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Palladium-Catalyzed Anilide *ortho*-Arylation and Subsequent One-Pot Cyclization to Phenanthridines

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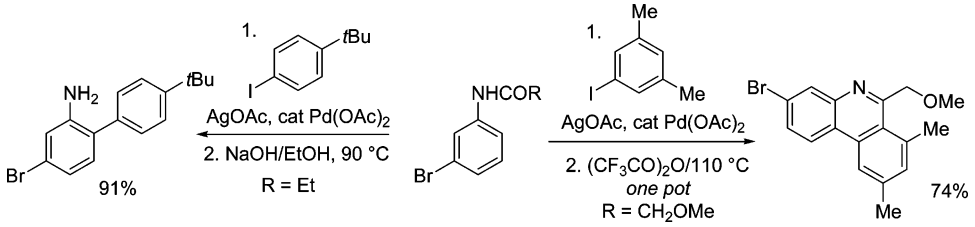


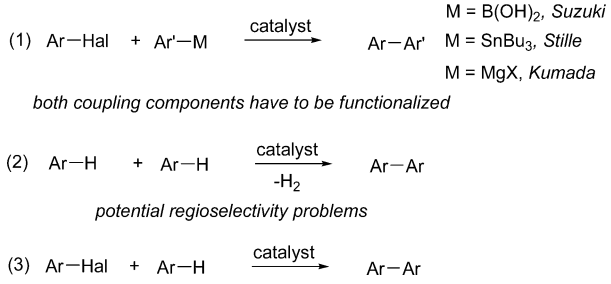
The palladium-catalyzed direct arylation of anilides possessing several *N*-acyl substituents has been demonstrated. Removal of the acyl group by base hydrolysis allows a short and efficient synthesis of 2-aryl or 2,6-diarylanilines. The method is functional group tolerant and allows the presence of chloride and bromide substituents on both the anilide and aryl iodide coupling components. The arylation products can be converted to phenanthridines by the reaction with trifluoroacetic anhydride.

Introduction

Palladium-catalyzed cross-coupling reactions of aryl halides with arylmetals have been developed to a remarkable extent and are now routinely used for the synthesis of aryl−aryl bonds.[1] However, this strategy requires installation of functionality on both coupling components (Scheme 1). Use of C−H bonds instead of other functional groups would result in shortening of synthetic sequences by allowing the use of readily available and simple starting materials.[2] From the viewpoint of atom economy and efficiency, it would be desirable to couple two C−H bonds forming a carbon−carbon bond. However, this approach is problematic for several reasons. The coupling of two molecules of benzene to biphenyl is energetically unfavorable by around 14 kJ/mol.[3]

This can be circumvented by using terminal oxidants; however, that often results in use of many equivalents of transition metal (copper) salts in the reactions, negating the atom efficiency resulting from use of C−H functionality. Another, and perhaps a more difficult, issue is achieving regioselectivity for this coupling process. A typical organic molecule contains a large number of C−H bonds, and the selective functionalization of the desired C−H bond may be challenging. In the case of simple arenes, for example, toluene, stoichiometric and catalytic C−H activation processes result in the formation of isomer mixtures.[4] A solution may be the coupling of a C−H bond with a carbon-leaving group bond. The first examples of transition-metal-promoted C−H/C−I and C−H/C−Cl couplings were reported by Tremont, Liebeskind, and Ohta.[5] Subsequently, it has been shown that many directing-group containing or even unfunc-

SCHEME 1. Cross-Coupling Reactions



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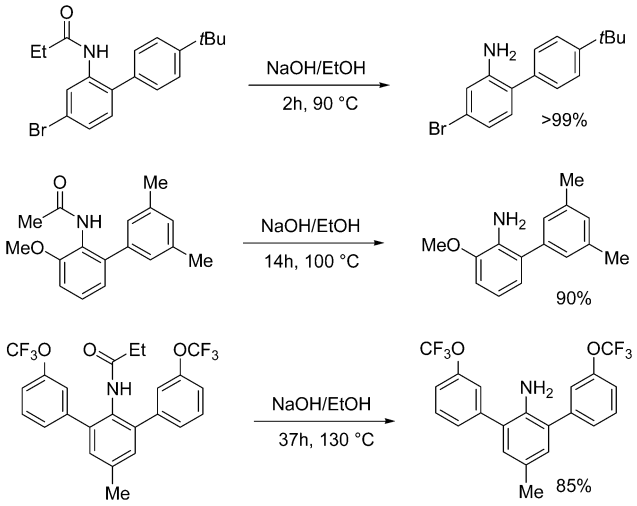
tionalized arenes can be arylated by aryl halides, boronates, stannanes, or aryliodonium salts under palladium, ruthenium, or rhodium catalysis.[6] We have shown that pyridines, benzylamines, benzamides, and benzoic acids can be arylated by aryl iodides, presumably under Pd(II)−Pd(IV) catalytic cycle conditions.[7] We have also reported that pivaloylated anilines can be efficiently arylated in trifluoroacetic acid under palladium catalysis, affording the *ortho*-arylated derivatives.[8] Sanford and co-workers simultaneously reported an analogous reaction between anilides and iodonium salts.[6e] This method has an unusual functional group tolerance—any halogens are allowed on the anilide coupling partner. Chloro and bromo substituents are tolerated on the aryl iodide. Up to 1000 turnovers were demonstrated for this reaction. However, the removal of the pivaloyl group affording the deprotected arylated anilines is difficult if not impossible. For this reason, use of other acylated anilides, for example, acetanilides, propionanilides, or trifluoroacetanilides, would be beneficial. We report here the scope of anilide arylation and the conditions for the removal of the acyl groups. Additionally, we report anilide one-pot arylation/cyclization forming diversely substituted phenanthridines.

Results and Discussion

1. Anilide Arylation. The initial optimization was carried out with respect to the acyl group of the anilide. The reactions were performed under the conditions previously utilized by our group for the arylation of pivalanilides.[8] The arylation of trifluoroacetanilides and ethoxycarbonylanilides was slow, and the formation of major amounts of biaryl homocoupling products was observed. Complete conversions were not obtained, presumably due to decomposition of palladium catalyst forming Pd(0). Under these conditions, formamide derivatives were transamidated to trifluoroacetamides. Aryl bromides cannot be used as arylating reagents. For example, the reaction between 2,3-dimethylpropionanilide and bromobenzene did not afford any product under the usual reaction conditions.

The arylation of propionyl and acetyl derivatives was successful (Table 1). The reactions are tolerant to halide substitution on the coupling components (entries 1−3, 7, and 8). However, low yield (34% isolated) was observed in the reaction of *p*-diiodobenzene with 4-methylpropionanilide (entry 11). Electron-rich (entries 1, 3−6, and 9−11) as well as electron-poor anilides are reactive. Aryl iodides of all electronic properties can be used; however, *ortho*-substitution is not tolerated. 2-Iodotoluene was unreactive in all attempted arylations. Typically, the yields are somewhat higher for propionyl derivatives (entry 4 vs 6 and entry 2 vs 7). Anilides substituted in 2- or 3-positions are monoarylated. For 4-substituted anilides, either diarylation (entries 4, 6, 10, and 11; CF_3CO_2H solvent) or monoarylation (entry 5; $CF_3CO_2H-CH_3CO_2H$ mixed solvent) is possible. Addition of acetic acid slows the reaction, resulting in the preferential formation of the monoarylation product. For slower reactions or diarylation, use of silver trifluoroacetate instead of silver acetate is beneficial (entries 4, 6, 10, and 11).

SCHEME 2. Removal of Acyl Groups



2. Deprotection. 2,6-Diarylanilines are used in the synthesis of ligands for Brookhart-type transition-metal-catalyzed olefin polymerization.[9] Access to these compounds requires multiple step syntheses from starting materials that may not be readily available.[9,10] If the anilide arylation can be followed by deprotection, a short and efficient pathway to such substances would be possible. We have previously demonstrated that pivalanilides are readily arylated in *ortho* positions under palladium catalysis.[8] However, we were not able to remove the pivalate group from arylated pivalanilides. Less bulky acetate and propionate groups can be removed by using sodium hydroxide in ethanol. Three deprotection reactions were optimized (Scheme 2), representing cases of different steric hindrance. Anilides possessing one *ortho*-substituent can be deprotected in a few hours at 90 °C. Harsher conditions are required for the removal of acyl group from compounds with one *ortho*-aryl and one non-aryl substituent. In this case, 100 °C and extended reaction times are required. The most difficult is the removal of an acyl group from diarylated derivatives. Heating to 130 °C for almost 2 days is required for complete deprotection.

3. Cyclization to Phenanthridines. During the arylation reactions, we observed the formation of minor amounts of a byproduct. The analysis of mass spectra of this byproduct showed the loss of H_2O from the arylated anilide. The molecular weight data and the fragmentation pattern are consistent with the formation of a phenanthridine derivative. Since the first phenanthridine synthesis by Pictet and Ankersmit,[11] many

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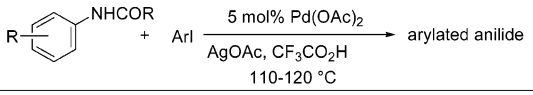
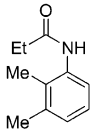
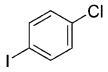
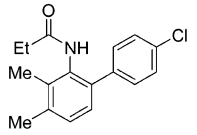
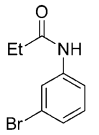
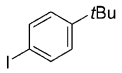
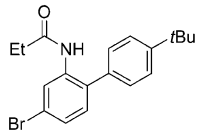
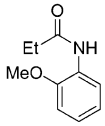
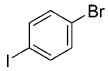
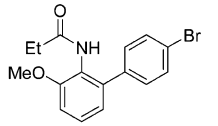
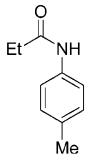
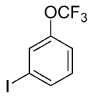
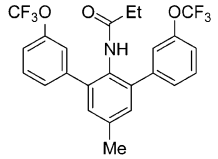
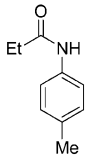
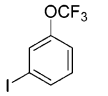
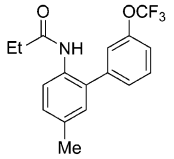
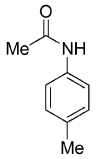
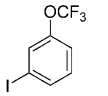
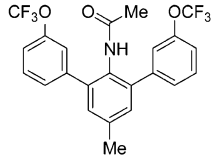
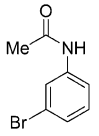
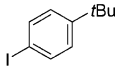
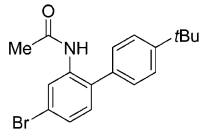
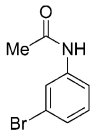
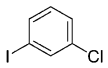
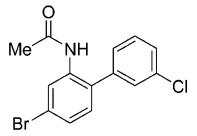
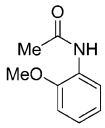
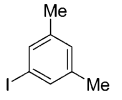
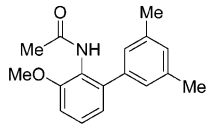
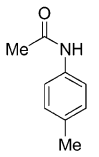
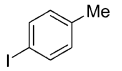
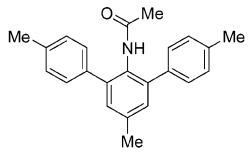
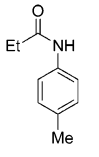
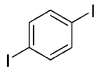
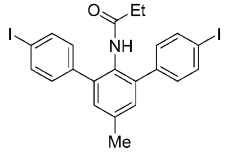
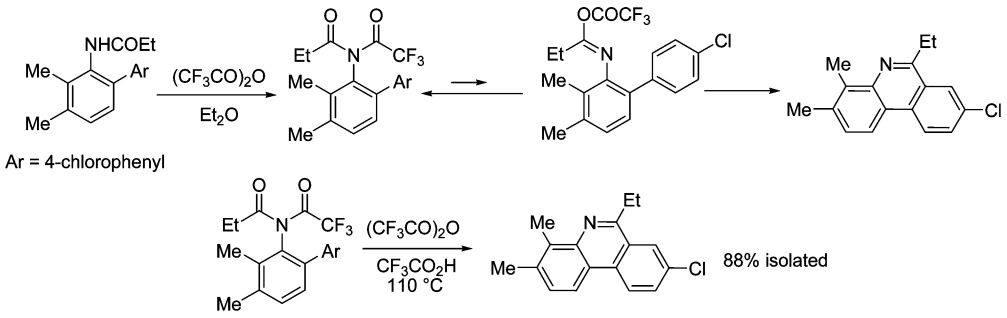
TABLE 1. Arylation of Anilides[a]



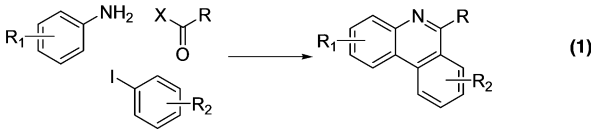
Entry	Amide	Aryl Iodide	Arylated Anilide	Yield
1				96%
2				91%
3				90% 28%[b]
4[c]				79%
5[d]				53%
6[c]				76%
7				82%
8				87%
9				82%
10[c]				74%
11[c]				34%

[a] $Pd(OAc)_2$ (5 mol %), AgOAc (1.3−2.3 equiv), ArI (3−4 equiv), anilide (1 equiv), CF_3CO_2H (0.5 mL), 110−120 °C, 1−8 h. [b] One equivalent of ArI used; conversion by GC reported. [c] Silver trifluoroacetate used instead of silver acetate. [d] CF_3CO_2H−CH_3CO_2H solvent (1:1).

SCHEME 3. Cyclization to Phenanthridines



methods for their construction have been developed.[12] For example, the Bischler−Napieralski-type cyclization has been used extensively for constructing the phenanthridines.[12d] However, most of the known procedures suffer from limited generality, harsh reaction conditions, and the requirement for multistep transformations. We focused on developing a convenient one-pot phenanthridine synthesis that would allow a construction of diversely substituted phenanthridines. Creation of phenanthridine skeleton from aryl iodide and acylated aniline would result in a highly modular synthetic approach (eq 1).



After a short investigation, we discovered that trifluoroacetic anhydride promotes the formation of phenanthridines from the *ortho*-arylated anilides.[13] Moreover, the transformation of arylated anilides to phenanthridines can be accomplished without isolating the intermediate arylation product. Simple addition of trifluoroacetic anhydride followed by heating to 110 °C resulted in formation of the phenanthridines (Table 2).

Phenanthridines containing methoxymethyl (entry 1), trifluoroethyl (entry 6), *N*-alkylphthalimido (entry 7), or various alkyl groups (entries 2−5, and 8) can be obtained. Bulky substituents at position 6 are tolerated (entries 3 and 5). The reaction proceeds well with both electron-poor (entries 1, 6, and 7) and electron-rich (entries 3−5, and 8) anilides. The cyclization step is faster for electron-rich aryl iodides. An X-ray structure of the product of entry 4 in Table 2 was obtained (Figure 1).

We isolated the intermediate formed by the reaction of trifluoroacetic anhydride with the arylated anilide (Scheme 3). Since the NMR spectra were inconclusive, the structure of the trifluoroacetylanilide was verified by X-ray crystallography (Figure 2), proving that *N*-trifluoroacetylation had occurred. It is known that amides are trifluoroacetylated on nitrogen.[14] However, the *N*-trifluoroacetylated derivative may need to exist in equilibrium with the *O*-acylated product in order for the cyclization to occur. The *N*-trifluoroacetylated species is cleanly converted to the phenanthridine upon heating in trifluoroacetic acid/trifluoroacetic anhydride mixture (Scheme 3). If trifluoroacetic anhydride is not added, cyclization is accompanied by partial hydrolysis of the *N*-trifluoroacetylated amide by adventitious water.

Conclusions

We have demonstrated that anilides possessing a number of different acyl groups can be arylated by aryl iodides under palladium catalysis. The arylation reactions proceed in trifluoroacetic acid solvent at 110−120 °C. The method employs stoichiometric silver acetate for iodide removal. Anilides and aryl iodides of all electronic properties are reactive. After the arylation, the anilide acyl group can be removed by base hydrolysis, affording 2-aryl- or 2,6-diarylaniline derivatives

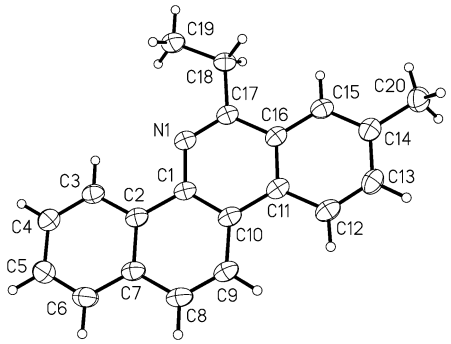


FIGURE 1. ORTEP view of 6-ethyl-8-methylbenzo[*c*]phenanthridine. Thermal ellipsoids are 40% equiprobability envelopes.

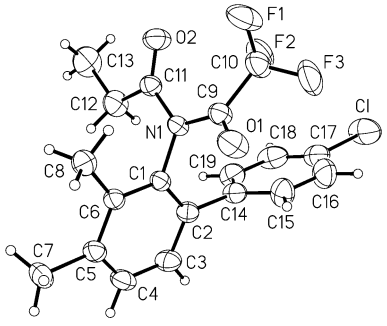


FIGURE 2. ORTEP view of 2-(4-chlorophenyl)-5,6-dimethyl-*N*-propionyl-*N*-trifluoroacetylaniline. Thermal ellipsoids are 40% equiprobability envelopes.

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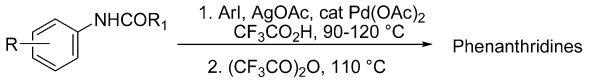
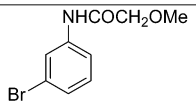
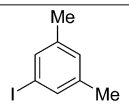
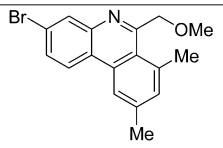
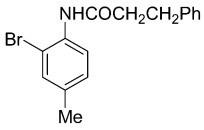
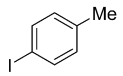
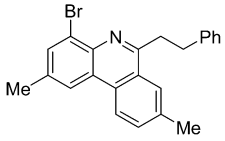
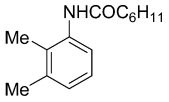
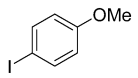
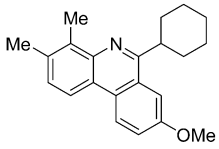
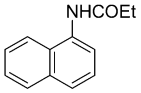
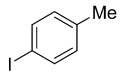
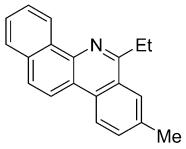
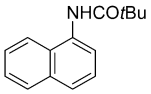
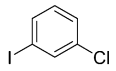
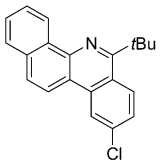
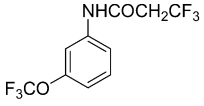
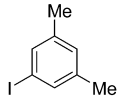
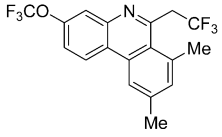
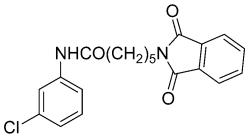
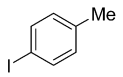
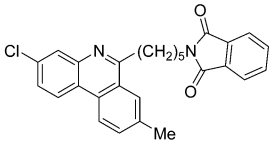
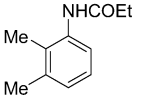
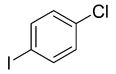
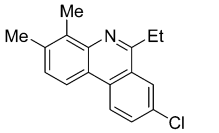
TABLE 2. Phenanthridine Synthesis[a]



Entry	Amide	Aryl Iodide	Phenanthridine	Yield
1				74%
2				68%
3				99%
4				83%
5				54%
6				66%
7				80%
8[b]				93%

[a] Anilide, $Pd(OAc)_2$ (5 mol %), AgOAc (1.3 equiv), ArI (3 equiv), CF_3CO_2H (0.5 mL), 90−120 °C; then add $(CF_3CO)_2O$ (2−3 equiv), 0.5−3 h at 110 °C. Isolated yields reported. [b] Cyclization of isolated 6-(4-chlorophenyl)-2,3-dimethyl-*N*-propionylaniline.

useful for the synthesis of ligands for transition-metal-catalyzed polymerization. The arylated anilides can be converted to phenanthridines by reaction with trifluoroacetic anhydride.

Experimental Section

General Procedure for Arylation of Anilides: A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %), AgOAc (1.3−2.3 equiv), iodide (3.0−4.0 equiv), substrate, and TFA (0.5 mL). The resulting solution was stirred and heated at 110−120 °C. The conversion was monitored by GC. After completion of the reaction, ether was added to the reaction mixture followed by filtration through a pad of Celite. The filtrate was evaporated under reduced pressure, and the residue was dried under vacuum to remove solvent. The residue was purified by flash chromatography.

2-(4-*tert*-Butylphenyl)-5-bromo-*N*-propionylaniline: 3-Bromo-*N*-propionylaniline (160 mg, 0.70 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), AgOAc (152 mg, 0.91 mmol), and 4-*tert*-butyliodobenzene (546 mg, 2.1 mmol) were dissolved in TFA (0.5 mL). Resulting solution was heated for 1.5 h at 110 °C. Purification by flash

chromatography (EtOAc/hexanes 1/9 to 1/6) gave 230 mg (91%) of crystalline material: mp 152−153 °C (EtOAc/hexanes), R_f = 0.45 (EtOAc/hexanes 1/4); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.61 (s, 1H), 7.54−7.48 (m, 2H), 7.31−7.25 (m, 3H), 7.22 (br s, 1H), 7.09 (d, 1H, J = 8.0 Hz), 2.25 (q, 2H, J = 7.5 Hz), 1.37 (s, 9H), 1.12 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 172.0, 151.7, 136.2, 134.2, 131.4, 130.5, 129.0, 127.2, 126.4, 124.0, 122.1, 35.0, 31.5, 31.0, 9.5; FT-IR (neat, cm^{-1}) ν 3250, 1655. Anal. Calcd for $C_{19}H_{22}BrNO$: C, 63.34; H, 6.15; N, 3.89. Found: C, 63.58; H, 6.20; N, 3.81.

4-Methyl-2,6-di-(3-trifluoromethoxyphenyl)-*N*-propionylaniline: 4-Methyl-*N*-propionylaniline (114 mg, 0.70 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), AgO_2CCF_3 (356 mg, 1.61 mmol), and 3-trifluoromethoxyiodobenzene (806 mg, 2.8 mmol) were dissolved in TFA (0.5 mL). Resulting solution was heated for 5.5 h at 120 °C. Purification by flash chromatography (EtOAc/hexanes 1/6) gave 266 mg (79%) of crystalline material: mp 156−157 °C (EtOAc/hexanes), R_f = 0.26 (EtOAc/hexanes 1/4); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.43 (dd, 2H, J = 7.7, 7.7 Hz), 7.36−7.30 (m, 2H), 7.25−7.18 (m, 6H), 6.48 (s, 1H), 2.43 (s, 3H), 1.93 (q, 2H, J = 7.6 Hz), 0.83 (t, 3H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 173.3, 149.1, 141.8, 139.7, 138.1, 131.1, 128.9, 128.8, 127.6, 121.6, 120.7 (q, J_{C-F} = 257.4 Hz), 120.0, 29.6, 21.2, 9.5; FT-IR (neat, cm^{-1}) ν 3220, 1652. Anal. Calcd for $C_{24}H_{19}F_6NO_3$: C, 59.63; H, 3.96; N, 2.90. Found: C, 59.39; H, 3.95; N, 2.92.

4-Methyl-*N*-propionyl-2-(3-trifluoromethoxyphenyl)aniline: 4-Methyl-*N*-propionylaniline (114 mg, 0.70 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), AgOAc (152 mg, 0.91 mmol), and 3-trifluoromethoxyiodobenzene (605 mg, 2.8 mmol) were dissolved in a 1:1 mixture of TFA and AcOH (0.5 mL). Resulting solution was heated for 6 h at 120 °C. Purification by flash chromatography (EtOAc/hexanes 1/6 to 1/2) gave 120 mg (53%) of crystalline material: mp 98.5−99.4 °C (EtOAc/hexanes); R_f = 0.15 (EtOAc/hexanes 1/4); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.07 (d, 1H, J = 8.2 Hz), 7.54−7.47 (m, 1H), 7.34−7.18 (m, 4H), 7.06 (s, 1H), 6.94 (br s, 1H), 2.36 (s, 3H), 2.24 (q, 2H, J = 7.6 Hz), 1.12 (t, 3H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 172.2, 149.6, 140.7, 134.7, 132.1, 131.8, 130.7, 130.5, 129.7, 127.9, 123.2, 121.9, 120.6 (q, J_{C-F} = 257.3 Hz), 120.4, 30.6, 21.0, 9.6; FT-IR (neat, cm^{-1}) ν 3229, 1654. Anal. Calcd for $C_{17}H_{16}F_3NO_2$: C, 63.15; H, 4.99; N, 4.33. Found: C, 63.08; H, 4.98; N, 4.28.

5-Bromo-2-(4-*tert*-butylphenyl)aniline: 5-Bromo-2-(4-*tert*-butylphenyl)-*N*-propionylaniline (80 mg, 0.22 mmol) and sodium hydroxide (44 mg, 1.11 mmol) were dissolved in EtOH (0.5 mL) and heated for 2 h at 90 °C in a closed vessel. After heating was finished, water was added to reaction mixture and the resulting solution was extracted with ether three times. Organic layer was dried over $MgSO_4$. Evaporation of solvent gave 67 mg (>99%) of crystalline material: mp 166−167 °C (EtOAc/hexanes); R_f = 0.62 (EtOAc/hexanes 1/4); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.48−7.42 (m, 2H), 7.36−7.31 (m, 2H), 6.96 (d, 1H, J = 7.7 Hz), 6.93−6.87 (m, 2H), 3.80 (br s, 2H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 150.7, 145.3, 135.7, 131.9, 128.8, 126.7, 126.1, 122.0, 121.6, 118.2, 34.8, 31.6; FT-IR (neat, cm^{-1}) ν 3382, 1615, 1484. Anal. Calcd for $C_{16}H_{18}BrN$: C, 63.17; H, 5.96; N, 4.60. Found: C, 63.32; H, 6.03; N, 4.50.

4-Methyl-2,6-di-(3-trifluoromethoxyphenyl)aniline: 4-Methyl-*N*-propionyl-2-(3-trifluoromethoxyphenyl)aniline (80 mg, 0.16 mmol) and sodium hydroxide (46 mg, 1.16 mmol) were dissolved in EtOH (0.3 mL) and heated for 37 h at 130 °C in a closed vessel. After heating was finished, water was added to reaction mixture and the resulting solution was extracted with ether three times. Organic layer was dried over $MgSO_4$. Evaporation of solvent and purification by flash chromatography (EtOAc/hexanes 1/8) gave 60 mg (85%) of crystalline material: mp 60−61 °C (hexanes); R_f = 0.64 (EtOAc/hexanes 1/4); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.51−7.41 (m, 4H), 7.38 (br s, 2H), 7.24−7.18 (m, 2H), 6.96 (s, 2H), 3.66 (br s, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 149.9, 141.9, 138.3, 131.0, 130.4, 127.9, 126.9, 122.1, 120.8 (q, J_{C-F} = 257.1 Hz), 120.0, 20.5 (signal for one carbon could not be detected); FT-IR (neat, cm^{-1}) ν 3370, 1603, 1250, 1216, 1152. Anal. Calcd for $C_{21}H_{15}F_6NO_2$: C, 59.02; H, 3.54; N, 3.28. Found: C, 59.29; H, 3.56; N, 3.38.

General Procedure for in situ Cyclization of Arylated Anilides: First, a standard procedure for *ortho*-arylation of anilides was performed without isolation of product. The reaction mixture was cooled to room temperature, and trifluoroacetic anhydride (TFAA, 2.0−3.0 equiv) was added. The vial was placed in an oil bath (110 °C) for 0.5−3 h. The conversion was monitored by GC. After completion of reaction, ether was added to reaction mixture and the reaction mixture was filtered through a pad of Celite. Filtrate was washed twice with aqueous $NaHCO_3$. Organic layer was dried over $MgSO_4$. Solvent was removed by evaporation in vacuum, and residue was purified by flash chromatography.

3-Bromo-6-methoxymethyl-7,9-dimethylphenanthridine: 3-Bromo-*N*-(2-methoxyacetyl)aniline (171 mg, 0.7 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), AgOAc (152 mg, 0.91 mmol), and 3,5-dimethyliodobenzene (487 mg, 2.1 mmol) were dissolved in TFA (0.5 mL). Resulting solution was heated for 2.5 h at 120 °C. After cooling to room temperature, trifluoroacetic anhydride (200 μL, 1.4 mmol) was added and reaction mixture was heated for 1.5 h at 110 °C. Filtration of the reaction mixture, basic extraction, and purification by flash chromatography (EtOAc/hexanes 1/10 to 1/5) gave 172 mg (74%) of crystalline material: mp 141−142 °C (EtOH/water); R_f = 0.45 (EtOAc/hexanes 1/4); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.39 (d, 1H, J = 8.9 Hz), 8.30 (d, 1H, J = 2.0 Hz), 8.28 (s, 1H), 7.70 (dd, 1H, J = 8.9, 2.0 Hz), 7.38 (s, 1H), 5.11 (s, 2H), 3.48 (s, 3H), 3.01 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 158.0, 143.8, 140.7, 137.2, 134.9, 134.0, 132.3, 130.2, 124.0, 123.6, 123.4, 122.2, 120.4, 78.4, 58.6, 23.8, 22.0; FT-IR (neat, cm^{-1}) ν 1619, 1596, 1568, 1097. Anal. Calcd for $C_{17}H_{16}BrNO$: C, 61.83; H, 4.88; N, 4.24. Found: C, 61.27; H, 4.81; N, 4.16.

3-Chloro-8-methyl-6-(5-phthalimidopentyl)phenanthridine: 3-Chloro-*N*-(ω-phthalimidocaproyl)aniline (259 mg, 0.7 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), AgOAc (175 mg, 1.05 mmol), and 4-methyliodobenzene (458 mg, 2.1 mmol) were dissolved in TFA (0.5 mL). The solution was heated for 3 h at 120 °C. After cooling to room temperature, trifluoroacetic anhydride (300 μL, 2.1 mmol) was added and reaction mixture was heated for 40 min at 110 °C. Filtration, basic extraction, and purification by flash chromatography (EtOAc/hexanes 1/4 to 1/1) gave 250 mg (80%) of crystalline material: mp 164−165 °C (EtOH/EtOAc); R_f = 0.23 (EtOAc/hexanes 1/4); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.45 (d, 1H, J = 8.5 Hz), 8.40 (d, 1H, J = 8.8 Hz), 8.06 (d, 1H, J = 2.2 Hz), 8.01 (s, 1H), 7.87−7.80 (m, 2H), 7.74−7.68 (m, 2H), 7.66 (dd, 1H, J = 8.5, 1.6 Hz), 7.53 (dd, 1H, J = 8.8, 2.2 Hz), 3.73 (t, 2H, J = 7.2 Hz), 3.36−3.28 (m, 2H), 2.62 (s, 3H), 2.04−1.91 (m, 2H), 1.86−1.74 (m, 2H), 1.65−1.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 168.6, 163.0, 144.3, 137.7, 134.0, 133.7, 132.5, 132.3, 130.4, 128.9, 126.8, 126.0, 125.4, 123.3, 123.2, 122.43, 122.37, 38.1, 36.1, 28.7, 27.2, 22.1 (one aliphatic carbon signal could not be detected); FT-IR (neat, cm^{-1}) ν 1774, 1718, 1396, 1371. Anal. Calcd for $C_{27}H_{23}ClN_2O_2$: C, 73.21; H, 5.23; N, 6.32. Found: C, 72.95; H, 5.24; N, 6.17.

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Supporting Information Available: Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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