DOI: 10.1002/adsc.200600306

Oxapolycycles from One-Pot Cross-Metathesis/Carbonyl Ylide Formation-Intramolecular Cycloaddition of α-Diazo-β-keto Esters

David M. Hodgson[a,*] and Deepshikha Angrish[a]

[a] Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK
Fax: (+44)-1865-285002; e-mail: david.hodgson@chem.ox.ac.uk

Received: June 26, 2006; Accepted: September 4, 2006

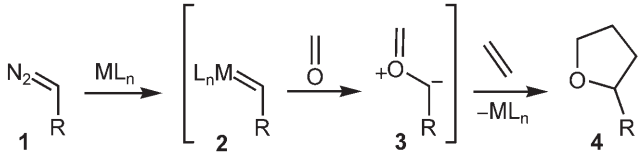
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Chemoselective cross-metathesis of unsaturated α-diazo-β-keto esters using Grubbs' 2nd generation catalyst, followed by $Rh_2(OAc)_4$-catalysed tandem carbonyl ylide formation-intramolecular cycloaddition is demonstrated. The two different catalytic metallocarbene transfer reactions have also been successfully carried out in a one-pot procedure, which allows rapid generation of molecular complexity in a single operation.

Keywords: carbonyl ylides; cross-metathesis; cycloaddition; diazo compounds; rhodium acetate

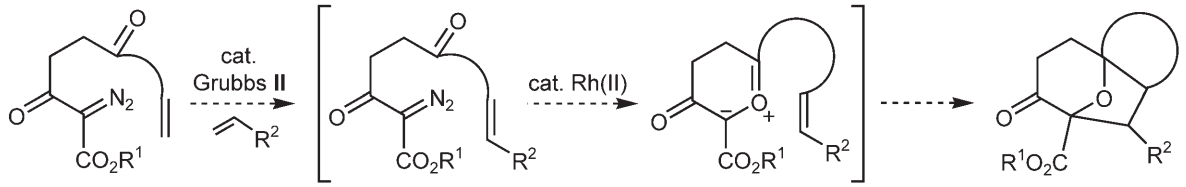
Introduction

Metallocarbenes **2**, obtained from transition-metal catalysed decomposition of diazo compounds **1**, are normally reactive intermediates that are known to undergo a number of synthetically useful transformations such as σ-bond (e.g., C–H, O–H) insertion, cyclopropanation, and ylide-based process.[1] Carbonyl ylides **3**, generated from the interaction of carbonyl functionality with metallocarbenes **2**, are capable of undergoing 1,3-dipolar cycloaddition with dipolarophiles to furnish reduced furans **4** (Scheme 1).[2] Such cascade process, catalysed by copper or rhodium complexes, were originally developed by Ibata and especially Padwa for the synthesis of oxapolycycles,[3] and are of interest because of the opportunities for rapid generation of molecular complexity in a single operation.



Scheme 1. Metal-catalysed 1,3-dipolar cycloaddition using diazo and carbonyl compounds.

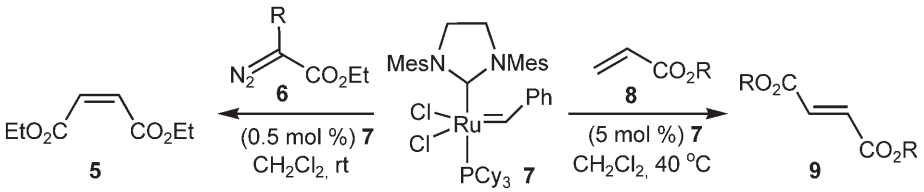
In the present paper, we report on advances in this process to generate more complex oxapolycycles by initial alkene cross-metathesis, followed by tandem carbonyl ylide formation/intramolecular 1,3-dipolar cycloaddition (Scheme 2).[4] Alkene cross-metathesis, has undergone tremendous development in recent times, making it currently one of the most mild and powerful processes for elaborating olefins for potential use in subsequent transformations.[5] The methodology is especially useful in its current form because of the (commercial) availability of Ru-based metathesis (pre-)catalysts exhibiting compatibility with a wide range of functional groups, although tolerance of diazo functionality was not established at the outset of our investigations.



Scheme 2. Cross-metathesis and carbonyl ylide formation/intramolecular cycloaddition strategy.

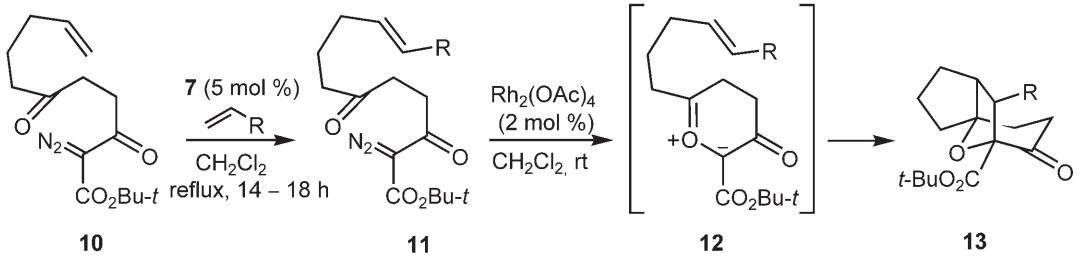
Results and Discussion

In earlier studies, we observed that Grubbs' 2nd generation catalyst **7**, the most commonly used catalyst for olefin metathesis, could also catalyse the coupling of diazoacetates (e.g. **6**, R = H) under mild conditions to give *cis*-olefins **5** (Scheme 3).[6] In contrast, olefin metathesis of acrylates **8** gives rise to *trans*-α,β-unsaturated carbonyl compounds **9**.[7]



Scheme 3. Maleates **5** and fumarates **9** using Grubbs' 2nd generation catalyst **7**.

Upon further exploration of the reactivity of catalyst **7** with more substituted diazoesters, we found that ethyl α-diazopropanoate **6** (R = Me)[8] was stable to catalyst **7** in CH_2Cl_2 at room temperature but underwent decomposition at reflux. However, the more stabilised α-diazo-β-keto ester **6** (R = COMe, derived from ethyl acetoacetate)[9] was stable to catalyst **7**, under typical metathesis conditions (5 mol% **7**, CH_2Cl_2, reflux, 14–18 h). This last result suggested that olefin metathesis might proceed in presence of such dicarbonyl-stabilised diazo functionality, and this could then allow straightforward diversity generation in unsaturated diazo compounds. The retained diazo functionality would subsequently be used to facilitate metal-catalysed carbene transfer reactions involving the newly elaborated olefin. Due to our interest in tandem carbonyl ylide formation-cycloaddition of diazo compounds, we selected unsaturated 2-diazo-3,6-diketo ester **10**[10] to test this concept (Scheme 4).

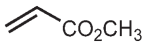
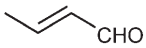
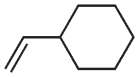
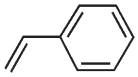
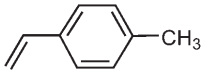
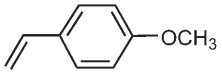
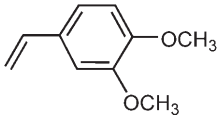
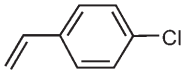
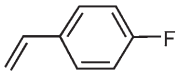
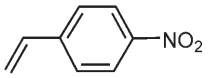
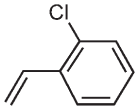
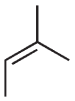
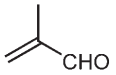


Scheme 4. Cross-metathesis/carbonyl-ylide formation/intramolecular cycloaddition using diazo ester **10**.

We first examined 2-diazo-3,6-diketo ester **10** with methyl acrylate, as the latter is known to undergo stereoselective cross-metathesis with terminal olefins,[5,7] and the resulting desired ester **11** [R = CO_2Me, previously prepared from **10** ($CN_2 = CH_2$) by cross-metathesis followed by diazo transfer] was already known to undergo 1,3-dipolar cycloaddition.[11] In the event, cross-metathesis proceeded smoothly with 2-diazo-3,6-diketo ester **10** and methyl acrylate (2.0 equivs.) with Grubbs' 2nd generation catalyst **7** (5 mol%, CH_2Cl_2, reflux, 16 h) to give the *E*-α,β-unsaturated ester **11** (R = CO_2Me) in good yield (74%) and complete *E*-stereoselectivity (Table 1, entry 1). Importantly, retention of the diazo functionality was observed. Cross-metathesis of unsaturated 2-diazo-3,6-diketoester **10** with various other olefins (5–10 equivs.)[12] was then examined using catalyst **7** (5 mol%) in CH_2Cl_2 at reflux for 14–18 h, and substituted alkenes **11** were obtained in good to excellent yields and generally with high stereoselectivity (Table 1).

Crotonaldehyde, vinyl cyclohexane and sterically demanding 3,3-dimethyl-1-butene were all good partners for the cross-metathesis process, with crotonaldehyde and 3,3-dimethyl-1-butene giving only *E*-isomers **11b** and **11d** (entries 2 and 4). Although styrene underwent efficient cross-metathesis (entry 5), more electron rich styrenes were increasingly reluctant partners (entries 6–8), as evidenced from the drop in yields. In the cases of the methoxystyrenes (entries 7 and 8), prolonged reaction times, further addition of catalyst, or use of a large excess of the methoxystyrene (15–20 equivs.) failed to drive cross-metathesis to completion. Styrenes bearing electron-withdrawing (Hal, NO_2) *para* or *ortho* substituents led to higher yields with excellent *trans*-selectivity (entries 9–12). Cross-metathesis with both amylene and methacrolein

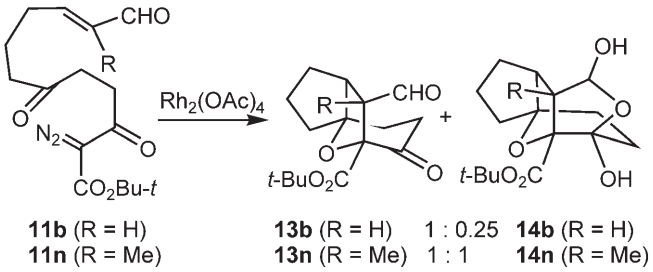
Table 1. Cross-metathesis and carbonyl ylide formation/cycloaddition using diazo ester **10**.

Entry	Olefin	Cross-metathesis % (E:Z)[a]	Cycloaddition %	Yield over 2 steps (%)	Yield in one pot (%)
1		**11a** 74 (E only)	**13a** 89	66	69
2		**11b** 76 (E only)	**13b** 85[b]	65	70[b]
3		**11c** 78 (85:15)	**13c** 78	61	63
4		**11d** 74 (E only)	–[c]	–	–[c]
5		**11e** 81 (E only)	**13e** 84	68	73
6		**11f** 69 (94:6)	**13f** 86	59	77
7		**11g** 46[d] (E only)	**13g** quant.	46	43
8		**11h** 36 (E only)	–[e]	–	–[e]
9		**11i** 76 (E only)	**13i** 82	62	68
10		**11j** 76 (96:4)	**13j** 88	67	75
11		**11k** 79 (E only)	**13k** quant.	79	76
12		**11l** 89 (96:4)	**13l** 78	69	80
13		**11m** 77 (-)	**13m** 74	57	79
14		**11n** 83 (E only)	**13n** 77[f]	64	86[f]

[a] Determined by ^{1}H NMR.
[b] Isolated as *ca.* 1:0.25 mixture of **13b** with hydrate **14b**.
[c] No cycloadduct observed.
[d] 74% based on recovered diazo ester **10**.
[e] Not carried out.
[f] Isolated as *ca.* 1:1 mixture of **13n** with hydrate **14n**.

proceeded efficiently to generate cycloaddition substrates **11m** and **n** bearing trisubstituted alkene dipolarophiles (entries 13 and 14).

With the above elaborated di/trisubstituted olefins **11** in hand, we examined their propensity to undergo tandem carbonyl ylide formation-intramolecular cycloaddition. In general, catalysis by $Rh_2(OAc)_4$ (2 mol%) in CH_2Cl_2 at room temperature for 3–4 h proceeded very efficiently to give the cycloadducts **13** in good to excellent yields (Table 1). However, *tert*-butyl-substituted alkene **11d** (generated from cross-metathesis of **10** and 3,3-dimethyl-1-butene, Table 1, entry 4) failed to undergo cycloaddition, suggesting a limitation of the chemistry with hindered alkene dipolarophiles.[13] Aryl-substituted dipolarophiles underwent efficient cycloaddition with no observable influence of the electronic nature of the aromatic ring being evident (entries 5–12).[14] Trisubstituted olefins **11m** and **n** gave the corresponding cycloadducts **13m** and **n** efficiently (74% and 77% yields, respectively).



11b (R = H) **13b** (R = H) 1 : 0.25 **14b** (R = H)
11n (R = Me) **13n** (R = Me) 1 : 1 **14n** (R = Me)

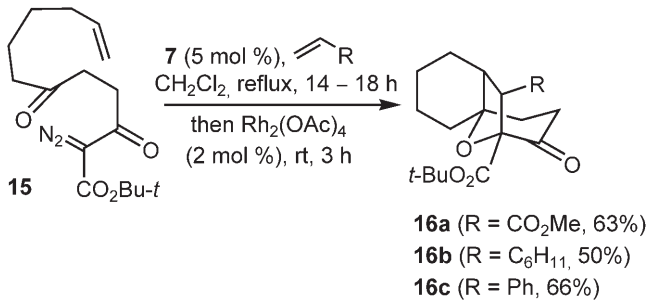
Scheme 5. Intramolecular carbonyl ylide cycloaddition with α,β-usaturated aldehyde dipolarophiles.

Interestingly, the cycloadduct **13n** from methacrolein was isolated as a 1:1 mixture with its cyclic hydrate **14n** [Scheme 5, with crotonaldehyde, hydrate **14b** formation was also observed but to a lesser extent], and provides another example of Woodward's well-known dictum "that enforced propinquity often leads on to greater intimacy".[15]

Single cycloadduct stereoisomers **13** were observed in all cases when starting with geometrically pure alkenes **11**. Stereochemistry was assigned on the basis that stereospecificity in this type of (intramolecular) cycloaddition with simple alkenes has been previously established.[11] Importantly, the use of more polarised alkenes in the present study does not lead to loss of stereospecificity (e.g., by encroachment of a stepwise reaction process). The current results expand the range of substituted alkene dipolarophiles that can be used in this (intramolecular) cycloaddition chemistry.

Having establishing the tolerance of diazo functionality in α-diazo-β-keto ester **10** to cross-metathesis using Grubbs' 2nd generation catalyst **7**, we studied the one-pot cross-metathesis/intramolecular carbonyl ylide cycloaddition cascade reaction. The latter was in order to examine the effectiveness of Rh(II) catalysis in the presence of spent (following metathesis) Ru catalyst (i.e., to see if the latter would affect the subsequent Rh(II)-catalysed transformation).[16] The one-pot cross-metathesis/carbonyl ylide cycloadditions were carried out using catalyst **7** (5 mol%) in CH_2Cl_2 at reflux for 14–18 h, followed by addition of $Rh_2(OAc)_4$ (2 mol%) after cooling to rt, and proceeded smoothly to yield the desired cycloadducts **13** in good to excellent yields, compared to the yields over 2 steps (Table 1). The one-pot protocol also proved effective using carbonyl-ylide precursor **15**[10] containing a 4- (rather than 3-) methylene-tethered dipolarophile (Scheme 6). Since hexenyl-tethered substrates possess slower rates of cycloaddition than the corresponding pentenyl systems,[17] it was interesting that no intermolecular trapping by excess methyl acrylate or fumarate (present from the cross-metathesis step) was observed in the one-pot synthesis of cycloadduct **16a**.

Tolerance of phthalic anhydride-derived α-diazo-β-keto ester **17**[18] to cross-metathesis and subsequent compatibility of the spent Grubbs' catalyst with $Rh_2(OAc)_2$-catalysed *in situ* oxidopyrylium (aromatic carbonyl ylide) **18** formation/intramolecular cycloaddition has also been established, to give cycloadducts **19** (Scheme 7).

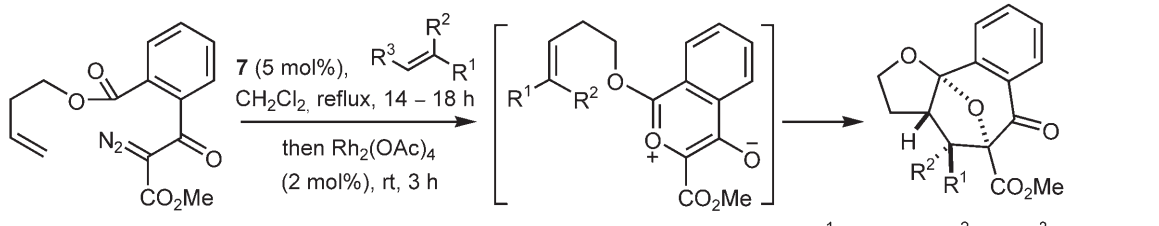


16a (R = CO_2Me, 63%)
16b (R = C_6H_{11}, 50%)
16c (R = Ph, 66%)

Scheme 6. One-pot cross metathesis/carbonyl ylide formation/cycloaddition of diazo ester **15**.

Conclusions

In conclusion, we have demonstrated the viability of directly coupling two powerful transition metal-catalysed carbene transfer reactions in a one-flask operation for the rapid assembly of complex oxapolycycles. This work also suggests opportunities for one-pot



19a (R^1 = CO_2Me, R^2 = H, R^3 = H, 68%)
19b (R^1 = Ph, R^2 = H, R^3 = H, 86%)
19c (R^1 = R^2 = R^3 = Me, 83%)
19d (R^1 = CHO, R^2 = Me, R^3 = H, 54%)

Scheme 7. One-pot cross metathesis/oxidopyrylium formation/cycloaddition of diazo ester **17**.

metathesis followed by other transformations involving pre-exisiting diazo functionality.

Experimental Section

General Remarks

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using DPX200 (200 MHz) or AV400 (400 MHz) spectrometers. Chemical shifts (δ) are reported in ppm relative to residual $CHCl_3$ (^{1}H NMR 7.26), or $CDCl_3$ (^{13}C NMR 77.4). Due to long relaxation time, C=N_2 was not observed in the ^{13}C NMR spectra. The multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet. Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded as thin films on NaCl plates or KBr discs, on a Bruker Tensor 27 FT-IR spectrophotometer; peaks are quoted as ν_{max} in cm^{-1}. Bands are characterised as broad (br), strong (s), medium (m) or weak (w). Mass spectra were obtained by the EPSRC National Mass Spectrometry Service at the University of Swansea, on a Micromass Quattro II low resolution triple quadrupole mass spectrometer using CI. All reactions were performed in flame-dried glassware under an atmosphere of argon. Solvents were degassed and dried over alumina under argon.[19] Reactions were monitored by TLC using commercially available aluminium plates precoated with silica (0.25 mm, Merck 60 F_{254}), which were developed using standard visualising techniques: UV fluorescence (254 nm) and/or potassium permanganate solution, heating. Flash chromatography was performed on Kieselgel 60 (40–63 μm).

General Procedure for Cross-Metathesis of Diazoester 10 and Olefins

Grubbs catalyst **7** (5 mol%) was added to a solution of *tert*-butyl 2-diazo-3,6-dioxo-10-undecenoate **10** (1.0 equiv.) and olefin (5–10 equivs.) in CH_2Cl_2 (c = 15–20 mM). The mixture was heated under reflux for 14–18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography. See Supporting Information for the characterisation of alkenes **11a–n**.

General Procedure for Tandem Carbonyl Ylide Formation-Cycloaddition

Rhodium acetate dimer (2 mol%) was added to a stirred solution of olefin **11** (obtained by cross-metathesis) in CH_2Cl_2 (c = 15–20 mM). After 3 h the reaction mixture was concentrated under reduced pressure and purified by flash chromatography. See Supporting Information for the characterisation of cycloadducts **13a–n**.

General Procedure for One-Pot Cross-Metathesis/Cycloaddition

Grubbs catalyst **7** (5 mol%) was added to a solution of α-diazo-β-keto ester (1.0 equiv.) and olefin (5–10 equivs.) in CH_2Cl_2 (c = 15–20 mM) and the reaction mixture was heated to reflux for 14–18 h. After cooling to room temperature rhodium acetate dimer (2 mol%) added and the reaction mixture was stirred at rt for 3 h. The mixture was then concentrated under reduced pressure and purified by flash chromatography. See supporting information for the characterisation of cycloadducts **13a–n**, **16a–c** and **19a–d**.

Acknowledgements

*We thank Dr. A. Labande for preliminary observations on the preparation of **13a**, the University of Oxford for a full Clarendon Fund bursary award (to D. A.) and the EPSRC National Mass Spectrometry Service Centre for mass spectra.*

References

[1] M. P. Doyle, M. A. McKervey, Y. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley and Sons, New York, **1998**.

[2] a) Ref.[1], pp. 289–354; b) M. C. McMills, D. Wright, in: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products,* Vol. 59, (Eds.: A. Padwa, W. H. Pearson), John Wiley and Sons, New York, **2002**, pp. 253–314; c) J. S. Clark, *Nitrogen, Oxygen and Sulfur Ylide Chemistry*, Oxford University Press, Oxford, **2002**; d) G. Mehta, S. Muthusamy, *Tetrahedron* **2002**, *58*, 9477–9504; e) D. A. Selden, D. M. Hodgson, in: *Comprehensive Organic Functional Group Transformations II*, Vol. 3, (Ed.: K. Jones), Elsevier, Oxford, **2004**, pp. 309–353; f) R. M. Savizky, D. J. Austin, in: *Modern Rhodium-Catalyzed Organic Reactions*, (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, pp. 433–454.

[3] a) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223–270; for recent examples, see: b) D. M. Hodgson, T. Brückl, R. Glen, A. H. Labande, D. A. Selden, A. G. Dossetter, A. J. Redgrave, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5450–5454; c) S. Muthusamy, J. Krishnamurthi, M. Nethaji, *Chem. Commun.* **2005**, 3862–3864; d) A. Padwa, J. Boonsombat, P. Rashatasakhon, J. Willis, *Org. Lett.* **2005**, *7*, 3725–3727; e) X. Zhang, R. Y. Y. Ko, S. Li, R. Miao, P. Chiu, *Synlett* **2006**, 1197–1200.

[4] Preliminary communication: D. M. Hodgson, D. Angrish, A. H. Labande, *Chem. Commun.* **2006**, 627–628.

[5] a) R. H. Grubbs, *Handbook of Metathesis*, Wiley-VCH, Weinheim, **2003**; b) A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

[6] a) D. M. Hodgson, D. Angrish, *Chem. Commun.* **2005**, 4902–4904; see also: b) D. M. Hodgson, D. Angrish, *J. Mol. Catal. A: Chem.* **2006**, *254*, 93–95.

[7] a) A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784; b) J. P. Morgan, R. H. Grubbs, *Org. Lett.* **2000**, *2*, 3153–3155; c) T. L. Choi, C. W. Lee, A. K. Chatterjee, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 10417–10418.

[8] a) M. Regitz, J. Hocker, A. Liedhegener, *Org. Synth. Coll. Vol. V* **1973**, 179–183; b) S. Bachmann, D. Fielen-

bach, K. A. Jørgensen, *Org. Biomol. Chem.* **2004**, *2*, 3044–3049.
[9] Y.-H. Lim, K. F. McGee, Jr., S. M. Sieburth, *J. Org. Chem.* **2002**, *67*, 6535–6538.
[10] D. M. Hodgson, P. A. Stupple, F. Y. T. M. Pierard, A. H. Labande, C. Johnstone, *Chem. Eur. J.* **2001**, *7*, 4465–4476.
[11] D. M. Hodgson, A. H. Labande, F. Y. T. M. Pierard, M. Á. E. Castro, *J. Org. Chem.* **2003**, *68*, 6153–6159.
[12] In most cases, lower yields were obtained when less than 5.0 equivs. of cross-metathesis partner was used.
[13] The methyl ester of **11d** also failed to undergo cycloaddition.
[14] D. M. Hodgson, R. Glen, G. H. Grant, A. J. Redgrave, *J. Org. Chem.* **2003**, *68*, 581–586.
[15] a) R. B. Woodward, *Pure Appl. Chem.* **1968**, *17*, 519–547; for a related observation, see: b) D. M. Hodgson, F. L. Strat, T. D. Avery, A. C. Donohue, T. Brückl, *J. Org. Chem.* **2004**, *69*, 8796–8803.
[16] For other one-pot processes involving alkene cross-metathesis, see: a) S. D. Goldberg, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2002**, *41*, 807–810; b) B. M. Trost, J. L. Gunzner, O. Dirat, Y. H. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 10396–10415; c) J. Cossy, F. Bargiggia, S. BouzBouz, *Org. Lett.* **2003**, *5*, 459–462.
[17] A. Padwa, S. F. Hornbuckle, G. E. Fryxell, Z. J. Zhang, *J. Org. Chem.* **1992**, *57*, 5747–5757.
[18] D. M. Hodgson, P. A. Stupple, C. Johnstone, *Arkivoc* **2003**, *7*, 49–58.
[19] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518–1520.

