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Palladium-Catalysed Ligand-Free Reductive Heck Cycloisomerisation of 1,6-En-α-Chloro-Enamides

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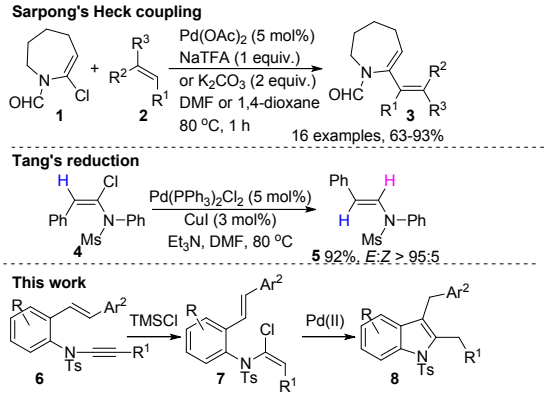
The first example of an intramolecular hydroarylation of 1,6-en-α-chloro-enamides was achieved by a palladium-catalysed ligand-free reductive Heck cycloisomerisation with no competing Heck-cyclised by-product.

Reductive processes in metal-catalysed organic synthesis are often well understood, involving common reductants such as dihydrogen, formates, formic acid and activated alcohols.[1] Similarly, palladium-catalysed hydroarylation (reductive Heck reactions) between arylhalides and alkenes, typically involve: (i) alkylamines, formates and activated alcohols as the hydride source in the process;[2] (ii) neutral or anionic aryl–Pd complexes, and electron-poor olefins and styrene (preferred olefin substrates for insertion);[2a,3 and] (iii) key aryl-Pd species, coordinatively saturated by ligands (phosphines, *N*-heterocyclic carbenes, halides and acetates) to inhibit β-H-Pd elimination side-reactions.[4]

Herein, we report a palladium-catalysed reductive Heck cyclisation of 1,6-enynamides. In contrast to the common features of reductive Heck reactions, we report here that: (i) hydroarylation of styrene occurred through an intramolecular hydride transfer[5] and an indolyl alkylpalladium(II)-pecies was reduced through an intermolecular hydride transfer likely from *i*-PrOH (or 1,4-dioxane[6]) as H-donor, confirmed by D-isotope exchange studies; (ii) chloride dissociation of an electrophilic α-chloro-enamide was realised in the absence of alkylammonium salts as halide abstractors and a cationic Pd(II)-enamide Heck coupling proceeded with both electron-neutral and electron-rich styrenes;[7] (iii) interestingly, the key enamide-Pd species was free from ligands saturation;[8] and (iv) no β-H-Pd elimination by-product was observed.



Scheme 1. Heck coupling and reduction of Chloro-enamides.

Ynamides and enamides are versatile functional groups that are finding use as fascinating building blocks for the synthesis of nitrogen-containing compounds.[9] Recently, Sarpong reported intermolecular Heck coupling reactions of bench-stable α-halo eneformamides in DMF or 1,4-dioxane[10] and Tang reported a reduction of the α-halo-enamide to the enamide using Et_3N as a reductant (Scheme 1).[11] In order to explore the balance of reactivity and stability of α-halo-enamides, we prepared more electrophilic α-chloro tosylmides **7a** and employed Sarpong's Heck conditions to test the potential intramolecular cyclisation of **7a**. However, our approach was distinct from Sarpong's Heck, in that a reductive Heck cyclised **8a** was obtained exclusively, rather than Heck cyclised **8a'** (Table 1, entries 1-3). Alternatively, using activated alcohols as the solvent (which was employed in alkenylpalladative reduction of ynamides by Anderson[12]), **8a** was also afforded in satisfying yields (entries 4-13). Surprisingly, when electron-rich palladium ligands were employed, which were expected to prohibit β–H-Pd elimination according to coordinatively saturation of Pd(II) and Pd(0), the reductive Heck cyclisation was supressed (entries 14-18). In general, $PdCl_2$ is more sustainable in 1,4-dioxane (entries 1 and 2) than that in *i*-PrOH, as the precipitation of palladium black was immediately observed in *i*-PrOH.

Based on the optimised results, entries 2 and 3 (Table 1) were applied to explore the substrate scope using 2-styryl-α-chloro-

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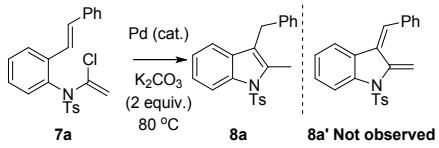
enamide derivatives **7** (Table 2). In order to overcome the hydrolytic lability of α-chloro-enamides, these species were prepared from *in-situ* generated HCl and addition to enynamides **6**, which were used directly without further isolation.[13]

Table 1. Optimization of conditions.[a]



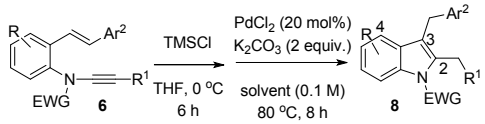
7a **8a** **8a' Not observed**

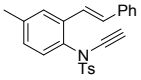
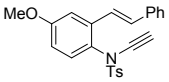
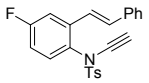
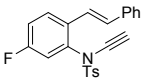
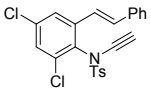
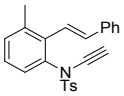
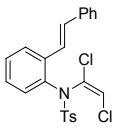
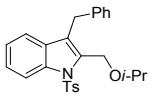
entry	catalyst (mol%)	solvent	yield[b] (%)
1	$PdCl_2$ (2.5)	1,4-dioxane	81
2	$PdCl_2$ (20)	1,4-dioxane	80
3	$PdCl_2$ (20)[c]	1,4-dioxane	N.R.[d]
4	$PdCl_2$ (20)	*i*-PrOH	93
5	$Pd(TFA)_2$ (10)	*i*-PrOH	81
6	none	*i*-PrOH	N.R.[d]
7	$PdCl_2$ (20)	MeOH	trace
8	$PdCl_2$ (20)	EtOH	N.R.[d]
9	$PdCl_2$ (20)	*t*-BuOH	dec.[e]
10	$PdCl_2$ (20)	toluene	dec.[e]
11	$PdCl_2$ (10)	*i*-PrOH	60
12	$PdCl_2$ (5)	*i*-PrOH	44
13	$PdCl_2$ (2.5)	*i*-PrOH	44
14	$PdCl_2$ (10), TMTU[f] (20)	*i*-PrOH	N.R.[d]
15	$PdCl_2$ (10), bipy[g] (10)	*i*-PrOH	dec.[e]
16	$Pd(PPh_3)_4$ (5)	1,4-dioxane	N.R.[d]
17	$Pd(PPh_3)_4$ (5), $(n\text{-}Bu)_3P$ (10)	1,4-dioxane	N.R.[d]
18	$Pd(PPh_3)_4$ (5), $(t\text{-}Bu)_3P$ (10)	1,4-dioxane	dec.[e]
19	$Pd_2(dba)_3$ (2.5)	*i*-PrOH	trace

[a.] **7a** (0.15 mmol), Pd catalyst, K_2CO_3 (0.3 mmol), solvent (4 mL), 80 °C, 6 h, N_2. [b.] Isolated yield. [c.] Without K_2CO_3. [d.] N.R. = no reaction. [e.] dec. = decomposition. [f.] TMTU = tetramethyl thiourea. [g.] Bipy = 2,2'-bipyridine.

In general, the one-pot, sequential cyclisation afforded 3-benzylindoles **8** in higher yields in *i*-PrOH than that in 1,4-dioxane (Table 2). When the styryl group contained electron-donating groups (entries 2 and 3, Table 2) and mildly electron-deficient groups ((entry 4, Table 2), the reductive Heck process proceeded to deliver products **8** in moderate to good yields. As for the ynamide fragment, terminal and internal aryl ynamides were tolerated ((entries 1, 5-9, Table 2). When the tosylamide was replaced by Ms- and Ns-amides, a better yield was obtained for Ns-variant in *i*-PrOH ((entry 9, Table 2). However, the substrates **6** were restricted to *para*-substituted aryl groups, cyclisation of *in-situ* generated **7** containing *ortho*-, *meta*-substituted aryl groups is more complicated with slow conversion (20 h), accompanied by complex mixtures (entries 10 and 11, Table 2). Noticeably, the substrates **6** bearing electron-poor styrene and electron-poor ynamide moieties were incompatible with the reaction conditions, where complex mixtures were formed. Replacing styryl and ynamidyl fragments of **6** with alkyl-substituted alkenes and alkyl ynamides respectively also led to complex mixtures.[14] We next assessed the benzene ring of indoles. The reactions (entries 12-17, Table 2) proceeded well to deliver products bearing electron-donating or electron-withdrawing groups on the aniline ring, although the yield dropped to 20% when C-4 was substituted (entry 17). Noticeably, when en-α,β-dichloro-enamide **9** was employed, an unusual competing C-O coupling was found to give an isopropoxide **10** (entry 18).[15]

Table 2. Substrate exploration.



entry	starting material **6**				**8**	yield[a] (%)
	R	EWG	R^1	Ar^2		
1	H	Ts	H	Ph	**8a**	79[b]; 50[c]
2	H	Ts	H	*p*-MeC_6H_4	**8b**	58[b]; 18[c]
3[d]	H	Ts	H	*p*-$OMeC_6H_4$	**8c**	73[b]; 42[c]
4	H	Ts	H	*p*-ClC_6H_4	**8d**	56[b]; trace[c]
5	H	Ts	Ph	Ph	**8e**	77[b]; 70[c]
6	H	Ts	*p*-MeC_6H_4	Ph	**8f**	47[b]; 50[c]
7	H	Ts	*p*-*t*-BuC_6H_4	Ph	**8g**	70[b]; 43[c]
8	H	Ms	H	Ph	**8h**	49[b]; 10[c]
9	H	Ns	H	Ph	**8i**	82[b]; 37[c]
10[d]	H	Ts	H	*o*-$OMeC_6H_4$	**8j**	23[b]; 10[c]
11	H	Ts	H	*m*-furanyl	**8k**	24[b]; 10[c]
12[d]					**8l**	67[b]; 23[c]
13[d,e]					**8m**	53[b]; 11[c]
14					**8n**	51[b]; N.R.[c]
15					**8o**	49[b]; N.R.[c]
16[d]					**8p**	39[b]; N.R.[c]
17					**8q**	20[b]; N.R.[c]
	starting material **9r**				**10r**	
18					 52[b]; trace[c]	

a. Isolated yield. [b.] Isopropanol was utilized as the solvent. [c.] 1,4-Dioxane was utilized as the solvent. [d.] The reaction was conducted at 100 °C for 18 hours. [e.] Demethylated by-product observed.

Given that the configuration of **8o** was confirmed by X-ray diffraction analysis (Figure 1),[16] we are able to propose that a novel Pd(0)-catalysed reductive Heck cycloisomerisation mechanism (Scheme 2) explains these observations. This is initiated by oxidative addition of Pd(0), generated by β-hydride elimination and reductive elimination *via* coordination of $PdCl_2$ with *i*-PrOH[17] or 1,4-dioxane[6]. The intramolecular coordination of the styrene may facilitate dissociation of the chloride anion to form the cationic Pd(II)-enamide species **A** from the highly electrophilic α-chloro-enamide **7**.[7]

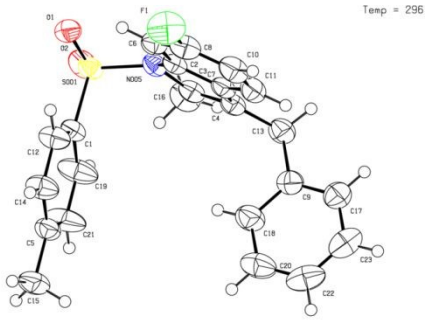
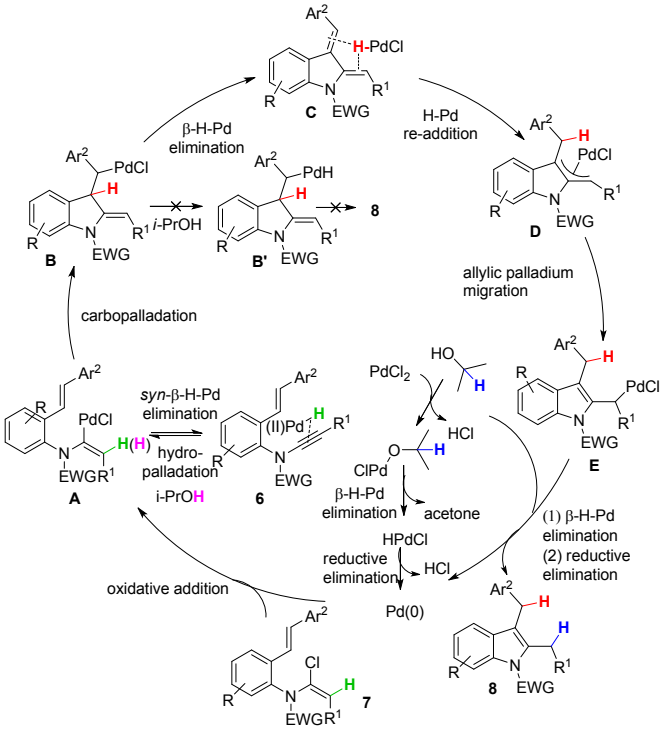


Figure 1. X-ray crystal structure of **8o**

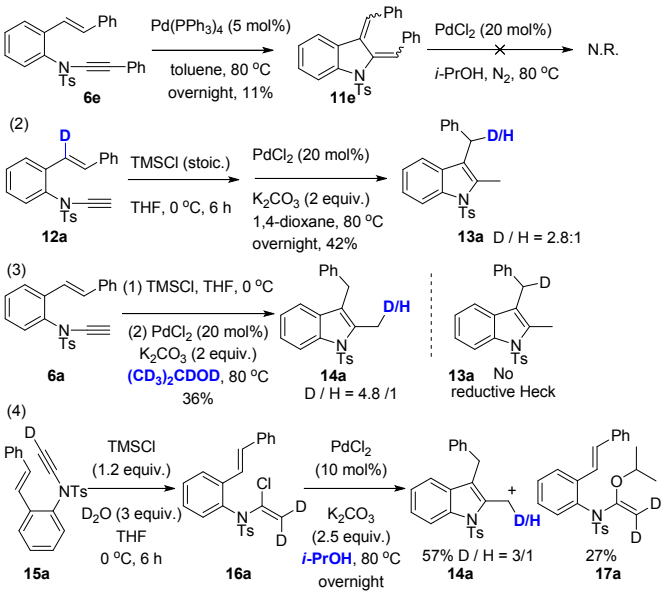
This is followed by an ionic Heck enamidation of the electron-rich styrene to afford diene **C**, which could be understood as arising from the styrene acting as a Lewis base attacking the electrophilic palladium(II).[7] There is a driving force for aromatisation through a pseudo-intramolecular reversible re-addition of Pd(II)-H species to the dienyl indoline,[18] which ligates Pd-H, to deliver the indolyl palladium species **D**. Upon alkene migration *via* the allylpalladium species, **E** was delivered. Then, there is a preference for Pd(II) to transfer methylene hydrogen from 1,4-dioxane or methinyl hydrogen from *i*-PrOH, through its coordination with the solvent / β-hydride elimination / reductive elimination to irreversibly afford **8**. If the cycle is not fast enough, reversible *syn*-β-H-Pd elimination of **A** and subsequent hydropalladation of ynamide **6** would occur,[19] allowing the proton exchange between substrate **7** and the solvent.

Our next focus was to seek out potential reductants and determine whether they contribute to the proposed reductive Heck cycloisomerisation sequence. Firstly, the dienyl indoline **11e**, acting as the presumptive intermediate **C** in Scheme 1, was prepared *via* cycloisomerisation of enynamide **6e**. When it was subjected to $PdCl_2$-catalysed, ligand-free conditions in *i*-PrOH, no reductive product **8e** was obtained, implying that the reductive process was not initiated by an intermolecular H-Pd species generated from $PdCl_2$ and *i*-PrOH. Secondly, to determine the source of the incoming hydrogen atom for the hydroenamidation of the styrene, we conducted a labelling experiment using **12a** with deuterium labeled at the styryl moiety. Interestingly, **13a** was obtained with deuterium migrated to the benzylic position, which elucidates that in the reduction of the styrene, the hydride source comes from the intramolecular H-Pd species, generated by β-H-Pd elimination and re-addition to the styrene.

Next, from various deuterium solvent screening (1,4-dioxane-d_8, DMF-d_7), we found that **6a** was converted to the mono-deuterated product in 2-propanol-d_8, without deuteration at the benzylic carbon. This indicates that before the reductive elimination of the C-Pd(II)-D bond, palladium is located at the methylene position, rather than the benzylic position, which excludes the possibility of a pathway to **8** *via* **B'**. Furthermore, this result confirmed that the solvent was indeed involved as a hydride donor in the reduction of the terminal alkylpalladium(II) species.



Scheme 2. Proposed overall mechanistic scheme.



Scheme 3. Deuterium labelling study

Finally, isotopomer **16a**, with two deuterium atoms on β-carbon of the α-chloro-enamide, was subjected to the reductive cycloisomerisation conditions. Interestingly, the indole **14a** was

delivered with one deuterium replaced by a hydrogen atom, accompanied by a C-O coupled isopropoxide **17a**. This reveals that *syn*-β-D-Pd elimination of **A** and re-addition to the ynamide **6** occurs reversibly, allowing D-H exchange of deuterated **A** with *i*-PrOH to take place.[20]

In conclusion, a palladium-catalysed ligand-free reductive Heck cycloisomerisation of aromatic 1,6-enynamides has been realised using *in-situ* generated 1,6-en-α-chloro-enamides in a one-pot stepwise protocol. Deuterium isotope labeling studies revealed that intramolecular hydride transfer, along with intermolecular hydride donation from the solvent, were both observed. Moreover, this indicates that there was a hydride exchange between the chloroenamide and *i*-PrOH. The mild, straightforward experimental condition will highten valuable potential towards the synthesis of complex azacyclic target compounds from acyclic units in both academic and industrial research settings.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 1890685 (**8o**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. The single crystal X-ray structure of product **8o** is included in the Supporting Information.

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