Organic LETTERS

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# Palladium(II)/*N*-Heterocyclic Carbene-Catalyzed Direct C−H Acylation of Heteroarenes with *N*-Acylsaccharins

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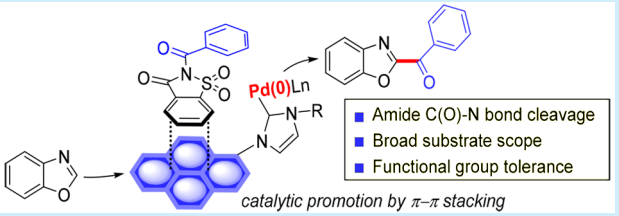
Supporting Information

**ABSTRACT:** *N*-Acylsaccharin represents a facile acyl group transfer agent to heteroarenes in the presence of Pd(II)/NHC complexes appended with a pyrene unit. Catalytic acylation of heteroarenes was enhanced by the noncovalent interaction between the pyrene unit and substrates. High functional group tolerance, broad substrate scope, and moderate to good yields of 2-acylated azoles are added features of this method.




Azoles, especially 2-substituted azoles (aryl and acyl), are an important structural motif prevalent in biological systems, pharmaceuticals, agriculture, and functional materials.[1,2] Of late, transition-metal-catalyzed organic transformations have emerged as one of the attractive and practical methods for forging C−C bonds which lead the way for the direct C-2 functionalization of azoles.[3] Besides the conventional synthesis[4] of 2-substituted azoles, other recent methods include the palladium-catalyzed carbonylative cross-coupling reaction (Figure 1a),[5] decarboxylative cross-coupling approach (Pd (Figure 1b)[6] Ni[7] and Co[8] catalyzed), cycloetherification method (Figure 1c),[9] and C−H functionalization via isocyanide insertion (Figure 1d).[10] Nevertheless, most of the reported methodologies suffer from certain drawbacks such as uptake of CO, harsh reaction conditions, longer reaction time, assembly of multicomponents, and demanding prefunctionalized substrates.[11] Amides could be an excellent choice as an electrophile as they are ubiquitous in Nature, which governs the biological, materials, and structural properties.[12] However, using amides as a functional group transfer agent is impaired due to the resonance stabilization, resulting from the orbital overlap between the nitrogen lone pair ($n_N \rightarrow \pi^*_{C=O}$) and the antibonding orbital of the carbonyl group.[12a] Recently, a trendsetting contribution by Garg et al. unveiled the utility of the stable and rigid amides as electrophilic coupling partners with the intervention of transition metal catalysts.[13] Strategically, the C(O)−N bond is activated by using twisted amides, which interrupt the resonance stabilization and pave the way for oxidative addition of transition-metal catalysts and subsequent elusive organic transformations.[14]

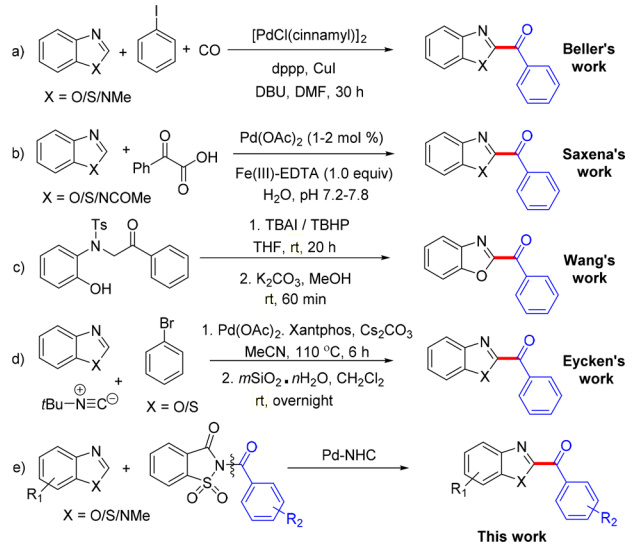



**Figure 1.** Synthesis of 2-acylated azoles: previous (a−d) and (e) this work.

Szostak and co-workers efficiently exploited the amides bestowed with geometrical distortion in many of the catalytic cross-coupling reactions.[15] In addition, amides proved to be a good acylating agent by reacting with aryl boronic acid,[13b,15a,16] organozinc halides,[17] alcohols,[13a] and cyclic and acyclic amines.[18] *N*-Functionalized saccharin, in particular, acted as an excellent functional group transfer agent (resonance energy 2.0 kcal/mol)[19] for acylation,[20] aryloxycarbonylation,[21] formylation,[22] and thiolation.[23] Accordingly, *N*-functionalized saccharin has gained impetus as an electrophilic transfer agent owing to its interesting traits: it is economical, easily accessible, and shelf-stable. Its geometric distortion enhanced the activation of the C(O)−N bond. Recently, our group has developed a method comprising tailor-made Pd−NHC catalyst bearing naphthalimide and bis-naphthalimide wingtip substituents on an NHC ligand promoting regioselective heteroannulation of tertiary propargyl alcohols and *o*-haloanilines to form 2-alkenylindoles.[24] Herein, we report a general and convenient synthesis of 2-acylazoles catalyzed by air-stable Pd−NHC complexes (attached with pyrene wingtip substituents) by the reaction of azoles with *N*-acylsaccharin via challenging amide C(O)−N bond activation.

**Received:** September 14, 2017

DOI: 10.1021/acs.orglett.7b02877
*Org. Lett.* XXXX, XXX, XXX−XXX

Initially, we set out to explore the effective Pd catalyst. Headway was made by designing and synthesizing a series of pyrene-based Pd−PEPPSI catalysts **D1**−**D5** with wingtip substituents such as ar-alkyl and alkyl groups (Figure 2).

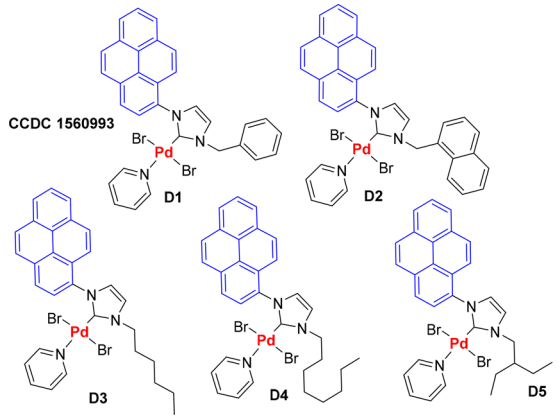
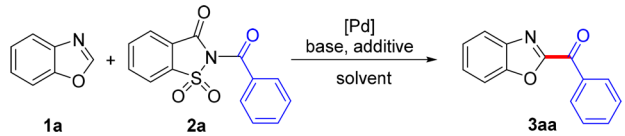



**Figure 2.** Structures of carbene ligands and synthesized pyrene based Pd−NHC catalysts.

Pyrene-substituted azolium salts **C1**−**C5** were prepared by treating the 1-(pyren-1-yl)-1*H*-imidazole with various ar-alkyl/alkyl halides. Subsequently, palladation of **C1**−**C5** with $PdCl_2$ furnished **D1**−**D5** complexes which were characterized by multinuclear NMR and HRMS (see the Supporting Information (SI)). The molecular structure of **D1** was determined by X-ray crystallography, and the Pd−$C_{carbene}$ distance was found to be 1.973(9) Å (see the SI). The catalytic efficacies of **D1**−**D5** were examined in acylation of heteroarenes by direct C−H bond functionalization reaction. We commenced our investigation by choosing benzoxazole **1a** as a coupling partner and *N*-benzoylsaccharin **2a** as an electrophilic source for the benzoyl group to form 2-benzoylated benzoxazole **3aa** in the presence of a well-examined palladium catalyst system ($Pd(OAc)_2/PPh_3$) and $K_2CO_3$ as a base in THF at 65 °C for 16 h (Table 1). Delightfully, the desired product **3aa** was observed, but in low yield (15%). Predictably, **3aa** was not observed in the absence of palladium salts (entries 1−2). To improve the yield of **3aa**, we screened phosphine ligands ($PCy_3$ and XPhos), bases ($Na_2CO_3$, NaO-*t*-Bu, KO-*t*-Bu, $Et_3N$, and DBU), additives (TBAB and DMAP), and solvents (THF, 1,4-dioxane, and MeCN) (entries 3−10). Combination of $Et_3N$, DMAP, and MeCN improved the yield of the acylation reaction to 35% (entry 11). When IPr was employed in lieu of the phosphine system, it gave 55% yield with $Et_3N$ as base and DMAP as an additive in MeCN at 65 °C for 16 h (entry 12). This result prompted us to evaluate our synthesized Pd−NHCs **D1**−**D5**. Meanwhile, use of the ligand **C1** with $Pd(OAc)_2$ under the same conditions improved the yield of **3aa** to 62% (entry 13). Interestingly, **D1** proved to be the best catalyst for acylation of heteroarenes (78%) (entry 14). No product was observed in the case of nonpolar solvents such as toluene and chloroform, whereas polar aprotic solvents were found to be effective (in the order of MeCN > DMF > DMSO) (entries 15−18). Changes in the time, temperature, and catalytic loading from 16 to 24 h (entry 19), 65−85 °C (entries 20 and 21), and 5−2.5 mol % (entry 22), respectively, deters the yield of **3aa**. Consistently, **D2**−**D5** (entries 23−26) was outperformed by **D1** in the acylation of heteroarenes.

Having established the new catalytic system, substrate scope for acylation was examined and a variety of 2-acylated azoles

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | base | catalyst | additive | solvent | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $K_2CO_3$ | | | THF | |
| 2 | $K_2CO_3$ | $Pd(OAc)_2/PPh_3$ | | THF | 15 |
| 3 | $Na_2CO_3$ | $Pd(OAc)_2/PPh_3$ | | THF | |
| 4 | NaO*t*-Bu | $Pd(OAc)_2/PPh_3$ | | dioxane | |
| 5 | KO*t*-Bu | $Pd(OAc)_2/PPh_3$ | | dioxane | |
| 6 | $Et_3N$ | $Pd(OAc)_2/PPh_3$ | | MeCN | 20 |
| 7 | $Et_3N$ | $Pd(OAc)_2/PPh_3$ | TBAB | MeCN | 25 |
| 8 | $Et_3N$ | $Pd(OAc)_2/PCy_3$ | DMAP | MeCN | 30 |
| 9 | $Et_3N$ | $Pd(OAc)_2$/XPhos | DMAP | MeCN | 20 |
| 10 | DBU | $Pd(OAc)_2/PPh_3$ | DMAP | MeCN | 15 |
| 11 | $Et_3N$ | $Pd(OAc)_2/PPh_3$ | DMAP | MeCN | 35 |
| 12 | $Et_3N$ | $Pd(OAc)_2$/IPr | DMAP | MeCN | 55 |
| 13 | $Et_3N$ | $Pd(OAc)_2$/**C1** | DMAP | MeCN | 62 |
| **14** | **$Et_3N$** | **D1** | **DMAP** | **MeCN** | **78** |
| 15 | $Et_3N$ | **D1** | DMAP | toluene | |
| 16 | $Et_3N$ | **D1** | DMAP | $CHCl_3$ | |
| 17 | $Et_3N$ | **D1** | DMAP | DMF | 38 |
| 18 | $Et_3N$ | **D1** | DMAP | DMSO | 10 |
| 19 | $Et_3N$ | **D1** | DMAP | MeCN | 60[c] |
| 20 | $Et_3N$ | **D1** | DMAP | MeCN | 72[d] |
| 21 | $Et_3N$ | **D1** | DMAP | MeCN | 70[e] |
| 22 | $Et_3N$ | **D1** | DMAP | MeCN | 66[f] |
| 23 | $Et_3N$ | **D2** | DMAP | MeCN | 55 |
| 24 | $Et_3N$ | **D3** | DMAP | MeCN | 65 |
| 25 | $Et_3N$ | **D4** | DMAP | MeCN | 69 |
| 26 | $Et_3N$ | **D5** | DMAP | MeCN | 60 |

[a]**1a** (1.0 equiv), **2a** (1.1 equiv), base (1.5 equiv), catalyst (5 mol %), additive (0.1 equiv), solvent (0.1 M), 65 °C, 16 h. Entries 1−10: ligand (10 mol %). Entries 11 and 12: ligand (6 mol %). [b]Percentage of yields as isolated. [c]For 24 h. [d]75 °C. [e]85 °C. [f]2.5 mol % of **D1**. IPr: [1,3-bis(2,6-diisopropyl phenyl)-1*H*-imidazol-3-ium] chloride, C1: [3-benzyl-1-(pyren-1-yl)-1*H*-imidazol-3-ium] bromide, TBAB: tetrabutylammonium bromide, DMAP: 4-(dimethylamino)pyridine.

could be synthesized (Scheme 1). Reaction of saccharin with *N*-acyl moieties bearing electron-donating substituents **3aa**−**ad** proceeds smoothly as compared to electron-withdrawing **3ae**−**al**. Interestingly, 2-acylation of azoles was extended to thiophenyl **3am** and 2-naphthyl derivatives **3an**. Substituents such as OMe, OEt, F, Cl, Br, CN, and $NO_2$ were well tolerated under the reaction conditions. Functional groups such as −CN[25] and $-NO_2$[26] known for its directing effect did not further participate in the C−H activation process.

Encouraged by this finding, we further examined the substrate scope of azoles. Both electron-donating **3ba**−**fa** and electron-withdrawing **3ga** substituents on azoles are compatible with the reaction conditions, resulting in moderate yields. Gratifyingly, this optimized protocol of acylation could be successfully employed to *N*-methylbenzimidazoles **3ha**−**ja** and benzothiazoles **3ka**−**ma**. However, longer reaction time and increase in catalyst loading is required to furnish the desired products (Scheme 2). Inspired by the work of Peris et al.[27] and our own recent report,[24] we envisioned the role of pyrene wingtip substituents on Pd−NHCs, which could promote the acylation of azoles. This anomalous enhancement in the catalytic reaction could be attributed to noncovalent interaction between ($\pi-\pi$



DOI: 10.1021/acs.orglett.7b02877
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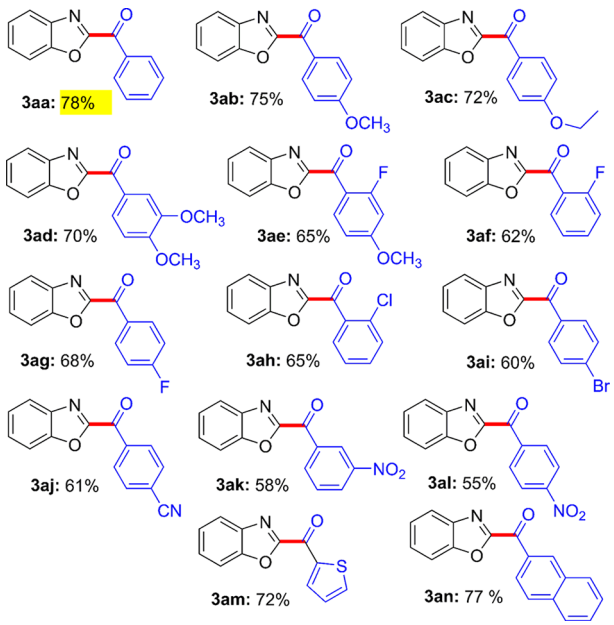
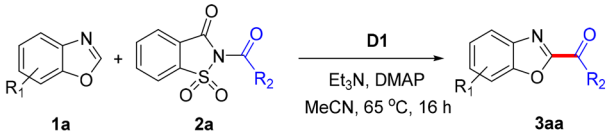
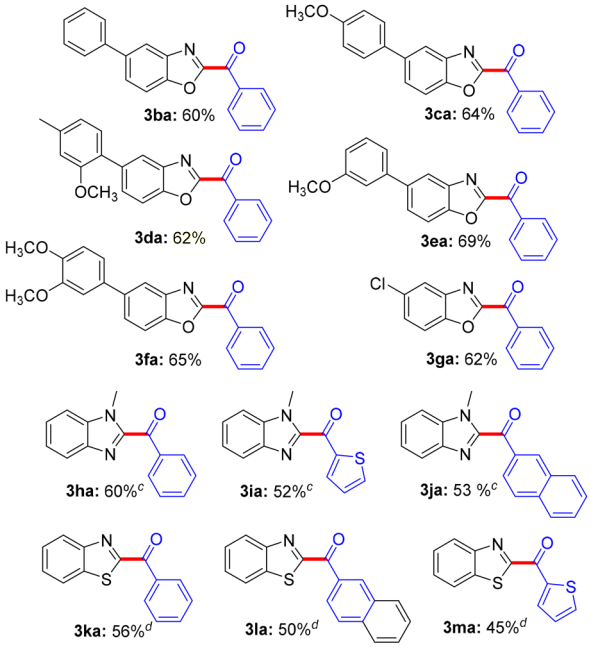
**Scheme 1. Scope of Amides in Pd−NHC-Catalyzed Direct C−H Acylation with Benzoxazole**[a,b]




[a]**1a** (1 equiv), **2a** (1.1 equiv) $Et_3N$ (1.5 equiv), **D1** (5 mol %), DMAP (0.1 equiv), MeCN (0.1 M), 65 °C, 16 h. [b]Isolated yields.

**Scheme 2. Scope of Azoles in Pd−NHC Catalyzed Direct C−H Acylation**[a,b]

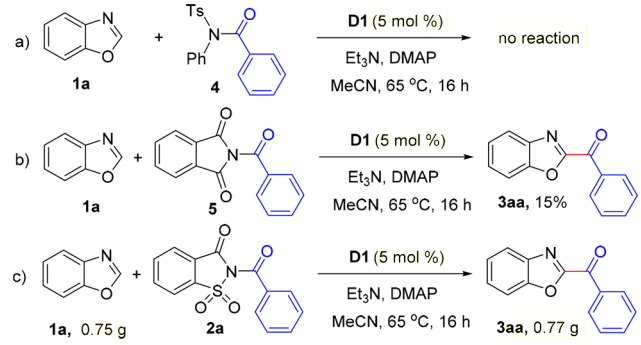



[a]**1a** (1 equiv), **2a** (1.1 equiv), $Et_3N$ (1.5 equiv), **D1** (5 mol %), DMAP (0.1 equiv), MeCN (0.1 M), 65 °C, 16 h. [b]Yields are isolated. [c]**D1** (7.5 mol %), 24 h. [d]**D1** (10 mol %), 36 h.

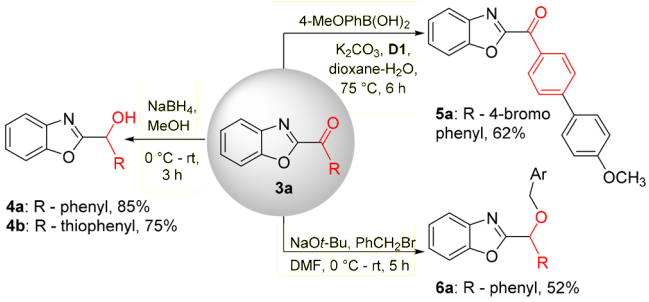
stacking) the appended pyrene moiety and substrates. To corroborate the aforementioned concept, we have introduced $\pi$-stacking additives, namely phenanthrene and pyrene, to the acylation reaction and followed the reaction by GC (see the SI). In addition, to ascertain the presence of the $\pi-\pi$ interactions between pyrene with **D1**, UV−vis absorption studies were performed in chloroform at room temperature. Notably, an increase in the absorption of pyrene was observed with an increment in concentration of **D1**, which supports the formation of donor−acceptor complex (D−A).[28] To substantiate the higher reactivity of *N*-benzoylsaccharin, **1a** was reacted with **4** and **5** under the optimized reaction conditions. Understandably, both proved to be poor electrophilic acyl transfer reagents (Scheme 3a,b). Furthermore, this reaction was found to be

**Scheme 3. Control Experiments for Pd−NHC-Catalyzed Direct C−H Acylation**




scalable under optimized conditions (Scheme 3c). Applicability of this protocol was realized by employing 2-acylated azoles as a valuable precursor for the synthesis of important organic derivatives (Scheme 4). On the basis of previous literature

**Scheme 4. Synthetic Diversification of 2-Acylated Derivatives**



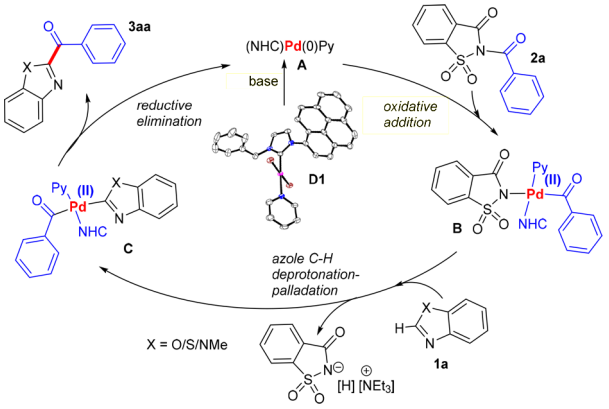

reports,[29] we proposed the plausible mechanism of Pd−NHC-catalyzed acylation of azoles. Acyl palladium complex **B** was generated by oxidative addition of *N*-acylsaccharin to an activated palladium complex **A**. The base removes the acidic proton from **1a** and generates the intermediate **C**. Eventually, **C** undergoes reductive elimination to form the desired product **3aa** (Scheme 5).

In summary, an efficient method for the acylation of heteroarenes by direct C−H bond functionalization using pyrene-based Pd−NHC catalyst **D1**−**D5** has been developed. Various benzoxazoles, a few examples of benzothiazole, and *N*-methylbenzimidazole were selectively converted into the corresponding 2-acylated products in high selectivity with synthetically useful yield. Functional group tolerance and broad substrate scope provide an attractive approach to access



DOI: 10.1021/acs.orglett.7b02877
Org. Lett. XXXX, XXX, XXX−XXX

**Scheme 5. Plausible Mechanism for Pd−NHC-Catalyzed Direct C−H Acylation**




2-acylated oxazoles. Experimental studies indicate that the high reactivity of the pyrene Pd−NHC system is likely due to noncovalent interaction of complexes with the substrates.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02877.

Detailed experimental procedures and spectral data for all compounds (PDF)

Crystallographic data for compound **D1** (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work is supported by the CSIR, India [01(2815)/14/EMR-II], and Seed Grant, VIT University, Vellore. S.K. acknowledges UGC, India, for JRF [no. F.2-4/2011(SA-I) dated 22 July 2014]. We thank VIT-SIF and IITM-SAIF for instrument facilities. We thank Dr. C. M. Nagaraja at IIT Ropar for assistance with the single-crystal XRD.

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DOI: 10.1021/acs.orglett.7b02877
*Org. Lett.* XXXX, XXX, XXX−XXX