Journal Name

COMMUNICATION

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

Yangyang Hou,†[a] Jing Ma,†[a] Hongyi Yang,[a] Edward Anderson,[b] Andy Whiting[c] and Na Wu*[a,c]

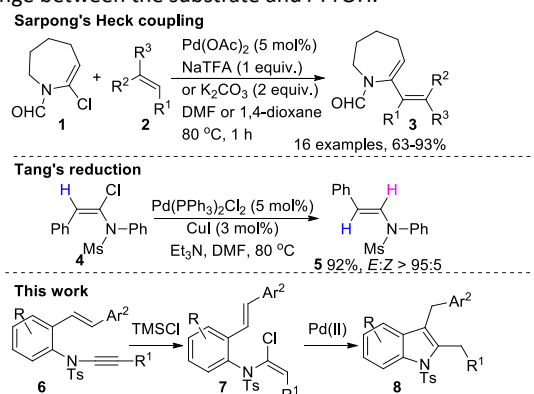**The first example of intramolecular hydroarylation of 1,6-en-α-chloro-enamides was achieved by palladium-catalysed ligand-free reductive Heck cycloisomerisation without Heck cyclised byproduct observed.**

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

Herein, we report a palladium-catalysed reductive Heck cyclisation of 1,6-enynamides. Compared with the common features of reductive Heck reactions, we found that (i) hydroarylation of styrene occurred through an intramolecular hydride transfer,[5] and the indolyl alkylpalladium(II) species was reduced through an intermolecular hydride transfer with i-PrOH or 1,4-dioxane as H-donors;[6] (ii) Chloride dissociation of the 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 electron-neutral and electron-rich styrenes;[7] (iii) Interestingly, the key enamide-Pd species was free from ligands saturation. No β-H-Pd elimination byproduct was observed. Deuterium isotope labeling studies further revealed that reductive Heck cyclisation involves an intramolecular hydride

transfer, intermolecular hydride donation from the solvent, and H-exchange between the substrate and i-PrOH.

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

Ynamides and enamides are versatile motifs that are finding use as fascinating building blocks for the synthesis of nitrogen-containing compounds.[8] Recently, Sarpong reported intermolecular Heck coupling reactions of bench-stable α-halo eneformamides in DMF or 1,4-dioxane.[9] Tang reported a reduction of the α-halo-enamide to the enamide using Et$_3$N as a reductant (Scheme 1).[10] In order to explore the balance of reactivity and stability of α-halo-enamides, we prepared a more electrophilic α-chloro tosylmides **7a**, and employed Sarpong's Heck condition to test intramolecular cyclisation of **7a**. Interestingly, it is distinct from Sarpong's Heck in that a reductive Heck cyclised **8a** was obtained exclusively, rather than Heck cyclised **8a'** (Table 1, entries 1-2). Alternatively, using activated alcohols as the solvent, which was employed in alkenylpalladative reduction of ynamides by Anderson,[11] also afforded **8a** in satisfying yields (entries 3-12). Surprisingly, when electron-rich 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 13-17).

[a] State Key Laboratory for the Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Pharmaceutical Science, Guangxi Normal University, Gulin, Guangxi, 541004, China. E-mail: wuna07@gxnu.edu.cn.

[b] Chemistry Research Laboratory, Oxford University, 12 Mansfield Road, Oxford, OX1 3TA, UK.
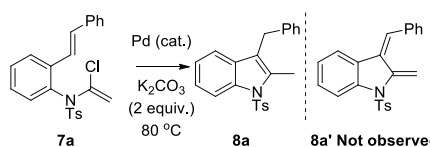
[c] Department of Chemistry, Durham University, South Road, Durham DH1 3LE, UK. E-mail: na.wu@durham.ac.uk.

† These authors contributed equally to this work.

Based on the optimised reults, entries 1 and 3 were applied to explore the substrate scope: 2-styryl-α-chloro-enamide derivatives **7** (Table 2). In order to overcome the hydrolytic lability of α-chloro-

Table 1. Optimization of conditions.[a]

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

[a] **7a** (0.15 mmol), Pd catalyst, K$_2$CO$_3$ (0.3 mmol), solvent (4 mL), 80 °C, 6 h, N$_2$. [b] isolated yield. [c] without K$_2$CO$_3$. [d] N.R. = no reaction. [e] dec. = decomposition. [f] TMTU = tetramethyl thiourea. [g] bipy = 2,2'-bipyridine.

enamides, they were prepared from *in-situ* generated HCl addition to enynamides **6** and used directly without further isolation.[12] In general, the one-pot equential cyclisation afforded 3-benzylindoles **8** in higher yields in *i*-PrOH than that in 1,4-dioxane. When the styryl group contained electron-donating groups (entries) and electron-mildly-deficient groups, 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. When the tosylamide was replaced by Ms- and Ns-amides, a better yield was obtained for Ns-variant in *i*-PrOH. However, cyclisation of **7** containing *ortho*-, *meta*-substituted aryl groups is more complicated with slow conversion (20 h), accompanied by complex mixtures. Noticeably, the substrates 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 with alkyl-substituted alkenes and alkyl ynamides respectively, also led to complex mixtures.[13] We next assessed the benzene ring of indoles. The reactions 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).[14]

The configuration of **8l** was further confirmed by X-ray diffraction analysis (Figure 1).[15] We propose that a novel Pd(0)-catalysed

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$_6$H$_4$	8b	58[b]; 18[c]
3[d]	H	Ts	H	*p*-OMeC$_6$H$_4$	8c	73[b]; 42[c]
4	H	Ts	H	*p*-ClC$_6$H$_4$	8d	56[b]; trace[c,e]
5	H	Ts	Ph	Ph	8e	77[b]; 70[c]
6	H	Ts	*p*-MeC$_6$H$_4$	Ph	8f	47[b]; 50[c]
7	H	Ts	*p*-*t*-BuC$_6$H$_4$	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$_6$H$_4$	8j	23[b]; 10[c]
11	H	Ts	H	*m*-furanyl	8k	24[b]; 10[c]
12					8l	67[b]; 23[c]
13[d]					8m	53[b]; 11[c]
14					8n	51[b]; N.R.[c]
15					8o	49[b]; N.R.[c]
16					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 condition. [c] 1,4-dioxane condition. [d] Demethylated byproduct was observed.

reductive Heck cycloisomerisation mechanism (Scheme 2) explains the observations. This is initiated by oxidative addition by Pd(0), generated by β-hydride elimination and reductive elimination *via* coordination of PdCl$_2$ with *i*-PrOH or 1,4-dioxane. 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]
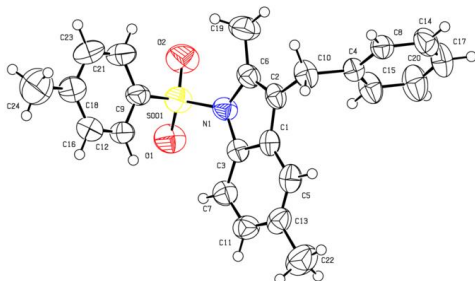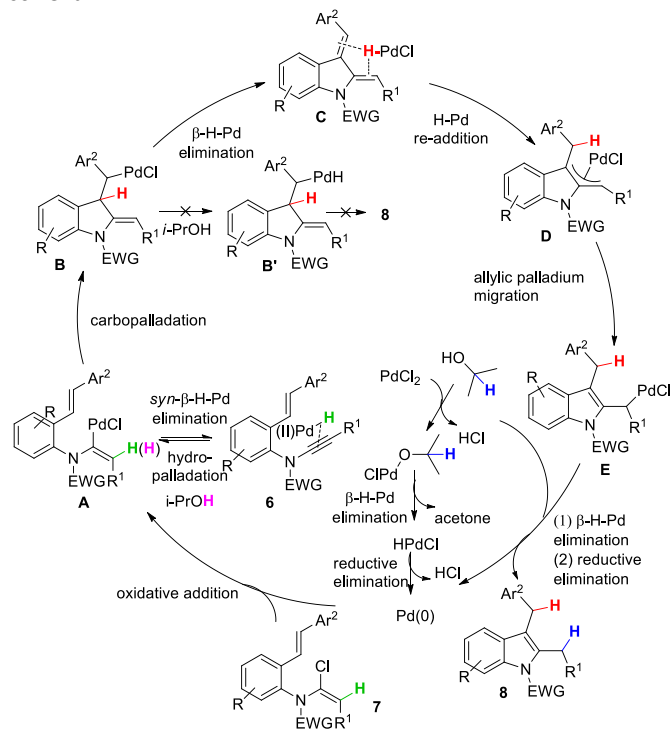

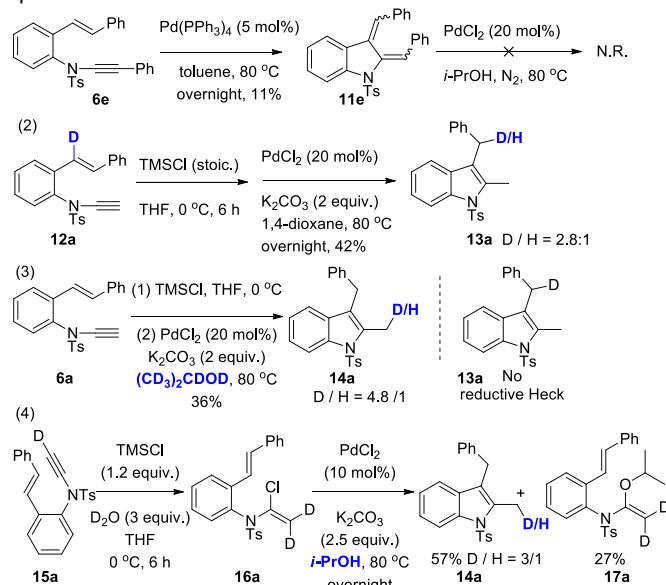**Figure 1**. X-ray crystal structure of **8l**

This is followed by ionic Heck enamidation of electron-rich styrenes 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 strong aromatisation driving force for pseudo-intramolecular reversible re-addition of Pd(II)-H species to the dienyl indoline,[16] which ligates Pd-H, to deliver indolyl palladium species **D**. Upon alkene migration *via* allylpalladium species, **E** was delivered. Followed by that, 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,[17] allowing for the proton exchange between substrate **7** and the solvent.

Scheme 2. Proposed mechanism.

Our next focus was to seek out potential reductants and determine whether they contribute to the proposed reductive Heck cycloisomerisation sequence. First, 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 condition in *i*-PrOH, no reductive product was obtained, implying that the reductive process was not initiated by an intermolecular H-Pd species generated from PdCl$_2$ and *i*-PrOH. To determine the source of the incoming hydrogen atom for the hydroenamidation of styrenes, we conducted 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 process of styrenes, the hydride source comes from the intramolecular H-Pd species, generated by β-H-Pd elimination and re-addition to styrenes.

Next, among various deuterium solvents screening (1,4-dioxane-d$_8$, DMF-d$_7$), we found **6a** is converted to the mono-deuterated product in 2-propanol-d$_8$, without deuteration at the benzylic carbon. This indicates that before reductive elimination of C-Pd(II)-D bond, palladium is located at the methylene position rather than the benzylic position, which excluded the possibility of pathway to **8** *via* **B'**. Furthermore, the result confirmed that the solvent was involved as a hydride donor in the reduction of the terminal alkylpalladium(II) species.

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 condition. 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** would occur reversibly, allowing for D-H exchange of deuterated **A** with *i*-PrOH.[18]

In conclusion, a palladium-catalysed ligand-free reductive Heck cycloisomerisation of aromatic 1,6-enynamides has been

COMMUNICATION   **Journal Name**

realised using *in-situ* generated chloroenamides in a one-pot stepwise protocol. Deuterium isotope labeling studies revealed that intramolecular H$^-$ transfer, along with intermolecular H$^-$ donation from the solvent, were both observed. Moreover, it indicated that there was a hydride exchange between the chloroenamide and *i*-PrOH.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1   (a) M. Ahlquist, G. Fabrizi, S. Cacchi and P. Norrby, *J. Am. Chem. Soc.*, 2006, **128**, 12785; (b) S. Raoufmoghaddam, S. Mannathan, A. J. Minnaard, J. G. de Vries and J. N. H. Reek, *Chem. – Eur. J.*, 2015, **21**, 18811; (c) K. Wu, N. Sun, B. Hu, Z. Shen, L. Jin and X. Hu, *Adv. Synth. Catal.*, 2018, **360**, 3038.
2   (a) G. Yue, K. Lei, H. Hirao and J. Zhou, *Angew. Chem. Int. Ed.*, 2015, **54**, 6531; (b) Z.-M. Zhang, B. Xu, Y. Qian, L. Wu, Y. Wu, L. Zhou, Y. Liu and J. Zhang, *Angew. Chem. Int. Ed.*, 2018, **57**, 10373; (c) L. Jin, J. Qian, N. Sun, B. Hu, Z. Shen and X. Hu, *Chem. Commun.*, 2018, **54**, 5752.
3   (a) B. P. Carrow and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 79; (b) X. Qin, M. W. Y. Lee and J. S. Zhou, *Angew. Chem. Int. Ed.*, 2017, **56**, 12723.
4   (a) Z. Wang, Z. Zhang and X. Lu, *Organometallics* 2000, **19**, 775; (b) N. Wu, L. Deng, L. Liu, Q. Liu, C. Li and Z. Yang. *Chem. Asian. J.*, 2013, **8**, 65.
5   For Pd-catalysed hydride transfer, see (a) H. Nakamura, S. Onagi and T. Kamakura, *J. Org. Chem.*, 2005, **70**, 2357; (b) H. Nakamura, M. Ishikura, T. Sugiishi, T. Kamakura and J.-F. Biellmann, *Org. Biomol. Chem.*, 2008, **6**, 1471; (c) N. Wu, A. Messinis, A. S. Batsanov, Z. Yang, A. Whiting and T. B. Marder, *Chem. Commun.*, 2012, **48**, 9986; (d) K. Shekarrao, P. P. Kaishap, S. Gogoi and R. C. Boruah, *Adv. Synth. Catal.*, 2015, **357**, 1187.
6   (a) S. Y. W. Lau, N. G. Andersen and B. A. Keay, *Org. Lett.*, 2001, **3**, 181; (b) J. A. M. Torre, P. Espinet and A. C. Albéniz, *Organometallics* 2013, **32**, 5428.
7   (a) J. Mo, L. Xu and J. Xiao, *J. Am. Chem. Soc.*, 2005, **127**, 751; (b) J. Mo and J. Xiao, *Angew. Chem. Int. Ed.*, 2006, **45**, 4152; (c) Z. Hyder, J. Ruan and J. Xiao, *Chem. Eur. J.*, 2008, **14**, 5555; (d) J. Ruan, J. A. Iggo, N. G. Berry and J. Xiao, *J. Am. Chem. Soc.*, 2010, **132**, 16689.
8   (a) G. Evano, N. Blanchard, G. Compain, A. Coste, C. S. Demmer, W. Gati, C. Guissart, J. Heimburger, N. Henry, K. Jouvin, G. Karthikeyan, A. Laouiti, M. Lecomte, A. Martin-Mingot, B. Métayer, B. Michelet, A. Nitelet, C. Theunissen, S. Thibaudeau, J. Wang, M. Zarca and C. Zhang, *Chem. Lett.*, 2016, **45**, 574; (b) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski and R. P. Hsung, *Acc. Chem. Res.*, 2014, **47**, 560; (c) Y. Zhang, K. A. DeKorver, H. Y. Li, A. G. Lohse, R. Hayashi, Z. J. Lu and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064;

(d) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840.
9   T. K. Beng, S. M. Wilkerson-Hill and R. Sarpong, *Org. Lett.*, 2014, **16**, 916.
10 W. Cao, P. Chen, L. Wang, H. Wen, Y. Liu, W. Wang and Y. Tang, *Org. Lett.*, 2018, **20**, 4507.
11 R. L. Greenaway, C. D. Campbell, H. A. Chapman and E. A. Anderson, *Adv. Synth. Catal.*, 2012, **354**, 3187; (b) C. D. Campbell, R. L. Greenaway, O. T. Holton, P. R. Walker, H. A. Chapman, C. A. Russell, G. Carr, A. L. Thomson and E. A. Anderson, *Chem. Eur. J.*, 2015, **21**, 12627.
12 K. Ohashi, S. Mihara, A. H. Sato, M. Ide and T. Iwasawa *Tetrahedron Lett.*, 2014, **55**, 632.
13 For unreactive substrate table, see supporting information.
14 For alkoxylation of 2-(chloromethyl)-1H-indole derivative, see: J.-R. Huang and C. Bolm, *Angew. Chem. Int. Ed.*, 2017, **56**, 15921.
15 CCDC 1890691 (**8l**) and 1890685 (**8o**) contain the supplementary crystallographic data for this paper. These 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 structures of products **8l** and **8o** are included in the Supporting Information.
16 (a) S. F. Vice, H. N. Carvalho, N. G. Taylor and G. I. Dmitrienko *Tetrahedron Lett.*, 1989, **30**, 7289; (b) X. Chen, G. Zheng, Y. Li, G. Song and X. Li, *Org. Lett.*, 2017, **19**, 6184.
17 G. Liu, W. Kong, J. Che and G. Zhu, *Adv. Synth. Catal.*, 2014, **356**, 3314.
18 For detailed mechanistic study, see supporting information.