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Site-Selective Pd-Catalyzed C(sp^3)–H Arylation of Heteroaromatic Ketones

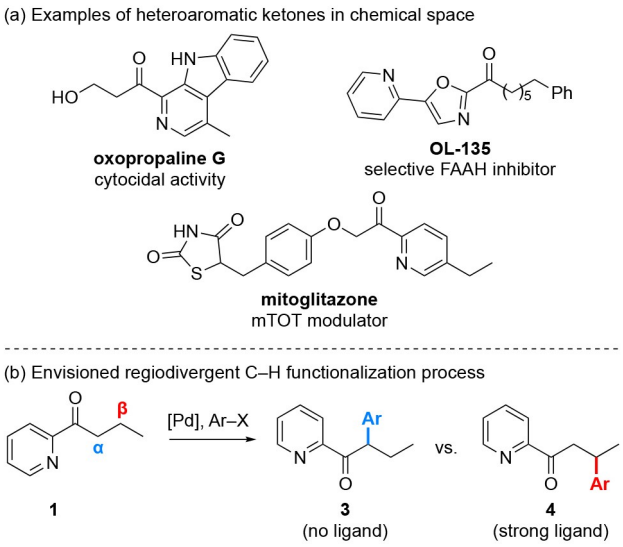
Anton Kudashev[a] and Olivier Baudoin*[a]

Abstract: A ligand-controlled site-selective C(sp^3)–H arylation of heteroaromatic ketones has been developed using Pd catalysis. The reaction occurred selectively at the α- or β-position of the ketone side-chain. The switch from α- to β-arylation was realized by addition of a pyridone ligand. The α-arylation process showed broad scope and high site- and chemoselectivity, whereas the β-arylation was more limited. Mechanistic investigations suggested that α-arylation occurs through C–H activation/oxidative addition/reductive elimination whereas β-arylation involves desaturation and aryl insertion.

Introduction

Heteroaromatic ketones represent a diverse chemical space present in numerous bioactive molecules, natural products, and other functional molecules (Scheme 1a).[1–3] Therefore, this class of compounds is the subject of regular studies in medicinal chemistry as a gateway to new drug candidates, usually through costly and time-consuming de novo synthesis.

In this context, the development of an operationally simple regiodivergent post-functionalization strategy is desirable to facilitate further discoveries. Toward this goal, we envisioned that a heterocycle-directed, site-selective Pd-catalyzed C–H activation process could, with minimal tuning, be developed to access diversely functionalized heteroaromatic ketones. While non-directed C(sp^2)–H activation strategies were successfully employed to functionalize heterocycles,[4] the site-selective functionalization of aliphatic chains remains a major challenge.[5] To date, this has been achieved either by employing particular reagents that change the selectivity-determining step,[6] or by designing new directing groups in combination with suitable ligands.[7] However, switching the selectivity by simply altering the reaction conditions has not yet been realized, to the best of our knowledge. Arylation at the α-position of heteroaromatic ketones was reported via Pd^0-catalyzed coupling of the corresponding enolate with an aryl iodide.[8] In addition, Pd^{II}-catalyzed nitrogen-directed C–H arylation was established as an efficient tool to arylate non-keto heteroarenes via 5-membered palladacycle intermediates.[9] On the other hand, the selective C(sp^3)–H arylation of the β-position of (hetero)aromatic ketones is limited to a Rh/Cu-catalyzed method involving in situ desaturation.[10,11] Pd-catalyzed β-arylation reactions involving such a desaturation/conjugate addition mechanism have been reported, but are limited to dialkylketones.[12,13] Importantly, no unified manifold for a facile selectivity switch exists, which prompted us to investigate such a possibility (Scheme 1b). We hypothesized that the α- versus β-selectivity in the arylation of heteroaromatic ketones such as **1** could be controlled by changing the reaction conditions to affect the coordination of the metal to the pyridine nitrogen. In particular, in the absence of a strong ligand, α-arylation should occur to produce ketone **3** through pyridine-directed C–H activation. Conversely, the presence of a strong exogeneous ligand could open up the desaturation/



Scheme 1. Regiodivergent arylation of heteroaromatic ketones: relevance and current work.

[a] A. Kudashev, Prof. Dr. O. Baudoin
Department of Chemistry
University of Basel
St. Johanns-Ring 19, CH-4056 Basel, Switzerland
E-mail: olivier.baudoin@unibas.ch

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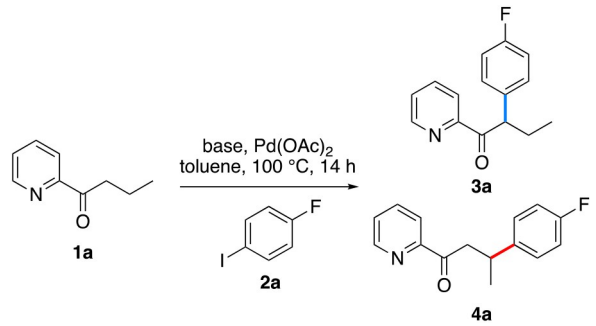
conjugate addition pathway leading to β-arylated ketone **4**. Given our earlier contributions to the fields of C(sp^3)–H activation[14] and migratory arylation,[15] we sought to explore the possibility of such a selectivity control.

Results and Discussion

We commenced our studies by investigating the effect of the base in the arylation of 2-butyrylpyridine **1a** with aryl iodide **2a** (Table 1). The strongest bases examined (K_3PO_4, Cs_2CO_3 and KOH) all furnished the α-arylated product **3a** as the major product together with a minor amount of product **4a** (entries 1–3). In contrast, the use of an acetate base selectively gave rise to the β-functionalized product, albeit in lower yields

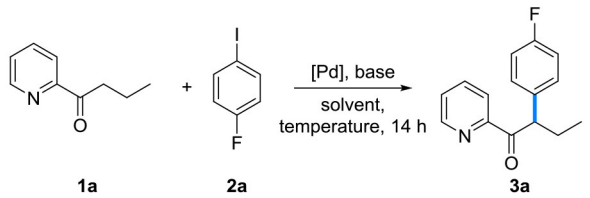
Table 1. Initial exploration of the site-selectivity.[a]



entry	base	% yield **3a** [b]	% yield **4a**[b]
1	K_3PO_4	15	5
2	Cs_2CO_3	45	1
3	KOH	37	6
4	KOAc	0	12
5	AgOAc	0	16

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), base (0.1 mmol), toluene (1 mL). [b] NMR yield using 1,1,2-trichloroethylene as an external standard.

Table 2. Optimization of α-selective arylation.[a]



entry	Base (equiv)	Solvent, *c*	*T*, °C	% yield **3a**[b]
1	Cs_2CO_3 (1)	TFT, 0.1 M	100	68
2	Cs_2CO_3 (2)	TFT, 0.1 M	100	78
3	Cs_2CO_3 (2)	mesitylene, 0.1 M	100	95
4[c]	Cs_2CO_3 (2)	mesitylene, 0.1 M	100	72
5[c]	Cs_2CO_3 (2)	mesitylene, 0.2 M	100	80 (77)
6[c][d]	Cs_2CO_3 (2)	mesitylene, 0.2 M	100	74
7[c][d][e]	Cs_2CO_3 (2)	mesitylene, 0.4 M	120	88 (75)

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), base (according to the table), solvent. [b] NMR yield using 1,1,2-trichloroethylene as an external standard, isolated yield in parenthesis. [c] Performed on 0.5 mmol scale. [d] Using 1.25 equiv of **2a**. [e] Using 5 mol% $Pd(OAc)_2$. TFT = α,α,α-trifluorotoluene.

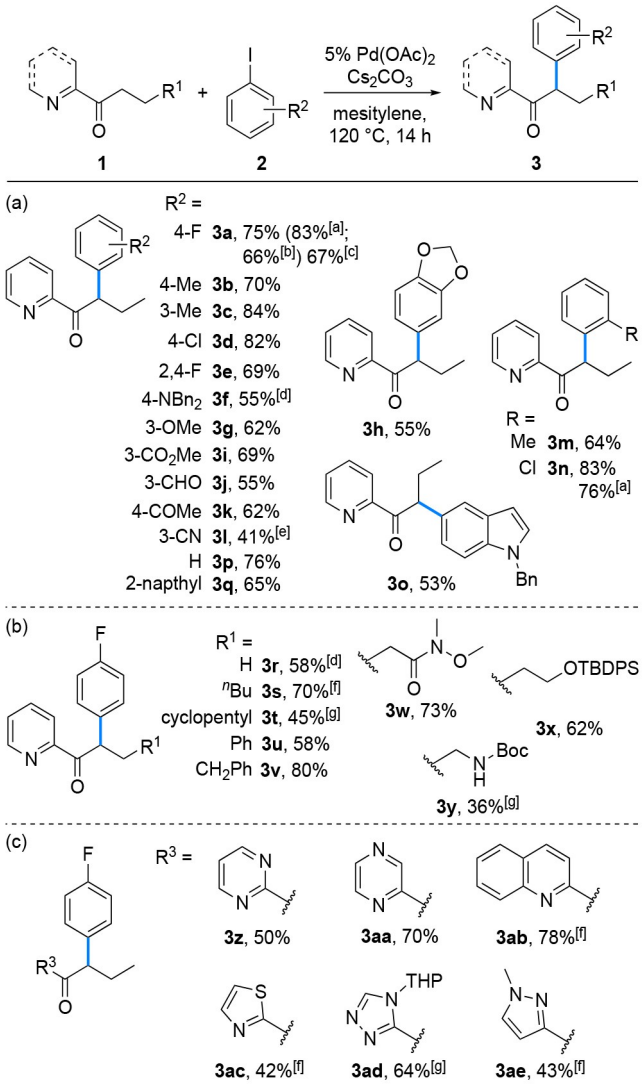
(entries 4–5). This preliminary study already demonstrated the feasibility of a conditions-based selectivity switch, and prompted us to further optimize each reaction separately.

It was possible to reach an optimum for the α-arylation reaction by tuning the stoichiometry and solvent (Table 2; see the Supporting Information for more details). The best performance was achieved in non-polar, aprotic solvents (entries 1–3), and in particular mesitylene (entry 3). Increasing the amount of Cs_2CO_3 to 2 equiv proved to be beneficial (entries 1–2). The reaction could be performed on a 5x scale at increasing concentrations (entries 4, 5 and 7), while simultaneously reducing the amount of required aryl iodide (entry 6) and palladium acetate (entry 7).

Under these conditions, the target α-arylated product **3a** was isolated in good yield on small (0.5 mmol, 77%) and preparative (2.5 mmol, 83%; 12.5 mmol, 66%) scale alike (Scheme 2a). In order to study the tolerance of these mildly basic conditions towards diverse substitution patterns, a range of aryl halides and heteroaromatic ketones were reacted. Starting off with the variation of substituents on the aryl iodide partner, both electron-deficient and electron-rich groups provided a good overall performance. Among these are alkyl groups (**3b**, **3c**), single or multiple halides (**3a**, **3d** and **3e**), a protected amine (**3f**) and protected phenols (**3g** and **3h**), products of which were obtained in good yields. Carbonyl substituents, such as unprotected ketone **3k** and aldehyde **3j**, as well as an ester **3i** were also formed in moderate yield. Interestingly, *ortho*-substituted aryl iodides were also reactive, and afforded target compounds **3m** and **3n** in good yields. Switching from an aryl iodide to a bromide was also possible with only a slightly lower efficiency (67% instead of 75%). Aryl chlorides proved to be unreactive, hence providing a handle for further functionalization (**3d**, **3n**). Finally, when aryl nitriles or heteroaryl iodides were used (**3l**, **3o**), a more moderate yield of product was obtained. This might be explained by inhibitive coordination of the aryl component to palladium and unproductive decay of the catalytically active species. Of note, further C–H arylation of **3o** at the indole ring was not observed. Finally, non-substituted and polycyclic aryl iodides, as represented by products **3p** and **3q**, were well tolerated.

Next, we investigated the reactivity of pyridyl ketones possessing different aliphatic chains (Scheme 2b). A shorter (**3r**) or a longer (**3s**) linear chain, as well as various terminal substituents (**3t**–**3v**) provided satisfying results (45–80% yields). Interestingly, the β-arylated product was not observed for substrates with R^1 = H and Ph, containing a more activated (i.e. primary or benzylic) β-position. Introducing functional groups gave varied, but satisfactory levels of performance: while Weinreb amide-bearing ketone **3w** and protected alcohol **3x** were obtained in good yields (62–73%), the Boc-protected amine **3y** was obtained in more modest yield (38%), presumably due to the same inhibitive coordination as mentioned before.

Obviously, the outcome of directed C–H activation reactions is heavily dependent on the nature of the directing group. To study the effect of the latter, we examined the reactivity of ketones with different heteroaromatic cores (Scheme 2c). We

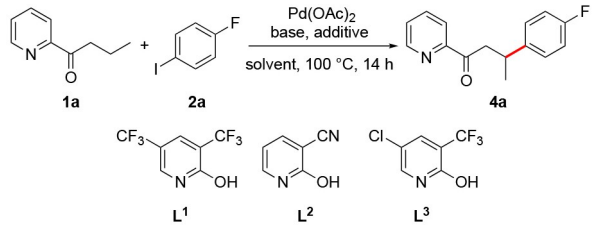


Scheme 2. Scope of the α-selective arylation of heteroaromatic ketones. Reaction conditions: **1** (0.5 mmol), **2** (0.625 mmol, 1.25 equiv), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (1 mmol, 2 equiv). [a] Using 2.5 mmol of ketone **1**. [b] Using 12.5 mmol of ketone **1**. [c] Using the aryl bromide instead of the iodide. [d] Using 0.5 mmol (1 equiv) of **2**. [e] Using 10 mol% $Pd(OAc)_2$. [f] Using 1 mmol (2 equiv) of **2**. [g] Using 0.75 mmol (1.5 equiv) of **2**.

were pleased to find that the developed protocol could be expanded beyond pyridine-based substrates. Indeed, substrates bearing pyrimidine, pyrazine or quinoline moieties, which are all able to coordinate to Pd, gave the corresponding products **3z**–**3ab** in moderate to good yields. Moreover, five-membered heterocycles, as shown with thiazole (**3ac**), 1,2,4-triazole (**3ad**) and pyrazole (**3ae**) derivatives, were found to be competent substrates and furnished the desired α-arylated ketones in moderate yields.

Next, we decided to investigate the β-selective arylation in greater detail, which proved to be a formidable task. Our attempts to optimize the reaction conditions are summarized in Table 3. While we were able to single out conditions to achieve a high α/β selectivity, simple base and solvent variations did

Table 3. Optimization of the β-arylation of ketone **1a**.[a]

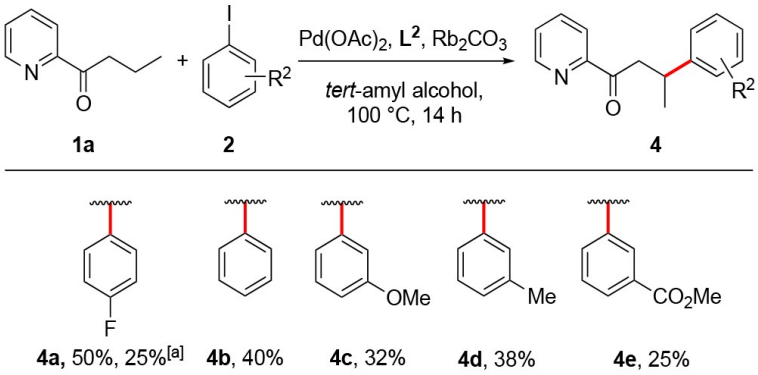


entry	base, additive (equiv)	solvent, c	ligand (mol%)	% yield **4a**[b]
1	AgOAc (1)	tol, 0.1 M	–	16
2	AgTFA (3) TFA (3)	*m*-xyl, 0.1 M	–	27
3	KOAc (1)	*t*-AmOH, 0.1 M	*N*-Ac-Gly (20)	21
4	K_2CO_3 (1.5)	*t*-AmOH, 0.1 M	**L**^{1} (20)	39
5[c]	Rb_2CO_3 (1.5)	*t*-AmOH, 0.2 M	**L**^{3} (20)	40
6[d]	Rb_2CO_3 (1)	*t*-AmOH, 0.2 M	**L**^{2} (20)	50

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), base (0.1 mmol), toluene (1 mL). [b] NMR yield using 1,1,2-trichloroethylene as an external standard. [c] Using 0.2 mmol of ketone **1a**. [d] Using 0.5 mmol of ketone **1a**. tol = toluene, *m*-xyl = *m*-xylene, *t*-AmOH = *tert*-amyl alcohol.

not increase the yield of the β-arylated ketone **4a** beyond 20% (entry 1). Inclusion of additives such as TFA, in combination with AgTFA, only marginally increased the yield (entry 2). Then, we turned our attention to the addition of stronger ligands, which were introduced by Yu and co-workers to accelerate various C–H activation reactions and, in some cases, modulate the site-selectivity.[16] Whereas mono-*N*-protected amino acids (MPAAs) such as *N*-Ac-Gly did not improve the yield (entry 3), the recently introduced pyridone ligands[17] were more successful, with electron-deficient pyridones **L**^{1}–**L**^{3} providing the best results (entries 4–6). After further optimization, it was possible to obtain the target β-arylated ketone **4a** in 50% yield on a 0.5 mmol scale using Rb_2CO_3 as the base and *tert*-amyl alcohol as the solvent (entry 6). Despite the moderate yield, a total selectivity for the β-position was observed. This is remarkable considering that a similar stoichiometric base (i.e., carbonate) is employed for α-selective reaction, and demonstrates a strong ligand control over the site-selectivity. In addition, no diarylated product was observed under these conditions. Further modifications such as ligand combinations did not furnish any tangible increase in isolated yield, despite extensive investigations.

With these conditions in hand, other aryl iodides were tested (Scheme 3). Unfortunately, despite the high selectivity observed for the corresponding β-arylated products, the yields were all lower than the one obtained with **2a**. Similar to the α-arylation, an aryl bromide was reactive albeit with a lower yield. Regrettably, it was not possible to transpose this reactivity towards other heteroaromatic ketones in synthetically useful yields. Therefore, the current results serve as a proof of concept that ligand-controlled selectivity switch is possible without modifying the substrates, but synthetic utility remains to be improved.



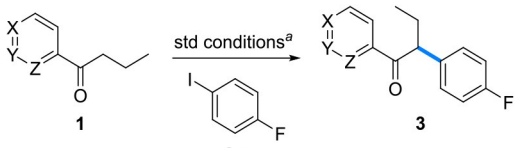
Scheme 3. Scope of the β-selective arylation of heteroaromatic ketones. Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), $Pd(OAc)_2$ (10 mol%), L^2 (20 mol%), Rb_2CO_3 (0.5 mmol). [a] Using the bromide instead of the iodide.

To get insights into the α-arylation process, we performed a series of comparative studies (Scheme 4). First off, to probe the competition between C–H activation and enolate arylation pathways, we compared the action of *t*-BuONa against Cs_2CO_3 (Scheme 4a). Sodium *tert*-butoxide is a strong base, which should facilitate rapid deprotonation at the α-position in a heteroaromatic ketone to form its corresponding enolate, thus shifting the process from C–H activation to enolate arylation.[8] Indeed, when model ketone **1a** was tested, both bases gave rise to product **3a**, albeit with a higher yield for Cs_2CO_3 (entries 1–2). In contrast, when butyrophenone **1b** lacking coordination ability was utilized, only *t*-BuONa provided the arylated product **3af** (entries 3–4). Moreover, the 3-pyridinyl ketone **1c** lacking directing ability only provided traces of product (entry 5). Likewise, whereas the 3-substituted pyrazole derivative **1d** provided α-arylated ketone **3ae** in moderate yield (entry 6, see also Scheme 2), the analogous 5-pyrazolyl ketone **1e** failed to react under the optimized conditions (entry 7). In parallel, we compared the performance of Cs_2CO_3 and *t*-BuONa on base-sensitive substrates containing a methyl ketone (product **3k**, see Scheme 2) or Weinreb amide (product **3w**). Whereas Cs_2CO_3 provided **3k** and **3w** in good yields, these products were not obtained in the presence of *t*-BuONa, with only decomposition being observed. Finally, a competitive reaction between ketones **1a** and **1b** under standard α-arylation conditions revealed a near-exclusive formation of **3a** when Cs_2CO_3 was employed, while a mixture of **3a** and **3af** was observed under *t*BuONa mediation (Scheme 4b). Taken together, these results indicate that the reaction employing Cs_2CO_3 requires coordination of Pd to the substrate nitrogen atom without preformation of the ketone enolate, whereas the latter is probably formed with *t*-BuONa. Moreover, the use of the less basic carbonate enables an increased chemoselectivity compared with *t*-BuONa. Similarly, the nature of β-arylation was investigated via comparative studies (Scheme 4c). As expected, butyrophenone **1b** did not yield any β-arylated product under optimized conditions (entry 1), thereby pointing again at the crucial coordination to the pyridine nitrogen atom. Increasing the number of methyl groups at the α-position dramatically decreased (entry 2) and even suppressed (entry 3) β-arylation, which excludes a direct C–H activation mechanism at the β-position and indicates that a desaturation mechanism is operative. A cross-over experiment with saturated pyridyl ketone **1a** and unsaturated phenyl ketone **1h** led to the exclusive formation of product **4a** (Scheme 4d), which indicates the intramolecular nature of this reaction.

Based on these elements and literature precedents on directed C–H activation,[9] as well as desaturation-mediated functionalization,[12,13] a unified mechanistic proposal is depicted in Scheme 5. Coordination of the pyridine to Pd^{II} (complex **I**) favors deprotonation with carbonate to give 5-membered palladacycle **II**. This deprotonation could occur through concerted metalation-deprotonation.[18] In the absence of a strong LX-type ligand, oxidative addition of the aryl iodide occurs to give Pd^{IV} intermediate **III**, which upon reductive elimination delivers the α-arylated product **3** with concomitant recycling of Pd^{II}. The presence of an LX-type ligand, and in particular pyridone,[19] induces the decoordination from pyridine (**II**→**IV**) and enables β-H elimination[20] to furnish **V**. In the latter, Pd^0 remains coordinated to the alkene, as indicated by the lack of cross-over in Scheme 4d. Oxidative addition of the aryl iodide and base-mediated abstraction of HI leads to **VI**, which undergoes migratory insertion to provide **VII** and, upon protonation, delivers β-arylated product **4** and recycled Pd^{II}. Obviously, we are aware that this mechanism is likely oversimplified and other pathways such as those involving Pd^0 catalysis[8] cannot be excluded at this point.

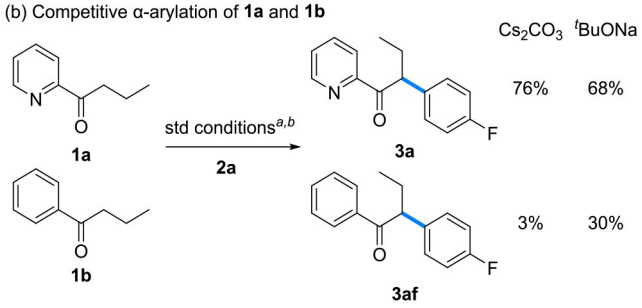
Finally, further functionalization of the obtained α-arylated products is possible (Scheme 6). In particular, compound **3n**, which possesses an *ortho*-chlorine atom was smoothly cyclized under standard Pd^0-catalyzed C–H arylation conditions[21] to obtain benzo[f]quinolinol **5a** in 85% yield, hence establishing a sequential C–H arylation route to this class of compounds.

(a) Control and comparative studies for α-arylation

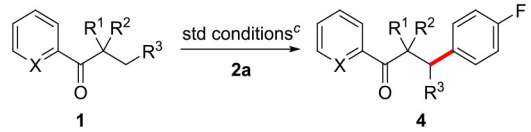


entry	X, Y, Z	base	**3** (% yield)
1	CH, CH, N (**1a**)	Cs_2CO_3	**3a** (75)
2	**1a**	*t*-BuONa	**3a** (52)
3	CH, CH, CH (**1b**)	Cs_2CO_3	–
4	**1b**	*t*-BuONa	**3af** (62)
5	CH, N, CH (**1c**)	Cs_2CO_3	**3ag** (traces)
6	–, NCH_3, N (**1d**)	Cs_2CO_3	**3ae** (43)
7	–, N, NCH_3 (**1e**)	Cs_2CO_3	–

(b) Competitive α-arylation of **1a** and **1b**

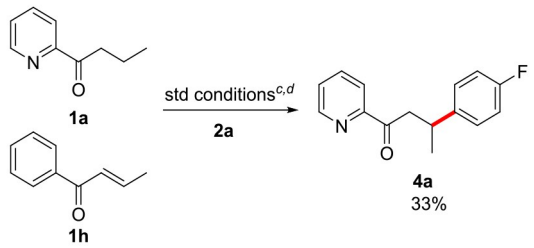


(c) Control experiments for β-arylation



entry	X, R_1, R_2, R_3	**3** (% yield)
1	CH, H, H, Me (**1b**)	–
2	N, Me, H, H (**1f**)	**4f** (traces)
3	N, Me, Me, H (**1g**)	–

(d) Cross-over experiment



Scheme 4. Control and comparative studies. [a] Reaction conditions: **1** (0.5 mmol), **2a** (0.625 mmol, 1.25 equiv), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 or *t*-BuONa (1 mmol), mesitylene, 120 °C, 14 h. [b] Additional 0.5 mmol (1 equiv) of **1b** was used. [c] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), $Pd(OAc)_2$ (10 mol%), L^2 (20 mol%), Rb_2CO_3 (0.5 mmol), *tert*-amyl alcohol, 100 °C, 14 h. [d] Additional 0.5 mmol (1 equiv) of **1h** was used. Yields in reactions (b)-(d) refer to NMR yields using 1,1,2-trichloroethylene as an external standard.

Conclusion

A switchable site-selective arylation of heteroaromatic ketones by employing Pd-catalyzed directed C–H activation was developed. The α-arylation reaction employed mildly basic conditions and proved efficient and chemoselective on a broad range of aryl iodide and ketone substrates, including various heteroarenes. Employing a pyridone ligand allowed to switch the selectivity towards β-arylation, without having to rely on substrate modification, albeit with a much lower efficiency and generality. This work demonstrates the feasibility of conditions-controlled site-selectivity in metal-catalyzed C(sp^3)–H functionalization.

Experimental Section

General procedure for α-arylation: To an oven-dried threaded culture tube (10 mL) equipped with a PTFE-coated magnetic stirrer cesium carbonate (2 equiv) was charged. The tube was then introduced into the glovebox, where palladium acetate (5% mol) was charged. The tube was closed with a septum and removed from the glovebox, then ketone **1**, aryl halide **2** (1.25 equiv) and mesitylene (0.4 M) were added by syringe. The septum was then replaced in a flow of argon with a screwcap and the reaction mixture was stirred in a heating block at 120 °C for 14 h. The reaction mixture was then cooled to r. t., diluted with CH_2Cl_2 (2 mL) and filtered over a pad of Celite. Solids were then washed with CH_2Cl_2 (2×2 mL) and the combined filtrate was evaporated at reduced pressure, dry-loaded onto Celite and subjected to column chromatography to yield the corresponding α-arylated product **3**.

General procedure for β-arylation: To an oven-dried threaded culture tube (10 mL) equipped with a PTFE-coated magnetic stirrer rubidium carbonate (1 equiv) and L^2 (20 mol%) were charged. The tube was then introduced into the glovebox, where palladium acetate (10% mol) was charged. The tube was closed with a septum and removed from the glovebox, then ketone **1**, aryl halide **2** (2 equiv) and *tert*-amyl alcohol (0.2 M) were added by syringe. The septum was then replaced in a flow of argon with a screwcap and the reaction mixture was stirred in a heating block at 100 °C for 14 h. The reaction mixture was then cooled to r. t., diluted with CH_2Cl_2 (2 mL) and filtered over a pad of Celite. Solids were then washed with CH_2Cl_2 (2x2 mL) and the combined filtrate was evaporated at reduced pressure, dry-loaded onto Celite and subjected to column chromatography to yield the corresponding β-arylated product **4**.

Acknowledgements

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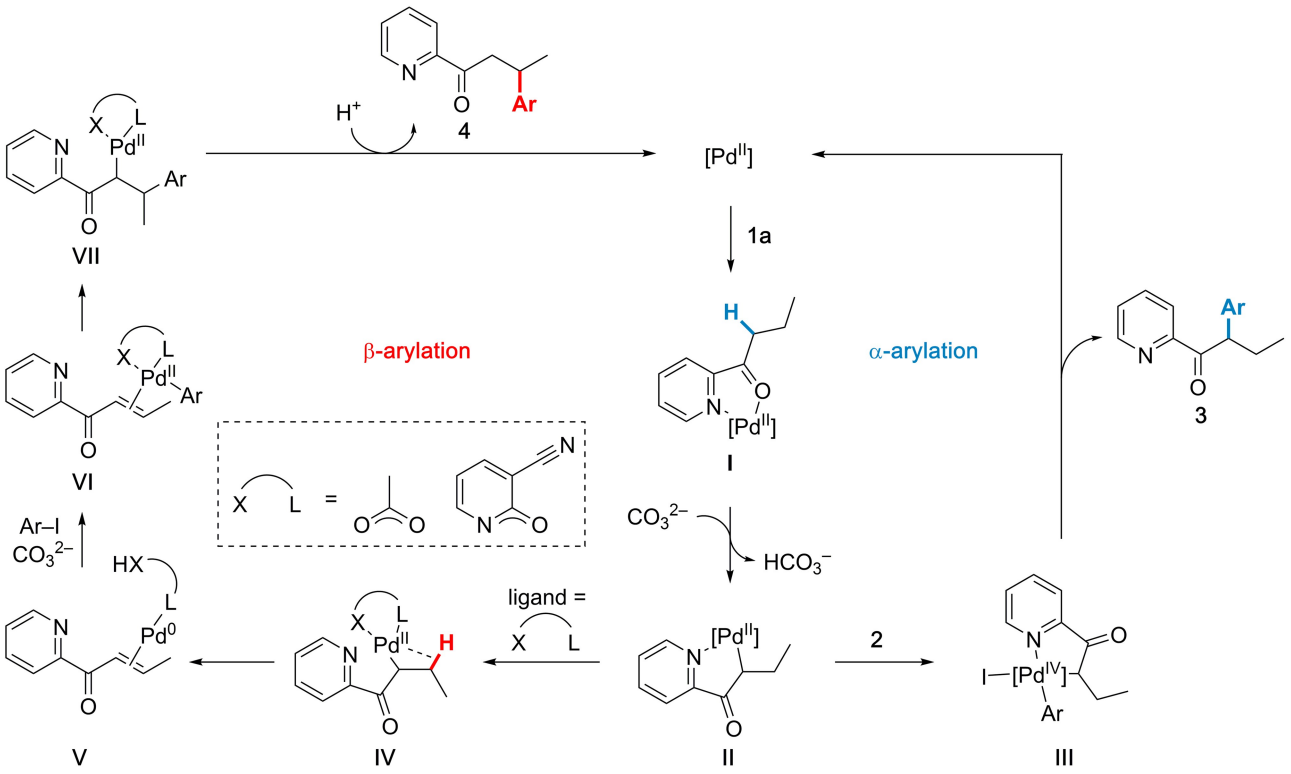
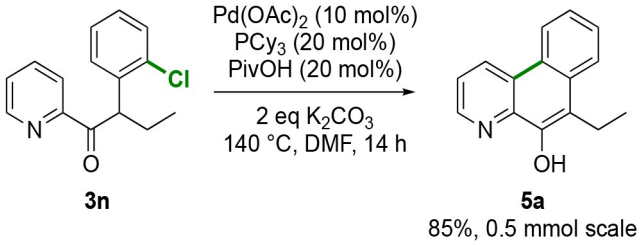
Conflict of Interest

The authors declare no conflict of interest.



Scheme 5. Mechanistic proposal.



Scheme 6. Post-functionalization reaction.

Keywords: arylation · C–H activation · palladium · site-selectivity

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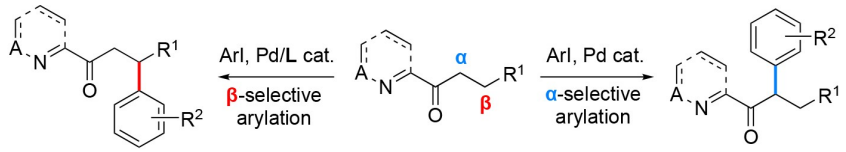

*A. Kudashev, Prof. Dr. O. Baudoin**

Site-Selective Pd-Catalyzed C(sp^3)–H Arylation of Heteroaromatic Ketones

Switching site-selectivity: Regiodivergent Pd-catalyzed arylation of α- and β-positions of the alkyl side-chain of heteroaromatic ketones is reported. The presence of a pyridone ligand orients the selectivity towards β-arylation, while its absence leads to α-arylation. Mechanistic studies suggest that α-arylation follows a C–H activation pathway, whereas β-arylation takes place through a C–H activation/desaturation/conjugate addition manifold. The method developed is mild and allows further functionalization of the products.