

# Two-directional cross-metathesis†

Annabella F. Newton,<sup>a</sup> Stephen J. Roe,<sup>b</sup> Jean-Christophe Legeay,<sup>a</sup> Pooja Aggarwal,<sup>a</sup> Camille Gignoux,<sup>a</sup> Nicola J. Birch,<sup>b</sup> Robert Nixon,<sup>c</sup> Marie-Lyne Alcaraz<sup>c</sup> and Robert A. Stockman<sup>\*a</sup>

Received 16th April 2009, Accepted 20th April 2009

First published as an Advance Article on the web 28th April 2009

DOI: 10.1039/b907720k

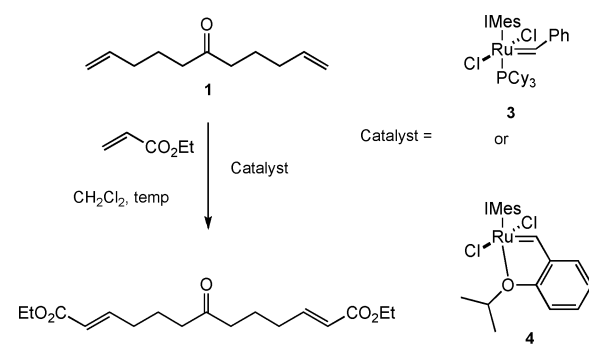
Two-directional cross-metathesis of a range of  $\alpha,\omega$  dienes with a variety of electron deficient alkenes has been accomplished. It was found that the process is quite general and gives complete selectivity for the *E,E*-dienes, making this a very useful and high yielding protocol for two-directional chain elongation.

Two-directional synthesis, wherein a symmetrical substrate chain is elongated either sequentially or simultaneously in two-directions by the same reaction, has become a widely used tactic in organic synthesis.<sup>1</sup> As two reactions are taking place on the same substrate, it is preferable for efficient synthesis that the type of reaction used to homologate is robust and high yielding. Over the past few years we have explored the tactic of combining two-directional synthesis and tandem reactions for the concise synthesis of natural products.<sup>2</sup> These syntheses used Horner-Wadsworth Emmons reactions for two-directional homologation of dialkenes by a two-step process involving initial oxidative cleavage followed by reolefination. More recently we have sought to shorten this sequence by the use of cross-metathesis.<sup>3</sup> Our recent synthesis of histrionicotoxin<sup>4</sup> used this approach, resulting in the shortest synthetic route to this natural product to date. With this initial success, we set about investigating the scope and generality of this type of process,<sup>5</sup> and herein we disclose our findings on the two-directional homologation of  $\alpha,\omega$ -dienes by cross-metathesis.

The conversion of diene **1** to dienoate **2** was used as our optimisation platform, as this transformation forms part of our strategy towards the synthesis of pinnaic acid,<sup>6</sup> and previously required 4 steps to accomplish (ketone protection, oxidative cleavage, olefination, deprotection). We investigated two cross-metathesis catalysts, Grubbs second-generation catalyst<sup>7</sup> (**3**) and the Hoveyda-Blechert catalyst<sup>8</sup> **4** (also known as the Grubbs-Hoveyda second generation catalyst). The results of our study are shown in Table 1.

The reactions were all carried out at room temperature in dichloromethane using 6 equivalents of ethyl acrylate. It was found that the reactions were relatively slow, but very clean, with minimal byproducts being formed when catalyst **4** was used. The use of catalyst **3** resulted in slower reaction, with incomplete conversion to the dihomologated product. Due to the length of the reactions, it was found that addition of the catalyst was best achieved in two

Table 1 Optimisation of conditions



Entry	Cat.	Cat. Loading <sup>a</sup> n X	Temp (°C)	Time (h)	Yield mono CM (%)	Yield double CM (%)
1	<b>3</b>	2 2.5	20	120	44	31
2	<b>4</b>	2 2.5	20	120	—	90
3	<b>4</b>	4 1.0	20	120	—	83
4	<b>4</b>	2 0.5	20	120	—	67
5	<b>4</b>	2 2.5	40	60	—	79

<sup>a</sup> n = number of additions of catalyst portion, X = catalyst portion in mol%.

portions, with the second portion being added in all cases 24 hours after the start of the reaction. It was found that having more additions of catalyst were not beneficial (entry 3). Similarly heating of the reaction was not found to influence the rate significantly. Thus it was determined that two additions of 2.5 mol% of catalyst **4**, with the reaction being run at room temperature gave an excellent yield of the dienoate **2**. With this information in hand, we then turned our attention to the exploration of the two-directional cross-metathesis of diene **1** with other alkenes. Our results are summarised in Table 2.

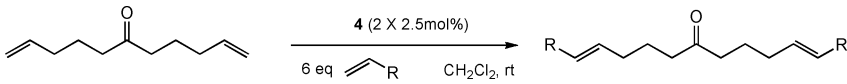
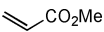
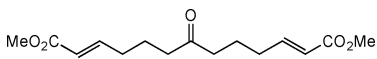
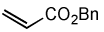
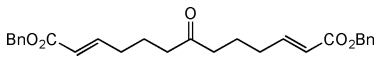
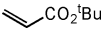
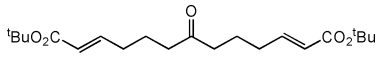

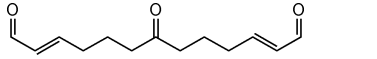

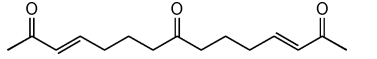
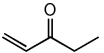
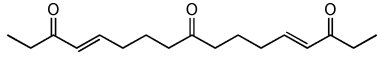
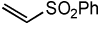
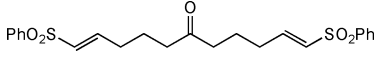
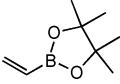
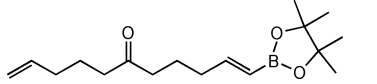

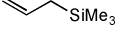

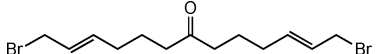
Acrylate esters were found to be good substrates for the reaction, with even the bulky *tert*-butyl acrylate participating well. Acrolein was also found to undergo the cross metathesis in 63% yield, with no mono-cross metathesis product being observed. Methyl vinyl ketone was found to be a less reactive substrate, with substantial amounts of mono-cross metathesis product being isolated under the standard conditions. It was found, however, that upon heating the reaction in a microwave (120 °C, 3.5 hours), good yields could be achieved. This is in contrast to ethylvinylketone, which reacted slowly but cleanly under the standard conditions to yield 87% of the doubly homologated product. It is unclear as to why there is such a difference between these two examples, and one can only surmise that methylvinylketone is more prone to

<sup>a</sup>School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, UK. E-mail: robert.stockman@nottingham.ac.uk; Fax: +44 (0)115 9513564; Tel: +44 (0)115 9513252

<sup>b</sup>School of Chemistry, University of East Anglia, Norwich, NR4 7TJ, UK  
<sup>c</sup>AstraZeneca, Bakewell Road, Loughborough, Leics, LE11 5RH, UK

† Electronic supplementary information (ESI) available: Experimental procedures and data. See DOI: 10.1039/b907720k

**Table 2** Investigation into range of cross-metathesis partners for ketone **1**

				
Entry	Substrate	Time (hrs)	Yield (%)	Major Product
1		120	78	
2		120	85	
3		120	78	
4		120	63 <sup>a</sup>	
5		3.5	76 <sup>b</sup>	
6		120	87	
7		96	73 <sup>c</sup>	
8		264	47	
9		120	—	No reaction
10		120	—	No reaction
11		192	35	

<sup>a</sup> 5 equivalents of acrolein were used. <sup>b</sup> This reaction was found to give mainly mono-CM product at room temperature, so microwave conditions (120 °C) were used. <sup>c</sup> Elevated temperatures (50 °C) were required to observe CM, and 2 × 5 mol% catalyst was used.

self-condensation and polymerization, and thus the long reaction times required at ambient temperatures allow these other processes to take place. Vinyl sulfone was also found to require heating, but this time 50 °C was found to be sufficient. Vinyl pinacol borane was found to give predominantly the mono-substituted product. Electron rich alkenes styrene and allyl trimethylsilane were found not to participate in the reaction, although allyl bromide was a successful substrate for double cross-metathesis, albeit in only 35% yield.

Having looked at the two-directional cross-metathesis of ketone **1**, we now set out to explore the effect of chain length and centrepiece functionality on the two-directional cross metathesis process. Our results are described in Table 3.

In general, substrates with alcohol functionality (entries 1, 3, 8, Table 3) were found to be detrimental to the reaction when compared with the corresponding ketone substrates (entries 2, 5, 11). Indeed, in the case of Entry 8 it was found that the alcohol substrate gave the product of mono cross-metathesis as the main product. The lack of reactivity is likely due to internal co-ordination of the alcohol to the alkylidene carbene, slowing the cross-metathesis. The reactions with alcohols were

also noticeably more prone to decomposing the starting materials compared to the ketone substrates. The exception to this was Entry 2, where due to the proximity of the ketone functionality to the alkenes, the majority of product was the result of the alkene functionality moving into conjugation with the ketone, thus generating a mixture of products, whereas the alcohol variant, (entry 1), actually underwent double cross-metathesis in moderate yield. Protected alcohol functions (Entry 8) and protected amines (Entries 5, 6, 9) were found to be good substrates, as was an amide function (Entry 11). It was found that if the starting material allowed the formation of a 6-membered ring through ring-closing metathesis, then this was the major product obtained (Entry 6). This observation might suggest that the reaction proceeds *via* initial ring-closing metathesis, followed by ring-opening cross metathesis. However, ring-closing metathesis products were not observed in any of the other experiments, although a few percent of mono-cross metathesis products were occasionally observed. We suggest therefore, that in the case of Entry 7, ring-closing metathesis is a competitive pathway to the first cross-metathesis, but the 6-membered product of ring-closing metathesis acts as a thermodynamic sink. Around 18% of double-cross metathesis

**Table 3** Investigation into range of cross-metathesis partners for ethyl acrylate

$  \begin{array}{c}  \text{2 X 2.5mol\%} \\  \text{Grubbs-Hoveyda II (catalyst)} \\  \text{6 eq } \text{CH}_2=\text{CHCO}_2\text{Et} \quad \text{CH}_2\text{Cl}_2, \text{ r.t.} \\  n, m = 1, 2, 3  \end{array}  $				
Entry	Substrate	Time (hrs)	Yield (%)	Major Product
1		89	44 <sup>a</sup>	
2		89	8	
3		120	14	
4		120	57	
5		190	66 <sup>b</sup>	
6		48	77	
7		48	77	
8		96	35	
9		120	67	
10		144	89	
11		120	90	
12		144	79	
13		144	—	No reaction
14		144	—	No reaction

<sup>a</sup> 12 equivalents of ethyl acrylate were used. <sup>b</sup> 2 × 4.3 mol% catalyst and 6 equivalents of ethyl acrylate were used. <sup>c</sup> This reaction was carried out at reflux.

product was observed in this reaction. Polar functionalities such as oxime and amine (entries 12,13) were found to not be compatible. Presumably these functionalities bind the catalyst, thus removing it from the catalytic cycle.

In conclusion, two-directional cross-metathesis offers a convenient, fairly functional group tolerant and high-yielding method of doubly homologating  $\alpha,\omega$  dialkenes to give exclusively the *E,E*-dienes, with the exception of 1,7-dienes, which preferentially give the product of ring-closing metathesis.

The authors thank EPSRC (EP/D500877, EP/E055346), AstraZeneca, University of East Anglia and University of Nottingham for funding.

## Notes and references

- (a) S. R. Magnuson, *Tetrahedron*, 1995, **51**, 2167; (b) C. S. Poss and S. L. Schreiber, *Acc. Chem. Res.*, 1994, **27**, 9.
- (a) R. A. Stockman, A. Sinclair, L. G. Arini, P. Szeto and D. L. Hughes, *J. Org. Chem.*, 2004, **69**, 1598; (b) M. Rejzek, R. A. Stockman and

- D. L. Hughes, *Org. Biomol. Chem.*, 2005, **3**, 73; (c) S. J. Roe and R. A. Stockman, *Chem. Commun.*, 2008, 3432.
- 3 A. F. Newton, M. Rejzek, M. L. Alcaraz and R. A. Stockman, *Beilstein J. Org. Chem.*, 2008, **4**, 4; J.-C. Legeay, W. Lewis and R. A. Stockman, *Chem. Commun.*, 2009, 2207.
- 4 M. S. Karatholuvhu, A. Sinclair, A. F. Newton, M. L. Alcaraz, R. A. Stockman and P. L. Fuchs, *J. Am. Chem. Soc.*, 2006, **128**, 12656.
- 5 For some one-off examples of two-directional metathesis see: J. S. Clark and O. Hamelin, *Angew. Chem., Int. Ed.*, 2000, **112**, 380; S. Purser, T. D. W. Claridge, B. Odell, P. R. Moore and V. Gouverneur, *Org. Lett.*, 2008, **10**, 4263; M. W. B. Pfeiffer and A. J. Phillips, *J. Am. Chem. Soc.*, 2005, **127**, 5334; J. S. Clark, D. M. Grainger, A. A. C. Ehkirch, A. J. Blake and C. Wilson, *Org. Lett.*, 2007, **9**, 1033–1036.
- 6 L. G. Arini, P. Szeto, D. L. Hughes and R. A. Stockman, *Tetrahedron Lett.*, 2004, **45**, 8371.
- 7 (a) M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953; (b) M. S. Sanford, J. A. Love and R. H. Grubbs, *J. Am. Chem. Soc.*, 2001, **123**, 6543.
- 8 (a) S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168; (b) S. Gessler, S. Randl and S. Blechert, *Tetrahedron Lett.*, 2000, **41**, 9973.