Discovery of Oxygen Induced Chemoselectivity in Pd-catalyzed C-H Functionalization: Cross Dehydrogenative Coupling *vs* C-H Amination

Sheba Ann Babu,[a,b] Sunil Varughese,[a,b] Jomon Mathew [c] and Jubi John *[a,b]

[a]Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram-695019, India.

[b]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India.

[c]Research and Post-graduate Department of Chemistry, St. Joseph's College, Devagiri, Calicut- 673008, India.

Email: jomonmathew@devagiricollege.org, jubijohn@niist.res.in

Abstract

The functionalization of unactivated C-H bonds at will for the strategic introduction of bonds or functionalities have been a matter of extensive investigation for the last couple of decades. We have come across a substrate namely, 5-benzoyl-pyrrolo[2,1-a]isoquinoline in which three different functionalizable C-H bonds were identified that could be judiciously transformed site selectively for the generation of complex polyring fused N-heterocycles. At first, we attempted a Pd-catalyzed cross-dehydrogenative coupling in 5-benzoyl-pyrrolo[2,1-a]isoquinoline towards the synthesis of 8H-indeno-pyrrolo[2,1-a]isoquinolinones. Later, we identified a hitherto unknown oxygen induced palladium catalyzed selective C-H amination in 5-benzoyl-pyrrolo[2,1-a]isoquinoline towards a pentacene viz., 9H-indolo-pyrrolo[2,1-a]isoquinoline. Finally, we came across an unexpected site selective C-H amination towards the formation of multiring fused benzazepine which is believed to form due to its stability and to the higher electron density at the reaction centre on isoquinoline ring.

Introduction

Organic synthesis has taken a huge stride with the advancements in the functionalization of unactivated C-H bonds directly to carbon-carbon or carbon-heteroatom bonds.1 The initial reports on selective C-H functionalization relied on free radical transformations2 and this was followed by the development of metal complexes that could activate C-H bonds.3 For the last 2 decades, organic chemists have taken up the challenge of designing substrates or environments that would enable selective functionalization of

unactivated C-H bonds.4 These developments have indeed shortened the way that retrosynthetic approaches are planned towards complex organic molecules thereby improving step and atom economy.

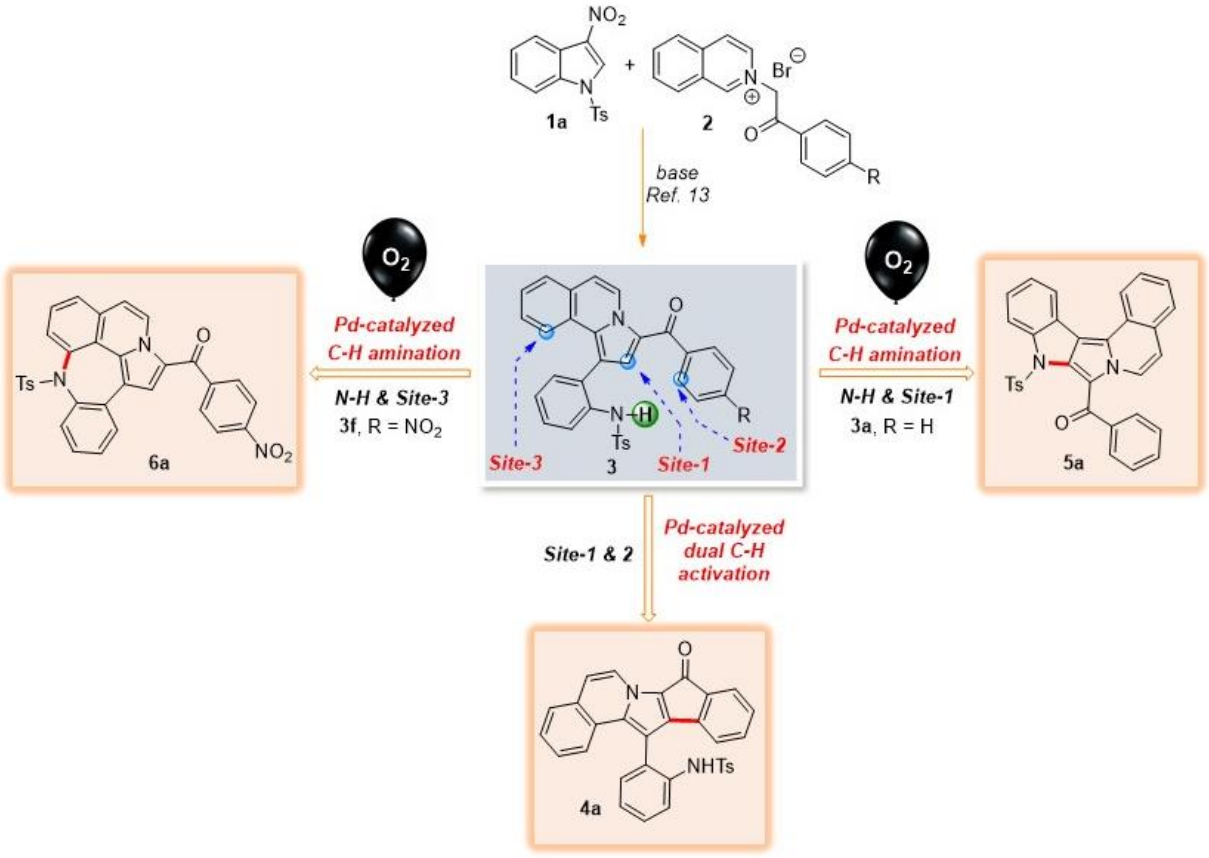
Cross-dehydrogenative coupling (CDC) or dual C-H activation is presently considered as an inevitable tool for the generation of carbon-carbon bonds both in intermolecular and intramolecular fashion.5 This powerful methodology which doesn't require any preactivation of reaction centers have been utilized for the synthesis of carbocycles and heterocycles under both transition metal catalyzed and metal-free conditions.6 Another equally important transformation is C-H amination which also is a heavily relied strategy for generating substituted amines or N-heterocycles.7 The initial reports in this line came from the groups of Stahl and Buchwald wherein the former reported Pd-cataylzed oxidative amination of unactivated alkenes towards substituted amines8 and the later reported Pd-catalyzed intramolecular C-H amination towards carbazoles.9

Achieving high position selectivity in C-H functionalization among similar reactive sites is still a challenging task for chemists.10 Site selective C-H functionalization is now a days effected by either utilizing the stereoelectronic differences in reactive centers or by installing appropriate directing groups that can limit the reactivity to particular centers of interest.11 In this article, we report our observations on site-selective C-H functionalization between three different reactive centers towards polyring fused N-heterocycles. In continuation on our interest in the chemistry of electrophilic benzannulated heterocycles,12 we recently reported an unexpected observation of pyrrolo[2,1-a]isoquinoline 3a formation from the reaction of electrophilic indoles and isoquinolinium methylides (Scheme 1).13

In the substrate 5-benzoyl-pyrrolo[2,1-a]isoquinoline 3a (Scheme 1), we identified two fucntionalizable C-H centers, at site-1 & site-2. Under Pd-catalyzed cross-dehydrogenative coupling conditions, we hypothesized that an intramolecular cyclization will happen between site-1 and site-2 affording 8H-indeno-pyrrolo[2,1-a]isoquinolinone moiety 4a. In addition, by tuning the reaction conditions, we postulated that a C-H amination could be effected between N-H and site-1 for the synthesis of 9-tosyl-9H-indolo-pyrrolo[2,1-a]isoquinoline 5a. These investigations resulted in unraveling an

oxygen induced chemoselectivity which to the best of our knowledge is unknown thus far. Finally, during the investigations on the generality of C-H amination reaction, we came across an unprecedented observation of formation of a polyring fused azepine 6a by the C-H amination between N-H and site-3. In this article, we describe in detail about our examinations on Pd-catalyzed cross-dehydrogenative coupling and C-H aminations towards polyring fused N-heterocycles.

Scheme 1. Pd-catalyzed site selective C-H functionalization in 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline towards polyring fused *N*-heterocycles

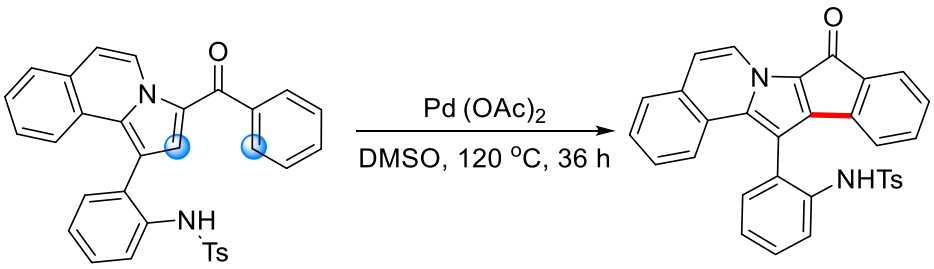


Results and Discussion

We initiated our investigations by synthesizing 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline **3a** from 3-nitro-*N*-tosyl indole **1a** and 2-(2-oxo-2-phenylethyl)isoquinolin-2-ium-bromide **2a** (Scheme 1).[13] By keeping **3a** as a substrate, we planned to examine the possibility of Pd-catalyzed cross-dehydrogenative coupling for activating C-H bonds at sites 1&2 as shown in Scheme 1. The test reaction was set up with **3a** in the presence 10 mol% of $Pd(OAc)_2$

in DMSO at 120 °C for 36 h (Scheme 2). As expected, we could isolate the product 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-one **4a** formed by dual C-H activation in 30% yield. The structure of **4a** was established with various spectroscopic methods and single crystal X-ray analysis.[14]

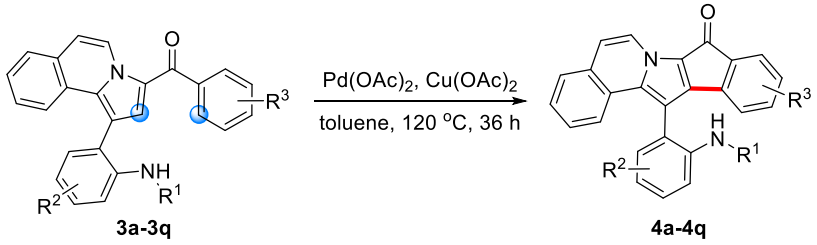
Scheme 2. Pd(II) mediated cross-dehydrogenative coupling of pyrrolo[2,1-*a*]isoquinolines



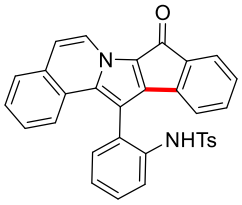
3a **4a** (30%)

The optimization of Pd(II) mediated cross-dehydrogenative coupling towards functionalized 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-one was carried out with **3a** as the substrate.[14] Under the optimized conditions [$Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv.), toluene, 120 °C, 36 h] for the Pd-catalyzed cross-dehydrogenative coupling towards functionalized 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-one, we explored the scope of the reaction using different 5-benzoyl pyrrolo[2,1-*a*]isoquinolines, the results of which are summarized in Table 1. Different starting substrates **3** for this study was synthesized by following our methodology from a series of electrophilic indoles and isoquinolinium salts.[13]

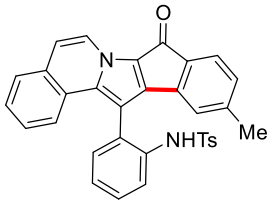
Table 1. Generality of Pd-catalyzed cross-dehydrogenative coupling[a]



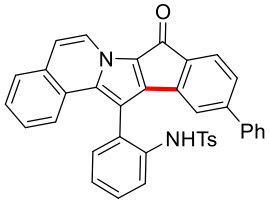
3a-3q **4a-4q**



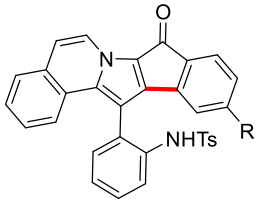
4a (84%)



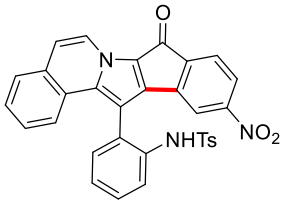
4b (70%)



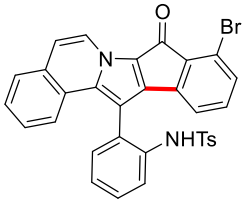
4c (64%)



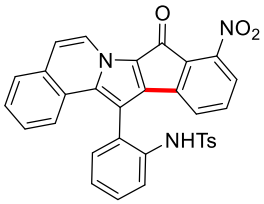
4d, R = F (40%)
4e, R = Cl (64%)



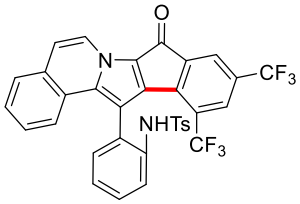
4f (70%)



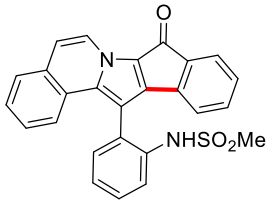
4g (50%)



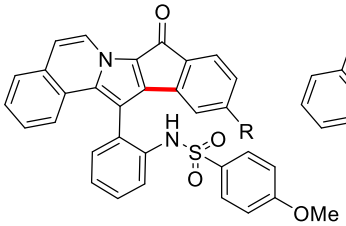
4h (40%)



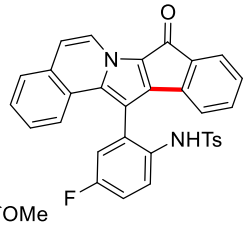
4i (53%)



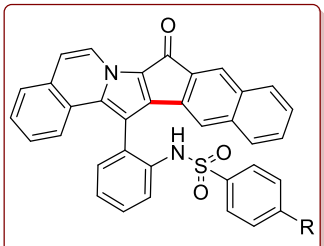
4j (60%)



4k, R = H (62%)
4l, R = CH_3 (55%)
4m, R = Cl (52%)
4n, R = NO_2 (51%)



4o (49%)



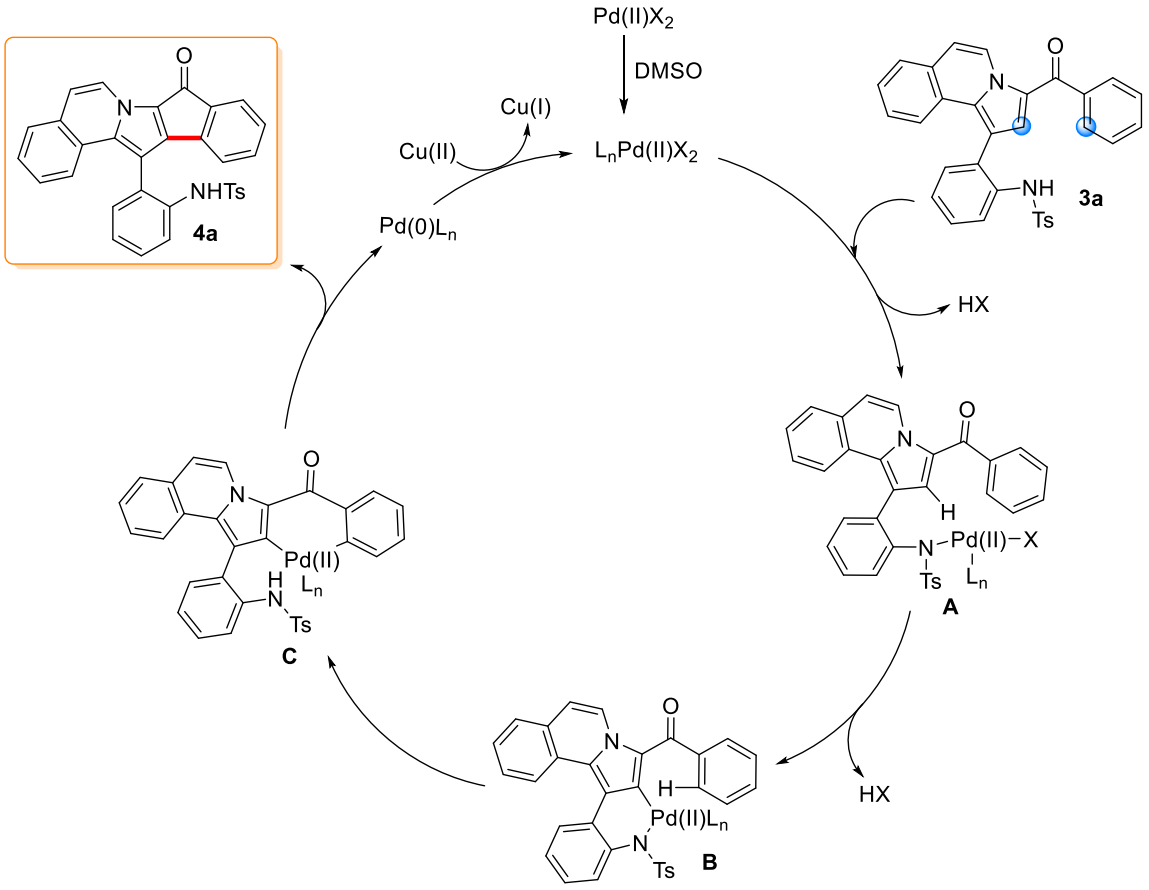
4p, R = CH_3 (60%)
4q, R = OCH_3 (55%)

[a]Reaction conditions: **3** (1.0 equiv., 0.20 mmol), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv.), toluene (2.0 mL), 120 °C, 36 h.

We initiated the studies (Table 1) by using 5-benzoyl pyrrolo[2,1-*a*]isoquinolines with substituents on the benzoyl moiety. In this line, we could introduce methyl (in **4b**) and phenyl (in **4c**) substituents on the indanone ring. Next, we were able to synthesize 8*H*-indenopyrrolo[2,1-*a*]isoquinolin-8-ones **4d** and **4e** with halogen substitutions (F and Cl) on the indanone ring. The Pd-catalyzed cross-dehydrogenative coupling conditions also worked well with a NO_2-group on the benzoyl moiety thereby furnishing **4f** in 70% yield. By the synthesis of **4g**, **4h** and **4i**, we could demonstrate that substituents can be introduced at any position of the indanone ring by starting with the appropriately functionalized 5-benzoyl pyrrolo[2,1-*a*]isoquinolines. We also tried reactions with substrates having different *N*-substituents such as -SO_2Me and -SO_2Ph-4OMe and all these afforded the corresponding products **4j** to **4n** in moderate to good yields. We could synthesize **4o** in 49% yield with a F-substituent on the aryl group attached to the pyrrole ring. Finally, the methodology could be extended for the synthesis of six-ring fused heteroacenes **4p** and **4q** by starting from suitably substituted 5-naphthoyl pyrrolo[2,1-*a*]isoquinolines.

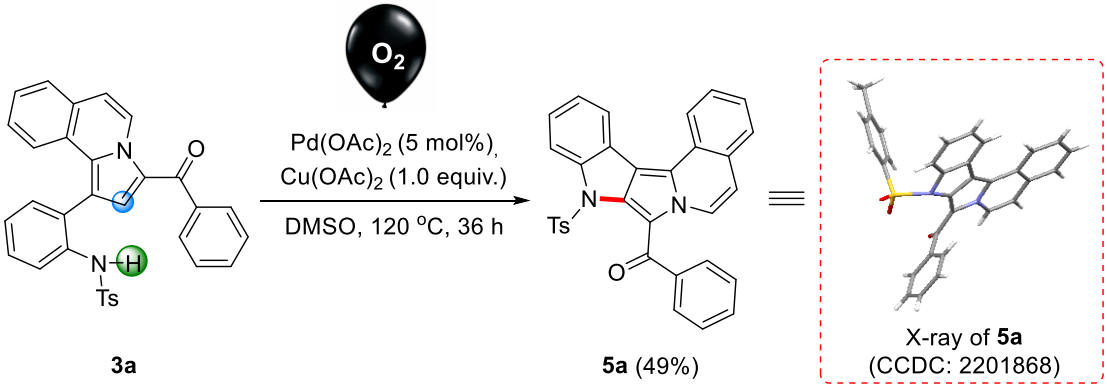
Based on our observations and by following reported literature, we propose a mechanism for the Pd-catalyzed cross-dehydrogenative coupling towards indenopyrrolo[2,1-*a*]isoquinolines (Scheme 3).[5,6,15] As per the theoretical investigations carried out by Zierkiewicz and Privalov and also based on the postulation of many others we believe that DMSO acts not only as a solvent but also as a ligand which stabilizes the active Pd-species.[16] The first step of the catalytic cycle will be the formation of N-Pd bond as in intermediate **A** from **3a** and the Pd-catalyst.[7,8] Next, a selective activation of the C-H bond in pyrrole ring takes place to form a six-membered palladacycle **B**.[9] A Fujiwara-Moritani type process is then believed to occur in intermediate **B** *via* a C-H bond activation in the benzoyl moiety to furnish the new six-membered cyclic Pd(II) intermediate **C**.[15,17] Subsequently, the reductive elimination occurs in **C** affording the product **4a** and Pd(0). Finally, the Pd(II) species is regenerated by the oxidation with $Cu(OAc)_2$ to complete the catalytic cycle.

Scheme 3. Plausible mechanism for the synthesis of indenopyrrolo[2,1-*a*]isoquinolines [X = OAc and L = DMSO]



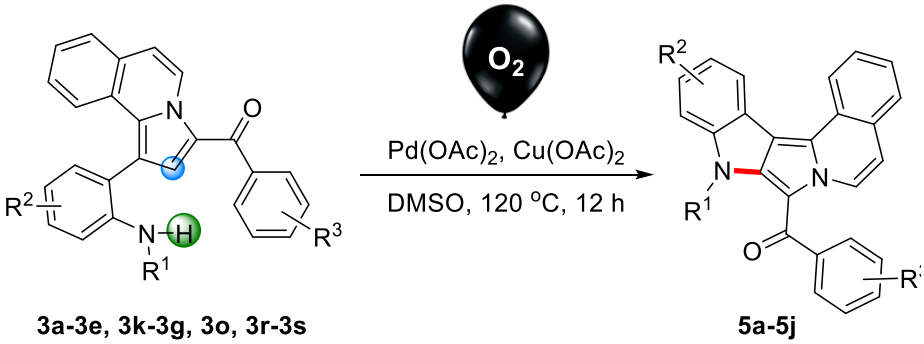
The metal-catalyzed intramolecular C−H amination provides a straightforward approach for the synthesis of *N*-containing heterocycles such as carbazoles, benzimidazoles, indazoles, indolines etc.[18] In this line, we targeted the C-H amination between the N-H and site-1 of pyrrolo[2,1-*a*]isoquinolines (Scheme 1) towards the synthesis of indolo-pyrrolo[2,1-*a*]isoquinoline. During our optimization studies on Pd-catalyzed cross-dehydrogenative coupling with **3a**, we came across a combination of $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.) under O_2 atmosphere in DMSO. The reaction at 120 °C was allowed to continue for 36 h after which we could isolate indolo-pyrrolo[2,1-*a*]isoquinoline **5a** in 49% yield along with **4a** in minor amounts (Scheme 4). Interestingly, in the present observation, the presence of oxygen has changed the course of the reaction furnishing the C-H amination product in major quantity and such an oxygen induced chemoselective transformation is rare.

Scheme 4. Pd(II) catalyzed site-selective C-H activation towards indolo[3',2':3,4]pyrrolo[2,1-*a*]isoquinoline

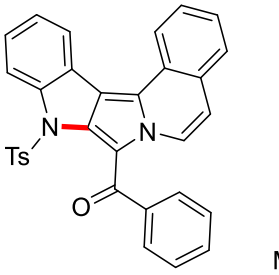


A systematic investigation was then carried out to find the best condition for Pd-catalyzed site selective C-H amination with **3a** as the substrate.[14] With the optimized conditions in hand [$Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.), DMSO, O_2, 120 °C, 12 h], we explored the scope of the reaction using different pyrrolo[2,1-*a*]isoquinolines, the results of which are summarized in Table 2. First, we repeated the Pd-catalyzed C-H amination with **3a** from which the product **5a** was obtained in 54% yield. Then, we changed the substituent at the *N*-atom from Ts- to 4-OMe-C_6H_4-SO_2- and from the reaction the corresponding indolo-pyrrolo[2,1-*a*]isoquinoline **5b** was isolated in 53% yield. We could synthesize indole fused pyrrolo[2,1-*a*]isoquinolines **5c** and **5d** with halogens such as F and Br on the indole ring in satisfactory yields. Next, we evaluated the variations in substitutions on the benzoyl group attached to the pyrrole ring. The reaction was found to be compatible with electronically diverse functionalities at the para position, including electron donating methyl (**5e**) and phenyl groups (**5f**). In addition, halogens such as F, Cl and Br on different positions of the benzoyl group were also tolerated under these reaction conditions affording the products **5g** to **5j**. In all the above cases, we could observe the formation of indenopyrrolo[2,1-*a*]isoquinolines in trace amounts.

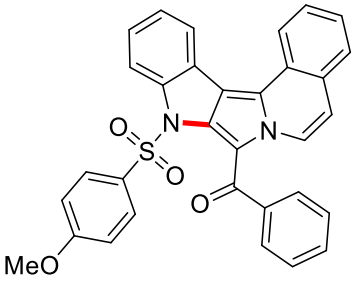
Table 2. Pd-catalyzed C-H amination of pyrrolo[2,1-*a*]isoquinolines towards indolopyrrolo[2,1-*a*]isoquinolines[a]



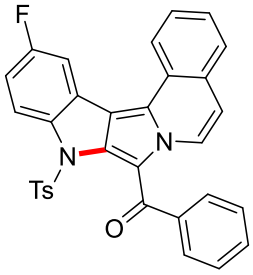
3a-3e, 3k-3g, 3o, 3r-3s **5a-5j**



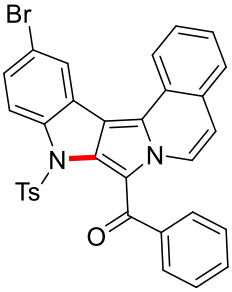
5a (54%)



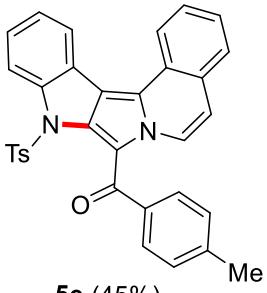
5b (53%)



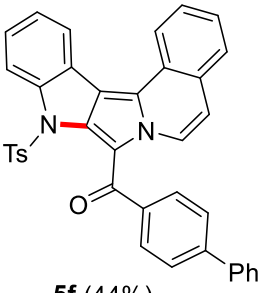
5c (50%)



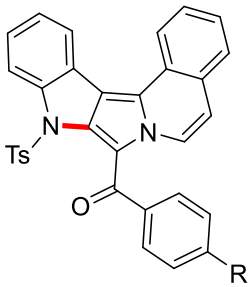
5d (49%)



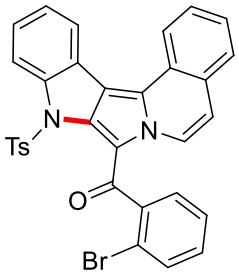
5e (45%)



5f (44%)



5g, R = 4-Cl (40%)
5h, R = 4-F (39%)
5i, R = 4-Br (40%)

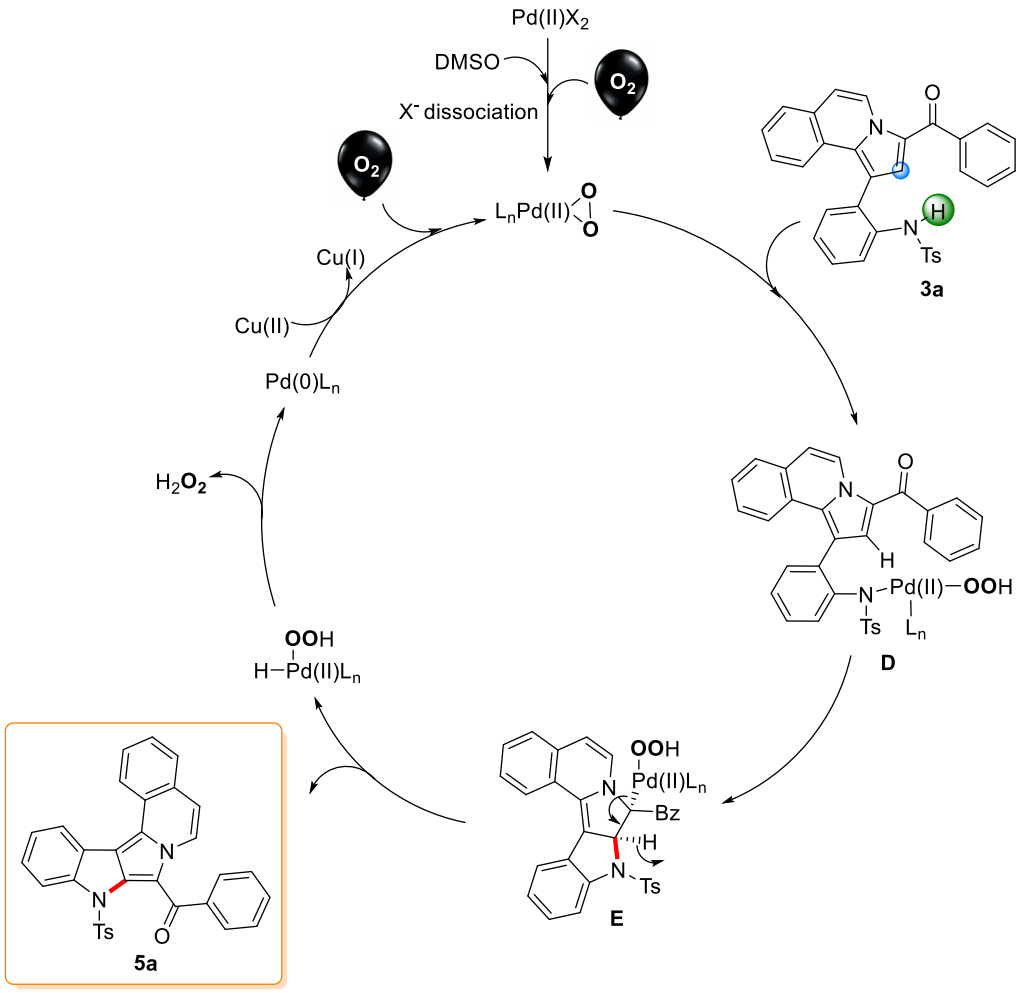


5j (41%)

[a]Reaction conditions: **3** (1.0 equiv., 100 mg), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.), O_2 (1.0 atm), DMSO (0.1 M), 120 °C, 12 h.

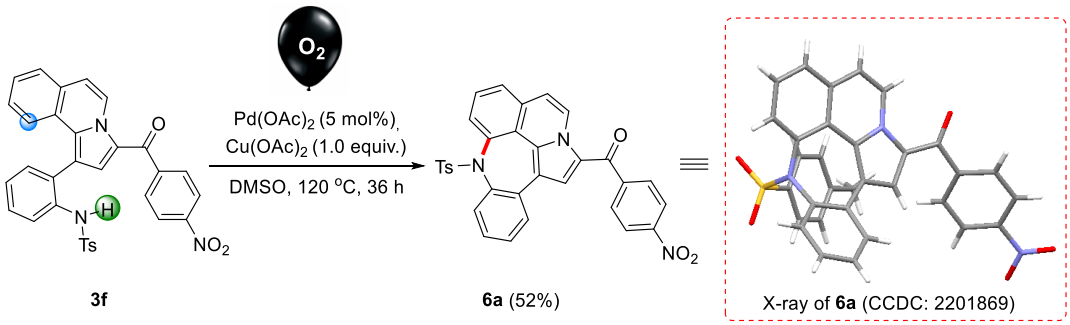
This oxygen-induced chemoselective synthesis of indolo-pyrrolo[2,1-*a*]isoquinoline **5** made us believe that oxygen might be involved from the start of the catalytic cycle. We hypothesize that initially DMSO interacts with the catalyst $Pd(OAc)_2$ to form a $Pd(0)(DMSO)_n$ species as per the theoretical investigations carried out by Zierkiewicz and Privalov.[16] Stahl and co-workers have investigated in detail on the Pd-catalyzed aerobic oxidations promoted by ligands.[19] By following the literature precedents,[20] we believe that $Pd(0)(DMSO)_n$ is then oxidized by oxygen to form the active η^2-peroxo-Pd(II) species. We consider that the presence of oxygen forces the reaction to take a Wacker-like pathway as proposed by Buchwald and Monguchi for the oxygen promoted Pd-catalyzed synthesis of carbazoles.[9,21] In this line, the complexation of η^2-peroxo-Pd(II) intermediate to the *N*-centre in **3a** takes place generating the amide **D**. Next, a Wacker-like addition of the Pd-species across the pyrrole double bond will give rise to the intermediate **E**. A β-hydride elimination then happens in **E** releasing the indolo-pyrrolo[2,1-*a*]isoquinoline **5** and H-Pd(II)Ln-OOH moiety. Reductive elimination happens in H-Pd(II)Ln-OOH releasing the $Pd(0)L_n$ and H_2O_2. The $Pd(0)L_n$ is then reoxidized by $Cu(OAc)_2$ and O_2 to continue the catalytic cycle (Scheme 5).

Scheme 5. Plausible mechanism for the O_2 induced Pd-catalyzed C-H amination for synthesis of *N*-Ts-indolopyrrolo[2,1-*a*]isoquinolines [X = OAc, L = DMSO]



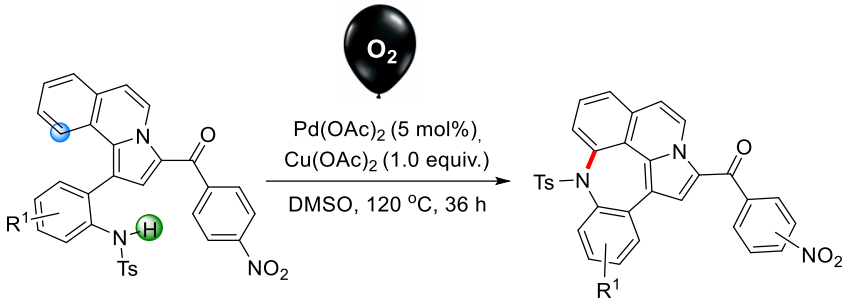
We came across a serendipitous observation of the activation of C-H bond in the isoquinoline ring (site-3, Scheme 1) in **3f** during the generality studies of Pd-catalyzed C-H amination. The reaction of appropriately functionalized 5-(4-nitro benzoyl)-pyrrolo[2,1-*a*]isoquinolines **3f** under the optimized conditions for O_2 promoted Pd-catalyzed C-H amination furnished tetra-ring-fused azepine **6a** in 52% yield. The structure of **6a** was established by various spectroscopic analysis and further confirmed by single crystal X-ray analysis (Scheme 6). We observed that the reaction does not proceed further after 36 h and from this reaction mixture we could recover unreacted **3f**.

Scheme 6. Pd-catalyzed site-selective C-H activation towards tetra-ring-fused azepine 6a

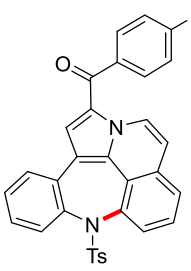


We were excited to observe the formation of this multiring fused azepine scaffold and we went on in exploring the scope of the reaction by starting from different 5-benzoyl-pyrrolo[2,1-*a*]isoquinolines with NO_2-group on the phenyl ring (Table 3). With this methodology, we could introduce halogens such as Br and F on the fused benzene ring thereby generating multiring fused azepines **6b**, **6c** and **6d** in moderate yields. Moreover, changing the nitro group to meta position of the benzene ring in the benzoyl substituent also gave a positive result and we isolated the corresponding product **6e** in 51% yield. As mentioned above, we could recover unreacted starting compounds in all cases.

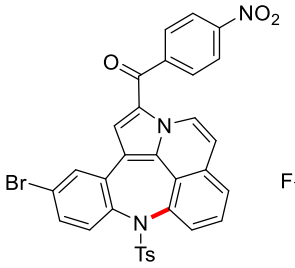
Table 3. Pd-catalyzed C-H amination of pyrrolo[2,1-*a*]isoquinolines towards multiring fused azepines[a]



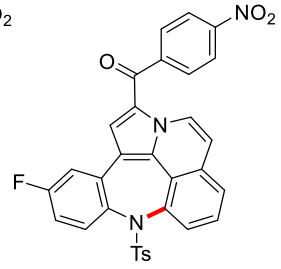
3f, 3t-3w **6a-6e**



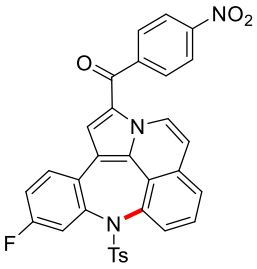
6a (52%)



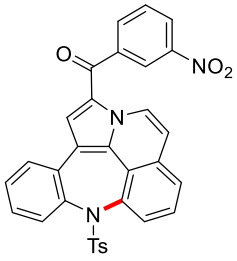
6b (50%)



6c (53%)



6d (45%)



6e (51%)

[a]Reaction conditions: **3** (1.0 equiv., 100 mg), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv.), O_2 (1.0 atm), DMSO (0.1 M), 120 °C, 36 h.

The factors influencing the site selective C-H functionalization towards different fused N-heterocycles were then analyzed. The single crystal X-ray structures of **3a** and **3f** (Figure 1) and density functional theory calculations at the B3LYP-D3/6-31G(d,p)[22] level showed that the orientation of tosylamine group, C-H bond electron density at the sites 1 and 3 and the thermodynamic stability of possible products will be decisive in the site selective C-H amination.

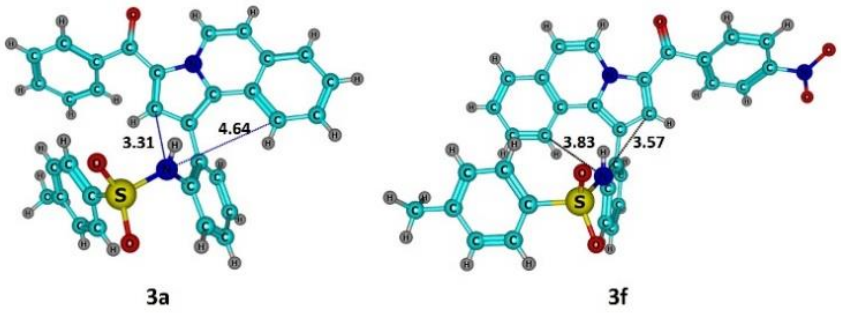


Figure 1. X-ray structures of 3a (CCDC: 2201867) and 3f (CCDC: 2174937). [N-C distances are given in Å].

The X-ray structure of **3a** shows the closeness of *N*-centre to site-1 (3.31 Å) compared to site-3 (4.64 Å). Therefore, the binding of $Pd(OAc)_2$ to nitrogen would lead to the C-H activation at site-1. It can further proceed to the C-H activation of phenyl ring (site-2) forming **4a** which is thermodynamically more stable than the possible C-H aminated products (Figure 2).

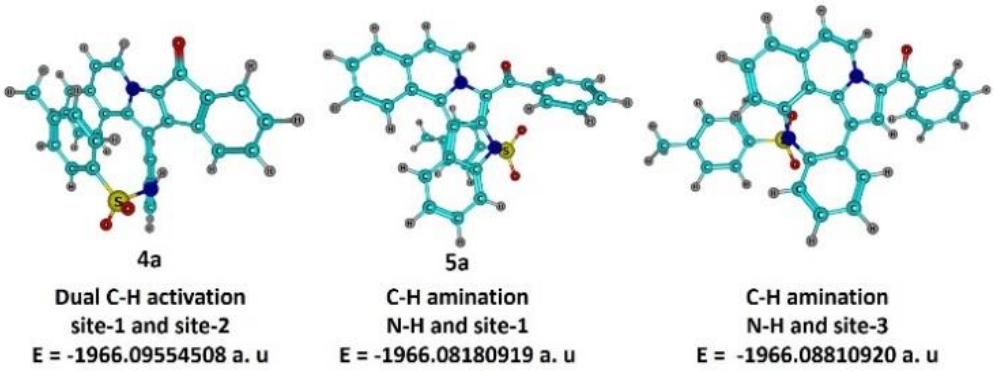


Figure 2. Optimized structures of the possible C-H activation products of 3a along with energy values.

Binding of oxygen to $Pd(OAc)_2$ would hinder the phenyl C-H activation and results in C-H amination to form **5a**. In the case of **3f**, dual C-H activation product is thermodynamically more stable than the possible C-H amination products and therefore **4f** forms (Figure 3). Binding of oxygen to Pd center hinders the activation of phenyl C-H (site-2) and the isoquinoline C-H undergoes activation to form **6a** albeit N is slightly closer to site-1 (3.57 Å) than site -3 (3.83 Å). This can be accounted to the higher electron density at site-3 and the stability of **6a** (more stable than site -1 C-H aminated product by 3 kcal/mol). Molecular

electrostatic potential at the carbon nucleus on site -1 is -14.74153 a. u while that at site -3 is -14.74500 a. u suggests a higher electron density at site-3 than site-1.[23]

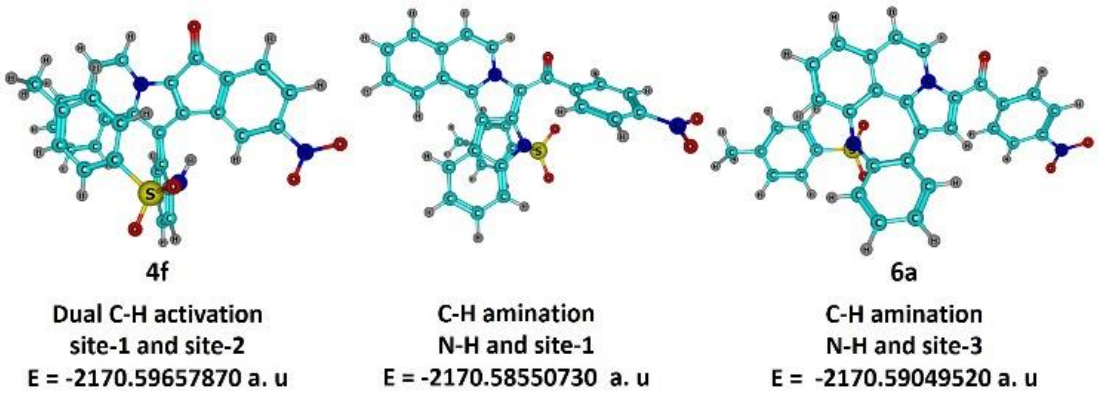


Figure 3. Optimized structures of the possible C-H activation products of 3f along with energy values.

Conclusions

To conclude, we have unraveled an interesting Pd-catalyzed site selective C-H functionalization towards multiring fused *N*-heterocycles. These observations were made on 5-benzoyl-pyrrolo[2,1-*a*]isoquinoline scaffold, where we could identify three sites for C-H functionalization and a *N*-centre which could participate in C-H amination. The experimental and theoretical investigations have shown that there is a preference for Pd-catalyzed cross dehydrogenative coupling towards 8*H*-indeno-pyrrolo[2,1-*a*]isoquinolinone derivatives. Then during our attempts for selective C-H amination, we came across a unique and previously unknown O_2 induced chemoselectivity forcing the formation of 9*H*-indolo-pyrrolo[2,1-*a*]isoquinoline scaffold over the CDC product. We believe that this selectivity is induced by O_2 which gets incorporated in the active Pd-species driving the reaction to take Wacker-type pathway leading to C-H amination When we tried the Pd-catalyzed C-H amination with a substrate bearing a NO_2-group on the benzoyl moiety of starting substrate, we found that the C-H amination was taking place preferentially at the isoquinoline ring. This result can be attributed to the higher electron density at the reactive centre on isoquinoline ring and also to stability of multiring fused benzazepine in comparison with the pentacene regioisomer. Currently we are investigating the reaction pathway in detail both experimentally and theoretically and also are trying to apply the site selectivity in similar scaffolds.

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest

ACKNOWLEDGMENT

SAB thank CSIR for research fellowship. JJ thanks CSIR (OLP-162539, HCP-029, MLP-064) and AICTE (GAP-161939) for financial assistance. The authors thank Prof. Mahesh Hariharan and Mr. Alex Andrews of IISER-Thiruvananthapuram for single crystal X-ray analysis. The authors also thank Mrs. Saumini Mathew and Mrs. Viji S. of CSIR-NIIST for recording NMR and mass spectra respectively.

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