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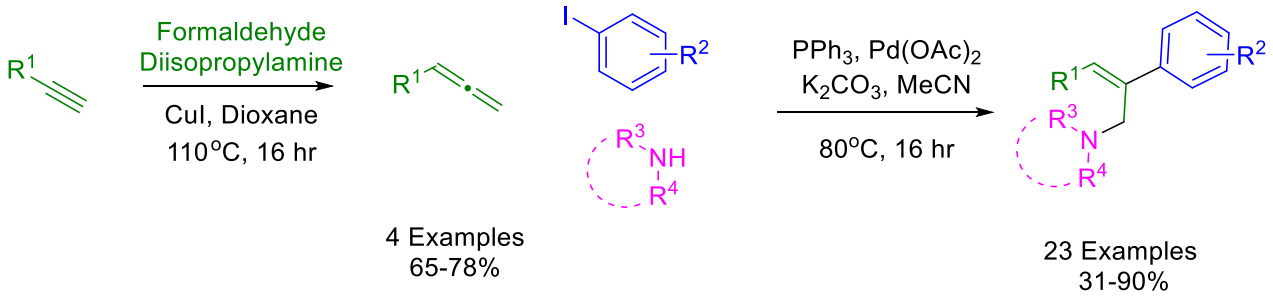

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Palladium catalysed three component cascade reaction for the efficient synthesis of diverse small molecules

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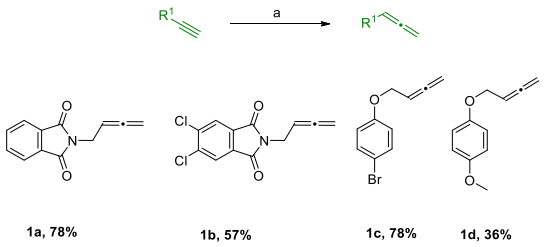
ABSTRACT

A three component palladium catalysed cascade reaction was employed in the regiospecific and stereoselective synthesis of novel substituted (*Z*) 2-butene 1,4 diamine analogues and substituted 4-aryloxy but-2-enyl amine analogues. Allenes were first synthesised from the corresponding alkynes using a Crabbé reaction and then reacted with a large range of commercially available aryl iodides and amines to generate a library of small molecules. The reaction is compatible with aryl iodides containing both electron donating and electron withdrawing groups. Amines of different sizes can also be utilised with no noticeable effect on the yield, regiospecificity or stereoselectivity.

One-pot multicomponent reactions (MCRs) are a powerful method for synthesizing complex molecular scaffolds in a single step.[1–3] Advantages in using MCRs over a linear reaction sequence to afford the same molecule include better yields, ease of synthetic access to analogues, and a single purification step.

Allenes are an underused functionality in organic synthesis, yet show great potential, as they may react with a vast array of functional groups.[4] The reaction of an aryl palladium (II) intermediate with an allene yields a highly reactive π-allyl palladium species which may then undergo an array of transformations. Examples of attack by nucleophiles,[5] electrophiles[6] and transmetallation have been reported.[7] As part of our ongoing interest in palladium catalysed cascade chemistry, we herein report the synthesis of a small library of novel substituted (*Z*) 2-butene 1,4 diamine analogues and substituted 4-aryloxy but-2-enyl amine analogues. *via* nucleophilic attack of the π-allyl palladium species by an amine, in order to investigate the effects of component sterics and electronic properties on reaction stereoselectivity and regioselectivity.

We started our investigation by synthesizing a range of allenes to be used in the palladium catalysed three component cascade reaction. A total of 4 allenes were prepared from *N*-propargyl phthalimides and *O*-propargyl phenols *via* a Crabbé reaction (Scheme 1) in good yields.



Scheme 1.A range of allenes were synthesized *via* a Crabbé reaction for use in the palladium catalysed cascade in good yields. a. Alkyne (2 eq), paraformaldehyde (5 eq), copper (I) iodide (1 eq) and diisopropylamine (4 eq), reflux in 1,4-dioxane, 16 hours.

The allenes were then used in the palladium catalysed cascade reaction. A wide array of commercially available amines and aryl iodides with different steric and electronic properties were used in the palladium catalysed cascade reaction (Scheme 2).

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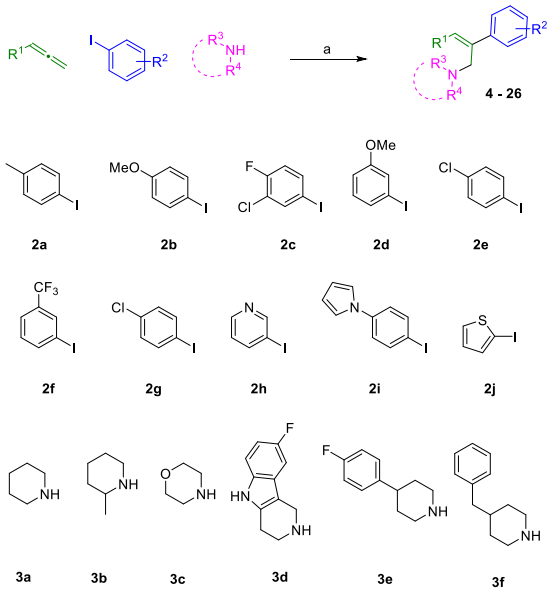


Scheme 2. The range and amines and aryl iodides used in the cascade reaction and the general reaction scheme. a. Allene (1 eq), K_2CO_3 (2 eq), aryl iodide (1 eq), amine (2 eq), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), reflux in MeCN, 18 hours.

The reaction of phthalimide based allenes (**1a** and **1b**) with a range of aryl iodides and amines were first assessed. Yields ranged from 31-90% and showed high stereoselectivity for the *Z*-isomer (Table 1). Aryl iodides with both electron donating and electron withdrawing groups are tolerated and do not seem to have a big effect on the yield, stereoselectivity or regiospecificity.

Table 1. A wide range of amines and aryl iodides give good yields and show high Z-isomer stereoselectivity.

Aryl Iodide	Amine	Allene	Product	Yield (%)	*E/Z*
2a	3a	1a	4	53	6:94
2j	3a	1a	5	78	0:100
2b	3a	1a	6	55	0:100
2c	3c	1a	7	76	17:83
2b	3c	1a	8	65	29:71
2c	3d	1a	9	73	22:78
2e	3d	1a	10	75	12:88
2f	3c	1a	11	74	21:79
2b	3e	1a	12	63	20:80
2d	3c	1a	13	90	16:84
2i	3c	1a	14	36	4:96
2f	3f	1a	15	31	10:90
2f	3b	1a	16	40	2:98
2h	3c	1a	17	36	0:100
2g	3c	1b	18	53	17:83
2f	3c	1b	19	61	12:88

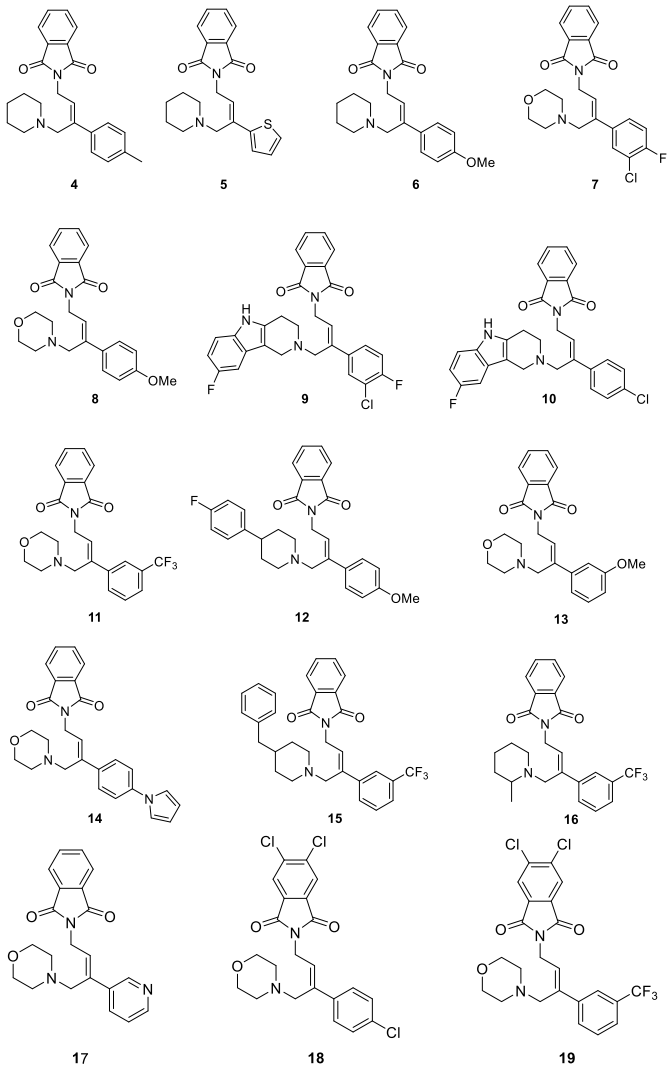


Figure 1. Major isomers (*Z*) of the products formed from phthalimide based allenes in the palladium catalysed cascade reaction.

The reaction of (**1c**-**1d**) with a range of aryl iodides was then assessed. Yields range from 31-67% with moderate selectivity for the *Z*-isomer (Table 2). The yields observed using the phenol based allenes were comparable to the phthalimide based allenes, however the reaction is less stereoselective.

Table 2. A wide range of amines gave good yields and showed moderate selectivity for the Z-isomer.

Aryl Iodide	Amine	Allene	Product	Yield (%)	*E/Z*
2f	3c	1c	20	43	26:74
2b	3c	1c	21	53	29:71
2g	3c	1c	22	36	25:75
2b	3c	1d	23	67	25:75
2g	3c	1d	24	64	25:75
2f	3c	1d	25	61	30:70

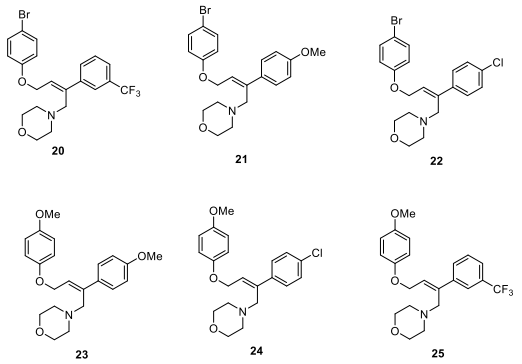


Figure 2. Major isomers (*Z*) of the products formed from phenol based based allenes in the palladium catalysed cascade reaction.

The proposed reaction mechanism is outlined in (Figure 3). Pd(II) is first reduced to Pd(0) using PPh_3. The aryl iodide then undergoes oxidative insertion with Pd(0). Allene insertion then displaces one of the PPh_3 ligands of the Pd(0), followed by migratory insertion of the aryl group. The complex can then undergo nucleophilic attack by the amine to liberate the product. The catalyst can be recovered through reductive elimination by a base.[8]

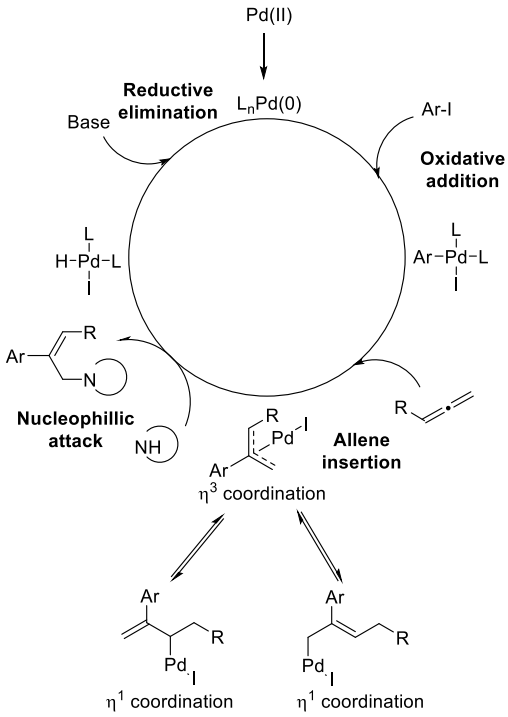
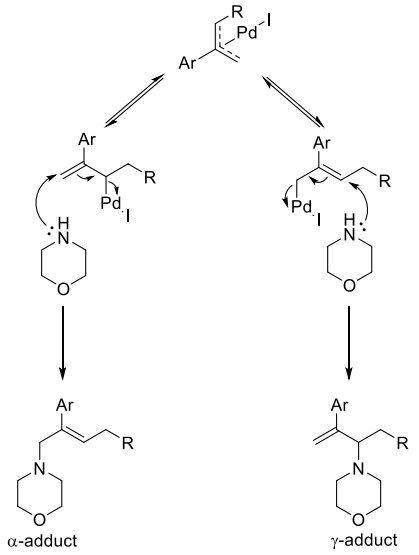


Figure 3. Proposed reaction mechanism for the three component palladium catalysed cascade reaction.

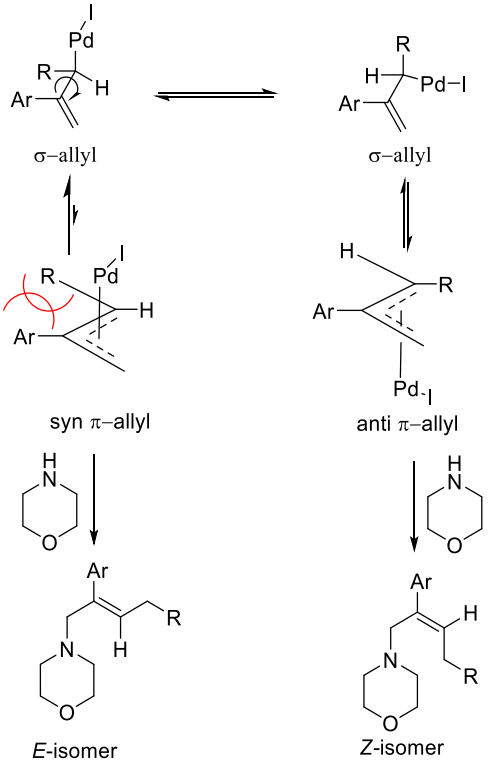
The regiospecific nature of the reaction can be explained by the equilibrium of the anti π-allyl complex with the two η^1 palladium complexes (scheme 3). It is expected that the nucleophile would preferentially attack the less sterically hindered complex to form the α-adduct. As was expected, only the α-adduct is observed.



Scheme 3. Regiochemical outcome of nucleophilic attack on both η^1 palladium complexes. Nucleophillic attack on the least hindered position is favoured.

If the γ-adduct was obtained, we would expect to see two germinal alkene protons in the ^{1}H NMR. Instead, we see a single vicinal alkene proton appears as a triplet showing the α-adduct is forming exclusively.

The two π-allyl palladium species can interconvert through rearrangement of the two σ- allyl species (scheme 4). The amine will proceed to attack the least hindered carbon on each π-allyl palladium complex and a mixture of *E*/*Z* isomers will be obtained. The higher preference for the *Z*-isomer seen with the reaction of phthalimide based allenes can be explained by its larger steric bulk, resulting is a more significant clash between the allene R group and the aryl ring in the syn π-allyl complex This further favours the formation of the anti π-allyl complex and the resulting *Z*-isomer. *E* and *Z* geometry was assigned following NOESY studies performed on similar molecules.[8] *E*/*Z* ratio was calculated by comparing the integrals of the alkenyl proton environment.



Scheme 4. Unfavourable interactions in the syn π-allyl complex leads to preferred formation of the anti-π allyl complex and the Z-isomer.

In summary, we have successfully prepared a wide range of substituted (*Z*) 2-butene 1,4 diamine analogues and substituted 4-aryloxy but-2-enyl amine analogues using a three component palladium catalysed cascade reaction with good yields, regiospecificity and stereoselectivity for the *Z*-isomer. A range of aryl iodides were used, including those with both electron withdrawing and electron donating groups. Amines of different steric bulk were also be used, with no noticeable effect on the yield, regiospecificity or stereoselectivity.

Acknowledgements

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