ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

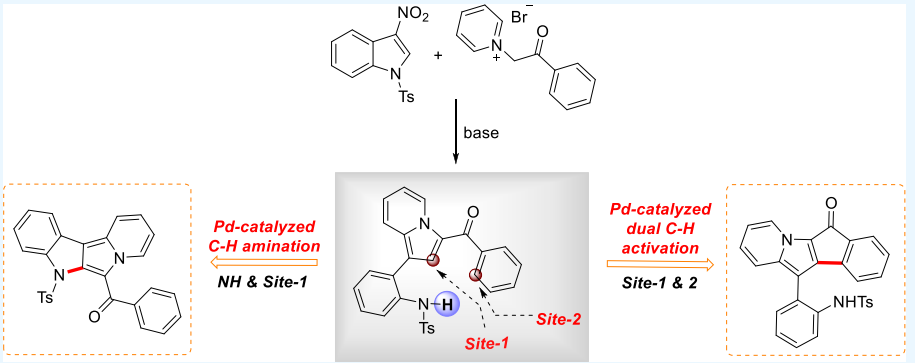
Tandem Reactions of Electrophilic Indoles toward Indolizines and Their Subsequent Transformations through Pd(II)-Mediated C−H Functionalization to Access Polyring-Fused *N*-Heterocycles

Sheba Ann Babu,* Aparna A, Malavika Mohan, Namitha Paul, Jomon Mathew,* and Jubi John*

Cite This: *ACS Omega* 2024, 9, 16196−16206

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A simple and efficient synthetic approach for generating a library of structurally novel indolizines has been developed via sequential 1,3-dipolar cycloaddition-ring opening processes. Using this methodology, a series of indolizines bearing different substituents were made in moderate to good yields. The presence of two functionalizable C−H bonds in these indolizine motifs makes them attractive for accessing fused indolizine scaffolds. In this line, we have introduced palladium-mediated site-selective C−H functionalizations, where the *N*-center and the two C−H centers of the indolizine moiety can be readily functionalized to generate fused *N*-heterocycles. Utilizing a Pd-mediated dual C−H activation of 5-benzoyl-substituted indolizine afforded 6*H*-indeno-indolizine, and a tetracene, viz., indolizino[2,1-*b*]indoles, was produced in the same substrate by the Pd-catalyzed selective C−H amination in the presence of oxygen.

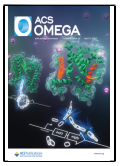
INTRODUCTION

Indolizines are an important class of nitrogen-containing heterocycles that exhibit a variety of biological activities, including anticancer, anti-inflammatory, anticonvulsant, and phosphodiesterase inhibitory effects (Figure 1).[1] Besides, indolizine motifs are also known to have diverse photophysical properties.[2] Due to the widespread use of this heterocyclic moiety as a preferred scaffold, organic chemistry and materials science researchers are looking into effective methods for synthesizing multisubstituted indolizine derivatives.

One such approach toward synthesizing functionalized indolizines[3] is based on the 1,3-dipolar cycloaddition of dipolarophiles, such as electron-deficient alkenes and alkynes with pyridinium ylides. Pyridinium ylides are considered versatile building blocks for synthetic heterocyclic chemistry. They are widely utilized as synthons for accessing heterocycles due to their ease of preparation and strong reactivity as nucleophiles, 1,3-dipoles, and electrophiles.[3] Shang's group successfully developed a base-catalyzed synthesis of indolizine via a 1,3-dipolar cycloaddition between pyridinium salt and alkyne (Scheme 1a).[4] It was shown that *N*-ethynylamides having an electron-withdrawing substituent at the triple bond could also be used similarly, giving access to a variety of 2-aminoindolizines (Scheme 1b).[5] Replacing electron-deficient alkynes with electron-deficient alkenes also extended the scope of the reaction. In this line, nitroolefins were reported to react with pyridinium ylides toward the synthesis of polysubstituted indolizines (Scheme 1c).[6] Dong *et al.* also reported a metal-free synthesis of indolizines from structure-specific alkenes such as chromones (Scheme 1d).[7] Despite these reports, the exploration of 1,3-dipolar cycloaddition of pyridinium ylides with electron-deficient aromatic systems toward the synthesis of indolizines with diverse substituents remains to be explored.

Recently, a significant focus has been on exploring the electrophilic reactivity of 3-nitroindoles.[8] Notably, it has been

Received: December 20, 2023
Revised: March 15, 2024
Accepted: March 20, 2024
Published: March 30, 2024



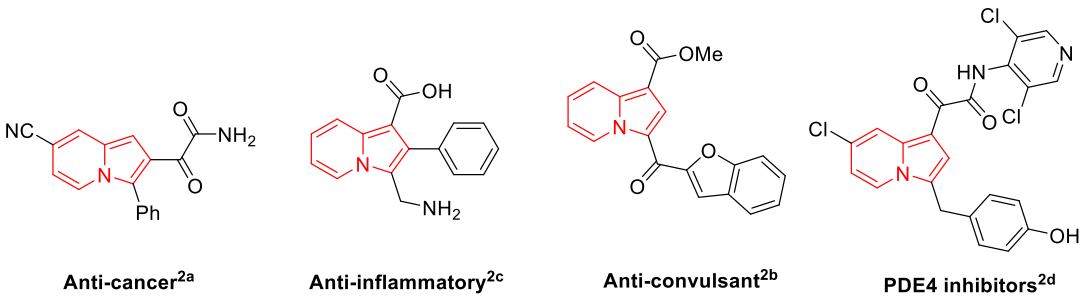
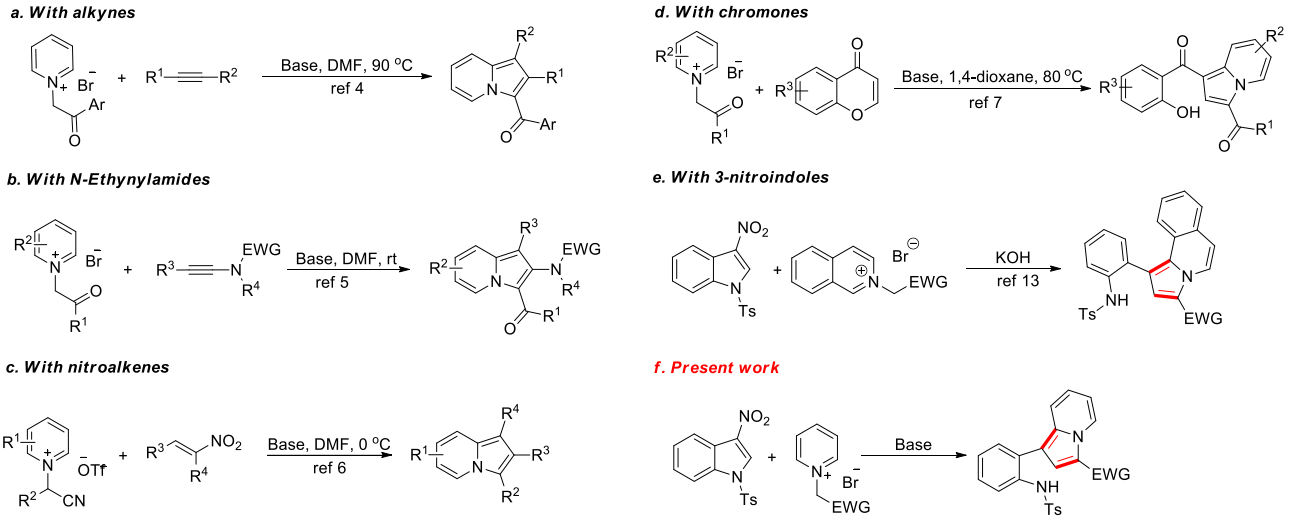


Figure 1. Bioactive indolizines.

Scheme 1. Synthesis of Heterocycles via Dipolar Cycloadditions of Heteroaromatic *N*-Ylides and Activated Alkynes/Alkenes



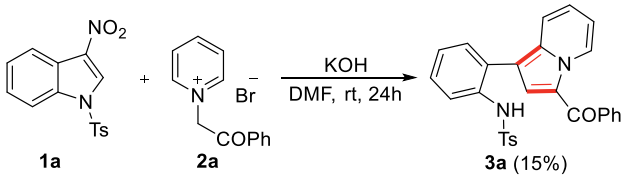
shown that incorporating electron-withdrawing motifs on the *N*-atom and the second or third position of the indole moiety resulted in reversing its intrinsic nucleophilic character, thus making the system quite electrophilic.[9] In this context, several research groups have investigated the chemistry of electrophilic indoles for synthesizing fused or functionalized indole/indoline compounds.[10] 3-Nitroindoles are prone to react with 1,3-dipoles in dipolar cycloaddition reactions toward annulated heterocycles.[11] Due to our continued fascination with the reactivity of electrophilic benzannulated heterocycles,[12] we were able to synthesize functionalized pyrrolo[2,1-*a*]-isoquinolines by treating electrophilic indoles with isoquinolinium methylides through a domino dipolar cycloaddition-ring opening reaction[13] (Scheme 1e). Inspired by the above reports, we envisioned that novel indolizine derivatives could be accessed from the reactions of electrophilic indoles and pyridinium *N*-ylides (Scheme 1f), which presents an alternative strategy for synthesizing complex derivatives of indolizines.

RESULTS AND DISCUSSION

With this plan in mind, the studies commenced with *N*-tosyl 3-nitroindole (**1a**) and 1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide (**2a**) as substrates. Initially, **1a** and **2a** were treated in DMF at room temperature with KOH (4.0 equiv) as the base (optimized conditions from our previous report).[13] As expected, after 24 h, we could isolate the functionalized indolizine **3a** in 15% yield, the structure of which was characterized by NMR and mass spectral analyses (Scheme 2).

Detailed optimization studies began with the model reaction of *N*-tosyl 3-nitroindole **1a** (1.0 equiv) and 1-(2-oxo-2-phenylethyl)pyridine-1-ium bromide **2a** (1.5 equiv) (Table 1). We observed an enhancement in the yield of **3a** to 52% (entry 2), on increasing the reaction temperature to 60 °C. After screening different solvents and bases (entries 2−12), the combination of CH_3CN and K_3PO_4 was the best choice. On optimizing the amounts of K_3PO_4 and **2a** (entries 13−17), it was found that the reaction proceeded efficiently with 4.0 equiv of K_3PO_4 and 1.2 equiv of **2a** (entry 17). Low yield was obtained by changing the concentration of the reaction to 0.1 as well as 0.3 mmol. For further improvement of yields, we also increased the reaction temperature, leading to a drop in the yield of **3a** to 30% (entry 15).

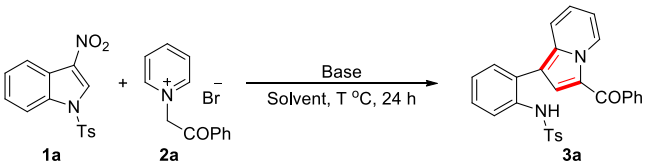
Scheme 2. Reaction of Pyridinium Methylides with Electrophilic Indole toward the Synthesis of Indolizines



The relative reactivity of pyridinium and isoquinolinium ylides is illustrated below indicating a greater reactivity for isoquinolinium ylide compared to pyridinium ylide (nucleophilicity parameter '*N*' = 19.46, nucleophile-specific sensitivity parameter 's_N' = 0.58 for the pyridinium makes it less reactive than the isoquinolinium equivalent: '*N*' = 20.08, 's_N' = 0.57).[3c] This is evident from our observations as the ring-opened product pyrrolo[2,1-*a*]isoquinoline is obtained at room

https://doi.org/10.1021/acsomega.3c10194
ACS Omega 2024, 9, 16196−16206

Table 1. Optimization Studies[a]



entry	oxidant	solvent	temp (deg C)	yield of **3a** (%)
1	KOH	DMF	rt	15
2	KOH	DMF	60	52
3	KOH	1,4-dioxane	60	30
4	KOH	CH_3CN	60	58
5	KOH	THF	60	27
6	DBU	CH_3CN	60	32
7	Et_3N	CH_3CN	60	traces
8	KO*t*Bu	CH_3CN	60	47
9	NaOH	CH_3CN	60	36
10	K_3PO_4	CH_3CN	60	64
11	LiOH	CH_3CN	60	traces
12	K_2CO_3	CH_3CN	60	traces
13[b]	K_3PO_4	CH_3CN	60	39
14[c]	K_3PO_4	CH_3CN	60	33
15	K_3PO_4	CH_3CN	90	30
16[d]	K_3PO_4	CH_3CN	60	74
17[e]	**K_3PO_4**	**CH_3CN**	**60**	77
18[f]	K_3PO_4	CH_3CN	60	65
19[g]	K_3PO_4	CH_3CN	60	26
20[h]	K_3PO_4	CH_3CN	60	33

[a]Reaction conditions: **1a** (1.0 equiv., 0.16 mmol), **2a** (1.5 equiv), base (4.0 equiv), solvent (0.15 mM), T °C, 24 h. [b]Base (3.0 equiv). [c]Base (5.0 equiv). [d]**2a** (1.1 equiv). [e]**2a** (1.2 equiv). [f]**2a** (1.3 equiv). [g]Solvent (0.1 mM). [h]Solvent (0.3 mM).

temperature for isoquinolinium ylide,[13] while pyridinium ylide requires heating of the reaction to obtain the desired indolizine in higher yields (Scheme 3).

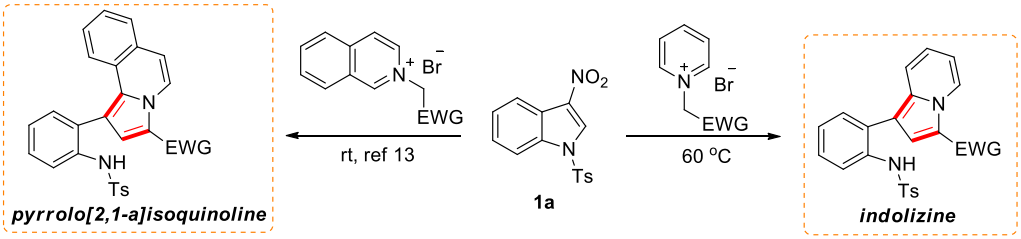
With the optimal conditions [**1a** (1 equiv), **2a** (1.2 equiv), K_3PO_4 (4 equiv), and CH_3CN (0.15 mM), 60 °C], a series of 3-nitroindoles and pyridinium salts were applied to establish the scope and generality of the protocol (Table 2). Initially, we examined the reactivity of different 3-nitroindoles on the model substrate 1-(2-oxo-2-phenylethyl)pyridine-1-ium bromide (**2a**). The reactions with electrophilic indoles substituted with halogens (Cl, Br, and F) progressed smoothly, yielding the corresponding products **3b**, **3c**, and **3d**. No desired product was obtained using 5-methoxy-3-nitroindole as the substrate (**3e**). The reaction with 3-nitro-1-[(4-nitrophenyl)-sulfonyl]-1*H*-indole yielded indolizine **3f** in moderate yield. Next, we investigated the nature of different types of pyridinium salts. In this regard, we tested various pyridinium salts bearing different electron-withdrawing groups. The products (**3g**−**3k**) were obtained in good yields from the reactions of pyridinium bromides (bearing different para-substituents on the phenyl ring) with **1a**. Finally, the pyridinium methylide **2l** with a naphthoyl group as the electron-withdrawing moiety furnished the corresponding indolizine in satisfactory yield (**3l**). With 3-nitro *N*-Boc indole, we could observe only the formation of an intractable band (**3m**). This can be due to the sensitivity of the *N*-Boc-3-nitroindole starting material, which easily loses the Boc group upon heating. The same was observed for ethoxycarbonyl- and cyano-substituted pyridinium salts, wherein the reaction failed to proceed smoothly (**3n, 3o**) but resulted in intractable reaction mixtures.

Based on our observations and literature precedents,[3e,6,7,13] we have postulated a mechanism for the reaction of electrophilic indoles with pyridinium methylide (Scheme 4). This reaction might proceed through a cascade mechanism involving 1,3-dipolar cycloaddition, ring opening, and subsequent aromatization (Scheme 4). The first step is the conversion of pyridinium salt **2a** to the corresponding *N*-ylide in the presence of a base. Next, a 1,3-dipolar cycloaddition takes place between *N*-tosyl-3-nitroindole **1a**, the dipolarophile, and the *N*-ylide, resulting in the formation of the corresponding cycloadduct **A**. The removal of HNO_2[3e] from **A** subsequently results in the formation of the unstable intermediate **B**. The desired product **3a** is produced by a strain-instigated breakage of the carbon−nitrogen bond due to aromatization.[7]

The idea of synthesizing heteroacenes prompted us to check the reactivity of these indolizines toward tetracenes via site-selective C−H activation. For the past few years, the scientific community has been exploring novel approaches toward functionalizing unactivated carbon−hydrogen bonds, creating C−C or C-heteroatom bonds.[14] Initially, the selective functionalization of C−H bonds at specific sites depended on free radical transformations[15] and later progressed with the emergence of metal complexes capable of activating C−H bonds.[16] Organic chemists, over the last two decades, have embraced the task of developing advanced methodologies and new strategies for C−H functionalization at unactivated sites.[17] Based on our previous report on C−H functionalization of pyrrolo[2,1-*a*]isoquinolines,[18] we hypothesized that a similar approach could be applied to achieving site-selective C−H functionalization of the indolizine moiety **3a** via cross-dehydrogenative coupling (CDC) and C−H amination reaction toward the formation of **4a** and **5a**, respectively, and disclose herein our findings (Scheme 5).

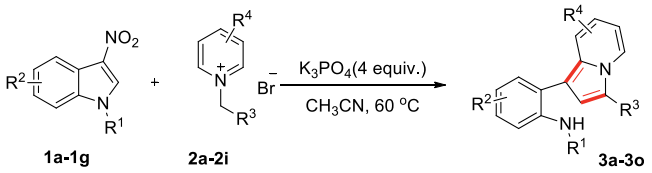
CDC,[19] a technique based on C−H activation, has emerged as an attractive and competitive way of producing a range of fused heterocyclic rings, through the direct coupling of two C−H bonds. In this line, we targeted the Pd-catalyzed CDC

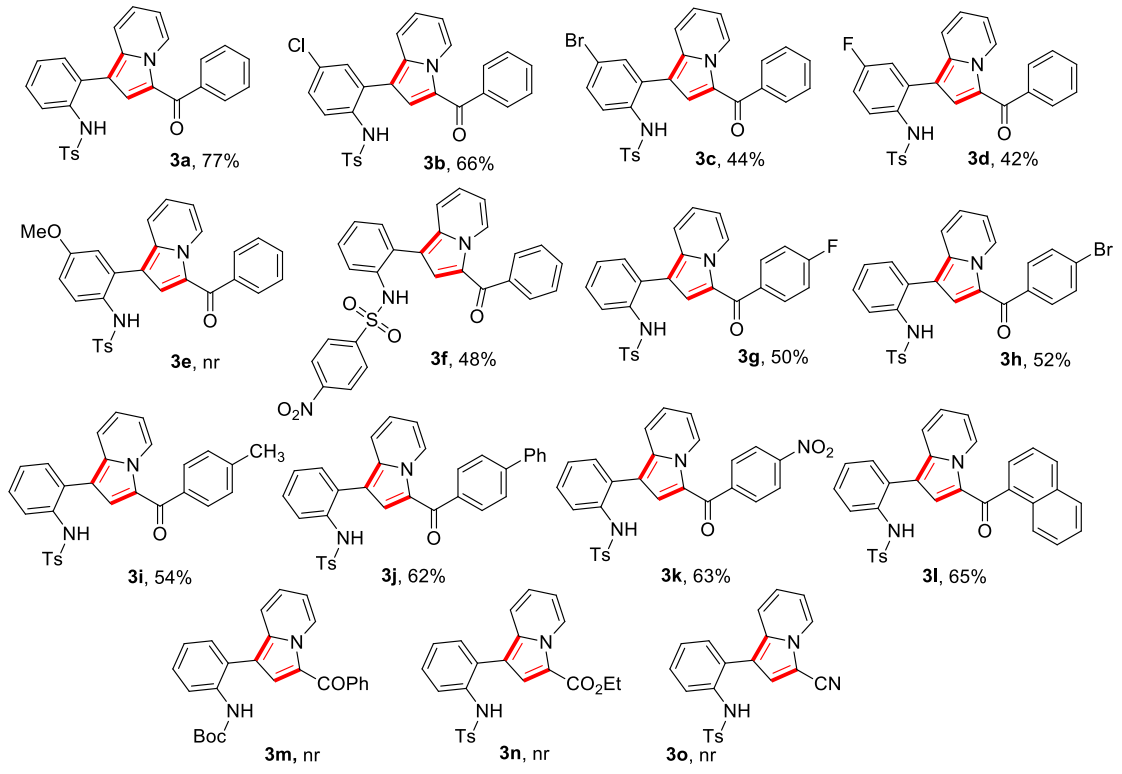
Scheme 3. Reactivities of Isoquinolinium and Pyridinium Ylides with Electrophilic Indoles



https://doi.org/10.1021/acsomega.3c10194
ACS Omega 2024, 9, 16196−16206

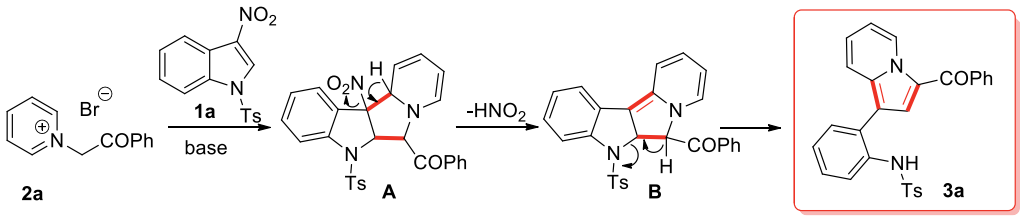
Table 2. Substrate Scope of the Reaction of Substituted Electrophilic Indoles with Pyridinium Methylides[a]



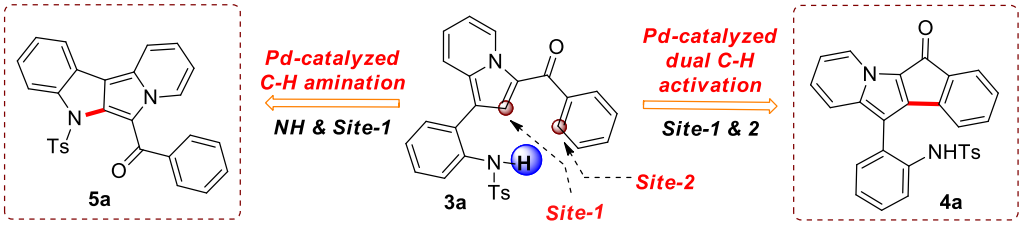


[a]Reaction conditions: **1** (1.0 equiv., 100 mg), **2** (1.2 equiv), K_3PO_4 (4.0 equiv), CH_3CN (0.15 mM), 60 °C, 24 h.

Scheme 4. Plausible Mechanism for the Cascade Reaction of Pyridinium Ylides with Electrophilic Indoles



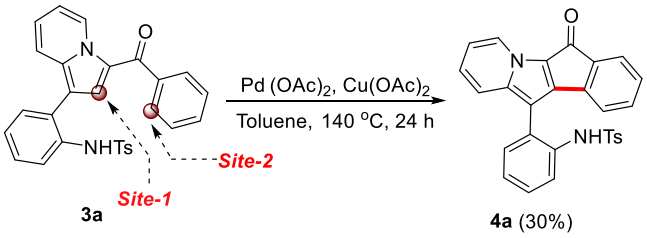
Scheme 5. Pd(II)-Mediated C−H Functionalization of Indolizines



reaction between site-1 and site-2 of indolizine **3a** toward *6H*-indeno-indolizine moiety **4a** (Scheme 5). To verify our hypothesis, we started the investigation by synthesizing *N*-[2-(3-benzoylindolizin-1-yl)phenyl]-4-methylbenzenesulfonamide **3a** from 3-nitro-*N*-tosyl indole **1a** and 1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide **2a** (Table 2). Initially, the reaction was carried out with **3a** using a catalyst system comprising $Pd(OAc)_2$ and $Cu(OAc)_2$ in toluene at 140 °C for 24 h (Scheme 6). Gratifyingly, we isolated the product *6H*-indeno[1,2-*b*]indolizin-6-one **4a** in 30% yield.

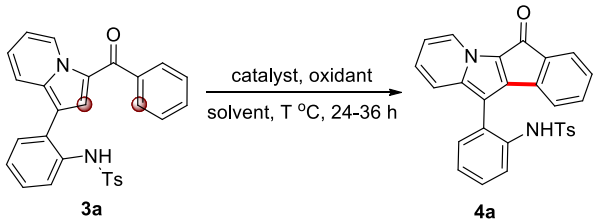
https://doi.org/10.1021/acsomega.3c10194
ACS Omega 2024, 9, 16196−16206

Scheme 6. Pd(II)-Mediated Dual C−H Activation of Indolizines



We commenced further optimization studies with **3a** as a test substrate to determine the impact of different reaction parameters, as illustrated in Table 3. Initially, the reaction was carried out by employing 20 mol % of $Pd(OAc)_2$ and 1.0 equiv of $Cu(OAc)_2$ in a toluene medium, and the desired product was obtained only in 30% yield after 24 h. On changing the oxidants from $Cu(OAc)_2$ to $K_2S_2O_8$ and AgOAc, we could not observe any increase in the yield of the reaction (Table 3, entries 1−3). Other palladium catalysts such as $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(tfa)_2$ afforded poor results, hence revealing that $Pd(OAc)_2$ is the best one (Table 3, entry 1). Low yield was obtained by increasing the amount of catalyst loading and oxidant (Table 3, entries 7 and 8). To our delight, increasing the reaction time to 36 h increased the yield up to 40% (Table 3, entry 9). This observation prompted us to further increase the reaction time to 60 h but did not positively affect the reaction (Table 3, entry 10). In order to improve the reaction conditions, we also screened various solvents, among which only toluene afforded the best yield (Table 3, entries 11−16). In all these cases, **3a** remained, which made us try another reaction with a catalyst system comprising $Pd(OAc)_2$ and AgOAc with PivOH as the solvent (Table 3, entry 17). Herein, we could observe an increase in the reaction yield up to 52%. We further tried the same reaction with different silver oxidants, such as Ag_2O and $AgCO_3$, and in all these cases, the reaction failed to proceed (Table 3, entries 18 and 19). In order to be sure whether the palladium catalyst is regenerated or not, we tried another reaction consisting of 1.0 equiv of $Pd(OAc)_2$ in the PivOH medium, which led to a yield of 92% (Table 3, entry 20), which stands as clear evidence for the low yield of the reaction due to catalyst poisoning.

Table 3. Optimization Studies[a]



entry	catalyst	oxidant	solvent	time (h)	yield of **4a** (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	24	30
2	$Pd(OAc)_2$	$K_2S_2O_8$	toluene	24	traces
3	$Pd(OAc)_2$	Ag(OAc)	toluene	24	30
4	$PdCl_2$	$Cu(OAc)_2$	toluene	24	traces
5	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	toluene	24	20
6	$Pd(tfa)_2$	$Cu(OAc)_2$	toluene	24	traces
7[b]	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	24	25
8[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	24	20
9	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	36	40
10	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	60	40
11	$Pd(OAc)_2$	$Cu(OAc)_2$	xylene	36	traces
12	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	36	trace
13	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	36	20
14	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	36	30
15	$Pd(OAc)_2$	$Cu(OAc)_2$	TFA	36	nr
16	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	36	Trace
17	**$Pd(OAc)_2$**	**AgOAc**	**PivOH**	**36**	**52**
18	$Pd(OAc)_2$	Ag_2O	PivOH	36	nr
19	$Pd(OAc)_2$	Ag_2CO_3	PivOH	36	nr
20[d]	$Pd(OAc)_2$	–	PivOH	36	92

[a]Reaction conditions: **3a** (1.0 equiv., 0.10 mmol), catalyst (20 mol %), oxidant (1.0 equiv), solvent (0.5 M), 140 °C. [b]Catalyst (30 mol %). [c]Oxidant (2.0 equiv). [d]Catalyst (1 equiv).

After the optimization studies, we explored the substrate scope of this reaction under both catalytic and stoichiometric amounts of $Pd(OAc)_2$ in PivOH. Initially, we started the reaction by using various benzoyl-substituted indolizines (Table 4), wherein we incorporated halogens such as fluorine (**4b**) onto the indanone ring. The reaction conditions also proved effective when both a CH_3 and NO_2 group were present on the benzoyl moiety, thereby furnishing **4c** and **4d** in good to moderate yields. We also tried reactions with a fluorine substituent on the aryl moiety of the pyrrole ring (**4e**), affording the corresponding product in good yield.

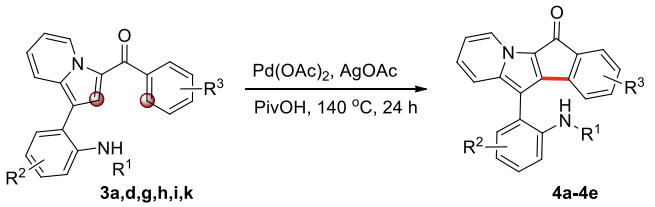
Based on our studies and reported literature, we put forward a mechanism for the formation of *6H*-indeno-indolizines via Pd-catalyzed CDC (Scheme 7).[19,20] The formation of the N−Pd bond, which can be observed in **A** formed from **3a** and the Pd-catalyst, will mark the beginning of the catalytic cycle.[21,22] The C−H bond in the pyrrole ring is then selectively activated to form a six-membered palladacycle **B**.[23] The newly formed palladacycle **C** is then believed to be produced via a Fujiwara-Moritani type reaction in intermediate **B** via the activation of a C−H bond in the benzoyl moiety.[19,24] Reductive elimination produces the product **4a** and Pd(0), which would then be reoxidized to Pd(II) upon oxidation with AgOAc, thus completing the catalytic cycle.

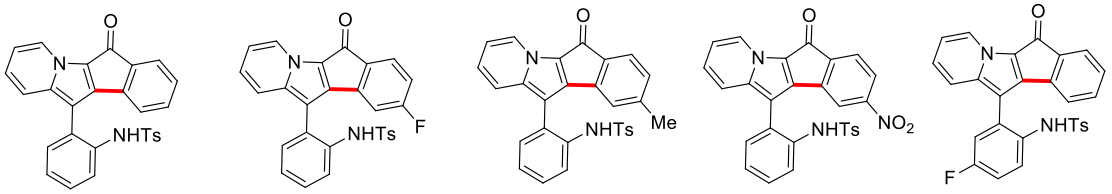
It is important to mention that C−H amination has also established itself as a powerful tool for generating substituted amines or *N*-heterocycles.[21−23] So by tuning the reaction conditions, we hypothesized that it is possible to facilitate a C−H amination between site-1 and the N−H center for the synthesis of indolizino[2,1-*b*]indole moiety **5a** (Scheme 5). During our optimization studies for the Pd-catalyzed dual C−H activation using **3a**, we came across a catalyst system comprising 5 mol % of $Pd(OAc)_2$ and 1.0 equiv of $Cu(OAc)_2$ in the presence of an O_2 atmosphere with DMSO as the solvent. The reaction at 120 °C after 36 h provided indolizino[2,1-*b*]indoles **5a** in 56% yield (Scheme 8). Interestingly, in the current observation, oxygen was present, altering the reaction's path to produce the C−H amination product.

We commenced our investigations with **3a** as the test substrate to find suitable reaction conditions for the palladium-catalyzed C−H amination using various Pd-catalysts, oxidants, and solvents (Table 5). Screening of various solvents such as DMSO, DMF, and toluene revealed DMSO to be the best (Table 5, entries 1−3). Other palladium catalysts such as $PdCl_2(PPh_3)_2$, $Pd(tfa)_2$, $PdCl_2$, and $Pd(dba)_2$ were screened, and we observed an increase in the yield of the reaction up to

https://doi.org/10.1021/acsomega.3c10194
ACS Omega 2024, 9, 16196−16206

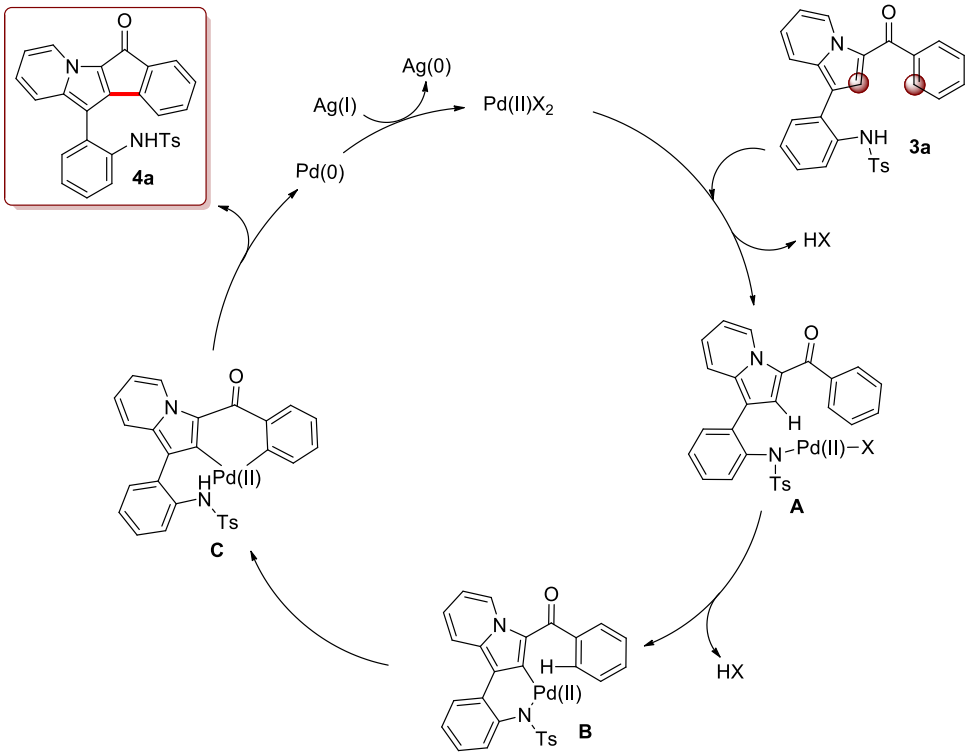
Table 4. Generality of Pd-Mediated Cross-Dehydrogenative Coupling[a]



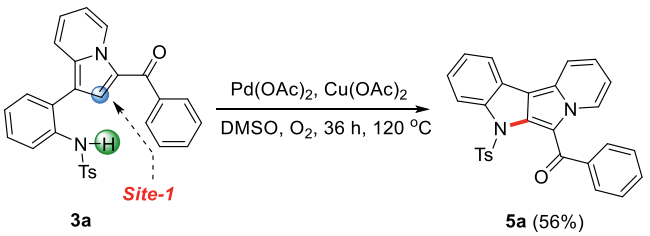


[a]Reaction conditions: 1. **3** (1.0 equiv., 100 mg), $Pd(OAc)_2$ (1.0 equiv), PivOH (0.5 M), 140 °C, 36 h. 2.* **3** (1.0 equiv., 100 mg), $Pd(OAc)_2$ (20 mol %), AgOAc (1.0 equiv), PivOH (0.5 M), 140 °C, 36 h.

Scheme 7. Mechanistic Postulate for 6*H*-Indeno-Indolizine Synthesis



Scheme 8. Pd(II)-Mediated C−H Amination of Indolizines

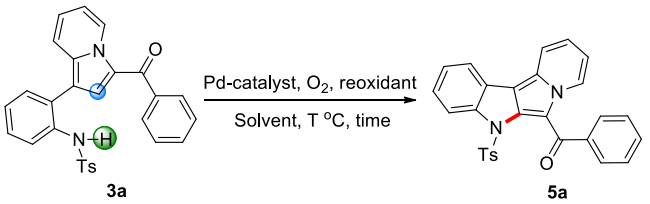


76% when $PdCl_2$ was used as the catalyst (Table 5, entries 4−7). Attempts to use different oxidants such as AgOAc, AgO, and benzoquinone were also unsuccessful, hence revealing $Cu(OAc)_2$ to be the best (Table 5, entries 8−10).

With the aforementioned optimized reaction protocol in hand [1.0 equiv of **3a**, 5 mol % of $PdCl_2$, 1.0 equiv of $Cu(OAc)_2$, O_2, DMSO, 120 °C, 36 h], we first evaluated the substrate scope using different indolizines, and the results are outlined in Table 6. Initially, we started the reaction with F, Cl, and Br substituents on the aryl part of the indole ring (**5b**, **5c**, **and 5d**), affording the corresponding products in good yield. The Pd-catalyzed C−H amination also worked well with electron-donating and electron-releasing substituents on the para position of the benzoyl moiety attached to the pyrrole ring (**5e**−**5i**) in 68−74% yields. We could also synthesize **5j** in

https://doi.org/10.1021/acsomega.3c10194
ACS Omega 2024, 9, 16196−16206

Table 5. Optimization Studies[a]



entry	catalyst	oxidant	solvent	time (h)	yield of **5a** (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	36	56
2	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	36	40
3	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	36	Nr
4	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	DMSO	36	44
5	$Pd(tfa)_2$	$Cu(OAc)_2$	DMSO	36	40
6	**$PdCl_2$**	**$Cu(OAc)_2$**	**DMSO**	**36**	**76**
7	$Pd(dba)_2$	$Cu(OAc)_2$	DMSO	36	40
8	$PdCl_2$	AgOAc	DMSO	36	Nr
9	$PdCl_2$	AgO	DMSO	36	Nr
10	$PdCl_2$	Benzoquinone	DMSO	36	Nr

[a]Reaction conditions: **3a** (1.0 equiv., 0.10 mmol), catalyst (5 mol %), oxidant (1.0 equiv), solvent (0.1 M), 120 °C.

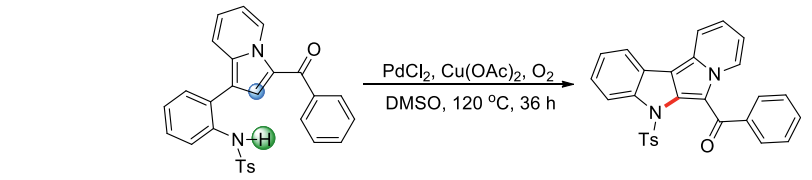
70% yield by starting from suitably substituted 5-naphthoyl indolizine.

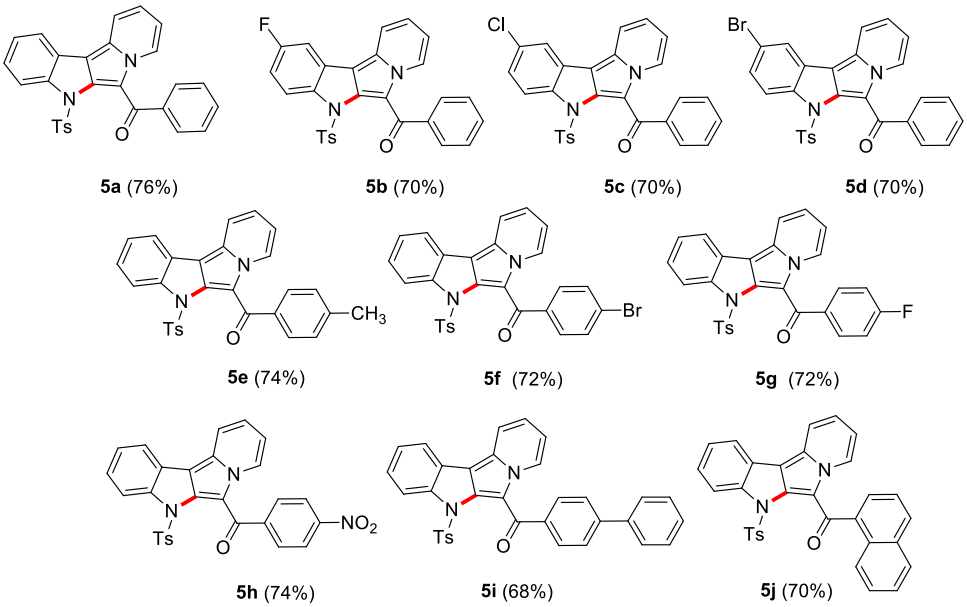
Based on our observations and literature precedents, we put forward a mechanism for the formation of indolizino[2,1-*b*]indoles via a Pd-catalyzed site-selective C−H activation (Scheme 9). According to the theoretical studies reported in the literature, we assume that, initially, DMSO and $PdCl_2$ interact to form a $Pd(0)(DMSO)_n$ species.[25] Stahl and co-workers have carried out extensive research on the ligand-supported Pd-catalyzed aerobic oxidations.[26] By adhering to the literature reports, we assume that the subsequent oxidation of Pd(0)(DMSO)n by oxygen takes place to produce the active η^2-peroxo-Pd(II) species.[27] Based on the reports of Buchwald and Monguchi on the palladium-catalyzed synthesis of carbazoles promoted by oxygen, we believe that oxygen's presence will compel the reaction to follow the Wacker-like pathway.[23,28] In this line, the intermediate η^2-peroxo-Pd(II) intermediate complexes with the *N*-center in **3a** to produce amide **A**. The intermediate **B** will then be produced when the Pd species undergoes a Wacker-type addition through the double bond of pyrrole. Then, in **B**, a β-hydride elimination takes place, releasing the H−Pd(II)L_n-OOH moiety and indolizino[2,1-*b*]indoles. Reductive elimination of H−Pd(II)-L_n-OOH produces $Pd(0)L_n$ and H_2O_2, which is further reoxidized by $Cu(OAc)_2$ and O_2 to Pd(II) species, thus completing the catalytic cycle.

CONCLUSIONS

In conclusion, this method proves effective for the synthesis of complex indolizines from various 3-nitroindoles and pyridinium methylides via 1,3-dipolar cycloaddition-ring opening reaction-aromatization cascade processes. This method was found to be general with a broad spectrum of functional groups

Table 6. Generality of the Pd-Catalyzed C−H Amination of Indolizines toward Indolizino[2,1-*b*]indoles[a]

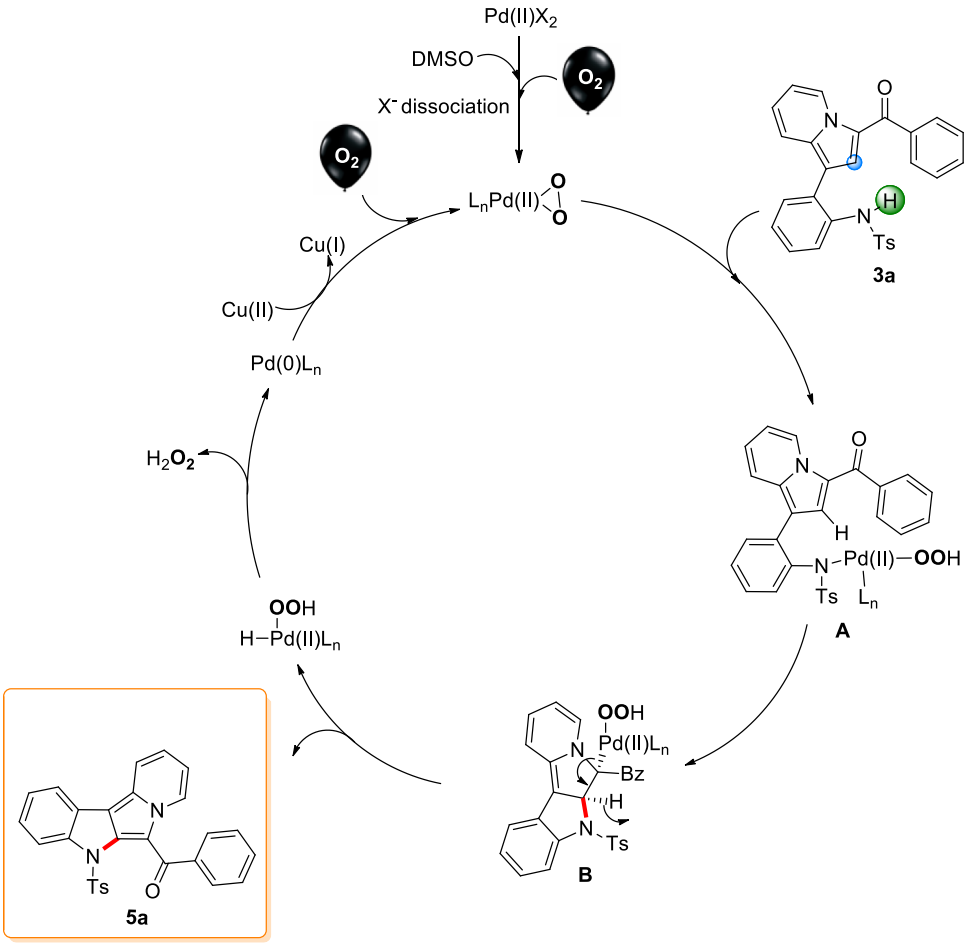




[a]Reaction conditions: **3a** (1.0 equiv., 100 mg), $PdCl_2$ (0.05 equiv), $Cu(OAc)_2$ (1.0 equiv), DMSO (0.1 M), O_2, 120 °C, 36 h.

https://doi.org/10.1021/acsomega.3c10194
ACS Omega 2024, 9, 16196−16206

Scheme 9. Proposed Mechanism for the Synthesis of Indolizino[2,1-*b*]indoles via Pd-Catalyzed C−H Amination



and serves as a simple, effective, and cost-efficient means of generating indolizine derivatives with moderate to good yields. In addition, we have also discovered an intriguing Pd-catalyzed site-selective C−H functionalization for the synthesis of polyring-fused *N*-heterocycles. In the present study, two C−H functionalization sites and an *N*-center could be found on the benzoyl-substituted indolizine scaffold, capable of participating in C−H amination. Both experimental and theoretical studies provide evidence that supports the formation of 6*H*-indeno-indolizine moiety derivatives via Pd-catalyzed CDC. A broad substrate scope further establishes the potential of this method. Presently, we are looking at ways to utilize the site selectivity in similar structural frameworks.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c10194.

Synthetic procedures, analytical details, and NMR spectra of all newly synthesized compounds PDF

■ AUTHOR INFORMATION

Corresponding Authors

Sheba Ann Babu − *Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram 695019, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*; Email: shebaannbabu@gmail.com

Jomon Mathew − *Research and Post-Graduate Department of Chemistry, St. Joseph's College, Devagiri, Calicut 673008, India*; Email: jomonmathew@devagiricollege.org

Jubi John − *Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram 695019, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*; orcid.org/0000-0003-0483-2026; Email: jubijohn@niist.res.in

Authors

Aparna A − *Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram 695019, India*

Malavika Mohan − *Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram 695019, India*

https://doi.org/10.1021/acsomega.3c10194
ACS Omega 2024, 9, 16196−16206

Namitha Paul − *Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram 695019, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c10194

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.A.B. thanks the CSIR for the research fellowship. J.J. thanks CSIR (HCP-41, HCP-49, and HCP-50), AICTE (GAP-161939), and DST-SERB for the CRG project (CRG/2023/001162) for financial assistance.

■ REFERENCES

(1) (a) Lucescu, L.; Ghinet, A.; Belei, D.; Rigo, B.; Dubois, J.; Bicu, E. Discovery of indolizines containing triazine moiety as new leads for the development of antitumoral agents targeting mitotic events. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3975−3979. (b) Szefler, B. Czelen, Potential inhibitory effect of indolizine derivatives on the two enzymes: nicotinamide phosphoribosyltransferase and beta lactamase, a molecular dynamics study. *J. Mol. Model* **2017**, *23*, 1. (c) Kumar, R. S.; Antonisamy, P.; Almansour, A. I.; Arumugam, N.; Periyasami, G.; Altaf, M.; Kim, H. R.; Kwon, K. B. Functionalized spirooxindole-indolizine hybrids: Stereoselective green synthesis and evaluation of anti-inflammatory effect involving TNF-α and nitrite inhibition. *Eur. J. Med. Chem.* **2018**, *152*, 417−423. (d) Purushothaman, B.; Arumugam, P.; Kulsi, G.; Song, J. M. Design, synthesis, and biological evaluation of novel catecholopyrimidine based PDE4 inhibitor for the treatment of atopic dermatitis. *Eur. J. Med. Chem.* **2018**, *145*, 673−690.

(2) (a) Kim, E.; Lee, Y.; Lee, S.; Park, S. B. Discovery, understanding, and bioapplication of organic fluorophore: a case study with an indolizine-based novel fluorophore, Seoul-Fluor. *Acc. Chem. Res.* **2015**, *48*, 538−547. (b) Lee, Y.; Cho, W.; Sung, J.; Kim, E.; Park, S. B. Monochromophoric design strategy for tetrazine-based colorful bioorthogonal probes with a single fluorescent core skeleton. *J. Am. Chem. Soc.* **2018**, *140*, 974−983.

(3) (a) Jacobs, J.; Van Hende, E.; Claessens, S.; De Kimpe, N. Pyridinium Ylids in Heterocyclic Synthesis. *Curr. Org. Chem.* **2011**, *15*, 1340−1362. (b) Kakehi, A. Reactions of pyridinium *N*-ylides and their related pyridinium salts. *Heterocycles* **2012**, *85*, 1529. (c) Allgäuer, D. S.; Mayer, P.; Mayr, H. Nucleophilicity Parameters of Pyridinium Ylides and Their Use in Mechanistic Analyses. *J. Am. Chem. Soc.* **2013**, *135*, 15216−15224. (d) Sowmiah, S.; Esperança, J. M. S. S.; Rebelo, L. P. N.; Afonso, C. A. M. Pyridinium salts: from synthesis to reactivity and applications. *Org. Chem. Front.* **2018**, *5*, 453−493. (e) Funt, L. D.; Novikov, M. S.; Khlebnikov, A. F. New applications of pyridinium ylides toward heterocyclic synthesis. *Tetrahedron* **2020**, *76*, 131415.

(4) Shang, Y.; Zhang, M.; Yu, S.; Ju, K.; Wang, C.; He, X. New route synthesis of indolizines via 1, 3-dipolar cycloaddition of pyridiniums and alkynes. *Tetrahedron Lett.* **2009**, *50*, 6981−6984.

(5) Brioche, J.; Meyer, C.; Cossy, J. Synthesis of 2-aminoindolizines by 1,3-dipolar cycloaddition of pyridinium ylides with electron-deficient ynamides. *Org. Lett.* **2015**, *17*, 2800−2803.

(6) Kucukdisli, M.; Opatz, T. A modular synthesis of polysubstituted indolizines. *Eur. J. Org Chem.* **2012**, *2012*, 4555−4564.

(7) Dong, K. K.; Huang, Q. Metal-free synthesis of novel indolizines from chromones and pyridinium salts *via* 1, 3-dipolar cycloaddition, ring-opening and aromatization. *Tetrahedron Lett.* **2019**, *60*, 1871−1874.

(8) (a) Gribble, G. W. Synthesis and Reactions of Nitroindoles. *Prog. Heterocycl. Chem.* **2020**, *31*, 83−117. (b) Rkein, B.; Bigot, A.; Birbaum, L.; Manneveau, M.; De Paolis, M.; Legros, J.; Chataigner, I. Reactivity of 3-nitroindoles with electron-rich species. *Chem. Commun.* **2021**, *57*, 27−44. (c) Rkein, B.; Manneveau, M.; Noël-Duchesneau, L.; Pasturaud, K.; Durandetti, M.; Legros, J.; Lakhdar, S.; Chataigner, I. How electrophilic are 3-nitroindoles? Mechanistic investigations and application to a reagentless [4 + 2] cycloaddition. *Chem. Commun.* **2021**, *57*, 10071−10074.

(9) (a) Roy, S.; Gribble, G. W. Nucleophilic amination of 2-iodo-3-nitro-1-(phenylsulfonyl)indole. *Tetrahedron Lett.* **2007**, *48*, 1003−1005. (b) Lee, S.; Chataigner, I.; Piettre, S. R. Facile Dearomatization of Nitrobenzene Derivatives and Other Nitroarenes with *N*-Benzyl Azomethine Ylide. *Angew. Chem., Int. Ed.* **2011**, *50*, 472−476. (c) Lee, S.; Diab, S.; Queval, P.; Sebban, M.; Chataigner, I.; Piettre, S. R. Aromatic C−C Bonds as Dipolarophiles: Facile Reactions of Uncomplexed Electron-Deficient Benzene Derivatives and Other Aromatic Rings with a Non-Stabilized Azomethine Ylide. *Chem.−Eur. J.* **2013**, *19*, 7181−7192. (d) Andreini, M.; Chapellas, F.; Diab, S.; Pasturaud, K.; Piettre, S. R.; Legros, J.; Chataigner, I. Addition of 4-(cyclohex-1-en-1-yl)morpholine on 3-nitroindole: an unprecedented dearomatizing process. *Org. Biomol. Chem.* **2016**, *14*, 2833−2839. (e) Cheng, Q.; Zhang, F.; Cai, Y.; Guo, Y.; You, S. Stereodivergent Synthesis of Tetrahydrofuroindoles through Pd-Catalyzed Asymmetric Dearomative Formal [3 + 2] Cycloaddition. *Angew. Chem., Int. Ed.* **2018**, *57*, 2134−2138.

(10) (a) Pelkey, E. T.; Chang, L.; Gribble, G. W. An abnormal Barton−Zard reaction leading to the pyrrolo[2,3-*b*]indole ring system. *Chem. Commun.* **1996**, 1909−1910. (b) T Pelkey, E.; Gribble, G. W. One-step syntheses of the pyrrolo[3,4-*b*]indole and pyrrolo[2,3-*b*]indole ring systems from 3-nitroindoles. *Chem. Commun.* **1997**, 1873. (c) Chataigner, I.; Hess, E.; Toupet, L.; Piettre, S. R. Activation of the Dienophilicity of Indoles in Normal Electron Demand [4 + 2] Cycloadditions under High Pressure. *Org. Lett.* **2001**, *3*, 515−518. (d) Trost, B. M.; Ehmke, V.; O'Keefe, B. M.; Bringley, D. A. Palladium-Catalyzed Dearomative Trimethylenemethane Cycloaddition Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 8213−8216. (e) Li, Y.; Tur, F.; Nielsen, R. P.; Jiang, H.; Jensen, F.; Jørgensen, K. A. Enantioselective Formal [4 + 2] Cycloadditions to 3-Nitroindoles by Trienamine Catalysis: Synthesis of Chiral Dihydrocarbazoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 1020−1024. (f) Cao, D.; Ying, A.; Mo, H.; Chen, D.; Chen, G.; Wang, Z.; Yang, J. [4 + 2] Annulation of 3-Nitroindoles with Alkylidene Malononitriles: Entry to Substituted Carbazol-4-amine Derivatives. *J. Org. Chem.* **2018**, *83*, 12568−12574. (g) Mei, M.-S.; Wang, Y.-H.; Hu, Q.; Li, Q.-H.; Shi, D.-Y.; Gao, D.; Ge, G.; Lin, G.-Q.; Tian, P. Enantioselective [3 + 2] annulation of isatin-derived MBH-carbonates and 3-nitroindoles enabled by a bifunctional DMAP-thiourea. *Chem. Commun.* **2020**, *56*, 10718−10721. (h) Ling, J.; Mara, D.; Roure, B.; Laugeois, M.; Vitale, M. R. Copper(I)-Catalyzed Dearomative [3 + 2] Cycloaddition of 3-Nitroindoles with Propargylic Nucleophiles: An Access to Cyclopenta[*b*]indolines. *J. Org. Chem.* **2020**, *85*, 3838−3848.

(11) (a) Gribble, G. W.; Pelkey, E. T.; Switzer, F. L. New Syntheses of Pyrrolo[3,4 *b*]indoles, Benzo[*b*]furo[2,3-*c*]pyrroles, and Benzo[*b*]-thieno[2,3-*c*]pyrroles. Utilizing the Reaction of Münchnones (1,3-Oxazolium-5-olates) with Nitroheterocycles. *Synlett* **1998**, *1998*, 1061−1062. (b) Roy, S.; Kishbaugh, T. L. S.; Jasinski, J. P.; Gribble, G. W. 1,3-Dipolar cycloaddition of 2- and 3-nitroindoles with azomethine ylides. A new approach to pyrrolo[3,4-*b*]indoles. *Tetrahedron Lett.* **2007**, *48*, 1313−1316. (c) Awata, A.; Arai, T. PyBidine/Copper Catalyst: Asymmetric exo′-Selective [3 + 2] Cycloaddition using Imino Ester and Electrophilic Indole. *Angew. Chem., Int. Ed.* **2014**, *53*, 10462−10465. (d) Gerten, A. L.; Stanley, L. M. Enantioselective dearomative [3 + 2] cycloadditions of indoles with azomethine ylides derived from alanine imino esters. *Org. Chem. Front.* **2016**, *3*, 339−343. (e) Liu, X.; Yang, D.; Wang, K.; Zhang, J.; Wang, R. A catalyst-free 1,3-dipolar cycloaddition of C,*N*-cyclic azomethine imines and 3-nitroindoles: an easy access to five-ring-fused tetrahydroisoquinolines. *Green Chem.* **2017**, *19*, 82−87.

(12) (a) Nitha, P. R.; Jayadev, V.; Pradhan, S. C.; Divya, V. V.; Suresh, C. H.; John, J.; Soman, S.; Ajayaghosh, A. Regulating Back ElectronTransfer through Donor and π-Spacer Alterations in Benzothieno [3, 2-*b*] indole-based Dye-sensitized Solar Cells.

Chem.-Asian J. **2020**, *15*, 3503−3512. (b) Krishnan R, A.; Babu, S. A.; Nitha, P. R.; Krishnan, J.; John, J. Synthesis of Benzothienobenzofurans *via* Annulation of Electrophilic Benzothiophenes with Phenols. *Org. Lett.* **2021**, *23*, 1814−1819. (c) Paul, D.; John, J. Recent Advances towards the Synthesis and Material Applications of Indoloindoles. *Chem.-Asian. J.* **2022**, *17*, No. e202200460. (d) Krishnan R, A.; Babu, S. A.; Ravi, N. P.; Thulasi, S.; John, J. Base-Mediated Annulation of Electrophilic Benzothiophene with Naphthols and Phenols: Accessing Benzothiophene-Fused Heteroacenes. *J. Org. Chem.* **2022**, *87*, 8017−8027. (e) Babu, S. A.; V, P. V.; Poulose, S.; Varughese, S.; John, J. Copper-Catalyzed Annulation of Electrophilic Benzannulated Heterocycles with 2-Aminopyridine and 2-Aminoquinoline: Direct Access toward Polyring-Fused Imidazo[1,2-*a*]pyridines. *J. Org. Chem.* **2023**, *88*, 10027−10039.

(13) (a) Babu, S. A.; A R, R.; Nitha, P. R.; Omanakuttan, V. K.; P, R.; Varughese, S.; John, J. Unprecedented access to functionalized pyrrolo[2,1-*a*]isoquinolines from the domino reaction of isoquinolinium ylides and electrophilic benzannulated heterocycles. *Org. Biomol. Chem.* **2021**, *19*, 1807−1817.

(14) (a) Labinger, J. A.; Bercaw, J. E. Understanding and exploiting C−H bond activation. *Nature* **2002**, *417*, 507−514. (b) Collet, F.; Dodd, R. H.; Dauban, P. Catalytic C−H amination: recent progress and future directions. *Chem. Commun.* **2009**, *34*, 5061. (c) Gutekunst, W. R.; Baran, P. S. C−H functionalization logic in total synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1976. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C-H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem., Int. Ed.* **2012**, *51* (36), 8960−9009. (e) Roudesly, F.; Oble, J.; Poli, G. Metal-catalyzed C-H activation/functionalization: The fundamentals. *J. Mol. Catal. A: Chem.* **2017**, *426*, 275−296. (f) Crabtree, R. H.; Lei, A. Introduction: C-H Activation. *Chem. Rev.* **2017**, *117*, 8481−8482. (g) Romero, A. H. Fused Heteroaromatic Rings via Metal-Mediated/Catalyzed Intramolecular C−H Activation: A Comprehensive Review. *Top. Curr. Chem.* **2019**, *377*, 21. (h) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. *Chem. Rev.* **2020**, *120*, 2613−2692. (i) Rej, S.; Das, A.; Chatani, N. Strategic evolution in transition metal-catalyzed directed C−H bond activation and future directions. *Coord. Chem. Rev.* **2021**, *431*, 213683.

(15) (a) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent Advances in Radical C−H Activation/Radical Cross-Coupling. *Chem. Rev.* **2017**, *117*, 9016−9085. (b) Xia, Y.; Wang, L.; Studer, A. Site-Selective Remote Radical C−H Functionalization of Unactivated C−H Bonds in Amides Using Sulfone Reagents. *Angew. Chem., Int. Ed.* **2018**, *57*, 12940−12944. (c) Song, S.-Z.; Meng, Y.-N.; Li, Q.; Wei, W.-T. Recent Progress in the Construction of C−N Bonds via Metal-Free Radical C(sp^3)−H Functionalization. *Adv. Synth. Catal.* **2020**, *362*, 2120−2134.

(16) (a) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. Selective Intermolecular Carbon-Hydrogen Bond Activation by Synthetic Metal Complexes in Homogeneous Solution. *Acc. Chem. Res.* **1995**, *28*, 154−162. (b) Shilov, A. E.; Shul'pin, G. B. Activation of C−H Bonds by Metal Complexes. *Chem. Rev.* **1997**, *97*, 2879−2932.

(17) (a) Crabtree, R. H. Alkane C−H activation and functionalization with homogeneous transition metal catalysts: a century of progress-a new millennium in prospect. *J. Chem. Soc., Dalton Trans.* **2001**, 2437−2450. (b) Dick, A. R.; Sanford, M. S. Transition metal catalyzed oxidative functionalization of carbon−hydrogen bonds. *Tetrahedron* **2006**, *37*, 2439. (c) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. Functionalization of Organic Molecules by Transition-Metal-Catalyzed C(sp^3)-H Activation. *Chem.−Eur. J.* **2010**, *16*, 2654−2672. (d) Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. Site-selective and stereoselective functionalization of unactivated C−H bonds. *Nature* **2016**, *533*, 230−234. (e) Davies, H. M. L.; Morton, D. Recent Advances in C−H Functionalization. *J. Org. Chem.* **2016**, *81*, 343−350. (f) Hartwig, J. F.; Larsen, M. A. Undirected, Homogeneous C−H Bond Functionalization: Challenges and Opportunities. *ACS Cent. Sci.* **2016**, *2*, 281−292. (g) Davies, H. M. L.; Morton, D. Collective Approach to Advancing C−H Functionalization. *ACS Cent. Sci.* **2017**, *3*, 936−943. (h) Berger, F.; Plutschack, M. B.; Riegger, J.; Yu, W.; Speicher, S.; Ho, M.; Frank, N.; Ritter, T. Site-selective and versatile aromatic C−H functionalization by thianthrenation. *Nature* **2019**, *567*, 223−228.

(18) Babu, S. A.; Varughese, S.; Mathew, J.; John, J. Discovery of Oxygen Induced Chemoselectivity in Pd-catalyzed C-H Functionalization: Cross-Dehydrogenative Coupling *vs* C-H Amination. *J. Org. Chem.* **2023**, *88*, 9877−9892.

(19) (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C−H bond activation strategy for C−C and C−N bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5068. (b) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon−Carbon Bonds by Oxidizing Two Carbon−Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215−1292. (c) Liu, J.; Xiong, X.; Chen, J.; Wang, Y.; Zhu, R.; Huang, J. Double C-H Activation for the C-C bond Formation Reactions. *Curr. Org. Synth.* **2018**, *15*, 882−903. (d) Campo, M. A.; Larock, R. C. Synthesis of fluoren-9-ones via palladium-catalyzed cyclocarbonylation of o-halobiaryls. *Org. Lett.* **2000**, *2*, 3675−3677. (e) Wang, G. W.; Yuan, T. T.; Li, D. D. One-pot formation of C-C and C-N bonds through palladium-catalyzed dual C-H activation: synthesis of phenanthridinones. *Angew. Chem., Int. Ed. Engl.* **2011**, *50*, 1380−1383. (f) Li, H.; Zhu, R.-Y.; Shi, W.-J.; He, K.-H.; Shi, Z.-J. Synthesis of Fluorenone Derivatives through Pd-Catalyzed Dehydrogenative Cyclization. *Org. Lett.* **2012**, *14*, 4850−4853. (g) Samanta, R.; Matcha, K.; Antonchick, A. P. Metal-Free Oxidative Carbon-Heteroatom Bond Formation Through C−H Bond Functionalization. *Eur. J. Org Chem.* **2013**, *2013*, 5769−5804. (h) Batra, A.; Singh, K. N. Recent Developments in Transition Metal-Free Cross-Dehydrogenative Coupling Reactions for C−C Bond Formation. *Eur. J. Org Chem.* **2020**, *2020*, 6676−6703.

(20) Wang, L.; Guo, W.; Zhang, X.-X.; Xia, X.-D.; Xiao, W.-J. Synthesis of Indolo [1,2-a]Quinoxalines *via* a Pd-Catalyzed Regioselective C−H Olefination/Cyclization Sequence. *Org. Lett.* **2012**, *14*, 740−743.

(21) (a) Roizen, J. L.; Harvey, M. E.; Du Bois, J. Metal-Catalyzed Nitrogen-Atom Transfer Methods for the Oxidation of Aliphatic C−H Bonds. *Acc. Chem. Res.* **2012**, *45*, 911−922. (b) Louillat, M.-L.; Patureau, F. W. Oxidative C−H amination reactions. *Chem. Soc. Rev.* **2014**, *43*, 901−910. (c) Hazelard, D.; Nocquet, P.-A.; Compain, P. Catalytic C−H amination at its limits: challenges and solutions. *Org. Chem. Front.* **2017**, *4*, 2500−2521. (d) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C−H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247−9301. (e) Timsina, Y. N.; Gupton, B. F.; Ellis, K. C. Palladium-Catalyzed C−H Amination of C(sp^2) and C(sp^3)−H Bonds: Mechanism and Scope for N-Based Molecule Synthesis. *ACS Catal.* **2018**, *8*, 5732−5776.

(22) (a) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. Dioxygen-Coupled Oxidative Amination of Styrene. *J. Am. Chem. Soc.* **2003**, *125*, 12996−12997. (b) Timokhin, V. I.; Stahl, S. S. Brønsted Base-Modulated Regioselectivity in the Aerobic Oxidative Amination of Styrene Catalyzed by Palladium. *J. Am. Chem. Soc.* **2005**, *127*, 17888−17893. (c) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. Aerobic Oxidative Amination of Unactivated Alkenes Catalyzed by Palladium. *J. Am. Chem. Soc.* **2005**, *127*, 2868−2869. (d) Scarborough, C. C.; Stahl, S. S. Synthesis of Pyrrolidines via Palladium(II)-Catalyzed Aerobic Oxidative Carboamination of Butyl Vinyl Ether and Styrenes with Allyl Tosylamides. *Org. Lett.* **2006**, *8*, 3251−3254. (e) Rogers, M. M.; Kotov, V.; Chatwichien, J.; Stahl, S. S. Palladium-Catalyzed Oxidative Amination of Alkenes: Improved Catalyst Reoxidation Enables the Use of Alkene as the Limiting Reagent. *Org. Lett.* **2007**, *9*, 4331−4334.

(23) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. Combined C−H Functionalization/C−N Bond Formation Route to Carbazoles. *J. Am. Chem. Soc.* **2005**, *127*, 14560−14561. (b) Tsang, W. C.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. Palladium-catalyzed

https://doi.org/10.1021/acsomega.3c10194
ACS Omega 2024, 9, 16196−16206

method for the synthesis of carbazoles via tandem C-H functionalization and C-N bond formation. *J. Org. Chem.* **2008**, *73*, 7603−7610.
(24) (a) Shiotani, A.; Itatni, H.; Inagaki, T. Selective coupling of dimethyl phthalate with palladium catalysts at atmospheric pressure. *J. Mol. Catal.* **1986**, *34* (1), 57−66. (b) Wu, Y.; Wang, J.; Mao, F.; Kwong, F. Y. Palladium-Catalyzed Cross-Dehydrogenative Functionalization of C(sp^2)-H Bonds. *Chem.—Asian J.* **2014**, *9*, 26−47.
(25) Zierkiewicz, W.; Privalov, T. A Theoretical Study of the Essential Role of DMSO as a Solvent/Ligand in the $Pd(OAc)_2$/DMSO Catalyst System for Aerobic Oxidation. *Organometallics* **2005**, *24*, 6019−6028.
(26) (a) Stahl, S. S. Palladium Oxidase Catalysis: Selective Oxidation of Organic Chemicals by Direct Dioxygen-Coupled Turnover. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (b) Diao, T.; Pun, D.; Stahl, S. S. Aerobic Dehydrogenation of Cyclohexanone to Cyclohexenone Catalyzed by $Pd(DMSO)_2(TFA)_2$: Evidence for Ligand-Controlled Chemoselectivity. *J. Am. Chem. Soc.* **2013**, *135*, 8205−8212. (c) Pun, D.; Diao, T.; Stahl, S. S. Aerobic Dehydrogenation of Cyclohexanone to Phenol Catalyzed by Pd(TFA)2/2-Dimethylaminopyridine: Evidence for the Role of Pd Nanoparticles. *J. Am. Chem. Soc.* **2013**, *135*, 8213−8221.
(27) (a) Gligorich, K. M.; Sigman, M. S. Mechanistic Questions about the Reaction of Molecular Oxygen with Palladium in Oxidase Catalysis. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612−6615. (b) Popp, B. V.; Stahl, S. S. Insertion of Molecular Oxygen into a Palladium−Hydride Bond: Computational Evidence for Two Nearly Isoenergetic Pathways. *J. Am. Chem. Soc.* **2007**, *129*, 4410−4422. (c) Popp, B. V.; Wendlandt, J. E.; Landis, C. R.; Stahl, S. S. Reaction of Molecular Oxygen with an NHC-Coordinated Pd0 Complex: Computational Insights and Experimental Implications. *Angew. Chem., Int. Ed.* **2007**, *46*, 601−604. (d) Scheuermann, M. L.; Boyce, D. W.; Grice, K. A.; Kaminsky, W.; Stoll, S.; Tolman, W. B.; Swang, O.; Goldberg, K. I. Oxygen-Promoted C-H Bond Activation at Palladium. *Angew. Chem., Int. Ed.* **2014**, *53*, 6492−6495. (e) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions. *Chem. Rev.* **2018**, *118*, 2636−2679.
(28) Monguchi, Y.; Okami, H.; Ichikawa, T.; Nozaki, K.; Maejima, T.; Oumi, Y.; Sawama, Y.; Sajiki, H. Palladium on Carbon-Catalyzed C−H Amination for Synthesis of Carbazoles and its Mechanistic Study. *Adv. Synth. Catal.* **2016**, *358*, 3145−3151.

https://doi.org/10.1021/acsomega.3c10194
ACS Omega 2024, 9, 16196−16206