Regioselective Mercury(I)/Palladium(II)-Catalyzed Single-Step Approach for the Synthesis of Imines and 2-Substituted Indoles

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Abstract: An efficient synthesis of ketimines was achieved through a regioselective Hg(I)-catalyzed hydroamination of terminal acetylenes in the presence of anilines. The Pd(II)-catalyzed cyclization of these imines into the 2-substituted indoles was satisfactorily carried out by a C-H activation. In a single-step approach, a variety of 2-substituted indoles were also generated via a Hg(I)/Pd(II)-catalyzed, one-pot, two-step process, starting from anilines and terminal acetylenes. The arylacetylenes proved to be more effective than the alkyl derivatives.

Keywords: mercury(I)-catalyzed alkyn hydroamination; imines; Pd-catalyzed oxidative cyclization; one-pot indole synthesis

1. Introduction

Imines are one of the most versatile functional groups in synthesis. Numerous studies have focused on their preparation [1–5], chemical structure and tautomeric or transimination equilibrium [6–8], and use as a precursor for the construction of more complex structures [9–12]. Due to their versatility, they play an important role in medicinal chemistry, serving as urease and protease inhibitors [13] as well as antimalarial, antibacterial, and antifungal agents [14]. They also exhibit activity against Mycobacterium tuberculosis [15] and tumor cells [16–19], and act as suppressors of HIV-1-gp120, related to the human immunodeficiency virus (HIV) [20] (Figure 1). Interestingly, imines are present in phytoplankton and shellfish as toxins [21].

Figure 1. Imine- and indole-containing compounds with pharmacological activity.

Likewise, indoles are widely distributed in natural products [22–24]. They occupy a prominent place as pharmacologically active compounds [25–28], including commercial therapeutic chemicals and active pharmaceutical ingredients [29–31]. The U.S. Food and
Drug Administration (FDA) has approved at least 43 indole-containing drugs [32,33]. For example, arbidol has shown efficient in vitro activity against the SARS-CoV-2 infections [34] and has been administered to infected patients [35–37] (Figure 1). Hence, the molecular structures of imines and indoles are of great value for medicinal and synthetic purposes.

Despite the variety of methods for the preparation of imines [1–5], their synthesis is mainly carried out with conventional procedures, such as the acid-catalyzed condensation of a carbonyl compound with a primary amine [1]. Among the relevant methodologies are the reduction of nitriles, oximes, and aliphatic nitro derivatives [38–41], the addition of an organometallic reagent to nitriles and amides [42,43], and the oxidation of alcohols and amines [44,45]. These methods are only practical, however, if there is an existing carbon–nitrogen formal bond in the substrate.

Intermolecular imine is usually synthesized by condensation reactions with an azeotropic agent [1], a desiccant [46], or a water scavenger [47] to remove water. Alkyne hydroamination arose as an alternative, being an attractive and elegant pathway with complete atom economy [48–51]. Barluenga et al. described several catalytic and noncatalytic hydroamination methods with terminal acetylenes (e.g., 2a) promoted by Tl(III) or Hg(II) salts [52]. They found that HgCl₂ acts through a nucleophilic attack of the aniline (1a) on the internal acetylene carbon, firstly forming terminal acetylene-HgCl complex 3 followed by its possible conversion into the aminoalkenylmercurial(II) chloride intermediate 4. The latter regenerates the Hg(II) catalyst by protonolysis to give the enamine, which is converted into the desired imine 5a (Scheme 1a) [53,54].

Our group has an ongoing interest in designing and carrying out the novel synthesis of heterocycles [69–71], and in particular of aza-heterocycles and indoles [72–75]. Accordingly, the aim of the present study was to assess the feasibility of preparing indoles in a one-pot process, involving the regioselective Hg(I)-catalyzed hydroamination of terminal alkynes to produce imines as intermediates, and their subsequent Pd(II)-catalyzed cross-coupling oxidative cyclization to afford the corresponding C-2-substituted indoles (Scheme 1c).

2. Results and Discussion

2.1. Synthesis of Imines

The properties of Hg(0) and Hg(II) salts have been examined [76], and these species have many chemical and industrial applications [77–79], including chemical transformations [80–82]. Curiously, the use of Hg(I) in organic synthesis is surprisingly rare and limited [83,84]. Our group has reported the inclusion of Hg₂Cl₂ as the catalyst for the solvent-free hydroamination of phenylacetylene (2a) with m-anisidine (1e) to furnish the corresponding imine 5e in quantitative yield [85]. Following up on that effort, the scope of the method was herein explored by varying the structure of anilines (1) and acetylenes (2) to develop an efficient synthesis of imines (5).

Unfortunately, when employing the previously described reaction conditions (room temperature, 24 h), the yields of the resulting imines depended on the anilines (Table 1). For example, with p-anisidine (1i) and 2a, imine 5i was furnished in a modest yield (61%, entry 2). The yield was improved by increasing

**Scheme 1.** (a) Imine synthesis by a Hg(II)-promoted alkyne hydroamination. (b) Indole synthesis from imines derived by a condensation reaction and Pd(II)-catalyzed oxidative cyclization. (c) Pd(II)-catalyzed indole synthesis from imines derived from Hg(I)-catalyzed alkyne hydroamination.
In contrast, indoles have been elaborated by diverse protocols [55], such as the well-known Fischer [56,57], Julia [58], Bartoli [59], and Gassman [60] procedures, each of which include a sigmatropic rearrangement at a high temperature. Other efficient approaches have involved organometallic reagents, as with the syntheses of indoles described by Castro [61], Larock [62], Fagnou [63], and Söderberg [64,65]. Most of them demand the use of ortho-halogenated and ortho-vinylated N-protected anilines or nitrobenzenes to build the indole A ring. Recently, imine substrates have proven valuable for indole synthesis, as demonstrated by the groups of Yoshikai [66], Xiao [67], and Zhang [68] (Scheme 1b).

Our group has an ongoing interest in designing and carrying out the novel synthesis of heterocycles [69–71], and in particular of aza-heterocycles and indoles [72–75]. Accordingly, the aim of the present study was to assess the feasibility of preparing indoles in a one-pot process, involving the regioselective Hg(I)-catalyzed hydroamination of terminal alkynes to produce imines as intermediates, and their subsequent Pd(II)-catalyzed cross-coupling oxidative cyclization to afford the corresponding C-2-substituted indoles (Scheme 1c).

2. Results and Discussion
2.1. Synthesis of Imines 5a–n by Hg(I)-catalyzed Hydroamination of Alkynes 2a–d with Anilines 1a–k

The properties of Hg(0) and Hg(II) salts have been examined [76], and these species have many chemical and industrial applications [77–79], including chemical transformations [80–82]. Curiously, the use of Hg(I) in organic synthesis is surprisingly rare and limited [83,84]. Our group has reported the inclusion of Hg2Cl2 as the catalyst for the solvent-free hydroamination of phenylacetylene (2a) with m-anisidine (1e) to furnish the corresponding imine 5e in quantitative yield [85]. Following up on that effort, the scope of the method was herein explored by varying the structure of anilines (1) and acetylenes (2) to develop an efficient synthesis of imines (5). Unfortunately, when employing the previously described reaction conditions (room temperature, 24 h), the yields of the resulting imines depended on the anilines (Table 1). For example, with p-anisidine (1i) and 2a, imine 5i was furnished in a modest yield (61%, entry 2). The yield was improved by increasing the reaction time (82%, entry 3) or by raising the temperature to 45 ºC with a reaction time of 4 h (87%, entry 4).

Table 1. Optimization of the preparation of N-arylimes 5e and 5i.

| Entry | 1 (Ar) | Catalyst | Additive (mol equiv.) | T (°C) | T (h) | 5 (Yield, %) |
|-------|--------|----------|----------------------|--------|-------|--------------|
| 1     | 1e     | Hg2Cl2   | —                    | 20     | 24    | 5e (99) c    |
| 2     | 1i     | Hg2Cl2   | —                    | 20     | 24    | 5i (61) d    |
| 3     | 1i     | Hg2Cl2   | —                    | 45     | 4     | 5i (87) d    |
| 4     | 1e     | Ag2CO3   | —                    | —      | —     | 5e (0) d     |
| 5     | 1e     | Hg2Cl2   | —                    | 60     | 2     | 5i (72)      |
| 6     | 1i     | Hg2Cl2   | Li2CO3 (0.2)         | 60     | 2     | 5i (91)      |
| 7     | 1i     | Hg2Cl2   | Li2CO3 (0.2)         | —      | —     | 5i (0)       |
| 8     | 1i     | Hg2Cl2   | Li2CO3 (0.2)         | 60     | 2     | 5i (78)      |
| 9     | 1i     | Hg2Cl2   | Li2CO3 (0.2)         | —      | —     | 5i (0)       |
| 10    | 1i     | Hg2Cl2   | Li2CO3 (0.2)         | —      | —     | 5i (0)       |

| a | 2a (1.0 mol equiv.), ArNH2 (1.0–1.1 mol equiv.), catalyst (10 mol%), and no solvent. | b | After purification by column chromatography. | c | [85]. |

Other parameters were evaluated, such as solvent, catalyst, and additive. Although solvent-free reaction conditions are always recommended for designing an optimal green methodology, three chlorinated solvents (chloroform, 1,2-dichloroethane, and DMSO) were compared for their ability to solubilize the reactants and additives. It is important to note that the third solvent, it was not detected with 1,2-dichloroethane, THF, and DMSO. When hydroquinone was added as a radical quencher, which did not modify the yield (entry 8) for 2a. After purification by column chromatography, the yield was improved by increasing the reaction time (82%, entry 3) or by raising the temperature to 45 ºC with a reaction time of 4 h (87%, entry 4).
chemistry methodology \[86\], three chlorinated solvents (chloroform, 1,2-dichloroethane, and methylene chloride), THF, and DMSO were assessed by heating at 60 °C for 2–12 h. Whereas imine 5i was obtained in fairly low yields (21–41%) with either the first or the third solvent, it was not detected with 1,2-dichloroethane, THF, and DMSO. When Ag$_2$CO$_3$ (Table 1, entry 5) and CuCl (not shown) were tested as the catalysts for 1e and 2a, the outcome was the recovery of the reactants but no trace of imine 5e.

Imines, usually water-sensitive, are converted into ketones by hydrolysis. For example, acetophenone (7a) can be formed from imines 5e or 5i. Therefore, anhydrous lithium carbonate was employed as the additive, which greatly improved the yield (Table 1, entries 6 and 7). Of course, under these optimal reaction conditions, the presence of Hg$_2$Cl$_2$ was essential for the transformation to take place. Due to a feasible light-induced Hg–Hg bond disproportionation \[87\], the generation of radicals was contemplated. Consequently, hydroquinone was added as a radical quencher, which did not modify the yield (entry 8) and thus ruled out this possibility.

In agreement with the findings of Barluenga et al. \[52–54\], the process was also catalyzed with HgCl$_2$ under the same reaction conditions, but a lower yield (78%) was observed (Table 1, entry 9). This suggests that Hg(I) and Hg(II) are both probably the catalytic species involved in the process. Considering the feasible generation of Hg(0) as a secondary product during the decomposition of Hg$_2$Cl$_2$ under an analogous reaction \[53,54\], the process was carried out in the presence of Hg(0), but no imine was found (entry 10). Hence, the participation of Hg(0) as a catalyst is unlikely. Moreover, there was no visual evidence of a dark-silver mirror residue in the Hg(I) trials. Actually, Hg(0) is a well-known poisoning catalyst in heterogeneous/homogeneous reactions \[88\].

To gain insights into the mechanism, 2a was reacted with Hg$_2$Cl$_2$ to examine its possible conversion into acetophenone (7a) as an intermediate. After heating at 45 °C for 1 h, however, only the recovery of 2a was achieved. Taking into account the potential formation of intermediate 7a in the middle of the reaction, a further trial was performed under the same reaction conditions (45 °C for 1 h) and in the presence of 1i and Hg$_2$Cl$_2$. The result was again the recovery of the starting material. Finally, after reacting a mixture of 1i and Hg$_2$Cl$_2$ at 45 °C for 1 h, no N-Hg complex was detected.

Once the reaction conditions were optimized (Table 1, entry 7), evaluation was performed for a series of anilines (1a–k) bearing substituents with diverse electron-demand at the three positions of the benzene ring, utilizing arylalkynes 2a–d as the terminal acetylenes (Table 2). In general, neither the electron-demand of the substituents nor their position in the benzene ring of the aniline showed any effect on the efficacy of the process. The only exception was the use of the halogenated anilines 1f and 1k, which gave rise to the corresponding imines in modest yields (Table 2, entries 6 and 11).

The high yields afforded by the unsubstituted phenylacetylene (2a) were also obtained with the terminal para-substituted phenylacetylenes 2b–d (Table 2, entries 9 and 12–14), supporting the idea that Hg(I) easily interacts with the triple bond regardless of the electron-demand of its substituent. Furthermore, the reaction was successful with terminal alkyl- and some aryl-acetylenes, including 4-cyanophenylacetylene (2c), propylacetylene (2e), cyclopropylacetylene (2f), and cyclohexylacetylene (2g), judging by the $^1$H NMR and MS/GC analyses of the crude mixtures. Nevertheless, the corresponding imines 5m (as a mixture of 5m/p-cyanoacetophenone (7b) (95:5)) and 5o–q were not stable enough to be isolated under the extraction conditions. Evidence of their formation was found unambiguously by the synthesis of the indoles (see Scheme 3).

Reactivity significantly decreased with the di-substitution of the triple bond. For instance, neither methylpropylacetylene (2h) nor phenylpropylacetylene (2i) reacted with p-anisidine (1i), even when the mixture was heated to 80 °C for 53 h, probably because both electronic and steric effects impede the addition of the aniline or do not allow for the formation of the σ-Hg(I)-acetylene complex (see below).
Table 2. Preparation of the series of N-arylimines 5a–n through the Hg(I)-catalyzed hydroamination of 2a–d with anilines 1a–k.

| Entry | 1     | 2 (R’) | R   | T (h) | 5 (Yield, %) |
|-------|-------|--------|-----|-------|--------------|
| 1     | 1a    | 2a (H) | H   | 4     | 5a (88)      |
| 2     | 1b    | 2a (H) | 2-Me| 4     | 5b (85)      |
| 3     | 1c    | 2a (H) | 2-OMe| 4    | 5c (87)      |
| 4     | 1d    | 2a (H) | 3-Me| 4     | 5d (83)      |
| 5     | 1e    | 2a (H) | 3-OMe| 4    | 5e (84)      |
| 6     | 1f    | 2a (H) | 3-Cl | 4    | 5f (53)      |
| 7     | 1g    | 2a (H) | 4-Me | 2    | 5g (91)      |
| 8     | 1h    | 2a (H) | 4-OMe | 2  | 5h (68)      |
| 9     | 1i    | 2a (H) | 4-OMe | 2  | 5i (91)      |
| 10    | 1j    | 2a (H) | 4-OMe | 2  | 5j (78)      |
| 11    | 1k    | 2a (H) | 2-Br-4-Me| 8 | 5k (42)      |
| 12    | 1l    | 2b (Me) | 4-OMe | 2  | 5l (91)      |
| 13    | 1i    | 2c (CN) | 4-OMe | 2  | 5m (90)      |
| 14    | 1i    | 2d (OMe) | 4-OMe | 2  | 5n (83)      |

a 2 (1.0 mol equiv.), ArNH2 (1.0–1.1 mol equiv.), Hg2Cl2 (5 mol%), Li2CO3 (0.2 mol equiv.), and no solvent. b The yield was estimated from the 1H NMR spectrum of the crude reaction mixture, resulting in the ratio products, which were then confirmed by the ratio and molecular ions by MS/GC analysis. The product was not isolated and used without purification in the next step.

All the imines prepared by this method were characterized by IR and NMR (1D and 2D), and in some cases, HRMS. The latter technique was performed in case of finding a discrepancy between the data reported in the literature and the melting point or physical state of the compound in the current effort. Imine 5i was crystallized in order to be subjected to X-ray crystallographic analysis (Figure 2), which demonstrated the expected E configuration of the double bond. However, the N-anisyl ring was not coplanar to the imine double bond, instead adopting a quasi-orthogonal conformation (torsion angle, C(8)-N(1)-C(1)-C(2) = 115.31(17), see Supplementary Materials), which indicates that the π-system is not conjugated. In contrast, the phenyl ring attached to the imine double bond displayed a planar conformation (torsion angle, C(11)-C(10)-C(8)-N(1) = 4.7(2), see Supplementary Materials).

Figure 2. Structure of 5i, as determined by single X-ray diffraction crystallography (ellipsoids at the 30% probability level).

2.2. One-Pot Synthesis of Indoles 6a–p by Subsequent Hg(I)- and Pd(II)-Catalyzed Conversion of Anilines 1a–g and 1i–k with Alkynes 2a–g

The Pd(II)-catalyzed conversion of imines/enamines into indoles has been performed by fairly similar methods [89–91], previously forming imine 5 or generating it in situ as the intermediate [66–68] (Scheme 1b). In all the approaches, the mechanism seems to start from the tautomerization of imine 5 to enamine 8, which undergoes a dehydrogenative
reaction by the metal to furnish the σ-Pd(II) complex 9 (Scheme 2). An aryl C–H activation affords palladacycle 10, bridging the aryl and the methylene moieties. By accomplishing the reductive elimination step, the internal oxidative cross-coupling reaction of 10 promotes the formation of the C-3/C-3a sigma bond of the corresponding indole 6 and Pd(0). The latter is oxidized back to Pd(II) by the oxidizing agent to renew the catalytic cycle. This aerobic oxidative cyclization reaction is only modestly efficient and regioselective in a one-pot reaction beginning from the aniline and the ketone [67]. With an excess of Cu(OAc)2, on the other hand, the reaction produces a couple of indoles in moderate yields (41–55%) [66].

Scheme 2. Indole synthesis from imines through a Pd(II)-catalyzed oxidative cross-coupling.

Considering the feasibility of the oxidative cyclization reaction from imines 5 to indoles 6, a one-pot reaction was explored that started from aniline 1i and phenylacetylene (2a) and progressed by a sequential Hg(I)/Pd(II)-catalyzed process. Diverse reagents were tested under aerobic conditions to find the proper oxidizing agent (Table 3). The reaction conditions were standardized and carried out in two steps. The first step consisted of applying the optimal reaction conditions found for the preparation of imines 5, thus fixing the temperature and reaction time at 40 °C and 2 h. The second step involved the addition of Pd(OAc)2 along with the oxidizing agent in DMSO as the solvent, and then stirring at 60 °C for 4.5 h.

Table 3. Selection of the oxidizing agent and optimization of the reaction conditions for the one-pot conversion of 1i and 2a into indole 6h a.

| Entry | Oxidant (mol equiv.) b | Additive (mol equiv.) | 5i/6h (Ratio) c (Yield, %) d |
|-------|----------------------|----------------------|-------------------------------|
| 1     | Cu(OAc)2 (3.0)       | Li2CO3 (0.2)         | 78:22                         |
| 2     | O2                   | Li2CO3 (0.2)         | 85:15                         |
| 3     | Cu(OAc)2/O2 (3.0)    | Li2CO3 (0.2)         | 46:54                         |
| 4     | KMnO4/O2 (3.0)       | Li2CO3 (0.2)         | 56:44                         |
| 5     | NMMO/O2 (3.0)        | Li2CO3 (0.2)         | 67:33                         |
| 6     | DTBP/O2 (3.0)        | Li2CO3 (0.2)         | 65:35                         |
| 7     | Cu(OTf)2/O2 (3.0)    | Li2CO3 (0.2)         | 100:0                         |
| 8     | Cu(OAc)2/O2 (1.0)    | Li2CO3 (0.2)         | 53:47                         |
| 9 e   | Cu(OAc)2/O2 (3.0)    | Li2CO3 (0.2)         | 13:87                         |
| 10 e  | Cu(OAc)2/O2 (3.0)    | Li2CO3 (0.2)         | 6h (45)                       |
| 11 e  | Cu(OAc)2/O2 (3.0)    | —                    | 6h (50)                       |
| 12 e  | Cu(OAc)2/O2 (3.0)    | EtCO2H (0.2)         | 6h (46)                       |
| 13 e  | Cu(OAc)2/O2 (3.0)    | Li2CO3 (0.2)         | 6h (52)                       |
| 14 e  | Cu(OAc)2 (3.0)       | —                    | 6h (80)                       |

a 1i (1.05 mol equiv.), 2a (1.0 mol equiv.), Li2CO3 (0.2 mol equiv.), Hg2Cl2 (0.05 mol equiv.), Pd(OAc)2 (0.1 mol equiv.), and DMSO (0.2 M). b Oxygen gas was used. c Calculated by 1H NMR of the reaction crude mixture. d After purification by column chromatography. e Pd(OAc)2 (0.2 mol equiv.) was employed. f The additive was added at the second step. NMMO = N-methylmorpholine N-oxide, DTBP = di-tert-butyl peroxide.
The synergic action of Cu(OAc)$_2$ and oxygen turned out to be the best oxidizing agent (Table 3, entries 8 and 9), although no significant conversion was shown when reacting each separately (entries 1 and 2). The addition of 0.2 mol equivalents of Pd(OAc)$_2$ was critical for improving the yield (entry 9). Interestingly, mixing all the catalysts with the oxidant and solvent (DMSO) under similar reaction conditions and as a single step did not provide any trace of the imine or the indole. A possible explanation is that the Hg(I) catalyst was inactivated by DMSO. Indeed, the first step was always inefficient with the use of this solvent (Table 1).

With the aim of optimizing the process, the additive was changed to K$_2$CO$_3$ and Cs$_2$CO$_3$ rather than Li$_2$CO$_3$, but without success (not shown in Table 3). Hence, the conversion depicted in Table 3 was carried out with or without the addition of Li$_2$CO$_3$ in the second step. The addition of an acid instead of Li$_2$CO$_3$ (entries 10–12) caused a non-significant decrease in the yield. A similar outcome was found without the presence of oxygen (entry 13). However, when both the additive and oxygen were removed from the whole process, the yield sharply increased (entry 14). The reaction temperatures and times with the best efficiency were determined, and the optimized method for the elaboration of 6h was applied to the entire series, mixing anilines 1a–g and 1i–k with acetylenes 2a–g, which gave the corresponding indoles 6a–p (Scheme 3). Most of the 2-arylindoles were obtained in good yields, regardless of the position of the substituent in the benzene ring.

One-pot synthesis of indoles 6a–p from a series of anilines 1a–g and 1i–k, and acetylenes 2a–g:

\[ \text{R}^1\text{Ph} + \text{HgO}_2 \rightarrow \text{R}^1\text{N} + \text{R}^1\text{N}^+ \]  
\[ \text{Cu(OAc)}_2 \]  
\[ \text{DMSO (0.2 M)} \]  
\[ \text{80 °C; 24 h} \]  
\[ \text{6a–p} \]

Scheme 3. a Yields in square brackets were obtained by conversion of imines 5a and 5i–j into indoles 6a and 6h–i (see Experimental Section). b Minor isomer 4-methyl-2-phenyl-1H-indole (6d') was detected (12% ratio) by GC/MS of the crude mixture, but could not be isolated. c Minor isomer 4-methoxy-2-phenyl-1H-indole (6e') was detected (7% ratio) by GC/MS of the crude mixture, but could not be isolated. d Minor isomer 4-chloro-2-phenyl-1H-indole (6f') was detected (19% ratio) by GC/MS of the crude mixture, but could not be isolated.
On the other hand, the indoles produced in low yields showed a certain correlation with the imines afforded in fairly modest yields (Table 2). For example, the in-situ formation of imine 5k delivered indole 6j in a low yield. The unstable and non-isolated imines 5m and 5o–q, generated by acetylenes 2c and 2e–g respectively, provided low yields of their corresponding indoles 6l and 6n–p. It is likely that the low yield of indole 6l was due to the low stability of the imine under the two-step reaction conditions, since the corresponding p-cyanoacetophenone (7b) was isolated in 20% yield. The reaction of aniline 1h and phenylacetylene (2a) resulted in a complex mixture of products. With the use of meta-substituted anilines 1d–f with 2a, a mixture of regioisomers 6d–f/6d–f’ was found, respectively. The 6-substituted indoles 6d–f were the major isomers, and the 4-substituted indoles 6d–f’ the minor ones. The latter could not be isolated (see caption, Scheme 3).

Analogous second-step reaction conditions (Pd(OAc)$_2$/Cu(OAc)$_2$, DMSO, 80 °C, 24 h) were evaluated for the preparation of indoles 6a and 6h–i from imines 5a and 5i–j, leading to lower yields than those obtained from the one-pot procedure (Scheme 3, square brackets). This suggests that a possible Hg/Pd transmetalation reaction during the one-pot process may foster the necessary catalytic activity to promote the oxidative cyclization of the in-situ formed imine and provide the indole. Actually, there are many examples of satisfactory palladium-catalyzed cross-coupling reactions involving a transmetalation process with organomercury substrates [80,92,93].

The series of indoles 6a–p was characterized by IR, $^1$H and $^{13}$C NMR (the signals were attributed by HMQC and HMBC experiments), and HRMS. Indoles 6e and 6l were isolated as colorless and pale reddish crystals respectively, and their structures were determined by single X-ray diffraction crystallography (Figure 3). Regarding 6e, the C-2-substituted benzene ring adopted a coplanar conformation in relation to the heterocycle (torsion angle: N(1)-C(1)-C(10)-C(15) = 1.8(3), see Supplementary Materials). A larger torsion angle can be appreciated for 6l (torsion angle: C(15)-C(10)-C(1)-N(1) = 32.41(18), see Supplementary Materials). Thus, it is likely that the π-system of the aromatic rings in 6e is stabilized by conjugation, despite the possible van der Waals repulsions triggered by the eclipsed conformation of the ortho C-H protons (C2-H and C11-H). Meanwhile, the coplanarity between the aromatic rings is lost for 6l, leading to the rotation of the sigma bond C1–C10. This is probably due to the presence of the cyano group, which compensates for the loss of stability caused by the conjugation of the aromatic rings. The latter loss is due to the instability caused by such ortho C-H and N-H repulsions.

![Figure 3. Structures of 6e (a) and 6l (b) as determined by single X-ray diffraction crystallography (ellipsoids at the 30% probability level).](image)

2.3. Mechanism of the Formation of Indoles 6a–p

Taking into account the aforementioned results as well as the role played by the catalysts through each step [54,66–68] in the one-pot process for 2a, two consecutive catalytic cycles can be suggested (Scheme 4). For the first event, the triple bond of 2a would be activated by a π-Hg(I) mercurinium cation complex I, and then probably stabilized by the formation of the alkynylmercury(I) II [83]. The addition of aniline 1 to either of the two possible complexes (I or II) would generate enamino-vinylmercury(I) III, followed by
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The second step would start with the tautomerization of imine 5 to enamine V, leading to the π-Pd(II) complex VI and the subsequent elimination of AcOH to deliver σ-Pd(II) complex VII (Scheme 4) [66–68]. Intramolecular aryl C–H activation would furnish palladacycle VIII, which would undergo a coupling reaction to give rise to the new C3-C3a sigma bond of heterocycle IX. The latter process would be associated with the reductive elimination of Pd(II) to form Pd(0), which would again be oxidized by the action of Cu(OAc)2. A final aromatization of IX would complete the synthesis of indoles 6.

Considering the possibility that an Hg/Pd transmetalation reaction takes place to improve the one-pot process with respect to the conversion of imines 5 to indoles 6, a plausible alternative reaction mechanism can be postulated. The Pd(II)-catalyzed transmetalation reaction may occur either with the vinylmercurial complex III [92,93] or the alkylmercurial complex IV to directly produce the σ-Pd(II) complex VII, which implies a shortcut capable of improving the process and avoiding the in-situ formation of imines 5.

Since modest efficiency of the mixture of the catalyst and oxidant agent Pd(OAc)2/Cu(OAc)2 was achieved for the one-pot conversion of anilines and ketones to indoles in only two cases [66], the Hg(II)-free reaction of aniline 1i with 2a in the presence of the Pd(OAc)2/Cu(OAc)2 couple was also tested. However, no indole was found [51]. Indeed, the alkyne was consumed only to generate 1,4-diphenylbuta-1,3-diyne, being the well-known, palladium-catalyzed, self-coupling product of terminal alkynes [94].

Given that Hg(II) was an active catalyst for promoting the formation of imine 5i (Table 1, entry 9), analogous alkynyl- and vinyl-mercury(II) (i.e., species I–III) could not be discarded as a competitive species [54]. Consequently, an assay was carried out with an HgCl2-catalyzed reaction of aniline 1i with 2a, followed by the Pd(OAc)2/Cu(OAc)2 couple-catalyzed cyclization in DMSO, which led to indole 6h in low yield (12%). This indicates that the mechanism of the reaction described in Scheme 4 is mainly driven by Hg(I) intermediates (i.e., species I–IV).

Scheme 4. Possible consecutive Hg(I)/Pd(II) catalytic cycles for the one-pot synthesis of indoles 6. Firstly, hydroamination provides imines 5 (Step 1), and then oxidative cyclization (Step 2) furnishes the indole frame.
3. Materials and Methods

3.1. General

Melting points were determined on a Krüss KSP 1N (KRÜSS GmbH, Hamburg, Germany) capillary melting point apparatus. IR spectra were recorded on Perkin-Elmer 2000 (PerkinElmer, Waltham, MA, USA) and Bruker Vertex 70 (ATR-FT) (Bruker Corporation, Billerica, MA, USA) spectrophotometers. \(^1\)H and \(^13\)C NMR spectra were captured on Varian Mercury (300 MHz) (Varian, Inc., Palo Alto, CA, USA), Varian VNMR (500 MHz) (Varian, Inc., Palo Alto, CA, USA), and Bruker 600 AVANCE III (600 MHz) (Bruker Corporation, Billerica, MA, USA) instruments, with CDCl\(_3\) as the solvent and TMS as the internal standard. Signal assignments were based on 2D NMR spectra (HMQC, HMBC, and/or ROESY). Mass spectra (MS) were recorded on Thermo Polaris Q-Trace GC Ultra (Finnigan Co., Waltham, MA, USA) and Hewlett-Packard 5971 A (Hewlett Packard Co., Houston, TX, USA) spectrometers. High-resolution mass spectra (HRMS) were obtained (in electron impact mode) on a Jeol JSM-GCMateII (JEOL, Ltd., Tokyo, Japan) spectrometer. X-Ray crystallographic measurements were collected on an Oxford XcaliburS diffractometer (Rigaku Co., Tokyo, Japan). Analytical thin-layer chromatography was performed with 0.25 plates coated with E. Merck (Darmstadt, Germany) silica gel 60 F254 and visualized with a short/long-wavelength UV lamp. Flash column chromatography was conducted over Natland International Co. (Morrisville, NC, USA) silica gel (230–400 and 230–400 mesh). All air moisture-sensitive reactions were conducted under N\(_2\) in oven-dried glassware. DMSO was distilled over CaH\(_2\), and Li\(_2\)CO\(_3\) and K\(_2\)CO\(_3\) were dried overnight at 250 °C prior to use. All other reagents were utilized without further purification. Warning: The hazardous wastes of mercury-containing silica gel and reaction residues were treated with sulfur and placed in high-density plastic containers for disposal, then handled by an authorized hazardous waste company.

3.2. General Method A for the Preparation of Imines 5a–n

To a round-bottomed flask (at room temperature and in the dark), the corresponding arylacetylene 2a–d (1.0 mol equiv.), Li\(_2\)CO\(_3\) (0.20 mol equiv.), the respective aniline 1a–k (1.05 mol equiv.), and mercury(I) chloride (0.05 mol equiv.) were successively added. The mixture was vigorously stirred at 60 ºC for 2–8 h. The organic layer was extracted with EtOAc (3 × 5 mL) and dried with Na\(_2\)SO\(_4\). The solvent was removed under vacuum and the residue was purified by column chromatography over silica gel treated with Et\(_3\)N (10% w/w) (40 g/g crude, hexane/EtOAc, 98:2) to afford imines 5a–n.

3.3. General Method B for the Preparation of Indoles 6a–p

To a round-bottomed flask (at room temperature and in the dark), the corresponding alkyl and arylacetylenes 2a–g (1.0 mol equiv.), the respective aniline 1a–g and 1i–k (1.05 mol equiv.), and mercury(I) chloride (0.05 mol equiv.) were successively added. The mixture was vigorously stirred at 60–60 °C for 2–8 h, and anhydrous DMSO (0.2 M), Cu(OAc)\(_2\) (1.5 mol equiv.), and Pd(OAc)\(_2\) (0.20 mol equiv.) were successively added. The mixture was stirred at 80 °C for 24 h, filtered over celite, and washed with EtOAc (4 × 20 mL). The organic layer was washed with brine (40 mL) and dried with Na\(_2\)SO\(_4\). The solvent was removed under vacuum and the residue was purified by column chromatography over silica gel (30 g/g crude, hexane/EtOAc, 98:2) to provide indoles 6a–p.

3.4. General Method C for the Preparation of Indoles 6a and 6h–i Starting from Imines 5a and 5i–j

In a round-bottomed flask (at room temperature), the respective imine 5a and 5i–j, anhydrous DMSO (0.2 M), Cu(OAc)\(_2\) (1.5 mol equiv.), and Pd(OAc)\(_2\) (0.20 mol equiv.) were mixed and stirred at 80 °C for 24 h. The crude reaction was filtered over celite and washed with EtOAc (4 × 20 mL). The organic layer was washed with brine (40 mL) and dried with Na\(_2\)SO\(_4\). The solvent was removed under vacuum and the residue was purified by column
chromatography over silica gel (50 g/g crude, hexane/EtOAc, 98:2) to obtain indoles 6a and 6h–i.

3.5. Preparation and Characterization of Imines 5a–n

3.5.1. (E)-N-(1-Phenylethylidene)aniline (5a)

Following general method A, a mixture of 2a (0.094 g, 0.92 mmol), Li2CO3 (0.014 g, 0.19 mmol), 1a (0.090 g, 0.97 mmol), and Hg2Cl2 (0.022 g, 0.047 mmol) was reacted for 4 h to furnish 5a (0.159 g, 88%) as a yellow solid. RF 0.72 (hexane/EtOAc, 7:3); mp 35–36 °C (Lit. 37 °C [10]; 42–43 °C [95]). IR (film): ν 3058, 3027, 1638, 1593, 1482, 1447, 1366, 1287, 1214, 1072, 1026, 783, 762, 730, 694 cm⁻¹. 1H NMR (500 MHz, CDCl3): δ 2.23 (s, 3H, CH3-2'), 6.78–6.82 (m, 2H, H-2'), 7.06–7.11 (m, 1H, H-4), 7.32–7.38 (m, 2H, H-3), 7.41–7.49 (m, 3H, H-3′, H-4′), 7.95–7.80 (m, 2H, H-2′). 13C NMR (125 MHz, CDCl3): δ 17.4 (CH3-2′), 119.3 (C-2), 123.2 (C-4), 127.1 (C-2′), 128.3 (C-3′), 128.9 (C-3), 130.4 (C-4′), 139.5 (C-1′), 151.7 (C-1), 165.4 (C-1′). HRMS (EI): m/z [M⁺] calcd for C14H13N: 195.1048; found: 195.1046.

3.5.2. (E)-2-Methyl-N-(1-phenylethylidene)aniline (5b)

Following general method A, a mixture of 2a (0.101 g, 0.99 mmol), Li2CO3 (0.015 g, 0.20 mmol), 1b (0.111 g, 1.04 mmol), and Hg2Cl2 (0.023 g, 0.049 mmol) was reacted for 4 h to give 5b (0.176 g, 85%) as a yellow solid. RF 0.77 (hexane/EtOAc, 7:3); mp 56–58 °C (Lit. 61 °C [10]). IR (film): ν 3063, 3016, 1637, 1597, 1578, 1482, 1447, 1366, 1287, 1221, 1114, 1026, 787, 765, 737, 692 cm⁻¹. 1H NMR (600 MHz, CDCl3): δ 2.10 (s, 3H, CH3Ar), 2.16 (s, 3H, CH3-2′), 6.65 (br d, 3J = 7.8 Hz, 2H, H-6), 7.00 (br dd, 3J = 7.8, 7.2 Hz, 1H, H-4), 7.17 (br dd, 3J = 7.7, 7.2 Hz, 1H, H-5), 7.21 (br d, 3J = 7.2 Hz, 1H, H-3), 7.43–7.49 (m, 3H, H-3′, H-4′), 7.99–8.02 (m, 2H, H-2′). 13C NMR (150 MHz, CDCl3): δ 17.4 (CH3-2′), 17.8 (CH3Ar), 118.4 (C-6), 123.2 (C-4), 126.3 (C-5), 127.1 (C-2, C-2′), 128.4 (C-3′), 130.3 (C-3), 130.4 (C-4′), 139.4 (C-1′), 150.3 (C-1), 164.9 (C-1′).

3.5.3. (E)-2-Methoxy-N-(1-phenylethylidene)aniline (5c)

Following general method A, a mixture of 2a (0.107 g, 1.05 mmol), Li2CO3 (0.015 g, 0.20 mmol), 1c (0.135 g, 1.10 mmol), and Hg2Cl2 (0.025 g, 0.053 mmol) was reacted for 4 h to afford 5c (0.205 g, 87%) as a yellow oil. RF 0.70 (hexane/EtOAc, 7:3). IR (film): ν 3059, 3001, 2957, 2934, 1684, 1635, 1590, 1489, 1448, 1366, 1242, 1208, 1180, 1115, 1046, 1026, 765, 746, 693 cm⁻¹. 1H NMR (500 MHz, CDCl3): δ 2.18 (s, 3H, CH3-3), 3.79 (s, 3H, CH3O), 6.78 (dd, 3J = 7.5, 1.7 Hz, 2H, H-6), 6.94 (dd, 3J = 7.5, 1.5 Hz, 1H, H-3), 6.96 (td, 3J = 7.5, 1.5 Hz, 1H, H-5), 7.08 (td, 3J = 7.5, 1.7 Hz, 1H, H-4), 7.42–7.48 (m, 3H, H-3′, H-4′), 7.97–8.03 (m, 2H, H-2′). 13C NMR (125 MHz, CDCl3): δ 17.8 (CH3-2′), 55.6 (CH3O), 111.5 (C-3), 120.5 (C-5), 120.8 (C-6), 124.1 (C-4), 127.3 (C-2′), 128.3 (C-3′), 130.4 (C-4′), 139.3 (C-1′), 140.5 (C-1), 1489.9 (C-2), 167.1 (C-1′) [96].

3.5.4. (E)-3-Methyl-N-(1-phenylethylidene)aniline (5d)

Following general method A, a mixture of 2a (0.096 g, 0.94 mmol), Li2CO3 (0.014 g, 0.19 mmol), 1d (0.106 g, 0.99 mmol), and Hg2Cl2 (0.022 g, 0.047 mmol) was reacted for 4 h to give 5d (0.163 g, 83%) as a yellow oil. RF 0.67 (hexane/EtOAc, 7:3); (Lit. mp 34 °C [10]). IR (film): ν 3059, 3001, 2958, 2834, 1684, 1634, 1594, 1485, 1447, 1367, 1363, 1288, 1261, 1193, 1148, 1045, 913, 852, 784, 765, 694 cm⁻¹. 1H NMR (500 MHz, CDCl3): δ 2.23 (s, 3H, CH3-2′), 2.35 (s, 3H, CH3Ar), 6.60 (dm, 3J = 7.5 Hz, 1H, H-6), 6.61–6.64 (m, 1H, H-2′), 6.90 (dm, 3J = 7.5 Hz, 1H, H-4), 7.23 (t, 3J = 7.5 Hz, 1H, H-5), 7.41–7.48 (m, 3H, H-3′, H-4′), 7.94–7.98 (m, 2H, H-2′). 13C NMR (125 MHz, CDCl3): δ 17.3 (CH3-2′), 25.5 (CH3Ar), 116.3 (C-6), 120.0 (C-2), 123.9 (C-4), 127.1 (C-2′), 128.3 (C-3′), 128.8 (C-5), 130.4 (C-4′), 138.7 (C-3′), 139.5 (C-1′), 151.7 (C-1), 165.2 (C-1′). HRMS (EI): m/z [M⁺] calcd for C15H15N: 209.1204; found: 209.1205.
3.5.5. (E)-3-Methoxy-N-(1-phenylethylidene)aniline (5e)

Following general method A, a mixture of 2a (0.096 g, 0.94 mmol), Li₂CO₃ (0.014 g, 0.19 mmol), 1e (0.122 g, 0.99 mmol), and Hg₂Cl₂ (0.022 g, 0.047 mmol) was reacted for 4 h to afford 5e (0.178 g, 84%) as a yellow oil. Rf 0.70 (hexane/EtOAc, 7:3). IR (film): ν 3452, 3369, 2929, 2837, 1602, 1496, 1464, 1292, 1206, 1158, 1038, 835, 764, 688. ¹H NMR (500 MHz, CDCl₃): δ 2.25 (s, 3H, CH₃-2’), 3.81 (s, 3H, CH₂O), 6.35–6.40 (m, 2H, H-2, H-6), 6.64 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H, H-4), 7.25 (t, J = 8.0 Hz, 1H, H-5), 7.42–7.49 (m, 3H, H-3”, H-4”), 7.95–7.98 (m, 2H, H-2”). ¹³C NMR (125 MHz, CDCl₃): δ 17.4 (CH₃-2’), 55.2 (CH₂O), 105.0 (C-2), 108.8 (C-4), 111.7 (C-6), 127.1 (C-2”), 128.3 (C-3”), 129.8 (C-5), 130.5 (C-4”), 139.4 (C-1”), 153.1 (C-1), 160.3 (C-3), 165.5 (C-1’) [97].

3.5.6. (E)-3-Chloro-N-(1-phenylethylidene)aniline (5f)

Following general method A, a mixture of 2a (0.111 g, 1.09 mmol), Li₂CO₃ (0.016 g, 0.22 mmol), 1f (0.145 g, 1.14 mmol), and Hg₂Cl₂ (0.026 g, 0.055 mmol) was reacted for 4 h to provide 5f (0.132 g, 53%) as a brown oil. Rf 0.76 (hexane/EtOAc, 7:3). IR (film): ν 3060, 2920, 1635, 1588, 1470, 1448, 1367, 1288, 1212, 1072, 864, 788, 763, 692 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 2.25 (s, 3H, CH₃-2’), 6.68 (dm, J = 8.1 Hz, 1H, H-6), 6.81 (t, J = 1.8 Hz, 1H, H-2), 7.07 (dm, J = 8.1 Hz, 1H, H-4), 7.27 (t, J = 8.1 Hz, 1H, H-5), 7.43–7.51 (m, 3H, H-3”, H-4”), 7.94–7.97 (m, 2H, H-2”). ¹³C NMR (150 MHz, CDCl₃): δ 17.9 (CH₃-2’), 118.0 (C-6), 119.8 (C-2), 123.5 (C-4), 127.5 (C-2”), 128.7 (C-3”), 130.4 (C-5), 131.1 (C-4”), 134.8 (C-3), 139.3 (C-1”), 152.2 (C-1), 166.6 (C-1’). HRMS (EI): m/z [M⁺] calcd for C₁₄H₁₂N₂: 229.0658; found: 209.0652 [13].

3.5.7. (E)-4-Methyl-N-(1-phenylethylidene)aniline (5g)

Following general method A, a mixture of 2a (0.096 g, 0.94 mmol), Li₂CO₃ (0.014 g, 0.19 mmol), 1g (0.105 g, 0.98 mmol), and Hg₂Cl₂ (0.022 g, 0.047 mmol) was reacted for 2 h to afford 5g (0.179 g, 91%) as a yellow oil. Rf 0.76 (hexane/EtOAc, 7:3); (Lit. 62 °C [10]). IR (film): ν 3449, 3363, 3023, 2920, 1683, 1633, 1516, 1505, 1447, 1364, 1288, 1266, 1219, 1026, 842, 827, 763, 692 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 2.24 (s, 3H, CH₃-2’), 2.35 (s, 3H, CH₃Ar), 6.70 (d, J = 7.8 Hz, 2H, H-2), 7.16 (d, J = 7.8 Hz, 2H, H-3), 7.41–7.49 (m, 3H, H-3”, H-4”), 7.94–7.99 (m, 2H, H-2”). ¹³C NMR (150 MHz, CDCl₃): δ 17.3 (CH₃-2’), 20.9 (CH₃Ar), 119.4 (C-2), 127.1 (C-2”), 128.3 (C-3”), 129.5 (C-3), 130.3 (C-4”), 132.6 (C-4), 139.7 (C-1”), 149.0 (C-1), 165.5 (C-1’). HRMS (EI): m/z [M⁺] calcd for C₁₅H₁₅N: 209.1204; found: 209.1210 [51].

3.5.8. (E)-4,N,N-dimethy lamino-N-(1-phenylethylidene)aniline (5h)

Following general method A, a mixture of 2a (0.099 g, 0.97 mmol), Li₂CO₃ (0.014 g, 0.19 mmol), 1h (0.139 g, 1.02 mmol) and Hg₂Cl₂ (0.023 g, 0.049 mmol) was reacted for 2 h to obtain 5h (0.158 g, 68%) as a brown solid. Rf 0.53 (hexane/EtOAc, 7:3); mp 90–92 °C. IR (film): ν 2918, 2803, 1622, 1510, 1446, 1364, 1222, 830, 760, 690 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 2.28 (s, 3H, CH₃-2’), 2.95 (s, 6H, (CH₂)₂N), 6.75–6.82 (m, 4H, H-2, H-3), 7.41–7.45 (m, 3H, H-3”, H-4”), 7.95–7.97 (m, 2H, H-2”). ¹³C NMR (125 MHz, CDCl₃): δ 17.3 (CH₃-2’), 41.2 ((CH₂)₂N), 113.5 (C-3), 121.0 (C-2), 127.0 (C-2”), 128.3 (C-3”), 130.1 (C-4”), 140.1 (C-1’), 141.7 (C-1), 147.4 (C-4), 165.0 (C-1’). HRMS (EI): m/z [M⁺] calcd for C₁₅H₁₇N₃: 238.1470; found: 238.1471 [98].

3.5.9. (E)-4-Methoxy-N-(1-phenylethylidene)aniline (5i)

Following general method A, a mixture of 2a (0.125 g, 1.23 mmol), Li₂CO₃ (0.018 g, 0.24 mmol), 1i (0.158 g, 1.28 mmol), and Hg₂Cl₂ (0.029 g, 0.06 mmol) was reacted for 2 h to furnish 5i (0.252 g, 91%) as a pale yellow crystalline solid. Rf 0.70 (hexane/EtOAc, 7:3); mp 93–94 °C (Lit. 86 °C [109,105]; Lit. 85–86 °C [50]). IR (KBr): ν 2954, 2929, 1616, 1576, 1510, 1443, 1365, 1284, 1240, 1210, 1032, 846, 771, 752, 699 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 2.26 (s, 3H, CH₃-2’), 3.82 (s, 3H, CH₂O), 6.73–6.79 (m, 2H, H-2), 6.89–6.94 (m, 2H, H-3), 7.41–7.49 (m, 3H, H-3”, H-4”), 7.95–7.98 (m, 2H, H-2”). ¹³C NMR (150 MHz, CDCl₃): δ
17.3 (C-2'), 55.5 (CH3O), 114.2 (C-3), 120.7 (C-2), 127.1 (C-2''), 128.3 (C-3'''), 130.3 (C-4''), 139.8 (C-1'''), 144.8 (C-1'), 155.9 (C-4), 165.7 (C-1'). HRMS (EI): m/z [M⁺] calcd for C15H15NO: 225.1154; found: 225.1164 [51,99].

3.5.10. (E)-4-Chloro-N-(1-phenylethylidene)aniline (5j)
Following general method A, a mixture of 2a (0.119 g, 1.17 mmol), Li2CO3 (0.017 g, 0.23 mmol), 1j (0.155 g, 1.22 mmol), and HgCl2 (0.027 g, 0.057 mmol) was reacted for 2 h to give 5j (0.209 g, 78%) as a yellow solid. Rf 0.76 (hexane/EtOAc, 7:3); mp 68-70 °C [Lit. 73-74 °C [99]]. IR (film): ʋ 3061, 2955, 2854, 1634, 1579, 1483, 1447, 1437, 1288, 1214, 1091, 1010, 844, 762, 692, 674 cm⁻¹. 1H NMR (500 MHz, CDCl3): δ 2.23 (s, 3H, CH3-2'''), 6.71-6.76 (m, 2H, H-2), 7.28-7.33 (m, 2H, H-3), 7.42-7.50 (m, 3H, H-3'', H-4''), 7.93-7.98 (m, 2H, H-2''). 13C NMR (125 MHz, CDCl3): δ 17.4 (CH3-2''), 120.8 (C-2), 127.2 (C-2''), 128.4 (C-3''), 128.5 (C-4), 129.0 (C-3), 130.7 (C-4''), 139.2 (C-1''), 150.2 (C-1), 166.2 (C-1') [13,51].

3.5.11. (E)-2-Bromo-4-methoxy-N-(1-phenylethylidene)aniline (5k)
Following general method A, a mixture of 2a (0.093 g, 0.91 mmol), Li2CO3 (0.013 g, 0.182 mmol), 1k (0.177 g, 0.95 mmol), and HgCl2 (0.021 g, 0.044 mmol) was reacted for 8 h to produce 5k (0.110 g, 42%) as a yellow oil. Rf 0.73 (hexane/EtOAc, 7:3). IR (film): ʋ 3057, 3026, 2921, 1645, 1634, 1578, 1480, 1447, 1366, 1293, 1221, 1044, 865, 828, 761, 692 cm⁻¹. 1H NMR (500 MHz, CDCl3): δ 2.19 (s, 3H, CH3-2''), 2.33 (s, 3H, CH3Ar), 6.68 (d, J = 8.0 Hz, 1H, H-6), 7.09 (dd, J = 8.0, 2.0 Hz, 1H, H-5), 6.43 (d, J = 2.0 Hz, 1H, H-3), 7.14-7.50 (m, 3H, H-3'', H-4''), 7.98-8.02 (m, 2H, H-2'). 13C NMR (125 MHz, CDCl3): δ 18.0 (CH3-2''), 20.5 (CH3Ar), 113.5 (C-2), 120.1 (C-6), 127.4 (C-2''), 128.4 (C-3'''), 128.7 (C-5), 130.7 (C-4''), 133.1 (C-3), 134.2 (C-4), 139.1 (C-1''), 147.4 (C-1), 167.6 (C-1'). HRMS (EI): m/z [M⁺] calcd for C15H14BrN: 287.0310; found: 287.0318.

3.5.12. (E)-4-Methoxy-N-(1-(p-tolyl)ethyldene)aniline (5l)
Following general method A, a mixture of 2b (0.118 g, 1.02 mmol), Li2CO3 (0.015 g, 0.20 mmol), 1l (0.132 g, 1.07 mmol), and HgCl2 (0.024 g, 0.051 mmol) was reacted for 2 h to generate 5l (0.221 g, 91%) as a yellow solid. Rf 0.73 (hexane/EtOAc, 7:3); mp 78-80 °C [Lit. 83 °C [10]]. IR (film): ʋ 2996, 2954, 2930, 2835, 1621, 1576, 1505, 1445, 1366, 1286, 1242, 1211, 1181, 1032, 846, 761, 699 cm⁻¹. 1H NMR (500 MHz, CDCl3): δ 2.22 (s, 3H, CH3-2''), 2.40 (s, 3H, CH3Ar), 3.81 (s, 3H, CH3O), 6.72-6.76 (m, 2H, H-2), 6.88-6.92 (m, 2H, H-3), 7.22-7.25 (m, 2H, H-3''), 7.84-8.77 (m, 2H, H-2''). 13C NMR (125 MHz, CDCl3): δ 17.2 (CH2-2''), 21.3 (CH3Ar), 55.5 (CH3O), 114.2 (C-3), 120.8 (C-2), 127.1 (C-2''), 129.0 (C-3''), 137.1 (C-1''), 140.5 (C-4''), 145.0 (C-1), 155.8 (C-4), 165.5 (C-1') [100].

3.5.13. (E)-4-(1-((4-methoxyphenyl)imino)ethyl)benzonitrile (5m)
Following general method A, a mixture of 2c (0.083 g, 0.65 mmol), Li2CO3 (0.010 g, 0.13 mmol), 1l (0.084 g, 0.68 mmol), and HgCl2 (0.014 g, 0.03 mmol) was reacted for 2 h, resulting in an inseparable mixture of 5m/7b (95:5) as an instable brown solid. The yield of compound 5m (0.147 g, 90%) was estimated by 1H NMR and GC/MS. Rf 0.48 (hexano/AcOEt, 7:3). 1H NMR (500 MHz, CDCl3): δ 2.28 (s, 3H, CH3-2''), 3.83 (s, 3H, CH3O), 6.73-6.78 (m, 2H, H-2), 6.91-6.95 (m, 2H, H-3), 7.72-7.75 (m, 2H, H-3''), 8.04-8.09 (m, 2H, H-2''). Signals attributed to 7b: 2.65 (s, CH3-2''), 3.74 (s, CH3O), 7.74-7.80 (m, H-3'').

3.5.14. (E)-4-Methoxy-N-(1-(4-methoxyphenyl)ethyldiene)aniline (5n)
Following general method A, a mixture of 2d (0.095 g, 0.72 mmol), Li2CO3 (0.011 g, 0.15 mmol), 1l (0.093 g, 0.76 mmol), and HgCl2 (0.017 g, 0.036 mmol) was reacted for 2 h to form 5n (0.152 g, 83%) as a pale yellow solid. Rf 0.57 (hexane/EtOAc, 7:3); mp 130-132 °C [Lit. 132-134 °C [95]]. IR (film): ʋ 2968, 2837, 1626, 1601, 1502, 1379, 1266, 1258, 1239, 1207, 1172, 1028, 833 cm⁻¹. 1H NMR (600 MHz, CDCl3): δ 2.22 (s, 3H, CH3-2''), 3.82 (s, 3H, CH3O-4), 3.86 (s, 3H, CH3O-4''), 6.72-6.76 (m, 2H, H-2), 6.88-6.92 (m, 2H, H-3), 6.93-6.96 (m, 2H, H-3''), 7.91-7.95 (m, 2H, H-2''). 13C NMR (150 MHz, CDCl3): δ 17.1 (C-2''), 55.4
3.6. Preparation and Characterization of Indoles 6a–p

3.6.1. 2-Phenyl-1H-indole (6a)

Following general method B, a mixture of 2a (0.080 g, 0.79 mmol), 1a (0.077 g, 0.83 mmol), and Hg_{2}Cl_{2} (0.019 g, 0.04 mmol) was stirred at 60 °C for 4 h. It was then reacted with DMSO (3.9 mL), Cu(OAc)_{2} (0.215 g, 1.18 mmol), and Pd(OAc)_{2} (0.035 g, 0.16 mmol) to yield 6a (0.120 g, 79%) as a brown solid. R_{f} 0.77 (hexane/EtOAc, 7:3).

Following general method C, a mixture of 5a (0.088 g, 0.45 mmol), DMSO (2.2 mL), Cu(OAc)_{2} (0.123 g, 0.68 mmol), and Pd(OAc)_{2} (0.020 g, 0.09 mmol) was reacted to yield 6a (0.054 g, 63%) as a pale brownish solid. R_{f} 0.77 (hexane/EtOAc, 7:3); mp 189–190 °C (Lit. 189–190 °C [66], 188–189 °C [101], 187–188 °C [102]). IR (ATR): ν 3439, 2919, 2853, 1455, 1230, 794, 770, 742, 690 cm^{-1}. 1H NMR (600 MHz, CDCl_{3}): δ 6.83 (dd, J = 2.1, 0.9 Hz, 1H, H-3), 7.12 (td, J = 7.8, 0.6 Hz, 1H, H-5), 7.19 (td, J = 7.8, 1.2 Hz, 1H, H-6), 7.30–7.33 (m, 1H, H-4'), 7.39 (dd, J = 7.8, 0.9 Hz, 1H, H-7), 7.41–7.46 (m, 2H, H-3), 7.63 (dd, J = 7.8, 0.9 Hz, 1H, H-4), 7.64–7.67 (m, 2H, H-2'), 8.32 (br s, 1H, NH). 13C NMR (150 MHz, CDCl_{3}): δ 100.0 (C-3), 110.9 (C-7), 120.3 (C-5), 120.7 (C-4), 122.4 (C-6), 125.2 (C-2'), 127.7 (C-4'), 129.0 (C-3'), 129.3 (C-3a), 132.4 (C-1'), 136.8 (C-7a), 137.9 (C-2).

3.6.2. 7-Methyl-2-phenyl-1H-indole (6b)

Following general method B, a mixture of 2a (0.077 g, 0.57 mmol), 1b (0.085 g, 0.79 mmol), and Hg_{2}Cl_{2} (0.018 g, 0.04 mmol) was stirred at 60 °C for 4 h. It was then reacted with DMSO (3.8 mL), Cu(OAc)_{2} (0.205 g, 1.13 mmol), and Pd(OAc)_{2} (0.034 g, 0.15 mmol) to provide 6b (0.10 g, 64%) as a brown solid. R_{f} 0.67 (hexane/EtOAc, 7:3); mp 114–116 °C (Lit. 112–118 °C [103]). IR (ATR): ν 3450, 1601, 1486, 1449, 1335, 1330, 1299, 804, 770, 737, 690 cm^{-1}. 1H NMR (500 MHz, CDCl_{3}): δ 2.52 (s, 3H, CH_{3}Ar), 6.81 (d, J = 2.5 Hz, 1H, H-3), 6.98 (dm, J = 7.5 Hz, 1H, H-6), 7.04 (t, J = 7.5 Hz, 1H, H-5), 7.30 (tm, J = 7.5 Hz, 1H, H-4'), 7.40–7.44 (m, 2H, H-3'), 7.47 (dm, J = 7.5 Hz, 1H, H-4), 7.64–7.68 (m, 2H, H-2'), 8.15 (br s, 1H, NH). 13C NMR (125 MHz, CDCl_{3}): δ 16.7 (CH_{3}Ar), 100.6 (C-3), 118.4 (C-4), 120.0 (C-7), 120.4 (C-5), 122.9 (C-6), 125.2 (C-2'), 127.6 (C-4'), 128.8 (C-3a), 129.0 (C-3'), 132.5 (C-1'), 136.4 (C-7a), 137.6 (C-2).

3.6.3. 7-Methoxy-2-phenyl-1H-indole (6c)

Following general method B, a mixture of 2a (0.086 g, 0.84 mmol), 1c (0.110 g, 0.89 mmol), and Hg_{2}Cl_{2} (0.020 g, 0.04 mmol) was stirred at 60 °C for 4 h. It was then reacted with DMSO (4.2 mL), Cu(OAc)_{2} (0.230 g, 1.27 mmol), and Pd(OAc)_{2} (0.038 g, 0.17 mmol) to furnish 6c (0.149 g, 79%) as an amber solid. R_{f} 0.67 (hexane/EtOAc, 7:3); mp 63–64 °C (Lit. 94–95 °C [66]). IR (ATR): ν 3429, 1608, 1581, 1505, 1485, 1453, 1401, 1332, 1316, 1258, 1225, 1097, 798, 772, 753, 730 cm^{-1}. 1H NMR (600 MHz, CDCl_{3}): δ 4.0 (s, 3H, CH_{3}O), 6.66 (d, J = 7.8 Hz, 1H, H-6), 6.81 (d, J = 2.4, 1H, H-3), 7.04 (t, J = 7.8 Hz, 1H, H-5), 7.24 (d, J = 7.8 Hz, 1H, H-4), 7.31–7.34 (m, 1H, H-4'), 7.42–7.46 (m, 2H, H-3'), 7.68–7.70 (m, 2H, H-2'), 8.56 (br s, 1H, NH). 13C NMR (150 MHz, CDCl_{3}): δ 55.3 (CH_{3}O), 100.2 (C-3), 102.1 (C-6), 113.3 (C-4), 120.5 (C-5), 125.1 (C-2'), 127.3 (C-7a), 127.6 (C-4'), 129.0 (C-3'), 130.4 (C-3a), 132.4 (C-1'), 137.5 (C-2), 145.9 (C-7). HRMS (EI): m/z [M^+] calcd for C_{15}H_{13}NO: 223.0997; found: 223.0994.

3.6.4. 6-Methyl-2-phenyl-1H-indole (6d). 4-Methyl-2-phenyl-1H-indole (6d')

Following general method B, a mixture of 2a (0.076 g, 0.75 mmol), 1d (0.084 g, 0.79 mmol), and Hg_{2}Cl_{2} (0.019 g, 0.04 mmol) was stirred at 60 °C for 4 h. It was then reacted with DMSO (3.7 mL), Cu(OAc)_{2} (0.204 g, 1.12 mmol), and Pd(OAc)_{2} (0.034 g, 0.15 mmol) to afford a mixture of 6d/6d' (88:12), which was separated to provide 6d (0.097 g, 63%) as a pale yellow solid. R_{f} 0.70 (hexane/EtOAc, 7:3); mp 186–187 °C (Lit. 189–190 °C [102], 190–192 °C [103]). IR (ATR): ν 3429, 1454, 1384, 1350, 1232, 814, 760, 741,
3.5.6. 6-Methoxy-2-phenyl-1H-indole (6e). 4-Methoxy-2-phenyl-1H-indole (6e′)

Following general method B, a mixture of 2a (0.085 g, 0.83 mmol), 1e (0.107 g, 0.87 mmol), and Hg₂Cl₂ (0.019 g, 0.04 mmol) was stirred at 60 °C for 4 h. It was then reacted with DMSO (4.4 mL), Cu(OAc)₂ (0.225 g, 1.24 mmol), and Pd(OAc)₂ (0.038 g, 0.17 mmol), leading to a mixture of 6e/6e′ (93:7) [66], which was separated by column chromatography over silica gel (30 g/g crude, hexane/EtOAc, 98:2) to give 6e (0.138 g, 75%) as a brown solid. Rf 0.60 (hexane/EtOAc, 7:3); mp 160–161 °C (Lit. 177–178 °C [66]; 173–176 °C [102]). IR (ATR): ν 3396, 1625, 1446, 1257, 1200, 1158, 1016, 823, 756 cm⁻¹. 1H NMR (600 MHz, CDCl₃): δ 3.86 (s, 3H, CH₃O), 6.76 (d, j = 1.8, 1H, H-3), 6.80 (dd, j = 8.4, 2.4 Hz, 1H, H-5), 6.90 (d, j = 2.4, 1H, H-7), 7.27–7.31 (m, 1H, H-4′), 7.41–7.44 (m, 2H, H-3′). 13C NMR (150 MHz, CDCl₃): δ 17.4, 30.1, 55.6 (CH₃O), 94.4 (C-7), 99.8 (C-3), 110.2 (C-5), 121.3 (C-4), 123.5 (C-3a), 124.7 (C-2′), 127.2 (C-4′), 129.0 (C-3′), 132.5 (C-1′), 136.8 (C-2), 137.6 (C-7a), 156.7 (C-6). Data for 6e: MS (70 eV): m/z 223 (M⁺, 77), 208 (100), 182 (15), 177 (3). Data for 6e′: MS (70 eV): m/z 223 (M⁺, 100), 208 (87), 180 (17), 127 (15), 89 (23), 77 (13). HRMS (EI): m/z [M⁺] calcd for C₁₅H₁₃NO: 223.0997; found: 223.0991.

3.6.6. 6-Chloro-2-phenyl-1H-indole (6f). 4-Chloro-2-phenyl-1H-indole (6f′)

Following general method B, a mixture of 2a (0.079 g, 0.77 mmol), 1f (0.103 g, 0.81 mmol), and Hg₂Cl₂ (0.019 g, 0.04 mmol) was stirred at 60 °C for 4 h. It was then reacted with DMSO (4.3 mL), Cu(OAc)₂ (0.211 g, 1.16 mmol), and Pd(OAc)₂ (0.034 g, 0.15 mmol), resulting in a mixture of 6f/6f′ (81:19), which was separated by column chromatography over silica gel (30 g/g crude, hexane/EtOAc, 98:2) to obtain 6f (0.109 g, 62%) as a yellow solid. Rf 0.70 (hexane/EtOAc, 7:3); mp 181–182 °C (Lit. 171–173 °C [104]; 182–183 °C [105]). IR (ATR): ν 3429, 1453, 1310, 1067, 876, 805, 758, 736, 688 cm⁻¹. 1H NMR (500 MHz, CDCl₃): δ 6.79 (d, j = 2.0 Hz, 1H, H-3), 7.09 (dd, j = 8.5, 1.5 Hz, 1H, H-5), 7.34 (br t, j = 7.5 Hz, 1H, H-4′), 7.39 (d, j = 1.5 Hz, 1H, H-7), 7.45 (t, j = 7.5 Hz, 2H, H-3′), 7.52 (d, j = 8.5 Hz, 1H, H-4), 7.65 (d, j = 7.5 Hz, 2H, H-2′), 8.32 (br s, 1H, NH). 13C NMR (125 MHz, CDCl₃): δ 100.0 (C-3), 110.8 (C-7), 121.0 (C-5), 121.5 (C-4), 125.2 (C-2′), 127.8 (C-3a), 128.0 (C-4′), 128.1 (C-6), 129.1 (C-3′), 131.9 (C-1′), 137.1 (C-7a), 138.6 (C-2). Data for 6f: MS (70 eV): m/z 229 (M⁺+2, 37), 227 (M⁺, 100), 190 (8), 165 (23), 114 (5), 89 (13), 77 (3). Data for 6f′: MS (70 eV): m/z 229 (M⁺+2, 30), 227 (M⁺, 100), 190 (8), 165 (17), 89 (15).

3.6.7. 5-Methyl-2-phenyl-1H-indole (6g)

Following general method B, a mixture of 2a (0.083 g, 0.81 mmol), 1g (0.092 g, 0.86 mmol), and Hg₂Cl₂ (0.019 g, 0.04 mmol) was stirred at 60 °C for 2 h. It was then reacted with DMSO (4.1 mL), Cu(OAc)₂ (0.222 g, 1.22 mmol), and Pd(OAc)₂ (0.036 g, 0.16 mmol) to produce 6g (0.103 g, 61%) as a pale-yellow solid. Rf 0.70 (hexane/EtOAc, 7:3); mp 214–215 °C (Lit. 216–218 °C [66]; 211–213 °C [102]; 218–220 °C [103]). IR (ATR): ν 3405, 1603, 1449, 1406, 1299, 1202, 1079, 804, 799, 737, 761, 686 cm⁻¹. 1H NMR (600 MHz, CDCl₃): δ 2.45 (s, 3H, CH₃), 6.75 (dd, j = 2.4, 0.6 Hz, 1H, H-3), 7.02 (dd, j = 8.4, 1.2 Hz, 1H, H-6), 7.28 (d, j = 8.4 Hz, 1H, H-7), 7.29–7.32 (m, 1H, H-4′), 7.41 (dd, j = 1.2, 0.6 Hz, 1H, H-4), 7.41–7.44 (m, 2H, H-3′), 7.63–7.66 (m, 2H, H-2′), 8.23 (br s, 1H, NH). 13C NMR (150 MHz, CDCl₃): δ 21.5 (CH₃), 99.5 (C-3), 110.5 (C-7), 120.3 (C-4), 124.0 (C-6), 125.0 (C-2′), 127.6 (C-4′), 129.0 (C-3′), 129.46 (C-5), 129.54 (C-3a), 132.5 (C-1′), 135.2 (C-7a), 137.9 (C-2).
3.6.8. 5-Methoxy-2-phenyl-1H-indole (6h)

Following general method B, a mixture of 2a (0.085 g, 0.83 mmol), 1i (0.106 g, 0.86 mmol), and HgCl₂ (0.019 g, 0.04 mmol) was stirred at 60 °C for 2 h. It was then reacted with DMSO (4.1 mL), Cu(OAc)₂ (0.222 g, 1.22 mmol), and Pd(OAc)₂ (0.036 g, 0.16 mmol) to give 6h (0.146 g, 80%) as a yellow solid. Rf 0.60 (hexane/EtOAc, 7:3).

Following general method C, a mixture of 5i (0.060 g, 0.27 mmol), DMSO (1.33 mL), Cu(OAc)₂ (0.073 g, 0.40 mmol), and Pd(OAc)₂ (0.012 g, 0.054 mmol) was reacted to afford 6h (0.037 g, 62%) as a pale brownish solid. Rf 0.60 (hexane/EtOAc, 7:3). mp 168–169 °C (Lit. 169–170 °C [66], 166–169 °C [101], 160–162 °C [102]). IR (KBr): υ 3415, 1615, 1479, 1208, 1148, 1030, 765 cm⁻¹. H NMR (600 MHz, CDCl₃): δ 3.87 (s, 3H, CH₃O), 6.76 (dd, J = 2.4, 1.2 Hz, 1H, H-6), 6.86 (dd, J = 9.0, 2.4 Hz, 1H, H-6), 7.09 (dd, J = 2.4 Hz, 1H, H-4), 7.29 (d, J = 9.0 Hz, 1H, H-7), 7.30–7.33 (m, 1H, H-4’), 7.41–7.46 (m, 2H, H-3’), 7.63–7.66 (m, 2H, H-2’), 8.21 (br s, 1H, NH). 13C NMR (150 MHz, CDCl₃): δ 55.8 (CH₃O), 99.9 (C-3), 102.3 (C-4), 111.6 (C-7), 112.6 (C-6), 125.1 (C-2’), 127.6 (C-4’), 129.0 (C-3’), 129.7 (C-3a), 132.0 (C-7a), 132.5 (C-1’), 138.6 (C-2), 154.5 (C-5).

3.6.9. 5-Chloro-2-phenyl-1H-indole (6i)

Following general method B, a mixture of 2a (0.085 g, 0.83 mmol), 1j (0.111 g, 0.87 mmol), and HgCl₂ (0.019 g, 0.04 mmol) was stirred at 60 °C for 2 h. It was then reacted with DMSO (4.1 mL), Cu(OAc)₂ (0.225 g, 1.24 mmol), and Pd(OAc)₂ (0.037 g, 0.17 mmol) to give 6i (0.134 g, 71%) as a yellow solid. Rf 0.60 (hexane/EtOAc, 7:3).

Following general method C, a mixture of 5j (0.081 g, 0.35 mmol), DMSO (1.77 mL), Cu(OAc)₂ (0.073 g, 0.53 mmol), and Pd(OAc)₂ (0.016 g, 0.07 mmol) was reacted to provide 6i (0.046 g, 57%) as a yellow solid. Rf 0.60 (hexane/EtOAc, 7:3); mp 195–196 °C (Lit. 196–197 °C [66], 198–200 °C [103]). IR (ATR): υ 3429, 1452, 1313, 1065, 876, 803, 754, 736, 687 cm⁻¹. 1H NMR (600 MHz, CDCl₃): δ 6.76 (d, J = 1.8 Hz, 1H, H-3), 7.14 (dd, J = 8.4, 1.8 Hz, 1H, H-6), 7.31 (d, J = 8.4 Hz, 1H, H-7), 7.35 (t, J = 7.5 Hz, 1H, H-4’), 7.45 (t, J = 7.5 Hz, 2H, H-3’), 7.59 (d, J = 1.8 Hz, 1H, H-4), 7.65 (d, J = 7.5 Hz, 2H, H-2’), 8.35 (br s, 1H, NH). 13C NMR (150 MHz, CDCl₃): δ 99.6 (C-3), 111.8 (C-7), 120.0 (C-4), 122.6 (C-6), 125.2 (C-2’), 125.9 (C-5), 128.1 (C-4’), 129.1 (C-3’), 130.3 (C-3a), 131.9 (C-1’), 135.1 (C-7a), 139.3 (C-2’).
99.3 (C-3), 102.2 (C-4), 111.5 (C-7), 112.3 (C-6), 125.0 (C-2'), 129.6 (C-1' or C-3a), 129.7 (C-3'), 129.8 (C-3a or C-1'), 131.9 (C-7a), 137.6 (C-4'), 138.8 (C-2), 154.5 (C-5).

3.6.12. 2-(4-Cyanophenyl)-5-methoxy-1H-indole (6l)

Following general method B, a mixture of 2e (0.078 g, 0.61 mmol), 1i (0.079 g, 0.64 mmol), and Hg2Cl2 (0.014 g, 0.03 mmol) was stirred at 60 °C for 2 h. It was then reacted with DMSO (3.1 mL), Cu(OAc)2 (0.167 g, 0.92 mmol), and Pd(OAc)2 (0.027 g, 0.12 mmol) to produce 6l (0.050 g, 33%) as yellow crystals. Rf 0.47 (hexane/EtOAc, 7:3); mp 191–192 °C (Lit. 195–196 °C [66]). IR (KBr): δ 3377, 2219, 1606, 1445, 1209, 1036, 876 cm⁻¹. 1H NMR (500 MHz, CDCl3): δ 3.87 (s, 3H, CH3), 6.88 (dd, J = 1.5, 0.5 Hz, 1H, H-3), 6.92 (dd, J = 8.7, 2.5 Hz, 1H, H-6), 7.09 (d, J = 2.5 Hz, 1H, H-4), 7.31 (dd, J = 8.7, 0.5 Hz, 1H, H-7), 7.69–7.73 (m, 4H, H-2', H-3'), 8.30 (br s, 1H, NH). 13C NMR (125 MHz, CDCl3): δ 55.8 (CH3O), 102.3 (C-4), 102.4 (C-3), 110.5 (C-4'), 112.0 (C-7), 114.3 (C-6), 118.8 (CN), 125.1 (C-2'), 129.4 (C-3a), 132.6 (C-7a), 132.8 (C-3'), 136.1 (C-2), 136.6 (C-1'), 154.8 (C-5). HRMS (EI): m/z [M⁺] calcd for C16H12N2O: 248.0950; found: 248.0943.

3.6.13. 5-Methoxy-2-(4-methoxyphenyl)-1H-indole (6m)

Following general method B, a mixture of 2d (0.075 g, 0.57 mmol), 1i (0.074 g, 0.60 mmol), and Hg2Cl2 (0.014 g, 0.03 mmol) was stirred at 60 °C for 2 h. It was then reacted with DMSO (3.1 mL), Cu(OAc)2 (0.156 g, 0.86 mmol), and Pd(OAc)2 (0.025 g, 0.11 mmol) to generate 6m (0.122 g, 84%) as a colorless crystalline solid. Rf 0.53 (hexane/EtOAc, 7:3); mp 218–219 °C (Lit. 218–219 °C [66]). IR (ATR): δ 3430, 1543, 1480, 1456, 1254, 1217, 1155, 1018, 829, 777 cm⁻¹. 1H NMR (600 MHz, CDCl3): δ 3.85 (s, 3H, CH3-O-C4'), 3.86 (s, 3H, CH2-O-C5'), 6.64 (d, J = 1.2 Hz, 1H, H-3), 6.83 (dd, J = 8.4, 2.4 Hz, 1H, H-6), 6.96–6.99 (m, 2H, H-3'), 7.10 (d, J = 2.4 Hz, 1H, H-4), 7.27 (d, J = 8.4 Hz, 1H, H-7), 7.56–7.59 (m, 2H, H-2'), 8.13 (br s, 1H, NH). 13C NMR (150 MHz, CDCl3): δ 55.4 (CH3O), 55.9 (CH3O), 98.7 (C3), 102.2 (C-4), 111.4 (C-7), 112.0 (C-6), 114.5 (C-3'), 125.3 (C-1'), 126.4 (C-2'), 129.9 (C-3a), 131.8 (C-7a), 138.7 (C-2), 154.5 (C-5), 159.3 (C-4').

3.6.14. 5-Methoxy-2-propyl-1H-indole (6n)

Following general method B, a mixture of 2e (0.088 g, 1.29 mmol), 1i (0.166 g, 1.35 mmol), and Hg2Cl2 (0.028 g, 0.06 mmol) was stirred at 60 °C for 2 h. It was then reacted with DMSO (6.5 mL), Cu(OAc)2 (0.352 g, 1.94 mmol), and Pd(OAc)2 (0.058 g, 0.26 mmol) to form 6n (0.093 g, 38%) as an amber solid. Rf 0.67 (hexane/EtOAc, 7:3); p.f. 64–65 °C (Lit. 64–65 °C [107]). IR (ATR): δ 3381, 2961, 1620, 1582, 1478, 1450, 1195, 1166, 1034, 831 cm⁻¹. 1H NMR (500 MHz, CDCl3): δ 1.00 (t, J = 7.5 Hz, 3H, H-3'), 1.73 (hex, J = 7.5 Hz, 2H, H-2'), 2.70 (t, J = 7.5 Hz, 2H, H-1'), 3.84 (s, 3H, CH3O), 6.17 (dd, J = 2.0, 1.0 Hz, 1H, H-3), 6.77 (dd, J = 8.5, 2.5 Hz, 1H, H-6), 7.00 (d, J = 2.5 Hz, 1H, H-4), 7.18 (d, J = 8.5 Hz, 1H, H-7), 7.74 (br s, 1H, NH). 13C NMR (125 MHz, CDCl3): δ 13.9 (C-3'), 22.5 (C-2'), 30.4 (C-1'), 55.9 (CH3O), 99.5 (C-3), 102.0 (C-4), 110.7 (C-6), 110.9 (C-7), 129.3 (C-3a), 130.9 (C-7a), 140.7 (C-2), 154.1 (C-5). HRMS (EI): m/z [M⁺] calcd for C17H15NO: 251.1154; found: 251.1153.

3.6.15. 2-Cyclopropyl-5-methoxy-1H-indole (6o)

Following general method B, a mixture of 2f (0.097 g, 1.47 mmol), 1i (0.189 g, 1.54 mmol), and Hg2Cl2 (0.033 g, 0.07 mmol) was stirred at 40 °C for 2 h. It was then reacted with DMSO (7.3 mL), Cu(OAc)2 (0.401 g, 2.21 mmol), and Pd(OAc)2 (0.065 g, 0.29 mmol) to provide 6o (0.107 g, 39%) as a yellow solid. Rf 0.67 (hexane/EtOAc, 7:3); mp 57–58 °C. IR (ATR): δ 3382, 2914, 1621, 1583, 1482, 1451, 1332, 1214, 1163, 1030, 837, 799, 770, 676 cm⁻¹. 1H NMR (600 MHz, CDCl3): δ 0.73–0.76 (m, 2H, CH2), 0.91–0.95 (m, 2H, CH2), 1.87–1.93 (m, 1H, H-1'), 6.07 (dd, J = 1.2, 0.6 Hz, 1H, H-3), 6.76 (dd, J = 9.0, 2.4 Hz, 1H, H-6), 6.98 (d, J = 2.4 Hz, 1H, H-4), 7.13 (d, J = 9.0 Hz, 1H, H-7), 7.83 (br s, 1H, NH). 13C NMR (150 MHz, CDCl3): δ 7.3 (2CH2), 8.9 (C-1'), 55.8 (CH3O), 97.5 (C-3), 101.9 (C-4), 110.7 (C-6), 110.8 (C-7), 129.1 (C-3a), 130.8 (C-7a), 142.6 (C-2), 154.1 (C-5). HRMS (EI): m/z [M⁺] calcd for C12H13NO: 187.0997; found: 187.0997 [66].
3.6.16. 2-(Cyclohex-1-en-1-yl)-5-methoxy-1H-indole (6p)

Following general method B, a mixture of 2g (0.096 g, 0.91 mmol), 1i (0.117 g, 0.95 mmol), and Hg₂Cl₂ (0.024 g, 0.05 mmol) was stirred at 40 °C for 2 h. It was then reacted with DMSO (4.5 mL), Cu(OAc)₂ (0.247 g, 1.36 mmol), and Pd(OAc)₂ (0.040 g, 0.18 mmol) to yield 6p (0.037 g 18%) as a brown solid. Rf 0.70 (hexane/EtOAc, 7:3); mp 108–110 °C. IR (KBr): ν 3063, 3016, 1637, 1597, 1578, 1482, 1447, 1366, 1287, 1221, 1114, 1026, 765, 728 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 2.23 (s, 3H, CH₃-2'), 6.78 – 7.02 (m, 1H, H-2'), 6.09 – 6.11 (m, 1H, H-2'), 6.37 (d, J = 1.5 Hz, H-3'), 2.42 – 2.46 (m, 2H, H-6'), 6.09 – 6.11 (m, 1H, H-2'), 6.37 (d, J = 1.5 Hz, H-3'), 2.42 – 2.46 (m, 2H, H-6'). HRMS (EI): m/z [M⁺] calcd for C₁₁H₁₃NO: 183.0631; found: 183.0632.

3.7. Single-Crystal X-ray Crystallography

Compounds 5i (yellow crystals, hexane/EtOAc, 98:2), 6e (colorless crystals, hexane/EtOAc, 98:2), and 6l (pale reddish crystals, hexane/EtOAc, 94:6) were prepared and mounted on glass fibers. Crystallographic measurements were performed with an areadetector with Mo Kα diffraction radiation (λ = 0.71073 Å; graphite monochromator) at room temperature (Table 4). Unit cell parameters were obtained from a least-squares refinement. Intensities were corrected for Lorentz and polarization effects. Multi-scan absorption correction was applied. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in accordance with electron density maps and idealized positions, and their atomic coordinates were refined by utilizing unit weights. After the structure was solved using SHELXT [108,109], it was implemented in WinGX [110], refined with SHELXL [111], and then visualized and plotted with the MERCURY program package [112].

| Structure | 5i | 6e | 6l |
|-----------|----|----|----|
| CCDC number | 2082632 | 2082633 | 2082634 |
| Empirical formula | C₁₅H₁₅NO | C₁₅H₁₅NO | C₁₆H₁₆N₂O |
| Molecular weight | 225.28 | 223.26 | 248.28 |
| Temperature | 292(2) K | 292(2) K | 292(2) K |
| Crystal size | 0.79 × 0.47 × 0.27 mm³ | 0.50 × 0.30 × 0.21 mm³ | 0.52 × 0.30 × 0.27 mm³ |
| Crystal system | monoclinic | orthorhombic | monoclinic |
| Space group | P₂₁/n | P₂₁₂₁ | P₂₁/c |
| Unit cell parameters | a = 10.0110(6) Å, α = 90° | a = 5.6782(3) Å, α = 90° | a = 7.0104(3) Å, α = 90° |
| | b = 8.7430(5) Å, β = 104.172(7)° | b = 8.0462(3) Å, β = 90° | b = 14.5242(8) Å, β = 98.202(4)° |
| | c = 14.6687(11) Å, γ = 90° | c = 25.5690(16) Å, γ = 90° | c = 12.5032(7) Å, γ = 90° |
| Volume | 1244.82(14) Å³ | 1168.19(11) Å³ | 1260.06(11) Å³ |
| Density | 1.202 mg/m³ | 1.269 mg/m³ | 1.309 mg/m³ |
| Absorption coefficient | 0.075 mm⁻¹ | 0.080 mm⁻¹ | 0.084 mm⁻¹ |
| Theta range | 3.655–29.183° | 3.187–29.557° | 2.936–29.453° |
| Reflections collected | 5094 | 3635 | 5405 |
| Independent reflections | 2839 | 2352 | 2909 |
| Observed reflections | 1999 | 2017 | 2171 |
| Final R indices | R₁ = 0.0505; wR₂ = 0.1110 | R₁ = 0.0387; wR₂ = 0.0841 | R₁ = 0.0450; wR₂ = 0.1001 |
| Goodness-of-fit on F² | 1.042 | 1.056 | 1.022 |

4. Conclusions

A new Hg(I)-catalyzed hydroamination of terminal acetylenes 2a–d in the presence of anilines 1a–k generated a series of ketimines 5a–n. An efficient consecutive Hg(I)/Pd(II)-catalyzed one-pot process led to the direct conversion of 1 and 2 into a series of 2-substituted...
Although good yields were found for most of the 2-arylindoles, the yields were fairly modest for halogenated, 2-alkyl, and 2-vinyl indoles. The latter limitation was possibly due to the low stability of the imine intermediate under these reaction conditions. Likewise, the direct Hg(I)-catalyzed preparation of the imines either provided low yields or made it impossible to avoid decomposition or hydrolysis to their corresponding acetophenones upon isolation from the reaction mixture. The reaction mechanism of this transformation was explored, finding that an Hg(I)–Pd(II) transmetalation step plausibly connects the consecutive cycles of Hg(I)-catalyzed enamine formation and Pd(II)-catalyzed oxidative cyclization.

Supplementary Materials: The following are available online. ¹H- and ¹³C-NMR spectra are available online. The CIF files of crystal structures have been deposited with the CCDC, and the crystal data and torsion angles for 5i, 6e, and 6l are also provided.

Author Contributions: R.U.G. contributed by developing the method, synthesizing compounds, performing NMR and HRMS spectra, and writing the experimental section; M.H.-M. carried out compound synthesis; A.M.-M. performed IR spectra and analyzed the results; F.D. contributed by doing the literature research, analyzing the results, and reviewing the manuscript; J.T. designed the project, provided tutorial guidance, discussed the results, acquired the financial resources, and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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