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Merging C−H Activation and Alkene Difunctionalization at Room Temperature: A Palladium-Catalyzed Divergent Synthesis of Indoles and Indolines

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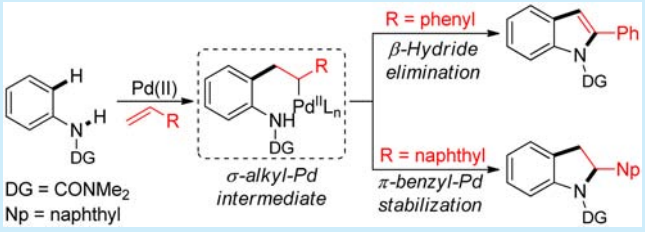
Supporting Information

ABSTRACT: A palladium-catalyzed 1,2-carboamination through C−H activation at room temperature is reported for the synthesis of 2-arylindoles, and indolines from readily available, inexpensive aryl ureas and vinyl arenes. The reaction initiates with a urea-directed electrophilic ortho palladation, alkene insertion, and β-hydride elimination sequences to provide the Fujiwara−Moritani arylation product. Subsequently, aza-Wacker cyclization, and β-hydride elimination provide the 2-arylindoles in high yields. Intercepting the common σ-alkyl-Pd intermediate, corresponding indolines are also achieved. The indoline formation is attributed to the generation of stabilized, cationic π-benzyl-Pd species to suppress β-hydride elimination.



Nitrogen-containing heterocycles, particularly indoles and indolines, are prevalent in numerous pharmaceuticals, natural products, agrochemicals, and functionalized materials.[1] Therefore, a significant effort has been devoted to their synthesis, and sustained progress has been made through Fisher,[2] Larock,[3] Buchwald,[4] and Hegedus[5] indole synthesis. In the past decade, the transition-metal-catalyzed C−H activation strategy has enabled the generation of indole moiety directly from anilines or protected anilines obviating rigorous prefunctionalizations. In this vein, two distinct strategies have been well explored: (a) intramolecular cyclization of *N*-arylenamines or -imines[6] and (b) intermolecular cyclization of anilines and alkynes.[7] We hypothesized that annulation of aniline derivatives with readily available and inexpensive olefins such as styrenes to afford 2-arylindoles and 2-arylindolines in intermolecular fashion will be synthetically attractive but challenging due to the facile β-hydride elimination. In fact, the potential of simple olefins was realized in the synthesis of *N*-arylindoles from diarylamines.[8] However, this methodology is limited due to the formation of inseparable mixture of regioisomers from unsymmetrical diarylamines and requires high temperature to occur. To exploit the full potential of C−H functionalization in the complex molecule synthesis,[9] development of expedient methods under mild conditions, particularly at room temperature,[10] is in high demand. Intrigued by the key mechanistic features, here we report a palladium-catalyzed divergent synthesis of 2-arylindole and indoline through a dehydrogenetive coupling of aryl urea and vinyl arene at room temperature.

Our initial screening with acetanilide and styrene in acetic acid at 110 °C was in vain due to the deleterious dimerization of styrene. Switching to other solvents such as 1,4-dioxane, the dimerization was reduced but not diminished. Therefore, we turned our attention to optimize this cascade reaction at room temperature. Cationic palladium complexes are known to undergo facile electrophilic palladation to aryl urea derivatives at room temperature.[10d,g−i] Gratifyingly, using *N*,*N*-dimethyl-*N*′-phenylurea and commercially available electrophilic Pd(tfa)$_2$, Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ complexes, the yield of the desired product was improved at room temperature. Palladium(II) acetate, in the presence of excess TsOH, is known to generate highly electrophilic palladium mono- or bistosylate species in situ.[11] Interestingly, ubiquitous Pd(OAc)$_2$ in combination with TsOH and inexpensive 1,4-benzoquinone (BQ) was found to be optimal for the catalytic turnover. Other oxidants such as O$_2$, *N*-ligands/O$_2$, Cu(OAc)$_2$, AgOAc, and even DDQ were ineffective. Presumably, BQ has a dual role as ligand as well as oxidant in palladium(II) catalysis, and the redox process is anticipated to be accelerated under acidic conditions.[12] Other directing/protecting groups such as pivalate, tosylate, *N*,*N*-diethyl-*N*′-phenylurea, *N*-methyl, etc. were less effective in this case. After a rigorous screening (for details, see the Supporting Information), we found that 10 mol % of Pd(OAc)$_2$ in combination with 1.0 equiv of TsOH and 2.0 equiv of 1,4-benzoquinone as terminal oxidant provided 2-phenylindole in 82% yield at room temperature from 1.0 equiv of phenylurea and 1.5 equiv of styrene (entry 10, Table 1). During optimization, it was also found that water is detrimental to the reaction outcome, but dioxygen has little or no effect.

Subsequently, we explored the substrate scope under the optimized reaction conditions. A wide variety of functional

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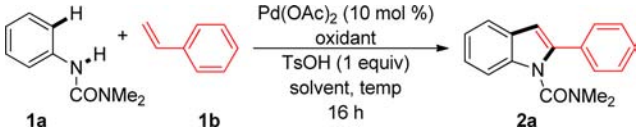
Table 1. Optimization of the Reaction Conditions[a]



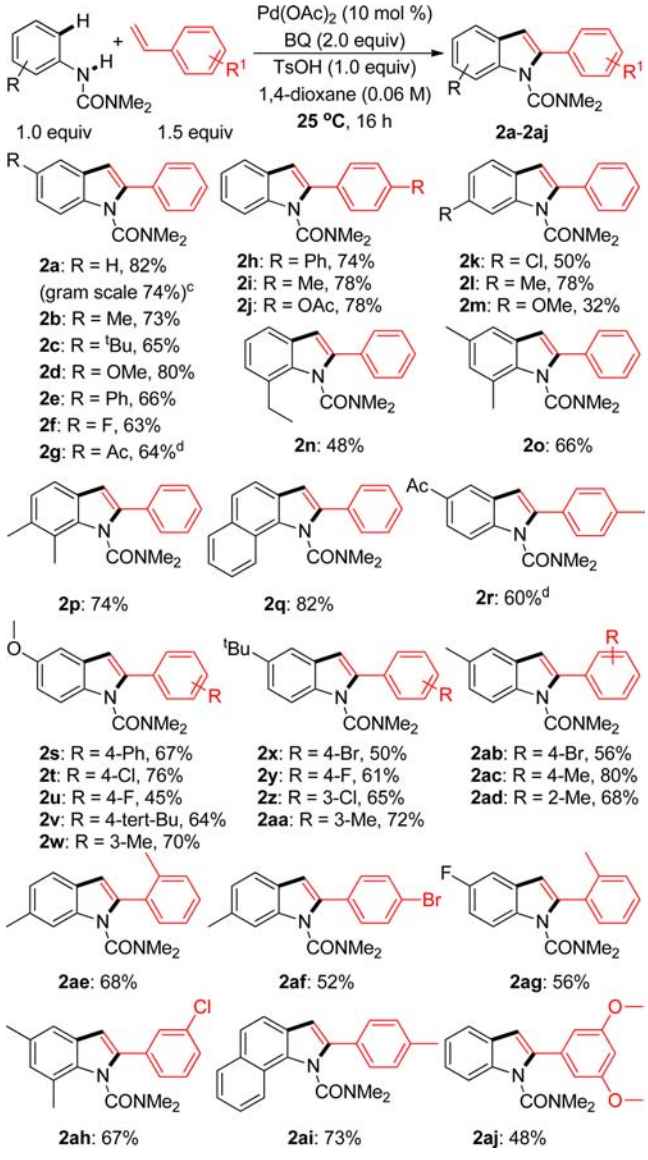
entry	oxidant	solvent	temp (°C)	yield[b] (%)
1	$Cu(OAc)_2$ (1 equiv)	toluene	110	trace
2	AgOAc (1 equiv)	toluene	110	8
3	BQ (1 equiv)	1,4-dioxane	110	10
4	BQ (1 equiv)	AcOH	110	7
5	BQ (1 equiv)	AcOH	50	13
6	BQ (1 equiv)	AcOH	25	18
7	BQ (2 equiv)	THF	25	58
8	BQ (2 equiv)	EtOAc	25	77
9	BQ (1 equiv)	1,4-dioxane	25	52
10	**BQ (2 equiv)**	**1,4-dioxane**	**25**	**82**
11	DDQ (2 equiv)	1,4-dioxane	25	trace
12	–	1,4-dioxane	25	12
13[c]	BQ (2 equiv)	1,4-dioxane	25	65
14	BQ (3 equiv)	1,4-dioxane	25	80
15	BQ (2 equiv)	1,4-dioxane/AcOH (2:1)	25	38

[a]All reactions were carried out in 0.1 mmol scale. [b]Yields refer to here are overall isolated yields. [c]2.0 equiv of TsOH was used.

groups on aniline as well as styrene were found to be compatible under this mild reaction protocol. Besides methoxy, alkyl, and aryl groups, halogens such as bromo (**2x**, **2ab**, **2af**, Scheme 1), chloro (**2k**, **2t**, **2z**, **2ah**, Scheme 1), and fluoro (**2f**, **2u**, **2y**, **2ag**, Scheme 1) remain intact which are useful for further cross-coupling reactions. Interestingly, the acyl group (**2g**, **2r**, Scheme 1) is well-tolerated under this protocol, which is a reactive functionality in the Fischer and Yoshikai method.[2,6f] An acid-sensitive −OAc (**2j**, Scheme 1) group is also stable, which demonstrates the mild nature of this protocol. The electronic nature has a prominent influence on the reaction outcome. In general, a moderate electron-donating group on the aniline has a positive influence due to the facile electrophilic palladation. However, highly electron-rich anilines are too reactive to provide the desired product. Similarly, neutral or moderately electron-rich and/or electron-defficient styrenes underwent annulation smoothly. Highly electron-deficient 3-nitrostyrene and pentafluorostyrene did not furnish any desired product, presumably due to the alkene deactivation for migratory palladium insertion. Interestingly, ortho-substituted anilines (**2n−q**, **2ah**, **2ai**, Scheme 1) also afforded good to high yields of the desired products, which are known to be difficult for electrophilic ortho palladation.[11] The meta-substituted anilines provided single regioisomeric indoles through ortho palladation from the sterically less hindered side (**2k−m**, **2ae**, **2af**, Scheme 1). All compounds are new entities and adequately characterized.[13]

From a mechanistic perspective, we realized that migratory insertion to the alkene results in an unstable σ-alkyl-Pd intermediate that could be intercepted for further functionalization.[14] The direct 1,2-carboamination strategy to generate indoline moiety was reported using norbornene[15] where β-hydride elimination is not feasible or using 1,3-dienes via π-allyl-Pd formation.[11] However, direct synthesis of 2-arylindolines through π-benzyl-Pd stabilization is not known. We chose

Scheme 1. Substrate Scope of Indoles[a,b]



[a]All reactions were carried out in 0.2 mmol scale. [b]Yields refer to the average of isolated yields of at least two experiments. [c]5 mol % of $Pd(OAc)_2$ was used. [d]Reaction time 30 h.

p-methoxy styrene as a model substrate to explore this divergent approach to indoline synthesis. Gratifyingly, the corresponding indoline was obtained in 48% isolated yield under the same reaction conditions (**3a**, Scheme 2). Remarkably, while *p*-acetoxystyrene (**2j**, Scheme 1) afforded indole selectively, the *p*-methoxy group favors indoline formation albeit in moderate yield. This subtle change in electronic nature leads to the generation of two distinct classes of compounds. This could be attributed to the formation of stabilized, cationic π-benzyl-Pd species that suppresses β-hydride elimination. Since naphthalenes have a better ability to stabilize π-benzyl-Pd species,[16] we decided to examine 1-vinylnaphthalene under the optimized conditions. As anticipated, the corresponding indoline was isolated in high yields with 1- and 2-vinylnaphthalenes. Remarkably, a number of urea derivatives with *ortho* substitution also provided the desired indolines in high yields (**3l−o**, Scheme 2).

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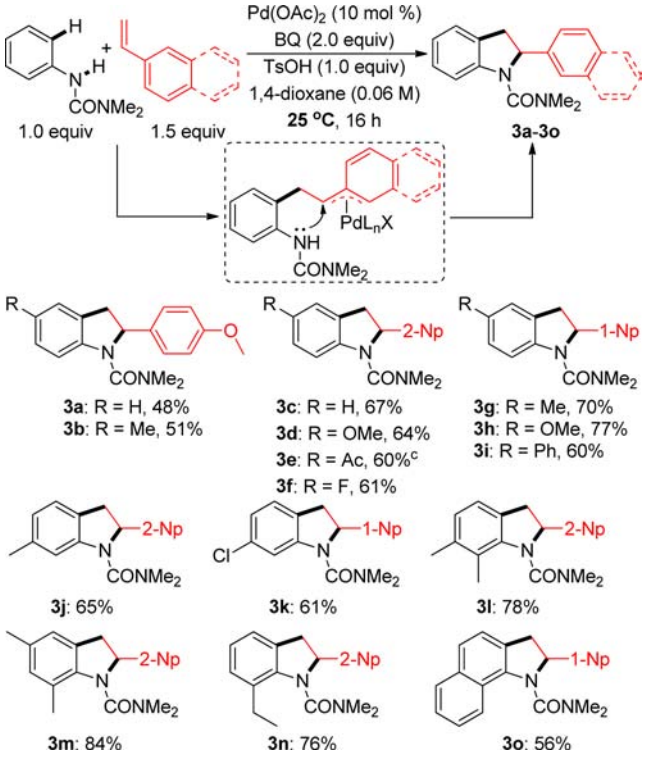
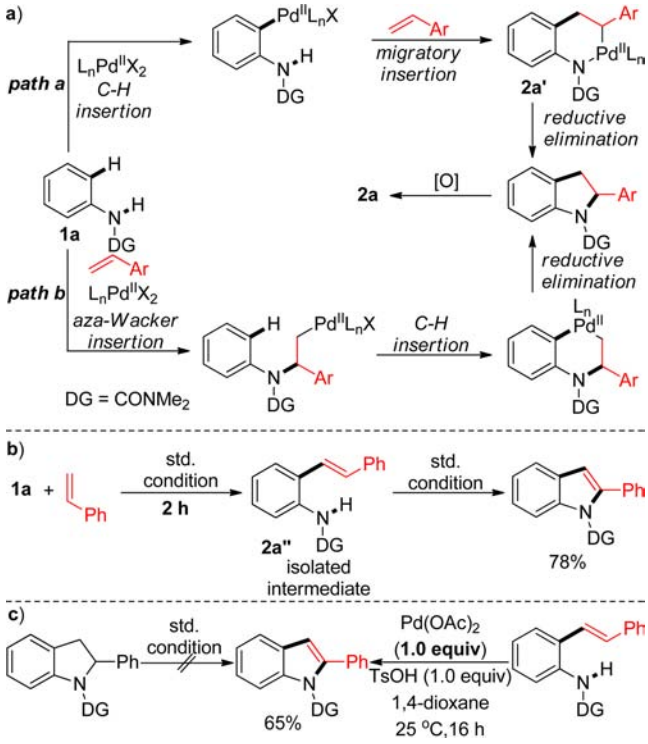
Scheme 2. Substrate Scope of Indolines[a,b]



[a]All reactions were carried out on a 0.2 mmol scale. [b]Yields refer to the average of isolated yields of at least two experiments. [c]Reaction time 30 h.

Mechanistically, the reaction may proceed in two distinct pathways. In path a, an electrophilic *ortho* palladation followed by migratory β-alkene insertion may lead to the intermediate **2a**′ (Scheme 3, a). Subsequently, reductive elimination to yield indolines and oxidation sequences may provide the desired 2-arylindoles. Alternatively, an initial aza-Wacker reaction followed by C−H arylation and oxidation cascade may lead to the desired product as shown in path b (Scheme 3, a). To understand the plausible mechanism, we performed several control experiments. From TLC, we observed that initially a polar, transient intermediate is formed which is converted into product during the reaction course. Therefore, the reaction was arrested after 2 h and the intermediate was isolated as Fujiwara−Moritani Heck arylation product **2a**″. Subsequently, this intermediate was subjected to the standard reaction conditions, and the desired 2-arylindole was obtained in 78% yield (Scheme 3, b). Therefore, the reaction may initiate through path a. To note, depending upon the π-benzyl-Pd stabilization ability, 8−12% corresponding indoles were also obtained along with the indolines (Scheme 2). Therefore, in the subsequent steps, either a concerted aza-Wacker cyclization followed by β-hydride elimination or initial 1,2-carboamination of styrenes to yield 2-arylindoline followed by oxidation to yield the desired product is plausible.[8] To probe this, 2-phenylindoline was synthesized separately and subjected to the standard conditions. The indoline remained intact, which eliminates the possibility of indoline formation/oxidation route (Scheme 3, c). It also demonstrates that indoles are kinetic in their origin through concerted β-hydride elimination. From the stoichiometric experiment it was observed that the Heck intermediate is converted to the corresponding indole in 65% yield with 1.0

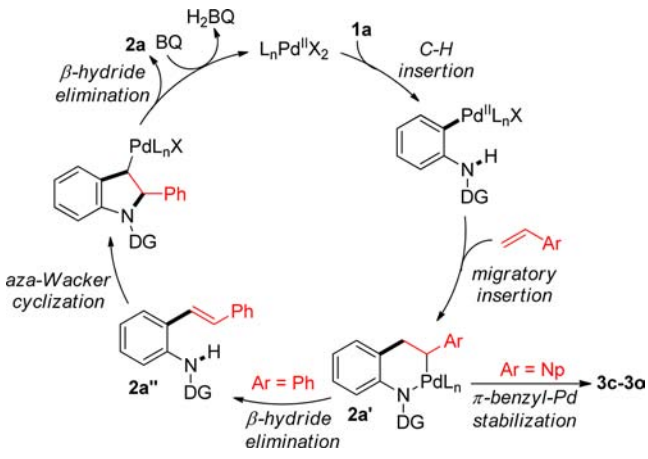
Scheme 3. Mechanistic Possibilities and Elucidations



equiv of $Pd(OAc)_2$/TsOH without 1,4-benzoquinone. Therefore, BQ may act as a ligand and oxidant to the palladium for catalytic turnover but may not be involved in the oxidation of indoline to indole directly.

From all these control experiments it is speculated that the reaction proceeds through a C−H insertion/carbopalladation/cyclization/aromatization cascade. The indolines are formed in a convergent manner from the σ-alkyl-Pd intermediate through π-benzyl-Pd stabilization as depicted in Scheme 4.

Scheme 4. Plausible Catalytic Cycle



Finally, the corresponding indole and indoline urea were hydrolyzed with saturated solution of potassium hydroxide in refluxing ethanol to afford the 2-arylindole and indoline in 85% and 80% yield, respectively.

In conclusion, we have developed a mild reaction protocol for the synthesis of 2-arylindole and indoline derivatives from arylureas and -styrenes at room temperature. The indoles are

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formed through C−H insertion/1,2-carboamination/ β-hydride elimination cascade, whereas the indolines are obtained through C−H insertion and 1,2-carboamination via π-benzyl-Pd stabilization. The present intermolecular technique incorporates a wide range of starting materials using a ubiquitous and inexpensive catalytic combination. The catalytic conversion is also reproducible on a gram scale with lower catalyst loading. Therefore, we anticipate that this methodology will find many applications in academia as well as in industrial processes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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