JOC The Journal of Organic Chemistry

Article

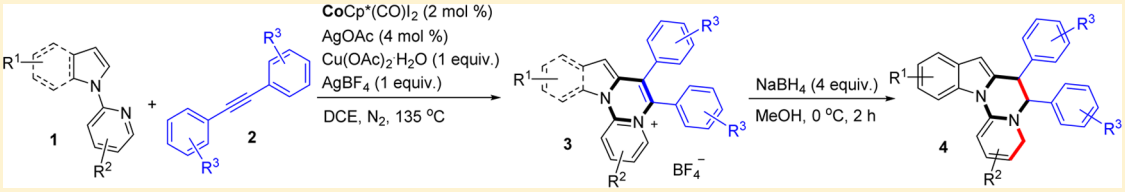
pubs.acs.org/joc

Cp*Co^{III}-Catalyzed Synthesis of Pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-iums via Tandem C−H Activation and Subsequent Annulation from 1-(Pyridin-2-yl)-1*H*-indoles and Internal Alkynes

Yuhan Yang, Bo Li, Wenmin Liu, Rumeng Zhang, Lintao Yu, Qin-Ge Ma, Rongrong Lv, Donghua Du, and Ting Li*

College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, Henan 473061, P. R. China

Supporting Information



ABSTRACT: A Cp*Co^{III}-catalyzed C2-selective C−H alkenylation/annulation cascade transformation of 1-(pyridin-2-yl)-1*H*-indoles with internal alkynes to afford pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-iums is presented. Moreover, 6,7-dihydro-4*H*-pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indole, a new functionalized *N*-fused indole core heterocycle, could be constructed effectively via reduction of pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-ium by $NaBH_4$.

INTRODUCTION

Indoles are important structural constituents of numerous pharmaceuticals, natural products, and biologically active molecules.[1] In addition, starting from indoles, a series of interesting nitrogen-containing heterocycles could be constructed effectively.[2] Therefore, the development of efficient synthetic methodologies that allow the synthesis and modification of indoles is a long-standing task for organic chemists, and there is continuing interest in new synthetic methods that would provide selective access to substituted indole derivatives.[3] Transition-metal-catalyzed C−H functionalization was recognized to be a powerful strategy in organic synthesis, and the past decade has witnessed the rapid development of transition-metal-catalyzed C−H functionalization transformations.[4] Especially, cobalt complexes as an effective catalyst for C−H activation transformations have attracted much attention by the synthestic community.[5] Recently, considerable progress has been achieved using high-valent cobalt complexes by Kanai/Matsunaga,[6] Ackermann,[7] Daugulis,[8] Glorius,[9] Ellman,[10] Chang,[11] and many others,[12] respectively.

On the other hand, fused polycyclic aromatic and polycyclic heteroaromatic compounds are embedded in a large number of compounds due to their potential utility in organic and polymeric functional materials.[13] Therefore, the synthesis of π-conjugated systems containing indole skeleton is highly desirable.[14] Yet, applications of the indole C−H functionalization process to cascade reactions providing access to more functionalized *N*-fused indole cores have been rare.[2] Thus, methods for efficiently providing a functionalized *N*-fused indole cores unit from readily available starting materials via a C−H activation process are interesting and in great demand. Several groups have already carried out the Co-catalyzed research on indole C-2 selective C−H bond activation with heteroatom-assisted chelation.[6b,c,15] In 2012, Yoshikai's group reported the stereoselective C2-alkenylation reaction of indoles with alkynes catalyzed by a low valent Co−pyphos catalyst (Scheme 1a).[16] Shortly after, Matsunaga and Kanai described the C2-selective C−H alkenylation/annulation cascade of *N*-carbamoyl indoles with alkynes to afford pyrroloindolones in one pot (Scheme 1b).[6c] Here, we present the Co-catalyzed C2-selective C−H alkenylation/annulation cascade transformation of 1-(pyridin-2-yl)-1*H*-indoles with internal alkynes to afford pyrido-[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-iums in one pot (Scheme 1c).[17]

RESULTS AND DISCUSSION

As demonstrated in Table 1, initially, the reaction of 1-(pyridin-2-yl)-1*H*-indole **1a** with 1.1 equiv of diphenylethyne **2a** was conducted under a N_2 atmosphere with 2% mol $[Cp^*RhCl_2]_2$ as the catalyst and 2.2 equiv of $Cu(OAc)_2{\cdot}H_2O$ as the oxidant in the presence of $AgBF_4$ (5% mol) for 24 h. Serendipitously, the unexpected red compound **3aa**, which contains the pyrido-[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-ium skeleton, was generated in about 4% isolated yield (entry 1). The definite structure of **3** was confirmed by X-ray crystallographic studies of **3ha**, as shown in Figure 1 (*vide infra*).[18] The formation of the pyrido[2′,1′:2,3]-pyrimido[1,6-*a*]indol-5-ium skeleton is interesting. To the best of our knowledge, efficient construction of pyrido[2′,1′:2,3]-pyrimido[1,6-*a*]indol-5-iums, a recurring structural motif found

Received: September 22, 2016
Published: October 25, 2016

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

Scheme 1. Cp*Co^{III}-Catalyzed Facile Synthesis of Pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-iums

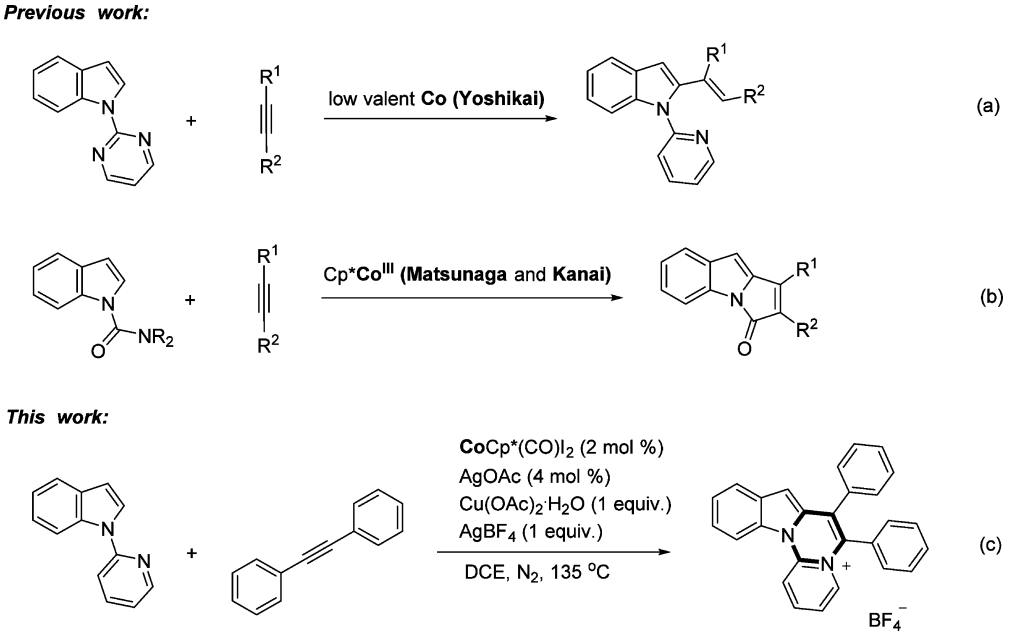
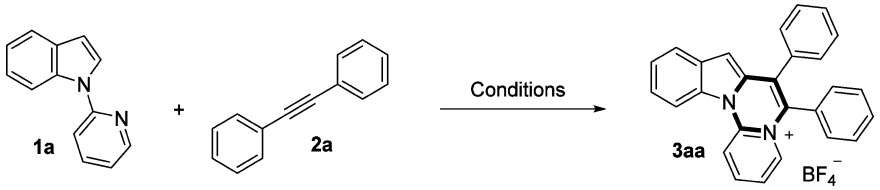


Table 1. Optimization of the Reaction Conditions[a]



entry	reaction conditions	yield (%)
1	[Cp*RhCl$_2$]$_2$ (2%), Cu(OAc)$_2$·H$_2$O (2.0), AgBF$_4$ (5%), 135 °C, PhMe	4
2	CoCp*(CO)I$_2$ (2%), Cu(OAc)$_2$·H$_2$O (2.0), AgBF$_4$ (1.0), 135 °C, PhMe	46
3	CoCp*(CO)I$_2$ (2%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 135 °C, PhMe	48
4	CoCp*(CO)I$_2$ (5%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 135 °C, PhMe	48
5	CoCp*(CO)I$_2$ (2%), AgOAc (4%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 135 °C, PhMe	76
6	CoCp*(CO)I$_2$ (2%), AgOAc (4%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 135 °C, PhCl	56
7	CoCp*(CO)I$_2$ (2%), AgOAc (4%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 135 °C, DCE	86
8	CoCp*(CO)I$_2$ (2%), AgOAc (4%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 135 °C, DMF	0
9	CoCp*(CO)I$_2$ (2%), AgOAc (4%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 125 °C, DCE	<5
10[b]	CoCp*(CO)I$_2$ (2%), AgOAc (4%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 135 °C, DCE	52
11	CoCp*(CO)I$_2$ (1%), AgOAc (4%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 135 °C, DCE	56
12	CoCp*(CO)I$_2$ (1%), KOAc (4%), Cu(OAc)$_2$·H$_2$O (1.0), AgBF$_4$ (1.0), 135 °C, DCE	trace

[a]Conditions: **1a** (0.20 mmol), **2a** (0.22 mmol, 1.1 equiv), [M], and solvent (2 mL) under a N$_2$ atmosphere for 24 h. Isolated products based on **1a**. [b]Reaction performed under air atmosphere.

in many pharmaceuticals and functional materials, have rarely been reported.[19] However, further studies to increase the yield of product **3aa** by using rhodium catalyst conditions failed. When CoCp*(CO)I$_2$ was used as the catalyst instead, the reaction was accelerated and compound **3aa** could be isolated in 46% yield (entry 2). Ongoing studies revealed that the addition of AgOAc would accelerate the transformation obviously (entries 2−5). We have also examined the solvent effects for this transformation (entries 5−8) and found DCE to be the most suitable solvent, which gave **3aa** in about 86% yield (entry 7). Further investigation demonstrated that the reaction temperature (135 °C), the N$_2$ atmosphere, and the amount of CoCp*(CO)I$_2$ catalyst loading were integrant for this transformation (entries 9−11). In addition, the use of KOAc as an alternative to the use of AgOAc and Cu(OAc)$_2$ was also tested, and only a trace amount of product **3aa** could be tested (entry 12).

Under the optimized reaction conditions in Table 1, we sought to further explore the scope and limitation of this reaction. First, a series of 1-(pyridin-2-yl)-1*H*-indoles were investigated (Scheme 2). It was found that installation of a Me substituent on the pyridyl C-2 or C-3 position would furnish products **3ca** or **3da** in 78% and 83% yields, respectively. In contrast, when the C-1 or C-4 position of the pyridyl directing group was blocked with a Me group, the reaction was completely suppressed, probably as a result of steric factors (**3ba** and **3ea**). The generality of the indole ring was next examined. Installation of a Me group at the C-4, C-5, C-6, or C-7 position on the indole ring had a negative influence on the transformation (**3fa**, **3ga**, **3ha**, and **3ia**). Yet, when the Me

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

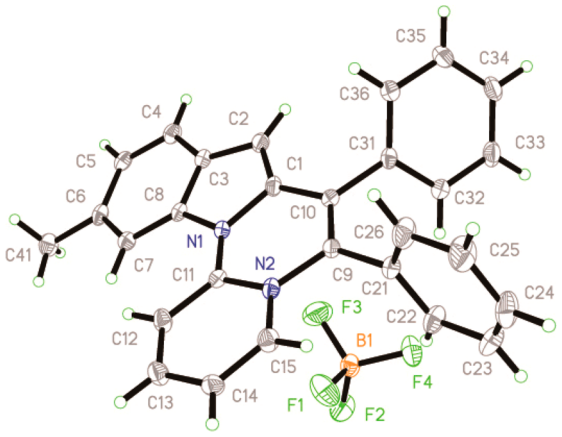


Figure 1. X-ray crystal structure of compound **3ha** (drawn at 50% ellipsoids).

group was at the C-3 position, the reaction was suppressed and **3ja** was isolated in about only 20% yield. The reaction also accommodated Cl, F, Br, I, NO_2, and OMe groups, thus affording products **3ka**, **3la**, **3ma**, **3na**, **3oa**, **3pa**, and **3qa** in good yields. Besides, when the C-5 position of the indole ring was fixed with a COOMe substituent, the reaction also worked well to provide **3ra** in 74% yields. Moreover, the transformation was not tolerant of the CN group, and product **3sa** could only be detected in about 10% yield. To further demonstrate the power of this cobalt catalytic system, other substrates were also tested. Under similar reaction conditions, substrates **1t** and **1u** could react with alkynes smoothly to afford the expected products pyrido[1,2-*a*]pyrido-[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-5-iums (**3ta**) and pyrido[1,2-*a*]pyrrolo[1,2-*c*]pyrimidin-5-iums in good yields (**3ua**, **3ug**), while substrate **1v** failed.

Consequently, the scope for the internal alkynes was further investigated (Scheme 3). Substrates bearing a Me group at the *meta* or *para* position on the phenyl ring proceeded smoothly (**3ab**, **3ac**), while that with a Me group at the *ortho* position failed to yield the desired product **3ad**, possibly due to the steric hindrance. Alkynes containing substituents including Cl and NO_2 at the *para* position on the phenyl ring were well tolerated to provide the corresponding products in good yields (**3ae**−**3af**). It is worthy to note that this methodology could be further extended to thiophene containing substrate **2g** to afford the corresponding product **3ag**, which was isolated in about 86% yield. Further studies revealed that aliphatic alkyne **2h** was not compatible with this transformation, and only trace **3ah** could be detected in the reaction mixture. In addition, the unsymmetrical alkyne **2i** was also tested and two regioisomeric salts were isolated with a 95:5 ratio in 81% combined yield (**3ai**). Moreover, we have also performed experiments with aryl silyl alkynes and aryl alkoxycarbonyl alkynes as the coupling alkyne. However, the reactions turned messy with only traces of the desired products detected.

It is reasonable to believe that the reaction first underwent C−H activation of substrate **1a**, followed by annulation of the alkyne to generate the target product **3aa**. To gain insight into the C−H cleavage step, substrate **1a** was allowed to react with excess CD_3OD (10 equiv) for 2 h under standard reaction conditions, and 84% deuterium incorporation at C−2 position as well as 78% (C−3 position of indole) and 84% (C−6 position of pyridine) deuterium incorporation was observed (Scheme 4, eq 1). This result clearly indicated that a reversible deprotonative C−H bond activation step might exist in the transformation. Subsequently, the kinetic isotope effect experiment on **1a** and **D-1a** (95% D) with alkyne **2a** was carried out under the standard conditions, resulting in a KIE value of 1.3 (see the Supporting Information), which indicated that the C−H cleavage of *N*-(2-pyridyl)indole is not likely to be the rate-limiting step for this transformation (Scheme 4, eq 2). As shown in eq 3, **3aa** was not obtained when treating **5a** under standard reaction conditions. The result suggested that the 2-alkenyl-substituted *N*-(2-pyridyl)indole **5a** was not the key intermediate of this Co-catalyzed cascade cyclization for the formation of **3aa**. Besides, the competition experiments with substrates bearing varied electronic properties were also investigated. As shown in Scheme 3, it was found that the formation of products derived from electron-deficient 1-(pyridin-2-yl)-1*H*-indole **1p** and electron-rich alkyne **2b** was favored in the transformation (Scheme 4, eq 4).

Based on these experiment results and the previous reports,[17] a tentative mechanism for the formation of compound pyrido-[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-ium is proposed as shown in Scheme 5. Initially, reaction of $CoCp^*(CO)I_2$ with AgOAc generates the catalytically active species $[Cp^*Co]^{2+}$ (**I**), which is followed by the nitrogen-directed reversible *ortho* cyclometalation to provide intermediate **II**. Then, coordination of the alkyne to intermediate **II** forms intermediate **III**, and the subsequent insertion reaction would provide the seven-membered cobaltacyclic intermediate **IV**. Reductive elimination of intermediate **IV** with the aid of $AgBF_4$ and $Cu(OAc)_2$ give the desired product **3aa** and regenerate the cobalt^{III} catalyst species to finish the catalystic cycle. The role of $AgBF_4$ is probably twofold. It not only offers a BF_4 ligand but also acts as an oxidant for the transformation.

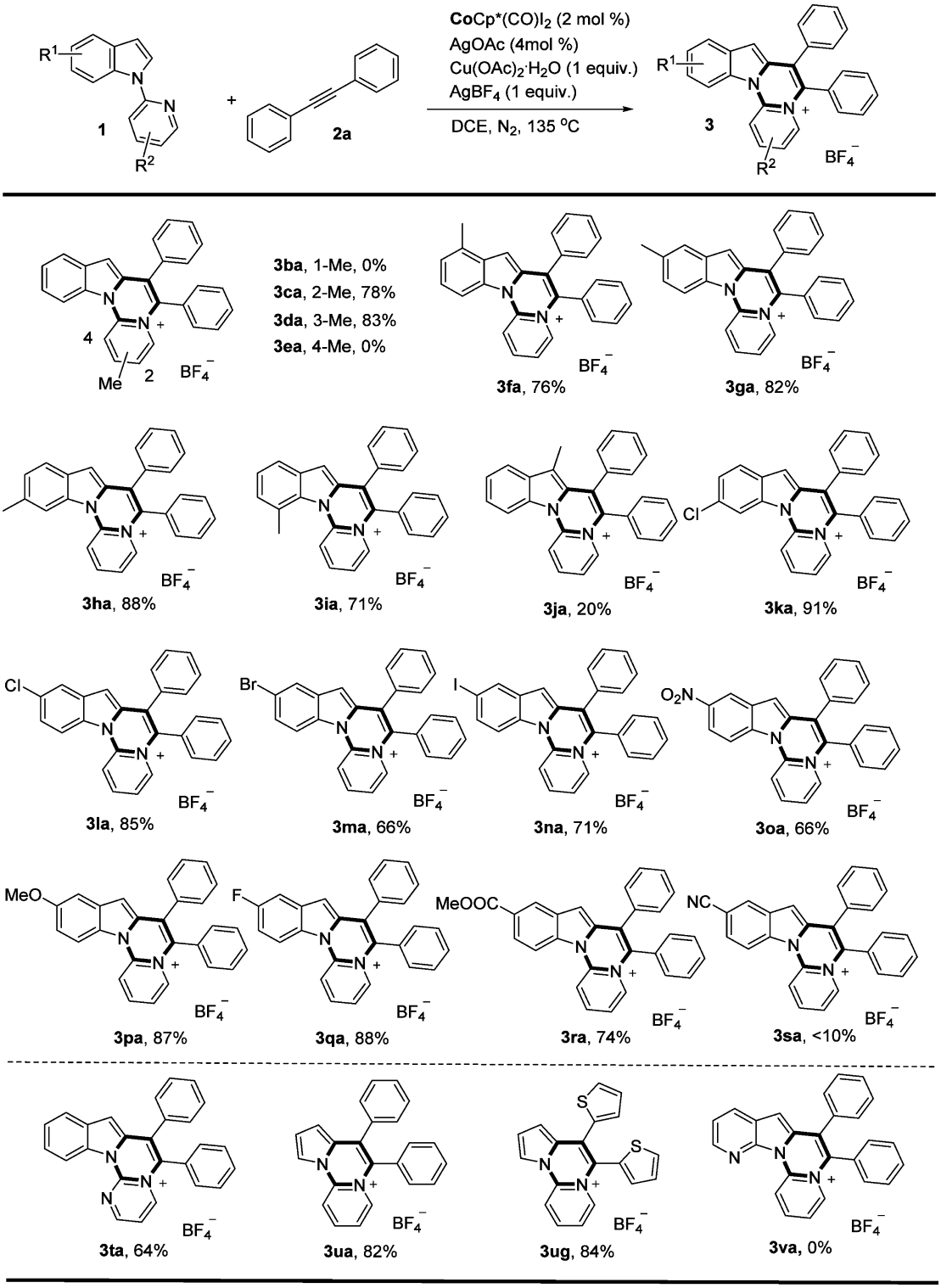
Besides, to demonstrate the synthetic potential of this transformation, 10 mmol scale reactions were conducted using **1a**, **1l**, and **1p** as substrates, and the reaction proceeded smoothly to provide products **3aa**, **3la**, and **3pa** in 75%, 81%, and 84% yields, respectively (Scheme 6). In addition, it was found that the C−H activation products could be readily reduced by $NaBH_4$ to give the addition products 6,7-dihydro-4*H*-pyrido[2′,1′:2,3]-pyrimido[1,6-*a*]indoles **4** in good yields (66% to 86% yields), and this transformation tolerated functional groups including F, Cl, OMe, and Me groups (Scheme 7). These transformations thus further strengthened the synthetic impact of this protocol for the preparation of new nitrogen-containing heterocycles starting from indoles. Moreover, we also characterized the UV−vis absorption of several representative products and found that the synthesized polycyclic compounds showed strong UV−vis absorption in the range of 440−480 nm as shown in Figure 2.

■ CONCLUSIONS

In conclusion, we have successfully developed a Cp*Co^{III}-catalyzed C−H annulation reaction of 1-(pyridin-2-yl)-1*H*-indole with internal alkynes toward the syntheses of pyrido-[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-iums in moderate to good yields. In addition, a new *N*-containing heterocycle, 6,7-dihydro-4*H*-pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indole, could be constructed effectively via reduction of pyrido[2′,1′:2,3]pyrimido-[1,6-*a*]indol-5-ium by $NaBH_4$. Evaluation of the biological activity of these products is underway in our laboratories. Given the simplicity of this reaction and the importance of heterocyclic quaternary ammonium salts as functional molecules in organic chemistry, we anticipate this transformation may find applications.

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

Scheme 2. Subsrate Scope for 1-(Pyridin-2-yl)-1*H*-indole[a]



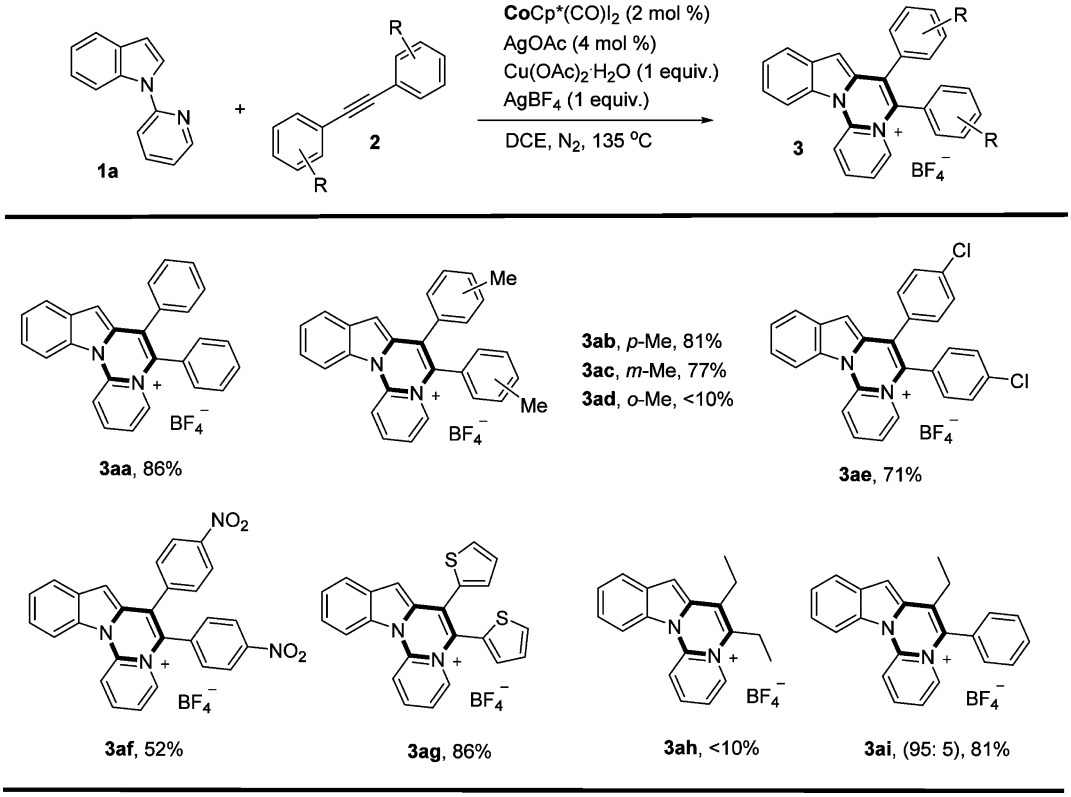
[a]Standard reaction conditions: A mixture of derivatives **1** (0.20 mmol), **2a** (0.22 mmol), $CoCp^*(CO)I_2$ (2 mol %), AgOAc (4 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.20 mmol), $AgBF_4$ (0.20 mmol), and DCE (2 mL) was added to a sealed Schlenk tube under a N_2 atmosphere. Then the mixture was stirred at 135 °C for 24 h. Isolated products based on **1**.

EXPERIMENTAL SECTION

General Remarks. All reactions were carried out in flame-dried sealed tubes with magnetic stirring. Unless otherwise noted, all experiments were performed under a N_2 atmosphere. Commercially available reagents and solvents were used without further purification except as noted. Products were purified by column chromatography on 200−300 mesh silica gels. All melting points were determined without correction. ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in DMSO-d_6 or $CDCl_3$. Splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). All chemical shifts are given as δ values (in ppm) with reference to

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

Scheme 3. Subsrate Scope for Alkynes[a]



[a]Standard reaction conditions: A mixture of derivatives **1a** (0.20 mmol), **2** (0.22 mmol), CoCp*(CO)I_2 (2 mol %), AgOAc (4 mol %), Cu(OAc)$_2$·H_2O (0.20 mmol), $AgBF_4$ (0.20 mmol), and DCE (2 mL) was added to a sealed Schlenk tube under a N_2 atmosphere. Then the mixture was stirred at 135 °C for 24 h. Isolated products based on **1a**.

tetramethylsilane (TMS) as an internal standard. Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). HRMS was performed on an FT-MS instrument using electrospray ionization (APCI or ESI). Crystallographic data were recorded on a diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Structures were solved by direct methods in SHELXS-97. Copies of the ^{1}H NMR and ^{13}C NMR spectra and crystallographic data in CIF are provided in the Supporting Information. Substrates including 1-(pyrimidin-2-yl)-1*H*-indole[21] and 2-(1*H*-pyrrol-1-yl)pyridine[22] were prepared by previously reported procedures.

General Procedure the Preparation of Substrates ***1***.[21] A mixture of indoles (5.0 mmol), 2-bromopyridine (6.0 mmol), and KOH (0.70 g, 12.5 mmol) in DMSO (5 mL) was vigorously stirred at 130 °C under a nitrogen atmosphere for 36 h. After the mixture was cooled to ambient temperature, the reaction mixture was diluted with EtOAc (20 mL) and washed with H_2O (2 × 20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL), and the combined organic phase was dried over Na_2SO_4. After filtration and evaporation of the solvents in vacuo, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 100:1−30:1) to afford the desired products.

General Procedure for the Preparation of Alkynes ***2***:[23] Pd-$(PPh_3)_2Cl_2$ (105 mg, 0.15 mmol, 5 mol %), 1,4- bis(diphenylphosphino)butane (128 mg, 0.30 mmol, 10 mol %), aryl halides (6.00 mmol, 2.00 equiv), and propiolic acid (212 mg, 3.00 mmol, 1.00 equiv) were combined with DBU (913 mg, 6.0 mmol, 2.00 equiv) in a small round bottomed flask. DMSO (15.0 mL) was added, and the flask was sealed with a septum. The resulting mixture was placed in an oil bath at 80 °C for 16 h. After that, the reaction was poured into 25 mL of saturated aqueous ammonium chloride solution and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, and filtered. The solvent was removed under vacuum, and the resulting crude product was adsorbed on silica and purified by column chromatography (Pentane/EtOAc).

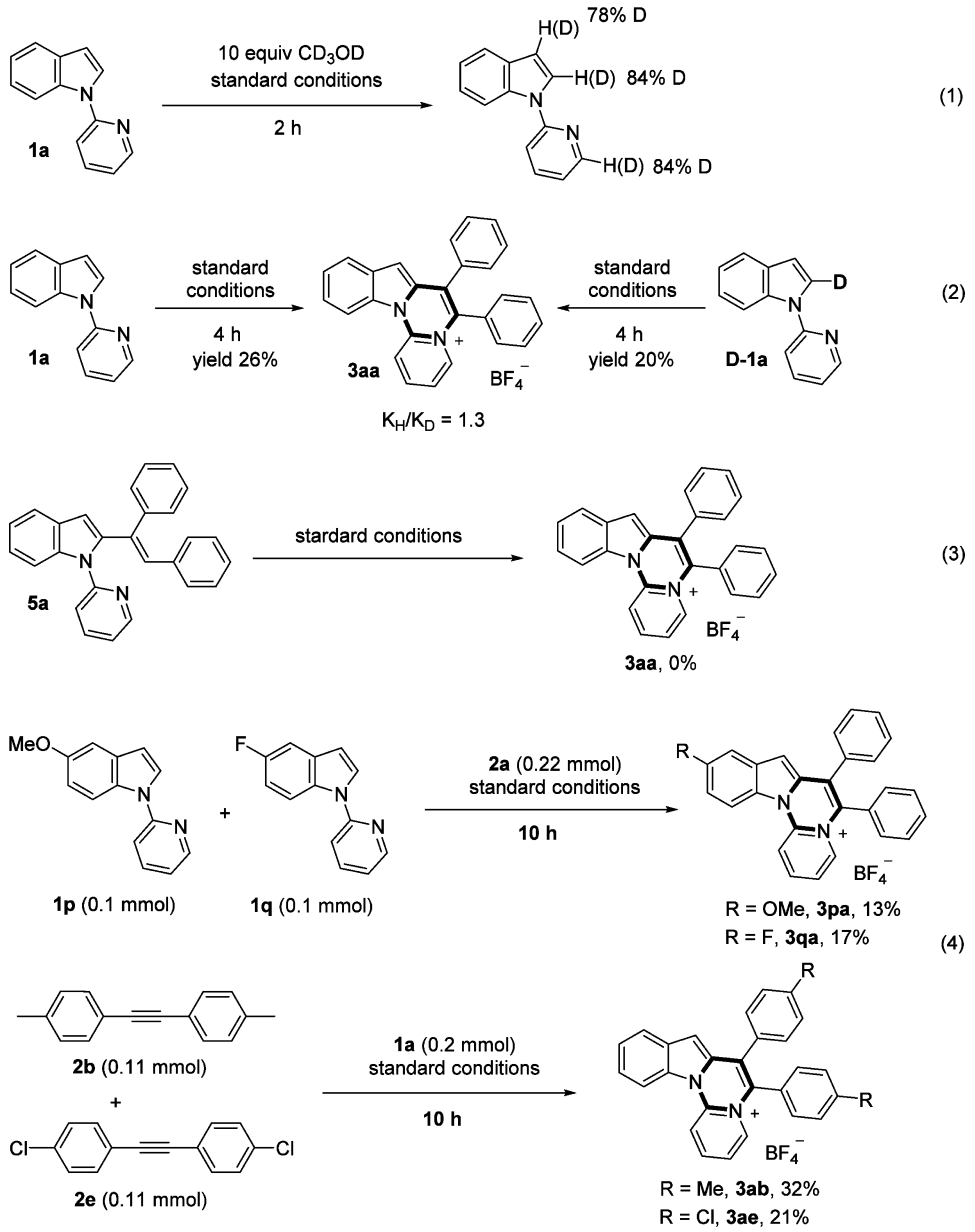
General Procedure for the Synthesis of ***3***. Synthesis of compound **3aa** is representative. A mixture of 1-(pyridin-2-yl)-1*H*-indole **1a** (0.20 mmol), 1,2-diphenylethyne **2a** (0.22 mmol), [CoCp*(CO)I_2] (2 mol %), AgOAc (4 mol %), Cu(OAc)$_2$·H_2O (0.20 mmol), $AgBF_4$ (0.20 mmol), and DCE (2 mL) was added to a sealed Schlenk tube under a N_2 atmosphere. Then the mixture was stirred at 135 °C (bath temperature, preheated) for the desired time (usually 24 h) until complete consumption of starting materials judged by TLC. Then the reaction mixture was filtered through a short plug of silica gel, washed with CH_2Cl_2, and concentrated; the residue was purified by chromatography with petroleum ether/EtOAc (v/v, 1/1) and then CH_2Cl_2/MeOH (v/v, 20/1) to afford pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-ium **3aa** in 86% yield.

*6,7-Diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3aa**).* Red solid (78.8 mg, 86%), mp 177−179 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (d, J = 8.7 Hz, 1H), 8.80 (d, J = 8.4 Hz, 1H), 8.70 (t, J = 7.7 Hz, 1H), 8.45 (d, J = 6.4 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.86−7.68 (m, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.50 (s, 5H), 7.37 (d, J = 12.2 Hz, 5H), 6.78 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.81, 143.72, 137.80, 133.26, 133.06, 133.04, 132.95, 131.98, 131.42, 130.91, 129.86, 129.76, 129.63, 129.33, 129.08, 128.53, 126.06, 126.02, 123.11, 120.67, 116.40, 116.04, 104.11. HRMS m/z (ESI) [M − BF_4] calcd for $C_{27}H_{19}N_2$, 371.1548; found, 371.1548.

*3-Methyl-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ca**).* Red solid (73.7 mg, 78%), mp 181−183 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (d, J = 9.0 Hz, 1H), 8.78 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 8.8 Hz, 1H), 8.15 (s, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.50 (s, 5H), 7.36 (d, J = 14.8 Hz, 5H), 6.75 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.21, 142.20, 135.23, 133.35, 132.96, 132.85, 132.81, 132.02, 131.31, 130.94, 130.59, 129.82, 129.67, 129.64, 129.28, 129.05, 128.61, 125.89, 123.03, 116.01, 115.95, 103.82, 17.92. HRMS m/z (ESI) [M − BF_4] calcd for $C_{28}H_{21}N_2$, 385.1705; found, 385.1704.

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

Scheme 4. Mechanism Studies



*2-Methyl-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3da**).* Red solid (78.4 mg, 83%), mp 186−188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.93 (d, J = 8.6 Hz, 1H), 8.32 (d, J = 7.1 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.64 (dd, J = 13.3, 7.0 Hz, 2H), 7.50 (s, 5H), 7.38 (t, J = 6.9 Hz, 3H), 7.34 (d, J = 7.6 Hz, 2H), 6.76 (s, 1H), 2.86 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.68, 143.15, 136.86, 133.32, 133.20, 132.97, 132.80, 131.96, 131.34, 130.86, 129.84, 129.82, 129.72, 129.25, 129.05, 127.59, 125.93, 125.84, 122.90, 122.02, 116.39, 115.02, 104.02, 22.34. HRMS m/z (ESI) [M − BF_4] calcd for $C_{28}H_{21}N_2$, 385.1705; found, 385.1704.

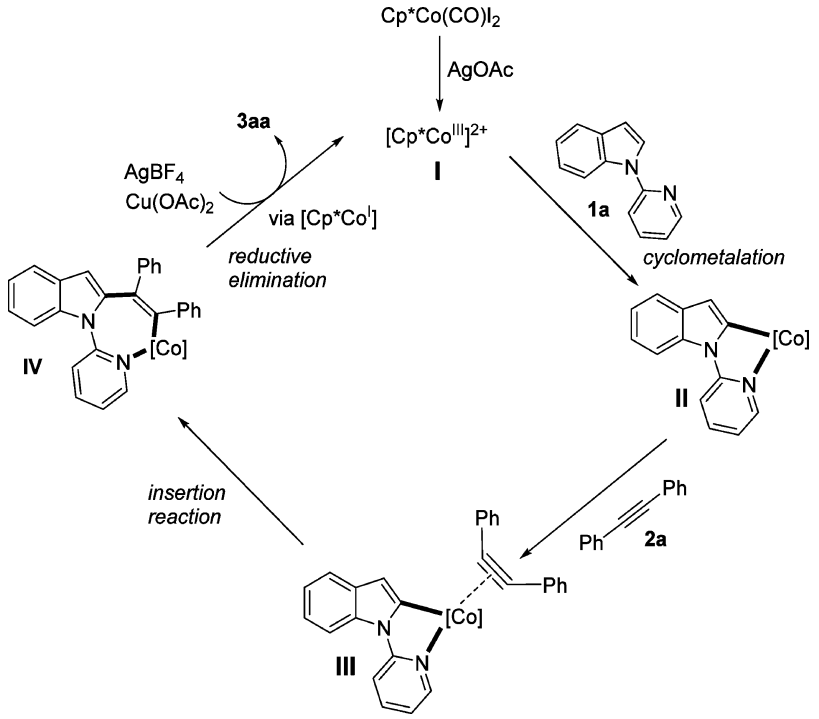
*9-Methyl-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3fa**).* Red solid (71.8 mg, 76%), mp 179−181 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (d, J = 8.7 Hz, 1H), 8.70 (t, J = 7.7 Hz, 1H), 8.64 (d, J = 8.5 Hz, 1H), 8.46 (d, J = 6.5 Hz, 1H), 7.77 (t, J = 6.7 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.50 (s, 6H), 7.38 (d, J = 12.0 Hz, 5H), 6.74 (s, 1H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.75, 143.70, 137.79, 133.23, 132.99, 132.85, 132.71, 132.33, 131.99, 131.03, 130.87, 129.84, 129.67, 129.35, 129.11, 128.61, 126.20, 126.14, 120.69, 116.40, 113.54, 102.24, 18.91. HRMS m/z (ESI) [M − BF_4] calcd for $C_{28}H_{21}N_2$, 385.1705; found, 385.1704.

*10-Methyl-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ga**).* Red solid (77.4 mg, 82%), mp 180−182 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (d, J = 8.9 Hz, 1H), 8.70 (d, J = 8.5 Hz, 2H), 8.42 (d, J = 6.8 Hz, 1H), 7.79 (s, 1H), 7.74 (s, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.50 (s, 5H), 7.38 (t, J = 6.8 Hz, 3H), 7.33 (d, J = 7.2 Hz, 2H), 6.71 (s, 1H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.64, 143.55, 137.68, 135.70, 133.30, 133.15, 132.93, 131.98, 131.76, 131.23, 130.88, 129.84, 129.62, 129.31, 129.08, 128.44, 127.54, 122.56, 120.44, 116.25, 115.73, 103.72, 21.49. HRMS m/z (ESI) [M − BF_4] calcd for $C_{28}H_{21}N_2$, 385.1705; found, 385.1704.

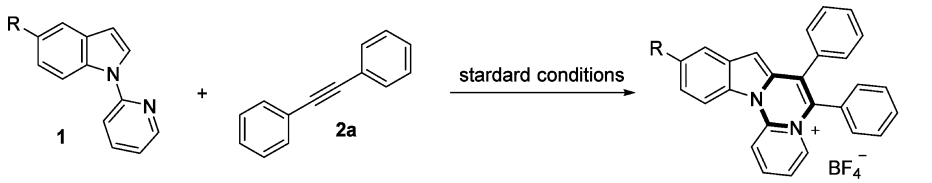
*11-Methyl-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ha**).* Red solid (82.2 mg, 87%), mp 183−185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (d, J = 8.7 Hz, 1H), 8.68 (t, J = 7.6 Hz, 1H), 8.63 (s, 1H), 8.42 (d, J = 6.2 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.75 (t, J = 6.4 Hz, 1H), 7.50 (s, 6H), 7.35 (d, J = 13.6 Hz, 5H), 6.73 (s, 1H), 2.68 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.64, 143.72, 137.71, 136.24, 133.37, 133.32, 132.53, 132.02, 130.85, 129.84, 129.61, 129.28, 129.25, 129.05, 128.62, 127.69, 122.65, 120.55, 116.44, 115.78, 104.05, 22.31. HRMS m/z (ESI) [M − BF_4] calcd for $C_{28}H_{21}N_2$, 385.1705; found, 385.1704.

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

Scheme 5. A Tentative Reaction Mechanism for the Transformation



Scheme 6. Gram-Scale Synthesis of C−H Activation Compounds 3aa, 3la, and 3pa



3aa, R = H, 10 mmol, 75%
3la, R = Cl, 10 mmol, 81%
3pa, R = OMe, 10 mmol, 84%

*12-Methyl-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ia**).* Red solid (67.1 mg, 71%), mp 184−185 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.31 (d, J = 8.9 Hz, 1H), 8.88 (d, J = 8.7 Hz, 1H), 8.77 (t, J = 8.0 Hz, 1H), 8.54 (d, J = 6.7 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.85 (t, J = 6.9 Hz, 1H), 7.68 (t, J = 8.1 Hz, 1H), 7.52 (s, 5H), 7.48−7.15 (m, 5H), 6.54 (s, 1H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 146.29, 143.58, 138.16, 134.17, 134.04, 133.22, 132.86, 131.85, 131.39, 131.06, 129.92, 129.61, 129.57, 129.49, 129.25, 128.86, 128.28, 127.03, 121.46, 116.67, 115.64, 115.40, 102.55, 31.15. HRMS m/z (ESI) [M − BF_4] calcd for $C_{28}H_{21}N_2$, 385.1705; found, 385.1704.

*8-Methyl-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ja**).* Red solid (18.9 mg, 20%), mp 178−180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (d, J = 8.9 Hz, 1H), 8.77 (d, J = 8.5 Hz, 1H), 8.65 (t, J = 7.9 Hz, 1H), 8.30 (d, J = 6.5 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 4.9 Hz, 2H), 7.59−7.44 (m, 5H), 7.34 (m, 6H), 1.68 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.68, 143.95, 137.54, 133.75, 132.92, 132.79, 132.00, 131.69, 130.65, 130.12, 129.83, 129.67, 129.20, 128.88, 127.28, 126.44, 125.82, 120.94, 120.27, 116.27, 115.88, 112.50, 103.53, 9.25. HRMS m/z (ESI) [M − BF_4] calcd for $C_{28}H_{21}N_2$, 385.1705; found, 385.1704.

*11-Chloro-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ka**).* Red solid (89.7 mg, 91%), mp 188−191 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (d, J = 8.8 Hz, 1H), 8.92 (s, 1H), 8.71 (t, J = 7.2 Hz, 1H), 8.48 (d, J = 6.2 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 6.2 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.50 (s, 5H), 7.36 (d, J = 17.4 Hz, 5H), 6.82 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 146.21, 143.43, 137.99, 133.79, 133.37, 133.12, 133.10, 131.94, 130.98, 130.66, 130.12, 129.89, 129.62, 129.40, 129.11, 128.51, 126.52, 124.28, 121.20, 116.78, 115.82, 103.96. HRMS m/z (ESI) [M − BF_4] calcd for $C_{27}H_{18}ClN_2$, 405.1159; found, 405.1158.

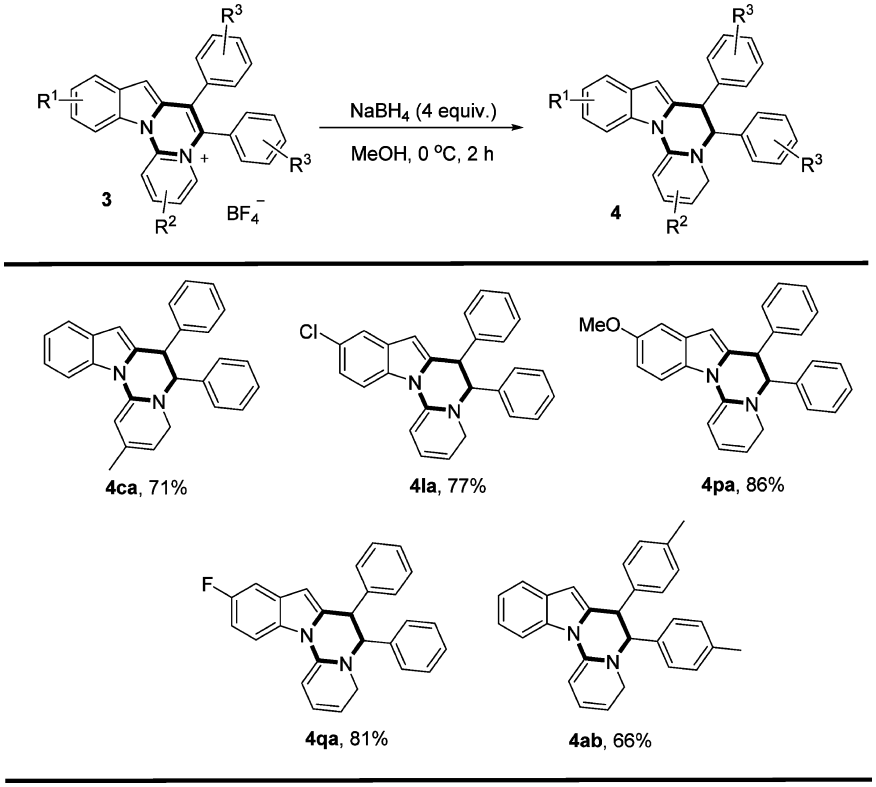
*10-Chloro-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3la**).* Red solid (83.8 mg, 85%), mp 186−188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, J = 8.7 Hz, 1H), 8.84 (d, J = 9.0 Hz, 1H), 8.73 (t, J = 7.7 Hz, 1H), 8.49 (d, J = 6.4 Hz, 1H), 8.11 (s, 1H), 7.81 (t, J = 6.6 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.51 (s, 5H), 7.38 (d, J = 16.3 Hz, 5H), 6.77 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 146.07, 143.46, 137.97, 134.37, 133.80, 133.05, 132.82, 131.89, 131.47, 131.00, 130.54, 129.89, 129.61, 129.58, 129.42, 129.14, 128.33, 125.63, 122.19, 121.07, 117.68, 116.44, 103.39. HRMS m/z (ESI) [M − BF_4] calcd for $C_{27}H_{18}ClN_2$, 405.1159; found, 405.1158.

*10-Bromo-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ma**).* Red solid (70.9 mg, 66%), mp 188−189 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.24 (d, J = 8.8 Hz, 1H), 8.86−8.65 (m, 2H), 8.49 (d, J = 6.5 Hz, 1H), 8.26 (s, 1H), 7.82 (t, J = 9.9 Hz, 1H), 7.81 (t, J = 6.5 Hz, 1H), 7.51 (s, 5H), 7.38 (dd, J = 25.0, 6.3 Hz, 5H), 6.78 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 146.09, 143.47, 138.00, 134.19, 133.83, 133.25, 133.05, 131.89, 131.78, 131.00, 129.89, 129.61, 129.43, 129.15, 128.33, 128.25, 125.31, 121.10, 118.79, 117.93, 116.50, 103.27. HRMS m/z (ESI) [M − BF_4] calcd for $C_{27}H_{18}BrN_2$, 449.0648; found, 449.0651.

*10-Iodo-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3na**).* Red solid (83.0 mg, 71%), mp 190−191 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.22 (d, J = 9.0 Hz, 1H), 8.72 (t, J = 8.0 Hz, 1H), 8.64 (d, J = 9.0 Hz, 1H), 8.48 (d, J = 6.7 Hz, 1H), 8.43 (s, 1H), 7.98 (d, J = 8.9 Hz,

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

Scheme 7. Application of the C−H Activation Products for the Construction of 6,7-Dihydro-4*H*-pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indoles 4[a]



[a]Standard reaction conditions: To a stirred solution of **3** (0.20 mmol) in dry MeOH (5 mL) at 0 °C was added $NaBH_4$ (0.80 mmol). Then the mixture was allowed to stir at 0 °C for 2 h. Isolated products based on **1a**.

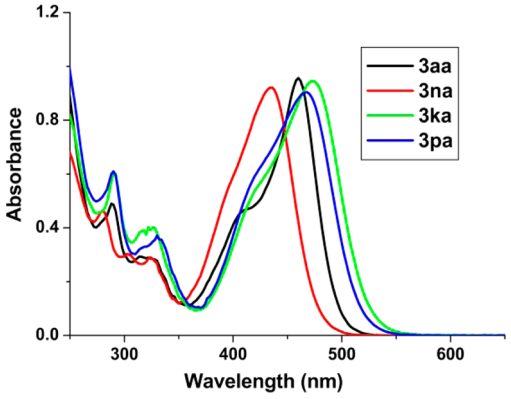


Figure 2. UV−vis absorption spectra of selected pyrido[2′,1′:2,3]-pyrimido[1,6-*a*]indol-5-iums compounds in CH_2Cl_2 at 1×10^{-6} M concentration.

1H), 7.79 (t, *J* = 6.9 Hz, 1H), 7.50 (s, 5H), 7.46−7.13 (m, 5H), 6.75 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 146.02, 143.49, 137.97, 133.79, 133.74, 133.71, 133.60, 133.07, 132.23, 131.90, 131.48, 130.98, 129.88, 129.60, 129.42, 129.14, 128.34, 121.03, 117.96, 116.55, 103.00, 91.47, 40.66, 40.45, 40.24, 40.04, 39.83, 39.62, 39.41. HRMS *m*/*z* (ESI) [M − BF_4] calcd for $C_{27}H_{18}IN_2$, 497.0509; found, 497.0516.

*10-Nitro-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3oa**).* Red solid (65.4 mg, 65%), mp 190−191 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.36 (d, *J* = 8.9 Hz, 1H), 9.05 (d, *J* = 9.4 Hz, 1H), 8.98 (s, 1H), 8.81 (t, *J* = 7.9 Hz, 1H), 8.56 (d, *J* = 6.7 Hz, 1H), 8.49 (d, *J* = 9.0 Hz, 1H), 7.89 (t, *J* = 6.9 Hz, 1H), 7.52 (s, 5H), 7.39 (m, 5H), 7.05 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 146.66, 145.02, 143.53, 138.45, 135.60, 134.36, 132.84, 131.85, 131.41, 131.11, 129.95, 129.61, 129.38, 129.21, 128.35, 122.01, 119.95, 119.02, 117.00, 116.84, 104.99. RMS *m*/*z* (ESI) [M − BF_4] calcd for $C_{27}H_{18}O_2N_3$, 416.1394; found, 416.1399.

*10-Methoxy-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3pa**).* Red solid (85.0 mg, 87%), mp 192−194 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (d, *J* = 9.0 Hz, 1H), 8.71 (d, *J* = 9.3 Hz, 1H), 8.66 (t, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 6.8 Hz, 1H), 7.72 (t, *J* = 6.9 Hz, 1H), 7.50 (s, 6H), 7.39 (d, *J* = 6.8 Hz, 3H), 7.36−7.25 (m, 2H), 6.71 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.74, 145.45, 143.18, 137.54, 133.66, 133.28, 133.08, 132.93, 131.96, 130.88, 129.84, 129.82, 129.63, 129.32, 129.07, 128.12, 127.53, 120.28, 117.11, 116.05, 115.52, 104.30, 103.84, 56.08. HRMS *m*/*z* (ESI) [M − BF_4] calcd for $C_{28}H_{21}ON_2$, 401.1654; found, 401.1661.

*10-Fluoro-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3qa**).* Red solid (83.8 mg, 88%), mp 182−184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (d, *J* = 8.9 Hz, 1H), 8.86 (d, *J* = 5.4 Hz, 1H), 8.71 (s, 1H), 8.47 (d, *J* = 6.2 Hz, 1H), 7.90−7.71 (m, 2H), 7.59 (s, 1H), 7.50 (s, 5H), 7.36 (d, *J* = 18.7 Hz, 5H), 6.78 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.08 (d, J_{C-F} = 242.4 Hz), 145.98, 143.43, 137.87, 134.62, 133.65, 132.92 (d, J_{C-F} = 11.1 Hz), 131.90, 130.98, 129.89, 129.62, 129.40, 129.13, 128.21, 120.89, 117.92 (d, J_{C-F} = 9.8 Hz), 114.02 (d, J_{C-F} = 25.8 Hz), 107.99 (d, J_{C-F} = 24.0 Hz), 103.83 (d, J_{C-F} = 4.4 Hz). HRMS *m*/*z* (ESI) [M − BF_4] calcd for $C_{27}H_{18}FN_2$, 389.1449; found, 389.1449.

*10-Methoxycarbonyl-6,7-diphenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ra**).* Red solid (76.4 mg, 74%), mp 195−197 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (d, *J* = 8.9 Hz, 1H), 8.93 (d, *J* = 9.1 Hz, 1H), 8.76 (t, *J* = 8.0 Hz, 1H), 8.66 (s, 1H), 8.50 (d, *J* = 6.8 Hz, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.83 (t, *J* = 7.0 Hz, 1H), 7.51 (s, 5H), 7.47−7.27 (m, 5H), 6.96 (s, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.40, 146.28, 143.58, 138.16, 135.12, 134.25, 133.68, 133.02, 131.92, 131.28, 131.02, 129.91, 129.64, 129.54, 129.46, 129.14, 128.52, 126.95, 125.89, 124.73, 121.44, 116.64, 116.22, 104.69, 52.92. HRMS *m*/*z* (ESI) [M − BF_4] calcd for $C_{29}H_{21}O_2N_2$, 429.1603; found, 429.1602.

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

6,7-Diphenylpyrimido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ta**). Red solid (58.8 mg, 64%), mp 176−178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.21 (d, J = 8.2 Hz, 1H), 8.79 (d, J = 6.2 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.85 (s, 1H), 7.78−7.72 (m, 1H), 7.72−7.61 (m, 1H), 7.44 (m, 10H), 6.89 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.18, 146.02, 145.73, 133.23, 133.09, 132.73, 132.62, 131.95, 131.19, 130.93, 129.98, 129.56, 129.22, 128.69, 128.59, 126.67, 126.44, 122.68, 118.41, 117.28, 105.19, 103.52. HRMS m/z (ESI) [M − BF_4] calcd for $C_{26}H_{18}N_3$, 372.1495; found, 372.1501.

6,7-Diphenylpyrido[1,2-a]pyrrolo[1,2-c]pyrimidin-5-ium (**3ua**). Red solid (66.9 mg, 82%), mp 131−133 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, J = 8.7 Hz, 1H), 8.86 (s, 1H), 8.66 (t, J = 7.8 Hz, 1H), 8.39 (d, J = 6.6 Hz, 1H), 7.78 (t, J = 6.7 Hz, 1H), 7.48 (s, 5H), 7.39−7.21 (m, 6H), 6.48 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 144.05, 141.15, 136.58, 133.37, 132.29, 130.78, 130.36, 129.85, 129.82, 129.62, 129.23, 129.00, 128.93, 128.31, 121.57, 119.28, 118.36, 116.05, 108.70. HRMS m/z (ESI) [M − BF_4] calcd for $C_{23}H_{17}N_2$, 321.1392; found, 321.1383.

6,7-Di(thiophen-2-yl)pyrido[1,2-a]pyrrolo[1,2-c]pyrimidin-5-ium (**3uq**). Red solid (70.6 mg, 84%), mp 136−138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (d, J = 8.8 Hz, 1H), 8.86 (s, 1H), 8.65 (t, J = 8.0 Hz, 1H), 8.59 (d, J = 6.8 Hz, 1H), 7.99 (d, J = 4.9 Hz, 1H), 7.81 (t, J = 7.0 Hz, 1H), 7.75 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.35 (d, J = 2.5 Hz, 1H), 7.31 (d, J = 3.5 Hz, 2H), 7.19−7.07 (m, 1H), 6.95 (d, J = 3.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 144.32, 141.27, 136.52, 135.66, 133.26, 132.99, 131.00, 130.14, 128.98, 128.77, 128.03, 127.66, 124.79, 123.63, 121.69, 119.35, 119.33, 115.90, 110.34. HRMS m/z (ESI) [M − BF_4] calcd for $C_{19}H_{13}N_2S_2$, 333.0520; found, 333.0515.

6,7-Di-p-tolylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ab**). Red solid (64.7 mg, 81%), mp 184−186 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, J = 8.9 Hz, 1H), 8.79 (d, J = 8.5 Hz, 1H), 8.68 (t, J = 7.8 Hz, 1H), 8.42 (d, J = 6.6 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.36 (dd, J = 23.2, 7.5 Hz, 4H), 7.23 (s, 4H), 6.78 (s, 1H), 2.34 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.67, 143.72, 140.51, 138.74, 137.72, 133.25, 133.04, 132.93, 131.82, 131.43, 130.54, 130.46, 129.70, 129.54, 128.48, 126.94, 126.01, 125.93, 123.08, 120.60, 116.37, 116.04, 104.07, 21.48, 21.31. HRMS m/z (ESI) [M − BF_4] calcd for $C_{29}H_{23}N_2$, 399.1861; found, 399.1864.

6,7-Di-m-tolylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ac**). Red solid (61.5 mg, 77%), mp 181−183 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (d, J = 8.9 Hz, 1H), 8.80 (d, J = 8.6 Hz, 1H), 8.69 (t, J = 8.0 Hz, 1H), 8.44 (d, J = 6.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.84−7.68 (m, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.4 Hz, 1H), 7.30 (dd, J = 17.7, 10.0 Hz, 4H), 7.19 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 7.5 Hz, 1H), 6.79 (s, 1H), 2.30 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.71, 143.70, 139.15, 138.22, 137.81, 133.20, 133.08, 133.00, 132.93, 132.23, 131.55, 131.42, 130.06, 129.98, 129.73, 129.71, 129.06, 128.94, 128.43, 126.77, 126.03, 125.96, 123.09, 120.66, 116.39, 116.05, 104.12, 21.41, 21.40. HRMS m/z (ESI) [M − BF_4] calcd for $C_{29}H_{23}N_2$, 399.1861; found, 399.1864.

6,7-Bis(4-chlorophenyl)pyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ae**). Red solid (74.9 mg, 71%), mp 201−203 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (d, J = 8.9 Hz, 1H), 8.82 (d, J = 8.5 Hz, 1H), 8.72 (t, J = 7.8 Hz, 1H), 8.53 (d, J = 6.5 Hz, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.75 (t, J = 7.1 Hz, 2H), 7.69−7.59 (m, 3H), 7.56−7.46 (m, 4H), 7.37 (d, J = 8.2 Hz, 2H), 6.87 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 146.14, 143.66, 138.26, 135.96, 134.30, 133.90, 132.98, 132.63, 132.13, 131.94, 131.59, 131.41, 130.19, 129.44, 128.50, 127.77, 126.24, 123.21, 120.78, 116.34, 116.04, 104.38. HRMS m/z (ESI) [M − BF_4] calcd for $C_{27}H_{17}Cl_2N_2$, 439.0763; found, 439.0766.

6,7-Bis(4-nitrophenyl)pyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3af**). Red solid (57.0 mg, 52%), mp 208−210 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (d, J = 8.9 Hz, 1H), 8.82 (d, J = 8.4 Hz, 1H), 8.72 (t, J = 7.8 Hz, 1H), 8.53 (d, J = 6.6 Hz, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.75 (t, J = 7.1 Hz, 2H), 7.66 (dd, J = 16.8, 7.8 Hz, 3H), 7.57−7.46 (m, 4H), 7.38 (d, J = 7.7 Hz, 2H), 6.87 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 146.13, 143.66, 138.25, 135.97, 134.30, 133.91, 132.98, 132.64, 132.12, 131.95, 131.60, 131.40, 130.18, 129.44, 128.50, 127.78, 126.23, 126.18, 123.19, 120.78, 116.34, 116.03, 104.38. HRMS m/z (ESI) [M − BF_4] calcd for $C_{27}H_{17}O_4N_4$, 461.1250; found, 461.1248.

6,7-Di(thiophen-2-yl)pyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ag**). Red solid (80.9 mg, 86%), mp 173−175 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (d, J = 8.8 Hz, 1H), 8.77 (d, J = 8.5 Hz, 1H), 8.68 (dd, J = 13.1, 7.1 Hz, 2H), 8.07 (d, J = 7.7 Hz, 1H), 7.99 (d, J = 4.8 Hz, 1H), 7.80 (dd, J = 12.0, 5.6 Hz, 2H), 7.73 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.4 Hz, 1H), 7.50 (s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 7.26 (s, 1H), 7.17 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 146.06, 143.73, 137.65, 135.60, 133.29, 133.22, 132.71, 132.18, 131.27, 131.09, 130.10, 128.75, 128.71, 127.71, 126.92, 126.48, 126.15, 125.19, 123.35, 120.75, 116.27, 116.07, 105.57. HRMS m/z (ESI) [M − BF_4] calcd for $C_{23}H_{15}S_2N_2$, 383.0677; found, 383.0679.

7-Ethyl-6-phenylpyrido[2′,1′:2,3]pyrimido[1,6-a]indol-5-ium (**3ai**). Two isomers in a ratio of 1:19 as determined by NMR analysis: red solid (66.4 mg, 81%), mp 143−145 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (d, J = 9.0 Hz, 1H), 8.65 (d, J = 9.3 Hz, 1H), 8.58 (t, J = 7.9 Hz, 1H), 8.25 (d, J = 6.5 Hz, 1H), 7.77 (d, J = 6.4 Hz, 3H), 7.72−7.60 (m, 4H), 7.52 (s, 1H), 7.47 (s, 1H), 2.58 (q, J = 7.0 Hz, 2H), 1.17 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.69, 144.63, 142.73, 137.30, 133.15, 132.28, 132.11, 131.42, 131.16, 130.67, 129.97, 129.89, 129.41, 128.51, 127.58, 127.36, 120.08, 117.13, 115.86, 115.28, 103.97, 102.10, 23.42, 13.37. HRMS m/z (ESI) [M − BF_4] calcd for $C_{23}H_{19}N_2$, 323.1543; found, 323.1546.

General Procedure for the Synthesis of **4**. Synthesis of compound **4ca** is representative. To a stirred solution of pyrido[2′,1′:2,3]pyrimido-[1,6-*a*]indol-5-ium **3ca** (0.20 mmol) in dry MeOH (5 mL) at 0 °C was added $NaBH_4$ (30 mg, 0.80 mmol). The mixture was allowed to stir at 0 °C for 2 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried over $MgSO_4$ and concentrated and purified by silica gel column chromatography using hexane/ethyl acetate (v/v = 50:1) as eluent to afford the product **4ca** as a colorless solid.

2-Methyl-6,7-diphenyl-6,7-dihydro-4H-pyrido[2′,1′:2,3]pyrimido-[1,6-a]indole (**4ca**). Colorless solid (55.2 mg, 71%), mp 91−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−6.79 (m, 13H), 5.85 (dd, J = 16.7, 13.9 Hz, 3H), 5.58 (d, J = 9.7 Hz, 1H), 3.68 (q, J = 18.5 Hz, 2H), 2.93−2.67 (m, 1H), 2.48−2.01 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.34, 137.59, 136.30, 135.15, 132.69, 132.07, 131.41, 130.29, 130.11, 129.04, 128.71, 127.88, 127.72, 127.49, 127.45, 125.82, 125.73, 122.25, 119.67, 107.67, 107.01, 95.92, 67.02, 49.05, 26.28, 21.49. HRMS m/z (ESI) calcd for $C_{28}H_{25}N_2$ [M + H$^+$], 389.2012; found, 389.2017.

10-Chloro-6,7-diphenyl-6,7-dihydro-4H-pyrido[2′,1′:2,3]-pyrimido[1,6-a]indole (**4la**). Colorless solid (63.0 mg, 77%), mp 100−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.25 (s, 1H), 7.23−6.90 (m, 11H), 6.01−5.82 (m, 3H), 5.68 (d, J = 10.0 Hz, 1H), 3.77 (q, J = 18.7 Hz, 2H), 3.31−2.72 (m, 1H), 2.32 (d, J = 16.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.23, 137.43, 137.16, 134.78, 132.63, 131.33, 130.88, 130.12, 127.95, 127.89, 127.59, 127.46, 126.00, 125.53, 125.44, 120.74, 119.05, 108.70, 106.42, 95.66, 66.99, 49.05, 26.28. HRMS m/z (ESI) calcd for $C_{27}H_{22}N_2Cl$ [M + H$^+$], 409.1472; found, 409.1477.

10-Methoxy-6,7-diphenyl-6,7-dihydro-4H-pyrido[2′,1′:2,3]-pyrimido[1,6-a]indole (**4pa**). Colorless solid (69.6 mg, 86%), mp 99−101 °C. ^{1}H (400 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.23−7.00 (m, 10H), 6.92 (s, 1H), 6.78 (d, J = 8.6 Hz, 1H), 6.34−5.80 (m, 3H), 5.67 (d, J = 9.7 Hz, 1H), 4.08−3.50 (m, 5H), 2.90 (t, J = 16.3 Hz, 1H), 2.33 (d, J = 16.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.38, 141.38, 137.49, 136.91, 135.06, 131.38, 130.31, 130.25, 129.57, 127.88, 127.74, 127.49, 127.42, 125.83, 125.68, 110.37, 108.55, 106.90, 102.22, 96.14, 67.12, 55.88, 49.03, 26.28. HRMS m/z (ESI) calcd for $C_{28}H_{25}N_2O$ [M + H$^+$], 405.1961; found, 405.1966.

10-Fluoro-6,7-diphenyl-6,7-dihydro-4H-pyrido[2′,1′:2,3]-pyrimido[1,6-a]indole (**4qa**). Colorless solid (63.6 mg, 81%), mp 99−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−6.99 (m, 12H), 6.77 (td, J = 9.1, 2.0 Hz, 1H), 5.88−5.78 (m, 2H), 5.60 (d, J = 10.0 Hz, 1H), 3.69 (q, J = 18.7 Hz, 2H), 2.90−2.77 (m, 1H), 2.25 (d, J = 16.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.19 (d, J = 233.9 Hz), 137.24, 134.84, 131.36, 130.15, 127.95, 127.91, 127.87, 127.57, 127.46, 125.97, 125.59, 108.55 (d, J = 26.3 Hz), 108.20 (d, J = 9.9 Hz), 104.84, 104.72 (d, J = 23.7 Hz), 67.08, 48.96, 26.18. HRMS m/z (ESI) calcd for $C_{27}H_{22}FN_2$ [M + H$^+$], 393.1762; found, 393.1767.

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

*6,7-Di-p-tolyl-6,7-dihydro-4H-pyrido[2′,1′:2,3]pyrimido[1,6-a]-indole (**4ab**).* Colorless solid (53.1 mg, 66%), mp 99−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 6.0 Hz, 1H), 7.02 (dd, J = 16.1, 7.7 Hz, 2H), 6.98−6.89 (m, 6H), 6.85 (d, J = 7.6 Hz, 2H), 6.03−5.73 (m, 2H), 5.59 (d, J = 9.9 Hz, 1H), 3.67 (q, J = 18.8 Hz, 2H), 2.99−2.68 (m, 1H), 2.33−2.30 (m, 1H), 2.19 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.20, 137.41, 135.00, 134.63, 134.11, 132.05, 131.17, 129.90, 129.60, 128.62, 128.50, 128.17, 127.44, 125.64, 120.54, 119.76, 119.63, 108.03, 106.63, 95.86, 66.86, 49.05, 26.29, 21.27, 21.15. HRMS m/z (ESI) calcd for $C_{29}H_{27}N_2$ [M + H$^+$], 403.2169; found, 403.2166.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02314.

Copies of ^{1}H and ^{13}C NMR spectra for all new products; UV−vis absorption spectra of selected compounds (PDF)
X-ray data of **3ha** (CCDC 1498398) (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chemlt2015@nynu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the Education Department Fund of Henan Province (14A150054, 17A150043) and Special Fund of Nanyang Normal University (ZX2016016).

■ REFERENCES

(1) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. 2, p 119. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930. (c) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080−3098. (d) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489−4497. (e) Zhou, G.; Wu, D.; Snyder, B.; Ptak, R. G.; Kaur, H.; Gochin, M. *J. Med. Chem.* **2011**, *54*, 7220−7231.

(2) See for examples: (a) Li, B.; Zhou, B.; Wang, Y.-H.; Shu, C.; Pan, Y.-F.; Lu, X.; Ye, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8245−8249. (b) Li, T.; Wang, Z.; Zhang, M.; Zhang, H.-J.; Wen, T.-B. *Chem. Commun.* **2015**, *51*, 6777−6780.

(3) For reviews about functionalization of indoles, see: (a) Dalpozzo, R. *Chem. Soc. Rev.* **2015**, *44*, 742. (b) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508−3549. (c) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608−9644. (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873−2920. (e) Beck, E. M.; Gaunt, M. J. *Top. Curr. Chem.* **2009**, *292*, 85.

(4) For selected reviews, see: (a) Herrerías, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546−2562. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624−655. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293−1314. (d) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281−295. (e) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443−1460. (f) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007−1020. (g) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, *44*, 1155−1171. (h) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900−2935 and references cited therein..

(5) For selected reviews on Co-catalyzed C−H bond functionalization, see: (a) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208−1219. (b) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948−8954. (c) Gandeepan, P.; Cheng, C.-H. *Acc. Chem. Res.* **2015**, *48*, 1194−1206. (d) Yoshikai, N. *ChemCatChem* **2015**, *7*, 732−734. (e) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498−525. (f) Wei, D.; Zhu, X.; Niu, J.-L.; Song, M.-P. *ChemCatChem* **2016**, *8*, 1242−1246.

(6) (a) Suzuki, Y.; Sun, B.; Sakata, K.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 9944−9947. (b) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 1491−1495. (c) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 5424−5431. (d) Andou, T.; Saga, Y.; Komai, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3213−3216. (e) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207−2211.

(7) (a) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8551−8554. (b) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3635−3638.

(8) (a) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2015**, *17*, 1204−1207. (b) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209−10212.

(9) (a) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508−4511. (b) Gensch, T.; Vasquez-Cespedes, S.; Yu, D.-G.; Glorius, F. *Org. Lett.* **2015**, *17*, 3714−3717. (c) Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vasquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722−17725.

(10) (a) Hummel, J. R.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 2400−2403. (b) Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490−498.

(11) (a) Pawar, A. B.; Chang, S. *Org. Lett.* **2015**, *17*, 660−663. (b) Patel, P.; Chang, S. *ACS Catal.* **2015**, *5*, 853−858.

(12) (a) Zhang, L.-B.; Hao, X.-Q.; Liu, Z.-J.; Zheng, X.-X.; Zhang, S.-K.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2015**, *54*, 10012−10015. (b) Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, Z.-J.; Zheng, X.-X.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2015**, *54*, 272−275. (c) Hao, X.-Q.; Du, C.; Zhu, X.; Li, P.-X.; Zhang, J.-H.; Niu, J.-L.; Song, M.-P. *Org. Lett.* **2016**, *18*, 3610−3613. (d) Li, L.; Wang, H.; Yu, S.; Yang, X.; Li, X. *Org. Lett.* **2016**, *18*, 3662−3665.

(13) (a) Mitschke, U.; Bäuerle, P. *J. Mater. Chem.* **2000**, *10*, 1471−1477. (b) Anthony, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 452−483. (c) Figueira-Duarte, T. M.; Müllen, K. *Chem. Rev.* **2011**, *111*, 7260−7314.

(14) See: (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019−4022. (b) Tan, X.; Liu, B.; Li, X.; Li, B.; Xu, S.; Song, H.; Wang, B. *J. Am. Chem. Soc.* **2012**, *134*, 16163−16166. (c) Shi, Z.; Tang, C.; Jiao, N. *Adv. Synth. Catal.* **2012**, *354*, 2695−2700. (d) Liu, B.; Hu, F.; Shi, B.-F. *Adv. Synth. Catal.* **2014**, *356*, 2688−2696. (e) Jayakumar, J.; Parthasarathy, K.; Chen, Y.-H.; Lee, T.-H.; Chuang, S.-C.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9889−9892. (f) Zheng, J.; You, S.-L. *Chem. Commun.* **2014**, *50*, 8204−8207. (g) Liu, X.; Li, X.; Liu, H.; Guo, Q.; Lan, J.; Wang, R.; You, J. *Org. Lett.* **2015**, *17*, 2936−2939. (h) Wang, W.; Niu, J.-L.; Liu, W.-B.; Shi, T.-H.; Hao, X.-Q.; Song, M.-P. *Tetrahedron* **2015**, *71*, 8200−8207.

(15) See selected recent examples: (a) Fallon, B. J.; Derat, E.; Amatore, M.; Aubert, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A.; Petit, M. *Org. Lett.* **2016**, *18*, 2292−2295. (b) Zell, D.; Bu, Q.; Feldt, M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 7408−7412. (c) Zhang, Z.-Z.; Liu, B.; Wang, C.-Y.; Shi, B.-F. *Org. Lett.* **2015**, *17*, 4094−4097. (d) Sauermann, N.; Gonzalez, M.; Ackermann, L. *Org. Lett.* **2015**, *17*, 5316−5319.

(16) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4698−4701.

(17) (a) Prakash, S.; Muralirajan, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1844−1848. (b) Lao, Y.-X.; Zhang, S.-S.; Liu, X.-G.; Jiang, C.-Y.; Wu, J.-Q.; Li, Q.; Huang, Z.-S.; Wang, H. *Adv. Synth. Catal.* **2016**, *358*, 2186−2191.

(18) CCDC 1498398 contains the supplementary crystallographic data for compound **3ha**; see Supporting Information for more details.

(19) Liu, W.; Khedkar, V.; Baskar, B.; Schürmann, M.; Kumar, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 6900−6905 and references therein.

(20) See selected examples for Rh(III) or Ru(II) catalyzed formal [4 + 2] annulation for salt synthesis, see: (a) Zhang, G.; Yang, L.; Wang, Y.; Xie, Y.; Huang, H. *J. Am. Chem. Soc.* **2013**, *135*, 8850−8853. (b) Luo, C.-Z.; Gandeepan, P.; Jayakumar, J.; Parthasarathy, K.; Chang, Y.-W.; Cheng, C.-H. *Chem. - Eur. J.* **2013**, *19*, 14181−14186. (c) Luo, C.-Z.; Gandeepan, P.; Cheng, C.-H. *Chem. Commun.* **2013**, *49*, 8528−8530. (d) Luo, C.-Z.; Jayakumar, J.; Gandeepan, P.; Wu, Y.-C.; Cheng, C.-H.

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345

Org. Lett. **2015**, *17*, 924−927. (e) Feng, B.; Wan, D.; Yan, L.; Kadam, V.; You, J.; Gao, G. *RSC Adv.* **2016**, *6*, 66407−66411.
(21) Xu, S.; Huang, X.; Hong, X.; Xu, B. *Org. Lett.* **2012**, *14*, 4614−4617.
(22) Wang, Z.; Song, F.; Zhao, Y.; Huang, Y.; Yang, L.; Zhao, D.; Lan, J.; You, J. *Chem. - Eur. J.* **2012**, *18*, 16616−16620.
(23) (a) Lerchen, A.; Vasquez-Cespedes, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2016**, *55*, 3208−3211. (b) Park, K.; Bae, G.; Moon, J.; Choe, J.; Song, K. H.; Lee, S. *J. Org. Chem.* **2010**, *75*, 6244−6251.

DOI: 10.1021/acs.joc.6b02314
J. Org. Chem. 2016, 81, 11335−11345