



Sequential Pd/Ru-catalysed allenylation/olefin metathesis/1,3-dipolar cycloaddition route to novel heterocycles

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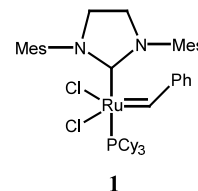
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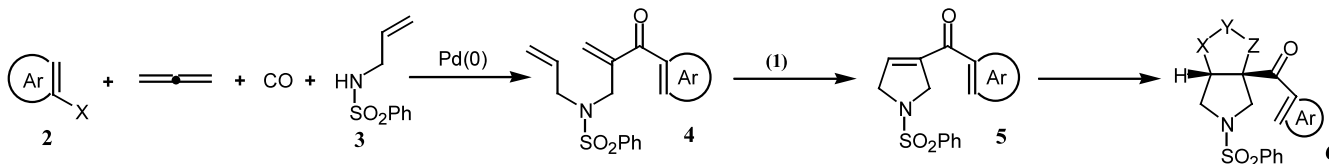
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Abstract—A novel sequential palladium/ruthenium-catalysed four component process is described involving carbonylation of an aryl/heteroaryl iodide followed by allenylation to generate (π -allyl) palladium species which are intercepted by nitrogen nucleophiles to afford 1,6-dienes. Subsequent Ring-Closing Metathesis (RCM) affords C-acyl-N-heterocycles in good yield. These heterocycles proved to be active dipolarophiles in sequential and cascade 1,3-dipolar cycloaddition reactions (1,3-DC) as exemplified by reactions with nitrones and azomethine ylides. © 2003 Elsevier Science Ltd. All rights reserved.

Carbon monoxide and allene are versatile building blocks in palladium-catalysed processes^{1,2} and they function as powerful relay switches in palladium-catalysed cyclisation–anion capture cascades.³ Recently we have developed a series of novel palladium-catalysed 3-component processes utilising either carbon monoxide or allene as relay switches.^{4–6} We have also interfaced our palladium-catalysed cascade chemistry with other transition metal-catalysed processes. Such bimetallic cascades include electrochemically driven Pd/Cr Nozaki–Hiyama–Kishi reaction,⁷ Pd/In Barbier type allylation,^{8,9} Pd/Ag Heck/1,3-DC,¹⁰ Pd/Ru Heck/metathesis,^{11,12} Pd/Ru termolecular queuing processes/metathesis,¹³ Rh/Pd cycloaddition–cyclisation–anion capture processes¹⁴ and Rh/Pd cycloaddition–Friedel Crafts reactions.¹⁵ In this paper we describe the combination of a Pd catalysed 4-component cascade with RCM and 1,3-DC.




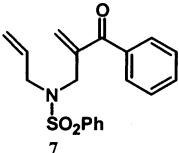
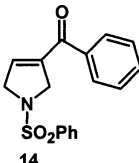
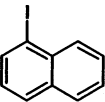
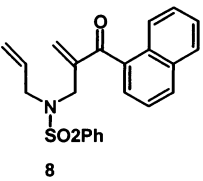
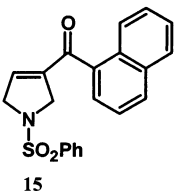
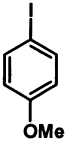
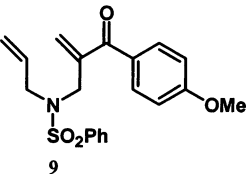
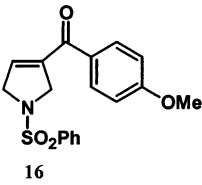
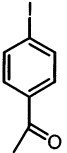
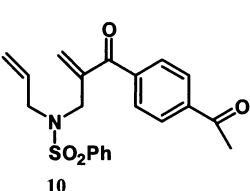
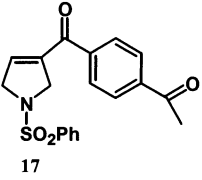

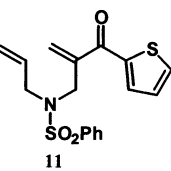
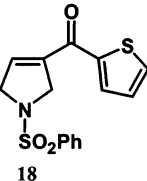
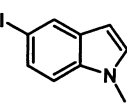
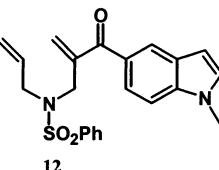
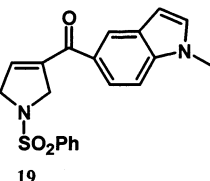
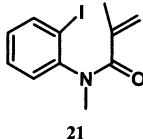
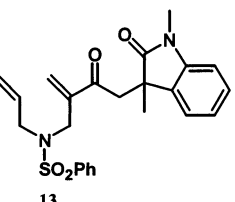
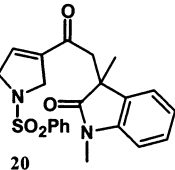
The development of second generation air stable, Ru catalysts such as **1**^{16–18} which exhibit higher thermal stability, wider functional group tolerance and accommodate a higher density of substitution on the double bond formed in RCM opens up new avenues for combination with Pd-catalysed multicomponent processes together with core organic reactions. Thus the four component process (Scheme 1) involving Pd/Ru catalysis combined with 1,3-DC has been developed. The initial reaction of aryl iodides **2** with carbon monoxide, allene and a nucleophile **3** in the presence Pd(0)



Scheme 1.

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Table 1. Four-component allenylation-amination cascades^a/RCM^b

Entry	Aryl Iodide	Product	Yield(%) ^c	RCM Product	Yield(%) ^c
1		 7	74	 14	88
2		 8	70	 15	90
3		 9	55	 16	71
4		 10	65	 17	93
5		 11	75	 18	94
6		 12	71	 19	89
7	 21	 13	65	 20	94

a. Reactions were carried out in toluene at 80°C for 32 h and employed 1.2 mmol aryl/heteroaryl iodide, 10 mol% Pd(OAc)₂, 20 mol% PPh₃, 2 mol eq. K₂CO₃ and 1 mmol of nucleophile 3.

b. Reactions were carried out in toluene at 70°C for 2–4 h and employed 5 mol% of catalyst 1.

c. Isolated yields

furnishes 1,6-dienes **4**, which undergo ruthenium catalysed RCM to give Δ^3 -pyrrolines **5**. The enones **5** undergo 1,3-DC with nitrones and azomethine ylides to produce bicyclic cycloadducts **6**. The overall process results in the formation of two rings, six bonds, three or four stereocentres and one or two tetrasubstituted carbon centres.

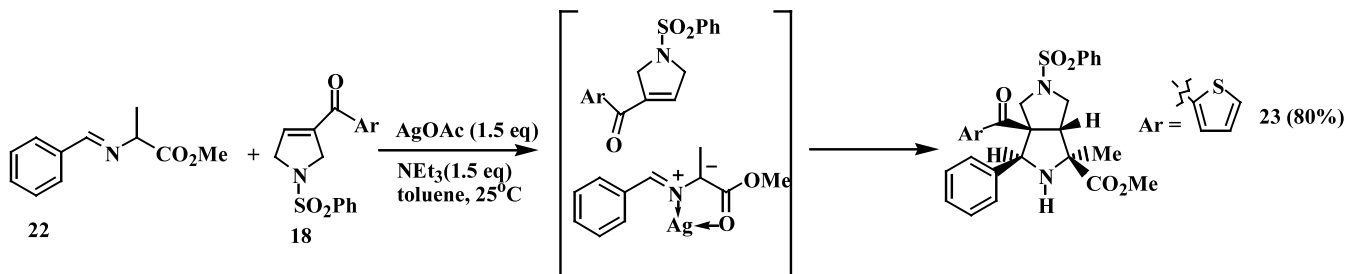
Thus, aryl/heteroaryl iodide **2** (1.2 mmol) react with CO (1 atm), allene (1 atm), Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), K₂CO₃ (2 mol equiv.), and *N*-allyl benzene-sulfonamide **3** (1 mmol), in toluene (70°C, 36 h) to afford **7–12** (Table 1, entries 1–7) in 55–75% yield. Subsequent RCM of these products produced the Δ^3 -pyrrolines **14–19** (Table 1) in excellent yields. This process is compatible with our cyclisation–anion capture methodology.³ Thus, **21** reacts with CO (1 atm), allene (1 atm) and nucleophile **3** (1 mol equiv.), in the presence of Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%) and K₂CO₃ (2 mol equiv.) in toluene at 70°C over 24 h to afford **13** in 65% yield (Table 1 entry 7). RCM on **13** furnishes **20** in 94% yield.

Next we briefly studied azomethine ylide cycloaddition of **18** with imine **22** (Scheme 2). Treating enone **18** (1 mmol), with imine **22** (1.2 mmol), silver acetate (1.5 mmol) and triethylamine (1.5 mmol) in toluene for 20 h

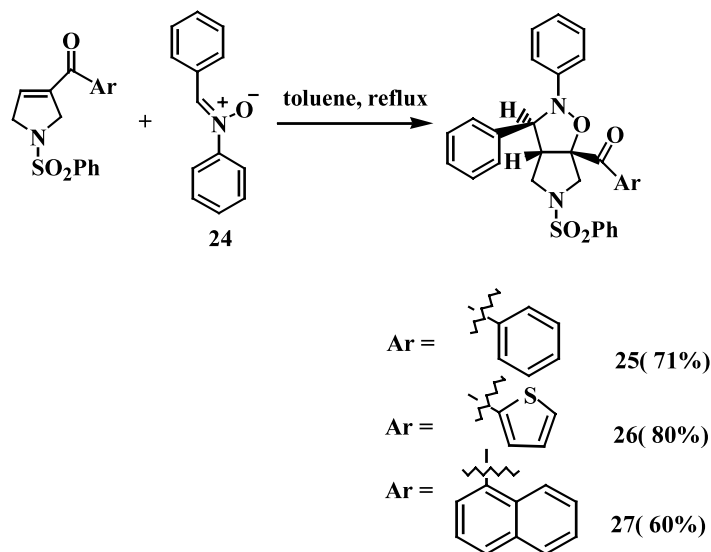
at room temperature afforded a single diastereoisomeric cycloadduct **23**. Product **23** arises via an *endo* transition state of the *syn*-dipole (Scheme 2) in 80% yield. The regio- and stereochemistry of the cycloadduct were established by NOE studies and conforms to that expected for our metal-catalysed proline synthesis.¹⁹

Reaction (toluene, 110°C, 44 h) of nitron **24** (1.5 mmol) with enones **14**, **15** and **18** (1 mmol) was then explored. In each case a single cycloadduct diastereomer **25–27**, arising from an *endo*-transition state, was obtained in good yield (Scheme 3). Performing these cycloadditions at 90°C afforded a 3.5:1 mixture of **28** and **29**, respectively, in 70% yield under kinetic control (Scheme 4),²⁰ whereas heating **28** in refluxing toluene affords thermodynamic isomer **26** via a retro-cycloaddition-1,3-DC sequence along with trace amounts of **18**, and nitron **24**. Thus, we have a synthetically useful temperature control of cycloaddition regiochemistry.

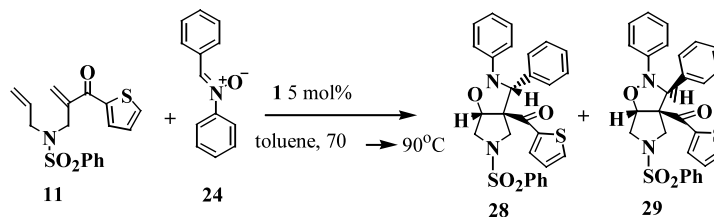
Finally a RCM/nitron cycloaddition cascade was achieved. Dienone **11** and nitron **24** were heated to 75°C with **1** (5 mol%) in toluene, for 2 h after which the temperature was raised to 90°C for 20 h affording a 3:1 mixture of cycloadducts **28** and **29** in a 59% overall yield (Scheme 4).



Scheme 2.



Scheme 3.



Scheme 4.

In conclusion we have demonstrated a novel sequential, Pd catalysed carbonylation/allene insertion/nucleophile incorporation followed by ruthenium-catalysed RCM for the synthesis of Δ^3 -pyrroline dipolarophiles as exemplified by both azomethine ylide and nitrone cycloadditions.

Acknowledgements

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20. Trace amounts of **27** were observed in some instances.