

Palladium catalysed tetramolecular queuing cascades of aryl iodides, carbon monoxide, amines and a polymer supported allene

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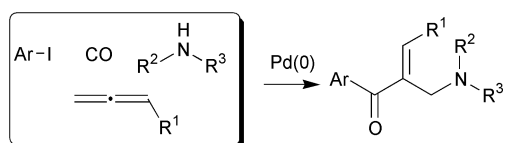
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Chemo- and regio-specific palladium catalysed four component processes, involving formation of 3 new bonds, initiated by oxidative addition of Pd(0) with aryl iodides followed by sequential incorporation of CO (1 atm), a polymer supported allene and an amine provides complex heterocycles with 3 points of diversity in good yield and excellent purity after cleavage.

A well designed cascade can deliver highly complex molecules whilst avoiding lengthy multistep procedures and the need for protection–deprotection of many functional groups.¹ This approach can be further enhanced by locating one of the reagents on a polymer support thus allowing the pure final product to be isolated by washing the resin and cleavage.

The objective of the present study was to explore the reactivity of a polymer bound allenic alcohol in a palladium catalysed four-component queuing cascade² (Scheme 1).

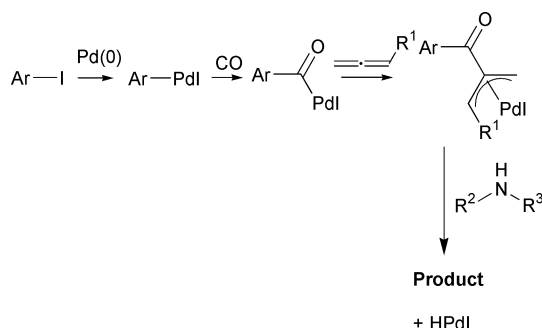


Scheme 1

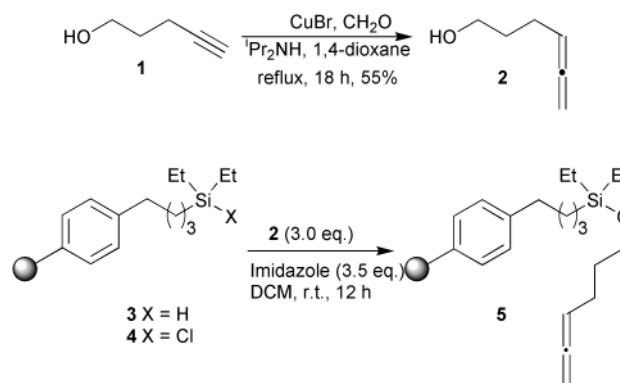
This cascade is initiated by addition of Pd(0) into the Ar–I bond, followed by CO insertion, allene insertion and capture of the resultant π -allylpalladium(II) complex by a secondary amine (Scheme 2).

In this preliminary study we attached hexa-4,5-dien-1-ol **2** (prepared from the alkyne **1** by a Crabbé³ reaction) to a gel-type polystyrene resin by means of a traceless silicon linker. The reason for this choice is three-fold: alkyl substituted allenes are particularly stable, the alcohol group is convenient for the introduction of further diversity and the cleavage conditions were anticipated to be particularly mild (Scheme 3).

The silane resin **3** (Argonaut Technologies, loading 1.59 mmol g⁻¹ SiH) was chlorinated and immediately loaded⁴ with the allenic alcohol **2** to give the resin **5** (loading 1.45 mmol g⁻¹).⁵ The colourless resin **5** was characterised by gel-phase ¹H NMR (250 MHz, CDCl₃) δ = 3.7 (CH₂CH=C=CH₂), 4.7



Scheme 2



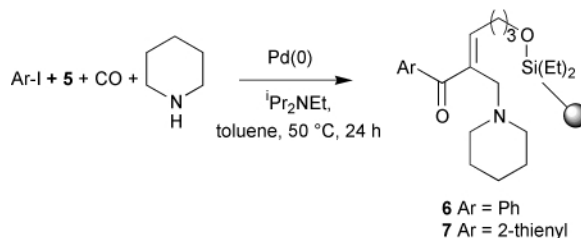
Scheme 3

(CH=C=CH₂), 5.1 (CH=C=CH₂) and FT-IR (KBr disc) 1953 cm⁻¹ (CH=C=CH₂ stretch).

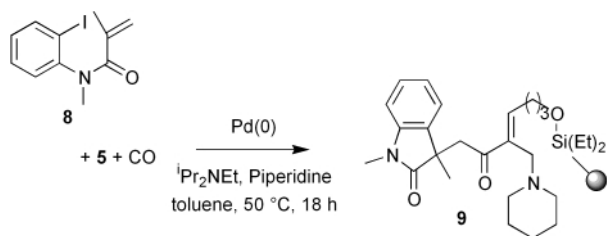
The experimental conditions for the palladium-catalysed cascade (Scheme 4) were as follows: resin **5** (1.0 mol eq.), iodobenzene or 2-iodothiophene (4.0 mol eq.), ⁱPr₂NEt (5.0 mol eq.), piperidine (4.0 mol eq.), Pd(OAc)₂ (0.1 mol eq.), tris(2-furyl)phosphine (0.2 mol eq.), toluene (10 ml mmol⁻¹) and a balloon containing carbon monoxide attached to the reaction vessel. After all the components were added to the flask containing the resin swollen in toluene, a sequence of evacuation (water pump–CO addition) was performed three times. Subsequently the flask was immersed in an oil bath at 50 °C and magnetically stirred for 24 h.

The reaction was monitored by FT-IR following the disappearance of the allene stretching band at 1953 cm⁻¹. After 24 h a small allenic peak was still present. The resin was washed with DMF, 1 : 1 DMF–H₂O, DCM, MeOH, dried and recycled in a second run to complete the conversion. The reaction was not optimised at this stage. The rate determining step appears to be the oxidative addition of Pd(0) into the Ar–I bond. Thus the iodoacrylamide **8** undergoes complete conversion to product in 18 h. In the case of **8** initial coordination of Pd(0) to the olefinic bond would facilitate the oxidative addition step, which is followed by a facile 5-*exo-trig* cyclisation, carbonylation, allene insertion and amine capture (Scheme 5).

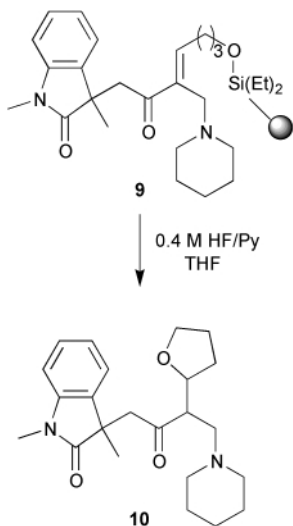
Cleavage of indolinone **9** was achieved using HF/Py (0.4 M HF/Py, THF). Reaction times longer than 25 min led to the formation of a diastereomeric mixture of tetrahydrofurans (1 : 1



Scheme 4



Scheme 5



Scheme 6

ratio by HPLC, 70% yield); **10** deriving from acid-catalysed intramolecular Michael addition (Scheme 6).

After exposing the resin for 20 min to the cleavage mixture the filtrate was quenched with a saturated solution of NaHCO_3 , extracted with AcOEt, the solvent removed *in vacuo* to afford the alcohol (60%) whose purity was 98% by HPLC-MS. The residue was acetylated (Ac_2O , pyridine, DMAP, DCM, 2 h, rt) and the acetate **11** was purified by silica gel chromatography (AcOEt-PE-triethylamine 50:50:2) and obtained in 90% yield from the alcohol (Scheme 7).

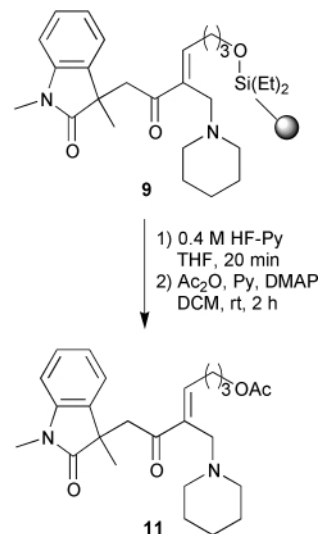
The loading of resin **9** was found to be 1.1 mmol g^{-1} (calculated on the yield of the crude product after cleavage).

Similarly the resins **12–14** were prepared. After cleavage and work-up the alcohols **15–17** were found to be 98% pure by HPLC-MS and no further purification was carried out.⁶

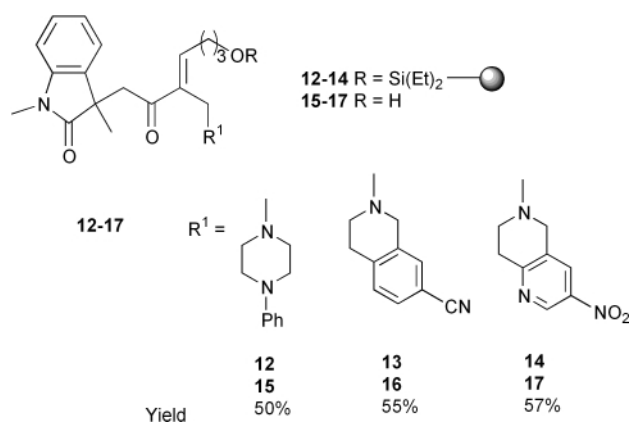
It is worth noting that all the products **11–17** were obtained as single stereoisomers.⁷

In conclusion, the resin supported allene **5** is an excellent scaffold for the construction of complex heterocycles. Further investigations using a broader range of anion capture agents and starter molecules are in progress.

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Scheme 7



Notes and references

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- The loading was the average of two determinations: 1) weight increase after washing and overnight drying *in vacuo*, 2) yield of **2** after cleavage (TBAF, 1.0 M in THF) and chromatographic purification (Et_2O -PE 1:1).
- Overall from **5** to **15–17**.
- In similar experiments we found that the C=C geometry is *Z* (NOE data): this stereochemical outcome is rationalised by attack of the amine on the more stable *anti* π -allylpalladium(II) complex (R. Grigg and M. Rasparini, unpublished data).