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Synthesis of carbo- and heterocycles via a palladium-catalysed allene insertion–nucleophile incorporation–Michael addition cascade

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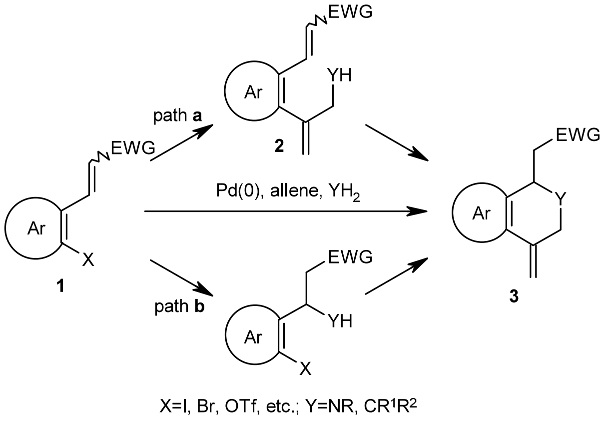
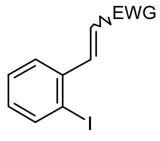
Abstract—A novel palladium catalysed three-component cascade process is described involving allenylation of an aryl iodide to generate a (π-allyl)palladium species which is intercepted by a carbon or nitrogen nucleophile followed by intramolecular Michael addition to afford carbo- and heterocycles in good yield.

In recent years allenes have become useful building blocks in palladium catalysed processes.[1] We have demonstrated that allenes are powerful relay switches in palladium catalysed cyclisation–anion capture cascades.[2] Reactions of aryl/vinyl palladium(II) intermediates with allene lead 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] As part of our ongoing interest in designing palladium catalysed allenylation processes in a tactical combination with core reactions, we explored combinations with Michael addition processes as the key step. The recent paper by Desmaele on related processes,[6] in which π-allylpalladium(II) species are generated from allylic acetates, encouraged us to present our work. In this communication we report three-component cascades in which a Michael acceptor is incorporated into the aryl iodide (Scheme 1).

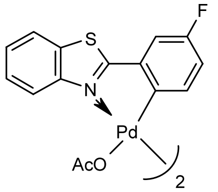


Scheme 1.

Thus, compound **1** reacts with allene and a nucleophile (YH_2) in the presence of palladium(0) to afford hetero- or carbocycles via path **a** or path **b**. Path **a** involves allene insertion followed by nucleophile attack to give intermediate **2** which then undergoes Michael addition to afford **3**. In path **b**, the Michael addition occurs first. For our initial studies we selected **4a**–**d** as dual aryl iodide/Michael acceptors.



4a (EWG=CO_2Me) (1:5 *cis:trans*)
4b (EWG=PhCO) (*trans*)
4c (EWG=CN) (2:1 *cis:trans*)
4d (EWG=NO_2) (*trans*)



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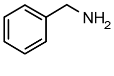
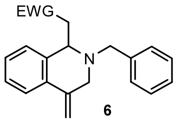
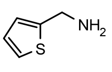
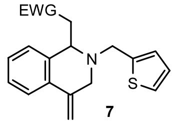
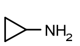
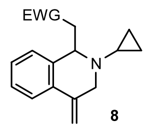
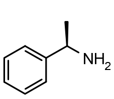
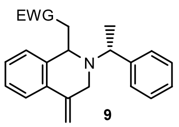
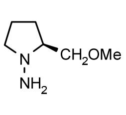
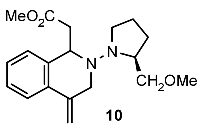
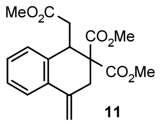
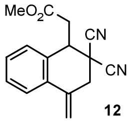
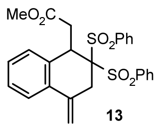
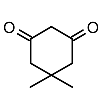
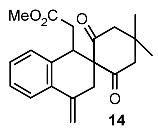
Thus, **4a–c** (1 mmol) reacted with allene (1 bar), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2 mol equiv.) and a primary amine (2 mol equiv.) in toluene (10 ml) at 80°C over 36 h to afford heterocycles **6–8** in good yield (Table 1). When a nitro group was employed as the electron withdrawing group (**4d**), palladacycle **5**[7] was used as the catalyst.

Table 1. Three-component allenylation–nucleophile incorporation–Michael addition cascades[a]

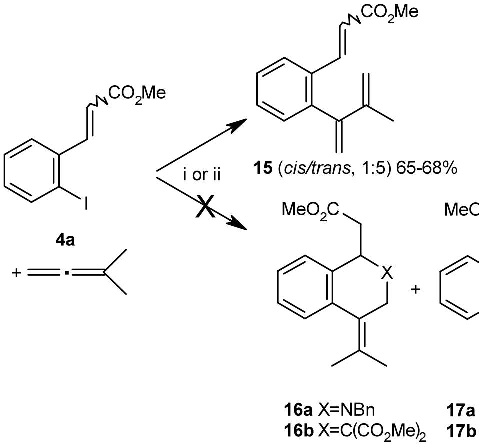
Entry	Nucleophile	Product	Yield (%)[b]
1		 **6**	**6a** 73 **6b** 76 **6c** 74 **6d** 60[c]
2		 **7**	**7a** 87 **7b** 90 **7c** 58 **7d** 64[c]
3		 **8**	**8a** 80 **8b** 80 **8c** 47 **8d** 68[c]
4		 **9**	**9a** 74[d] **9b** 74[d]
5		 **10**	**10a** 77[e]
6	$CH_2(CO_2Me)_2$	 **11**	**11a** 64[f]
7	$CH_2(CN)_2$	 **12**	**12a** 42[f]
8	$CH_2(SO_2Ph)_2$	 **13**	**13a** 60[f]
9		 **14**	**14a** 64[f]

[a] All reactions were carried out in toluene at 80 °C for 36 h and employed **4a-d** (1 mmol), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2 mol eq.) and amine (2 mol eq.) or carbon pronucleophile (1.2 mol eq.). [b] isolated yields. [c] palladacycle **5** (10 mol%) and 16 h reaction time. [d] 1:1 mixture of diastereoisomers. [e]2:1 mixture of diastereoisomers. [f] Cs_2CO_3 as base.

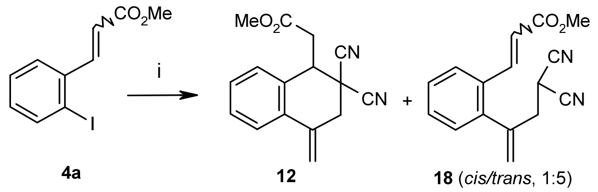
Next, we briefly studied the diastereoselectivity of the Michael addition (Table 1, entries 4 and 5). Thus, using *R*-(+)-α-methylbenzylamine afforded **9a** as a 1:1 and **9b** as a 2:1 mixture of diastereoisomers, whereas SAMP afforded **10a** as a 2:1 diastereomeric mixture.

Carbon nucleophiles (1.2 mol equiv.) were also successfully incorporated into this three-component cascade process to afford carbocycles with a tetra-substituted carbon centre in good yield (Table 1, entries 6–8). Finally, on the carbocyclic theme, we employed dimedone (1.2 mol equiv.) as the pronucleophile to synthesise spirocyclic compound **14a** in 64% yield.

We also showed that the mechanism of the reaction with **4a** is more likely to proceed via path **a** than path **b**. Thus, **4a** afforded the β-hydride eliminated product **15**, rather than the carbo- or heterocyclic compounds **16a**,**b** or **17a**,**b**, when reacted with dimethylallene, benzylamine and K_2CO_3 or with dimethylallene, dimethyl malonate and Cs_2CO_3 (Scheme 2). No Michael adduct, which might result from the reaction of **4a** or **15** with

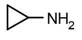
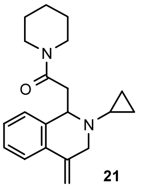
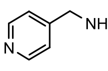
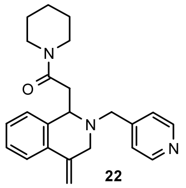
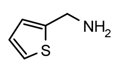
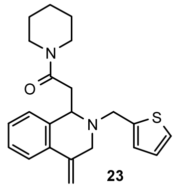
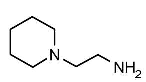
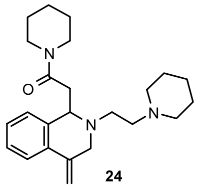
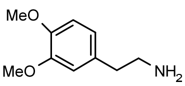
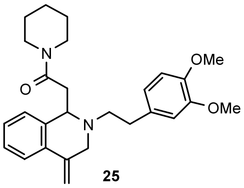
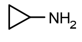
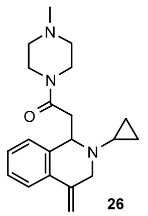
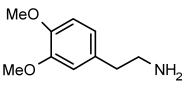
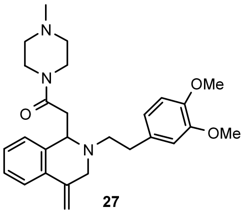


Scheme 2. *Reagents and conditions*: (i) methyl 2-iodocinnamate, **4a** (*cis*/*trans*, 1:5) (1 mmol), dimethylallene (3 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2 mol equiv.), NH_2Bn (2 mol equiv.), toluene, 80°C, 36 h, 65%. (ii) methyl 2-iodocinnamate **4a** (*cis*/*trans*, 1:5) (1 mmol), dimethylallene (3 mol equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (2 mol equiv.), $CH_2(CO_2Me)_2$ (1.2 mol equiv.), toluene, 80°C, 36 h, 68%.



Scheme 3. *Reagents and conditions*: (i) methyl 2-iodocinnamate **4a** (*cis*/*trans*, 1:5) (1 mmol), allene (1 bar), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (2 mol equiv.), CH_2CN_2 (1.2 mol equiv.), toluene, 80°C, 24 h.

Table 2. Three-component cascade with vinyl amide Michael acceptors[a]

Entry	Substrate	Nucleophile	Product	Yield (%)[b]
1	19		 **21**	77
2	19		 **22**	85
3	19		 **23**	56
4	19		 **24**	65
4	19		 **25**	65
5	20		 **26**	86
6	20		 **27**	90

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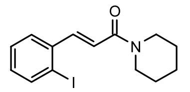
[a] All reactions were carried out in DMF at 80 °C for 18 h and employed $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), K_2CO_3 (2 mol eq.) and amine (2 mol eq.) [b] isolated yields.

either benzylamine or dimethyl malonate, was detected in these reactions. A control experiment, in which allene was omitted as a reagent and benzylamine used as the nucleophile, was also carried out but again no Michael adduct, resulting from the reaction of **4a** with benzylamine, was detected.

Further evidence for the reaction proceeding via path **a**, rather than path **b**, was gained from the reaction with malononitrile. When the reaction was left for 24 h, a mixture of compounds **12** and **18** was observed in the ^1H NMR spectrum of the crude product (Scheme 3). Increasing the reaction time to 36 h resulted in the sole formation of **12**. The mechanism for reactions with **4b–d** has yet to be probed.

A further facet of this high yielding cascade, of particular medicinal chemistry importance, is revealed when heterocyclic amides **19** and **20** are employed as the electron withdrawing group on the Michael acceptor. In these cases the catalyst system comprised 2.5 mol% Pd_2dba_3/10 mol% tris(2-furyl)phosphine/K_2CO_3 (2 mol equiv.) in DMF and the products **21**–**27** were obtained in excellent yield (Table 2).



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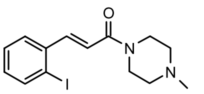

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In conclusion, we have demonstrated a novel three-component palladium catalysed allene insertion/nucleophile incorporation/Michael addition cascade for the synthesis of carbo- and heterocycles. Further work is in hand incorporating monosubstituted allenes into this cascade to study the regioselectivity of the palladium catalysed process and the diastereoselectivity of the Michael addition step.

Acknowledgements

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