

**STUDIES ON THE SELECTIVE INTRAMOLECULAR
BIARYL COUPLING REACTION OF 2-TRIFLYLOXY-
6-HALOBENZANILIDES USING A PALLADIUM REAGENT[†]**

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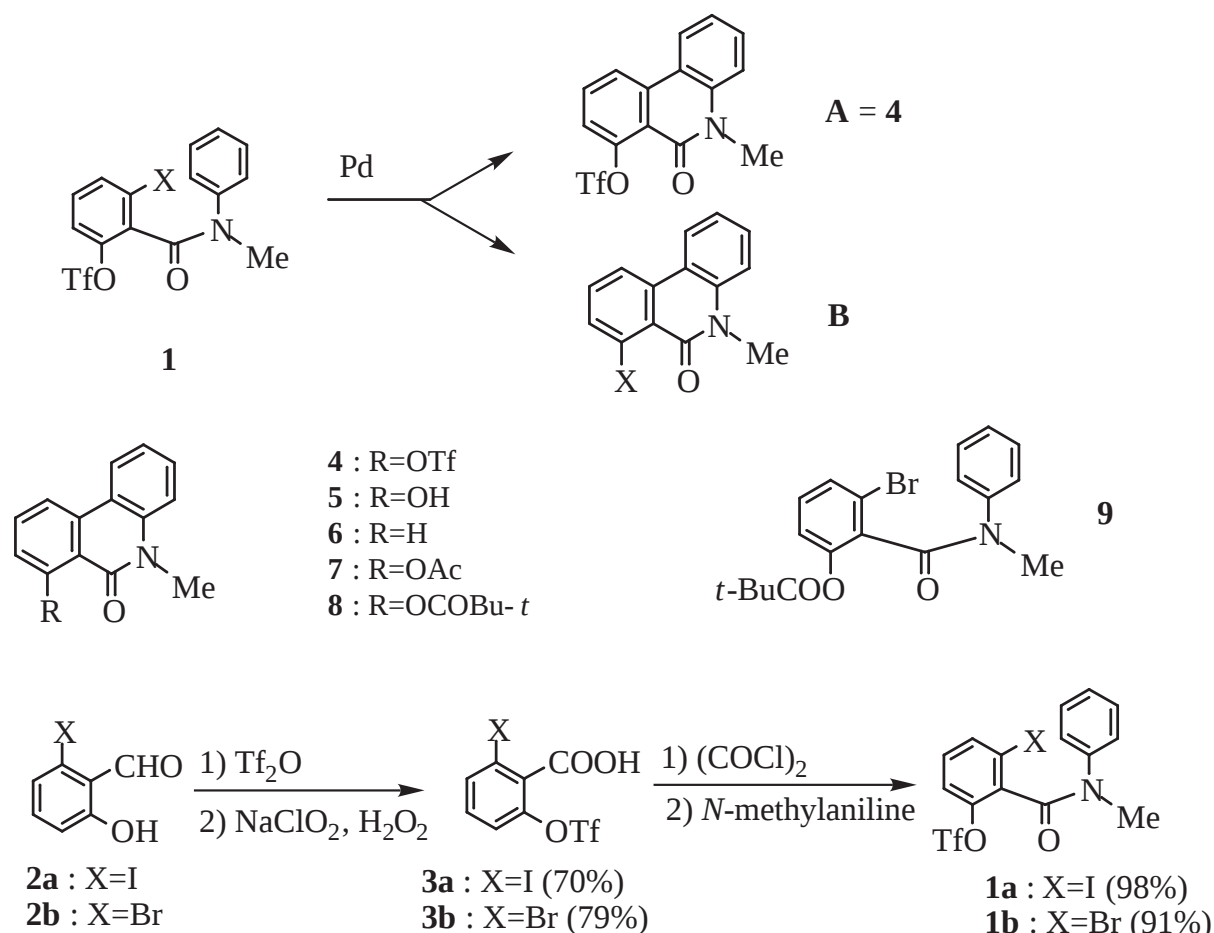
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Abstract-The aryl-aryl coupling reaction of 2-triflyloxy-6-halobenzanilides using a palladium reagent under several reaction conditions was examined. The 6-iodo compound gave triflyloxyphenanthridone selectively in excellent yield under the conditions for the ordinary Heck reaction.

Palladium-assisted aryl-aryl coupling reactions, such as the Heck and Suzuki-Miyaura reactions, have been used to synthesize condensed aromatic compounds.¹ Recently, we found that intramolecular coupling reaction between aromatic halides and arenes using palladium reagents was a very versatile way to synthesize condensed aromatic compounds.^{2,3} Moreover, we reported that a novel palladium reagent prepared from Pd(OAc)₂, 1,3-diphenylphosphinepropane (DPPP), and Bu₃P was suitable for coupling reactions not only between aryl triflates and arenes, but also between aryl halides and arenes.⁴ In order to examine the ability of triflyloxy and halogen groups to be the leaving group in biaryl coupling reactions using this palladium reagent, we investigated the coupling reactions of benzanilides (**1**) possessing both groups on the benzoyl moiety. If each leaving group on **1** can be arbitrarily differentiated under certain reaction conditions, triflyloxyphenanthridone (**A=4**) or halophenanthridone (**B**) can be synthesized selectively. Here, we describe the results of biaryl coupling reactions of **1** in the presence of the palladium reagent under different conditions.

The starting materials, 2-trifluoromethanesulfonyloxy-6-iodo-*N*-methylbenzanilide (**1a**) and 2-bromo-6-trifluoromethanesulfonyloxy-*N*-methylbenzanilide (**1b**), were prepared as shown in Scheme 1. The reaction of 2-hydroxy-6-iodobenzaldehyde (**2a**)⁵ with Tf₂O, followed by oxidation gave iodobenzoic acid (**3a**) in 70% yield. Subsequent treatment of **3a** with oxalyl chloride and *N*-methylaniline afforded **1a** in 98% yield. Benzanilide (**1b**) was synthesized from 2-bromo-6-hydroxybenzaldehyde (**2b**)⁶ via the same reaction sequence in 72% total yield. The biaryl coupling reaction of **1** was examined using the palladium

[†] Dedicated to Professor A. I. Meyers for the celebration of his 70th birthday.



Scheme 1

Table 1. Results of coupling reactions of 2-trifluoromethanesulfonyloxy-6-halo-N-methylbenzanilides (**1**) to phenanthridones in DMF.

run	Pd(OAc) ₂ (eq.)	phosphine (P/Pd) ^{a)}	base ^{b)}	temp.	time	yield (%) ^{c)}				
						4	5	6	7	8
1a	1	0.2	PPh ₃ (2)	Ag ₂ CO ₃	reflux	30 min	92	-	-	-
	2	0.2	PPh ₃ (2)	Ag ₂ CO ₃	rt	26 h	91	-	-	-
	3	1.0	<i>n</i> -Bu ₃ P (1), DPPP (1)	<i>i</i> -Pr ₂ NEt	reflux	30 min	-	11	76	-
	4	1.0	<i>n</i> -Bu ₃ P (1), DPPP (1)	<i>i</i> -Pr ₂ NEt	rt	26 h	57	14	-	-
	5 ^{d)}	0.1	-	AcOK	100°C	30 min	-	29	-	50
	6 ^{d)}	0.1	-	NaOCOCMe ₃	100°C	30 min	-	13	-	75
1b	7 ^{e)}	0.2	PPh ₃ (2)	Ag ₂ CO ₃	reflux	2 h	33	-	-	-
	8	1.0	PPh ₃ (2)	Ag ₂ CO ₃	reflux	45 min	53	24	8	-
	9 ^{f)}	0.2	P(<i>o</i> -Tol) ₃ (2)	Ag ₂ CO ₃	reflux	1 h	30	6	-	-
	10	1.0	P(<i>o</i> -Tol) ₃ (2)	Ag ₂ CO ₃	reflux	2 h	72	9	7	-
	11	1.0	<i>n</i> -Bu ₃ P (1), DPPP (1)	<i>i</i> -Pr ₂ NEt	reflux	45 min	-	6	71	-
	12 ^{g)}	1.0	<i>n</i> -Bu ₃ P (1), DPPP (1)	<i>i</i> -Pr ₂ NEt	rt	48 h	-	-	-	-
	13 ^{d)}	0.1	-	AcOK	100°C	30 min	-	13	-	36
	14 ^{d)}	0.1	-	NaOCOCMe ₃	100°C	30 min	-	15	-	- ^{h)}

^{a)} Molar ratio between phosphine and Pd. ^{b)} 2 Eq. of base was added unless otherwise noted. ^{c)} Isolated yield. ^{d)} 2 Eq. of *n*-Bu₄NCl and 5.5 eq. of base were added. ^{e)} **1b** was recovered in yield of 53%. ^{f)} **1b** was recovered in yield of 37%. ^{g)} **1b** was recovered in yield of 80%. ^{h)} **9** was obtained in yield of 42%.

reagent under several reaction conditions. The results are summarized in Table 1. Reaction of **1a** using the palladium reagent under the ordinary Heck reaction conditions mainly gave the coupling product (**4**) possessing the OTf group, indicating that the iodo group is more reactive than the triflyloxy group (see runs 1, 2 and 4). Using the palladium reagent⁴ prepared from Pd(OAc)₂, DPPP, and Bu₃P, a deoxygenated coupling product (**6**) was obtained in 76% yield (see run 3). The reaction of **1a** under phosphine-free reaction conditions⁸ (see runs 5 and 6) gave products (**7** or **8**) with the OTf group replaced by the RCOO group together with **5**. The reaction of **4** under the same reaction conditions gave the hydrolyzed product (**5**) in 70% yield and no substituted product (**7**).⁸ These facts indicate that the nucleophilic substitution reaction of the triflyloxy group occurred before the biaryl coupling reaction. The reaction of **1b** with equimolar amount of Pd(OAc)₂ and monodentate phosphine ligand gave mainly the coupling product (**4**) (see runs 8 and 10).

In conclusion, the biaryl coupling reaction of 2-triflyloxy-6-halobenzanilides (**1**) using palladium reagent mainly produced **4** possessing the OTf group; especially, **1a** gave **4** exclusively. However, each leaving group on **1** cannot be differentiated arbitrarily.

EXPERIMENTAL

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO A-102 or JASCO FT/IR 350 spectro-photometer and ¹H-NMR spectra in deuteriochloroform on a Hitachi R-1500 (60 MHz) or a Varian VXR-500 (500 MHz) spectrometer unless otherwise stated. NMR data are reported in ppm downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants are given in Hertz. MS spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out on silica gel (Wako gel C-200 or Merck, silica gel 60, No. 9385). All experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous MgSO₄, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. Pd(OAc)₂ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified Pd(OAc)₂.

2-Trifluoromethanesulfonyloxy-6-iodobenzoic acid (**3a**)

To a mixture of 2-hydroxy-6-iodobenzaldehyde (**2a**)⁵ (1.6 g, 6.45 mmol) and dry NEt₃ (1.8 mL, 12.9 mmol) in dry CH₂Cl₂ (30 mL) at 0°C was added triflic anhydride (1.7 mL, 10.1 mmol) in CH₂Cl₂ (10 mL). The whole was stirred for 5 min at the same temperature. The mixture was diluted with CH₂Cl₂ and washed with 1 N HCl, aqueous sat. NaHCO₃ and brine. The residue dissolved in CHCl₃-hexane (1 : 1) was subjected to column chromatography on silica gel. Elution with CHCl₃-hexane (1 : 1) gave 2-trifluoromethanesulfonyloxy-6-iodobenzaldehyde (1.74 g, 71%) as colorless plates (from hexane) mp 59-60.5°C. IR (KBr) cm⁻¹: 1710, 1420, 1140. ¹H-NMR (60 MHz) δ : 7.29-8.14 (3H, m, aromatic protons), 10.07 (1H, s, CHO). *Anal.* Calcd for C₈H₄O₄F₃IS : C, 25.30; H, 1.06. Found : C, 25.37; H, 1.28.

A solution of sodium chlorite (80%; 715 g, 7.91 mmol) in water (5 mL) was added to a stirred mixture of triflate-benzaldehyde (1.0 g, 2.63 mmol) prepared above, sodium phosphate monobasic dihydrate (100 mg, 0.64 mmol), and 31% hydrogen peroxide (0.87 mL, 7.92 mmol) in MeCN (20 mL) and water (3 mL) and

then the whole was stirred at 10°C for 15 h. After the decomposition of excess hydrogen peroxide with 10% aqueous sodium sulfite solution, the mixture was made to acidic with 1 N hydrochloric acid and extracted with ether. The residue was recrystallized from hexane to give **3a** (1.03 g, 99%) as colorless needles, mp 105.5-107°C. IR (KBr) cm^{-1} : 2900, 1720, 1410, 1140. $^1\text{H-NMR}$ (60 MHz) δ : 7.10-7.54 (2H, m, aromatic protons), 7.95 (1H, dd, $J=7$, 2 Hz), 8.33 (1H, s, COOH). *Anal.* Calcd for $\text{C}_8\text{H}_4\text{O}_5\text{F}_3\text{IS}$: C, 24.26; H, 1.02. Found: C, 24.20; H, 1.20.

2-Trifluoromethanesulfonyloxy-6-iodo-*N*-methylbenzanilide (**1a**)

A few drops of dry DMF and oxalyl chloride (0.3 mL, 3.1 mmol) were added to a solution of **3a** (1.0 g, 2.52 mmol) in dry CH_2Cl_2 (20 mL) under ice-cooling and the mixture was refluxed for 2 h. Then the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of *N*-methylaniline (0.7 mL, 6.46 mmol) in dry CH_2Cl_2 (10 mL) and dry NEt_3 (0.45 mL, 3.23 mmol) and the whole was stirred for 1 h at rt. The reaction mixture was concentrated to dryness and diluted with CH_2Cl_2 , then washed with 10% HCl, aqueous sat. NaHCO_3 solution and brine. The residue dissolved in AcOEt-benzene was subjected to column chromatography on silica gel. Elution with AcOEt-hexane (1 : 2) gave **1a** (1.20 g, 98%) as colorless prisms (from ether-hexane) mp 60.5-62.5°C. IR (KBr) cm^{-1} : 1650, 1420, 1140. $^1\text{H-NMR}$ (60 MHz, rotamer) δ : 3.25 (2/7x3H, s, NCH_3), 3.50 (5/7x3H, s, NCH_3), 6.79-8.00 (8H, m, aromatic protons). *Anal.* Calcd for $\text{C}_{15}\text{H}_{11}\text{NO}_4\text{F}_3\text{IS}$: C, 37.10; H, 2.29; N, 2.89. Found: C, 36.94; H, 2.46; N, 2.79.

2-Bromo-6-trifluoromethanesulfonyloxybenzoic acid (**3b**)

To a mixture of 2-bromo-6-hydroxybenzaldehyde (**2b**)⁶ (2.0 g, 9.95 mmol) and dry NEt_3 (2.8 mL, 20.0 mmol) in dry CH_2Cl_2 (20 mL) at 0°C was added triflic anhydride (4.2 g, 14.9 mmol) in CH_2Cl_2 (10 mL). The whole was stirred for 30 min at the same temperature. The mixture was diluted with CH_2Cl_2 and washed with 1 N HCl, aqueous sat. NaHCO_3 and brine. The organic layer was dried over anhydrous MgSO_4 . The residue dissolved in CHCl_3 -hexane (1 : 2) was subjected to column chromatography on silica gel. Elution with CHCl_3 -hexane (1 : 2) gave 2-bromo-6-trifluoromethanesulfonyloxybenzaldehyde (2.83 g, 86%) as colorless plates (from hexane) mp 54-55°C. IR (KBr) cm^{-1} : 1710, 1425, 1135. $^1\text{H-NMR}$ (60 MHz) δ : 7.27-7.85 (3H, m, aromatic protons), 10.36 (1H, s, CHO). *Anal.* Calcd for $\text{C}_8\text{H}_4\text{O}_4\text{BrF}_3\text{S}$: C, 28.85; H, 1.21. Found: C, 28.97; H, 1.45.

A solution of sodium chlorite (80%; 2.03 g, 18.0 mmol) in water (20 mL) was added to a stirred mixture of triflate-benzaldehyde (2.0 g, 6.0 mmol) prepared above, sodium phosphate monobasic dihydrate (234 mg, 1.5 mmol), and 31% hydrogen peroxide (1.8 mL, 18.0 mmol) in MeCN (50 mL) and water (5 mL) and then the whole was stirred at 10°C for 15 h. After the decomposition of excess hydrogen peroxide with 10% aqueous sodium sulfite solution, the mixture was made to acidic with 1 N hydrochloric acid and extracted with ether. The residue was recrystallized from hexane to give **3b** (1.93 g, 92%) as colorless needles, mp 94-95.5°C. IR (KBr) cm^{-1} : 2900, 1715, 1135. $^1\text{H-NMR}$ (60 MHz) δ : 7.37-7.78 (3H, m, aromatic protons), 8.20 (1H, s, COOH). *Anal.* Calcd for $\text{C}_8\text{H}_4\text{BrF}_3\text{O}_5\text{S}$: C, 27.53; H, 1.16. Found: C, 27.80; H, 1.45.

2-Bromo-6-trifluoromethanesulfonyloxy-*N*-methylbenzanilide (**1b**)

A few drops of dry DMF and oxalyl chloride (1.5 mL, 17.2 mmol) were added to a solution of **3b** (3.0 g, 8.59 mmol) in dry CH₂Cl₂ (300 mL) under ice-cooling and the mixture was stirred for 1 h at 10°C. Then the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of *N*-methylaniline (1.1 mL, 10.3 mmol) in dry CH₂Cl₂ (30 mL) and dry NEt₃ (1.6 mL, 11.2 mmol) and the whole was stirred for 5 h at rt. The reaction mixture was concentrated to dryness and diluted with CH₂Cl₂, then washed with 10% HCl, aqueous sat. NaHCO₃ solution and brine. The residue dissolved in AcOEt-hexane (1 : 8) was subjected to column chromatography on silica gel. Elution with AcOEt-hexane (1 : 8) gave **1b** (3.45 g, 91%) as colorless plates (from pet. ether) mp 73.5-75°C. IR (KBr) cm⁻¹: 1665, 1425, 1140. ¹H-NMR (60 MHz, rotamer) δ : 3.25 (1/9H, s, NCH₃), 3.50 (8/9H, s, NCH₃), 7.06-7.52 (8H, m, aromatic protons). *Anal.* Calcd for C₁₅H₁₁NO₄BrF₃S : C, 41.11; H, 2.53; N, 3.53. Found : C, 41.40; H, 2.66; N, 3.16.

General Procedure for the Coupling Reaction of Benzanilides (**1**) (runs 1~4 and 7~10 in Table 1)

The reaction of **1** (0.3 mmol) with Pd(OAc)₂, a phosphine ligand, and a base in dry DMF (8 mL) was carried out using Pd(OAc)₂ and the phosphine ligand in the ratios indicated in Table 1, and 2 mol equivalents of base for the times and temperatures indicated in Table 1. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in hexane-AcOEt (4 : 1) was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (4 : 1) gave 7-hydroxy-5-methylphenanthridin-6(5*H*)-one (**5**) and successive elution with the same solvent gave 5-methylphenanthridin-6(5*H*)-one (**6**)^{2a} and then 7-trifluoromethanesulfonyloxy-5-methylphenanthridin-6(5*H*)-one (**4**).

7-Hydroxy-5-methylphenanthridin-6(5*H*)-one (**5**) : mp 125-127°C (from ether) as colorless needles. IR (CHCl₃) cm⁻¹: 3020, 1635. ¹H-NMR (500 MHz, CDCl₃) δ : 3.75 (3H, s, NCH₃), 7.01(1H, dd, *J*=8.1, 0.9 Hz, C₈-H), 7.34 (1H, ddd, *J*=8.8, 6.7, 1.3 Hz, C₂-H), 7.40 (1H, br d, *J*=8.5 Hz, C₄-H), 7.54 (1H, ddd, *J*=8.5, 6.7, 1.3 Hz, C₃-H), 7.61 (1H, t, *J*=8.1 Hz, C₉-H), 7.67 (1H, dd, *J*=8.1, 0.9 Hz, C₁₀-H), 8.22 (1H, dd, *J*=8.5, 1.3 Hz, C₁-H), 13.32 (1H, s, OH). FAB-MS (positive ion mode) *m/z*: 226 [M+1]⁺. *Anal.* Calcd for C₁₄H₁₁NO₂·1/10H₂O : C, 74.06; H, 4.97; N, 6.17. Found : C, 73.86; H, 5.14; N, 5.97.

5-Methylphenanthridin-6(5*H*)-one (**6**) : mp 109-110.5°C (from hexane) as colorless needles. The synthetic sample was identified with the authentic sample.^{2a}

7-Trifluoromethanesulfonyloxy-5-methylphenanthridin-6(5*H*)-one (**4**) : mp 155-156.5°C (from CHCl₃-hexane) as colorless needles. IR (KBr) cm⁻¹: 1650, 1425, 1150. ¹H-NMR (500 MHz, CDCl₃) δ : 3.79 (3H, s, NCH₃), 7.34 (1H, t, *J*=8.1 Hz, C₂-H), 7.37 (1H, d, *J*=8.1 Hz, C₄-H), 7.41 (1H, br. d, *J*=8.2 Hz, C₈-H), 7.60 (1H, td, *J*=8.1, 1.3 Hz, C₃-H), 7.78 (1H, t, *J*=8.2 Hz, C₉-H), 8.24 (1H, dd, *J*=8.2, 0.8 Hz, C₁₀-H), 8.34 (1H, br. d, *J*=8.1 Hz, C₁-H). *Anal.* Calcd for C₁₅H₁₀NO₄F₃S : C, 50.42; H, 2.82; N, 3.92. Found : C, 50.57; H, 3.10; N, 3.97.

General Procedure for the Coupling Reaction of Benzanilides (**1**) in the Presence of

Palladium under Phosphine-free Conditions (runs 5, 6, 11, and 12 in Table 1)

The reaction of **1** (0.3 mmol) with 0.1 equivalent of Pd(OAc)₂, 2 equivalents of *n*-Bu₄NCl, and 5.5 equivalents of base in dry DMF (8 mL) was carried out for the times indicated in Table 1 at 100°C. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in CHCl₃ was subjected to column chromatography on a silica gel. Elution with hexane-AcOEt (4 : 1) gave 7-hydroxy-5-methylphenanthridin-6(5*H*)-one (**5**) and successive elution with the same solvent gave 7-acetoxy-5-methylphenanthridin-6(5*H*)-one (**7**) or 5-methyl-7-pivaloyloxyphenanthridin-6(5*H*)-one (**8**). In the cases of **1b** using sodium pivalate as base, elution with hexane-AcOEt (4 : 1) gave **5** and successive elution gave 2-bromo-*N*-methyl-6-pivaloyloxybenzanilide (**9**). 7-Acetoxy-5-methylphenanthridin-6(5*H*)-one (**7**) : mp 140.5-142°C, colorless needles (from ether). IR (CHCl₃) cm⁻¹: 1760, 1635. ¹H-NMR (500 MHz) δ : 2.49 (3H, s, OCOCH₃), 3.72 (3H, s, NCH₃), 7.20 (1H, dd, *J*=8.0, 1.2 Hz, C₈-H), 7.30 (1H, ddd, *J*=8.3, 7.0, 0.8 Hz, C₂-H), 7.36 (1H, br d, *J*=8.5 Hz, C₄-H), 7.54 (1H, ddd, *J*=8.5, 7.0, 1.5 Hz, C₃-H), 7.73 (1H, t, *J*=8.0 Hz, C₉-H), 8.20 (1H, dd, *J*=8.0, 1.2 Hz, C₁₀-H), 8.24 (1H, dd, *J*=8.3, 1.5 Hz, C₁-H). *Anal.* Calcd for C₁₆H₁₃NO₃ : C, 71.90; H, 4.90; N, 5.24. Found : C, 71.77; H, 5.19; N, 5.19.

5-Methyl-7-pivaloyloxyphenanthridin-6(5*H*)-one (**8**) : 129.5-131°C, colorless prisms (from ether). IR (KBr) cm⁻¹: 1740, 1650. ¹H-NMR (500 MHz) δ : 1.49 (9H, s, C(CH₃)₃), 3.70 (3H, s, NCH₃), 7.13 (1H, dd, *J*=7.9, 0.8 Hz, C₈-H), 7.28 (1H, ddd, *J*=8.5, 6.7, 1.3 Hz, C₂-H), 7.34 (1H, br. d, *J*=8.5 Hz, C₄-H), 7.53 (1H, ddd, *J*=8.5, 6.7, 1.3 Hz, C₃-H), 7.71 (1H, t, *J*=7.9 Hz, C₉-H), 8.19 (1H, br d, *J*=7.9 Hz, C₁₀-H), 8.24 (1H, dd, *J*=8.5, 1.3 Hz, C₁-H). *Anal.* Calcd for C₁₉H₁₉NO₃ : C, 73.77; H, 6.19; N, 4.53. Found : C, 73.73; H, 6.30; N, 4.50.

2-Bromo-6-pivaloyloxy-*N*-methylbenzanilide (**9**) : mp 124-125.5°C, colorless needles (from ether-hexane). IR (CHCl₃) cm⁻¹: 1750, 1640. ¹H-NMR (500 MHz, rotamer) δ : 1.35 and 1.39 (total 9H, s, C(CH₃)₃), 3.21 and 3.47 (total 3H, s, NCH₃), 6.99-7.51 (total 8H, m, aromatic protons). *Anal.* Calcd for C₁₉H₂₀NO₃Br : C, 58.47; H, 5.17; N, 3.59. Found : C, 58.61; H, 5.35; N, 3.48.

Treatment of Triflyloxyphenanthridone (**4**) with Palladium under Phosphine-free Conditions

A mixture of **4** (100 mg, 1.4 mmol), Pd(OAc)₂ (10 mg, 0.03 mmol), *n*-Bu₄NCl (170 mg, 0.6 mmol), and AcOK (160 mg, 1.65 mmol) in dry DMF (10 mL) was heated for 2 h at 100°C. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in CHCl₃ was subjected to column chromatography on a silica gel. Elution with hexane-AcOEt (4: 1) gave **5** (44 mg, 70%) and successive elution with the same solvent gave the starting material (**4**) (28 mg, 28%). These samples were identified using the respective authentic samples.

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- 8 Treatment of **1a** with AcOK in the presence of *n*-Bu₄NCl in dry DMF for 30 min at 100°C afforded 2-acetoxy-6-iodo-*N*-methylbenzanilide and 2-hydroxy-6-iodo-*N*-methylbenzanilide in yields of 44% and 44%, respectively.