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Iridium Catalyzed Regiocontrolled Direct Amidation of Isoquinolones and Pyridones

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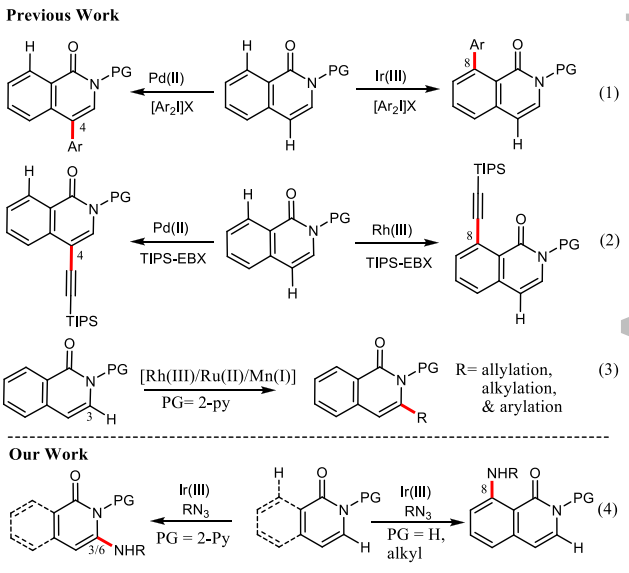
Abstract. Iridium catalyzed highly regiocontrolled C3/C8 amidation of isoquinolones and C6 amidation of 2-pyridones has been successfully accomplished with various azides. The optimized method is operationally simple with a broad substrate scope. The protocol has been found to be scalable.

Keywords: Regiocontrol; Amidation; Isoquinolone; Pyridone; Iridium(III)

Transition metal catalyzed site selective functional group introduction into the heteroatom containing organic molecules becomes an attractive area for synthetic chemists.[1] Nitrogen containing heterocycles like quinolones and pyridones are widely present in several natural products, pharmaceutical compounds, agrochemicals and functional materials.[2] Consequently, development of effective methods to directly introduce important functional groups in regioselective fashion to the isoquinolone[3] and pyridone[4-6] scaffolds is a demanding area of research.

Recently, the Hong group elegantly described the transition metal catalyst controlled site-selective arylation[3a-b] of isoquinolone moieties (Scheme 1, eq 1). Interestingly, they also revealed proper directing group guided regioselective alkynylation of 4-quinolone derivatives.[3d] Quite recently, Patil and co-workers also showed the catalyst controlled C4 and C8-selective alkynylation of isoquinolone derivatives (Scheme 1, eq 2).[3e] In this context, another nitrogen containing important heterocyclic scaffold 2-pyridone moiety was also widely explored for C3[4], C4[5] and C6-selective[6] direct functionalization under transition metal catalyzed conditions by us and other groups in recent years. Incidentally, during C6-selective functionalization of 2-pyridone scaffold, introduction of functional groups like alkyl[6h], aryl[6e, 6k] or allyl[6n,6o] groups at the C3 position of isoquinolone scaffold was also described in the literature (Scheme 1, eq 3). Based on previous pioneering works on isoquinolone[3,6] and pyridone[4-6], we hypothesized that C8 selectivity of isoquinolone can be achieved through the transition metal catalyzed activation of corresponding C-H bond via the carbonyl group coordination. The key aspect for the C3/C6 position functionalization of isoquinolone/2-pyridone moiety is the proper directing group placement at the corresponding nitrogen atom. Since the Buchwald-Hartwig amination of arylhalides, significant progress has been observed in the transition metal catalyzed amination of unactivated C-H bonds.[7-8] Despite admirable advancement on transition metal catalyzed direct regioselective functionalization of isoquinolone and pyridone scaffold, at per our best of knowledge there is no report on direct transition metal catalyzed site-selective amidation of isoquinolone scaffold. In continuation of our recent studies on iridium catalysis and amination,[9] herein we report a site-selective iridium catalyzed C3 and C8 amidation of isoquinolone and C6 amidation of 2-pyridone (Scheme 1, eq 4).



Scheme 1. Site Selective C-H Functionalization of Isoquinolones.

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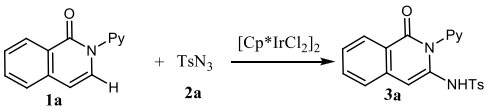
Based on the above assumptions, we started our investigation with 2-(pyridin-2-yl)isoquinolin-1(2*H*)-one (**1a**) and *p*-toluenesulfonyl azide (**2a**) in presence of $[Ru(p\text{-}cymene)_2Cl_2]_2$ (2 mol%), $AgSbF_6$ (8 mol%) in 1,2-dichloroethane at 85 °C (Table 1, entry 1). We were glad to find that the desired C3-amidated product was formed albeit in lower yield. Further, the reaction was screened with another transition metal catalyst $[Cp^*RhCl_2]_2$ to improve the yield (Table 1, entry 2). Gratifyingly, the desired product was isolated with improved 62% yield. When the reaction was performed under $[Cp^*IrCl_2]_2$ catalyst and $AgSbF_6$ as halide abstractor, the reaction proceeded with satisfying 81% desired product yield (Table 1, entry 3). To improve the yield further, reaction conditions were screened with additional 20 to 50 mol% acetate source (Table 1, entries 4-5).

Table 1. Optimization for the synthesis of iridium catalyzed amidation of isoquinolne[a)]

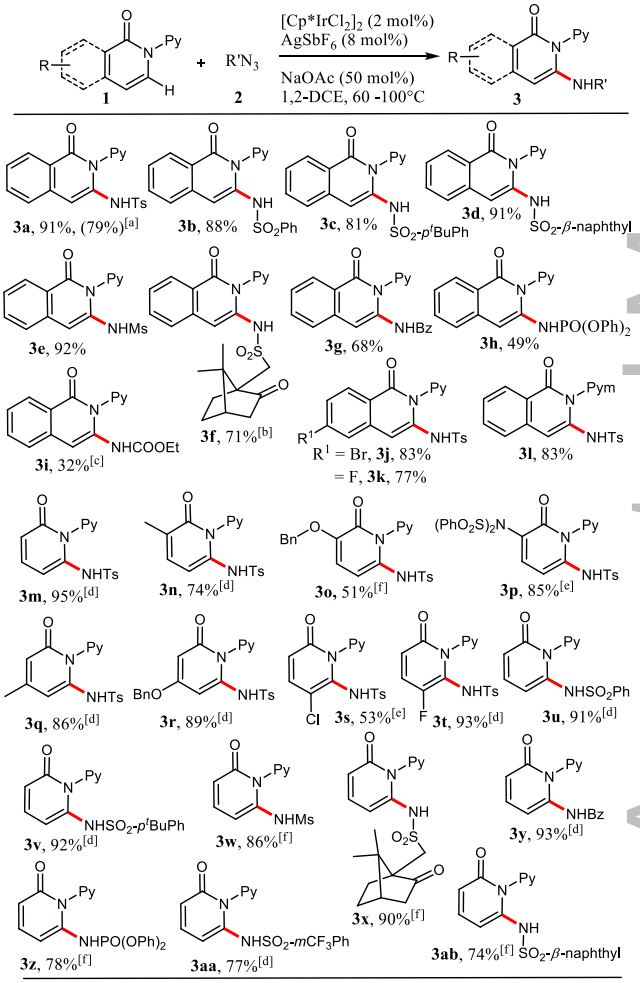


Entry	Solvent	Ag salt	Additive (mol%)	Yield[b)]
1[c)]	DCE	$AgSbF_6$	-	15
2[d)]	DCE	$AgSbF_6$	-	62
3	DCE	$AgSbF_6$	-	81
4	DCE	$AgSbF_6$	NaOAc (20)	83
5	**DCE**	**$AgSbF_6$**	**NaOAc (50)**	**91**
6[e)]	DCE	$AgSbF_6$	NaOAc (50)	53
7	DCE	$AgNTf_2$	NaOAc (50)	87
8	DCE	AgOAc	NaOAc (50)	trace
9	DCE	$AgNO_3$	NaOAc (50)	trace
10	MeCN	$AgSbF_6$	NaOAc (50)	15
11	EtOH	$AgSbF_6$	NaOAc (50)	33
12	dioxane	$AgSbF_6$	NaOAc (50)	trace
13	DMSO	$AgSbF_6$	NaOAc (50)	n.d.

[a)]Reaction Conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $[Cp^*IrCl_2]_2$ (2 mol%), Ag salt (8 mol%), NaOAc (50 mol%), 12 h, 85 °C, 0.1 M. [b)]Isolated Yields. [c)]Catalyst used $[Ru(p\text{-}cymene)Cl_2]_2$ (2 mol%) [d)]Catalyst used $[Cp^*RhCl_2]_2$ (2 mol%). [e)]$[Cp^*IrCl_2]_2$ (1 mol%).

Finally, we were happy to obtain 91% isolated yield of desired product with 50 mol% acetate additive. However, the decrease in catalyst loading lowered the yield (Table 1, entry 6). Furthermore, $AgNTf_2$ as silver salt provided comparable yield in 87% (Table 1, entry 7). Other silver salts did not provide isolable amount of desired product (Table 1, entries 8-9). Other solvents having different polarity were not found much successful in this transformation (Table 1, entries 10-13).

With the optimized reaction conditions in our hand, the generality of the regiocontrolled amidation was screened with the 2-pyridyl protected isoquinolone and 2-pyridone derivatives (Scheme 2). Reaction was efficiently proceeded with various aryl sulfonylazides (Scheme 2, **3a**-**3d**). Further, aliphatic sulfonylazides also worked smoothly (Scheme 2, **3e**-**3f**). Interestingly, sterically more crowded sulfonylazide like (1*R*)-(−)-10-camphorsulfonylazide provided good yield of the desired product (Scheme 2, **3f**). To our delight, chemically different other azides like benzoyl azide and diphenyl phosphoryl azide afforded the C3-amidated quinolones with good to moderate yield (Scheme 2, **3g**-**3h**). Notably, coupling of isoquinolone with aziodoformate also worked albeit in poor yield (Scheme 2, **3i**). But, other azides like phenyl azide or benzyl azide did not furnish the desired products. Furthermore, except **3g** there was no other probable Curtius rearranged product observed during the reaction with benzoyl azide.[10] C6-haloisoquinolones offered very good yields of the desired products keeping the window open for further modification of isoquinolone ring (Scheme 2, **3j**-**3k**). Additionally, 2-pyrimidyl protected isoquinolone also afforded C3-amidated product in 83% yield (Scheme 2, 3**l**).



Scheme 2: C3 and C6 selective amidation of isoquinolones and 2-pyridones; Reaction Conditions: **1** (0.1 mmol), **2** (0.12 mmol), $[Cp^*IrCl_2]_2$ (2 mol%), $AgSbF_6$ (8 mol%), NaOAc (50 mol%), 12 h, 85 °C, 0.1 M. [a)] **1a** in 3 mmol scale, 36 h. [b)] Reaction time 24h.[c)] N_3CO_2Et was used 0.3

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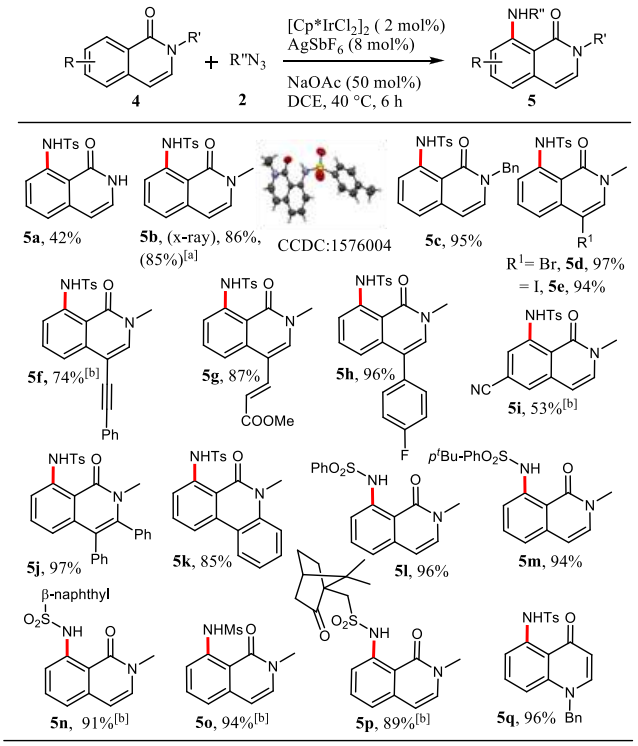
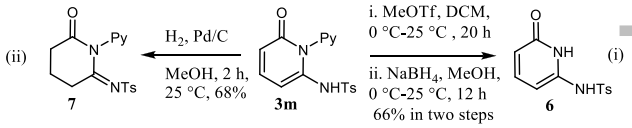
mmol. [d] at 60 °C. [e] at 100 °C. [f] at 80 °C. Pym = 2-pyrimidyl

We next explored the site-selective amidation of the 2-pyridone scaffold. Importantly, most electron deficient C6 position of 2-pyridone ring was amidated under the optimized conditions with admirable degree of regioselectivity (Scheme 2, **3m**-**3ab**). Electronically and sterically variant functional groups at the C3, C4 and C5 position of pyridyl protected 2-pyridone furnished the expected C6 amidated products with moderate to excellent yields. Electron donating groups at the C3 and C4 position of 2-pyridone moiety were well tolerated with moderate to very good yields (Scheme 2, **3n**-**3r**). However, electron withdrawing groups like CN, CF_3 or acetyl functional group at the C3 position of 2-pyridone and free hydroxyl group at the C4 position did not furnish the corresponding desired products in isolable amount. Halogens at the C5 position of 2-pyridone scaffold accomplished the desired products in moderate to excellent yield (Scheme 2, **3s**-**3t**). Further, sulfonylazides having wide steric and electronic profile afforded desired C6 amidated 2-pyridones under developed conditions (Scheme 2, **3u**-**3ab**) in good to excellent yields. For practical utility, **1a** could be converted into its C3-amidated product **3a** with 30-fold increased scale in 79% desired product yield (Scheme 2, **3a**).



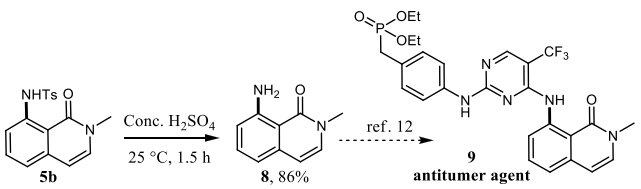
Scheme 3: C8 selective amidation of isoquinolones and 4-pyridone; Reaction Conditions: **4** (0.1 mmol), **2** (0.12 mmol), $[Cp^*IrCl_2]_2$ (2 mol%), $AgSbF_6$ (8 mol%), NaOAc (50 mol%), 6 h, 40 °C, 0.1 M. [a] **1a** in 2.5 mmol scale, 36 h. [b] at 80 °C.

Next, we examined the possibility of C8 amidation of isoquinolone derivative **4** (Scheme 3). Strikingly, the C8 amidated product was obtained in 42% yield from the parent isoquinolone scaffold without any protection group under the developed conditions (Scheme 3, **5a**). Further, the *NH*-alkyl protected isoquinolone derivatives afforded desired products in excellent yields (Scheme 3, **5b**-**5c**). C4-Halogen substituted iosquinolone derivatives accomplished the desired C8 amidated products in excellent yields (Scheme 3, **5d**-**5e**). Furthermore, alkyne, alkene or aryl substitution at this position of isoquinolone accomplished desired products in good to excellent yields (Scheme 3, **5f**-**5h**). Isoquinolone having electron withdrawing group like cyano group at its C6 position also afforded desired product albeit in moderate yield and at higher temperature (Scheme 3, **5i**). Importantly, more conjugated 3,4-diphenylisoquinolone or phenanthridone moieties also furnished desired amidated product in excellent yields (Scheme 3, **5j**-**5k**). Subsequently, various aromatic and aliphatic sulfonyl azides worked uninterruptedly to provide desired C8 amidated products with excellent yields (Scheme 3, **5l**-**5p**). Nitrogen containing relevant 4-quinolone scaffold was also amidated at its C5 position in high yield (Scheme 3, **5q**). The structure of the C8 amidated product **5b** was unequivocally confirmed by single x-ray crystallography (See supporting information for more details).[11] For scalability, **4b** could be converted into its C8-amidated product **5b** with 25-fold increased scale in 85% desired product yield (Scheme 3, **5b**).



Scheme 4: Transformations of C6 amidated 2-pyridone molecule

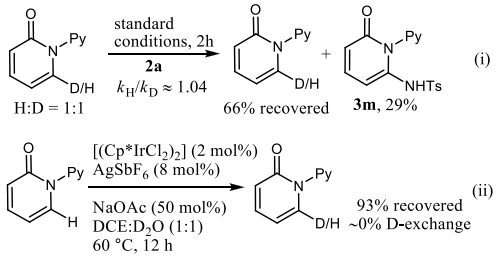
To confirm the extended synthetic utility of this developed reaction, further required modifications were carried out (Scheme 4). The pyridyl protecting group from the product **3m** was successfully removed *via* quaternization-reduction[12] to accommodate C6 amidated free pyridone derivative **6** in good yield (Scheme 4i).



Scheme 5: C8 Amidated isoquinolone product modification to bioactive compound.

Furthermore, the compound **3m** was partially reduced under atmospheric hydrogenation conditions to provide compound **7** (Scheme 4ii).

In addition to directing group deprotection and functional group transformations, C8 amidated isoquinolone derivative **5b** was undergone tosyl group deprotection to obtain 8-amino-2-methylisoquinolone **8**. Importantly, compound **8** could be easily extended to the known antitumor agent **9** (Scheme 5).[13]



Scheme 6: Kinetic isotope effect

To understand the plausible mechanism for this regioselective amidation, kinetic-isotope effect was calculated in competitive and parallel experiments (Scheme 6i). KIE value was obtained 1.08 by ^{1}H NMR analysis of the mixture of recovered starting materials from competitive experiments, while it was found 1.04 by isolating remaining starting materials from parallel experiments. Here in, both the studies recommended that C-H bond activation at C6-position of 2-pyridone was not the rate determining step in this transformation. No significant H/D-scrambling was observed at the C6 position of 2-pyridone moiety when **1m** was exposed with DCE/D_2O under standard reaction conditions (Scheme 6ii). This outcome reveals that more likely C-H bond metallation step is irreversible.

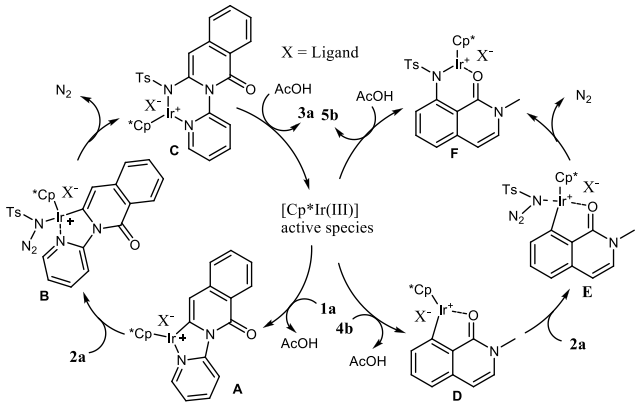


Figure 1: Plausible Mechanism

Based on the experiments and previous literatures [10a, 14], a plausible mechanism is shown in Figure 1. Initially, an active iridium complex is generated *via* ligand exchange with the help of Ag-salt. Next, upon coordination with the nitrogen atom of pyridine ring of **1a,** followed by acetate assisted C-H bond cleavage[14c-e] furnishes cyclometalated intermediate **A**. Afterwards, tosyl azide (**2a**) reacts with complex **A** to produce five-membered complex **B**. Further, release of N_2 and migratory insertion of complex **B** produced six-membered cyclic complex **C**. Finally, protodemetalation of **C** produces our desired amidated product **3a**. Alternatively, formation of an iridium nitrenoid species from **B** can occur through oxidative manner followed by insertion of the nitrenoid moiety to the the iridacycle may produce **C**.[14e-g] For the formation of C8 amidated product, coordination of active iridium complex with the keto group of **4b** and acetate assisted C-H bond cleavage generates the iridacycle complex **D.** Presumably, next few steps follow the similar way as previously described to provide **E** and **F**. Subsequent protodemetalation of **F** forms desired compound **5b**.

In summary, we have developed the iridium-catalyzed direct regioselective C3/C8-amidation of isoquinolones and C6-amidation of 2-pyridones using various azides. The substrate scope was broad with wide functional group tolerance. This amidation approach does not require extra oxidants and release N_2 as sole by-product. Due to ubiquitous availability of amidated isoquinolones and pyridones in bioactive natural products and pharmaceuticals, this protocol is expected to gather significant attention from industry and academia.

Experimental Section

Representative Method for the Synthesis of 3a and 5b:

1a (0.1 mmol) was taken in a 10 mL screw cap vial charged with a magnetic stirring bar and dissolved in 1 mL 1,2-DCE. Then [(Cp*$IrCl_2)_2$] (2 mol%), $AgSbF_6$ (8 mol%), NaOAc (50 mol%) and tosyl azide (0.12 mmol) were added to the reaction mixture. The reaction mixture was allowed to stir at 85 °C for 12 h under air. After completion of the reaction, it was directly loaded to the silica gel column and the product was purified by eluting with hexane-ethyl acetate mixture (1:1 to 0.5:9.5) to get product **3a** as pale yellow solid in 91% yield (35.6 mg). In a similar manner, compound **4b** was allowed to react under above mentioned conditions at 40 ºC for 6 h. The reaction mixture was directly loaded to the silica gel column and the product **5b** was purified by eluting with hexane-ethyl acetate mixture (9:1 to 1:1) in 86% yield (28.2 mg) as white solid.

Acknowledgements

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[11] CCDC 1576004 (**5b**) contains 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.

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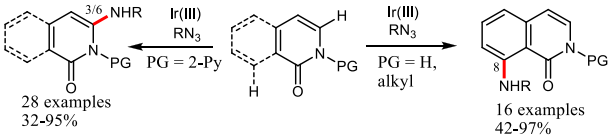

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