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Synthesis of triazolo- and tetrazolo-tetrahydroisoquinolines and isoquinolines via temperature controlled palladium catalysed allene/azide incorporation/intramolecular 1,3-dipolar cycloaddition cascades

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Abstract—A novel palladium catalysed three-component process is described involving an allene, an aryl iodide containing an activated alkene and $TMSN_3$. The cascade proceeds via a (π-allyl)palladium species which is intercepted by azide anion followed by stereoselective intramolecular 1,3-dipolar cycloaddition of the organoazide to afford substituted triazolo- and tetrazolo-tetrahydroisoquinolines in good yield. These latter products undergo extrusion of nitrogen to afford isoquinolines at 100 °C.
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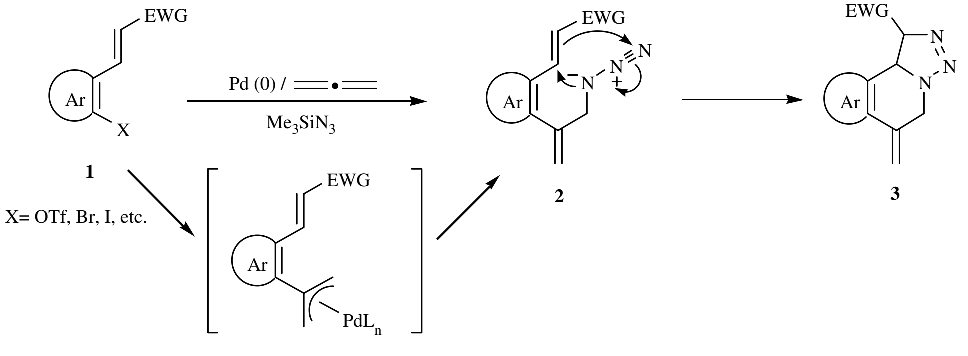
Triazoles and isoquinoline derivatives are important constituents of a diverse range of pharmaceutical and natural products. Isoquinolines occur mainly at the 1,2,3,4-tetrahydro oxidation level in a large number of alkaloids.[1] Triazoles have found broad use in pharmaceuticals, agrochemicals and dyes[2] whilst tetrazoles are widely used as carboxylic acid bioisosteres.[3] Recently, copper catalysed 1,3-dipolar cycloaddition reactions of azides and alkynes have been exploited in biology, for example, in cell surface labeling of *Escherichia coli*,[4] and activity-based protein profiling in vivo.[5] Sharpless and co-workers[6] have recently synthesised a potent and highly selective inhibitor of human α-1,3-fucosyltranferase via the 1, 3-dipolar cycloadditon of an azide and an alkyne.



Scheme 1.

Keywords: Multicomponent reaction; Catalysis; Cycloaddition.

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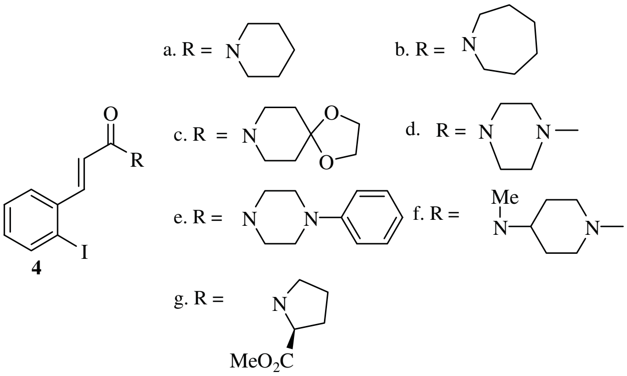
We have been developing novel high diversity palladium catalysed cascade processes in tactical combination with a variety of core reactions, such as the Diels–Alder,[7] 1,3-dipolar cycloaddition[8] and Michael addition[9] to generate novel complex heterocycles in one pot processes. Recently, we have reported palladium catalysed allene/azide capture/intermolecular cycloaddition cascades which furnish triazoles in good yield.[10,11] Yamamoto and co-workers.[12,13] have also reported processes which used allyl acetates to generate the π-allyl palladium species. In this letter, we report palladium catalysed three-component cascades in which a dipolarophile is incorporated into an aryl iodide (Scheme 1).

Thus **1** reacts with allene and Me_3SiN_3 in the presence of Pd(0) to afford allyl azide **2** which then undergoes intramolecular 1,3-dipolar cycloaddition to afford **3**. For our initial studies, we selected **4a**–**g** as dual aryl iodide/dipolarophiles.

Thus **4a**–**f** (1 mol equiv) were reacted with allene (1 bar), $TMSN_3$ (2 mol equiv), $Pd_2(dba)_3$ (2.5 mol%), tris (2-furyl) phosphine (TFP) (10 mol%) and KOAc (2 mol equiv) in DMF at 70 °C for 24 h to afford cycloadducts **5**–**10** as single diastereoisomers in good yield. (Table 1).

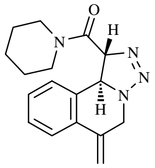
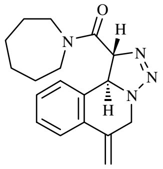
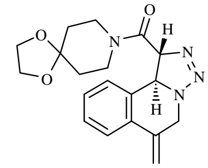
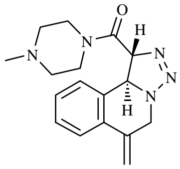
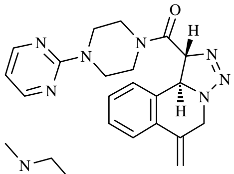
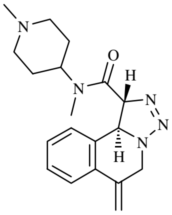
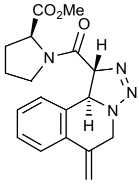
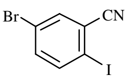
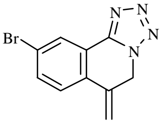
The stereochemistry of the cycloadducts was established by NOE studies.[14] Next, we studied the alkene face selectivity when a chiral auxiliary was present on the amide. Thus **4g** under essentially the same palladium catalysed conditions afforded a 3:1 diastereoisomer mixture of **11** in 72% yield. An analogous cascade employing the nitrile group as dipolarophile also proceeded under the same conditions. The product in this case is a tetrazole (Table 1, entry 8).



We further investigated the reaction of **4a**–**c** with substituted allenes. 1,2-Dimethyl allene, (5 mol equiv) reacted with $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), KOAc (2 mol equiv) and $TMSN_3$ (2 mol equiv) in DMF at 70 °C over 24 h to afford cycloadducts **13**–**15** regioselectively in good yield (Table 2, entries 1–3).

When the reaction of **4a**–**e** was run at 70 °C for 24 h, the excess allene gas vented and the mixture heated to 100 °C for another 24 h fragmentation–aromatisation ensued and the substituted isoquinolines **16**–**20** were obtained in 70–78% yields (Table 3). A possible mechanism for the formation of substituted isoquinolines is shown (Scheme 2). This rearrangement may be a free radical process but, at present, we have no data bearing on this.

Table 1. Three-component allene–nucleophile incorporation–intramolecular 1,3-dipolar cycloaddition cascades[a]

Entry	Substrate	Product	Yield[b] (%)
1	**4a**	 **5**	80
2	**4b**	 **6**	78
3	**4c**	 **7**	78
4	**4d**	 **8**	75
5	**4e**	 **9**	84
6	**4f**	 **10**	72
7	**4g**	 **11**	72[c]
8		 **12**	62[d]

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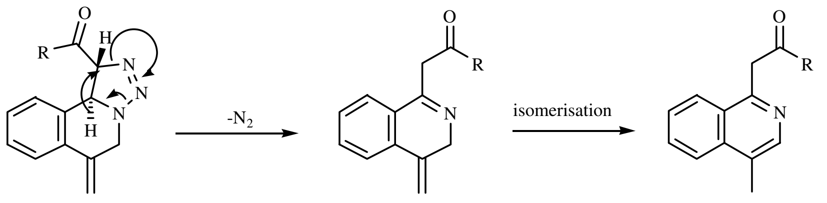
[a] All reactions were carried out in DMF at 70 °C for 24 h and employed $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), KOAc (2 mol equiv) and Me_3SiN_3 (2 mol equiv).

[b] Isolated yield.

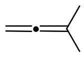
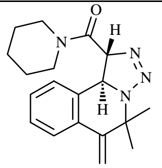
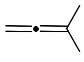
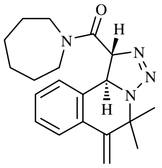
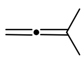
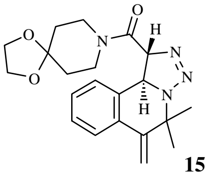
[c] Diastereomer ratio 3:1.

[d] Reaction was carried out for 48 h.



Scheme 2.

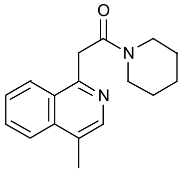
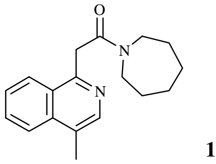
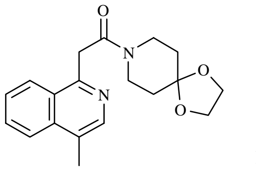
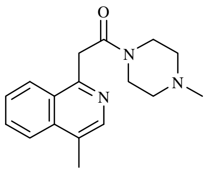
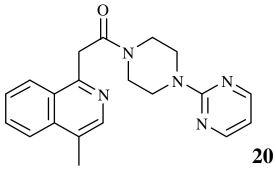
Table 2. Three-component allene–nucleophile incorporation–intramolecular 1,3-dipolar cycloaddition cascades with substituted allenes[a]

Entry	Substrates	Allene	Products	Yield[b] (%)
1	**4a**		 **13**	65
2	**4b**		 **14**	71
3	**4c**		 **15**	68

[a] All reactions were carried out in DMF at 70 °C for 24 h and employed $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), KOAc (2 mol equiv) Me_3SiN_3 (2 mol equiv) and 1,2-dimethylallene (5 mol equiv).

[b] Isolated yields.

Table 3. Three-component cascades forming substituted isoquinolines[a]

Entry	Substrates	Products	Yield[b] (%)
1	**4a**	 **16**	78
2	**4b**	 **17**	76
3	**4c**	 **18**	70
4	**4d**	 **19**	75
5	**4e**	 **20**	70

[a] All reactions were carried out in DMF initially at 70 °C for 24 h, then at 100 °C for a further 24 h and employed substrate (1 mmol), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), KOAc (2 mol equiv) and Me_3SiN_3 (2 mol equiv).

[b] Isolated yields.

In conclusion, we have demonstrated that palladium catalysed allene/azide capture/intramolecular 1,3-dipolar cycloaddition cascades provide substituted triazolo- and tetrazolo-tetrahydroisoquinolines or, at higher temperature, the corresponding substituted isoquinolines in good yield. The formation of **5–11** and **13–15** involves the formation of one C–C bond, three C–N bonds, two rings and two stereocentres.

Acknowledgements

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References and notes

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14. Typical NOE values for **5**–**11** are: irradiation of H_a enhances the signals for H_b (3.8–4.2%) and H_h (6.4–7.4%), irradiation of H_b enhances the signals for H_a (1.8–2.1%), H_d (1.7–2.1%) and H_h (3.4–3.7%), irradiation of H_c enhances the signals for H_d (31.8–32%) and H_e (5.3–6.3%) whilst irradiation of H_f enhances the signals for H_e (24.0–25.8%) and H_g (11.5–14.5%).