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A new mechanistic pathway under Sonogashira reaction protocol involving multiple acetylene insertions†

Roderick C. Jones,*[a] Allan J. Canty,*[a] Tom Caradoc-Davies,[b] Noel W. Davies,[c] Michael G. Gardiner,[a] Philip J. Marriott,[d] Christian P. G. Rühle[d] and Vicki-Anne Tolhurst[a]

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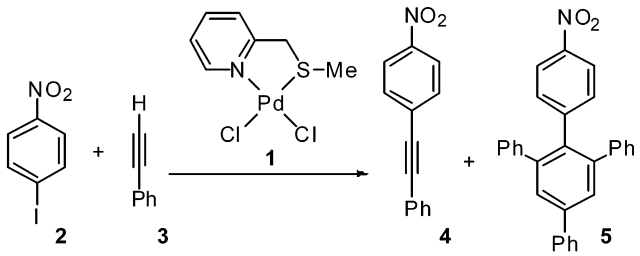
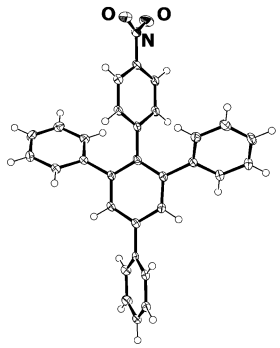
An unreported product outcome from an intended Sonogashira coupling is presented. The generality of this finding has been demonstrated by screening of a range of pre-catalysts. Mechanistic studies are consistent with the tetra-aryl benzene product forming by interception of the aryl halide oxidative addition intermediate by repeated acetylene insertion.

Formation of carbon-carbon bonds using protocols discovered by Sonogashira,[1a] Cassar,[1b] and Heck[1c] has developed into widely utilised processes for the coupling of C(sp^2) halides (R^1X) with alkynes ($R^2C{\equiv}CH$) to form $R^1C{\equiv}CR^2$, mediated predominantly by palladium pre-catalysts.[1,2] Except for Glaser coupling to form $R^2C{\equiv}CC{\equiv}CR^2$, byproducts[2b,d,h,i] have been rarely reported for Sonogashira coupling.[1c,2c,d,13] Herein we report the unexpected formation of $C_6H_2R^1(R^2)_3$ (**5**) that was discovered during catalytic activity screening of a class of N~S chelated Pd(II) complexes under Sonogashira reaction protocol, Scheme 1. Reaction conditions could be optimised to selectively give either the anticipated product, $R^1C{\equiv}CR^2$ (**4**), or **5** in high yield using a 2-organothiomethylpyridine ligand ($pyCH_2SMe$). The formation of **5** was subsequently also identified in reactions mediated by various common pre-catalyst systems. Catalytic and stoichiometric reaction studies are consistent with the synthesis of **5** occurring *via* the insertion of three phenylacetylene molecules following the oxidative addition of the aryl halide.

Complex **1**[4] was initially examined as a precatalyst under conditions typical for Sonogashira catalysis, with Na_2CO_3 as a base,[2a,j,5a] $^nBu_4NCl$ as a salt additive,[2a,5b] 1 mol% Pd,[5c,d] in *N*,*N*-dimethylacetamide (DMA)[2i,j] over a temperature range 25–140 °C for 24 h under argon. 4-Iodonitrobenzene (**2**) reacts with phenylacetylene (**3**) at 25 °C to give the anticipated product **4** in 95% yield, together with 5% of the known compound[6] 1-(4-nitrophenyl)-2,4,6-triphenylbenzene (**5**). Reactions conducted at higher temperatures gave the Sonogashira product **4** in lower yield and, at 120 °C, **5** involving incorporation of three alkyne fragments was obtained (41%) without any Sonogashira product **4**, rising to 63% yield at 140 °C. The use of additional alkyne in the reaction (1 : 3 ratio of **2**:**3**) gave only minor yield improvement. Product **5** was characterised by ^1H NMR spectroscopy and X-ray crystallography, and also synthesised independently for comparison of spectroscopic, HPLC and GC-MS data.[7]



Temp. (°C)	Yield (%) 4	5
140	0	63
120	0	41
80	66	20
25	95	5



Scheme 1 Optimised synthesis of Sonogashira coupling product (**4**) and tetra-aryl species (**5**), and molecular structure of **5**. Reaction conditions: **2** (1.5 mmol), **3** (2.25 mmol), **1** (1 mol%), Na_2CO_3 (3.0 mmol), $^nBu_4NCl$ (2.25 mmol), DMA (5 mL), 24 h under Ar.‡

We explored other pre-catalysts and protocols searching for related findings to better understand the occurrence of byproducts in Sonogashira catalysis. Reaction of **2** with **3** using the widely employed pre-catalyst[1a,b,2,5e] $PdCl_2(PPh_3)_2$ (**6**) under similar conditions to those reported initially by Sonogashira (0.5 mol% **6**, 1 mol% CuI, room temperature, in Et_2NH)[1a] gave **4** only (95% yield) and, under these conditions, catalyst **1** gave a lower yield of **4** (32%), **5** was not observed, and a minor amount of Glaser product (16%). Reaction of **2** and **3** under the conditions of Scheme 1 at 120 °C using **6** gave **4** (76%) and a product of molecular weight 427, indistinguishable from **5** by GC-MS (18%). Similarly, the bidentate ligand complexes $PdCl_2(L_2)$ (L_2 = 1,2-bis(diphenylphosphino)ethane[2i,5e] and 1,10-phenanthroline) gave both **4** (84, 87%) and **5** (11, 10%) at 120 °C, but 2,2′-bipyridine led to GC-MS data showing the absence of **4** and at least two species of molecular weight 427, the major component being

[a]*School of Chemistry, University of Tasmania, Hobart, Tasmania, Australia. E-mail: Allan.Canty@utas.edu.au; Fax: +61 3 62262858; Tel: +61 3 6226 2162*
[b]*Australian Synchrotron, Clayton, Victoria, Australia*
[c]*Central Science Laboratory, University of Tasmania, Hobart, Tasmania, Australia*
[d]*Australian Centre for Research on Separation Science (ACROSS), School of Applied Sciences, RMIT University, Melbourne, Victoria, Australia*

† Electronic Supplementary Information (ESI) available: Experimental procedures, synthesis and characterisation of **5** and **7**, X-ray crystallographic data (CIF) for **5** and **7** (CCDC Numbers: 755775 and 755776), and results for catalysis. See DOI:10.1039/c001109f/

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indistinguishable from **5** (overall yield 66%: the isolation of isomeric products with **1** is discussed later in regard to certain aryl halide substrates).

The incorporation of two alkyne units into a fulvene product 1,3-$(Me_3Si)_2C_5H_2CHPh$ in palladium mediated reactions of the vinyl halide PhCH=CHI with $Me_3SiC{\equiv}CH$ has been reported.[3] A mechanistic proposal for this outcome entailed repeated insertion of *two* acetylenes with the alkenyl species formed from oxidative addition of PhCH=CHI, followed by cyclisation *via* intramolecular migration of the alkenyl group onto the terminal alkene functionality of the C_6 fragment and finally product release by β-H elimination. Preliminary mechanistic findings in our study are consistent with a similar mechanism for the formation of the six-membered cyclised product **5** based on *three* acetylene insertions. Our evidence is not consistent with alternative well established mechanisms for cyclo-oligomerisation of acetylenes known for a wide range of metal complexes,[2g,8,9] including palladium reagents (see below).[8a,b,d-k9a,d-f]

We prepared and characterised $PdI(C_6H_4\text{-}4\text{-}NO_2)(pyCH_2SMe)$ (**7**)[10] (Fig. 1) as an anticipated intermediate in Sonogashira catalysis following oxidative addition of the aryl iodide to a Pd(0) complex. In stoichiometric reactions, **7** reacted with PhC≡CH (3.5 equiv, Scheme 1 conditions) giving **4** (18% yield) and **5** (22% yield) at 25 and 120 °C, respectively, with complete selectivity in accord with the outcomes discussed above for the catalytic reactions of complex **1** at these temperatures. The relatively low yields of **4** and **5** result from competing PhC≡CH cyclo-oligomerisation by Pd(0) following product release. Indeed, in the absence of aryl halide **2**, complex **1** under the conditions of Scheme 1 at both 25 and 120 °C supports cyclo-oligomerisation of PhC≡CH, giving $C_4H_2Ph_2$, $C_6H_3Ph_3$ (main product) and $C_8H_4Ph_4$. Low yields of $C_6H_3Ph_3$ in catalysis (of **2** and **3**) with **1** importantly highlights the relatively rapid oxidative addition of **2** to *in situ* formed Pd(0) relative to cyclotrimerisation of **3** in both temperature regimes.

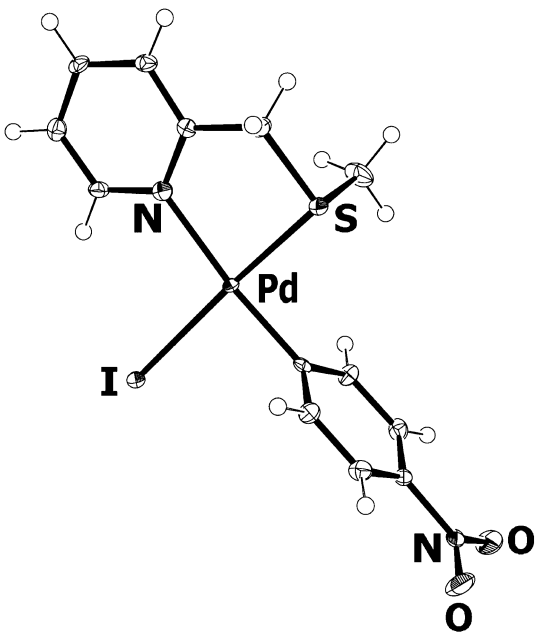
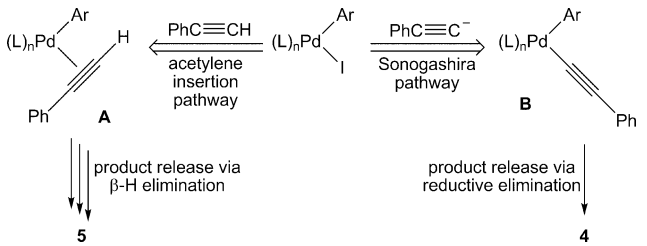


Fig. 1 Molecular structure of $PdI(C_6H_4\text{-}4\text{-}NO_2)(pyCH_2SMe)$ (**7**).

During catalysis (of **2** with **3**) using **1**, Scheme 1 conditions, added PhC≡CPh is not incorporated ($1,2,4,6\text{-}Ph_4C_6H_2$ or more highly Ph substituted benzenes are not formed) and added $4\text{-}NO_2C_6H_4C{\equiv}CPh$ (**4**) does not increase yields of **5**. These observations suggest that **4**, if liberated from palladium as the Sonogashira product in Scheme 1, is not incorporated into catalysis to form **5** *via* a mixed acetylene cyclotrimerisation pathway.

These results are consistent with the view that **5** is formed *via* a partial Sonogashira process involving insertion of three PhC≡CH molecules into a $Pd^{II}C_6H_4\text{-}4\text{-}NO_2$ intermediate. The participating ligands involved in the competing reaction pathways are shown in Scheme 2. The insertion of PhC≡CH (**A**) averts the release of the Sonogashira product **4** *via* involvement of $PhC{\equiv}C^-$ (**B**), leading to the tetra-aryl benzene product **5**. It is noteworthy that added CuI (10 mol%) at 120 °C does not affect the reaction specificity (0% **4**, 42% **5**, no Glaser coupling, Scheme 1 conditions), despite the increased acetylide availability that would promote the formation of the Sonogashira product **4**.



Scheme 2 Graphical depiction of the key product discriminating stages of the competing acetylene insertion (tetra-aryl benzene product pathway: **A**) and acetylide involvement (Sonogashira product pathway: **B**).

We have demonstrated that there are ligand effects on the selectivity of these reaction outcomes. The acetylene insertion pathway is favoured at higher temperature and, in particular, by bidentate ligands. It is feasible that this requires hemilability[9b,c,11] that would be facilitated at higher temperature. In this regard, the contrasting behaviour of 1,10-phenanthroline and the more flexible 2,2′-bipyridine ligated pre-catalysts is noted (mainly **4** for the former, exclusively acetylene insertion chemistry for the latter).

The rate of reductive elimination from Pd^{II}-aryl complexes featuring electron withdrawing *para*-substituents is known to be reduced in related Pd mediated C–C coupling reactions.[12] It was thus of interest to investigate variously activated aryl halide substrates to establish any effects on the product distribution. The expectation was to steer the outcome towards conventional Sonogashira products in the case of less activated aryls if species **B**, Scheme 2, undergoes faster reductive elimination giving **4**. In the case of phenyl iodide, for example, we still observed complete selectivity for insertion chemistry over the Sonogashira product at 120 °C, although a range of products corresponding to incorporation of three phenyl acetylenes have been identified that we have been unable to structurally assign as yet. We hope to report on these products at a later stage along with a mechanistic understanding of this intriguing selectivity which is likely to have its basis in either the insertion or cyclisation processes.

We have reported a new reaction pathway leading to a previously unreported product outcome arising from Sonogashira reaction condition protocols. Initially identified during catalytic activity screening of a class of N~S chelated Pd(II) complexes, but later

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confirmed as occurring using a range of previously reported pre-catalysts, this structural assignment is clearly of importance in the broader context of byproduct identification for this widely used catalytic C–C coupling reaction. Mechanistic studies are consistent with the tetra-aryl benzene product forming by interception of the aryl halide oxidative addition product by insertion of three molecules of phenylacetylene and, for $PdCl_2(pyCH_2SMe)$ (**1**) as pre-catalyst, the reaction can be tuned to give either the Sonogashira product or tetra-aryl benzene in high yield. The extensive studies of the general applicability of this new finding and a more detailed exploration of mechanistic issues have commenced.

We thank the Australian Research Council for financial support. Data for the structure solutions of **5** and **7** were obtained on the PX2 and PX1 beamlines, respectively, at the Australian Synchrotron, Victoria, Australia.

Notes and references

‡ **5** was isolated by HPLC with yields calculated by GC-MS with 1-(4-methyl-3-nitrophenyl)-2,4,6-triphenylbenzene as standard. The standard was obtained by Suzuki coupling of 2,4,6-(triphenyl)phenylboronic acid with 4-methyl-3-nitro-iodobenzene, using a modification of the protocol reported using 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl [S-PHOS] as a ligand.[13]

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