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LETTERS

Highly regioselective palladium/copper-catalysed cross-coupling reactions of terminal alkynes and allenes

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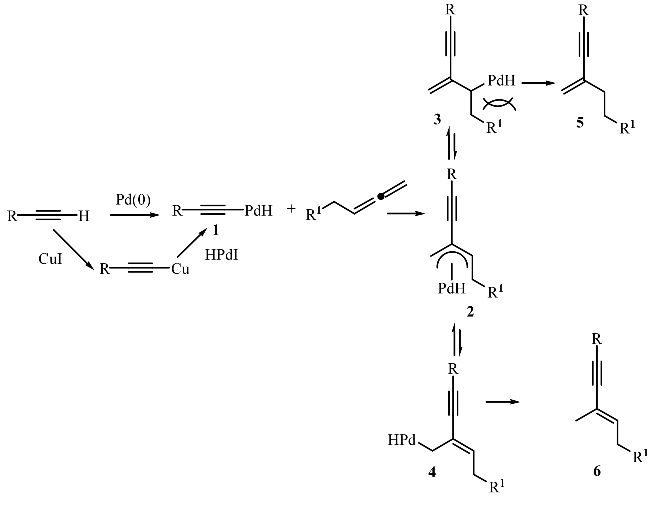
Abstract—The Pd/Cu-catalysed cross-coupling reaction of heterocyclic terminal alkynes and allene/allenyl heterocycles affords novel trisubstituted en-ynes in good yield.

Conjugated en-yne moieties are important building blocks found in a variety of biologically active compounds.[1–3] Various transition metal catalysts have been successfully employed for the cross-coupling reactions of terminal alkynes to alkynes[4] and allenes[5–7] to synthesise 1,3-en-ynes. However transition metal catalysed coupling of terminal alkynes and allenes invariably results in regio-and stereo-isomeric mixtures of en-ynes. Moreover most of the reported examples of palladium catalysed cross-coupling of terminal alkynes and allenes involve the use of allenes bearing electron-withdrawing substituents[5,8]

Palladium catalysed reactions of allenes are proving a remarkably fertile source of new reactions.[9,10] We have demonstrated the use of allene in a series of 100% atom economic palladium catalysed cascade reactions.[11,12] Typical examples are reactions of allenes and phenols to produce phenoxymethyl 1,3-dienes and reactions of allene, carbon monoxide and *N*- or *O*- nucleophiles such as amines or phenols to give methacrylamides or methacrylate esters. As part of our ongoing interest in developing atom economic processes, we explored the Pd/Cu catalysed cross-coupling reactions of heterocyclic terminal alkynes with both allene and allenyl heterocycles (Scheme 1). Thus, oxidative addition product **1** carbopalladates allenes to produce an equilibrating mixture of η^3- complex **2**, and η^1-complexes **3** and **4**. Reductive elimination of **3** and **4** produces **5** and **6**, respectively. Steric/electronic properties of the substitutents will play a dominant role in the regioselectivity of these processes and the extent of equilibration.



Scheme 1.

Keywords: bimetallic catalysis; en-ynes; peptidomimetics; trisubstituted alkenes.

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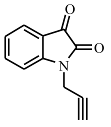
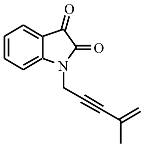
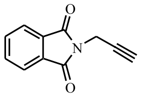
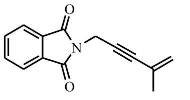
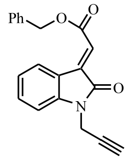
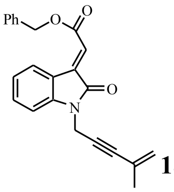
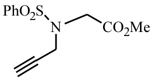
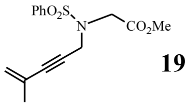
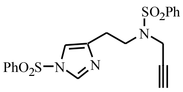
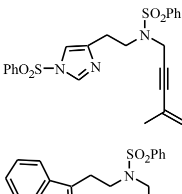
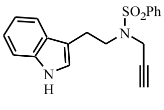
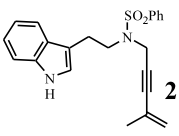
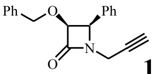
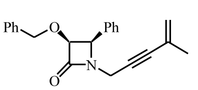
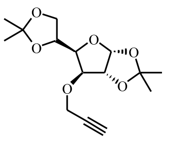
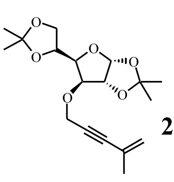
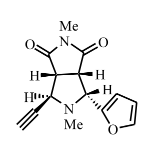
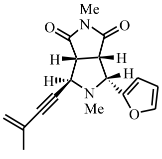
Initially we selected the parent allene (1 atm) to explore the Pd/Cu catalysed cross-coupling process. Alkynes (Tables 1 and 2) were synthesised via *N*-alkylation of the corresponding heterocycles/sulfonamides (except for **15**). Alkyne **15** was synthesised via 1,3-dipolar cycloaddition of an azomethine ylide generated in situ from *N*-methyl propargylamine, 2-furaldehyde and *N*-methylmaleimide in toluene at 110°C.[13] The alkynes **7**–**15** (1 mmol) reacted with allene (1 atm), $Pd(OAc)_2$ 5 mol%, TFP 5 mol%, and CuI 5 mol% in toluene at 80°C for 16 h to afford 1,3-en-ynes in good yield (Table 1). When the reactions were performed in the absence of the CuI co-catalyst the en-ynes were obtained in very low yield. The use of the sterically hindered phosphine TDMPP [tris(2,4,6-trimethoxyphenyl)phosphine] in conjunction with CuI also gave comparable yields of en-ynes. Next, we explored the use of novel allenyl heterocycles as the coupling partner. Allenyl heterocycles **28**–**35** (Table 2) were synthesised using the Crabbe reaction[14] which employs a terminal alkyne, diisopropylamine, paraformaldehyde and copper bromide and forms allenes, via a 1-carbon chain extension, in 50–70% yield (Scheme 2).

Table 1. En-yne coupling reactions employing allene gas[a]

Entry	Alkyne		Product		Yield (%)[b]
1		**7**		**16**	72
2		**8**		**17**	76
3		**9**		**18**	56
4		**10**		**19**	81
5		**11**		**20**	81
6		**12**		**21**	60
7		**13**		**22**	63
8		**14**		**23**	60
9		**15**		**24**	78

a. All reactions were carried out in toluene at 80 °C employing alkyne (1 mmol), allene (1 atm), 5 mol% $Pd(OAc)_2$, 5 mol% TFP and 5 mol% CuI. b. Isolated yield.

Alkynes **8**, **12**, **13** react with allenes **28**–**30**, $Pd(OAc)_2$ 5 mol%, TFP 5 mol% and CuI 5 mol% in toluene at 80°C for 16 h to afford trisubstituted 1,3-en-ynes in good yield (Table 2, entries 1–3). Only the *E* isomer was obtained in all cases. The stereochemistry of the trisubstituted en-ynes was established by NOE studies. When alkynes **25**–**27** were employed, a modified catalyst system consisting of $Pd(OAc)_2$ 5 mol%, TFP 10 mol% and CuI 10 mol% in toluene at 60°C for 2–4 h was used (Table 2, entries 4–9). Once again the reactions were stereoselective affording only the *E*-isomers **39**–**44** in 50–80% yield. Note that this methodology offers access to unusual peptidomimetics such as **41**.

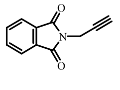
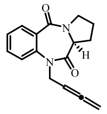
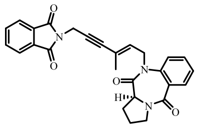
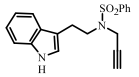
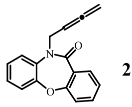
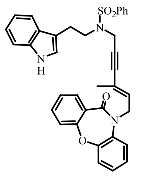
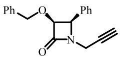
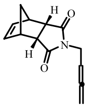
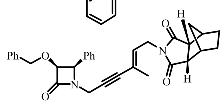
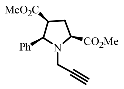
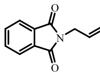
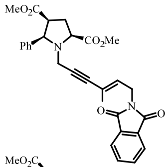
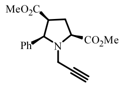
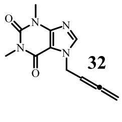
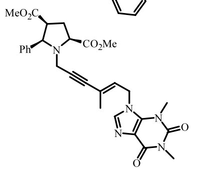
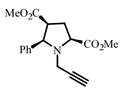
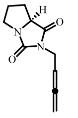
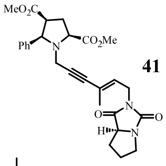
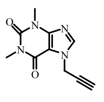
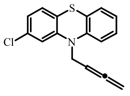
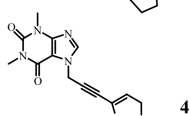
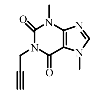
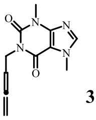
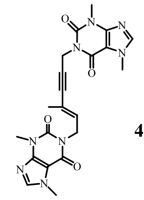
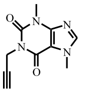
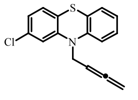
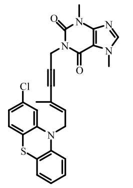
At present, the precise role of cuprous iodide in the mechanism is unclear. The coupling reaction is far more efficient in the presence of cuprous iodide and does not occur at all in the absence of palladium suggesting an alkynyl Pd(II) complex **1** as the active species. The latter arises via transmetallation of a first formed alkynyl copper species (Scheme 1). Additional roles for the cuprous iodide could include scavenging the phosphine and possibly acting as a redox cycle for Pd(II) to Pd(0). The observed selectivity for the *E*-isomer **6** suggests that the η^1–η^3 equilibria in Scheme 1 favour the η^1-complex **4** due to steric interactions.

In conclusion, we have demonstrated efficient and selective Pd/Cu catalysed cross-coupling reactions of alkynes and allenes which afford complex trisubstituted en-ynes in good yield.

Acknowledgements

We thank Avecia Lifesciences Molecules, Leeds University and the EPSRC for support.

Table 2. En-yne coupling reaction employing substituted allenes[a,b]

Entry	Alkyne	Allene	Product	Yield (%)[c]
1	 **8**	 **28**	 **36**	58[a]
2	 **12**	 **29**	 **37**	62[a]
3	 **13**	 **30**	 **38**	54[a]
4	 **25**	 **31**	 **39**	60[b]
5	 **25**	 **32**	 **40**	75[b]
6	 **25**	 **33**	 **41**	80[b]
7	 **26**	 **34**	 **42**	50[b]
8	 **27**	 **35**	 **43**	70[b]
9	 **27**	 **34**	 **44**	64[b]

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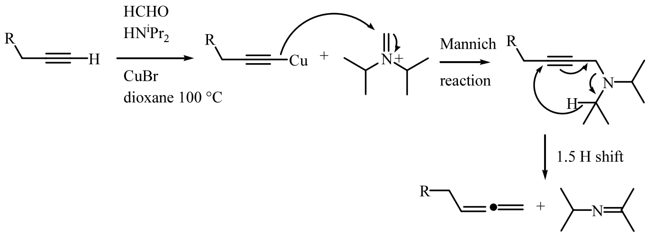
a. Reactions were carried out in toluene for 16 h at 80 °C employing alkyne (1 mmol), allene (1.2 mmol), 5 mol% $Pd(OAc)_2$, 5 mol% TFP and 5 mol% CuI.

b. Reactions were carried out in toluene for 2 – 4 h at 60 °C employing alkyne (1mmol), allene (1.2 mmol), 5 mmol%, $Pd(OAc)_2$, 10 mol% TFP and 10 mol% CuI.

c. Isolated yields.



Scheme 2.

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