Synthesis of 3-substituted pyrrolidines via palladium-catalysed hydroarylation.

Joseph B. Sweeney,[†,*] Julien Doulcet,[‡] and Bimod Thapa[‡]

Summary. Metal-catalysed reactions have revolutionised synthetic chemistry, allowing access to unprecedented molecular architectures with powerful properties and activities. Nonetheless, some transformations remain sparse in number, or out of reach, even with the diverse modern catalytic chemical arsenal, including bimolecular alkene hydroarylation reactions. We report here the first palladium-catalysed alkene hydroarylation to give 3-aryl pyrrolidines, a class of small molecule with potency in a diverse range of biological scenarios. Thus, whereas N-acyl pyrrolines usually undergo palladium-catalyzed arylation to give alkene products, the corresponding reactions of N-alkyl pyrrolines deliver products of hydroarylation, pyrrolidines. The process has broad substrate scope and can be used to directly deliver drug-like molecules in a single step from readily available precursors.

Keywords. Catalytic; hydroarylation; pyrrolidine; leishmaniasis; dopaminergic; serotonergic; HDAC inhibitors.

Introduction. Small molecules with saturated and unsaturated heterocyclic cores are ubiquitous in biochemistry, and there has been intense attention paid to the manufacture of such structures in academia and industry. Nitrogen-containing saturated rings are particularly privileged structures in biology, and there has therefore been intense interest in the design and use of these heterocycles as drug-like molecules: ca. 60% of currently FDA-approved small molecule drugs contain such a motif.[1] Within the N-heterocycle-containing drug library, the pyrrolidine motif is a very frequently seen structure, and these five-membered rings are widely used in drug discovery, with even relatively simple pyrrolidines often possessing great potency (Figure 1).

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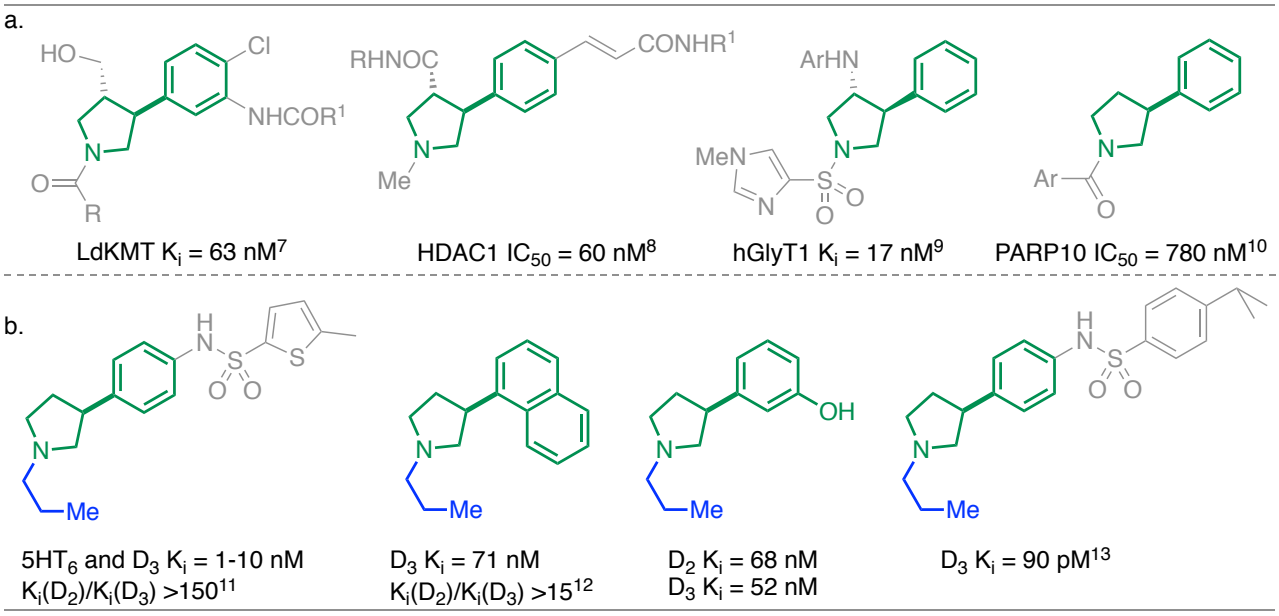
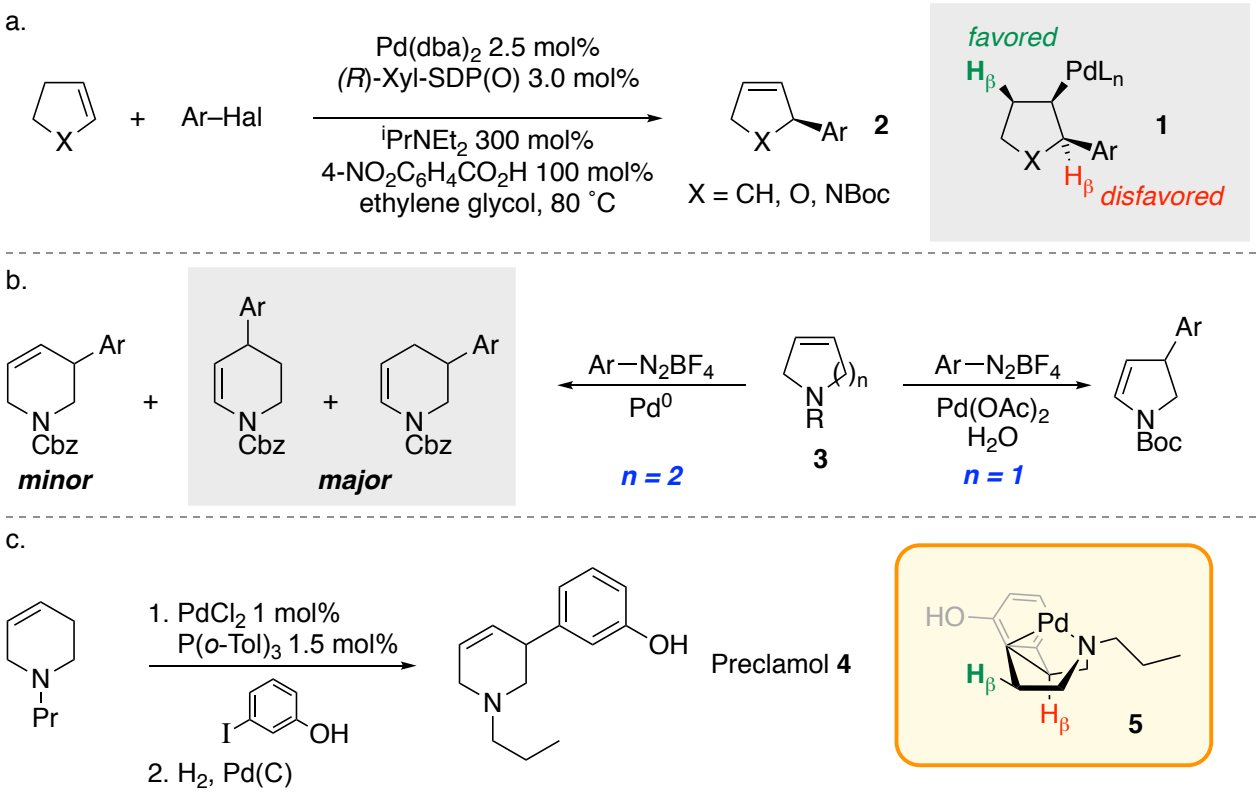
Figure 1. Saturated five-membered nitrogen heterocycles. a. 3-Aryl pyrrolidines are privileged structures, exhibiting powerful effects in a diverse range of biological scenarios, such as leishmaniasis, histone deacetylation, neurotransmission and gene transcription; b. 1-Propyl-3-aryl pyrrolidines are potent and selective ligands for serotonin and dopamine receptors.



Methods to deliver functionalised pyrrolidines directly by catalytic processes are relatively scarce, with the majority of reported methods involving ring-construction, rather than peripheral modification of intact pyrrolidines. In addition, certain classes of substituted pyrrolidines lend themselves rather more favourably to ring modification than others: thus, whilst there have been elegant efforts for both non-catalytic[2, 3, 4] and catalytic[5, 6] conversion of unsubstituted pyrrolidines to 2-substituted derivatives, there are few methods which efficiently deliver 3-substituted pyrrolidines, a structural class with diverse biological activity.[7, 8, 9, 10, 11, 12, 13] For the latter compounds, there is usually a requirement for a directing group[14, 15, 16] or N-protection, which limits direct access to structurally simple bioactive N-H, or N-alkyl pyrrolidines (such as bioactive N-propyl compounds, Figure 1b).

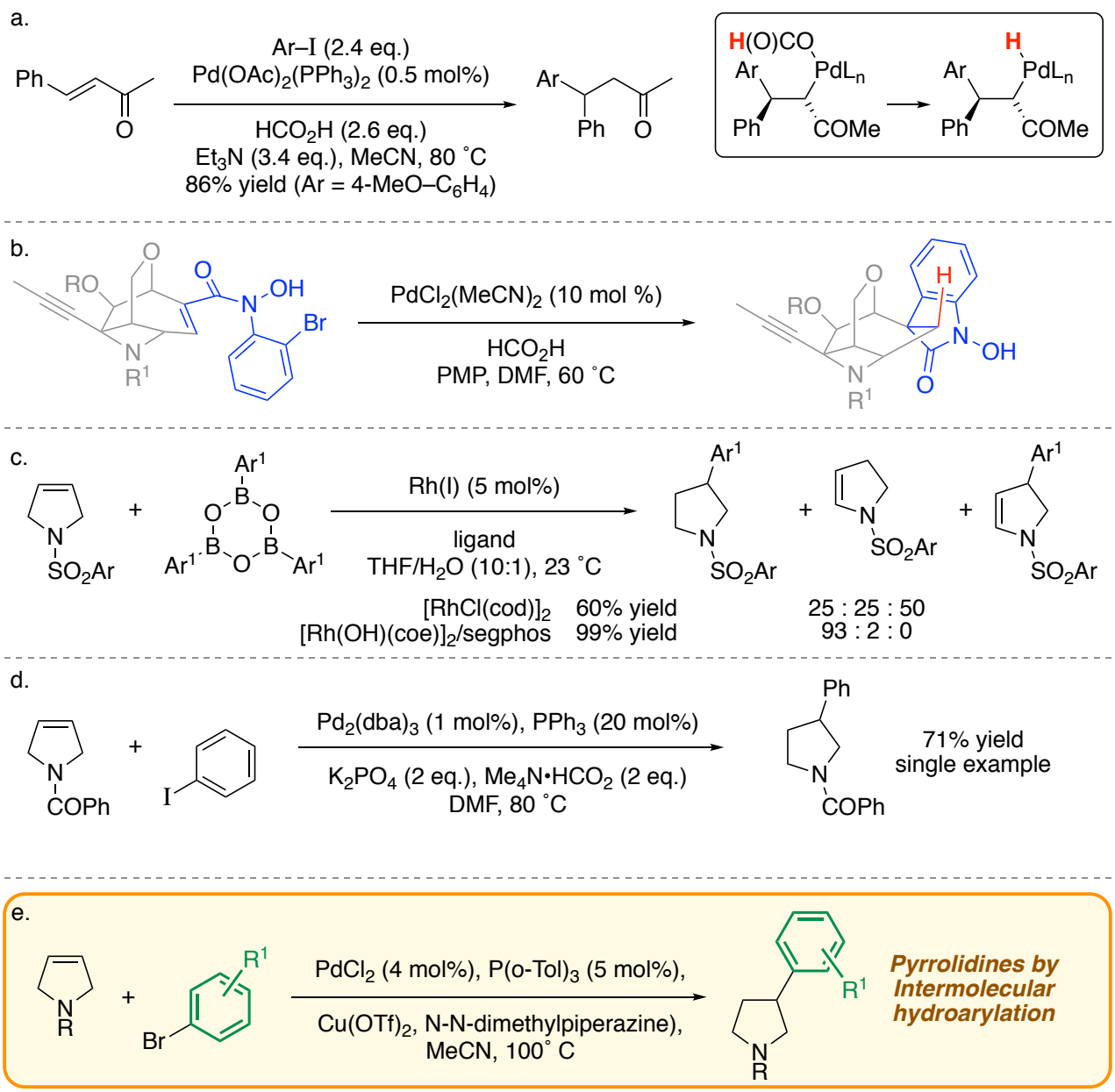
The Mizoroki-Heck ('MH') reaction[17, 18] was the first reported method[19, 20] to execute direct, substoichiometric catalytic modification of simple alkenes; for cycloalkenes, the MH reaction proceeds by overall functionalization of an sp^3– rather than an sp^2–CH bond, due to the stereoelectronic control for β-hydride elimination in the key palladium(II) intermediates **I** (Figure

Figure 2. Mizoroki-Heck arylation of unsaturated heterocycles proceed by overall sp^3-functionalization. a. Carba- and heterocycloalkene MH arylation favours allylic functionalisation, controlled by stereoelectronics; b. Mizoroki-Heck-Matsuda arylations of N-Acyl pyrrolines and tetrahydropyridines often give mixtures of products; c. MH arylations of N-alkyl tetrahydropyridines are controlled by chelation.



2a). In addition to the parent cycloalkene systems, the reaction can by applied to 2,3-dihydropyrans[21, 22] (**2**, X=O) and the analogous N-acyl pyrrolines[23, 24, 25, 26, 27, 28] (**2**, X=N–C[O]R) (Figure 2), but the reactions can be unpredictable (cf. Figure 2a and 2b). MH reactions of N-H or N-alkyl azacycloalkenes can be further complicated by competing oxidation processes, and there are few reports of effective MH reactions for this class of substrate; since many biologically active piperidines and pyrrolidines have this substitution pattern, this is a drastic limitation to the method. In addition, higher N-alkyl analogues (which can possess enhanced activity,[29] Figure 1b) are difficult to access directly using existing MH methodology, often requiring deacylation-alkylation strategies. We recently reported[30] conditions to effect MH reaction of 1-propyl tetrahydropyridine, in an improved, gram-scale, protecting group-free route to the drug molecule preclamol (3-PPP, **4**) (Figure 2c). The observed regiochemistry was ascribed to the intermediacy of a chelated palladium complex **5**.

Figure 3. Reductive Mizoroki-Heck processes are rare, and confined to a small number of reaction types. a. Conjugate-type additions; b. Intramolecular; c. Rh-catalysed pyrroline hydroarylation; d. N-Acylpyrroline reductive MH; e. This work: **reductive Mizoroki-Heck reaction – palladium-catalyzed hydroarylation of pyrrolines**



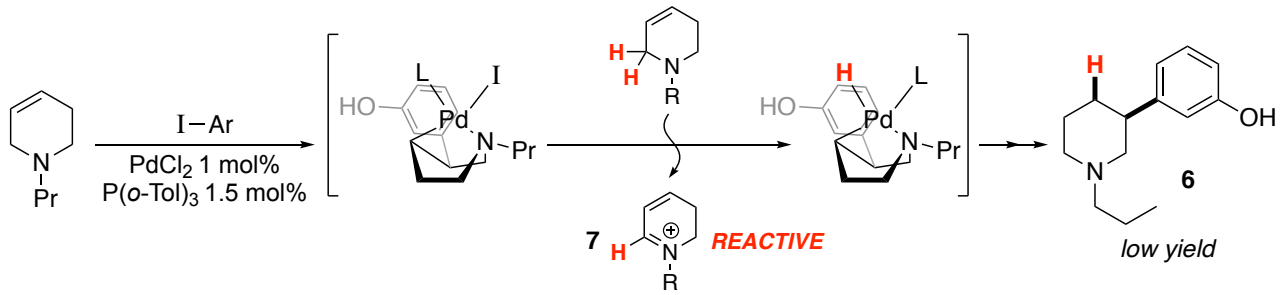
In theory, interception of **I** and **5** by a hydride source could lead to saturated products, rather than alkenes; in practice, such hydroarylation reactions[31, 32] are narrowly confined to conjugate-like additions (Figure 3a),[33] constrained alkenes,[34, 35] and intramolecular processes (Figure 3b).[36, 37, 38, 39] Though a rhodium-catalysed process has been reported (Figure 3c),[40] to date, only one intermolecular palladium-catalysed hydroarylation reaction to give pyrrolidines has been described (Figure 3d);[41] we report here the first broad-scope palladium-catalysed hydroarylation of pyrrolines (Figure 3e), directly furnishing 3-substituted pyrrolidines efficiently.

Results and discussion.

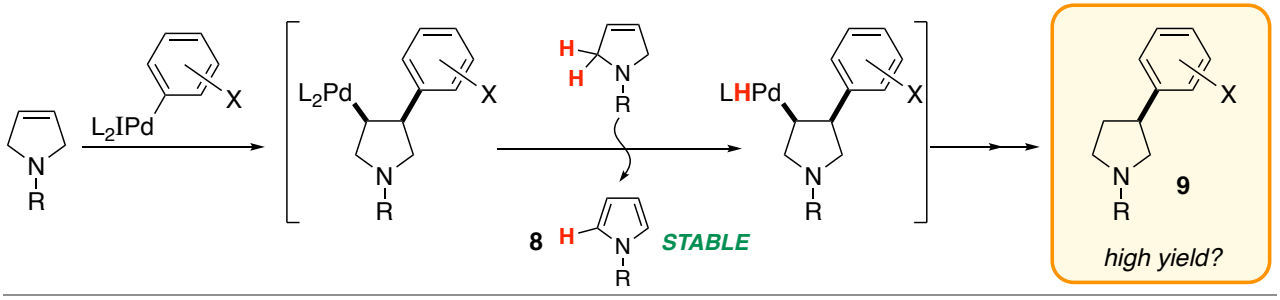
During the course of the optimisation of the route to preclamol shown in Figure 2c, it became clear that redox side-reactions were significant competitors to the desired arylation process; in addition to mono-arylated product, hydroarylated product **6** was also obtained (Figure 4a). We supposed that the hydride necessary to deliver **6** originated in the substrate (present in excess), leading to dihydropyridiniums **7**, reactive species notorious for their propensity for side-reaction (such as dimerization[42]), and we deduced that this would explain the relatively low yields of MH products compared with carbo cycloalkenes. Based on this analysis, we proposed that reaction of the lower homologue, pyrroline, should proceed more efficiently, since the analogous oxidised by-product (pyrrole **8**, Figure 4b) would be stable and therefore would neither initiate nor participate in further side-reactions. If this were the case, we assumed that the latter reaction would cleanly deliver hydroarylated product (pyrrolidine **9**) rather than the traditional, olefinic product.

Figure 4. Hijacking redox side-reactions to deliver **an efficient alkene hydroarylation reaction.**

a. Tetrahydropyridine MH reaction: redox processes are deleterious

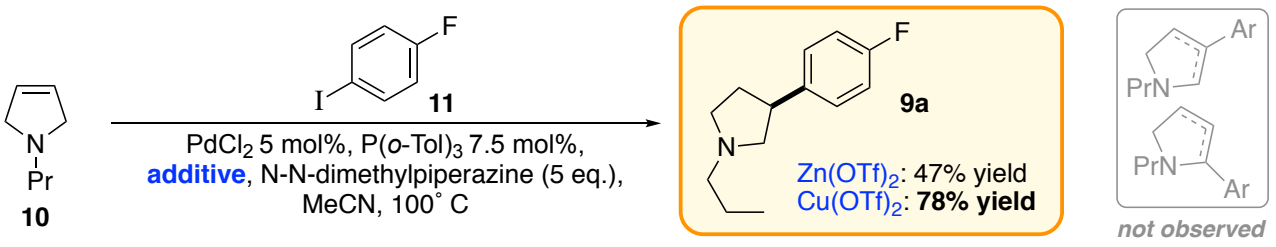


b. Pyrroline MH reaction: **harnessing pyrrole stability to favor hydroarylation**



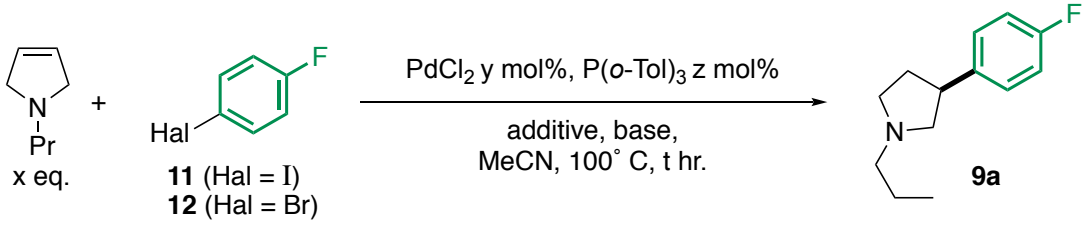
We were, therefore, gratified to observe that reaction of pyrroline **10** with iodide **11** under the MH conditions previously identified in the tetrahydropyridine series gave pyrrolidine **9a** as the

Figure 5. N-Alkyl pyrroline arylation: an efficient bimolecular reductive Mizoroki-Heck reaction



only coupled product (Figure 5); N-propyl pyrrole was also obtained, in approximately equal yield, confirming the hydride source to be the excess substrate, and validating the original hypothesis. Encouraged by the first-pass reaction, we next undertook a screening study (key data given in Table 1), which indicated conditions using bromide **12** as substrate with 4 mol% loading of Pd catalyst (entry 11) as being optimal, when considering stoichiometry, reaction time and yield.

Table 1. Optimisation of reaction conditions



Entry	x/eq.	y/mol%	z/mol%	Hal	Additive[a]	Base[b]	t/hr	Yield/%[c]
1	4	5	5	I	$AgNO_3$	DABCO	17	20
2	4	5	7.5	I	$Cu(OTf)_2$	DMpip[d]	17	78
3	4	5	7.5	I	$Zn(OTf)_2$	DMpip[d]	17	47[e]
4	4	5	7.5	Br	$Cu(OTf)_2$	DMpip[d]	17	77
5	4	5	7.5	Br	$Zn(OTf)_2$	DMpip[d]	17	32[f]
6	3	1	1.5	Br	$Cu(OTf)_2$	DMpip	17	62 (83[g])
7	3	5	7.5	Br	none	DMpip	20	0[h]
8	3	1	1.5	Br	$Cu(OTf)_2$	DMpip	90	71 (83[g])
9	3	2	3	Br	$Cu(OTf)_2$	DMpip	26	71
10	3	3	4.5	Br	$Cu(OTf)_2$	DMpip	26	78
11	3	4	6	Br	$Cu(OTf)_2$	DMpip	17	77
12	3	5	7.5	Br	$Cu(OTf)_2$	DMpip	17	80
13	2.5	3	4.5	Br	$Cu(OTf)_2$	DMpip	26	75
14	2.5	5	7.5	Br	$Cu(OTf)_2$	DMpip	26	76

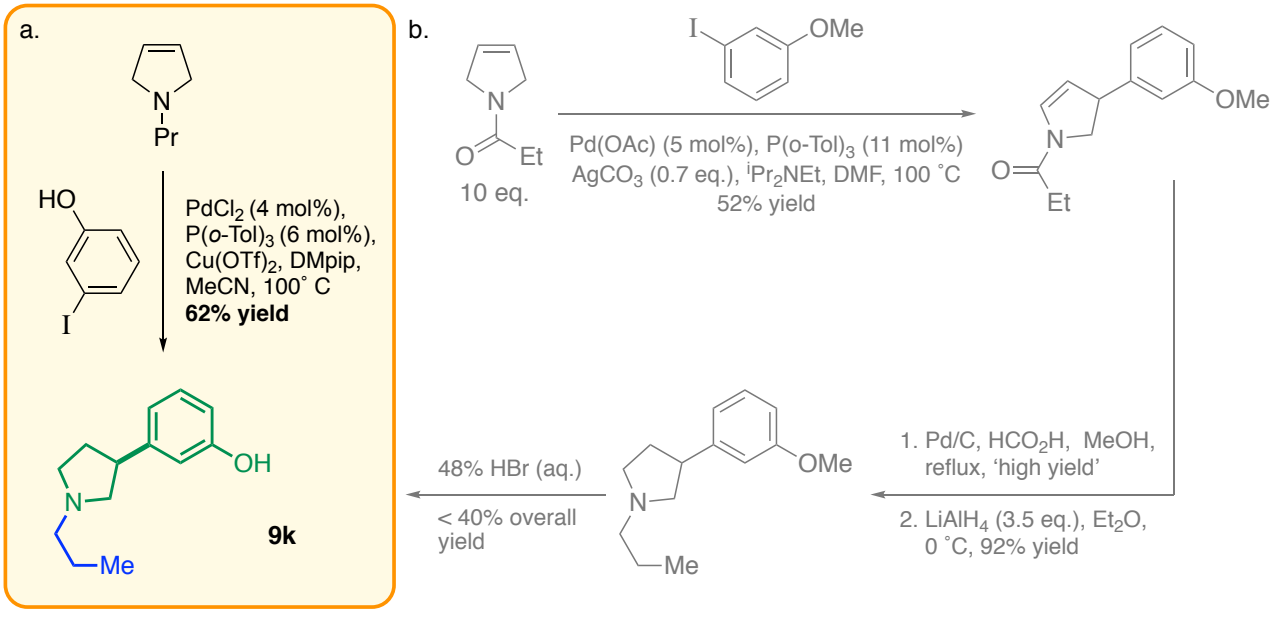
[a] 1 equivalent; [b] 5 equivalents; [c] Calculated from ^{1}H NMR; [d] N,N-dimethylpiperazine; [e] fluorobenzene obtained in 26% yield; [f] fluorobenzene obtained in 61% yield; [g] yield based on remaining starting material; [h] fluorobenzene obtained in 97% yield.

Traditional silver(I) additives delivered low yield of coupled product (entry 1), but the use of $Zn(OTf)_2$ was productive (entries 3 and 5), though less efficient than $Cu(OTf)_2$ (cf. entries 2 and 3, and entries 4 and 5) whilst only protodehalogenation was observed (in 97% yield) when no additive was present (entry 7); these data indicate that the additive is acting as a Lewis acid (vide infra).

Having identified an efficient and practical protocol, we next moved to examine the scope of the process, and were gratified to observe that a diverse range of aryl bromides underwent the reductive MH reaction, delivering 3-substituted pyrrolines **9a-9t** generally in good yields (Figure 6). The process was also applicable to N-benzylpyrroline, giving the synthetically tractable pyrrolidines **13a** and **13b**.

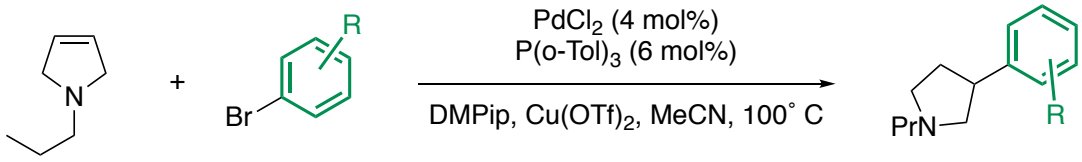
The power of this method is exemplified in the preparation of nanomolar dopamine antagonist **9k**, which is accessed in one step using the protocol described above, compared to the multi-step process which is the only previously described synthetic strategy to obtain **9k** (Figure 7).

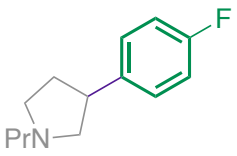
Figure 7. Palladium-catalysed hydroarylation of pyrrolines: an improved entry to dopamine receptor antagonists. a. This work: one-step synthesis of nanomolar compound **9k**; b. Reported synthesis of **9k**.[13]



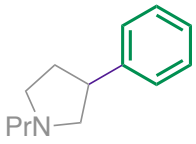
With regard to the precise mechanism in play, it is not unreasonable to assume that an intermediate such as cationic complex **14** (Figure 8) is involved: **14** (formed by ligand exchange of halide for pyrroline, promoted by $Cu(OTf)_2$[43, 44]) can rapidly be converted to palladium hydride **15**

Figure 6. Scope of pyrroline reductive Mizoroki-Heck arylation[a]

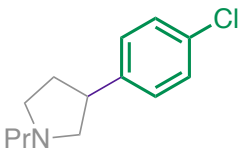




9a 60% yield[b]



9b 68%



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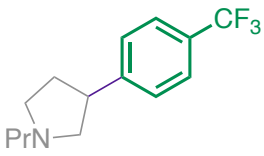
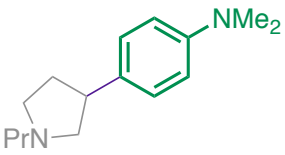
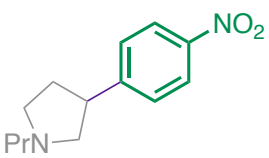


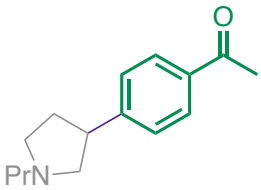
9d 60%



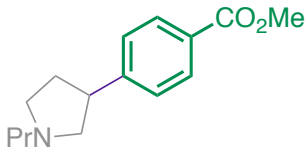
9e 19%



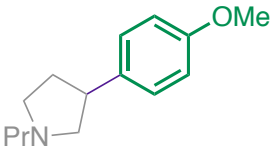
9f 50%



9g 70%



9h 19%



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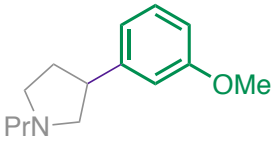

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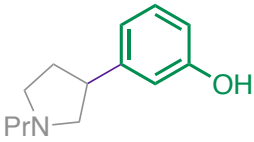

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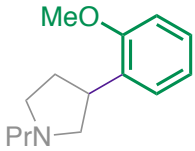

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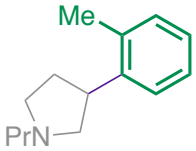

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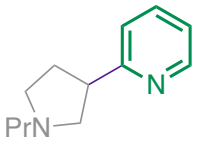

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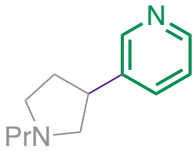

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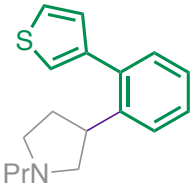

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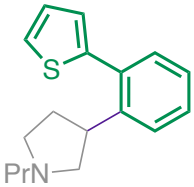

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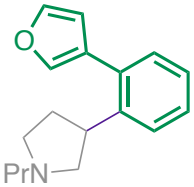

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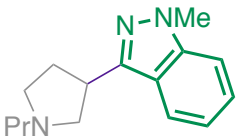

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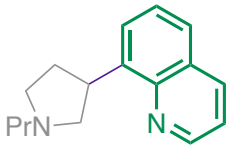

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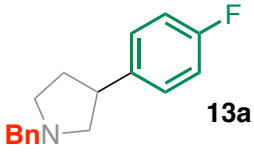
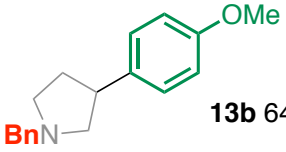


13a 54%

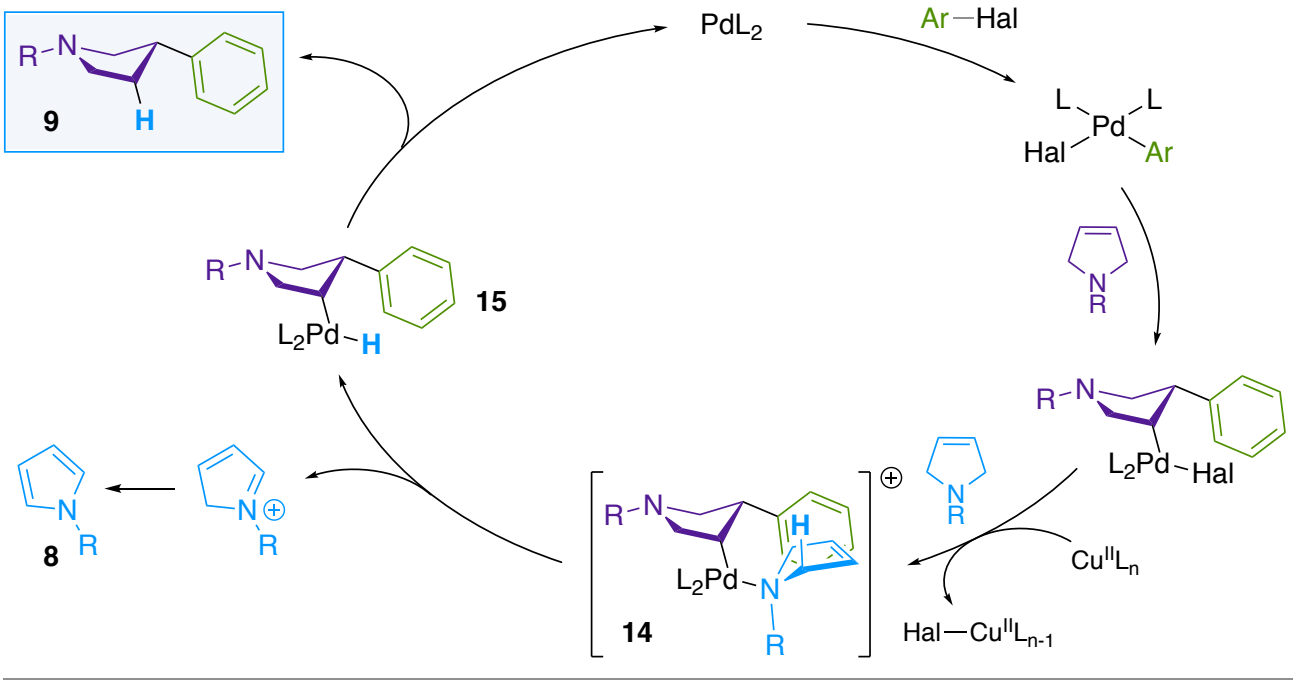


13b 64%

[a] Conditions: Aryl bromide, *N*-propyl-3-pyrroline (3 eq.), $PdCl_2$ (4 mol%), $P(o\text{-Tol})_3$ (6 mol%), *N*,*N*-dimethylpiperazine (5 eq), $Cu(OTf)_2$ (1 eq), MeCN (1 mM), sealed vial, 100 °C, 17 h; [b] isolated yield

(generating pyrrole **8** as by-product), which reductively eliminates the hydroarylated product and returns the catalyst to the cycle.

Figure 8. Plausible mechanism for palladium-catalysed pyrroline hydroarylation



In summary, we have described the first broad-scope palladium-catalysed hydroarylation to prepare pyrrolidines: the method is operationally simple and delivers potent bioactive small molecules in short order, and in good yields. The precise mechanistic features of these reactions are a focus of our research at this time and these data will be disclosed elsewhere, in due course.

Experimental procedures. *General procedure for hydroarylation*. To a 20 mL microwave vial was added $PdCl_2$ (21 mg, 0.12 mmol, 0.04 eq.), P(*o*-Tol)$_3$ (54 mg, 0.18 mmol, 0.06 eq.), *N*,*N*-dimethylpiperazine (2.1 mL, 15 mmol), aryl bromide (3 mmol), $Cu(OTf)_2$ (1.08 g, 3 mmol), *N*-propyl-3-pyrroline (1.17 mL, 9 mmol) and acetonitrile (3 mL). The vial was closed and then heated at 100 °C for 17 h. The reaction mixture was then allowed to cool to room temperature and was then diluted with CH_2Cl_2 (10 mL). Then Et_2O (100 mL) was added and the mixture was washed with NH_4OH (aq., 28%, 100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried ($MgSO_4$)

and evaporated under reduced pressure. The crude product was purified by column chromatography, affording the pure product. Full experimental procedures and spectral data are contained in the Supplemental Information

Acknowledgements. The authors acknowledge financial support from the University of Huddersfield. J.B.S. is grateful to the Royal Society, for the award of an Industry Fellowship.

Author contributions. J.D. and B.T. carried out all experiments, under the supervision of J.B.S. The ideas were conceived by J.B.S. Reactions were conceived and designed by J.B.S. The manuscript was written by J.B.S.

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