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ARYL-ARYL COUPLING REACTION CATALYZED BY A PALLADIUM REAGENT PREPARED FROM $Pd(OAc)_2$ AND $n\text{-}Bu_3P$†

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Abstract - A palladium reagent prepared from $Pd(OAc)_2$ (0.2 eq) and $n\text{-}Bu_3P$ (0.6 eq) catalyzed an aryl-aryl coupling reaction. This procedure is effective for coupling reactions of aryl triflate possessing no oxygen groups with arene, and of aryl iodide with arene.

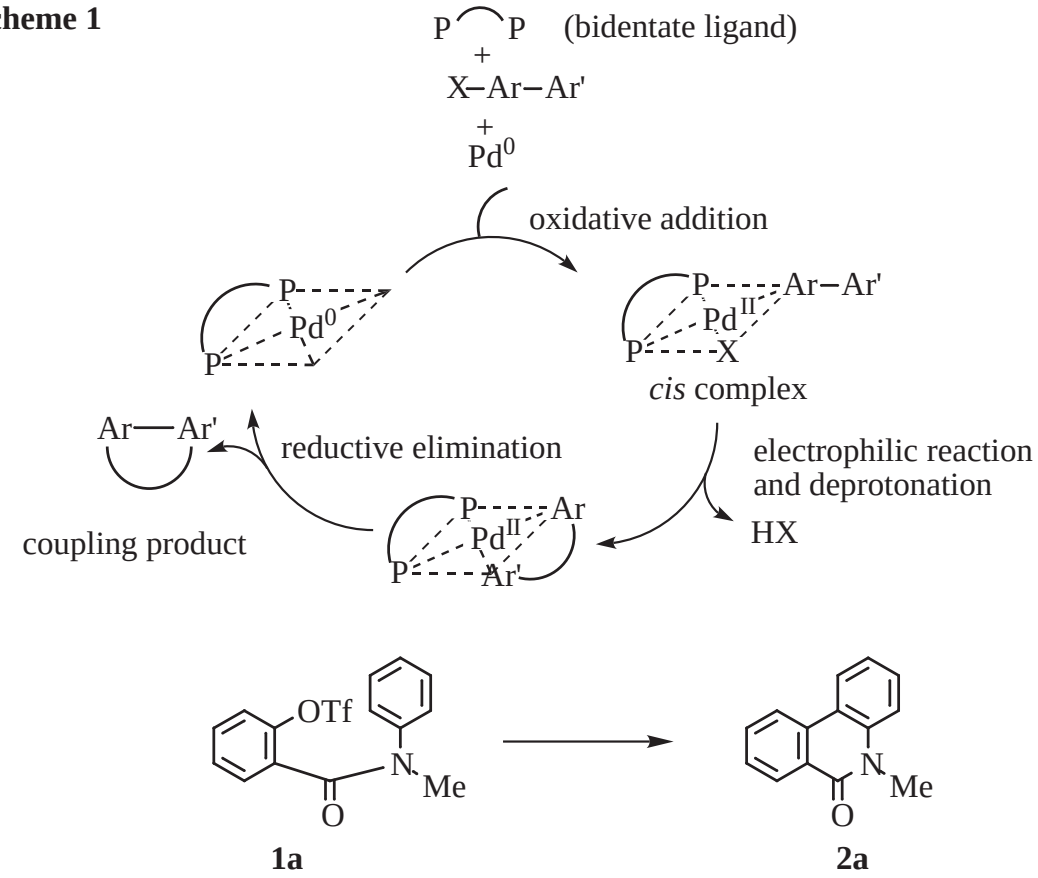
In our studies of the synthesis of fully aromatized benzo[*c*]phenanthridine alkaloids, we found that a novel Pd reagent prepared from $Pd(OAc)_2$, a bidentate ligand DPPP, and $n\text{-}Bu_3P$ was very versatile for coupling reactions between aromatic triflate and arene.[1] We synthesized several benzo[*c*]phenanthridine alkaloids, using this novel method for intramolecular biaryl coupling reactions, not only between aryl triflates and arenes, but also between aryl halides and arenes.[2] However, a stoichiometric amount of palladium reagent was usually required to obtain a coupling product between an aromatic triflate and arene in a high and satisfactory yield, although the cyclization reaction proceeded even in the presence of 0.3 eq of $Pd(OAc)_2$ if a few equivalents of phosphine ligand were used.[1] We investigated the catalytic ability of this method. Here, we describe our examination of the reaction conditions for biaryl coupling reactions including aryl triflate and arene, and aryl halide and arene, using a catalytic amount of Pd reagent.

As previously reported,[1] we speculated that a biaryl coupling process[3] (electrophilic reaction of palladium(II) complex with aryl ring, deprotonation, and reductive elimination of palladium) proceeds more easily when using a bidentate ligand, because there is an obligatory *cis* arrangement, in contrast to the *trans* arrangement of monodentate ligands in the complex[4] (see Scheme 1), and because they are less bulky due to a smaller cone angle.[5] Several bidentate ligands were effective for intramolecular coupling reactions between aryl triflate and arene[1b] and *N*-ethyldiisopropylamine ($^{i}Pr_2NEt$) was superior to silver carbonate as the base in the coupling reaction of aryl triflate (**Ia**) and arene[1b] (see runs 1 and 5 in Table 1). However, even when using $^{i}Pr_2NEt$, a stoichiometric amount of palladium reagent was still required to get a coupling product in an excellent yield (see runs 5-8 in Table 1). Since a monodentate ligand coordinates to a

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

square-planer palladium complex in a *trans* manner,[4] the coupling reaction process might be sluggish. Surprisingly, on using monodentate ligands, such as PPh_3 and P(*o*-Tol)$_3$, in addition to equimolar $Pd(OAc)_2$ and n-Bu_3P, reaction proceeded quickly with very high yield (see runs 9 and 10 in Table 1). Then, we postulated the the mechanism of the monodentate ligand shown in Scheme 2. Thus, monodentate ligands co-ordinate to palladium to form a *trans* complex and then isomerize to a *cis* complex to yield the biaryl coupling product *via* three steps process mentioned above.

Scheme 1



1a **2a**

Table 1. Results of coupling reactions of 2-[(trifluoromethanesulfonyl)oxy]-*N*-methyl-*N*-phenylbenzamide (**1a**) to *N*-methylphenanthridone (**2a**) in DMF under reflux

run	$Pd(OAc)_2$ (eq.)	n-Bu_3P (eq.)	ligand (L/Pd)[b]		base[c]	time	yield (%) **2a**	yield (%) **1a**
1[a]	1.0	1.0	DPPP	(1)	Ag_2CO_3	5 h	93	—
2[a]	0.3	0.3	DPPP	(1)	Ag_2CO_3	100 h	26	61
3[a]	0.3	1.0	DPPP	(1)	Ag_2CO_3	55 h	58	15
4[a]	0.3	3.0	DPPP	(1)	Ag_2CO_3	2 h	71	—
5[a]	1.0	1.0	DPPP	(1)	$^iPr_2NEt$	30 min	92	—
6	1.0	—	DPPP	(1)	$^iPr_2NEt$	4 h	15	59
7	0.2	0.2	DPPP	(1)	$^iPr_2NEt$	4 h	42	56
8	0.5	0.5	DPPP	(1)	$^iPr_2NEt$	3 h	72	6
9	1.0	1.0	PPh_3	(2)	$^iPr_2NEt$	30 min	82	—
10	1.0	1.0	P(*o*-Tol)$_3$	(2)	$^iPr_2NEt$	30 min	97	—

a) See reference 1. b) Molar ratio between ligand and Pd. c) Two mol equivalents of base were added.

Therefore, the coupling reaction[6] using a three molar ratio between Pd and the ligand was examined, and the results are given in Table 2. Of note, a highly active Pd reagent[7] prepared from $Pd(OAc)_2$ (0.2 eq) and n-Bu_3P (0.6 eq) catalyzed the reaction to provide the expected product in high yield (see run 4 in Table 2). This procedure was applied to the coupling reaction of benzanilides (**1b-f**) and naphthylamides (**3**) (see Tables 3 and 4). In the case of aryl triflates (**1b**, **3a**, and **3b**) possessing oxygen substituents and bromo amides (**1d** and **1f**), the expected product was obtained in poor to moderate yields in comparison with **1a**. However, this procedure was effective for the coupling reaction of iodo amides (**1c**, **1e** and **3c-f**) and **3c-f** provided benzo[*c*]phenanthridines (**3**) in high yield along with naphthobenzoazepinones (**5**). Synthetic samples (**4**, **5e**, and **5f**) were identified with the corresponding authentic samples.[8] The structures of the products (**5c** and **5d**) were elucidated from spectral data, especially ^{1}H-NMR data, in which **5c** showed only one singlet signal due to an aromatic proton and **5d** showed three singlet signals

Scheme 2

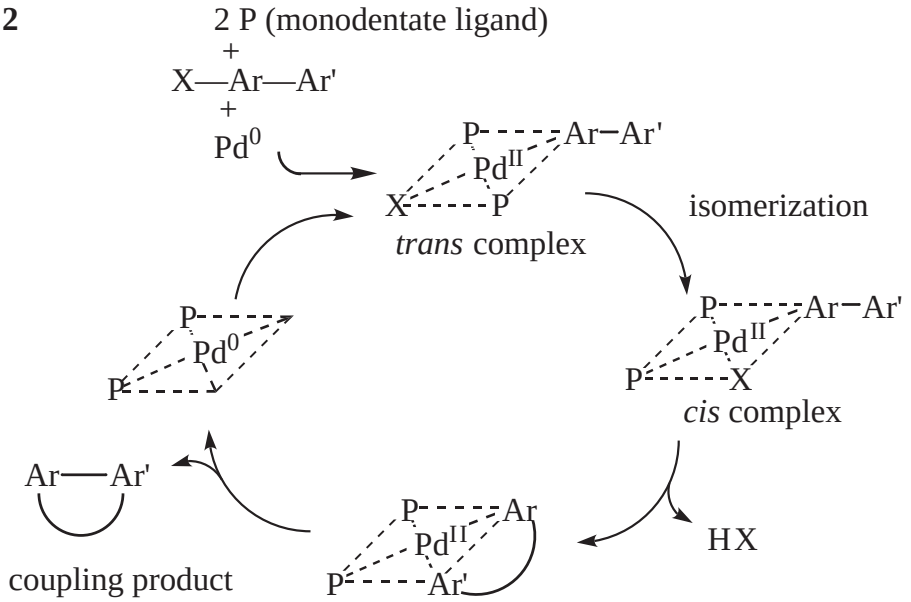
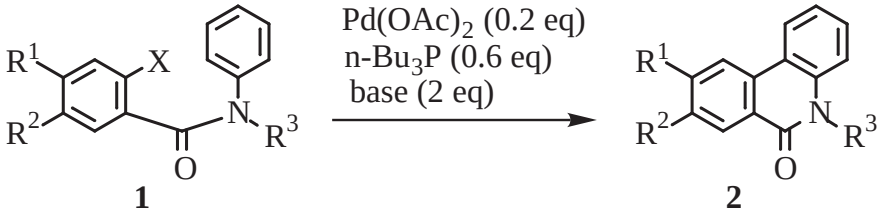


Table 2. Results of coupling reactions of 2-[(trifluoromethanesulfonyl)oxy]-*N*-methyl-*N*-phenylbenzamide (**1a**) to *N*-methylphenanthridone (**2a**) in DMF under reflux

run	$Pd(OAc)_2$ (eq.)	phosphine (L/Pd)[a]	base[b]	time	yield (%) **2a**	yield (%) **1a**
1	1.0	n-Bu_3P (3)	$^i Pr_2NEt$	30 min	92	—
2	1.0	PPh_3 (3)	$^i Pr_2NEt$	1 h	84	15
3	1.0	DPPP (1.5)	$^i Pr_2NEt$	30 min	86	—[c]
4	0.2	n-Bu_3P (3)	$^i Pr_2NEt$	30 min	84	—
5	0.2	PPh_3 (3)	$^i Pr_2NEt$	3 h	13	71
6	0.2	P(*o*-Tol)$_3$(3)	$^i Pr_2NEt$	3 h	39	46
7	0.2	DPPP (1.5)	$^i Pr_2NEt$	1 h	39	—[d]

a) Molar ratio between ligand and Pd. b) Two mol equivalents of base were added. c) *N*-Methyl-*N*-phenylbenzamide was obtained in 3-5% yield. d) *N*-Methyl-*N*-phenylbenzamide was obtained in 50% yield.

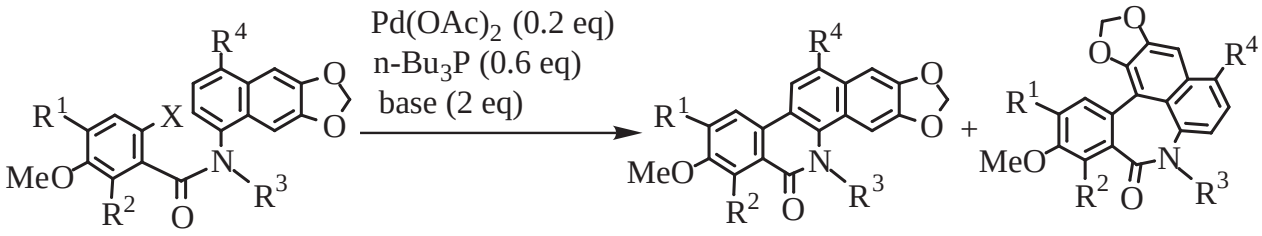


1 **2**

Table 3. Results of coupling reactions of benzanilides (**1b~1f**) in DMF under reflux

	X	R^1	R^2	R^3	base	time	yield (%) **2**	yield (%) **1**
1b	OTf	H	OMe	Me	$^iPr_2NEt$	3 h	59[a)]	3
1c	I	H	H	Me	Ag_2CO_3	15 min	90	–
1d	Br	H	H	Me	Ag_2CO_3	2 h	64	18
1e	I	H	H	MOM	Ag_2CO_3	30 min	97	–
1f	Br	$-OCH_2O-$		MOM	Ag_2CO_3	3.5 h	51	35

a) *N*-Methylphenanthridone (**2a**, R^1=R^2=H, R^3=Me) was obtained in 8% yield.



3 **4** **5**

Table 4. Results of coupling reactions of amides (**3**) in DMF under reflux

	X	R^1	R^2	R^3	R^4	base	time	yield (%) **4**	yield (%) **5**
3a	OTf	H	OMe	Me	H	$^iPr_2NEt$	4 h	11[a)]	–
3b	OTf	OMe	H	Me	H	$^iPr_2NEt$	5 h	6[a)]	–
3c	I	H	OMe	Me	H	Ag_2CO_3	30 min	83	15
3d	I	OMe	H	Me	H	Ag_2CO_3	30 min	59	3
3e	I	H	OMe	MOM	H	Ag_2CO_3	30 min	74	22
3f	I	H	OMe	Me	OMe	Ag_2CO_3	30 min	80	14

a) Starting material was recovered in 70~72% yield.

due to aromatic protons, in addition to multiple signals due to three successive aromatic protons (see EXPERIMENTAL).

In conclusion, this procedure is effective for coupling reactions of aryl triflates possessing no oxygen substituents and arene, and aryl iodide and arene.

EXPERIMENTAL

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol on a JASCO A-102 or JASCO FT/IR 350 spectro-

photometer and ^{1}H-NMR spectra in deuteriochloroform on a Varian VXR-200 (200 MHz) or -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 $MgSO_4$, 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 filrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

General Procedure for the Coupling Reaction of Triflate-amide (1a) used in Tables 1 and 2

The reaction of **1a** (108 mg, 0.3 mmol) with $Pd(OAc)_2$, a ligand, and/or n-Bu_3P and a base in dry DMF (8 mL) was carried out under reflux using $Pd(OAc)_2$, a ligand, and n-Bu_3P in the ratios indicated in Tables 1 and 2, and 2 mol equivalents of base for the time indicated in the Tables. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue was dissolved in hexane-AcOEt (4 : 1) and subjected to column chromatography on silica gel. Elution with hexane-AcOEt (4 : 1) gave the coupling product (**2a**)[1] and further elution with hexane-AcOEt (4 : 1) gave the starting material (**1a**). In run 7 in Table 2, elution with hexane-AcOEt (4 : 1) gave **2a**.[1] Further elution with the same solvent gave *N*-methyl-*N*-phenylbenzamide and then the starting material (**1a**). These samples were identified using authentic samples.

General Procedure for the Coupling Reaction of Benzanilides (1b-f) and Amides (3) with Palladium and n-Bu_3P Used in Tables 3 and 4

The reaction of **1b-f** and **3** (0.3 mmol) with 0.2 equivalent of $Pd(OAc)_2$, 0.6 equivalent of n-Bu_3P, and 2 mol equivalents of base in dry DMF (8 mL) was carried out under reflux for the times indicated in Tables 3 and 4. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (4 : 1) gave naphthobenzoazepinones (**5**), and successive elution with the same solvent gave the respective phenanthridones (**4**). In the cases of **3a** and **3b**, elution with hexane-AcOEt (4 : 1) gave **4a** and **4b**, respectively, and successive elution gave the corresponding starting material.

9,10-Dimethoxy-7-methyl-1,2-methylenedioxynaphtho[1,8-*cd*][2]benzazepin-8(7*H*)-one (**5c**) : mp 202-204˚C, pale yellow needles (from hexane-AcOEt). IR (KBr) cm^{-1}: 1660. ^{1}H-NMR (200 MHz) δ : 3.40 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 6.11 (2H, s, OCH_2O), 6.92 (1H, d, *J*=9.0 Hz, C_{11}-H), 6.97 (1H, s, C_3-H), 7.16 (1H, dd, *J*=7.1, 1.6 Hz, C_6-H), 7.27 (1H, dd, *J*=7.9, 7.1 Hz, C_5-H), 7.34 (1H, dd, *J*=7.9, 1.61 Hz, C_4-H), 7.39 (1H, d, *J*=9.0 Hz, C_{12}-H). High resolution FAB-MS Calcd for $C_{21}H_{18}NO_5$: 364.1185. Found : 364.1138.

10,11-Dimethoxy-7-methyl-1,2-methylenedioxynaphtho[1,8-*cd*][2]benzazepin-8(7*H*)-one (**5d**) : mp

232.5-236˚C, colorless needles (from hexane-AcOEt). IR (KBr) cm^{-1}: 1630. ^{1}H-NMR (500 MHz) δ : 3.45 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 6.12 (2H, s, OCH_2O), 7.02 (1H, s, C_3-H), 7.12 (1H, dd, *J*=7.5, 1.0 Hz, C_6-H), 7.20 (1H, s, C_{12}- H), 7.29 (1H, dd, *J*=7.5, 7.5 Hz, C_5-H), 7.36 (1H, d, *J*=7.5 Hz, C_4-H), 7.61 (1H, s, C_9- H). High resolution FAB-MS Calcd for $C_{21}H_{18}NO_5$: 364.1185. Found : 364.1214.

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6 The coupling reaction of **1a** using $Pd(OAc)_2$ (0.2 eq), n-Bu_3P (0.4 eq) and $^iPr_2NEt$ (2 eq) in DMF (8 mL) under reflux for 30 min gave **2a** (63% yield) and the starting material (**1a**) (20% yield), indicating that the reaction using a three molar ratio between Pd and the ligand is superior. (see run 4 in Table 2)

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