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## Sequential and Cascade Olefin Metathesis - Intramolecular Heck Reaction.

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Abstract. The sequential or cascade combination of olefin metathesis with intramolecular Heck reactions provides access to fused-, bridged- and spiro-cyclic ring systems in good yield. © 1998 Elsevier Science Ltd. All rights reserved.

Application of the olefin metathesis reaction<sup>1</sup> to target molecule synthesis is growing rapidly<sup>2</sup> following the introduction of well defined metathesis - active metallocarbene catalysts. Metallocarbenes of ruthenium,<sup>3</sup> tungsten<sup>4</sup> and molylbenum<sup>5</sup> have attracted the broadest range of applications and asymmetric processes employing chiral catalysts are now being developed.<sup>6</sup>

Applications of the Heck reaction<sup>7</sup> have grown rapidly following the development of the intramolecular version for the construction of bridged-, fused- and spiro-cyclic systems and tetrasubstituted carbon centres.<sup>8</sup>

The combination of the intramolecular Heck reaction with olefin metathesis, either sequentially or in a cascade process, offers unique opportunities for target molecule synthesis. The metathesis step can either precede or follow the intramolecular Heck reaction. In this communication we focus on processes where metathesis proceeds first and creates the functionality utilised by a subsequent intramolecular Heck reaction.

Our general approach to bridged-, fused- and spiro-cyclic systems is summarised in Scheme 1a-c, and a series of sequential bridged-ring forming metathesis - Heck processes are summarised in Table 1. The metathesis reactions proceeded to completion within a few hours at room temperature in DCM with 1-5 mol%  $(Cy_3P)_2Ru(=CHPh)Cl_2$  for 5- and 7-membered ring formation. Reactions forming 8-membered rings required ca 20h with entry 5 (Table 1) also requiring heating at 40°C when 60% conversion to product was achieved after 20h.

The Heck reactions proceeded to completion in 2-4h at 110°C (Table 1) except for entries 4 (60% conversion after 48h at 150°C) and 6 (68% conversion after 3h at 110°C). In the last two entries of Table 1 mixtures of double bond isomers were produced.



 Table 1 Bridged - ring forming sequential metathesis - Heck reactions

a. Isolated yields. Metathesis employed 1-5 mol%  $(Cy_3P)_2Ru(=CHPh)Cl_2$  in DCM at 25°C for 2 - 4h (entries 1 - 4) or 20h (entries 5 and 6). Yield for entry 5 is based on 60% conversion

b. Isolated yields. Heck reactions employed  $10 \mod \% \operatorname{Pd}(\operatorname{OAc}_2/20 \mod \% \operatorname{PPh}_3, \operatorname{Et_4NCl}(1 \mod eq), K_2CO_3$  (2 mol eq) in DMF at 110°C for 2 - 4h. Entry 4 required 150°C for 48h (60% conversion). Yields for entries 4 and 6 are based on 60 and 68% conversion respectively.



The potential for engineering cascade processes is illustrated by carrying out both steps of entry 1 (Table 1) in toluene. When carried out in two steps an overall yield of 72% was obtained whereas the one-pot process in toluene with sequential addition of catalysts proceeded in 51%. The lower yield in toluene compared to the DCM/DMF 2-step process is a result of incomplete conversion of the metathesis (carried out at 25°C) product in the Heck reaction (carried out at 110°C). When carried out as a cascade (both catalysts added at the beginning) in toluene the yield was 54% but the process was slow (54h).

The formation of fused rings is illustrated by the two-step sequences  $(1) \rightarrow (2) \rightarrow (3)$  and  $(4) \rightarrow (5) \rightarrow (6)$ . These employed the respective Ru and Pd catalysts noted above. The conversion of  $(4) \rightarrow (6)$  can be achieved as a one-pot sequence in toluene to afford a 10:1 mixture of (6) and the corresponding trans-isomer in 83% overall yield. The stereochemistry of the major cis-isomer was assigned on the basis of positive n O e enhancements between the ring junction protons.



A spirocycle forming 2-step process is provided by the sequence  $(7) \rightarrow (8) \rightarrow (9)$ .



The conversion of  $(7) \rightarrow (8)$  proceeds in 50% yield when the Ru catalyst is employed and the Pd catalysed spirocyclisation of (8) generates (9) in 70% yield.

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