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Use of Commercially Available Ruthenium Fischer-Type Carbenes for Ring-Closing Metathesis Reactions: Scope and Limitations of an *in situ* Activation Procedure

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Abstract: An evaluation of two commercially available Fischer-type ruthenium carbenes in a range of ring-closing diene and enyne metathesis reactions has been carried out. A method to activate such catalysts for ring-closing reactions is presented.

Keywords: activation; enyne metathesis; Fischer carbenes; ring-closing metathesis; ruthenium

Over the past fifteen years the ruthenium-mediated ring-closing metathesis reaction has become a major tool for synthetic organic chemists allowing for synthesis of small and medium rings, macrocyles and heterocycles in both academic and industrial settings.[1,2] In response to a growing demand for ever more challenging substrates, the development of new catalysts is a similarly active field. An increasing number of ruthenium catalysts are now commercially available, with the Grubbs and Hoveyda 1st and 2nd generation catalysts[3] (**1**–**4**) still seeing the most use (Figure 1).[4,5] Recent attempts by the Nolan and Grela groups to provide a "users guide" to allow for catalyst selection have highlighted the plethora of choices available and the difficulty in selecting a catalyst for any given transformation.[6]

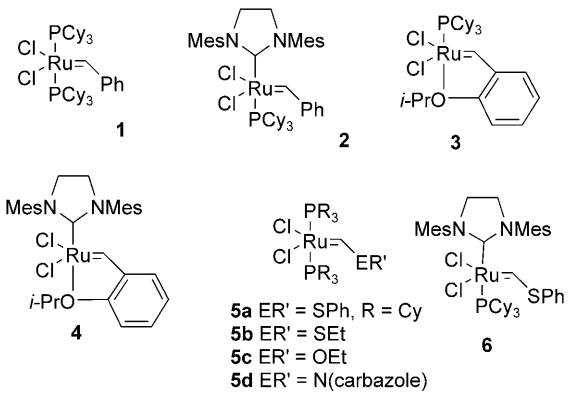
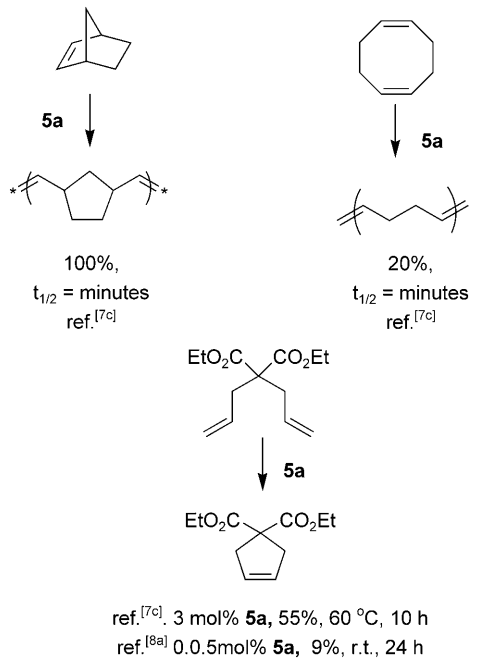


Figure 1. Common metathesis catalysts.

One series of catalyst absent from these recent reviews are the electron-rich Fischer-type carbene complexes such as **5a–d**.[7] In particular, complex **5a** is commercially available, shows comparable stability and shelf life to the original Grubbs catalyst **1**, is of similar price on laboratory scale and has been manufactured and used industrially.[8] As such this catalyst might be expected to feature in a range of synthetic applications, but to date has received limited use for the popular ring-closing reactions most often employed in natural product and medicinal chemistry syntheses.[9]

Although some early transition metal Fischer-type carbenes had been reported to undergo metathesis chemistry,[10] an initial evaluation of comparable ruthenium complexes in ring-closing reactions indicated a lack of reactivity,[11] and indeed reaction with ethyl vinyl ether (generating **5c**) has been used to quench ruthenium-catalyzed ring-opening metathesis polymerizations.[12] However, subsequent work by the Ciba group,[7b] Ozawa,[7a,d] and Grubbs,[7c] in the early years of this century showed that these catalysts were effective for a number of ring-opening polymerization reactions of highly strained cyclic olefins (norbornene and dicyclopenadiene) leading to the commercialization of **5a** (Scheme 1).[8] Unfortunately the reactivity of **5a** for promoting ring-opening of less hindered cyclic olefins such as 1,5-cyclooctadiene or ring-closing reactions remained low. For example, use of **5a** gave only 50% conversion for the usually facile ring-closing of diethyl diallylmalonate (DEDAM) with 3 mol% catalyst at 60 °C (Scheme 1).[7c,8a]

Despite this modest result we felt that catalyst **5a** and its second generation variant **6**, could be effective in promoting ring-closing reactions if the initial, less reactive Fischer-type carbene could be converted *in situ* to a more reactive alkylidene by taking advantage of their reactivity in certain ring-opening reactions. For example, initial reaction of **5a** with dicyclopentadiene (DCPD) is expected to afford **7** which reacts

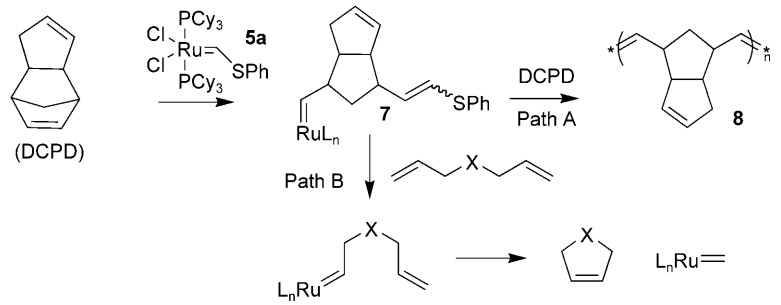


Scheme 1. Use of catalyst **5a** in ring-opening and ring-closing reactions.

further with DCPD *via* path A to give the expected polymer **8**. However, if DCPD is limiting, **7** could be intersected with other substrates which could undergo ring-closing chemistry *via* path B (Scheme 2). In this paper we describe our results on the use of catalysts **5a** and **6** in a range of ring-closing metathesis reactions and outline the scope and limitations of activating these catalysts *via* an initial ring-opening event.

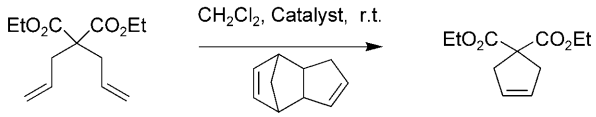
Our work started with a study of the benchmark ring-closing metathesis reaction of DEDAM. Treatment of a 0.25 M dichloromethane solution of DEDAM at room temperature with 0.5 mol% of catalysts **1** or **2** led to complete and clean conversion to the cyclized product in 18 and 2.5 h, respectively. In contrast, use of catalyst **5a** or **6** under otherwise identical conditions (catalyst loading, solvent, temperature, concentration) led to low conversion even after prolonged reaction times. However when 1.5 mol% of dicyclopentadiene (DCPD) was used in conjunction with the ruthenium catalyst we were pleased to observe a significantly improved reaction rate and conversion for catalyst **5a** and a marginal improvement for **6** (Table 1). A slight increase in the catalyst loading of **5a** to 1 mol% in conjunction with 3 mol% of DCPD gave complete conversion for the ring-closing reaction of DEDAM in 18 h and demonstrated that the proposed *in situ* method of activation for catalyst **5a** was indeed viable.

Support for the mechanistic proposal was sought by evaluating both initiation rate and the fate of the DCPD using NMR studies. A 0.5 M solution of DCPD is polymerized by 1.5 mol% **5a** within 1 hour to give an intractable solid. However, under the con-

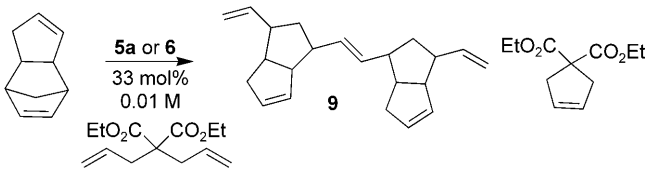


Scheme 2. Proposed activation of catalyst **5a** for ring-closing metathesis.

Table 1. Ring-closing metathesis of DEDAM.



Catalyst	Loading (mol%)	10 min	1 h	2.5 h	18 h	48 h
1	0.5	45	53	73	100	
2	0.5	9	76	100		
5a	0.5	0.5	4	11	36	46
6	0.5	0.5	4	7	12	12
5a, DCPD	0.5, 1.5	16	60	82	95	95
6, DCPD	0.5, 1.5	11	46	61	72	73
5a, DCPD	1, 3	-	-	-	100	



Scheme 3. Dimer **9** is the main DCPD by-product formed from the activation protocol.

ditions used to promote the RCM of DEDAM the catalyst loading with respect to DCPD is considerably higher (33 mol%) and the concentration of the catalytic components very low (typically < 0.01 M). Under these loading/dilution conditions, in the *absence* of DEDAM, full conversion of DCPD to polymeric material is complete within 2 h using catalyst **5a** and 10 min using catalyst **6**. Integration of the catalyst carbene proton (17.60 ppm for **5a** and 17.34 ppm for **6**) over the course of the reaction shows only marginal decrease of this species, implying only small amounts of the available catalyst are required to achieve this conversion. In the presence of DEDAM full consumption of DCPD is achieved in 2 h for both catalysts, along with decrease of the starting catalyst by about 50% (based on reduction in the ^{1}H NMR of the carbene proton). The DCPD is predominantly converted to dimeric species **9**, the structure of which has been confirmed by both NMR and mass spectroscopy following isolation. This result lends credence to the mechanism outlined in Scheme 2 where the polymerisation pathway (path A) is intersected by the diene prior to formation of polymer **8** (Scheme 3).

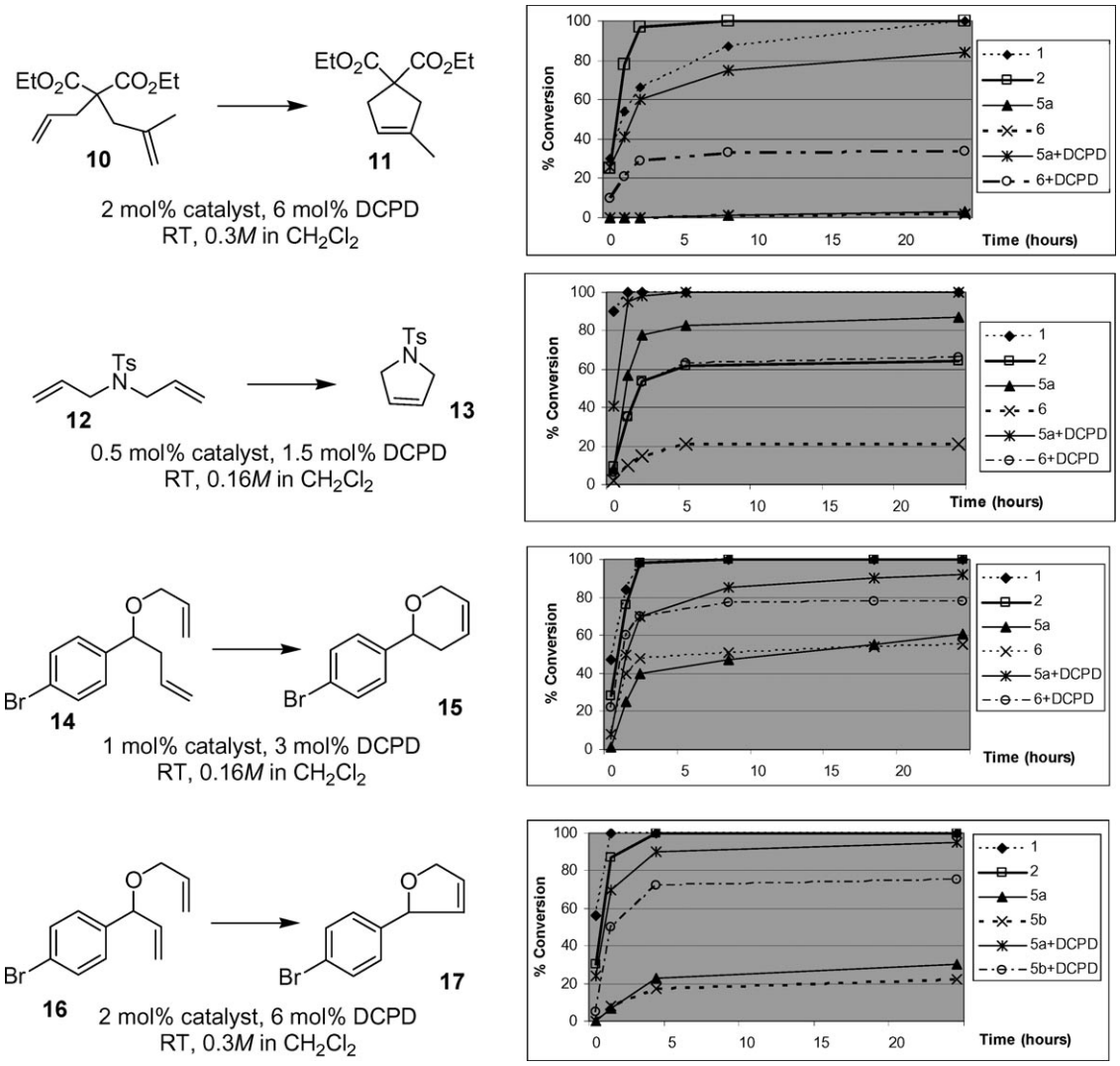
Based on these results a range of other ring-closing reactions were investigated to compare the reactivity of catalysts **5a** and **6** to **1** and **2** in the presence and absence of DCPD (Scheme 4). Catalysts **1** and **2** were generally found to be efficient promoters for these transformations leading to complete conversion within a few hours.[13,14] In contrast, under the same conditions (loading, concentration, solvent, temperature) catalysts **5a** or **6** were less effective leading to lower rates and incomplete conversion. For all reactions addition of a catalytic quantity of DCPD (3 equiv. with respect to catalyst) gave a significant increase in reactivity, with the results being most striking for catalyst **5a** when reactivity close to that obtained with catalyst **1** was restored. As with the DEDAM example the activation of catalyst **6** with DCPD is less effective than **5a**, but still leads to some increase with respect to the non-activated catalyst.

Careful inspection of the crude reaction mixtures by both ^{1}H NMR and HPLC indicate undetectable levels of any DCPD incorporation into the substrates via cross-metathesis pathways. Removal of the non-polar dimeric impurity **9** resulting from the DCPD can be achieved using standard chromatographic or crystallisation techniques, which are typically employed to remove ruthenium residues following RCM reactions. For example, purification of compound **13** by flash column chromatography (ethyl acetate:hexanes) efficiently removed ruthenium residues and DCPD impurities to afford analytically pure material in 87% isolated yield.

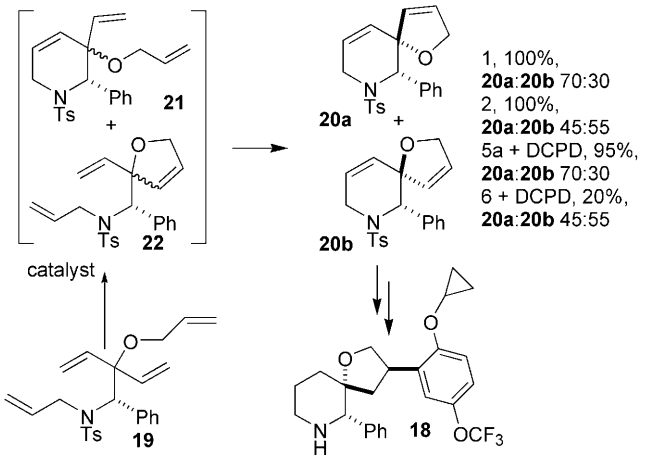
We recently reported a synthesis of the NK1-receptor antagonist **18** which used the double ring-closing metathesis reaction of tetraene **19** as a key step,[15] and hence this transformation was examined using the new protocol (Scheme 5). As previously reported, reaction of **19** with 10 mol% **1** gave complete conversion to the spirocyclic compounds **20a** and **20b** in a 70:30 ratio in favour of **20a**. Reaction with **2** also gave complete conversion, with a slight preference for **20b**.[15c] In contrast, reaction of **19** with catalysts **5a** or **6** gave less than 1% of spirocyclic products with small amounts of mono-cyclized intermediates **21** and **22** observed (23% and 10%, respectively, for reaction with **5a** and **6**). We were pleased to observe that use of 10 mol% **5a** in conjunction with 20 mol% DCPD gave a 68% yield of spirocyles (97% conversion of tetraene to combined intermediates and products). Increasing the catalyst loading of **5a** to 15 mol% with 20 mol% DCPD allowed for 95% conversion of **19** to the desired products.

Of particular interest was the stereoselectivity obtained in this reaction, which mirrored that obtained with catalyst **1** (and other "first generation" type catalysts[3,15c]), both with respect to final product ratio (70:30 **20a**:**20b**) and relative ratio of mono-cyclized intermediates detected as the reaction progressed. Activation of catalyst **6** with DCPD was less effective and only 20% yield of spirocyles and 58% conversion of starting material to intermediates was obtained even after prolonged reaction times. In this case the stereochemical distribution of mono-cyclized intermediates and product was comparable to that obtained using second generation catalysts such as **2.**

Finally, two ring-closing enyne metathesis reactions were studied to assess the utility of catalysts **5a** and **6** in for this process and to evaluate whether the *in situ* activation method would be effective in these cases.[16] (Scheme 6). The results for these transformations are somewhat in contrast to those obtained for the previous diene metathesis reactions. Catalyst **5a** was found to be a modest promoter for both enyne metathesis reactions and, in contrast to the diene reactions, the addition of DCPD did not significantly alter either the rate or conversion. Instead either an increase in catalyst loading or reaction time was found to be the most effective method to achieve conversion with **5a**. The second generation catalyst, **6** was found to be a poor promoter for both reactions with or without DCPD. Interestingly, in our hands catalyst **2** showed only modest reactivity for these transformations de-



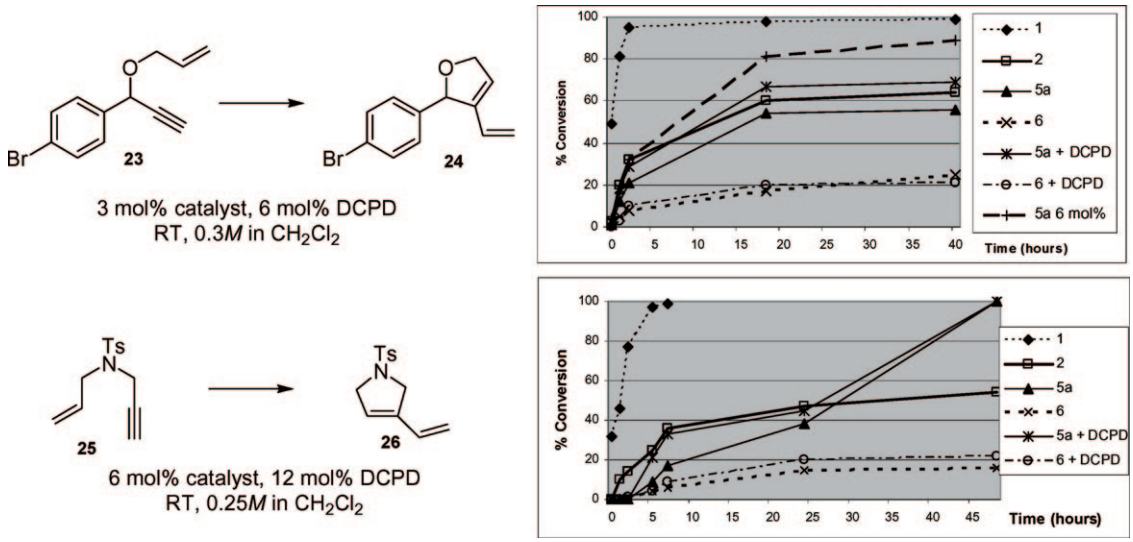
Scheme 4. Ring-closing metathesis of dienes with catalysts **5a** and **6**.



Scheme 5. Ring-closing metathesis of **19** with catalyst **5a** and **6**.

spite a number of literature examples documenting high conversions for such transformations.[17]

In conclusion, an evaluation of the utility of the commercially available ruthenium Fischer-type carbenes **5a** and **6** for a range of standard ring-closing alkene and enyne metathesis reactions has been carried out. For diene ring-closing reactions both catalysts are significantly less reactive than their carbon equivalents, however activation by addition of a catalytic amount of DCPD allows for an initial ring opening reaction to generate a more reactive alkylidene catalyst which then promotes the ring-closing reaction. This was found to be particularly effective for catalyst **5a** which showed comparable reactivity to **1** and could even be used for a challenging double ring-closing reaction. The same activation protocol was less effective when applied to enyne ring-closing reactions; however for these processes catalyst **5a** was modestly active even in the absence of additional acti-



Scheme 6. Enyne ring-closing metathesis reactions with catalyst **5a** and **6**.

vation and with a slight increase in loading and/or reaction time could give acceptable results.

As such another commercially available and bench stable catalyst can be included in the arsenal of available catalysts for ring-closing reactions, and catalyst **5a** provides a viable alternative to the Grubbs and Hoveyda first generation catalysts in case of supply problems. In contrast, the second generation variant **6** performed poorly for both diene and enyne metathesis reactions, showed only modest improvement with DCPD and at this time does not provide a realistic replacement for the standard second generation catalysts.

Experimental Section

General Procedure for the Ring-Closing Metathesis Reaction: Cyclisation of Diene 12

Diene **12** (1.50 g, 6.0 mmol) was dissolved in dichloromethane (36 mL). The solution was partitioned into 6 scintillation vials (6 mL, 1.0 mmol each) and each was de-gassed by subsurface nitrogen purge. To each of the first four vials was added 5 μmol of one of the catalysts **1** (4.1 mg), **2** (4.2 mg), **5a** (4.3 mg) and **6** (4.4 mg). In a separate flask a 0.5 M solution of dicyclopenadiene in dichloromethane was prepared. To the final two vials dicyclopenadiene, (30 μL, 0.5 M in dichloromethane, 15 μmol) was added followed by 5 μmol of either catalyst **5a** (4.3 mg) or **6** (4.4 mg). The progress of the reaction was monitored by HPLC analysis; purified samples of starting material **12** and product **13** were used to provide analytical standards. If required, isolation of the product was achieved by concentration and flash column chromatography to afford **13** having analytical data in accord with literature values.

Acknowledgements

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References

[1] For recent (2000-) reviews of ruthenium-catalyzed ring-closing alkene metathesis see:- a) A. Fürstner *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; b) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; c) M. A. Walters, *Progress in Heterocyclic Chemistry* **2003**, *15*, 1; d) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; e) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199; f) M. D. McReynolds, J. M. Dougherty, P. R. Hanson, *Chem. Rev.* **2004**, *104*, 2239; g) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; h) T. J. Donohoe, A. J. Orr, M. Bingham, *Angew. Chem.* **2006**, *118*, 2730; *Angew. Chem. Int. Ed. Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 2664; i) A. Michaut, J. Rodriguez, *Angew. Chem.* **2006**, *118*, 5870; *Angew. Chem. Int. Ed.* **2006**, *45*, 5740.

[2] A number of journals have dedicated issues to the topic of olefin metathesis, see: a) *Tetrahedron* **1999**, *55*, 8141–8262; b) *J. Mol. Cat. A.* **2006**, *254*, 1–208; c) *J. Organomet. Chem.* **2006**, *691*, 5077–5524; d) *Adv. Synth. Catal.* **2007**, *349*, 1–265.

[3] In this paper the term "first generation catalyst" describes catalysts lacking the dihydroimidazole ligand (e.g., **1**, **3** and **5a**) and "second generation catalyst" those with the dihydroimidazole ligand, (e.g., **2**, **4** and **6**).

[4] a) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100; b) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953; c) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am.*

Chem. Soc. **2000**, *122*, 8168; d) S. Gessler, S. Randl, S. Blechert, *Tetrahedron Lett.* **2000**, *41*, 9973; e) J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, Jr., A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791.

[5] For other ruthenium olefin metathesis catalysts see refs.[1,2] and, inter alia: a) A. Fürstner, J. Grabowski, C. W. Lehmann, *J. Org. Chem.* **1999**, *64*, 8275; b) J. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc.* **1999**, *121*, 2674; c) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247; d) L. Jafarpour, H. J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 5416; e) T. Weskamp, F. J. Kohl, W. Hieringer, D. Gleich, W. A. Herrmann, *Angew. Chem.* **1999**, *111*, 2573; *Angew. Chem. Int. Ed.* **1999**, *38*, 2416; f) A. Fürstner, O. Guth, A. Duffels, G. Seidel, M. Liebl, B. Gabor, R. Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811; g) K. Grela, S. Harutyunyan, A. Michrowska, *Angew. Chem.* **2002**, *114*, 4210; *Angew. Chem. Int. Ed.* **2002**, *41*, 4038; h) H. Wakamatsu, S. Blechert, *Angew. Chem.* **2002**, *114*, 832; *Angew. Chem. Int. Ed.* **2002**, *41*, 794;; i) H. Wakamatsu, S. Blechert, *Angew. Chem.* **2002**, *114*, 2509; *Angew. Chem. Int. Ed.* **2002**, *41*, 2403; j) A. Michrowska, R. Bujok, S. Harutyunyan, V. Sashuk, G. Dolgonos, K. Grela, *J. Am. Chem. Soc.* **2004**, *126*, 9318; k) M. Bicnick, R. Bujok, M. Cabaj, N. Lugan, G. Lavigne, D. Arlt, K. Grela, *J. Am. Chem. Soc.* **2006**, *128*, 13652.

[6] a) H. Clavier, S. P. Nolan, *Chem. Eur. J.* **2007**, *13*, 8029; b) M. Bieniek, A. Michrowska, D. L. Usanov, K. Grela, *Chem. Eur. J.* **2008**, *14*, 806.

[7] a) H. Katayama, H. Urushima, T. Nishioka, C. Wada, M. Nagao, F. Ozawa, *Angew. Chem.* **2000**, *112*, 4687; *Angew. Chem. Int. Ed.* **2000**, *39*, 4513; b) P. A. van der Schaaf, R. Kolly, H. J. Kirner, F. Rime, A. Muhlebach, A. Hafner, *J. Organomet. Chem.* **2000**, *606*, 65; c) J. Louie, R. H. Grubbs, *Organometallics* **2002**, *21*, 2153; d) H. Katayama, M. Nagao, F. Ozawa, *Organometallics* **2003**, *22*, 586.

[8] a) P. A. van der Schaaf, A. Hafner, A. Muhlebach, *Patent WO* 99/00396, **1999**; b) catalysts **5a** and **6** are available from Strem in research quantities.

[9] For one example of the failure of **5a** in a RCM reaction see R. N. Chapman, P. S. Arora, *Org. Lett.* **2006**, *8*, 5825.

[10] a) T. J. Katz, N. Acton, *Tetrahedron Lett.* **1976**, *17*, 4251; b) T. J. Katz, S. J. Lee, M. A. Shippey, *J Mol. Catal.* **1980**, *8*, 219.

[11] Z. Wu, S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1995**, *117*, 5503.

[12] W. Weck, B. Mohr, B. R. Maughon, R. H. Grubbs, *Macromolecules* **1997**, *30*, 6430.

[13] Reactions were monitored by HPLC and/or NMR. To allow for convenient analysis, catalyst loadings for each substrate were chosen to give reaction times in the order of hours. A preliminary evaluation of the reactivity of each substrate with catalyst **1** was used to guide this choice.

[14] Compounds **14**, **16** and **23** were prepared by addition of allylmagnesium chloride, vinylmagnesium bromide and propargylmagnesium bromide to 4-bromobenzaldehyde respectively, followed by reaction of the resulting alcohol with allyl bromide and sodium hydride. New compounds were characterised by standard methods.

[15] a) D. J. Wallace, C. J. Cowden, D. J. Kennedy, M. S. Ashwood, I. F. Cottrell, U. H. Dolling, *Tetrahedron Lett.* **2000**, *41*, 2027; b) D. J. Wallace, J. M. Goodman, D. J. Kennedy, A. J. Davies, C. J. Cowden, M. S. Ashwood, I. F. Cottrell, U. H. Dolling, P. J. Reider, *Org. Lett.* **2001**, *3*, 671; c) D. J. Wallace, *Tetrahedron Lett.* **2005**, *46*, 591; d) D. J. Wallace, *J. Mol. Catal. A* **2006**, *254*, 78.

[16] For reviews of ring-closing enyne metathesis see: a) C. S. Poulsen, R. Madsen, *Synthesis* **2003**, 1; b) S. T. Diver, A. J. Geissert, *Chem. Rev.* **2004**, *104*, 1317; c) M. Mori, *Adv. Synth. Catal.* **2007**, *349*, 121.

[17] Enyne methathesis reactions are often run under ethylene atmospheres to promote turnover (M. Mori, N. Sakakibara, A. Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082). To avoid confounding results ethylene was not used in this study and may have compromised the reactions with catalyst **2** compared to literature results.

