JOC*Note*

Synthesis of Indolo[1,2-*f*]phenanthridines from Palladium-Catalyzed Reactions of Arynes

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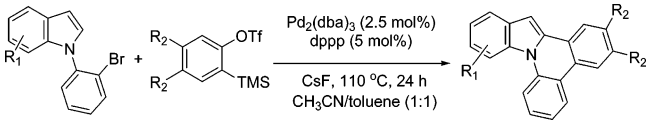
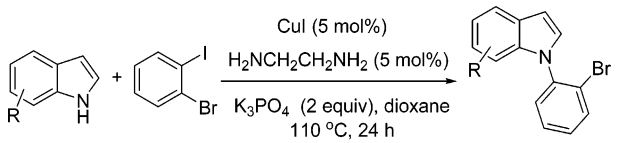


A novel convenient approach for the construction of indolo-[1,2-*f*]phenanthridine was developed from the reaction of arynes with 1-(2-bromophenyl)-1*H*-indole in the presence of palladium catalyst.

Phenanthridine heterocycles are of interest in many aspects. They not only widely occur in natural products,[1] but they also show a broad spectrum of biological activities and unusual pharmacological properties that make them suitable for antineoplastic applications.[2] In addition, the high-charge mobility of this heterocyclic system provides pronounced photoconducting and photovoltaic properties, which are key features in the field of dye lasers and electroluminescence.[3] Much attention has been focused on the efficient synthesis of phenanthridines over recent decades, and a variety of methods have been developed.[4] Although these methods provide reliable routes for the preparation of phenanthridines, most of them require multistep syntheses and strictly anhydrous conditions. The development of direct and efficient procedures for these classes of compounds has been the target of synthetic organic chemistry.

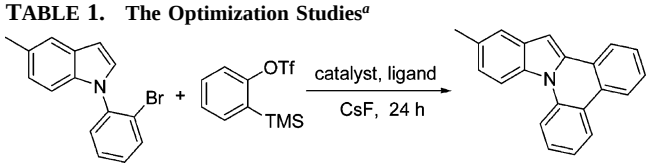
The transition-metal-catalyzed reactions of arynes have attracted considerable attention recently.[5] The cyclotrimerization of aryne catalyzed by palladium was reported in 1998,[6] and subsequent studies demonstrated that the cocyclizations of arynes with a variety of alkynes,[7] diynes,[8] allyl derivatives,[9] allenes,[10] CO_2,[11] and CO[12] could be performed in the presence

SCHEME 1



R=H, 4-Me, 5-Me, 5-OMe, 6-OMe, 5-CN, 4-COOMe

TABLE 1. The Optimization Studies[a]



entry	catalyst and ligand	solvent	*T* (°C)	yield[b] %
1	5% $Pd(PPh_3)_4$	CH_3CN and toluene (1:1)	110	56
2	2.5% $Pd_2(dba)_3$	CH_3CN and toluene (1:1)	110	22
3	2.5% $Pd_2(dba)_3$ + 10% PPh_3	CH_3CN and toluene (1:1)	110	30
4	2.5% $Pd_2(dba)_3$ + 5% dppp	CH_3CN and toluene (1:1)	110	76
5	2.5% $Pd_2(dba)_3$ + 5% dppp	CH_3CN and toluene (1:1)	110	58[c]
6	2.5% $Pd_2(dba)_3$ +5% dppp	CH_3CN and toluene (1:1)	110	31[d]
7	2.5% $Pd_2(dba)_3$ + 5% dppp	CH_3CN and toluene (1:1)	80	46
8	2.5% $Pd_2(dba)_3$ + 5% dppp	CH_3CN	80	54
9	2.5% $Pd_2(dba)_3$ + 5% dppp	toluene	110	2
10	2.5% $Pd_2(dba)_3$ + 5% dppp	DME	80	43
11	2.5% $Pd_2(dba)_3$ + 5% dppp	THF	67	trace

[a] Reaction conditions: 1-(2-bormophenyl)-5-methylindole (0.5 mmol), *o*-trimethylsilyl phenyltriflate (0.5 mmol), CsF (1.5 mmol), CH_3CN:toluene = 3:3 mL, external temperature, 24 h. [b] HPLC yield using 1,10-phenanthroline as the internal standard. [c] Reaction time was 12 h. [d] Reaction time was 6 h.

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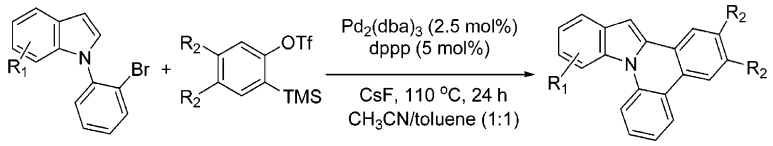
TABLE 2. Scope of the Annulation Reaction[a]



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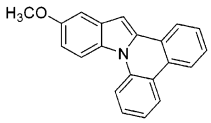
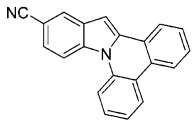
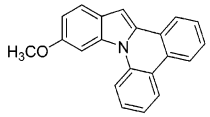
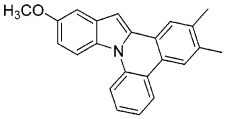
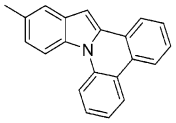
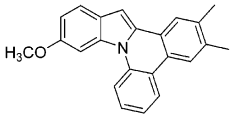
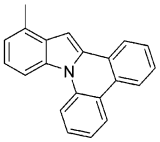
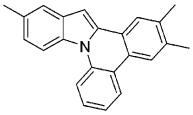
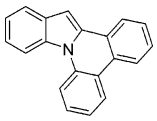
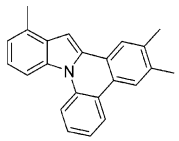
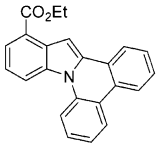
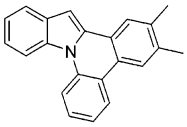
1	5-OMe	H		87	7	5-CN	H		68
2	6-OMe	H		88	8	5-OMe	Me		91
3	5-Me	H		72	9	6-OMe	Me		93
4	4-Me	H		78	10	5-Me	Me		73
5	H	H		61	11	4-Me	Me		69
6	4-CO_2Me	H		81	12	H	Me		60

[a] Reaction conditions: derivatives of indole (0.5 mmol), *o*-trimethylsilyl phenyltriflate (0.5 mmol), CsF (1.5 mmol), $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), dppp (5 mol %), CH_3CN:toluene = 3:3 mL, 110 °C (external temperature), 24 h. [b] Isolated yield.

of transition-metal catalysts. More recently, Liu et al. have shown that the coupling reaction between the two reactive substrates, an aryne and an organopalladium species, can be carried out to generate the cross-coupling products.[13] Herein, we report a mild and highly efficient route for the synthesis of indolo[1,2-*f*]phenanthridine from arynes and 1-(2-bromophenyl)-1*H*-indoles catalyzed by palladium complex under mild conditions. This reaction process involves the palladium-catalyzed carboannulation of arynes.

The key starting compounds of 1-(2-bromophenyl)-1*H*-indoles were accessed via a Hartwig−Buchwald C−N coupling reaction (Scheme 1).[14] This straightforward method offered the possibility of preparing a wide range of substituted 1-(2-bromophenyl)-1*H*-indoles.

The reaction of 1-(2-bormophenyl)-5-methylindole and benzyne, which was generated from in-situ elimination of *o*-trimethylsilyl phenyltriflate by CsF, was first studied using a catalytic amount of $Pd(PPh_3)_4$ as the catalyst in a mixture of 1:1 CH_3CN and tolune at 110 °C for 24 h. The annulation product of 11-methylindolo[1,2-*f*]phenanthridine was isolated in 56% yield (Table 1, entry 1). With $Pd_2(dba)_3$·$CHCl_3$ as catalyst, the reaction was dependent on the auxiliary phosphine ligands. In the absence of phosphine ligand, the annulation

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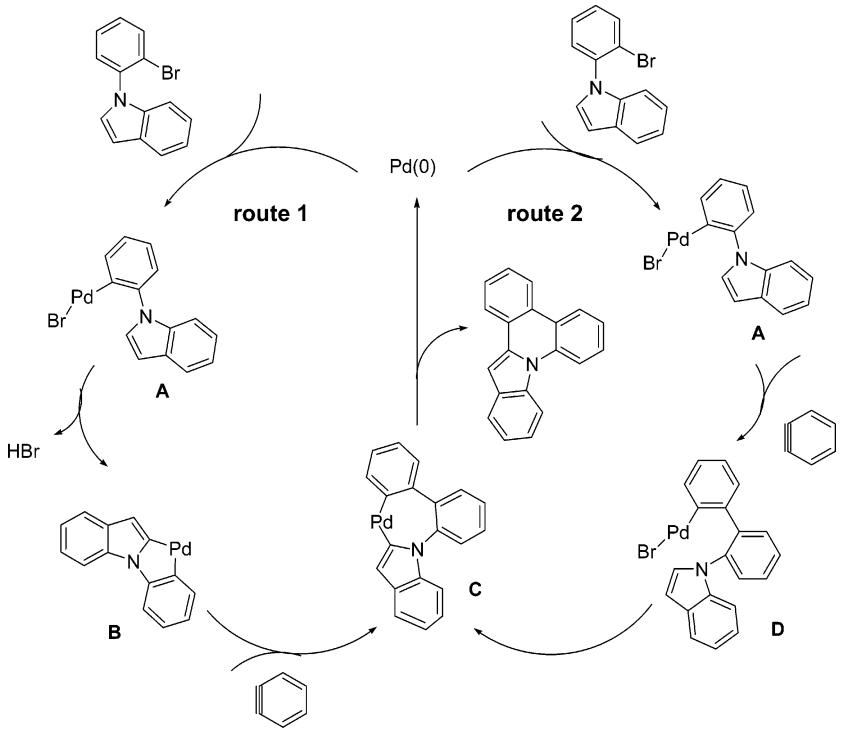
SCHEME 2



product was produced in poor yield (Table 1, entry 2). The use of PPh_3 afforded more annulation product (Table 1, entry 3), and the yield was improved to 76% when using dppp (1,3-bis-(diphenylphosphino)propane) as the phosphine ligand (Table 1, entry 4). Shortening the reaction time and decreasing the reaction temperature led to the lower yields (Table 1, entries 5−7). The choice of solvent was crucial for the success of the reaction, and the mixture of 1:1 CH_3CN and tolune was superior to other solvents such as CH_3CN, toluene, DME, and THF alone (Table 1, entries 8−11).

The reaction scope and limitations were investigated, and the results are summarized in Table 2. The reaction of 1-(2-bromophenyl)-5-methoxy-1*H*-indole and 1-(2-bromophenyl)-6-methoxy-1*H*-indole with *o*-trimethylsilyl phenyltriflate proceeded smoothly under the catalytic conditions to give the corresponding annulated products in high isolated yields (Table 2, entries 1−2). Employment of 1-(2-bromophenyl)-4-methyl-1*H*-indole and 1-(2-bromophenyl)-5-methyl-1*H*-indole as substrates resulted in 78% and 72% yields, respectively (Table 2, entries 3−4). However, when 1-(2-bromophenyl)-1*H*-indole (Table 2, entry 5) was used as the starting material, only a 61% yield was obtained (Table 2, entry 5). Clearly, the electron-donating substitutes on phenyl ring were beneficial to the annulation reaction. On the other hand, the indoles with electron-withdrawing substitutes on phenyl ring also worked well in this annulation reaction (Table 2, entries 6−7). Dimethylbenzyne was successfully employed in this annulation process, and moderate to high yields were obtained (Table 2, entries 8−12). Good fluorescence quantum yields were observed for the above new compounds (see Supporting Information).

On the basis of these experiments, the following plausible mechanism for this useful phenanthridine synthesis was proposed (Scheme 2). The Pd(0) complex first undergoes the oxidative addition[15] with 1-(2-bromophenyl)-1*H*-indole to give the arylpalladium intermediate **A**, followed by the C−H activation to generate the palladacycle **B**, which reacts with the aryne to afford intermediate **C**. The subsequent reductive elimination yields the final product and regenerates the Pd(0) catalyst. One other possible pathway, which is closely related to the one proposed by Liu and Larock,[13c] is that the arylpalladium intermediate **A** reacts with the aryne to afford intermediate **D**. The following intramolecular C−H activation generates the palladacycle **C**, which affords the final product via the reductive elimination.

In conclusion, we have demonstrated a palladium-catalyzed annulation reaction by aryne and 1-(2-bromophenyl)-1*H*-indoles, which allows an efficient synthesis of indolo[1,2-*f*]phenanthridine under mild conditions and in good yields. Further studies to elucidate the reaction mechanism and to extend the scope of the reaction are in progress.

Experimental Section

Representative Procedure for the Reaction of 1-(2-Bromophenyl)indole with Benzyne. 1-(2-Bromophenyl)indole (136 mg, 0.5 mmol), CsF (228 mg, 1.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (13 mg, 0.0125 mmol), and dppp (10 mg, 0.025 mmol) were placed in an oven-dried flask. CH_3CN (2 mL) and toluene (2 mL) were added under N_2. *o*-(Trimethylsilyl)phenyl triflate (149 mg, 0.5 mmol) in CH_3CN (1 mL) and toluene (1 mL) was added dropwise. After the completion of the addition, the reaction mixture was allowed to react at 110 °C for 24 h. Then, the reaction mixture was cooled to room temperature and was filtered through a pad of cellite. The filtrate was distilled under reduced pressure, and the product was obtained by flash chromatography on a silica gel column.

T2-5 Indolo[1,2-*f*]phenanthridine. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.56 (d, J = 8.4 Hz, 1 H), 8.39 (d, J = 8.4 Hz, 1 H), 8.34

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(d, $J = 8$ Hz, 1 H), 8.24 (m, 1 H), 8.15 (m, 1 H), 7.84 (d, $J = 7.6$ Hz, 1 H), 7.59 (t, $J = 7.6$ Hz, 1 H), 7.50 (m, 2 H), 7.36 (m, 3 H), 7.28 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.2, 133.9, 130.3, 128.7, 128.2, 127.8, 126.8, 126.1, 124.1, 124.0, 123.0, 122.4, 122.1, 122.0, 121.8, 121.0, 116.3, 114.2, 96.2. HRMS (ESI) calcd for $C_{20}H_{13}N$: $[M + H]^+$ 268.1121; found, 268.1113. Yellow powder, mp 140−142 °C.

T2-12 6,7-Dimethylindolo[1,2-*f*]phenanthridine. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.51 (d, $J = 8.4$ Hz, 1 H), 8.38 (d, $J = 6.8$ Hz, 1 H), 8.24 (d, $J = 8.0$ Hz, 1 H), 7.90 (s, 1 H), 7.82 (s, 1 H), 7.54 (t, $J = 8.0$ Hz, 1 H), 7.39 (m, 2 H), 7.32 (t, $J = 7.8$ Hz, 1 H), 7.17 (m, 1 H), 2.39 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.7, 135.6, 135.4, 133.7, 130.4, 127.9, 124.62, 124.59, 123.8, 123.6, 122.9, 122.7, 122.1, 121.54, 121.52, 120.7, 116.1, 114.1, 95.1, 20.2, 19.8. HRMS (ESI) calcd for $C_{22}H_{17}N$: $[M + H]^+$ 296.1434; found, 296.1425. Yellow powder, mp 103−105 °C.

Acknowledgment. We thank the support of Natural Science Foundation of China (No. 20571063).

Supporting Information Available: The experimental procedure and spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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