and Sanford in an unpublished study. See: M. S. Sanford, Ph.D. dissertation, California Inst. of Technology, 2001. Diss. Abstr. Int. B, 62 (2002) 5114. We thank Prof. Sanford for providing us with a copy of the relevant thesis sections and for helpful discussions.

[14] S. Diver, A.J. Giessert, Chem. Rev. 104 (2004) 1317.

[15] Experimental details of the preparation of this and other P1 surrogates will be provided in a forthcoming full paper.