JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

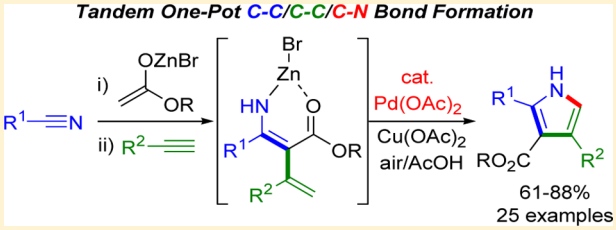
Tandem One-Pot Synthesis of Polysubstituted NH-Pyrroles Involving the Palladium-Catalyzed Intramolecular Oxidative Amination of the Zinc Bromide Complex of β-Enamino Esters

Ju Hyun Kim, Suh Young Choi, Jean Bouffard, and Sang-gi Lee*

Department of Chemistry and Nano Science (BK 21 Plus), Ewha Womans University, 120-750 Seoul, Korea

Supporting Information

ABSTRACT: The Pd-catalyzed oxidative olefin amination of the zinc bromide complex intermediate, formed by the sequential reaction of nitriles with a Reformatsky reagent and 1-alkynes, affords pyrrole derivatives in good to excellent yields. This tandem protocol provides a simple, efficient, and atom- and pot-economical way to quickly build polysubstituted NH-pyrroles starting from readily available reagents in a regiocontrolled manner with a broad substrate scope and high functional group tolerance. In contrast, the Pd-catalyzed oxidative olefin amination of an isolated α-vinyl-β-enamino ester did not proceed effectively, but the reaction efficiency can be restored by addition of *n*-BuZnBr or $Zn(OAc)_2$, indicating the crucial role of the zinc complex in this transformation. The synthetic utility of this protocol is exemplified by the rapid synthesis of pyrrolophenanthrenes and pyranopyrrolones through selective Pd- and Cu-catalyzed C−C and C−O bond-forming reactions.



INTRODUCTION

The pyrrole moiety is a widespread scaffold found in natural products, biologically active compounds,[1] as well as in dyes, pigments, and other functional materials.[2] This broad utility has made pyrroles long-standing synthetic targets and has spurred extensive efforts toward the development of efficient methods to prepare this important heterocyclic compound.[3] Recent advances in transition-metal-catalyzed reactions have provided new approaches for the construction of the pyrrole ring.[4] For example, the direct pyrrole-forming annulation using 1-alkynes remained elusive until the discovery of silver-catalyzed alkyne-isocyanide click reactions (Scheme 1a).[5a,b] Pd- or Pd/Cu-catalyzed addition/cyclization/tautomerization cascades via propargyl amines were also recently reported (Scheme 1b).[5c,d] In spite of these advances, many of the methods can only provide *N*-substituted pyrroles, requiring an extra synthetic step to remove the *N*-substituent for further synthetic elaboration. Others offer a limited scope with respect to the accessible substitution patterns about the pyrrole ring.[6] Therefore, the development of an efficient and direct method for the synthesis of regiocontrolled polysubstituted NH-pyrroles starting from readily available reagents remains an incomplete task.

During our continuing studies on the tandem use of the Blaise reaction,[7] we have found that the Blaise reaction intermediate **A**, formed by reaction of nitriles **1** with Reformatsky reagents, could react chemo- and regioselectively with 1-alkynes to afford the corresponding α-vinylated β-enamino esters. Mechanistic studies suggested that a zinc bromide complex of α-vinylated β-enamino ester **B** was formed as a second intermediate.[8] We envisioned that the vinylated intermediate **B** may serve as a viable substrate for palladium-catalyzed intramolecular oxidative aminations to provide pyrroles **3**, given that, under the reaction conditions, the intermediate **B** may be in equilibrium with the unchelated isomer **B′**, facilitating the cyclization step (Scheme 1). In a preliminary communication, the intermediate **B** (R^2 = *o*-Cl-Ph), formed by tandem reaction of **A** with *o*-chlorophenyl acetylene, was utilized as a common precursor for palladium catalyst-controlled divergent synthesis of pyrrole and quinoline.[9] Herein, we report the details and expand on our studies of this simple protocol that provides an efficient and atom- and pot-economic way to quickly build regiodefined pyrrole frameworks. Furthermore, we also report for the first time our important finding that the Pd-catalyzed oxidative olefin amination of the isolated α-vinyl-β-enamino ester does not proceed effectively, but that the reaction efficiency can be restored by addition of $Zn(OAc)_2$ or *n*-BuZnBr, indicating that the use of zinc complex intermediate **B** is crucial for the intramolecular oxidative olefin amination reaction. Finally, we disclose here a new divergent conversion of a pyrrole having chlorophenyl and ester functionalities to pyrrolophenathrene and pyranopyrrolone derivatives, demonstrating the synthetic utility of this tandem process.

RESULTS AND DISCUSSION

While large numbers of efficient transition-metal-catalyzed intramolecular oxidative olefin aminations have been de-

Received: July 24, 2014
Published: September 12, 2014

dx.doi.org/10.1021/jo501672c | J. Org. Chem. 2014, 79, 9253−9261

Scheme 1. Examples for the Syntheses of Pyrrole Rings Using 1-Alkyne Synthons, and Our Tandem Strategy for One-Pot Synthesis of Polysubstituted NH-Pyrroles

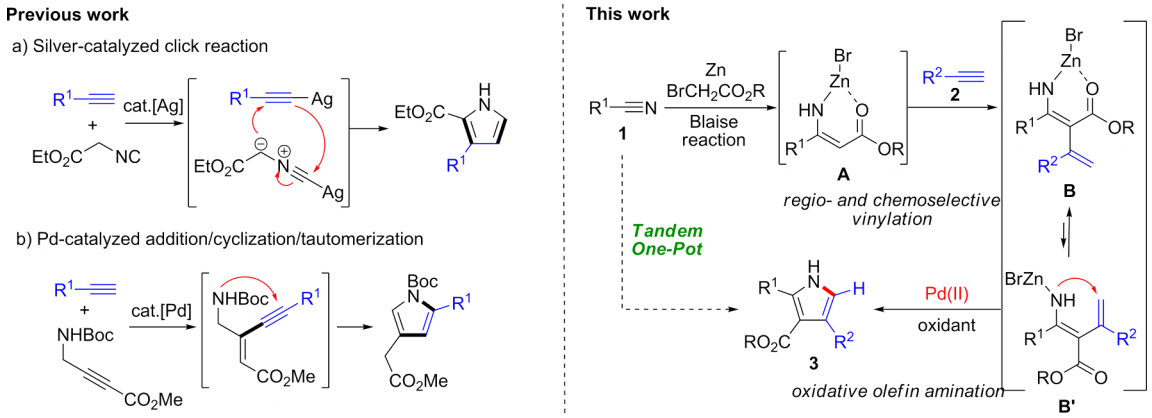
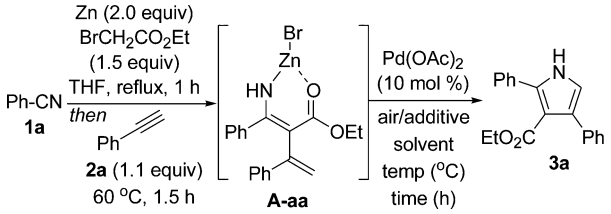


Table 1. Optimization of the Reaction Conditions[a]



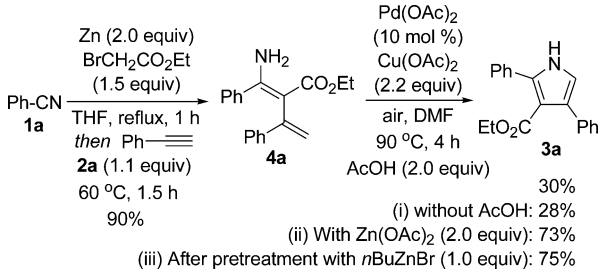
entry	additive (equiv)	solvent	°C/h	yield (%)[b]
1	$Cu(OAc)_2$ (2.2)/AcOH (2.0)	DMF	90/4	85
2	$Cu(OAc)_2$ (2.2)/AcOH (1.0)	DMF	90/4	70
3	$Cu(OAc)_2$ (3.0)/AcOH (2.0)	DMF	90/1	88
4	$Cu(OAc)_2$ (3.0)	DMF	110/4	52
5	$Cu(OAc)_2$ (3.0)	DMSO	110/3	48
6	$Cu(OAc)_2$ (3.0)	DMF/H_2O	110/3	37
7[c]	$Cu(OAc)_2$ (2.2)/AcOH (2.0)	DMF	90/24	48
8[d]	$Cu(OAc)_2$ (2.2)/AcOH (2.0)	DMF	90/12	
9		DMSO	110/12	15
10	AcONa (1.0)	DMSO	110/12	<5
11	pyridine (0.2)	toluene	110/24	13
12	Phen (0.2)	MeOH	110/24	<5

[a]Reaction conditions: A solution of **A-aa** was prepared from **1a** (2.29 mmol), Zn (4.59 mmol), ethyl bromoacetate (3.44 mmol), and **2a** (2.52 mmol) in THF (0.7 mL). This solution was then diluted with the indicated solvent (6.0 mL), and $Pd(OAc)_2$ and additives were added. [b]Isolated yields. [c]Reaction under a N_2 atmosphere. [d]Reaction in the absence of $Pd(OAc)_2$. Phen = phenanthroline.

scribed,[10] the use of N-zincated amines as nitrogen sources has not been reported. To test the feasibility of our tandem strategy, we first investigated the $Pd(OAc)_2$-catalyzed oxidative olefin amination of intermediate **A-aa** (R^1 = Ph, R = Et, X = H), formed by the sequential reaction of benzonitrile (**1a**) first with the Reformatsky reagent generated in situ from ethyl α-bromomoacetate and zinc, followed with phenylacetylene (**2a**) (Table 1). To our delight, the intramolecular oxidative olefin amination of **A-aa** could be achieved upon treatment with 10 mol % $Pd(OAc)_2$, 2.2 equiv of $Cu(OAc)_2$, and 2.0 equiv of AcOH in DMF under air for 4 h at 90 °C to afford the desired pyrrole **3a** in 85% overall yield (Table 1, entry 1).[11] Reducing the amount of AcOH to 1.0 equiv decreased the yield of **3a** to 70% (Table 1, entry 2). By contrast, increasing the amount of the $Cu(OAc)_2$ oxidant to 3.0 equiv slightly raised the yield to 88% and shortened the reaction time to 1 h (Table 1, entry 3). In the absence of AcOH, the yield of **3a** was substantially depressed (Table 1, entries 4–6). Carrying out the reaction under a nitrogen atmosphere dramatically decreased the yield of **3a** to only 48% after 24 h (Table 1, entry 7). A control reaction in the absence of $Pd(OAc)_2$ did not proceed, and no trace of pyrrole **3a** was detected by TLC (Table 1, entry 8). Other reaction conditions, developed by Larock,[12] Stahl,[13] and Stoltz,[14] among others,[15] for Pd^{II}-catalyzed aerobic oxidative olefin aminations, such as $Pd(OAc)_2$/DMSO, $Pd(OAc)_2$/NaOAc/DMSO, $Pd(OAc)_2$/pyridine in toluene, and other closely related variants, were not effective (Table 1, entries 9–12). Moreover, under the standard reaction conditions (Table 1, entry 1), the isolated α-vinylated β-enamino ester **4a** could also afford pyrrole **3a**, but only in a modest 30% yield (Scheme 2). These results suggest that the tandem reaction of N-zincated intermediate **A-aa** may have some advantages for Pd^{II}-catalyzed oxidative olefin amination. Additional empirical evidence supports the unforeseen zinc additive effect: (i) A similarly low yield (28%) of **3a** was observed from the reaction of **4a** in the absence of AcOH. (ii) The reaction efficiency with **4a** could be restored in the presence of $Zn(OAc)_2$ (2.0 equiv) to afford **3a** in 73% yield. (iii) Pretreatment of **4a** with 1.0 equiv

dx.doi.org/10.1021/jo501672c | J. Org. Chem. 2014, 79, 9253–9261

Scheme 2. Zinc Additive Effect on the Oxidative Olefin Amination of Isolated α-Vinylated β-Enamino Ester 4a



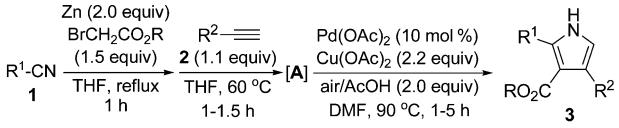
of *n*BuZnBr, possibly generating intermediate **A-aa**, also increased the yield of **3a** to 75% under the standard reaction conditions. The observed zinc additive effect appears consistent with the formation of a zinc complex of the β-enamino ester that may prevent the formation of inactive palladium complexes.

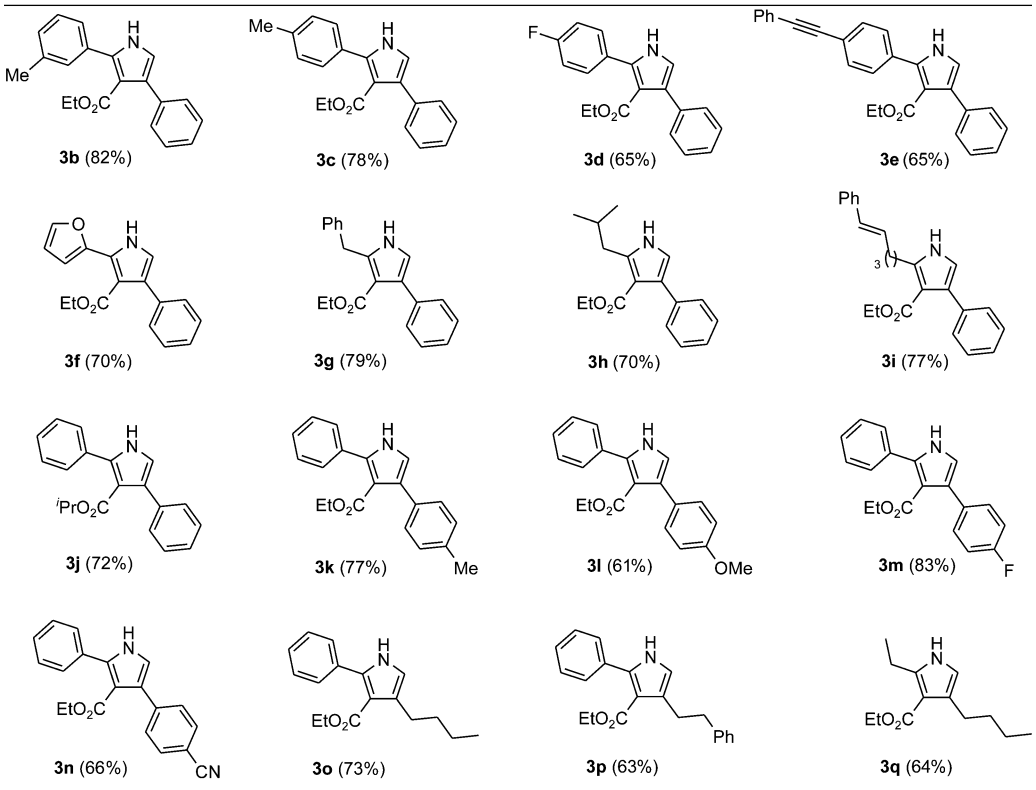
Under optimized reaction conditions, a variety of pyrroles **3** can be synthesized in a tandem one-pot manner (Table 2). Aromatic nitriles with methyl (**1b** and **1c**), fluorine (**1d**), and alkyne substituents (**1e**), as well as the heteroaromatic nitrile **1f**, were well tolerated and reacted with phenylacetylene **2a** to give the pyrroles **3b**–**3f** in high yields (65–82%). Benzyl nitrile (**1g**) and sterically demanding isovaleronitrile (**1h**) were also successfully incorporated to result in the corresponding pyrroles **3g** and **3h** in high yields. Formation of pyrrole **3i** from the aliphatic nitrile **1i** having an olefinic moiety suggested that the vinylene group is more reactive than the internal olefin under oxidative olefin amination conditions.

Variation of the Reformatsky reagent did not affect the reaction efficiency, as shown for **3j** bearing an isopropyl ester in 72% yield. The scope of the reaction with respect to alkynes was also investigated with benzonitrile **1a**. Aromatic alkynes with electron-donating methyl (**2b**) or methoxy (**2c**) groups, and electron-withdrawing fluorine (**2d**) and nitrile (**2e**) substitutents, in addition to aliphatic 1-hexyne **2f** (R^2 = *n*-Butyl) and 4-phenylbutyne (**2g**, R^2 = $PhCH_2CH_2$) were all successfully incorporated in the corresponding pyrroles **3k**–**3p** in comparably good yields. The 2,4-dialkylated pyrrole **3q** could also be synthesized in 64% yield using propionitrile (**1j**) and 1-hexyne (**2f**).

When we investigated the present protocol with the 2-halogenated phenylacetylenes **2h** (X = Cl) and **2i** (X = Br), it was found that the regioselectivity of the vinylation largely depended on the reaction temperature (Scheme 3). For example, the tandem reaction of the Blaise reaction intermediate with 2-chlorophenylacetylene **2h** in THF at reflux (80 °C bath temperature) for 2 h gave the two regioisomers **4h** and **4h′** in a 5 to 1 ratio, as determined by ^{1}H NMR analysis of

Table 2. Tandem One-Pot Synthesis of Various Pyrroles[a]

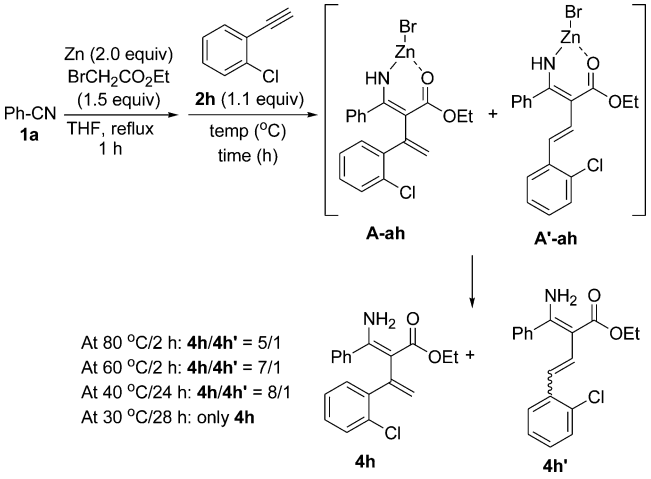




[a]Reactions were carried out under the optimized conditions shown in entry 1 of Table 1. Isolated yields are shown.

dx.doi.org/10.1021/jo501672c | J. Org. Chem. 2014, 79, 9253–9261

Scheme 3. Effects of Temperature on the Regioselectivity of Vinylation

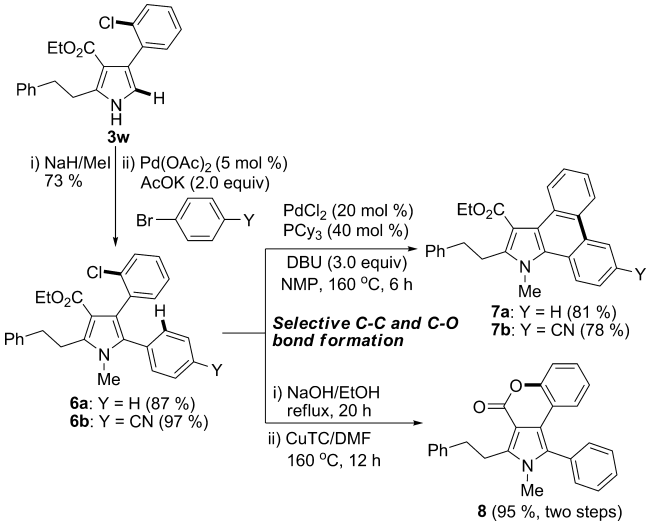


the crude reaction mixture. Decreasing the reaction temperature could suppress the formation of regioisomer **4h′**. Carrying out the vinylation at 30 °C for a prolonged reaction time (28 h) allowed for the isolation of the regioisomerically pure **4h**.

After establishing the optimal conditions for tandem vinylation reaction with 2-halogenated phenylacetylenes, the intermediate **A-ah** (X = Cl) was subjected to the standard oxidative olefin amination reaction conditions to afford the corresponding pyrrole **3r** in 62% yield. Under the same reaction conditions, however, the intermediate **A-ai** (X = Br) bearing an aryl bromide afforded a mixture of pyrrole **3s** (40%) and the undesired quinoline **5** (13%) (Scheme 4). Formation of quinoline **5** suggests that the rate of reoxidation of Pd(0), generated during the catalytic cycle, to Pd(II) competes with that of its oxidative addition to the Ar−Br bond, funnelling the intermediate through a Buchwald−Hartwig aryl amination reaction pathway.[16] Under optimized reaction conditions, a variety of pyrroles (**3t**−**3z**) having an *o*-chlorophenyl substituent at the 3-position were successfully synthesized in good yields.[9,17]

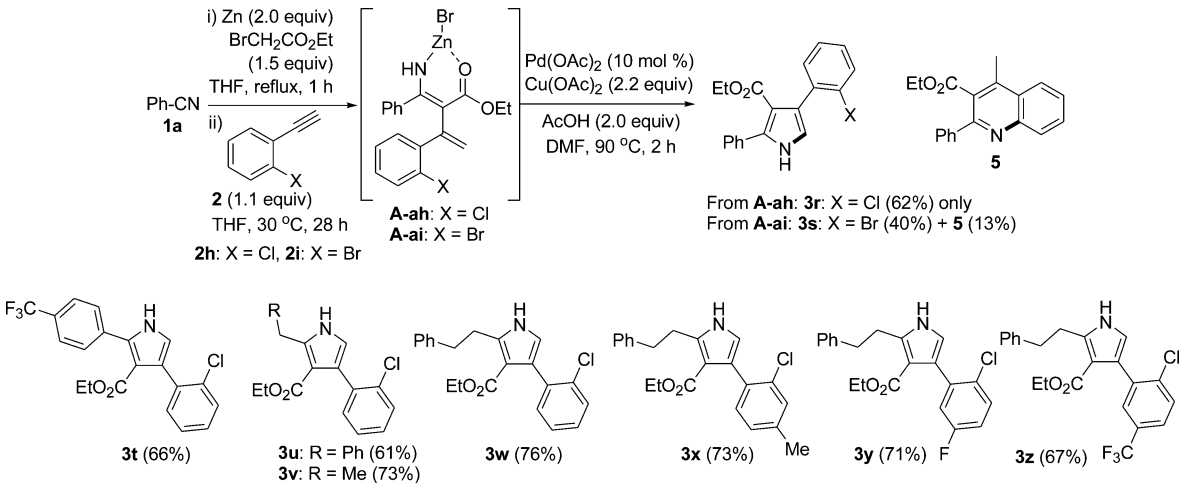
The *o*-chlorophenyl and ester functionalities offered synthetic handles for further elaboration of these pyrroles. For example, the pyrrole **3w**, formed by the sequential reaction of 3-phenylpropionitrile (**1k**) with a Reformatsky reagent and 1-chloro-2-ethynylbenzene (**2i**), could be converted to pyrrolophenathrenes **7a** and **7b**, and pyranopyrrolone **8**, demonstrating the synthetic utility of our tandem protocol (Scheme 5).

Scheme 5. Divergent Transformations of 3w to 7 and 8 via Selective C−C and C−O Bond Formations



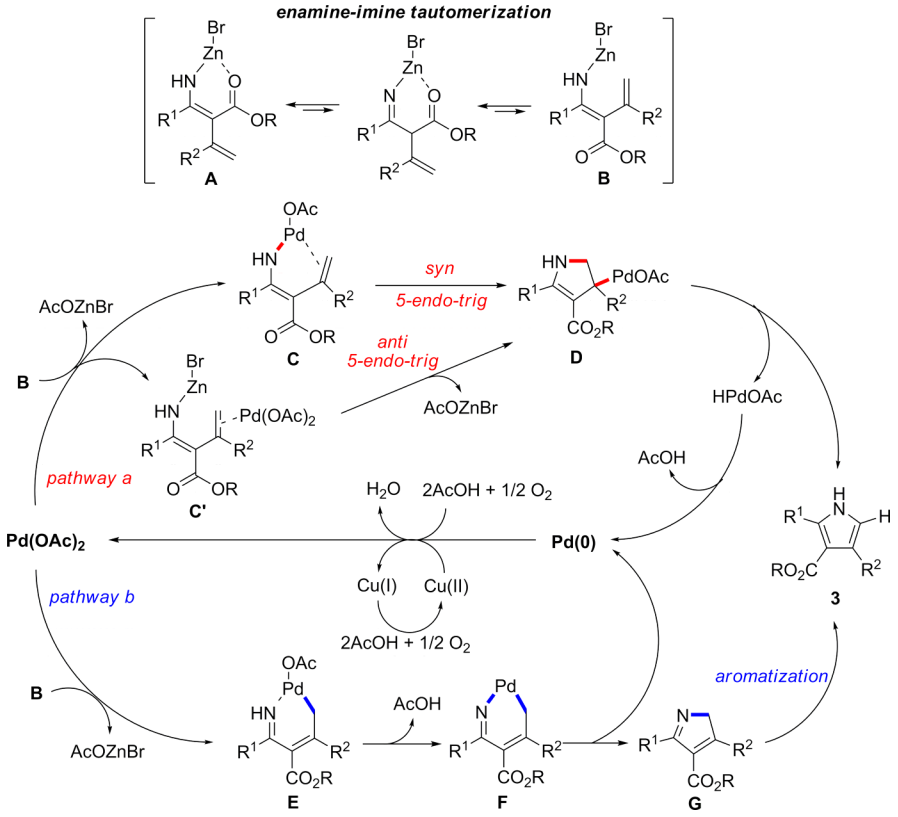
These classes of compounds were shown to have anticancer potency, as well as interesting photoconducting and optoelectronic properties.[18] After *N*-methylation of **3w**, affording **S1**, the C−H at the 2-position was directly arylated with bromobenzenes under the action of a palladium catalyst to afford **6a** (87%) and **6b** (97%) in high yields. These compounds served as common starting materials for selective C−C and C−O coupling reactions leading to **7** and **8**, respectively. Thus, a palladium-catalyzed intramolecular C−H bond arylation of **6a** and **6b** afforded the corresponding pyrrolophenathrene derivatives **7a** (81%) and **7b** (78%) in high yields.[19] Alternatively, a CuTC-mediated C−O coupling,[20] following hydrolysis of the ester group of **6a** giving corresponding carboxylic acid (**S2**), allowed access to pyranopyrrolone **8** in a 95% overall yield over two steps.

Scheme 4. Tandem Synthesis of Pyrroles with 2-Halogenated Phenylacetylenes



dx.doi.org/10.1021/jo501672c | J. Org. Chem. 2014, 79, 9253−9261

Scheme 6. Proposed Mechanism for the Formation of Pyrrole 3



Our mechanistic proposal for the formation of pyrrole **3** is outlined in Scheme 6. To facilitate the oxidative ring formation, the N-zincated nitrogen atom and olefin can adopt a more suitable geometry through the unchelated isomer **B**, which may be in equilibrium with **A** under the reaction conditions via enamine−imine tautomerization. One possible catalytic reaction pathway is a 5-*endo-trig* aminopalladation/β-H elimination cascade route (pathway *a* in Scheme 6). The transformation begins with a direct ligand substitution of $Pd(OAc)_2$, resulting in aminopalladate complex **C** and/or formation of palladium complex **C′**. A 5-*endo-trig* cyclization through either a *syn*-aminopalladation of **C** or an *anti*-aminopalladation of **C′** gives the intermediate **D**,[21] and subsequent β-H elimination affords pyrrole **3**. The resulting palladium hydride is then reoxidized back to $Pd(OAc)_2$ by $Cu(OAc)_2$ and O_2/AcOH.[22] Another possible catalytic pathway that cannot be ruled out is γ-nucleophilic substitution, forming the γ-C-palladate **E** (pathway *b* in Scheme 6). Extrusion of AcOH from **E**, affording **F**, followed by reductive elimination, results in intermediate **G**, which isomerizes quickly to give product **3**.

CONCLUSION

We have developed a novel tandem palladium-catalyzed intramolecular oxidative olefin amination of the zinc bromide complex of α-vinylated β-enamino esters, which are formed by the sequential reaction of nitriles with a Reformatsky reagent and 1-alkynes, to afford 2,3,4-trisubstituted NH-pyrroles in good yields for a diverse range of substrates. This protocol provides a simple, efficient, and atom- and pot-economical way for the regioselective assembly of pyrrole rings. Unforeseen zinc additive effects on the Pd^{II}-catalyzed oxidative olefin amination of isolated α-vinylated β-enamino esters have also been uncovered. The synthetic utility of the present protocol has been demonstrated through the divergent transformation of a pyrrole bearing 2-chlorophenyl and ester functionalities into pyrrolophenathrenes and a pyranopyrrolone via C−C and C−O bond formations. Given these advantages, this procedure may hold considerable promise in drug discovery and in the development of functional materials.

EXPERIMENTAL SECTION

General Methods. THF was distilled from sodium benzophenone ketyl prior to use. Anhydrous DMF and other reagents were purchased and used directly without further purification. The nitriles bearing alkyne (**1e**) and olefin moieties (**1i**) were synthesized according to the reported procedures.[23] 1-Chloro-2-ethynylbenzene (**2i**) was synthesized according to the reported procedures.[24] The NMR spectra were recorded at 300 MHz for ^{1}H, and 75.5 or 63.0 MHz for ^{13}C. HRMS data were obtained by electron ionization with a magnetic sector-electronic sector double focusing mass analyzer.

General Procedure for Tandem Synthesis of Pyrroles 3. To a stirred suspension of commercial zinc dust (300 mg, 4.59 mmol) in THF (0.7 mL) at reflux was added a solution of methanesulfonic acid in THF (1.0 M, 0.15 mL). After 5 min of stirring, the nitrile (2.29 mmol) was added at once. While maintaining the THF at reflux, alkyl bromoacetate **1** (3.44 mmol) was added over 1 h using a syringe pump, and the resulting reaction mixture was stirred for an additional 1 h. To this reaction mixture was added 1-alkyne **2** (2.52 mmol), and the mixture was stirred for 1.5−2 h (followed by TLC). After cooling to room temperature, the reaction mixture was diluted with DMF (6.0 mL), and then palladium(II) acetate (52 mg, 0.23 mmol), copper(II) acetate (917 mg, 5.05 mmol), and acetic acid (0.26 mL, 4.59 mmol) in DMF (6 mL) were added. The resulting mixture was heated in a preheated oil bath at 90 °C under air until the vinylated intermediate was entirely consumed, as monitored by TLC. The reaction mixture was allowed to cool to room temperature, quenched with saturated aqueous Na_2CO_3 (3 mL), and then diluted with saturated aqueous

dx.doi.org/10.1021/jo501672c | J. Org. Chem. 2014, 79, 9253−9261

NH_4Cl (50 mL). The organic compounds were extracted with ethyl acetate (30 mL × 3), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding NH-pyrroles **3**.

*Ethyl 2,4-Diphenyl-1H-pyrrole-3-carboxylate (**3a**) [CAS: 63324-78-7].* Yield: 85% (568 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; brown solid; mp: 48−50 °C (lit:[25] viscous oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.1 Hz, 3H), 3.94 (q, J = 7.1 Hz, 2H), 6.45 (d, J = 2.6 Hz, 1H), 7.22−7.39 (m, 10H), 9.00 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 60.0, 110.6, 117.7, 126.3, 127.3, 127.8, 127.9, 128.1, 128.7, 129.0, 132.4, 135.5, 137.0, 166.3 ppm.

*Ethyl 2-(4-Methylphenyl)-4-phenyl-1H-pyrrole-3-carboxylate (**3b**).* Yield: 78% (546 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; pale yellow solid; mp: 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 3H), 2.33 (s, 3H), 4.01 (q, J = 7.1 Hz, 2H), 6.59 (d, J = 2.6 Hz, 1H), 7.08−7.46 (m, 9H), 8.69 (brs, 1H) ppm ;^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 21.4, 60.0, 110.7, 117.3, 126.4, 127.6, 127.8, 128.7, 128.9, 129.1, 129.6, 135.7, 137.3, 138.0, 166.1 ppm. HRMS (EI) Calcd m/z for $C_{20}H_{19}NO_2$ $[M]^+$: 305.1416. Found: 305.1414.

*Ethyl 2-(3-Methylphenyl)-4-phenyl-1H-pyrrole-3-carboxylate (**3c**).* Yield: 82% (574 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; brown solid; mp: 80−82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 3H), 2.32 (s, 3H), 4.02 (q, J = 7.1 Hz, 2H), 6.60 (d, J = 2.4 Hz, 1H), 7.0−7.5 (m, 9H), 8.71 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 21.5, 60.0, 110.9, 117.4, 126.0, 126.4, 127.6, 127.9, 128.1, 128.9, 129.1, 129.4, 132.4, 135.6, 137.2, 137.8, 166.1 ppm. HRMS Calcd m/z for $C_{20}H_{19}NO_2$ $[M]^+$: 305.1416. Found: 305.1417.

*Ethyl 2-(4-Fluorophenyl)-4-phenyl-1H-pyrrole-3-carboxylate (**3d**).* Yield: 65% (462 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; pale yellow solid; mp: 104−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.1 Hz, 3H), 3.98 (q, J = 7.1 Hz, 2H), 6.58 (d, J = 2.6 Hz, 1H), 7.00 (t, J = 8.7 Hz, 2H), 7.22−7.43 (m, 7H), 8.83 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 60.0, 110.8, 115.1(d, J = 21.9 Hz), 117.6, 126.5, 127.7, 127.8, 128.6 (d, J = 3.0 Hz), 129.1, 130.8 (d, J = 8.3 Hz), 135.4, 136.2, 162.6 (d, J = 247.6 Hz), 166.0 ppm. HRMS (EI) Calcd m/z for $C_{19}H_{16}FNO_2$ $[M]^+$: 309.1165. Found: 309.1167

*Ethyl 4-Phenyl-2-[4-(phenylethynyl)phenyl]-1H-pyrrole-3-carboxylate (**3e**).* Yield: 65% (584 mg); Eluents: *n*-hexane/EtOAc = 5/1; light yellow solid; mp: 158−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, J = 7.1 Hz, 3H), 4.10 (q, J = 7.1 Hz, 2H), 6.84 (d, J = 2.6 Hz, 1H), 7.26−7.31 (m, 1H), 7.36−7.42 (m, 5H), 7.43−7.46 (m 2H), 7.50−7.53 (m, 2H), 7.54−7.59 (m, 4H), 8.76 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 60.2, 89.3, 90.6, 111.7, 118.0, 123.1, 123.3, 126.7, 128.0, 128.2, 128.5, 128.7, 129.1, 131.6, 131.8, 132.2, 135.3, 136.1, 165.8 ppm. HRMS (EI) Calcd m/z for $C_{27}H_{21}NO_2$ $[M]^+$: 391.1572. Found: 391.1572.

*Ethyl 2-(Furan-2-yl)-4-phenyl-1H-pyrrole-3-carboxylate (**3f**)[25] [CAS: 319905-68-5].* Yield: 70% (452 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; viscous brown liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J = 7.1 Hz, 3H), 4.15 (q, J = 7.1 Hz, 2H), 6.48 (dd, J = 3.5, 1.6 Hz, 1H), 6.72 (d, J = 2.6 Hz, 1H), 7.24−7.38 (m, 7H), 9.06 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 60.0, 109.8, 112.2, 117.5, 126.5, 127.7, 128.0, 128.1,129.3, 135.6, 141.5, 146.1, 165.4 ppm.

*Ethyl 2-Benzyl-4-phenyl-1H-pyrrole-3-carboxylate (**3g**) [CAS: 856118-83-7].* Yield: 79% (553 mg); Eluents: *n*-hexane/EtOAc = 5/1; brown solid; mp: 88−90 °C (lit:[26b] 94−95 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, J = 7.1 Hz, 3H), 4.15 (q, J = 7.1 Hz, 2H), 4.33 (s, 2H), 6.50 (d, J = 2.3 Hz, 1H), 7.24−7.40 (m, 10H), 8.10 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 34.1, 59.6, 110.1, 116.1, 126.4, 127.0, 127.4, 127.6, 129.0, 129.3, 129.5, 135.8, 138.0, 138.3, 165.7 ppm.

*Ethyl 2-(2-Methylpropyl)-4-phenyl-1H-pyrrole-3-carboxylate (**3h**).* Yield: 70% (436 mg); Eluents: *n*-hexane/EtOAc = 5/1; viscous brown liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6H), 1.15 (t, J = 7.1 Hz, 3H), 1.93−2.06 (m, 1H), 2.78 (d, J = 7.2 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 6.55 (d, J = 2.3 Hz, 1H), 7.21−7.42 (m, 5H), 8.35 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.6, 29.4, 37.0, 59.5, 110.1, 115.7, 126.2, 127.2, 127.6, 129.4, 136.1, 139.8, 165.9 ppm. HRMS (EI) Calcd m/z for $C_{17}H_{21}NO_2$ $[M]^+$: 271.1572. Found: 271.1571.

*Ethyl 4-Phenyl-2-[(4E)-5-phenylpent-4-en-1-yl]-1H-pyrrole-3-carboxylate (**3i**).* Yield: 77% (635 mg); Eluents: *n*-hexane/EtOAc = 5/1; viscous brown liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, J = 7.1 Hz, 3H), 1.77−1.86 (m, 2H), 2.34−2.42 (m, 2H), 2.90 (t, J = 7.3 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 6.35 (d, J = 2.4 Hz, 1H), 6.52 (d, J = 11.6 Hz, 1H), 7.23−7.32 (m, 5H), 7.33−7.37 (m, 5H), 7.87 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 27.1, 27.8, 29.7, 59.4, 109.5, 115.7(115.67), 115.7(115.73), 126.2, 126.8, 127.1, 127.6, 128.4, 128.9, 129.4, 132.5, 136.0, 137.6, 140.0, 165.8 ppm. HRMS (EI) Calcd m/z for $C_{24}H_{25}NO_2$ $[M]^+$: 359.1885. Found: 359.1884.

*Propan-2-yl 2,4-Diphenyl-1H-pyrrole-3-carboxylate (**3j**).* Yield: 72% (504 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; yellow solid; mp: 40−42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, J = 6.2 Hz, 6H), 4.90−4.98 (m, 1H), 6.62 (d, J = 2.4 Hz, 1H), 7.23−7.48 (m, 10H), 8.69 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 67.5, 111.6, 117.4, 126.4, 127.6, 127.9, 128.1, 128.2, 128.9, 129.2, 130.8, 132.5, 135.6, 136.7, 165.6 ppm. HRMS (EI) Calcd m/z for $C_{20}H_{19}NO_2$ $[M]^+$: 305.1416. Found: 305.1414.

*Ethyl 4-(4-Methylphenyl)-2-phenyl-1H-pyrrole-3-carboxylate (**3k**).* Yield: 77% (539 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; brown solid; mp: 126−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.1 Hz, 3H), 2.35 (s, 3H), 4.02 (q, J = 7.1 Hz, 2H), 6.61 (d, J = 2.6 Hz, 1H), 7.14 (d, J = 7.9 Hz, 2H), 7.27−7.37 (m, 5H), 7.44−7.47 (m, 2H), 8.66 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.3, 60.0, 111.0, 117.3, 127.6, 128.1, 128.2, 128.6, 128.8, 128.9, 132.5, 132.6, 136.0, 136.9, 166.1 ppm. HRMS (EI) Calcd m/z for $C_{20}H_{19}NO_2$ $[M]^+$: 305.1416. Found: 305.1412.

*Ethyl 4-(4-Methoxyphenyl)-2-phenyl-1H-pyrrole-3-carboxylate (**3l**).* Yield: 61% (450 mg); Eluents: *n*-hexane/EtOAc = 5/1; yellow solid; mp: 112−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J = 7.1 Hz, 3H), 3.82 (s, 3H), 4.05 (q, J = 7.1 Hz, 2H), 6.70 (d, J = 2.6 Hz, 1H), 6.88−6.92 (m, 2H), 7.34−7.41 (m, 5H), 7.45−7.52 (m, 2H), 8.54 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 55.3, 59.9, 110.8, 113.3, 117.2, 127.3, 128.0 (127.99), 128.0 (128.03), 128.2, 128.8, 130.2, 132.6, 137.0, 158.4, 166.1 ppm. HRMS (EI) Calcd m/z for $C_{20}H_{19}NO_3$ $[M]^+$: 321.1365. Found: 321.1364.

*Ethyl 4-(4-Fluorophenyl)-2-phenyl-1H-pyrrole-3-carboxylate (**3m**).* Yield: 83% (589 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 2/1; viscous brown liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, J = 7.1 Hz, 3H), 4.05 (q, J = 7.1 Hz, 2H), 6.72 (d, J = 1.6 Hz, 1H), 7.03 (t, J = 8.6 Hz, 2H), 7.30−7.41 (m, 5H), 7.50−7.53 (m, 2H), 8.55 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 60.0, 111.1, 114.5 (d, J = 21.1 Hz), 117.3, 127.0, 128.3 (128.31), 128.3 (128.33), 128.9, 130.7 (d, J = 8.3 Hz), 131.5 (d, J = 3.0 Hz), 132.5, 137.3, 162.0 (d, J = 244.6 Hz), 165.7 ppm. HRMS (EI) Calcd m/z for $C_{19}H_{16}FNO_2$ $[M]^+$: 309.1165. Found: 309.1166.

*Ethyl 4-(4-Cyanophenyl)-2-phenyl-1H-pyrrole-3-carboxylate (**3n**).* Yield: 66% (479 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; light yellow solid; mp: 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J = 7.1 Hz, 3H), 4.06 (q, J = 7.1 Hz, 2H), 6.81 (d, J = 2.6 Hz, 1H), 7.39−7.41 (m, 3H), 7.51−7.54 (m, 4H), 7.60−7.63 (m, 2H), 8.79 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 60.2, 109.8, 110.8, 118.1, 119.5, 126.2, 128.3, 128.6, 129.0, 129.7, 131.7, 132.1, 138.1, 140.6, 165.4 ppm. HRMS (EI) Calcd m/z for $C_{20}H_{16}N_2O_2$ $[M]^+$: 316.1212. Found: 316.1212.

*Ethyl 4-Butyl-2-phenyl-1H-pyrrole-3-carboxylate (**3o**).* Yield: 73% (454 mg); Eluents: *n*-hexane/EtOAc = 7/1 to 5/1; brown solid; mp: 74−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.35−1.47 (m, 2H), 1.55−1.65 (m, 2H), 2.70−2.80 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 6.54 (d, J = 2.4 Hz, 1H), 7.29−7.39 (m, 3H), 7.44−7.48 (m, 2H), 8.25 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.1, 22.8, 26.6, 32.7, 59.4, 110.5, 116.2, 127.6, 127.7, 127.9, 129.1, 133.1, 137.6, 166.1 ppm. HRMS (EI) Calcd m/z for $C_{17}H_{21}NO_2$ $[M]^+$: 271.1572. Found: 271.1570.

*Ethyl 2-Phenyl-4-(2-phenylethyl)-1H-pyrrole-3-carboxylate (**3p**).* Yield: 63% (462 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; brown solid; mp: 78−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3H), 2.89−2.95 (m, 2H), 3.00−3.07 (m, 2H), 4.13 (q, J = 7.1 Hz,

dx.doi.org/10.1021/jo501672c | J. Org. Chem. 2014, 79, 9253−9261

2H), 6.43 (d, J = 2.2 Hz, 1H), 7.15−7.20 (m, 1H), 7.22−7.37 (m, 7H), 7.42−7.45 (m, 2H), 8.36 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 28.9, 37.1, 59.5, 110.6, 116.5, 125.7, 126.7, 127.9, 128.3, 128.6, 129.2, 133.1, 137.8, 142.7, 165.8 ppm. HRMS (EI) Calcd m/z for $C_{21}H_{21}NO_2$ $[M]^+$: 319.1572. Found: 319.1569.

*Ethyl 4-Butyl-2-ethyl-1H-pyrrole-3-carboxylate (**3q**) [CAS: 594864-19-4].* Yield: 64% (328 mg); Eluents: *n*-hexane/EtOAc = 7/1; brown solid; mp: 54−56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 7.5 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.33−1.44 (m, 2H), 1.50−1.60 (m, 2H), 2.59−2.73 (m, 2H), 2.93 (q, J = 7.5 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 6.36 (d, J = 2.0 Hz, 1H), 8.56 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 14.1, 14.5, 21.4, 22.8, 26.8, 32.8, 59.2, 109.1, 113.9, 126.9, 142.0, 166.4 ppm.

*Ethyl 4-(2-Bromophenyl)-2-phenyl-1H-pyrrole-3-carboxylate (**3s**).* Yield: 40% (170 mg); Eluents: *n*-hexane/EtOAc = 5/1 to 3/1; brown solid; mp: 170−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.1 Hz, 3H), 3.92 (q, J = 7.1 Hz, 2H), 6.55 (d, J = 2.3 Hz, 1H), 7.10−7.15 (m, 1H), 7.23−7.35 (m, 5H), 7.49−7.52 (m, 2H), 7.58 (d, J = 7.9 Hz, 1H), 8.83 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 59.8, 111.6, 118.0, 125.2, 126.5, 126.8, 128.1, 128.2, 129.1, 131.8, 132.2, 137.1, 137.5, 165.4 ppm. HRMS (EI) Calcd m/z for $C_{19}H_{16}BrNO_2$ $[M]^+$: 369.0364. Found: 369.0365.

*Ethyl (Z)-2-Aminophenylmethylidene-3-(o-chlorophenyl)-3-butenoate (**4h**).* Eluents: *n*-hexane/EtOAc = 7/1; yellow solid; mp: 72−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, J = 7.1 Hz, 3H), 4.06 (q, J = 7.1 Hz, 2H), 5.14 (d, J = 1.6 Hz, 1H), 5.33 (d, J = 1.6 Hz, 1H), 6.97−7.06 (m, 3H), 7.19−7.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 59.3, 99.4, 123.3, 126.0, 127.2, 127.7, 128.2, 128.7, 129.9, 130.1, 132.0, 138.7, 141.2, 142.3, 160.3, 170.0 ppm. HRMS (EI) Calcd m/z for $C_{19}H_{18}ClNO_2$ $[M]^+$: 327.1026. Found:327.1023.

*Ethyl (Z)-2-Aminophenylmethylidene-4-(o-chlorophenyl)-3-butenoate (**4h′**).* Eluents: *n*-hexane/EtOAc = 7/1; yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (t, J = 7.1 Hz, 3H), 4.33 (q, J = 7.1 Hz, 2H), 6.55 (d, J = 16.3 Hz, 1H), 6.96−7.05 (m, 2H), 7.08−7.10 (m, 1H), 7.10 (d, J = 16.3 Hz, 1H), 7.21−7.27 (m, 1H), 7.39−7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 60.1, 96.6, 121.3, 125.1, 126.6 (126.60), 126.6 (126.64), 127.6, 128.6, 128.8, 129.6, 129.7, 132.5, 137.6, 138.2, 162.5, 170.3 ppm. HRMS (EI) Calcd m/z for $C_{19}H_{18}ClNO_2$ $[M]^+$: 327.1026. Found:327.1024.

Procedures for the Synthesis of Pyrrolophenanthrene 7 and Pyranopyrrolone 8. *Synthesis of N-Methylated Pyrrole **S1**.* To a solution of the pyrrole **3t** (1.77 g, 5.00 mmol) in DMF (6.0 mL) was added NaH (144 mg, 6.00 mmol) at 0 °C. After stirring for 10 min, iodomethane (0.38 mL, 6.0 mmol) was added, and the reaction mixture was stirred at room temperature for an additional 2 h. The reaction was quenched by the addition of H_2O and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-Hexane/EtOAc = 7/1) to afford *N*-methylated pyrrole **S1** as a pale yellow solid (1.34g, 73% yield). Yield: 73% (1.34 g); Eluents: *n*-hexane/EtOAc = 7/1; pale yellow solid; mp: 40−42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, J = 7.1 Hz, 3H), 2.92−2.98 (m, 2H), 3.19−3.24 (m, 2H), 3.22 (s, 3H), 4.07 (q, J = 7.1 Hz, 2H), 6.36 (s, 1H), 7.13−7.28 (m, 8H), 7.37−7.40 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 28.0, 33.5, 36.1, 59.2, 111.5, 121.0, 122.8, 126.0, 126.2, 127.8, 128.5, 128.8, 128.9, 131.7, 134.7, 135.9, 139.5, 141.5, 165.2 ppm. HRMS (EI) Calcd m/z for $C_{22}H_{22}ClNO_2$ $[M]^+$: 367.1339. Found: 367.1340.

*Synthesis of Pentasubstituted Pyrroles **6a, 6b**.* A mixture solution of bromobenzene (1.00 mmol), *N*-methylated pyrrole **S1** (1.00 mmol), KOAc (196 mg, 2.00 mmol), and $Pd(OAc)_2$ (11 mg, 0.05 mmol) in DMAc (3.0 mL) placed in a Schlenk tube was heated at 150 °C for 5 h. The reaction was quenched with H_2O at room temperature and extracted with ethyl acetate (30 mL × 3), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford pyrroles **6**.

*Ethyl 4-(2-Chlorophenyl)-1-methyl-2-(2-phenylethyl)-5-phenyl-1H-pyrrole-3-carboxylate (**6a**).* Yield: 87% (386 mg); Eluents: *n*-hexane/EtOAc = 10/1; white solid; mp: 96−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J = 7.1 Hz, 3H), 3.04−3.21 (m, 2H), 3.12 (s, 3H), 3.38−3.45 (m, 2H), 4.06 (dq, J = 10.6, 7.1 Hz, 1H), 4.17 (dq, J = 10.6, 7.1 Hz, 1H), 7.08−7.17 (m, 5H), 7.25−7.37 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 28.3, 31.5, 36.2, 59.1, 111.2, 121.2, 125.8, 126.3, 127.6 (127.55), 127.6 (127.60), 128.1, 128.5 (128. 45), 128.5 (128.50), 128.9, 130.7, 131.6, 131.9, 132.5, 135.5, 136.2, 139.6, 141.5, 165.3 ppm. HRMS (EI) Calcd m/z for $C_{28}H_{26}ClNO_2$ $[M]^+$: 443.1652. Found: 443.1653.

*Ethyl 4-(2-Chlorophenyl)-5-(4-cyanophenyl)-2-(2-phenylethyl)-1-methyl-1H-pyrrole-3-carboxylate (**6b**).* Yield: 97% (455 mg); Eluents: *n*-hexane/EtOAc = 5/1; pale yellow solid; mp: 124−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J = 7.1 Hz, 3H), 3.00−3.13 (m, 2H), 3.07 (s, 3H), 3.27−3.41 (m, 2H), 4.00 (dq, J = 10.7, 7.1 Hz, 1H), 4.09 (dq, J = 10.7, 7.1 Hz, 1H), 7.02 (dd, J = 7.5, 1.8 Hz, 1H), 7.07 (dd, J = 7.2, 1.0 Hz, 1H), 7.10−7.19 (m, 5H), 7.22−7.34 (m, 4H), 7.49 (d, J = 8.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 28.3, 31.8, 36.0, 59.3, 110.9, 111.9, 118.7, 122.6, 126.0, 126.4, 128.2, 128.5, 128.7, 128.9, 129.9, 130.9, 131.9, 132.3, 135.3, 135.4, 136.4, 140.9, 141.3, 164.9 ppm. HRMS (EI) Calcd m/z for $C_{29}H_{25}ClN_2O_2$ $[M]^+$: 468.1605. Found: 468.1602.

*Synthesis of Pyrrolophenanthrene Derivatives **7a** and **7b**.* Pyrrole **6** (0.30 mmol), $PdCl_2$ (11 mg, 0.06 mmol), and PCy_3 (34 mg, 0.12 mmol) were introduced in a thick-wall Pyrex pressure tube, equipped with a magnetic stirring bar. DBU (0.14 mL, 0.90 mmol) and DMF (5 mL) were added, and then the solution was purged with a nitrogen stream for 5 min. The sealed tube was placed in a preheated oil bath at 160 °C, and the reaction mixture was stirred for 6 h. After cooling to room temperature, the suspension was filtered through Celite and washed with CH_2Cl_2 (30 mL), and then the filtrate was concentrated in a reduced pressure. The residue was purified by chromatography on silica gel to afford the pyrrolophenanthrene derivatives **7**.

*Ethyl 1-Methyl-2-(2-phenylethyl)-1H-dibenzo[e,g]indole-3-carboxylate (**7a**).* Yield: 81% (99 mg); Eluents: *n*-hexane/EtOAc = 7/1; pale yellow solid; mp: 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, J = 7.1 Hz, 3H), 2.94−2.99 (m, 2H), 3.24−3.29 (m, 2H), 3.83 (s, 3H), 4.47 (q, J = 7.1 Hz, 2H), 7.12−7.18 (m, 2H), 7.19−7.29 (m, 3H), 7.48−7.59 (m, 4H), 8.26−8.34 (m, 1H), 8.60−8.69 (m, 2H), 8.70−8.78 (m, 1H) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.5, 27.8, 34.8, 36.3, 60.6, 60.6, 108.8, 119.1, 121.4, 123.2, 123.8, 124.0, 124.4, 124.6, 125.6, 126.2, 126.4, 127.8, 127.9, 128.5, 128.6, 129.0, 129.4, 140.9, 142.6, 167.6 ppm. HRMS (EI) Calcd m/z for $C_{28}H_{25}NO_2$ $[M]^+$: 407.1885. Found: 407.1887.

*Ethyl 7-Cyano-1-methyl-2-(2-phenylethyl)-1H-dibenzo[e,g]-indole-3-carboxylate (**7b**).* Yield: 78% (101 mg); Eluents: *n*-hexane/EtOAc = 3/1; white solid; mp: 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, J = 7.1 Hz, 3H), 2.97−3.03 (m, 2H), 3.27−3.34 (m, 2H), 3.81 (s, 3H), 4.51 (q, J = 7.1 Hz, 2H), 7.12−7.18 (m, 2H), 7.22−7.31 (m, 3H), 7.53−7.65 (m, 3H), 8.28 (d, J = 8.8 Hz, 1H), 8.49 (d, J = 7.7 Hz, 1H), 8.62 (dd, J = 8.2, 1.3 Hz, 1H), 8.91 (d, J = 1.4 Hz, 1H) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.5, 28.1, 35.1, 36.4, 61.0, 107.1, 109.6, 119.8, 121.6, 121.9, 123.1, 125.5, 125.8, 125.9, 126.7, 127.6, 127.8 (127.78), 127.8 (127.84), 127.9, 128.6, 128.8, 128.9, 129.1, 140.6, 144.2, 167.3 ppm. HRMS (EI) Calcd m/z for $C_{29}H_{24}N_2O_2$ $[M]^+$: 432.1838. Found: 432.1837.

*Synthesis of 4-(2-Chlorophenyl)-1-methyl-5-phenyl-2-phenylethyl-1H-pyrrole-3-carboxylic Acid (**S2**).* To a solution of pyrrole **6a** (444 mg, 1.0 mmol) in EtOH (20 mL) was added NaOH (280 mg, 7 mmol), and the mixture was stirred at reflux for 20 h. After removal of ethanol in vacuo, the residue was diluted in water (5 mL). After cooling to 0 °C, the resulting solution was acidified to pH < 3 with 6.0 N HCl and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization (CH_2Cl_2/*n*-hexane) to afford the pyrrole **S2** as a white solid. Yield: 99% (412 mg); white solid; mp: 202−204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92−3.0 (m, 2H), 3.07 (s, 3H), 3.32 (t, J = 7.4 Hz, 2H), 7.03−7.13 (m, 5H), 7.15−7.32 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 31.7, 36.2, 110.3, 121.6, 125.8, 126.2, 127.7, 127.8, 128.1, 128.5, 128.8, 129.0, 130.8, 131.5, 132.4, 132.6, 135.4,

dx.doi.org/10.1021/jo501672c | J. Org. Chem. 2014, 79, 9253−9261

135.6, 141.1, 141.6, 170.1 ppm. HRMS (EI) Calcd m/z for $C_{26}H_{22}ClNO_2$ $[M]^+$: 415.1339. Found: 415.1340.

*Synthesis of 2-Methyl-1-phenyl-3-(2-phenylethyl)chromeno[3,4-c]pyrrol-4(2H)-one (**8**).* Pyrrole **S2** (125 mg, 0.30 mmol) and copper(I)-thiophene-2-carboxylate (127 mg, 0.60 mmol) in DMF (3 mL) were introduced in a pressure tube, equipped with a magnetic stirring bar. The pressure tube was placed in a preheated oil bath at 160 °C, and then the reaction mixture was stirred for 15 h. After it cooled down to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) solution, and the mixture was extracted with ethyl acetate (30 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford pyranopyrrolone derivative **8** as a pale yellow solid. Yield: 95% (108 mg); pale yellow solid; mp: 146−148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (s, 3H), 3.05 (t, J = 7.2 Hz, 2H), 3.42 (t, J = 7.2 Hz, 2H), 6.82−6.91 (m, 1H), 7.02−7.14 (m, 3H), 7.16−7.28 (m, 5H), 7.31−7.39 (m, 2H), 7.48−7.57 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 31.3, 36.1, 104.9, 116.8, 117.4, 117.9, 122.6, 123.5, 126.4, 126.9, 127.0, 128.5, 128.9, 129.3, 131.3, 131.9, 138.8, 141.0, 151.5, 159.7 ppm. HRMS (EI) Calcd m/z for $C_{26}H_{21}NO_2$ $[M]^+$: 379.1572. Found: 379.1568.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sanggi@ewha.ac.kr (S.-g.L.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the financial support for this work from the Korea Research Foundation (NRF-2011-0016344). We thank Dr. Sung Hong Kim at the Daegu Center of the Korea Basic Science Institute for mass spectral analysis.

■ REFERENCES

(1) (a) Jones, R. A. *Pyrroles, Part II*; Wiley: New York, 1992. (b) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*, 2nd ed.; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Elsevier: Oxford, UK, 1996; p 207. (c) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (e) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213. (f) Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F., III; Schenck, R. J.; Trippe, A. J. *J. Org. Chem.* **2008**, *73*, 4443. (g) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (h) Huffman, J. W. *Curr. Med. Chem.* **1999**, *6*, 705.

(2) (a) Müllen, K., Wegner, G., Eds. *Electronic Materials: The Oligomer Approach*; Wiley-VCH: Weinheim, Germany, 1998. For reviews, see: (b) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465. (c) Novak, P.; Müller, K.; Santhanam, K. S. V.; Haas, O. *Chem. Rev.* **1997**, *97*, 207. (d) Curran, D.; Grimshaw, J.; Perera, S. D. *Chem. Soc. Rev.* **1991**, *20*, 391. For recent selected reports, see: (e) Takase, M.; Yoshida, N.; Narita, T.; Fujio, T.; Nishinaga, T.; Iyoda, M. *RSC Adv.* **2011**, *2*, 3221. (f) Blangy, V.; Heiss, C.; Khlebnikov, V.; Letondor, C.; Evans, H. S.; Neier, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1688. (g) Wienk, M. M.; Turbiez, M.; Gilot, J.; Janssen, R. A. *J. Adv. Mater.* **2008**, *20*, 2556. (h) Wu, D.; Descalzo, A. B.; Weik, F.; Emmerling, F.; Shen, Z.; You, X. Z.; Rurack, K. *Angew. Chem., Int. Ed.* **2007**, *47*, 193. (i) Chen, Y.; Zeng, D.; Xie, N.; Dang, Y. *J. Org. Chem.* **2005**, *70*, 5001. (j) Domingo, V. M.; Aleman, C.; Brillas, E.; Julia, L. *J. Org. Chem.* **2001**, *66*, 4058. (k) Lee, C. F.; Yang, L. M.; Hwu, T. Y.; Feng, A. S.; Tseng, J. C.; Luh, T. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992.

(3) (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans.1* **1999**, 2849. (c) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J. C. *Chem. Soc. Rev.* **2012**, *41*, 3929. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215. (f) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29. (g) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (h) Tarasova, O. A.; Nedolya, N. A.; Vvedensky, V. Yu.; Brandsma, L.; Trofimov, B. A. *Tetrahedron Lett.* **1997**, *38*, 7241.

(4) For recent selected reports, see: (a) Chen, G.-Q.; Zhang, X.-N.; Wei, Y.; Tang, X.-Y.; Shi, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8492. (b) Yu, Y.; Wang, C.; He, X.; Yao, X.; Zu, L. *Org. Lett.* **2014**, *16*, 3580. (c) Shi, Z.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 4892. (d) Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696. (e) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140. (f) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, 135. (g) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, *2*, 629. (h) Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176. (i) Nagata, H.; Sugimoto, Y.; Ito, Y.; Tanaka, M.; Yoshimatsu, M. *Tetrahedron* **2014**, *70*, 1306. (j) Chattopadhyay, B.; Gevorgyan, V. *Org. Lett.* **2011**, *13*, 3746. (k) Parr, B. T.; Green, S. A.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 4716. (l) Kim, C.-E.; Park, S.; Eom, D.; Seo, B.; Lee, P. H. *Org. Lett.* **2014**, *3*, 789.

(5) (a) Gao, M.; He, C.; Chen, H.; Bai, R.; Cheng, B.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6958. (b) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953. (c) Trost, B. M.; Lumb, J.-P.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740. (d) Merkul, E.; Boersch, C.; Frank, W.; Müller, T. J. J. *Org. Lett.* **2009**, *11*, 2269.

(6) For selected papers, see: (a) Narayan, R.; Daniliuc, C.-G.; Würthwein, E.-U. *Eur. J. Org. Chem.* **2012**, 6021. (b) Tang, Q.; Zhang, C.; Luo, M. *J. Am. Chem. Soc.* **2008**, *130*, 5840. (c) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384. (d) Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 597. (e) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140. (f) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (g) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2836. (h) Ghosh, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1918.

(7) For selected examples, see: (a) Kim, J. H.; Lee, S.-g. *Org. Lett.* **2011**, *13*, 1350. (b) Chun, Y. S.; Lee, J. H.; Kim, J. H.; Ko, Y. O.; Lee, S.-g. *Org. Lett.* **2011**, *13*, 6390. (c) Kim, J. H.; Shin, H.; Lee, S.-g. *J. Org. Chem.* **2012**, *77*, 1560. (d) Chun, Y. S.; Kim, J. H.; Choi, S. Y.; Ko, Y. O.; Lee, S.-g. *Org. Lett.* **2012**, *14*, 6358. (e) Chun, Y. S.; Xuan, Z.; Kim, J. H.; Lee, S.-g. *Org. Lett.* **2013**, *15*, 3162.

(8) (a) Chun, Y. S.; Ko, Y. O.; Shin, H.; Lee, S.-g. *Org. Lett.* **2009**, *11*, 3414. (b) Kim, J. H.; Chun, Y. S.; Lee, S.-g *J. Org. Chem.* **2013**, *78*, 11483.

(9) Kim, J. H.; Bouffard, J.; Lee, S.-g. *Angew. Chem., Int. Ed.* **2014**, *53*, 6435.

(10) For recent selected reports, see: (a) Cheng, J.; Chen, P.; Liu, G. *Org. Chem. Front.* **2014**, *1*, 289. (b) Weinstein, A. B.; Schuman, D. P.; Tan, Z. X.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 11867. (c) Kong, A.; Blakey, S. B. *Synthesis* **2012**, *44*, 1190. (d) Redford, J. E.; McDonald, R. I.; Rigsby, M. L.; Wiensch, J. D.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 1242. (e) Lu, Z.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 1234. (f) Kim, H. J.; Cho, S. H.; Chang, S. *Org. Lett.* **2012**, *14*, 1424. (g) Ye, X.; Liu, G.; Popp, B. V.; Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031. (h) Lu, J.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 3694. (i) Rogers, M. M.; Kotov, V.; Chatwichien, J.; Stahl, S. S. *Org. Lett.* **2007**, *9*, 4331. (j) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246.

(11) Tsvelikhovsky and Buchwald applied this type of conditions for aza-Wacker type intramolecular cyclization to *N*-arylated 2-vinylated anilines, resulting in indole derivatives; see: (a) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14048. (b) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 16917. See also the pioneering work of Hegedus: (c) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415.

(12) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584.
(13) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164.
(14) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892.
(15) For selected reviews, see: (a) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.
(16) For recent reviews, see: (a) Jiang, L.; Buchwald, S. L. *Metal-Catalyzed Cross Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 699−760. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (c) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; Vol. *1*, pp 1051−1069. (d) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (f) Surry, D. S.; Buchwarld, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (g) Hartwig, J. F. *Nature* **2008**, *455*, 314.
(17) Characterization data for these compounds; see the Supporting Information of ref 9.
(18) Selected recent papers; see: (a) Zhou, J.; Yang, W.; Wang, B.; Ren, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12293. (b) Cacchi, S.; Fabrizi, G.; Oggiamani, A.; Iazzettia, A. *Org. Biomol. Chem.* **2012**, *10*, 9142. (c) Zeng, W.; Lee, B. S.; Sung, Y. M.; Huang, K.-W.; Li, Y.; Kim, D.; Wu, J. *Chem. Commun.* **2012**, *48*, 7684. (d) Cao, J.; Miao, M.; Chen, W.; Wu, L.; Huang, X. *J. Org. Chem.* **2011**, *76*, 9329. (e) Hirano, K.; Inaba, Y.; Takasu, M.; Oishi, S.; Takemoto, Y.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 9068. (f) Budén, M. E.; Vaillard, V. A.; Martin, S. E.; Rossi, R. A. *J. Org. Chem.* **2009**, *74*, 4490. (g) Wu, D.; Descalzo, A. B.; Weik, F.; Emmerling, F.; Shen, Z.; You, X.-Z.; Rurack, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 193. (h) Pla, D.; Marchal, A.; Olsen, C. A.; Francesh, A.; Cuevas, C.; Albericio, F.; Alvarez, M. *J. Med. Chem.* **2006**, *49*, 3257. (i) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796.
(19) Wu, T.-C.; Hsin, H.-J.; Kuo, M.-Y.; Li, C.-H.; Wu, Y.-T. *J. Am. Chem. Soc.* **2011**, *133*, 16319.
(20) Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L.; Ruchirawat, S. *J. Org. Chem.* **2007**, *72*, 9379.
(21) Pd(II)-catalyzed 5-*endo-trig* cyclization; see: Kandukuri, S. R.; Schiffner, J. A.; Oestreich, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 1265.
(22) For selected reviews on Pd(II)-catalyzed reactions using molecular oxygen as the sole oxidant, see: (a) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (b) Shi, Z.; Zhang, C.; Cui, Y.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (c) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780.
(23) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292.
(24) Fenwick, A. E. *Tetrahedron. Lett.* **1993**, *34*, 1815.
(25) Katritzky, A. R.; Huang, T.-B.; Voronkov, M. V.; Wang, M.; Kolb, H. *J. Org. Chem.* **2000**, *65*, 8819.
(26) (a) Matiychuk, V. S.; Martyak, R. L.; Obushak, N. D.; Ostapiuk, Y. V.; Pidlypnyi, N. I. *Chem. Heterocycl. Compd.* **2004**, *40*, 1218. (b) Sonn, A.; Litten, W. *Chem. Ber.* **1933**, *66*, 1512.