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Letter

Divergent Syntheses of Indoles and Quinolines Involving N1−C2−C3 Bond Formation through Two Distinct Pd Catalyses

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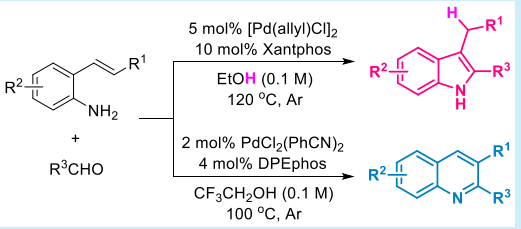
ABSTRACT: Pd-catalyzed annulative couplings of 2-alkenylanilines with aldehydes using alcohols as both the solvent and hydrogen source have been developed. These domino processes allow divergent syntheses of two significant *N*-heterocycles, indoles and quinolines, from the same substrate by tuning reaction parameters, which seems to invoke two distinct mechanisms. The nature of the ligand and alcoholic solvent had a profound influence on the selectivity and efficiency of these protocols. Particularly noteworthy is that indole formation was achieved by overcoming two significant challenges, regioselective hydropalladation of alkenes and subsequent reactions between the resulting Csp^3−Pd species and less reactive imines.

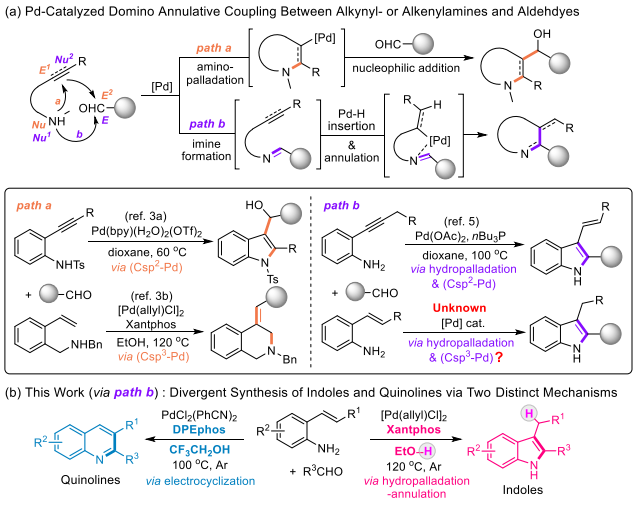


Transition-metal-catalyzed domino annulations enable several transformations in one operation with high selectivity and efficiency, leading to synthesis of a diverse range of carbo- and heterocycles from relatively simple starting materials.[1] In these reactions, the subsequent reactions occur as a consequence of the functionality achieved in the prior step. Thus, switching the reacting sequence may allow access to diverse scaffolds. In recent years, catalytic reactions to transform common substrates or intermediates into distinct molecular scaffolds have increasingly been explored. In this regard, use of different ligands often allows modulation of chemo- and/or regioselectivity, resulting in selective formation of divergent products.[2]

Pd-catalyzed cyclization of nitrogen-containing unsaturated compounds is a straightforward method for constructing *N*-heterocycles such as indoles and quinolines.[1a−i] When aldehydes are added as another reactant in this process, two reaction pathways could occur: (1) aminopalladation followed by nucleophilic addition of the resulting Pd species to aldehydes (Scheme 1a, path a) or (2) initial imine formation followed by annulative coupling (path b).

For path a, Han and Lu reported a cationic Pd-catalyzed domino aminopalladation, nucleophilic addition with aldehydes, and protonation to afford 2-aryl-3-hydroxymethylindoles involving the alkenylpalladium (Csp^2−Pd) species (left upper quadrant in the box of Scheme 1a).[3a] Recently, Huang successfully demonstrated such reactions with alkenylamines by controlling β-hydride elimination of the resulting alkylpalladium (Csp^3−Pd) species,[4] which is highly challenging (left lower quadrant).[3b] In this protocol, only electron-donating alkyl groups on the N atom could promote the reaction, while free NH_2 gave only the corresponding imines resulting from the reaction with aldehydes.

Scheme 1. Divergent Domino Reactions for Selective Formation of *N*-Heterocycles



In contrast, a different reaction order in Pd catalysis (path b) was observed by Yamamoto's group. The initial imine formation triggers hydropalladation of an alkyne moiety followed by annulative addition of the resulting Csp^2−Pd species to imine, leading to 3-alkenylindoles by forming the N1−C2−C3 bonds of the pyrrole nucleus of indoles (right

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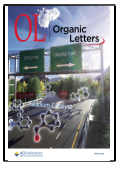

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upper quadrant).[5] Related cationic Pd-catalyzed tandem processes involving initial hydropalladation and sequential intramolecular addition of alkyne-tethered carbonyl compounds using ethanol as a hydrogen source were also reported by Han and Lu.[6] Inspired by these prior studies,[3b,5,6] we envisioned that initially formed imines from 2-alkenylanilines and aldehydes might undergo regioselective hydropalladation of alkenes followed by annulative coupling of the resulting Csp^3–Pd species with an imine to give indoles (right lower quadrant).

Here, we disclose the realization of this proposal. Pd-catalyzed annulative couplings of 2-alkenylanilines with aldehydes led to divergent syntheses of indoles and quinolines, which are both significant heterocycles due to their ubiquity and broad applications (Scheme 1b).[7,8] In sharp contrast to prior work using 2-alkynylanilines,[9,10] alcohols were used as both the hydrogen source[11] and solvent rather than a nucleophile, in the reactions presented herein.

Considering several reports on the effect of *N*-protecting groups in aminopalladation,[3,12] we first examined various *N*-protecting groups under Huang's conditions[3b] to identify one with a delicately balanced nucleophilicity for aminopalladation and imine/iminium ion formation.[13] Among them, *N*-Boc, *N*-alkyl, and NH_2 free derivatives afforded the desired products, and NH_2 free anilines were the optimal substrate for this reaction, promoting rapid imine formation rather than aminopalladation.

Subsequently, we conducted an extensive investigation of this process using **1a** and PhCHO. Ideally, suitable ligands could stabilize the speculated Csp^3–Pd species and allow switching of the regioselectivity of the proposed reaction. After careful examination of the reaction parameters, we found that a reagent blend consisting of $[Pd(allyl)Cl]_2$ and Xantphos in EtOH afforded **3a** along with a smaller amount of **4a**.[13] When the solvent was changed to F-containing alcohol, the ratio of **4a** to **3a** increased (entries 5 and 6). Selectivity for **4a** was markedly improved by switching the ligand from Xantphos to DPEphos in F-containing alcohol solvents (entries 13–16). From the evaluation of bidentate phosphine ligands (Table 1, bottom), we observed preliminary relationships among ligand bite angle, reactivity, and selectivity.[14] With the exception of dppf, bisphosphine ligands with bite angles of ~110° showed good efficiency for indole formation, and the use of Xantphos (108°) provided the best result, while DPEphos had an optimal bite angle (104°) for quinoline formation.

Although Conditions A and B selectively provided **3a** and **4a**, respectively, the selectivity for **3a** over **4a** and the yields of both were only moderate. In addition, although the ratio of **4a** to **3a** was generally good under Conditions B, a non-negligible amount of an indoline side product (e.g., **5a**)[13] was always observed. Therefore, a variety of additives were examined to determine more effective conditions, but no beneficial effect was obtained in any case.

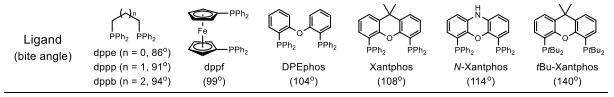
Under Conditions A and B, the reaction of (*Z*)-**1a** also afforded **3a** and **4a**, respectively, in comparable selectivity but lower yields compared to (*E*)-**1a** (entry 7 vs 8, entry 19 vs 20). During the course of these studies, we observed that substituents residing on the aromatic moiety of anilines had a very intriguing effect on the reactivity and selectivity of indole formation. When **1b** (R = Me) was used as a substrate, both yield and ratio of products were significantly improved to afford **3b** as the sole product in 90% yield (entry 9), while this was unsuitable for quinoline formation (entry 21). While the reason for this substituent effect in indole synthesis remains unclear at this stage, we surmised that the steric effect of *ortho*-Me substituent might render the imine's C atom being in close proximity to a speculated Csp^3–Pd species (arising from hydropalladation of alkene) to cause a more favorable subsequent reaction (for a detailed explanation, see the Supporting Information).[13]

It should be noted that both cationic Pd(II) species[3a,15] and typical Lewis acids were unable to promote this reaction for formation of **3a**, whereas all tested Lewis acids afforded **4a** in low to moderate yield.[13] These findings suggest that indole formation under Conditions A is unlikely to involve Lewis acid catalyzed electrophilic cyclization via imine activation, which might be involved in the synthesis of quinolines under Conditions B.[16] Control experiments indicated that all the

Table 1. Optimization Studies

Entry	1	Pd Catalyst (mol%)	Ligand (mol%)	Solvent	3 (%)[a]	4 (%)[a]
1	**1a**	$Pd(OAc)_2$ (2.5)	Xantphos (5.5)	EtOH	-	-
2	**1a**	$PdCl_2(PhCN)_2$ (2.5)	Xantphos (5.5)	EtOH	(38)	(20)
3	**1a**	$[Pd(allyl)Cl]_2$ (2.5)	Xantphos (5.5)	EtOH	(44)	(22)
4	**1a**	$[Pd(allyl)Cl]_2$ (2.5)	Xantphos (5.5)	*i*PrOH	10	7
5	**1a**	$[Pd(allyl)Cl]_2$ (2.5)	Xantphos (5.5)	TFE	(23)	(31)
6	**1a**	$[Pd(allyl)Cl]_2$ (2.5)	Xantphos (5.5)	HFIP	(23)	(32)
7	**1a**	$[Pd(allyl)Cl]_2$ (5)	Xantphos (10)	EtOH	(55)	(25)
8[b]	**1a**	$[Pd(allyl)Cl]_2$ (5)	Xantphos (10)	EtOH	(24)	(11)
9[c]	**1b**	$[Pd(allyl)Cl]_2$ (5)	Xantphos (10)	EtOH	**(90)**	-
10	**1a**	$[Pd(allyl)Cl]_2$ (5)	-	EtOH	-	4
11	**1a**	-	Xantphos (10)	EtOH	-	-
12	**1a**	-	-	EtOH	-	-
13	**1a**	$Pd(OAc)_2$ (2.5)	DPEphos (5.5)	TFE	4	(54)
14	**1a**	$[Pd(allyl)Cl]_2$ (2.5)	DPEphos (5.5)	TFE	7	(42)
15	**1a**	$PdCl_2(PhCN)_2$ (2.5)	DPEphos (5.5)	TFE	6	(55)
16	**1a**	$PdCl_2(PhCN)_2$ (2.5)	DPEphos (5.5)	HFIP	-	29
17	**1a**	$PdCl_2(PhCN)_2$ (2.5)	DPEphos (5.5)	EtOH	trace	13
18	**1a**	$PdCl_2(PhCN)_2$ (2.5)	DPEphos (5.5)	*i*PrOH	-	-
19[d]	**1a**	$PdCl_2(PhCN)_2$ (2)	DPEphos (4)	TFE	3	**(56)**
20[b,d]	**1a**	$PdCl_2(PhCN)_2$ (2)	DPEphos (4)	TFE	-	(31)
21[d]	**1b**	$PdCl_2(PhCN)_2$ (2)	DPEphos (4)	TFE	25	-
22[d]	**1a**	$PdCl_2(PhCN)_2$ (2)	-	TFE	-	13
23[d]	**1a**	-	DPEphos (4)	TFE	-	-
24[d]	**1a**	-	-	TFE	-	2

- **Conditions A** : 5 mol% $[Pd(allyl)Cl]_2$, 10 mol% ligand in EtOH (0.1 M) at 120 °C for 24 h under Ar
- **Conditions B** : 2 mol% $PdCl_2(PhCN)_2$, 4 mol% ligand in CF_3CH_2OH (0.1 M) at 100 °C for 24 h under Ar



Ligand (bite angle)	dppe (86°) / dppp (91°) / dppb (94°)	dppf (99°)	DPEphos (104°)	Xantphos (108°)	*N*-Xantphos (114°)	*t*Bu-Xantphos (140°)
Conditions A[e]	0~4/0~11	(44)/(28)	0/trace	**(55)**/(25)	21/14	0/0[f]
Conditions B[e]	0/0	0/0	3/**(56)**	0/24	0/0[f]	0/7[f]

[a]Determined by ^1H NMR. Values in parentheses indicate isolated yields. [b]Using (*Z*)-**1a** instead of (*E*)-**1a**. [c]For 4 h. [d]At 100 °C. [e]Yields of **3a**/**4a**. [f]Using 2.5 mol % Pd catalyst and 5.5 mol % ligand at 120 °C.

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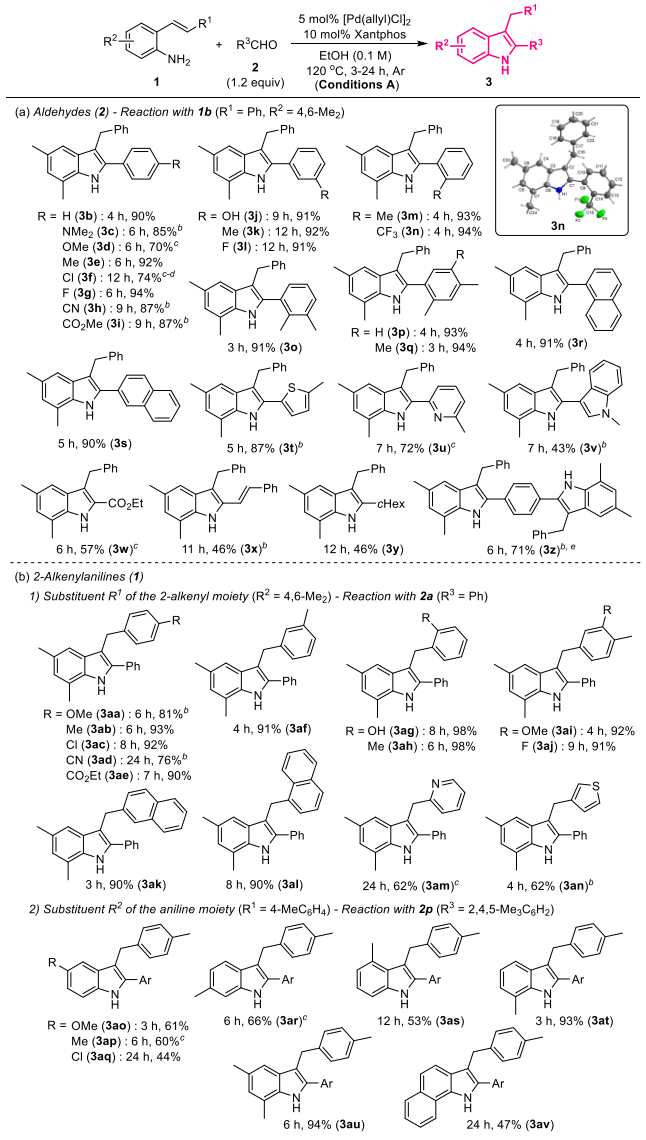
Org. Lett. 2020, 22, 9151–9157

reaction components (Pd, ligand, alcohol) were necessary for both reactions to occur (entries 10−12 and 22−24).

With viable catalytic systems for each indole and quinoline synthesis, we explored the substrate scope of these processes. First, we examined the reaction of various aldehydes with **1b** under Conditions A (Scheme 2a). In general, a variety of

Scheme 2. Substrate Scope: Indoles[a]



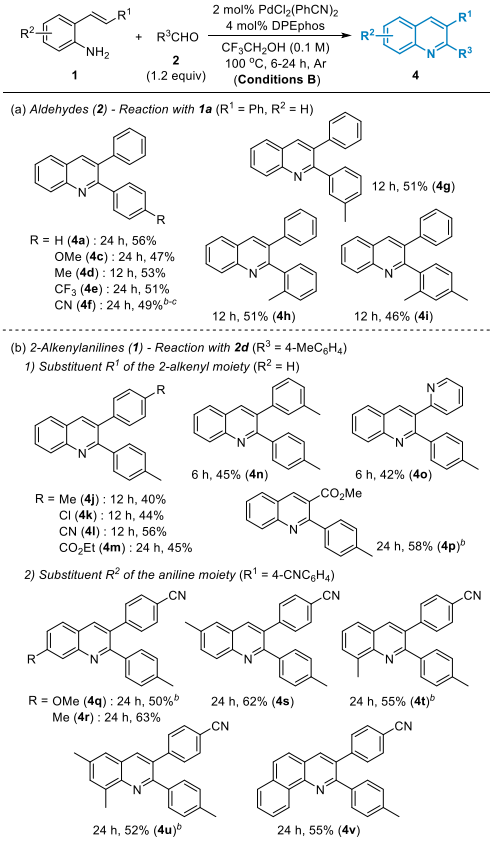
[a]Isolated yields. Quinoline byproducts (e.g., **4a**) were obtained in ≤5% yields unless otherwise noted. [b]Quinolines were obtained in 5−15% ^{1}H NMR yields. [c]Quinolines were obtained in 15−25% ^{1}H NMR yields. [d]Inseparable mixture of **3f** and dechlorinated product (i.e., **3b**) was obtained with a 10:1 ratio in 74% combined yield. [e]2.1 equiv of **1b** and 1 equiv of terephthalaldehyde were used.

arylaldehydes were well tolerated with little electronic and steric dependence, leading to diversely substituted indoles (**3a**−**s**) in high yields with good to excellent selectivities. Heteroaryl- (**3t**-**v**), ester- (**3w**), alkenyl- (**3x**), and secondary alkyl-substituted (**3y**) aldehydes proved to be suitable, while the reaction failed with primary alkylaldehydes. The reaction with terephthalaldehyde proceeded uneventfully to afford bisindole **3z** in 71% yield.

Next, we explored the substituent effect (R^1) at the alkene moiety of **1** (Scheme 2b-1). Various (hetero)aryl-substituted alkenes smoothly underwent this reaction to afford **3aa**−**an** in good to high yields. Unfortunately, alkyl-substituted alkenes resulted in low conversion. The effects of substituents (R^2) residing on the aromatic moiety of **1** were also investigated (Scheme 2b-2). As mentioned earlier, a methyl substituent at the *ortho* position had a significant influence on chemical reactivity, forming **3at**−**au** with excellent yields and selectivities. In contrast, other substituents (e.g., OMe, OH, F) located at the same position had deleterious effects, producing low yields (7−24%) of the desired products.

As shown in Scheme 3, diversely substituted **1** and **2** could also be successfully employed to give the corresponding 2,3-

Scheme 3. Substrate Scope: Quinolines[a]



[a]Isolated yields. In most cases, indole (e.g., **3a**) and indoline (e.g., **5a**) byproducts were obtained in 0−≤5% and 10−25% ^{1}H NMR yields, respectively, unless otherwise noted. [b]Indoline byproducts were not observed. [c]**7b** was obtained in 14% yield.

diaryl-substituted quinolines **4**, albeit in moderate yields. We note that various functional groups were commonly well tolerated in both indole- and quinoline-forming reactions except for a nitro group. No matter where the NO_2 group resided in **1** and **2**, no reaction occurred or only imine intermediates were observed.

A series of control experiments were performed to gain mechanistic insight into these reactions.[13] Imine intermediates such as **6a** were observed during the reaction progress. Therefore, probable intermediates (**6a**−**b**) were synthesized and subjected to Conditions A and B. Each reaction resulted in formation of **3b** and **4a** in 88% and 40% yield, respectively

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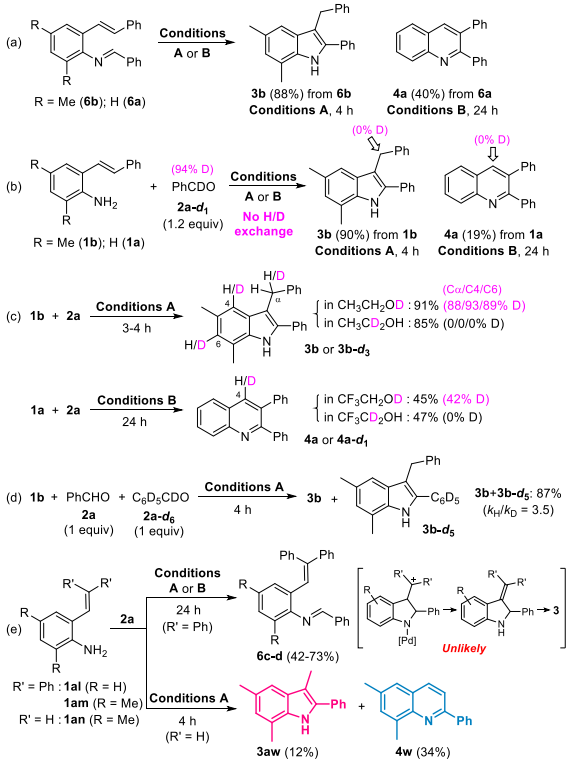
Org. Lett. 2020, 22, 9151−9157

(Scheme 4a); the latter result is distinct from a related Pd catalysis reported by Jiang.[17]

Scheme 4. Mechanistic Studies



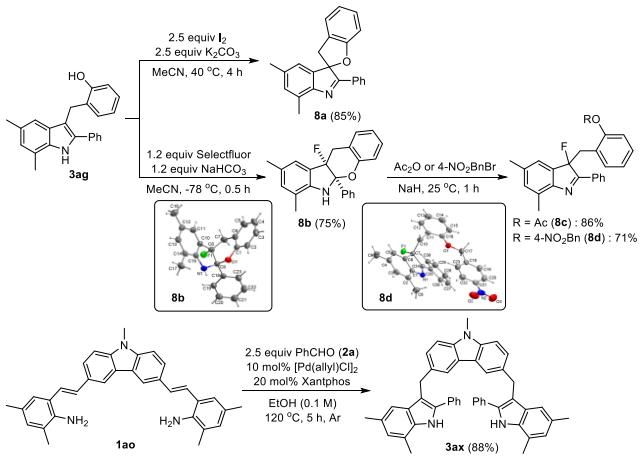
Next, deuterium-labeling experiments were carried out. The reaction of **1b** or **1a** with PhCDO afforded **3b** or **4a** with no deuterium incorporation (Scheme 4b), excluding the involvement of initial oxidative addition of an imine C−D bond to Pd[17] followed by carbopalladation or hydropalladation to an alkene moiety. When the reaction of **1b** with **2a** was carried out in CH_3CH_2OD under Conditions A, indole **3b** with deuterium at the benzylic position of the C3 substituent (88% D) was formed, whereas no deuterium incorporation was observed in CH_3CD_2OH (Scheme 4c, upper).[11e−g] Similarly, quinoline **4a** deuterated at the C4 position (42% D) was obtained using CF_3CH_2OD under Conditions B, while deuterium was not incorporated into **4a** in CF_3CD_2OH (Scheme 4c, lower). These findings indicate that the incoming hydrogen atoms for the benzylic position of the C3 substituent of **3b** and for the C4 position of **4a** are derived from O−H groups[11c−i] instead of the αC−H bond of alcohols.[6,11j−p] Moreover, as mentioned, quinoline synthesis was accompanied by some byproducts, such as *N*-benzylanilines (**7**) generated by reduction of **6**[18] and their cyclized products, indolines (e.g., **5a**).[13] Interestingly, **7** deuterated at the benzylic position was also obtained in the reactions using ROD-type solvents. Competition experiments with deuterium-labeled **2a** demonstrated a kinetic isotope effect of 3.5 (Scheme 4d), suggesting that C−H bond cleavage of imine[17] may be involved in the rate-determining step.

Reactions employing β,β-disubstituted (**1al**−**am**) and terminal alkenes (**1an**) as a substrate were undertaken to demonstrate that Lewis acid catalyzed Prins-type reactions[10,11q,r] are a possible mechanistic pathway in the indole-forming process. The former failed to give the desired indoles, while the latter produced 3-methylindole **3aw** along with **4w**, albeit in low yields (Scheme 4e). This constitutes evidence against an electrophilic pathway involving a carbocationic intermediate and ethanol as a proton source in the indole-forming reaction under Conditions A.

Although more detailed investigations are needed to clarify the mechanism, our experimental findings suggest that these two reactions proceed through different mechanistic pathways.[13] For quinoline (**4**) synthesis, the reaction seems to take place through 6π-electrocyclization of imine intermediates (**6**) promoted by Lewis acidic Pd salt.[16] In sharp contrast, indole (**3**) formation presumably commences with regioselective insertion of the alkene moiety of **6** into the Pd−H bond.[19] Then, subsequent reactions between the resulting Csp^3−Pd species and imine moiety may occur through either oxidative addition/reductive elimination[17] or carbopalladation/β-hydride elimination,[5,6] followed by isomerization to afford **3**.

To highlight the synthetic utility of this transformation, dearomatization of indoles, a powerful tool for construction of spiroindolenine and polycyclic indoline skeletons,[20] was undertaken (Scheme 5). I_2-mediated cyclization[21] and

Scheme 5. Synthetic Applications



fluoroetherification[22] of **3ag** proceeded smoothly to afford spiroindolenine **8a** and fused indoline **8b**, respectively. Subsequent acetylation or benzylation gave indolenines **8c**−**d** containing a fluorinated quaternary carbon center through ring opening. On the other hand, 3-(indolylmethyl)carbazole derivatives are known as highly efficient hosts for phosphorescent OLEDs[23a] and as colorimetric/fluorometric detectors of DNA.[23b] Reaction of carbazole-tethered **1ao** with PhCHO was readily accomplished to afford **3ax** in 88% yield.

In summary, we developed Pd-catalyzed domino annulative processes, one of which involves the significant challenges associated with controlling both regioselective hydropalladation and reaction of alkylpalladium species with less reactive imines. We demonstrated that exquisite tuning of reaction parameters such as ligand and solvent could modulate the reaction propensity and pathway for formation of different molecular frameworks from the same substrate. In these protocols, alcohols were used as the hydrogen source as well as solvent, delivering hydrogen atoms from O−H groups rather than the αC−H of alcohols. To the best of our knowledge, this represents the first example of Pd-catalyzed domino couplings between alkenes and imines generated in situ from amines and

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aldehydes, leading to construction of two different *N*-heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02898.

Full experimental details and characterization data (PDF)

Accession Codes

CCDC 2012360 and 2012365−2012366 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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