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INTERNAL ARYL-ARYL COUPLING REACTION USING A NOVEL AND HIGHLY ACTIVE PALLADIUM REAGENT PREPARED FROM Pd(OAc)$_2$, DPPP, and Bu$_3$P

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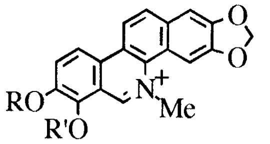
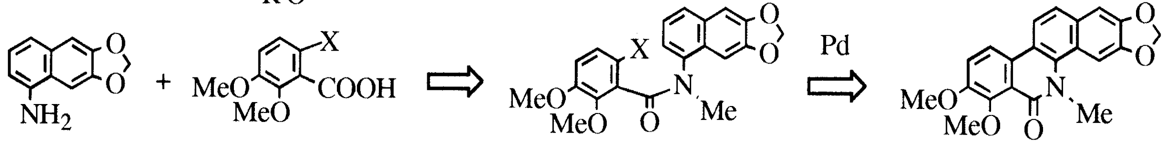
A novel Pd reagent prepared from equimolar Pd(OAc)$_2$, DPPP, and Bu$_3$P (method B) was useful for the internal biaryl coupling reaction of not only triflate-amide but also halo-amide.

KEY WORDS internal biaryl coupling; aryl triflate-arene coupling; aryl halide-arene coupling; bidentate ligand; Pd reagent

Recently, attention has been focused on benzo[*c*]phenanthridine alkaloids because of their potent pharmacological activities.[1] Among these, the chelerythrine type of alkaloids, especially chelerythrine (**1**),[2] isofagaridine (**2**),[3] and sanguinarine (**3**)[4] inhibit protein kinase C, DNA topoisomerase I, lipoxygenase, and other enzymes. The internal cross coupling reaction with Pd catalyst has been utilized for the synthesis of condensed aromatic compounds,[5] and we have recently succeeded in a convenient synthesis of oxychelerythrine (**7**), including a biaryl coupling reaction of halo-amides (**6**, X=I or Br), prepared from amine (**4**) and acid (**5**, X=I or Br), by Pd(OAc)$_2$, PPh$_3$ or POT (tris[2-methylphenyl]phosphine) and Ag$_2$CO$_3$ in DMF under reflux (method A).[6] To investigate the generality of this method, we applied method A to an amide possessing triflate (OTf) instead of halogen as a leaving group. However, method A was ineffective for triflate-amide as described below. We thus developed a novel combination system, Pd(OAc)$_2$, DPPP (1,3-bis[diphenylphosphino]propane) and Bu$_3$P in the presence of base (method B). Here, we describe the results of an internal aryl-aryl coupling reaction under such reaction conditions.



R = R' = Me chelerythrine (**1**)
R = H, R' = Me isofagaridine (**2**)
R, R' = CH$_2$ sanguinarine (**3**)



4 **5** **6** oxychelerythrine (**7**)

First, the biaryl coupling reaction of triflate-amide (**8a**)[7] to phenanthridone (**9a**) by method A[6] was examined. As shown in Table 1, the coupling reaction did not proceed even with equimolar Pd reagent (see runs 1-2). As Suzuki's method[9] gave **9a** along with hydrolysis product (see run 3), we planned to develop a more efficient new method. Since bidentate ligands such as DPPP have lower cone angles[10a] and P-Pd-P angles[10b] than monodentate ligands, and coordinate to the Pd in the square-planar Pd complex in an obligatory *cis* arrangement in contrast to the *trans* arrangement of monodentate ligands in the complex,[11] we considered that DPPP would be less bulky than PPh$_3$ and suitable for a biaryl coupling (coordination-insertion) process for steric reasons.[11] Moreover, since the Pd reagent prepared

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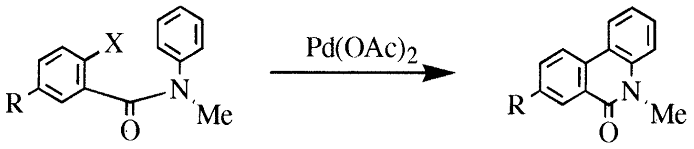


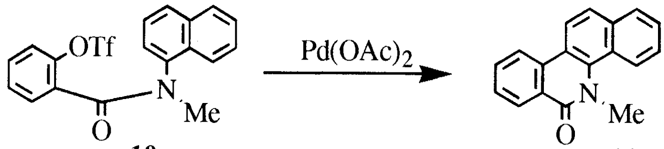
8a X = OTf R = H
8b X = I R = H
8c X = Br R = H
8d X = OTf R = OMe

9a R = H
9b R = OMe

Table 1. Results of Cyclization Reaction of *N*-Methyl-*N*-phenyl-2-substituted Benzamide (**8**)[a]

	Run	Pd (eq.)	Ligand (L/Pd)[b]	Bu_3P	Base	Solvent	Time	Yield (%)	
								9	S.M.
8a	1	$Pd(OAc)_2$ (0.2)	PPh_3 (2)	—	Ag_2CO_3	DMF	3 h	NR[c]	
	2	$Pd(OAc)_2$ (1.0)	PPh_3 (2)	—	Ag_2CO_3	DMF	5 h	NR	
	3	$(Ph_3P)_2PdCl_2$ (0.27)	—	—	NaOPiv	DMA[d]	1 h	69[e]	—
	4	$Pd(OAc)_2$ (1.0)	DPPP (1)	—	Ag_2CO_3	xylene	190 h	10	77
	5	$Pd(OAc)_2$ (1.0)	DPPP (1)	—	Ag_2CO_3	DMF	190 h	21	24
	6	$Pd(OAc)_2$ (1.0)	—	1.0	Ag_2CO_3	DMF	96 h	27	62
	7	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	DMF	5 h	93	—
	8	$Pd(OAc)_2$ (1.0)	POT (2)	1.0	Ag_2CO_3	DMF	10 h	13	71
	9	$Pd(OAc)_2$ (0.3)	DPPP (1)	0.3	Ag_2CO_3	DMF	100 h	26	61
	10	$Pd(OAc)_2$ (0.3)	DPPP (1)	1.0	Ag_2CO_3	DMF	55 h	58	15
	11	$Pd(OAc)_2$ (0.3)	DPPP (1)	3.0	Ag_2CO_3	DMF	2 h	71	—
	12	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	benzene	11 h	37	62
	13	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	xylene	9 h	59	35
	14	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	$^iPr_2NEt$	DMF	30 min	92	—
	15	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	—	DMF	30 min	77	—
	16	$Pd(OAc)_2$ (1.0)	DPPB[f] (1)	1.0	$^iPr_2NEt$	DMF	30 min	89	—
8b	17	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	DMF	15 min	93	—
	18	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	$^iPr_2NEt$	DMF	1.5 h	98	—
8c	19	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	DMF	20 min	93	—
	20	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	$^iPr_2NEt$	DMF	1.5 h	90	—
8d	21	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	DMF	3.5 h	76	—
	22	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	$^iPr_2NEt$	DMF	30 min	88	—
	23	$Pd(OAc)_2$ (1.0)	DPPB[f] (1)	1.0	$^iAg_2CO_3$	DMF	30 min	87	—

a) All reactions were carried out under an argon atmosphere using $Pd(OAc)_2$, ligand, and Bu_3P in the ratio indicated in the table and 2 mol equivalents of base under reflux unless otherwise noted. b) Molar ratio between ligand and $Pd(OAc)_2$. c) No reaction occurred and starting material was recovered in a yield of more than 80%. d) Heating at 140°C. e) Hydrolysis product (**8**, X=OH) was obtained in 28% yield. f) 1,4-Bis(diphenylphosphino)butane.



10 **11**

Table 2. Results of Cyclization Reaction of *N*-Methyl-*N*-(1-naphthyl)-2-[(trifluoromethanesulfonyl)oxy]benzamide (**10**)[a]

Run	$Pd(OAc)_2$(eq.)	Ligand(L/Pd)[b]	Bu_3P	Base	Solvent	Temp.	Time	Yield (%)
1	1.0	DPPP (1)	1.0	Ag_2CO_3	DMF	refl.	20 min	97
2	0.3	DPPP (1)	3.0	Ag_2CO_3	DMF	refl.	3 h	70
3	1.0	DPPP (1)	1.0	$^iPr_2NEt$	DMF	refl.	20 min	96

a) All reactions were carried out under an argon atmosphere using $Pd(OAc)_2$, ligand, and Bu_3P in the ratio indicated in the table, and 2 mol equivalents of base. b) Molar ratio between ligand and $Pd(OAc)_2$.

from $Pd(OAc)_2$-Bu_3P is highly active,[12] we supposed that the zerovalent Pd prepared from Bu_3P would have a strong oxidative addition ability. We applied each method to **8a** (see runs 5 and 6) and the desired product (**9a**) was obtained in yields of only 21% and 27%, respectively. Surprisingly, however, the DPPP-Bu_3P combination system afforded **9a** in an excellent yield (see run 7). Although the cyclization reaction proceeds even in the presence of 0.3 eq. of $Pd(OAc)_2$, several equivalents of Bu_3P were necessary to obtain the desired product in good yield (see runs 9-11 in Table 1 and run 2 in Table 2). On using equimolar $Pd(OAc)_2$, DPPP, Bu_3P, and Hünig base in DMF, the reaction proceeded in a short time and the product (**9a**) was obtained in excellent yield (see run 14). Application of our novel method to halo-amides (**8b**[6] and **8c**[6]) gave **9a** in excellent yields (see runs 17-20 in Table 1).

Next, we carried out cyclization reactions of other triflates (**8d**[13] and **10**[14]) using our novel method B. The results shown in Table 1 (see runs 21-22) and Table 2 indicate that the present method is very useful for the internal coupling reaction between aryl triflates and arenes. Moreover, the bidentate ligand DPPB also was effective for the coupling reaction (see runs 16 and 23 in Table 1).

Consequently, the novel combination system consisting of equimolar $Pd(OAc)_2$, DPPP , and Bu_3P and two molar equivalents of base is very efficient and powerful for the internal ary-aryl coupling reaction of not only triflate-amides (**8a**, **8d**, and **10**) but halo-amides (**8b** and **8c**). Mechanistic and synthetic studies on benzo[*c*]phenanthridine alkaloids are currently underway using our novel method.

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13) Triflate-amide (**8d**) was prepared from 3-methoxysalicylic acid and monomethylaniline *via* amidation in the presence of P_2O_5, followed by trifylation with Tf_2O with a total yield of 48%.
14) Triflate-amide (**10**) was prepared from salicylic acid and *N*-methyl-1-naphthylamine[15] *via* amidation in the presence of P_2O_5, followed by trifylation with Tf_2O with a total yield of 43%.
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