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Ring opening–cross metathesis of unstrained cycloalkenes

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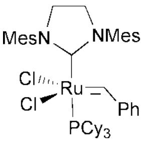
Unstrained cycloalkenes undergo ruthenium-catalysed ring opening–cross metathesis reactions with simple α,β-unsaturated carbonyl compounds under mild conditions.

Over the last decade, olefin metathesis has emerged as a powerful tool for the formation of carbon–carbon double bonds.[1] Due to their excellent activity and functional group tolerance, ruthenium complexes with sterically demanding *N*-heterocyclic carbene (NHC) ligands (**1** and **2**) have proved to be an important development in this field. Our group[2] and others[3] have investigated the catalytic properties of the readily prepared phosphine-free catalyst **2**. In the case of cross metathesis (CM) with α,β-unsaturated carbonyl compounds catalysed by **1**, the formation of the relatively unstable acceptor substituted carbene species was rejected.[4] However, Grubbs *et al.* have demonstrated that β-carbonyl ruthenium carbene species generated from diazoacetate are highly active, reacting in stoichiometric quantities with cyclohexene to afford new ruthenium carbene complexes.[5] Little is known about the ring opening–cross metathesis (ROM-CM) of unstrained cycloolefins,[6] and since **1** and **2** can promote highly efficient CM reactions with α,β-unsaturated carbonyl compounds,[2] we wondered if catalytic ROM-CM reactions of low-strain cycloolefins could be accomplished *via* highly reactive β-carbonyl ruthenium carbene intermediates.



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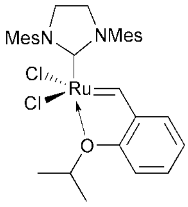
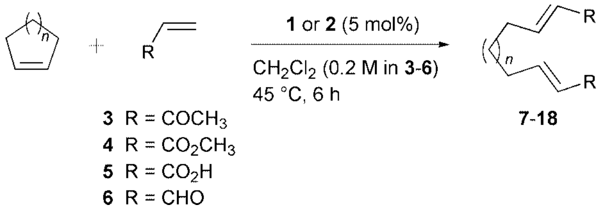


2

Cy = Cyclohexyl
Mes = 2,4,6-trimethylphenyl

Preliminary studies were carried out with cyclohexene and various electron deficient olefins. We found that methyl vinyl ketone (**3**), methyl acrylate (**4**), acrylic acid (**5**) and acrylaldehyde (**6**) were suitable substrates for ROM-CM, whereas vinyl sulfones, nitriles and amides gave poor results. Encouraged by these findings, we investigated the ROM-CM of unstrained cycloolefins (Scheme 1) such as cyclopentene, cyclohexene and cycloheptene (3.0 eq.), with simple α,β-unsaturated carbonyl compounds **3**–**6**.† It was also decided to compare the activity of catalysts **1** and **2** in these reactions. The results of these experiments are outlined in Table 1.



Scheme 1

In almost all cases moderate to excellent yields of ring opened double-cross products (**7**–**18**) were obtained. In addition, several trends were observed. Firstly, as expected,[2] phosphine-free catalyst **2** gave better cross product yields than **1**; secondly, the order of reactivity of the cycloalkene substrates was cycloheptene ⩾ cyclopentene > cyclohexene presumably due to ring strain. In addition, acrylic acid gave especially good results over the range of substrates.

Having established that efficient ROM-CM of unstrained cycloolefins is possible, we wished to extend this methodology to both functionalised and heterocyclic compounds. Thus, **19**–**25** were subjected to ROM-CM conditions, using catalyst **2** (5 mol%) and CM partners **3**, **4** and **5** (Table 2). Given the high reactivity of cyclopentene, the failure of 5- and 6-membered *N*-heterocycles **19** and **20** to give ring-opened products was somewhat surprising. In these reactions, only dimerisation of the electron deficient olefin occurred. At this time it is not known if this lack of ROM reactivity is attributable to either an internal complexation of the heteroatom to ruthenium during the catalytic cycle, or to the electron withdrawing effect of the tosyl-protected nitrogen atom on the 'allylic' double bond. In this regard it is interesting to note that dihydrofuran **23** gave only moderate yields of double-cross product. In the case of **21**, the 7-membered analogue of **19** and **20**, this effect is obviously less important than relief from ring strain, as good CM product yields were obtained. This is supported by the fact that the yields of **32**, **33** and **34** are in good correlation with those of **35**, **36** and **37** derived from **22**, where the olefin double bond is one methylene unit further removed from the heteroatom. Epoxycyclooctene **24** also gave smooth conversion to **41**, **42** and **43**, however bicyclic lactone **25** did not react, possibly due to steric factors.

Given that neither polymeric nor terminal olefinic products were detected even in the presence of excess cycloolefin, it is clear that the first step in the catalytic cycle is reaction between **1** or **2** and the electron deficient olefin to afford reactive carbene intermediates of general type **47**, which then ring-open the substrate to form a second alkylidene **48** (Scheme 2).

Table 1 Performance of **1** and **2** in ROM-CM with electron deficient alkenes

Product[a]	Yield (%)[b] using cat. **2**	Yield (%)[b] using cat. **1**
7 $n = 1$, R = $COCH_3$	86	62
8 $n = 1$, R = CO_2CH_3	90	79
9 $n = 1$, R = CO_2H	83	57
10 $n = 1$, R = CHO	83	30
11 $n = 2$, R = $COCH_3$	54	26
12 $n = 2$, R = CO_2CH_3	66	47
13 $n = 2$, R = CO_2H	80	38
14 $n = 2$, R = CHO	45	5
15 $n = 3$, R = $COCH_3$	87	87
16 $n = 3$, R = CO_2CH_3	97	80
17 $n = 3$, R = CO_2H	83	70
18 $n = 3$, R = CHO	90	75

[a] Only the *E*-isomers were detected in all cases. [b] Determined by ^1H NMR using (*E*)-stilbene as an internal standard.

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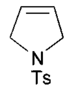
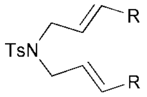
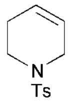
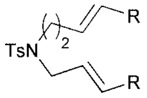
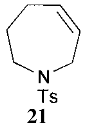
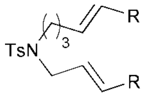
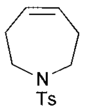
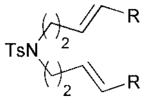
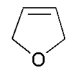
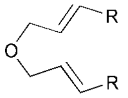
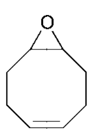
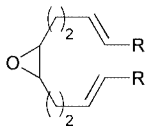
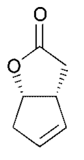
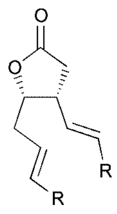
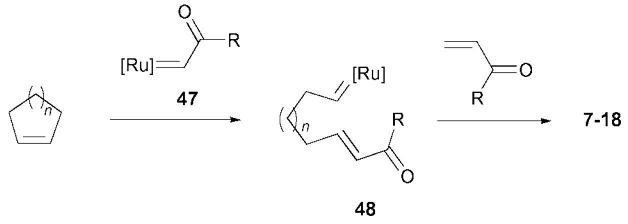
Table 2 ROM-CM of functionalised cycloolefins

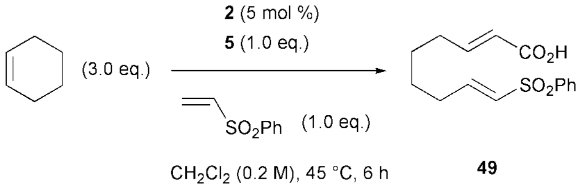
Cycloolefin	Products with **3**, **4** and **5** (% Yield)[a,b]			
 **19**		**26** **27** **28**	$R = COCH_3$ $R = CO_2CH_3$ $R = CO_2H$	(0) (0) (0)
 **20**		**29** **30** **31**	$R = COCH_3$ $R = CO_2CH_3$ $R = CO_2H$	(0) (0) (0)
 **21**		**32** **33** **34**	$R = COCH_3$ $R = CO_2CH_3$ $R = CO_2H$	(79) (70) (85)
 **22**		**35** **36** **37**	$R = COCH_3$ $R = CO_2CH_3$ $R = CO_2H$	(75) (90) (82)
 **23**		**38** **39** **40**	$R = COCH_3$ $R = CO_2CH_3$ $R = CO_2H$	(42) (0) (60)
 **24**		**41** **42** **43**	$R = COCH_3$ $R = CO_2CH_3$ $R = CO_2H$	(84) (92) (80)
 **25**		**44** **45** **46**	$R = COCH_3$ $R = CO_2CH_3$ $R = CO_2H$	(0) (0) (0)

[a] Only the *E*-isomers were detected in all cases. [b] Determined by ^{1}H NMR using (*E*)-stilbene as an internal standard.

The intermediacy of **48** suggested that a ring opening double cross metathesis reaction with two different CM partners could be possible. In order to test this, cyclohexene (3.0 eq.) was ring opened in the presence of **2** (5 mol%), **5** (1.0 eq) and phenyl vinyl sulfone (1.0 eq.) to give 25% yield (by ^{1}H NMR) of double cross product **49** (Scheme 3).



Scheme 2



Scheme 3

In summary, the novel ROM-CM of relatively unstrained carbo- and heterocycles to give ring opened bis-α,β-unsaturated carbonyl compounds has been described. Phosphine free catalyst **2** has been shown to possess a superior activity compared to **1** in these reactions. The bis-functionalisation of cyclohexene with two different CM partners using a ROM-CM strategy has also been demonstrated. Further investigations along these lines are in progress in our laboratories.

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Notes and references

† All new compounds were purified by column chromatography and fully characterised. Representative procedure: a solution of cyclohexene (0.40 mL, 3.95 mmol), **2** (125.4 mg, 0.2 mmol) and **5** (0.18 mL, 2.62 mmol) in CH_2Cl_2 (13 mL, 0.2 M in **5**) was stirred at 45 °C for 6 h under a nitrogen atmosphere, after which time the solvent was evaporated and (*E*)-stilbene added as an internal standard. The product yield was determined by ^{1}H NMR analysis of the crude mixture.

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