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# Bimetallic catalytic cascade ring closing metathesis— intramolecular Heck reactions using a fluorous biphasic solvent system or a polymer-supported palladium catalyst

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## Abstract

The combination of ring closing metathesis and intramolecular Heck reactions in a cascade gives bridged ring systems in good yield. Two methods using either a fluorous biphasic solvent system or a polymer-supported palladium catalyst overcome the observed incompatibility of the catalysts. © 2000 Elsevier Science Ltd. All rights reserved.

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Ring closing metathesis (RCM) allows the synthesis of a wide variety of cyclic systems<sup>1</sup> from the corresponding acyclic dienes. RCM is catalysed by a number of metallocarbene complexes amongst the most popular of which is the ruthenium benzylidene complex,<sup>2</sup> (Cy<sub>3</sub>P)<sub>2</sub>Ru(=CHPh)Cl<sub>2</sub>, **1**. This catalyst has numerous properties which recommend its use to the organic chemist such as its relative air and moisture stability, ease of synthesis and tolerance of many common functional groups.

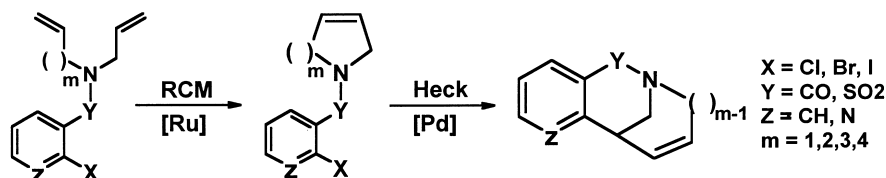
The Heck reaction is a well-established process for the coupling of unsaturated halides with olefins.<sup>3</sup> This reaction is catalysed by a wide variety of palladium(0) species, often generated in situ from the corresponding palladium(II) salt.<sup>3</sup>

In a recent communication<sup>4</sup> we reported the combination of RCM and Heck reactions for the synthesis of bridged rings (Scheme 1). However, attempts to perform these reactions as cascade processes, that is by addition of all reagents required for both transformations at the beginning of the procedure, were unsuccessful when  $m > 1$  (i.e. when the ring formed by RCM is greater than five-membered). In these cases the majority of the isolated material was derived from Heck reaction of the starting material. The reason for the failure of the RCM step was poisoning of the

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ruthenium benzylidene **1** by the palladium species used to catalyse the Heck reaction. This poisoning was found to be present with a variety of Heck catalysts and precursors (Table 1, entries 2–4) in the RCM of *N,N*-diallyl-2-bromobenzenesulphonamide, **2** (Scheme 1, X = Br, Y = SO<sub>2</sub>, Z = CH, m = 1). Phosphine ligands, unsurprisingly, also strongly retarded RCM in line with the observations of Grubbs<sup>5</sup> (Table 1, entries 5 and 6). The inorganic bases used in these Heck reactions, however, were shown to have no effect on the outcome of the RCM process (Table 1, entries 7 and 8), perhaps in part because of their low solubility in the reaction media.



Scheme 1.

Table 1  
Effect of additives on RCM<sup>a</sup>

Entry	Additive	Amount <sup>b</sup>	Yield (%) <sup>c</sup>
1	None	NA	>95
2	Pd(OAc) <sub>2</sub>	10 mol%	10
3	Hermann's Catalyst <sup>6</sup>	10 mol%	<5
4	Pd(Ph <sub>3</sub> P) <sub>4</sub>	10 mol%	<5
5	Ph <sub>3</sub> P	20 mol%	8
6	Cy <sub>3</sub> P	20 mol%	5
7	K <sub>2</sub> CO <sub>3</sub>	2 eq	>95
8	Tl <sub>2</sub> CO <sub>3</sub>	2 eq	93

a: A mixture of 5 mol **1** and the additive was stirred in toluene at rt for 10 min. **2** was then added and the mixture stirred at rt for a further 1 h.

b: Amount of additive added relative to **2**. This represents the amount present in a typical Heck reaction

c: Calculated from <sup>1</sup>H NMR.

Efforts to achieve the cascade synthesis of bridged rings were focused on methods which would separate the two catalysts. One such method used a palladium catalyst immobilised on polystyrene-bound triphenylphosphine.<sup>7</sup> The success of this method was ascribed to poor polymer swelling at room temperature, limiting access to the palladium species and phosphine ligands. At higher temperatures, however, swelling increased allowing access to the palladium catalyst and promoting efficient Heck cyclisation. Thus, carrying out the RCM at room temperature and the Heck reaction (with polymer supported Pd, PS–Pd) at 110°C, ensured that both catalysts could be added together and the desired cascade achieved.

A second approach was also developed using a fluorous biphasic system<sup>8</sup> where an immiscible mixture of organic and perfluorous solvent was used. In this protocol the palladium Heck catalyst was sequestered in the perfluorous phase using a triaryl phosphine, **3**, bearing a perfluoroalkyl side chain.<sup>9</sup> RCM, therefore, proceeded to completion unimpeded. On heating to perform the Heck reaction, however, the biphasic solvent system (2:2:3 v/v/v toluene:hexane:perfluoromethyl

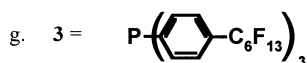
cyclohexane) became monophasic allowing the Heck reaction to occur in the bulk solvent and not merely in the vicinity of the phase boundaries.

The results of these studies are shown in Table 2. As expected, the simple combination of reagents was useful for the cascade RCM/Heck reaction only when the ring formed in the RCM process was five-membered (Table 2, entry 1). The use of the polymer-bound palladium catalyst<sup>7</sup> proved the more successful of the cascade processes with yields better than those observed when the reactions were performed sequentially (Table 2, entries 1–5).

Table 2  
Cascade RCM-intramolecular Heck reactions for bridged ring synthesis<sup>a</sup>

Entry	Substrate	Product	Sequential (%) <sup>b</sup>	Combination (%) <sup>c</sup>	PS – Pd (%) <sup>d</sup>	FBS (%) <sup>e</sup>
1			62	65	71	0
2			48	22	73	67
3 <sup>f</sup>			69	37	73	43
4			55	0	80	57
5 <sup>f</sup>			40	25	58	37

- a. In a typical cascade process all reagents were added at the beginning of the procedure. RCM was performed at rt and the mixture heated to 110 °C to initiate the Heck when RCM was complete.
- b. Yield observed when RCM (1-5 mol% **1**, toluene, rt, 1-8 h) and the Heck reaction (10 mol% Pd(OAc)<sub>2</sub>, 20 mol% Ph<sub>3</sub>P, 2eq Ti<sub>2</sub>CO<sub>3</sub>, toluene, 110 °C, 16h) were performed separately.
- c. Yield observed when the catalyst systems outlined in b were simply combined at the start of the cascade process.
- d. Yield observed with 10 mol% polystyrene bound palladium catalyst,<sup>7</sup> 2eq Ti<sub>2</sub>CO<sub>3</sub>, toluene, 110 °C, 16h.
- e. Yield observed with 10 mol% Pd(OAc)<sub>2</sub>, 20 mol% **3**<sup>8,9</sup>, 2eq Ti<sub>2</sub>CO<sub>3</sub>, perfluorous solvent system, 110 °C, 16h).
- f. In both these cases mixtures of the possible isomeric products were obtained. The major product only is shown.



The fluororous biphasic approach was not successful for the reaction of *N,N*-diallyl-2-bromobenzenesulphonamide (Table 2, entry 1) due to the forcing Heck reaction conditions required to give the strained product. The perfluorophosphine **3** decomposed at the elevated temperatures required. This thermal instability is also thought to be responsible for the generally lower yields observed for the fluororous biphasic approach compared to those seen with the polymer-bound palladium catalyst. Further studies are currently underway using alternative perfluorophosphines. Where the formation of isomers was observed in the Heck reaction (Table 2, entries 3 and 5) product distribution was effectively identical for all methods used.

The results reported herein, together with previous reports from our group employing Pd/Cr,<sup>10</sup> Pd/Rh<sup>11</sup> and Pd/In,<sup>12</sup> emphasise the power of bimetallic catalysis and the potential for this area to rival and ultimately outstrip multienzyme processes with their inbuilt restrictions on substrate and bond processing type.

## Acknowledgements

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