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BIARYL COUPLING REACTIONS OF 3-METHOXY-*N*-(2-IODOPHENYL)-*N*-METHYLBENZAMIDE AND 3-METHOXYCARBONYL-*N*-(2-IODOPHENYL)-*N*-METHYLBENZAMIDE USING PALLADIUM REAGENT

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Abstract – We examined palladium-assisted biaryl coupling reactions of 3-methoxy and 3-methoxycarbonyl benzanilides, and propose an aspect of the mechanism involved in forming a biaryl bond using Pd reagent.

Palladium-assisted biaryl coupling reactions have been used to synthesize many polycyclic aromatic compounds.[1] Recently, we reported that an intramolecular biaryl coupling reaction of 2-halo-*N*-arylbenzamides using palladium reagents was a convenient, versatile method for synthesizing condensed aromatic lactams, some of which can be transformed into polycyclic aromatic alkaloids.[2] Moreover, we successfully synthesized benzonaphthazepine, a new skeletal compound, and pyrrolophenanthridine (Amaryllidaceae) alkaloids, utilizing a Pd-assisted biaryl coupling reaction with regioselective C–H activation *via* the intramolecular coordination of an amine to Pd.[3] Subsequently, we applied the biaryl coupling reaction using Pd to the synthesis of quinazoline alkaloids[4] and graphislactones.[5]

Buchwald *et al*. recently proposed three possible mechanisms for the formation of oxindole from α-chloroacetanilide *via* Pd-catalyzed C–H functionalization: electrophilic substitution, carbopalladation (Heck-type reaction), and C–H activation.[6] Considering Buchwald *et al*.'s proposal, the three reaction mechanisms for the formation of the biaryl bond using Pd, as shown in Chart 1, would be possible.[7]

To determine some of the mechanistic aspects of the Pd-mediated biaryl coupling reaction, we examined cyclization reactions of 3-methoxy-*N*-(2-iodophenyl)-*N*-methylbenzamide (**1a**), which possesses an

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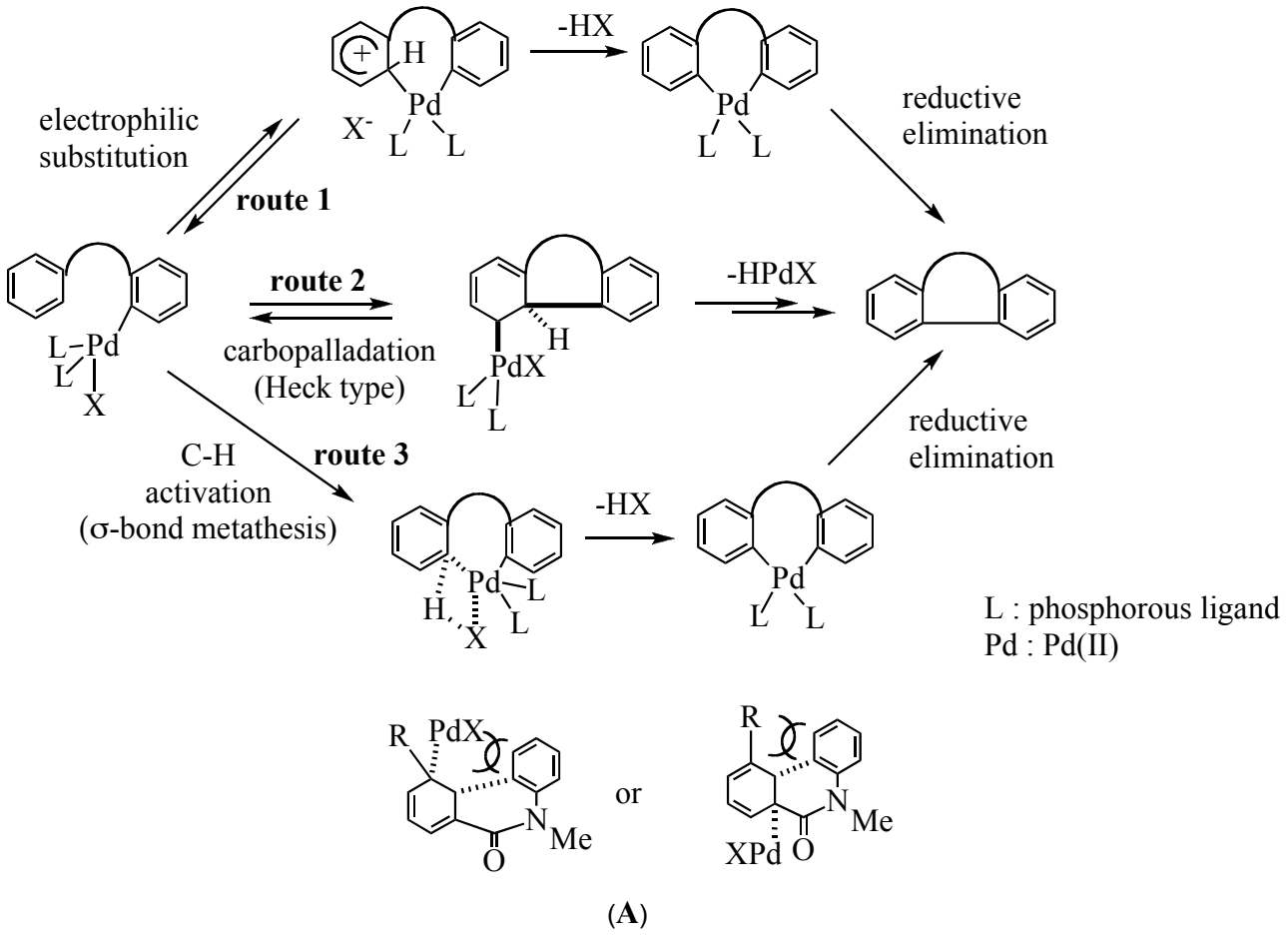
This paper is dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

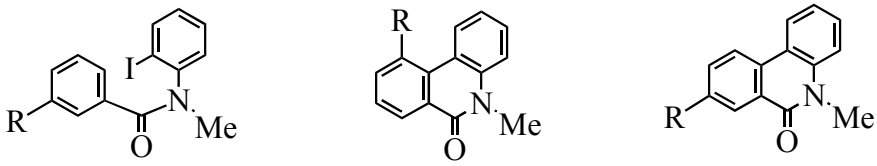
electron-donating group on the benzoyl part, and 3-methoxycarboyl-*N*-(2-iodophenyl)-*N*-methylbenzamide (**1b**), which possesses an electron-withdrawing group on the benzoyl part, under several reaction conditions using 0.1 eq of $Pd(OAc)_2$, 0.2 eq of PPh_3, and 2 eq of K_2CO_3 in DMF. The starting materials (**1**) for the coupling reaction were prepared from the appropriate benzoic acids and 2-iodoanilines. Successive treatment of 3-methoxybenzoic acid with oxalyl chloride and 2-iodoaniline produced the amide (**4**), which was methylated with methyl iodide to afford **1a**. The amidation of 3-methoxycarbonylbenzoic acid with 2-iodo-*N*-methylaniline[8] gave **1b**.



(**A**)

Chart 1

The results of coupling reactions at several reaction temperatures are summarized in Table 1 and show that the reaction time of **1a** and **1b** until the completion of coupling reaction is not influenced by the electronic character of the substituents, whereas the substituent effect on the regioselectivity in biaryl coupling reaction is observed. Since, in the classical aromatic electrophilic substitution mechanism (route 1), electron donating groups should increase the rate of reaction, this result indicates that the biaryl coupling reaction using Pd reagent would not proceed *via* the classical aromatic electrophilic substitution process such as route 1, although reports related with electrophilic substitution mechanism have been presented.[1f, 9, 10]



1 **2** **3**

a : R =OMe **b** : R =COOMe

Table 1. Results of coupling reaction of benzanilides (**1**) to phenanthridones (**2** and **3**)[a)]

substance	temp. (˚C)	time (h)	yield	ratio[b)] **2** : **3**
1a	reflux	0.15	93	1.0 : 1
	100	0.25	92	0.81 : 1
	50	5.5	92	0.67 : 1
1b	reflux	0.15	78	0.3 : 1
	100	0.5	qunat	0.16 : 1
	50	5.0	quant	0.10 : 1

a) All reactions were carried out in DMF using 0.1 eq of $Pd(OAc)_2$, 0.2 eq. of PPh_3, and 2 eq of K_2CO_3 unde argon atmosphere.
b) Determined by HPLC and NMR analysis.

The Heck-type reaction process should usually proceed *via cis* addition and *syn*-β-elimination. Therefore, since route 2 would be less likely,[7a] an alternative mechanism involving *anti*-elimination or isomerization and *syn*-elimination was proposed.[11] In our case, when the biaryl coupling reaction proceeds *via* the Heck-type process, such as route 2, we postulated that the *para*-product (**3**) would always be the major product because of the steric repulsion in the intermediate group (**A**), regardless of the character of the substituent group. However, we found that the substituent can affect the ratio of the product of the biaryl coupling reaction,[12] and therefore postulated that route 2 is a less plausible mechanism for the Pd-mediated arylation of aromatics. We thus propose that formation of the biaryl bond proceeds *via* a C–H activation process (route 3).

Detailed investigations of the substituent effect on the regioselectivity of Pd-mediated biaryl coupling are now in progress, although we have reported a tentative mechanism for the reaction.[12]

EXPERIMENTAL

Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO FT/IR 350 spectrophotometer and ^{1}H-NMR spectra in deuteriochloroform on Varian Mercury 300 or VXR-500 spectrometers. NMR spectral data are reported in parts per million downfield from tetramethylsilane as the internal standard (δ 0.0), and the coupling constants are given in Hertz. MS spectra were obtained on a VG-70SE. Analytical HPLC was performed

with a Shimadzu SPD-6A on a silica gel column (Chemcosorb 5Si-U). Column chromatography was carried out on a Merck silica gel (230–400 mesh). All the extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered; the filtrate was concentrated to dryness under reduced pressure. $Pd(OAc)_2$ was treated with boiling benzene, and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

***N*-(2-Iodophenyl)-3-methoxybenzamide (4)**

A few drops of dry DMF and oxalyl chloride (0.60 mL, 6.57 mmol) were added to a solution of 3-methoxybenzoic acid (500 mg, 3.29 mmol) in dry CH_2Cl_2 (25 mL) and the mixture was stirred for 3 h under ice cooling. Then, the reaction mixture was concentrated to dryness under reduced pressure. A solution of 2-iodoaniline (720 mg, 3.29 mmol) in dry CH_2Cl_2 (15 mL) and dry NEt_3 (0.55 g, 3.94 mmol) was added to this residue and the whole was stirred for 3 h at rt. The reaction mixture was concentrated to dryness, diluted with $CHCl_3$, and then washed with 10% HCl, aqueous 5% NaOH solution, and brine. The residue in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (4:1) gave **4** (836 mg, 72%) as colorless needles (from Et_2O), mp 94–95.5˚C. IR (KBr) cm^{-1}: 3270, 1650, 1520. ^{1}H-NMR (500 MHz) δ : 3.89 (3H, s), 6.89 (1H, dd, *J*=8.0, 1.5 Hz), 7.12 (1H, ddd, *J*=8.0, 2.0, 1.0 Hz), 7.41 (1H, ddd, *J*=8.0, 8.0, 1.5 Hz), 7.43 (1H, dd, *J*=8.0, 8.0 Hz), 8.29 (1H, br s), 8.45 (1H, dd, *J*=8.0, 1.5 Hz). *Anal*. Calcd for $C_{14}H_{12}NO_2I$: C, 47.61; H, 3.43; N, 3.97. Found : C, 47.62; H, 3.35; N, 3.84.

***N*-(2-Iodophenyl)-3-methoxy-*N*-methylbenzamide (1a)**

Methyl iodide (0.84 mL, 12.75 mmol) was added to a suspension of **4** (3. 0g, 8.49 mmol) and NaH (60%, 1.02 g, 25.47 mmol) in dry DMF (90 mL). After stirring for 15 min at rt, the excess NaH was decomposed with ice water, and extracted with AcOEt. The organic layer was washed with brine. The residue in AcOEt was subjected to column chromatography on a silica gel. Elution with hexane:AcOEt (1:1) gave **1a** (2.78 g, 89%) as colorless prisms (from Et_2O), mp 105–106˚C. IR (KBr) cm^{-1}: 1635. ^{1}H-NMR (500 MHz) δ : 3.38 (3H, s), 3.67 (3H, s), 6.77 (1H, dd, *J*=7.8, 2.0 Hz), 6.89-6.95 (3H, m), 7.04-7.08 (2H, m), 7.21 (1H, dd, *J*=7.0, 7.0 Hz), 7.82 (1H, br d, *J*=7.8 Hz). *Anal*. Calcd for $C_{15}H_{14}NO_2I$: C, 49.07; H, 3.84; N, 3.82. Found : C, 49.21; H, 4.01; N, 3.66.

3-Carbomethoxy-*N*-(2-iodophenyl)-*N*-methylbenzamide (Methyl 3-[*N*-(2-Iodophenyl)-*N*-methylcarbamoyl]benzoate) (1b)

A mixture of 3-methoxycarbonylbenzoic acid (4.00 g, 22.0 mmol) in a few drops of dry DMF and thionyl chloride (2.40 mL, 33.0 mmol) was first refluxed for 15 min and then concentrated to dryness under reduced pressure. A solution of 2-iodo-*N*-methylaniline[12] (5.10 g, 22.0 mmol) in dry CH_2Cl_2 (26 mL) and dry NEt_3 (3.70 mL, 26.4 mmol) was added to this residue and the whole was stirred for 1 h at rt. The reaction mixture was concentrated to dryness and diluted with AcOEt, and then washed with 10% HCl and brine. The residue in $CHCl_3$ was subjected to column chromatography on silica gel. The elution with

hexane:AcOEt (2:1) gave **1b** (7.39 g, 85%) as colorless needles (from hexane-AcOEt), mp 85–87˚C. IR (KBr) cm^{-1}: 1720, 1645. ^{1}H-NMR (500 MHz) δ : 3.39 (3H, s), 3.86 (3H, s), 6.90 (1H, br t, *J*=7.5 Hz), 7.14 (1H, br d, *J*=7.5 Hz), 7.22-7.26 (2H, m), 7.56 (1H, br d, *J*=7.5 Hz), 7.78 (1H, br d, *J*=7.5 Hz), 7.90(1H, br d, *J*=7.5 Hz), 8.07 (1H, br s). *Anal*. Calcd for $C_{16}H_{14}NO_5I$: C, 48.63; H, 3.57; N, 3.54. Found : C, 48.86; H, 3.66; N, 3.34.

General Procedure for the Coupling Reaction of Phenylbenzamides (1)

Phenylbenzamide (**1**) (0.2 mmol) was reacted with $Pd(OAc)_2$ (4.5 mg, 20 mol%), triphenylphosphine (10.5 mg, 40 mol%), and K_2CO_3 (55.3 mg, 400 mol%) in dry DMF (2 mL) at the temperatures and for the times indicated in Table 1. Then, the reaction mixture was diluted with AcOEt, and the precipitates were removed by filtration. The filtrate was washed with brine.

Biaryl Coupling Reaction of 3-Methoxy-*N*-(2-iodophenyl)-*N*-methylbenzamide (1a)

The residue was dissolved in $CHCl_3$ and was subjected to column chromatography on silica gel. Elution with hexane:isopropyl ether (2:1) gave 5-methyl-10-methoxyphenanthridin-6(5*H*)-one (**2a**) and successive elution with the same solvent gave 5-methyl-8-methoxyphenanthridin-6(5*H*)-one (**3a**)

5-Methyl-10-methoxyphenanthridin-6(5*H*)-one (2a) : colorless prisms (from Et_2O), mp 167.5-168.5˚C. IR (KBr) cm^{-1}: 1730. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.83 (3H, s), 4.09 (3H, s), 7.30 (2H, m), 7.31 (1H, dd, *J*=8.5, 1.0 Hz), 7.54 (1H, ddd, *J*=8.5, 7.3, 1.0 Hz), 7.54 (1H, dd, *J*=7.5, 7.3 Hz), 8.28 (1H, dd, *J*=7.5, 1.0 Hz), 9.30 (1H, dd, *J*=8.5, 1.0 Hz). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N,5.85. Found: C, 75.30; H, 5.82; N, 5.81.

5-Methyl-10-methoxyphenanthridin-6(5*H*)-one (3a) : colorless needles (from hexane), mp 133-135˚C. (lit.[13] 134-135.5˚C)

Biaryl Coupling Reaction of Methyl 3-[*N*-(2-Iodophenyl)-*N*-methylcarbamoyl]benzoate (1b)

The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. Elution with $CHCl_3$:acetone (30:1) gave a mixture of coupling products, which was separated by preparative thin layer chromatography using $CHCl_3$. The upper zone gave 10-methoxycarbonyl-5-methylphenanthridin-6(5*H*)-one (**2b**) and the lower zone gave 8-methoxycarbonyl-5-methylphenanthridin-6(5*H*)-one (**3b**).

10-Methoxycarbonyl-5-methylphenanthridin-6(5*H*)-one (2b) : colorless needles (from AcOEt), mp 154-155˚C. IR (KBr) cm^{-1}: 1720, 1650. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.81 (3H, s), 3.96 (3H, s), 7.24 (1H, ddd, *J*=7.8, 7.2, 1.2 Hz), 7.44 (1H, dd, *J*=8.4, 1.2 Hz), 7.56 (1H, ddd, *J*=8.4, 7.2, 1.5 Hz), 7.61 (1H, dd, *J*=7.5, 7.5 Hz), 7.79 (1H, dd, *J*=7.5, 1.2 Hz), 7.88 (1H, dd, *J*=7.5, 1.2 Hz), 8.68 (1H, dd, *J*=7.8, 1.5 Hz). High resolution MS (FAB) *m/z* : Calcd for $C_{16}H_{14}NO_3$ $[M+1]^+$: 268.0974. Found: 268.0999.

8-Methoxycarbonyl-5-methylphenanthridin-6(5*H*)-one (3b) : colorless needles (from $CHCl_3$-hexane), mp 211-213˚C. IR (KBr) cm^{-1}: 1720, 1650. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.84 (3H, s), 4.00 (3H, s), 7.36 (1H, ddd, *J*=7.2, 6.9, 1.5 Hz), 7.45 (1H, dd, *J*=8.7, 0.9 Hz), 7.62 (1H, ddd, *J*=7.2, 6.9, 1.5 Hz),

8.30-8.35 (2H, m), 8.39 (1H, dd, *J*=8.7, 1.8 Hz), 9.21 (1H, dd, *J*=1.8, 0.9 Hz).. *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N,5.24. Found: C, 71.72; H, 4.96; N, 5.37.

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