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Synthesis of spiro- and fused heterocycles by palladium catalysed carbo- and heteroannulation cascades of allenes

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Two novel palladium catalysed cascade processes involving the generation of a (π-allyl)palladium intermediate from allenes in an intra- or intermolecular fashion, followed by regioselective intramolecular nucleophilic addition of amines, alcohols or malonates provide spiro- or linear fused heterocycles in good yield.

The importance and versatility of palladium catalysed processes involving allenes for the construction of carbon–carbon and carbon–heteroatom bonds is amply documented in a recent review.[1]

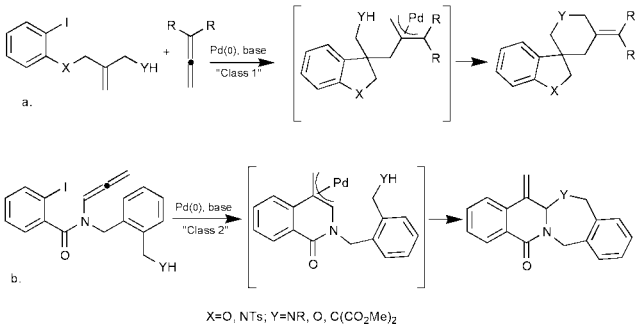
We have demonstrated that allenes are powerful relay switches in palladium catalysed polycomponent (poly)-cyclisation anion capture cascades.[2] Reaction of aryl/vinyl palladium(II) intermediates with allene leads to the formation of (π-allyl)palladium species able to undergo a wide range of transformations including attack by nucleophiles,[3] electrophiles[4] or transmetallation.[5]

The tactical combination of these transformations in an inter- and/or intramolecular fashion[6] enables expeditious increments of the molecular complexity of the products that are limited only by the ingenuity of the chemist.

We now report two novel palladium catalysed cascades ('Class 1' and 'Class 2') characterised by intramolecular anion capture[2] as the termination step. Both cascades are initiated by oxidative addition of Pd(0) into an Ar–I bond. In the 'Class 1' process this step is followed by an *exo-trig* cyclisation, intermolecular allene insertion and intramolecular capture of the resultant (π-allyl)palladium complex with a tethered nucleophile (amine or malonate anion) (Scheme 1a). This cascade results in the formation of three bonds and a spiro-fused ring system.

In the 'Class 2' process the (π-allyl)palladium complex is generated by an *exo-dig* cyclisation of the Ar–Pd species onto a proximal 1,2-dienamide. Subsequent interception of the resulting (π-allyl)palladium(II) species by a nucleophile leads to bicyclic lactams with formation of two rings and two new bonds (Scheme 1b).

The substrates for 'Class 1' process (Y = NR, $C(CO_2Me)_2$) were prepared in two steps by displacement of the allylic chlorides **1** or **3** with amines or dimethyl malonate (Scheme 2).

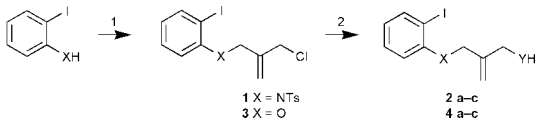


Scheme 1

Substrates **2a–c** and **4a–b** were then reacted with allene (1.0 bar) or 3-methylbuta-1,2-diene (dimethylallene) in the presence of a base and Pd(0) to afford the spirocyclic products in good yield[7] (Table 1). When dimethylallene was employed, exclusive formation of the regioisomer arising from attack at the less hindered end of the (π-allyl)palladium moiety was observed in all the cases.

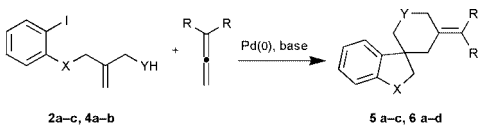
We then focused our attention on a fully intramolecular process: a scaffold precursor **7** was synthesised in 57% overall yield from 2-bromobenzaldehyde (Scheme 3).

The formyl group was then exploited for the introduction of the desired nucleophiles (Scheme 4). The *N*-propargyl amides were then isomerised to the relatively labile *N*-allenyl amides



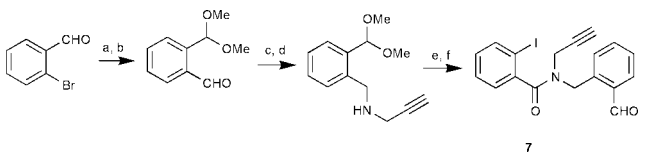
Scheme 2 *Reagents and conditions*: (1) 2-iodo-*N*-tosylaniline, NaH, 3-chloro-2-chloromethylpropene, DMF, rt, 48 h, 95% or 2-iodophenol, 3-chloro-2-chloromethylpropene, K_2CO_3, MeCN, reflux, 2 h, 91%; (2) primary amine (see Table 1), K_2CO_3, MeCN, reflux, 18 h (**2a**, 64%; **2b** 54%; **4a**, 61%, **4b**, 60%) or dimethyl malonate, K_2CO_3, CH_3CN, reflux, 18 h (**2c**, 80%, **4c**, 84%).

Table 1 Class 1 processes



Entry	X	Y	R	Base[a]	Product	Yield (%)[b]
1 (**2a**)	NTs	*N*-Cyclopropyl	H	K_2CO_3	**5a**	59
2 (**2b**)	NTs	NBn	H	K_2CO_3	**5b**	54
3 (**2b**)	NTs	NBn	Me	K_2CO_3	**5c**	56
4 (**2c**)	NTs	$C(CO_2Me)_2$	H	Cs_2CO_3	**5d**	66
5 (**2c**)	NTs	$C(CO_2Me)_2$	Me	Cs_2CO_3	**5e**	72
6 (**4a**)	O	NBn	H	K_2CO_3	**6a**	55
7 (**4a**)	O	NBn	Me	K_2CO_3	**6b**	59
8 (**4b**)	O	*N*-Cyclopropyl	H	K_2CO_3	**6c**	65
9 (**4b**)	O	*N*-Cyclopropyl	Me	K_2CO_3	**6d**	66

[a] For experimental, see ref. 7. [b] Isolated analytically pure products.



Scheme 3 *Reagents and conditions*: (1) MeOH, $CH(OMe)_3$, Dowex 50W X8-200, reflux, 18 h, 92%; 2) THF, *n*-BuLi, −78 °C, 30 min, then DMF, −78 °C to rt, 98%; (3) propargylamine, $MgSO_4$, DCM, 100%; (4) MeOH, $NaBH_4$, 0 °C, 95%; (5) 2-iodobenzoyl chloride, TEA, DCM, 0 °C to rt, 69%; (6) Montmorillonite K10, DCM, rt 10 min, 97%.

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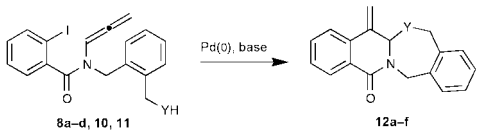
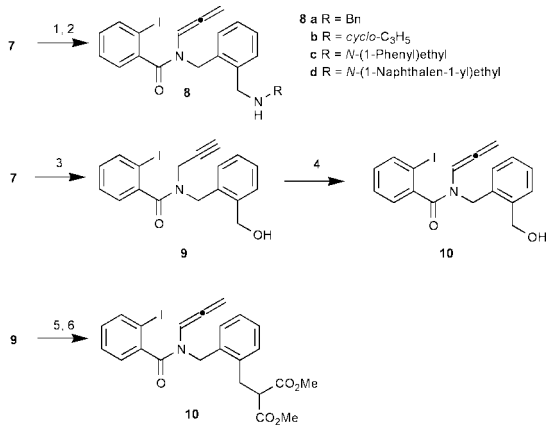
Table 2 Class 2 processes



Entry	Y	Base[a]	Time (h)	Product	Yield (%)[d]
1 (**8a**)	NBn	K_2CO_3	24	**12a**	63
2 (**8b**)	*N*-Cyclopropyl	K_2CO_3	24	**12b**	55
3 (**8c**)	*N*-(1-Phenyl)ethyl	Ag_2CO_3	24	**12c**[b]	52
4 (**8d**)	*N*-(1-Naphthalen-1-yl)ethyl	Ag_2CO_3	24	**12d**[c]	54
5 (**10**)	O	Cs_2CO_3	48	**12e**	50
6 (**11**)	$C(CO_2Me)_2$	Cs_2CO_3	48	**12f**	45

[a] For experimental, see ref. 8. [b] 1.2 : 1 mixture of diasteroisomers (HPLC). [c] 1.5 : 1 mixture of diastereoisomers (^{1}H NMR). [d] Isolated analytically pure products.



Scheme 4 *Reagents and conditions*: (1) Primary amine, $MgSO_4$, DCM, then MeOH, $NaBH_4$ 0 °C, 10 min, (**8a**, 85%, **8b**, 76%, **8c**, 71%, **8d**, 84%); (2) THF, *t*-BuOK (1.0 eq.), 0 °C, 1 min; (3) MeOH, $NaBH_4$ 0 °C, 10 min, 87%; (4) THF, *t*-BuOK (2.0 eq.), 0 °C, 1 min; (5) MsCl, TEA, DCM, 0 °C then DMF, sodium dimethyl malonate, 0 °C to rt, 60%; (6) THF, *t*-BuOK (2.0 eq.), 0 °C, 1 min.

immediately prior to the last Pd(0) catalysed step. The best conditions employed *t*-BuOK (1.1 eq. or 2.1 eq. when alcohols or malonates were used) in THF at 0 °C for 1 min. The transformation is nearly instantaneous and longer reaction times result in further isomerisation to *N*-prop-1-ynyl amides and to the formation of alcoholysis products.

All the substrates **8a**–**d** and **10**–**11** cyclised in 24–48 h in toluene at 50 °C in the presence of Pd(0) and an inorganic base[8] (Table 2).

We employed two chiral amines (**8c** and **8d**) in order to establish if the stereocenter α- to the nitrogen is able to induce a diastereofacial preference during the nucleophilic attack on the (π-allyl)palladium complex. When K_2CO_3 was employed, in both the cases a 1 : 1 mixture of diasteroisomers was obtained. Little improvement was achieved using Ag_2CO_3 (entry 3) or by increasing the steric hindrance around the nitrogen (entry 4). However, the two diasteroisomers were easily separated by crystallisation from EtOH.

A stronger base (entry 11) and longer reaction times were required (entry 10) for the less nucleophilic alcohol and malonate moieties.

In conclusion we have shown that this methodology permits access to unusual spiro- and fused heterocyclic frameworks.

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Notes and references

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6 For a recent example of an intramolecular (π-allyl)palladium capture: L. E. Overman and M. D. Rosen, *Angew. Chem., Int. Ed.*, 2000, **39**, 4596.
7 Typical experimental conditions for 'Class 1' process: substrate (0.3 mmol), allene (1.0 bar, 100 ml one-neck pressure dram vessel) or dimethylallene (4.0 eq.), base (2.0 eq.), tri(2-furyl)phosphine (0.2 eq.), $Pd(OAc)_2$ (0.1 eq.), toluene (5.0 ml), 110 °C, 18 h.
8 Typical experimental conditions for 'Class 2' process: substrate (1.0 mmol), base (2.0 eq.), tri(2-furyl)phosphine (0.2 eq.), $Pd(OAc)_2$ (0.1 eq.), toluene (5 ml), 50 °C, 24–48 h.