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Spiro-oxindoles via bimetallic [Pd(0)/Ag(I)] catalytic intramolecular Heck-1,3-dipolar cycloaddition cascade reactions

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Abstract—The combination of an intramolecular Heck reaction with a subsequent Ag(I) catalysed imine→azomethine ylide→cycloaddition cascade is described for the formation of novel spiro-oxindoles. The reaction proceeds regiospecifically with good to excellent stereoselectivity and creates two new rings, three bonds and three stereocentres.

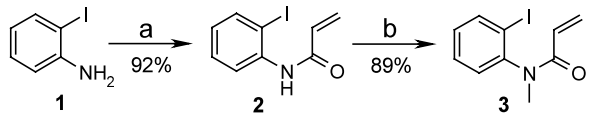
We have recently developed a significant number of sequential and cascade tactical combinations[1,2] in which two disparate ring forming reactions are combined to provide one-pot access to target molecules possessing a high degree of molecular complexity. We now report a combination of two powerful ring forming processes, the intramolecular Heck reaction and our imine→azomethine ylide→cycloaddition, in which the former Pd-catalysed process generates the dipolarophile for the latter Ag(I)-catalysed process. The Heck substrate **3** was produced as outlined in Scheme 1.

The cascade process (Scheme 2) utilised a $Pd(OAc)_2$/PPh_3 precatalyst combination for the intramolecular Heck reaction which affords **4** in situ. The known instability of **4**[3] dictated a search for mild reaction conditions. Using dichloromethane as solvent allowed the reaction to be carried out at room temperature. A subsequent Ag(I) catalysed imine→azomethine ylide→cycloaddition cascade leads to spiro-oxindoles regiospecifically in good yield with a reaction time of 16–18 h for the total cascade.

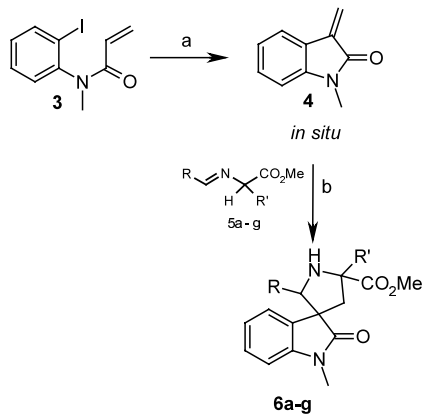
The cycloadducts comprise a ca. 4:1 to >9:1 mixture of two stereoisomers (Table 1).

Although it is not unknown for Heck reactions to occur at room temperature,[4] it is unusual that the reaction should be so efficient in dichloromethane. The constant removal of the Heck product **4** from the reaction mixture by the cycloaddition cascade counteracts its instability.

The silver(I) salt, in the presence of base, generates a metallo-azomethine ylide, which generally cycloadds both regio- and stereospecifically to dipolarophiles.[5] At room temperature, the kinetic *syn*-dipole has the imine



Scheme 1. (a) 1.1 equiv. of Et_3N, 1.1 equiv. of $CH_2CHCOCl$, DCM, rt; (b) NaH, MeI, DMF, 0°C to rt.



Scheme 2. (a) 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3, 1 equiv. of K_2CO_3; (b) 1 equiv. of imine (**5a**–**g**, see Table 1), 10 mol% of Ag_2O, 1 equiv. of DBU, DCM, rt.

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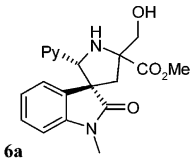
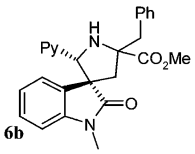
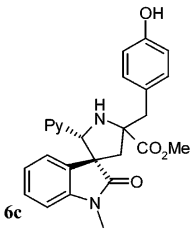
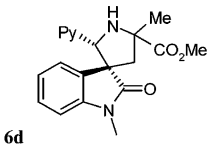
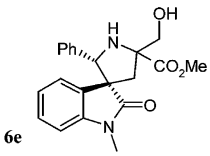
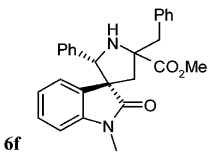
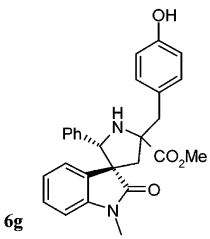
Table 1. Product ratios of spiro-oxindoles resulting after the Heck-1,3-dipolar cycloaddition reaction

Entry	Imine	Product	Yield (%)	Isomer Ratio[a]
1	**5a** R = 3-Py, R' = CH_2OH	 **6a**	68	>9:1
2	**5b** R = 3-Py, R' = CH_2Ph	 **6b**	67	6.4:1
3	**5c** R = 3-Py, R' = 4-OH-Bn	 **6c**	68	5.4:1
4	**5d** R = 3-Py, R' = CH_3	 **6d**	72	9.0:1
5	**5e** R = Ph, R' = CH_2OH	 **6e**	59	>9:1
6	**5f** R = Ph, R' = CH_2Ph	 **6f**	62	7.8:1
7	**5g** R = Ph, R' = 4-OH-Bn	 **6g**	63	4.2:1

[a] Isomer ratios determined from the ^1H NMR spectrum of the crude reaction mixture

nitrogen and the carbonyl oxygen of the ester moiety coordinated to the silver, locking the dipole conformation (Fig. 1).

The stereochemistry of the major isomer of product **6a** was determined by X-ray crystallography (Fig. 2), indicating that the 1,3-dipolar cycloaddition proceeded with *endo*-selectivity. However, the stereochemistry of this isomer is such that the metallo-azomethine ylide involved must have had *anti* conformation (Fig. 1).

Significant *syn–anti* dipole isomerisation is rare in Ag(I)-catalysed cycloaddition reactions. It occurs when structural features conspire to slow the cycloaddition step; sterically hindered 1,1-disubstituted amide dipolarophiles are particularly prone to this process.[6]

It was suspected that the minor isomer arose from the *syn*-dipole. Unfortunately in each of the cases **6a–g** it did not prove possible to isolate a suitable crystal of a minor isomer for X-ray structure determination. A separate experiment was therefore carried out using an imine derived from methyl glycinate (Scheme 3). In this case the isomer ratio **7a**/**7b** was 1.2:1 and crystals of both the major and minor isomers were obtained and their structures determined by X-ray crystallography (Fig. 3). As expected, the minor isomer resulted from the *syn*-dipole.

Syn-dipole. *Anti*-dipole

Figure 1.

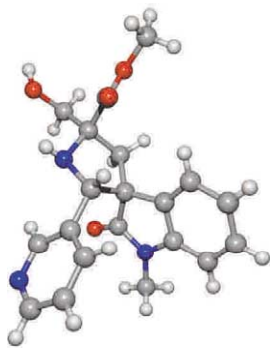
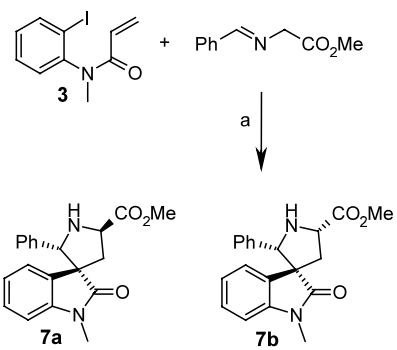
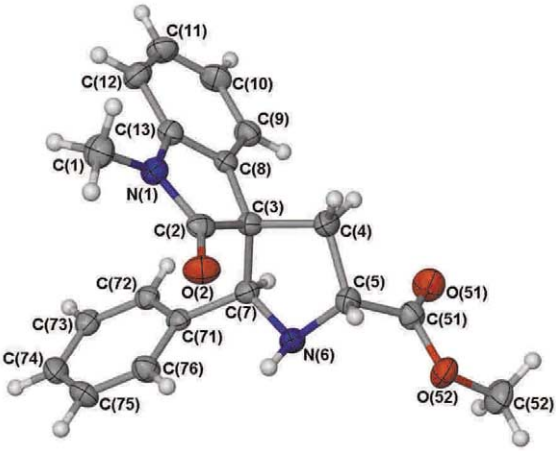


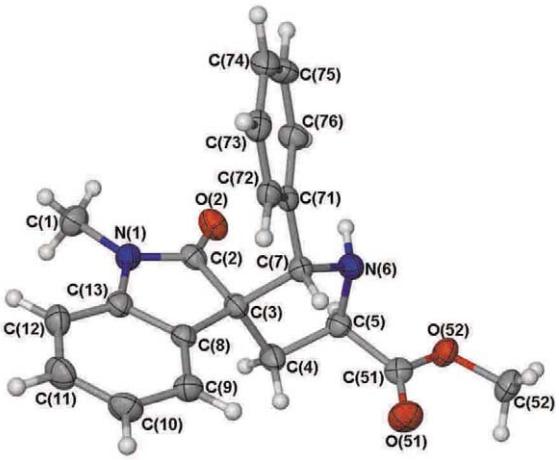
Figure 2. X-Ray crystal structure of the major stereoisomer of product **6a**.



Scheme 3. (a) 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3, 1 equiv. of K_2CO_3, 10 mol% of Ag_2O, 1 equiv. of DBU, DCM, rt.



Major isomer **7a**



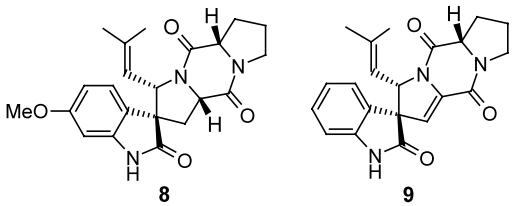
Minor isomer **7b**

Figure 3. X-Ray crystal structures of both stereoisomers of product **7**.

Further studies are currently ongoing to determine the diversity of functionality within the dipole that is tolerated in the cascade. Although the bimetallic cascade is demonstrated for imines of α-amino esters it is potentially applicable to the substantial range of aminomethyl substrates exemplified in our publications.[7]

In conclusion, this bimetallic catalytic cascade offers access to novel spiro-oxindole analogues, the reaction proceeding with good to excellent stereoselectivity. The spiro-oxindole moiety is the core structure in a number of natural products, which offer potentially valuable medicinal properties. Typical examples are the Spirotryprostatins A **8** and B **9**, which were recently isolated from the fermentation broth of *Aspergillus fumigatus*.[8]

These spiro-oxindole alkaloids inhibit the cell cycle in the G2/M phase of tsFT210 cells with IC_{50}s of 197.5 μM for **8** and 14 μM for **9**, thus, having the potential to act as antineoplastic agents. Recent synthetic work by Danishefsky[9] has identified more active unnatural analogues. The synthesis of such analogues, together with the natural products,[10] is currently attracting much attention.



Acknowledgements

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