Merging π-acid and Pd catalysis: dearomatising spirocyclisation/cross coupling cascade reactions of alkyne-tethered aromatics.

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ABSTRACT: A one-pot protocol for the dearomatising spirocyclisation/cross coupling of alkyne-tethered indoles/pyrroles is described. Mechanistic studies support a process by which palladium complexes generated *in situ* act as both π-acid and cross coupling catalysts. Overall, this facilitates an efficient cascade process that enables the simultaneous preparation of synthetically challenging quaternary spirocyclic carbons and tetrasubstituted alkenes in a single operation. KEYWORDS spirocycles, dearomatisation, cross coupling, palladium, catalysis

# Introduction

Alkynes are amongst the most versatile synthetic handles in chemistry, widely used for the formation of C–C bonds,1 with several methods for alkyne difunctionalisation known (*e.g.* **1** → **2** where X = alkyl/aryl andY = H,2 NR,3 O,4 S,5 Se,6 halide,7 alkyl/aryl,8 boryl,9 Scheme 1A). Intramolecular alkyne hydrocarbation processes are also important,10,11 and have been recently examined as an approach for the synthesis of quaternary spirocycles, which are of significant current interest in medicinal chemistry12 Our published conversion of indole-tethered ynones **3** into spirocycles **5** (Scheme 1B) is typical of this type of reaction,10b in which alkyne activation with a π-acidic catalyst [usually Ag(I) or Au(I)] promotes dearomatising spirocyclisation13 via nucleophilic attack from a tethered aromaticto form a vinyl metal intermediate (**4**), followed by fast protodemetallation to form spirocycle **5**. However, due to the ease with which such vinyl metal species undergo protodemetallation when Ag- or Au-π-acidic catalysts are used,14 to date we have been unable to intercept **4** (or related intermediates) with any external electrophile other than a proton,10 meaning that tetrasubstituted alkenes are inaccessible via these methods.

Our aim in this study was to move away from traditional Au/Ag-based π-acids,10,14 and develop an alternative catalyst system in which the transiently-formed vinyl metal species can engage in cross coupling, thus enabling quaternary spirocycles and tetrasubstituted alkenes to be prepared in a single synthetic operation. To the best of our knowledge, there are no published methods that enable this transformation to be performed directly using indole- or pyrrole-tethered alkynes;15 using existing methods, it is necessary to first generate a vinyl halide via dearomatising spirocyclisation with an electrophilic halogenation reagent, and then perform a separate cross coupling reaction.7b-d Direct methods to make all-carbon tetrasubstituted alkenes from alkynes are known,8 but examples that proceed with concomitant dearomatising spirocyclisation are limited to oxidative radical coupling reactions16,17 or formal [3+2]-spiroannulation processes, generally from phenol/anisole derivatives.18 A prominent example, described by Patil and co-workers in 2017, is summarised in Scheme 1C.17 This reaction, which is based on a clever application of Au(I)/visible light photoredox catalysis,19 enables a range of spirocyclic dienones **7** to be prepared in good yields (51–80%) from anisole precursors of the form **6**; however, the use of relatively high loadings of two precious metal catalysts is not ideal, and its reliance on aryldiazonium salts may also explain why only simple benzene derivatives have been used as coupling partners to date.

Scheme 1. Alkyne difunctionalisation reactions



To develop a more general reaction system, we prioritised the exploration of Pd-based catalyst systems and simple aryl/alkyl halide coupling partners.20 We postulated that one way that this could be achieved was to use *in situ*-generated Pd(II) oxidative addition complexes (*e.g*. **A** in Scheme 1D) as a π-acids (*i.e.* replacing the Ag(I) and Au(I) complexes more commonly used in such chemistry) to activate the alkyne towards spirocyclisation (**9 → 10**). The idea was that activating the alkyne in this way would simultaneously deliver the coupling partner to the reaction site, thus facilitating both dearomatising spirocyclisation and cross coupling, provided that reductive elimination (**10 → 11**) out-competes protodemetallation (Scheme 1D). Herein, the successful realisation of this new approach is reported, enabling the high yielding merged dearomatising spirocyclisation/cross coupling of various indole- and pyrrole-based precursors **8** with a wide range of coupling partners. Mechanistic studies suggest that this novel cascade process operates as planned, via a mechanism of the type outlined in Scheme 1D.

# Results and Discussion

We began by attempting the dearomatising spirocyclisation/cross coupling sequence using indole **12a** and 4-iodotoluene **13a** to make spirocycle **14a** with common Pd complex/ligand combinations under basic conditions. Selected screening results are summarised in Table 1, with more extensive details included in the Supporting Information (SI).

Table 1. Selected optimisation results



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| entry | catalyst  (X mol%) | base  (X equiv) | solvent | yield [%]a  **14a**  **15** | |
| 1 | Pd(PPh3)2Cl2 (5) | K2CO3 (2) | PhMe | 31 | 53 | |
| 2 | Pd(OAc)2 (5)  PCy3 (10) | K2CO3 (2) | PhMe | 41 | 42 | |
| 3 | Pd(PPh3)4 (5) | K2CO3 (2) | PhMe | 90 | 0 | |
| 4 | Pd(PPh3)4 (5) | Et3N (2) | PhMe | 91 | 0 | |
| 5 | Catcat (5) | Et3N (2) | PhMe | 91 | 0 | |
| 6b | Pd(PPh3)4 (2) | Et3N(2) | PhMe | 73 | 0 | |
| 7b | Catcat (2) | Et3N (2) | PhMe | 91 | 0 | |
| 8b | Catcat (2) | Et3N (1.1) | PhMe | 91 | 0 | |
| 9b | Catcat (2) | Et3N (1.1) | MeCN | 94 | 0 | |
| 10 | Catcat (1) | Et3N (1.1) | MeCN | 78 | 0 | |
| 11b | Catcat (2) | - | MeCN | 0 | 22 | |
| 12b | - | Et3N (1.1) | MeCN | 0 | 0 | |

[a] Yield determined by 1H NMR, using CH2Br2 as an internal standard. [b] Reaction time 5 h.Catcat = *trans-*PdBr(*N*-succinimide)(PPh3)2.

We were pleased to find that the desired cross-coupled spirocycle **14a** could be prepared using this method, although in some cases side product **15** was also formed, likely via activation of the alkyne with the palladium(II) pre-catalyst, followed by protodemetallation. However, the use of either Pd(PPh3)4 or commercially available Catcat [Catcat *= trans*-PdBr(*N*-succinimide)(PPh3)2]21 with triethylamine as base was effective at preventing side-product formation, promoting up to 94% conversion into the desired cross-coupled spirocycle **14a** (entries 3–9). The use of 2 mol% Catcat (entry 9) was found to be optimal; the catalyst loading can be reduced further and still give reasonable conversion into **14a** (see entry 10, 1 mol%) but around 5% of the starting material **12a** remained under these conditions. Both base (entry 11) and catalyst (entry 12) were shown to be essential to the success of this process, and we did not observe any direct C-3 arylation, despite this being a known dearomative process for indoles.20c

Two potential mechanisms for this transformation are presented in Scheme 2. One possibility (**Cycle 1**, Scheme 2) is that following *in situ* generation of an active Pd(0) species **A**, oxidative addition into the carbon-halogen bond of the coupling partner **13a** generates a Pd(II) complex **B**, which following ligand dissociation, could coordinate to the alkyne of **12a** and activate it towards attack from the electron rich indole C-3 position, to furnish a spirocyclic Pd(II)-complex **D**. Proton abstraction and reductive elimination would then complete the catalytic cycle and furnish cross coupled spirocycle **14a**. This mechanism, which we postulated at the start of this project, is supported by the knowledge that similar palladium(II) species are well known to promote addition reactions across alkynes with other nucleophiles,1a-b, 3b, 8a, 8e and is also consistent with the well-studied mechanisms of related dearomative ynone activation processes.22

Scheme 2. Mechanistic possibilities



Alternatively, rather than undergoing oxidative addition with **13a**, Pd(0) species **A** could instead coordinate to the alkyne of **12a** to form complex **E** and promote spirocyclisation at this stage form a Pd(0)-complex **F**, before going on to engage in oxidative addition with coupling partner **13a** to form Pd(II)-complex **D** and then joining the other cycle (**Cycle 2**, Scheme 2).Indeed, it is possible that these related mechanisms both operate. A third alternative mechanism involving oxidative addition, alkyne carbopalladation, formation of a 6-membered palladacycle and reductive elimination (see SI, Scheme S1 for a scheme depicting this possibility) appears less likely, because the carbopalladation step would have to proceed with the opposite regioselectivity to that typically observed in intermolecular carbopalladation reactions of electron deficient alkynes.23a

Additional insight on the mechanism is provided by the control experiments summarised in Scheme 3. First, we ran the reaction in the absence of coupling partner **13a** under the three sets of conditions shown in Scheme 3a. All three resulted in modest conversion (12–33%) into hydrocarbation product **15**. These results confirm that spirocyclisation is not entirely dependent on the presence of aryl iodide **13a** and add some support to the possibility of a spirocyclisation of the type **A →** **E → F** (**Cycle 2**, Scheme 2) operating in the cross-coupling reaction. However, they certainly do not rule out **Cycle 1**, and indeed, the inefficiency of the spirocyclisation in the absence of aryl iodide **13a** suggests that both Catcat and Pd(PPh3)4 (or indeed any Pd complex formed in situ from them) are weaker π-acids than the active species in the optimised reaction, as might be expected. This suggests that the mechanism depicted in **Cycle 1** is much more likely to be dominant, with the oxidative addition complex (see **B** in Scheme 2) being the best π-acid in this reaction system. Oxidative addition was expected to be fast using aryl iodides such as **13a**, and this assumption is supported by kinetic studies (see SI), which show that the reaction is zero-order in iodide **13a**. This confirms that oxidative addition is not rate limiting. In view of this, and the low reactivity of the palladium pre-catalyst in the absence of aryl iodide, we believe that the chances of any palladium species present in the reaction acting as a π-acid for dearomatising spriocyclisation before oxidative addition (as in **Cycle 2**) is unlikely.24 Another (less likely) mechanistic scenario that was considered is that the reaction proceeds via sequential palladium-catalysed dearomatising hydrocarbation (**12 → 15**), followed by a Heck reaction of the resulting alkene with iodide **13a** (**15 → 14a**). However, this possibility was ruled out by treating a purified sample of spirocycle **15** under the standard reaction conditions with coupling partner **13a**, which resulted in no reaction (full recovery of the starting material **15**, Scheme 3b), confirming that the conversion of **15** into **14a** is not a viable process under these conditions.

Scheme 3. Control experiments.



We then went on to examine the generality of the optimised reaction conditions (entry 9 of Table 1). First, other indoles with C-2 substituents were tested, and changes at various positions of the indole scaffold were well tolerated, with spirocycles **14a**–**h** all being prepared in high yields (Scheme 4A).Spirocycles **16a**–**e** were also generated with similar efficiency from indole precursors lacking a C-2 substituent (Scheme 4B). Crucially, there was no evidence of competing C-2 substituted side products (*i.e*. carbazole-type frameworks)9d being formed in any case, which is important, given the proclivity of 2*H*-indoles to react through their C-2 positions (either directly, or indirectly via 1,2-migration),in related reaction systems.25

It was also shown that ynones tethered to pyrroles via their 3-position are viable substrates, with spirocycles **17a**–**h** all beingisolated in good to excellent yields using the standard method (Scheme 4C). The 2- and 5-methyl substituents were a requirement in these examples (analogous starting materials lacking this substitution did not react), but these results are significant nonetheless, given the rarity of dearomatising spirocyclisation reactions of 3-pyrroles.26 X-ray crystallographic data was obtained for a derivative of **17b**,27,28 corroborating the structural assignments.

Of particular note, the method is compatible with a wide range of more challenging cross coupling partners (Scheme 4D). For example, 4-morpholine-, 4-methoxy- 4-ester-, 2-methyl and 2-methoxy substituted aryl iodides were all tested and were all found to work well (**18a**–**c**, **18g**–**h**). Aniline coupling partners were less straightforward, with 4-iodoanilines **13e** and **13f** both being unsuccessful in the reaction, although not all anilines are incompatible, demonstrated by the successful coupling of 3-iodoaniline **13g**¸which delivered **18h** in high yield. Isatin (**18i**), pyrazine (**18l**) and pyridine variants (**18j**–**m**) all worked well, which is significant given the importance of these nitrogen-containing motifs in medicinal chemistry. Coupling to sp3 hybridised benzyl/naphthyl halides has also been demonstrated (**18o**–**p**), although it seems that relatively activated alkyl halides are required for such sp3 coupling and spirocyclisation reactions to proceed effectively, with the analogous reactions using iodo-cyclopentane and 3-bromo-1-phenyl propane (not shown in the Scheme) both failing to deliver any of the cross coupled product. Finally, merged spirocyclisation/cross coupling with simultaneous installation of thiophene (**18q**), cyclopentenone (**18r**), alkyne (**18s**) and pyrazole (**18t**) motifs were all successful, and the formation of naphthyl derivative **18u** from triflate **13w** shows that aryl triflates can also be used as coupling partners in this reaction.29

In terms of special cases (Scheme 4E), we found that by using 1,4-diiodobenzene (**13s**)as the coupling partner, and changing the stoichiometry accordingly, double dearomatising spirocyclisation/cross coupling can be achieved, with compound **19** preparedin 91% yield as a 1:1 mixture of diastereoisomers. X-ray crystallographic data supports the formation of this interesting three-component product.27,30

Finally, we have shown that the method need not be limited to reactions initiated by oxidative addition into carbon-halogen bonds. Thus, the high yielding conversion of indole-tethered ynones **12a** and **12e** into allylated spirocycles **20a** and **20b** was achieved, with a η-3 palladium(II) π-allyl complex (formed *in situ* from allyl phosphonate **13t**) the most likely active palladium species that promotes spirocyclisation and allylation. Competing direct allylation of the indole C-3 position (which is known in related systems)20a,d,f was not observed. Full details of the optimisation of this reaction variant are included in the SI.

Scheme 4. Scope of dearomatising spirocyclisation/cross coupling cascade.



Unless stated the following standard conditions were used: indole/pyrrole ynone **12** (1 equiv.), coupling partner **13** (1.1 equiv.), Catcat (2 mol%), Et3N (1.1 equiv.), CH3CN, 60 °C for the designated time. The yields quoted are of isolated products following column chromatography. [a] 1.5 equiv. coupling partner **13**. [b] PhMe used as solvent in place of CH3CN. [c] 1.5 equiv. Et3N.

In summary, an operationally simple, high yielding one-pot dearomatising spirocyclisation/cross coupling cascade for the conversion of indole/pyrrole-tethered ynones into functionalised spirocycles containing tetrasubstituted alkenes, has been developed. The reaction exploits the ability of palladium complexes to fulfil two roles in the reaction, serving as both a π-acids to activate the alkyne towards dearomatising spirocyclisation, and as cross coupling catalysts. Mechanistic studies support the mechanism postulated at the start of this study (see Scheme 1D and **Cycle 1**, Scheme 2). The versatility of the reaction in terms of the range of cross coupling partners is arguably the most important feature of this synthetic method, which is especially notable for the wide range of nitrogen-containing and/or reactive coupling partners that are compatible.

ASSOCIATED CONTENT

**Supporting Information**.

Experimental procedures, spectroscopic data, images of NMR spectra, additional mechanistic information and optimisation details. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors.

ACKNOWLEDGMENT

We would like to thank the Engineering and Physical Sciences Research Council (EP/N035119/1, H. E. H.), the Leverhulme Trust (for an Early Career Fellowship, ECF-2015-13, W. P. U.) and the University of York (T. C. S. and W. P. U.) for financial support. We are also grateful to Dr. A. C. Whitwood and S. Hart (both University of York) for X-ray crystallography. Finally, we thank Dr Jason M. Lynam (University of York) for useful discussions and insight into the mechanistic studies.

ABBREVIATIONS

Catcat = *trans*-PdBr(*N*-succinimide)(PPh3)2.

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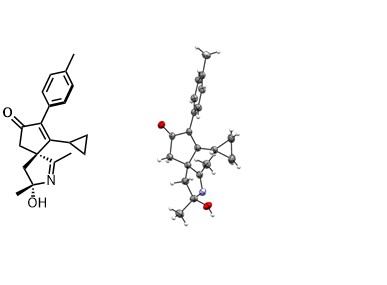
[24] Indeed, fast oxidative addition appears to be a requirement for the success of these reactions, given that the analogous reaction using 4-bromotoluene in place of 4-iodotoluene (see SI- Table S1, entry 28) resulted in a low yields of **14a** (16%) as well as **15** (28%), which suggest that competing spirocyclisation reactions with palladium species before oxidative addition may be competitive in this scenario.

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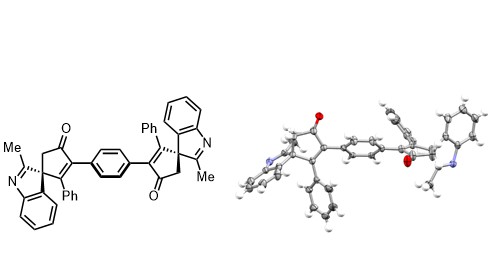
[27] CCDC 1857126 and 1882430 contain the crystallographic data for a hydrated derivative of compound **17b** and compound **19** respectively, see: [www.ccdc.cam.ac.uk/data\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)

[28] Compound **17b** crystallized as a hydrated derivative, as the diastereoisomer shown below:



[29] The fact that this aryl triflate example worked better than the aryl bromide examples tested (see SI) suggests that halide loss (*c.f*. **B** to **C** in Scheme 2) may influence the overall efficiency of the reaction. Note that a 16% yield of hydrocarbation product **15** was also obtained in this reaction.

[30] Crystals were grown from the 1:1 diastereomeric mixture of compound **19**, with the crystal used for the X-ray data being the single diastereoisomer shown below:



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