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SYNTHESIS OF BENZO[*C*]PHENANTHRIDINE ALKALOIDS USING A PALLADIUM-CATALYZED ARYL-ARYL COUPLING REACTION

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Abstract – A synthesis of (fully aromatized) benzo[*c*]phenanthridine alkaloids was accomplished using an intramolecular palladium-catalyzed aryl-aryl coupling reaction of halo- or triflyloxyarenes.

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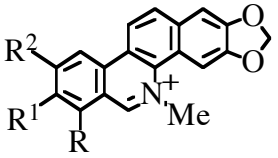
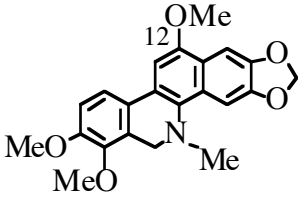
9) Conclusion

Fully aromatized benzo[*c*]phenanthridine alkaloids have a broad range of potent pharmacological properties such as anti-tumor and antiviral activities, and the inhibition of DNA topoisomerase I.[1, 2c] The development of convenient and effective methods for synthesizing these alkaloids has been the subject of recent attention.[2, 3] However, the reported methods have several disadvantages, including numerous steps, low total yield, and/or lack of generality. We have been studying the development of more concise and versatile synthetic methods for these alkaloids and recently developed a convenient method for the synthesis of benzo[*c*]phenanthridine alkaloids (**1**~**6**), using an intramolecular palladium-assisted aryl-aryl

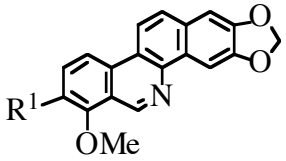
coupling reaction of 2-halo-*N*-arylbenzamides.[4] Subsequently, we developed a new palladium reagent, which was effective for the intramolecular coupling of 2-OTf-*N*-arylbenzamides.[4e-g, 4i] In this review, we report the results of applying this methodology.



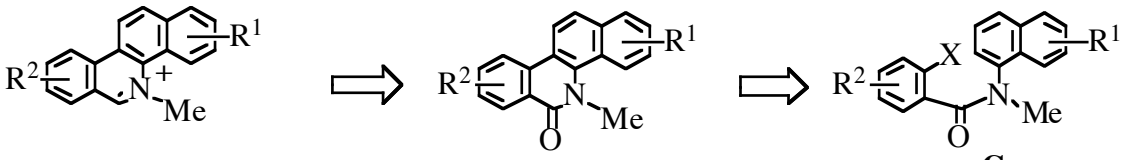
$R = R^1 = OMe, R^2 = H$ chelerythrine (**1**)
$R = H, R^1 = R^2 = OMe$ nitidine (**2**)
$R = OMe, R^1 = OH, R^2 = H$ fagaridine (**3**)



12-methoxydihydrochelerythrine (**4**)



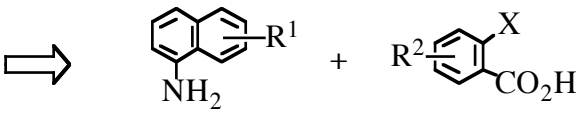
$R^1 = OMe$ norchelerythrine (**5**)
$R^1 = OH$ decarine (**6**)



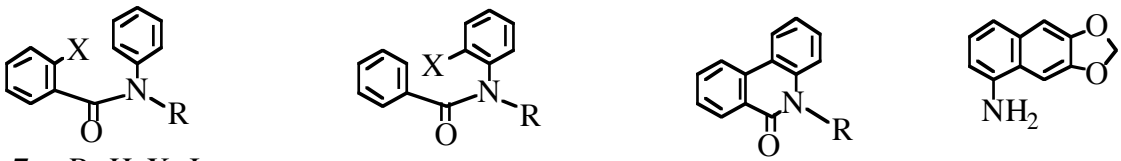
benzo[*c*]phenanthridine (**A**) benzo[*c*]phenanthridone (**B**)

C

X= I, Br, OTf



D **E**



7a : R- H, X=I
7b : R=Me, X=I
7c : R= Me, X=Br

8a : R= H, X=I
8b : R=MOM, X=I

9a : R=H
9b : R=Me

11

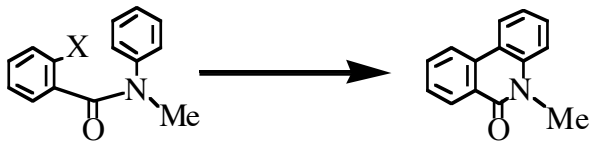
Scheme 1

1) Introduction

Palladium-assisted aryl-aryl coupling reactions have been used to synthesize many polycyclic aromatic compounds.[5] We envisioned that the palladium-assisted aryl-aryl coupling reaction of 2-halo-*N*-naphthylbenzamides (**C**), prepared from naphthylamine (**D**) and 2-halobenzoic acid (**E**), would provide a concise and direct synthesis of benzo[*c*]phenanthridine alkaloid (**A**) *via* benzo[*c*]phenanthridone (**B**) (Scheme 1).

As a preliminary study for the synthesis of these alkaloids, we examined a palladium-assisted coupling reaction of benzanilides (**7** and **8**). Ames *et al*. had reported in 1984 that a secondary amide (**7a**) with a halogen atom on the benzoyl moiety did not give rise to a coupling product (**9a**), whereas a secondary amide (**8a**) with the halogen atom on the aniline ring provided the expected product (**9a**) in poor to moderate yield.[6] Ames *et al*. reported also that a coupling reaction of bromo amide (**7c**) with a palladium reagent produced phenanthridone (**9b**) in 50% yield.[6] Thus, we expected that the reaction of the tertiary amide (**7b**), being more reactive than **7c**, would proceed smoothly. With the aim of improving the yield, the coupling reaction of **7b** and **7c** was re-examined using purified $Pd(OAc)_2$,[7] a phosphine ligand, and a

Table 1. Coupling reaction of 2-halo-*N*-methyl-*N*-phenylbenzamide (**7**)[a)]



7b X=I
7c X=Br

9b

	run	$Pd(OAc)_2$ (eq.)	ligand	base	solvent	temp.	time	yield (%) **9b**	yield (%) **7**
7b	1	0.05	PPh_3	Ag_2CO_3	DMF	Reflux	40 min	79	-
	2	0.2	PPh_3	Ag_2CO_3	DMF	Reflux	15 min	93	-
	3	0.2	P(*o*-tol)$_3$	Ag_2CO_3	DMF	Reflux	15 min	93	-
	4	0.2	PPh_3	Ag_2CO_3	DMF	30-35°C	35 h	85	-
	5	0.2	PPh_3	Ag_2CO_3	xylene	30-35°C	23 h	93	-
	6	0.2	PPh_3	Ag_2CO_3	benzene	Reflux	10 min	98	-
	7	0.2	PPh_3	Ag_2CO_3	CH_3CN	Reflux	15 min	95	-
	8	0.2	PPh_3	$^iPr_2NEt$	DMF	Reflux	4.5 h	21	7
	9	0.2	PPh_3	$^iPr_2NEt$	benzene	Reflux	6 h	45	14
	10	0.2	-	Ag_2CO_3	DMF	Reflux	20 min	90	-
	11	0.2	-	AcONa	DMF	Reflux	25 min	96	-
7c	12	1.0	PPh_3	Ag_2CO_3	DMF	Reflux	60 h	75	7
	13	0.2	P(*o*-tol)$_3$	Ag_2CO_3	DMF	Reflux	1.5 h	99	-

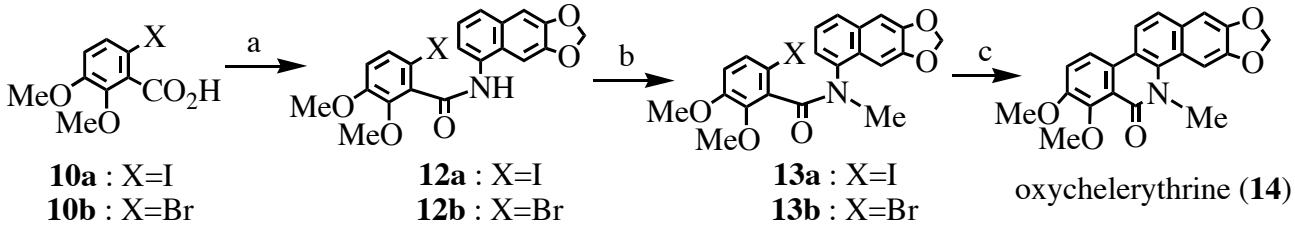
a) All reactions were carried out using $Pd(OAc)_2$ and ligand in a ratio of 1 : 2 and 2 mol equivalents of base.

base. The results are summarized in Table 1.[4a, c] It was found that Ag_2CO_3 was superior to diisopropylethylamine as a base. When using 0.2 eq. of $Pd(OAc)_2$, PPh_3, and Ag_2CO_3, the choice of solvent did not appear to significantly affect the coupling reaction of **7b** (runs 4-7 in Table 1). We chose DMF as the solvent because of the solubility of the starting materials for the synthesis of benzo[*c*]phenanthridine skeleton in this solvent. Interestingly, good results were obtained when no phosphine ligand was employed (runs 10 and 11 in Table 1).[8] Conversely, the coupling reaction of **7c**

proceeded slowly even when using a stoichiometric amount of $Pd(OAc)_2$ in the presence of PPh_3 in DMF (run 12 in Table 1). Upon changing to tri(*o*-tolyl)phosphine [$P(o\text{-tol})_3$] as ligand, the reaction proceeded smoothly with 0.2 eq. of $Pd(OAc)_2$, giving **9b** in an excellent yield (run 13 in Table 1).

2) Synthesis of chelerythrine (1)[4a, c]

As the coupling reaction of **7b** and **7c** using a palladium reagent was successful, we investigated the total synthesis of chelerythrine (**1**) utilizing this method. Starting materials (**13a** and **13b**) for the synthesis of **1** were prepared from 2-iodobenzoic acid (**10a**) or 2-bromobenzoic acid (**10b**) and naphthylamine (**11**) as shown in Scheme 2. The coupling reaction of both halo amides (**13**) with $Pd(OAc)_2$, PPh_3 or $P(o\text{-tol})_3$, and Ag_2CO_3 in DMF under reflux afforded oxychelerythrine (**14**) in excellent yield as shown in Table 2, although iodo amide (**13a**) was more reactive than bromo amide (**13b**). Given that **14** had previously been converted into chelerythrine (**1**),[9] the synthesis of **14** indicates a formal synthesis of **1**.



Scheme 2 Synthesis of oxychelerythrine (**14**)
Reagents and Conditions : (a) (i) $(COCl)_2$, CH_2Cl_2, reflux, (ii) 6,7-methylenedioxy-1-naphthylamine (**11**), CH_2Cl_2, Et_3N, 58% from **10a**, 77% from **10b**; (b) MeI, NaH, DMF, rt, 96% from **12a**, 93% from **12b**; (c) Pd reagent, see Table 2.

Table 2. Coupling reaction of 6-halo-2,3-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (**13**) to oxychelerythrine (**14**) in DMF under reflux[a)]

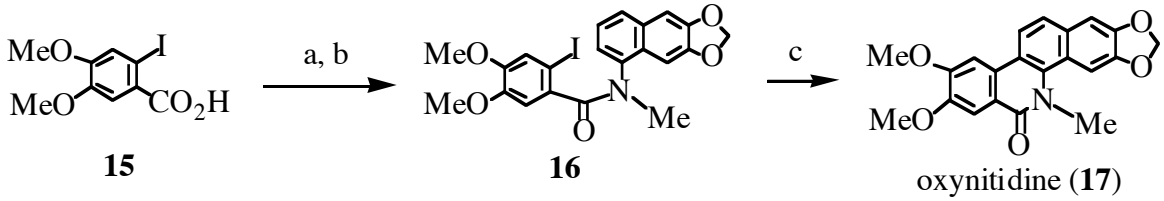
	run	$Pd(OAc)_2$ (eq)	ligand	base	time	yield (%)
13a	1	0.2	PPh_3	Ag_2CO_3	20 min	85
	2	0.2	$P(o\text{-tol})_3$	Ag_2CO_3	20 min	94
13b	3	0.2	PPh_3	Ag_2CO_3	2 h	79
	4	0.2	$P(o\text{-tol})_3$	Ag_2CO_3	3 h	96

a) All reactions were carried out using $Pd(OAc)_2$ and ligand in a ratio of 1 : 2 and 2 mol equivalents of base.

3) Synthesis of nitidine (2)[4b]

The starting material (**16**) for the synthesis of nitidine (**2**) was prepared from naphthylamine (**11**) and 2-iodobenzoic acid (**15**) as shown in Scheme 3. The coupling reaction of **16** was examined, and the results are summarized in the Table 3. Using 0.2 eq. of $Pd(OAc)_2$, PPh_3 or $(o\text{-tol})_3P$, and Ag_2CO_3 in DMF, which

had created successful reaction conditions for the synthesis of chelerythrine (**1**),[4c] the reaction of **16** did not proceed in a satisfactory yield, even when (*o*-tol)$_3$P was used as the ligand (run 3 in Table 3). Using one equivalent of Pd(OAc)$_2$, the coupling reaction proceeded in high yield (runs 2 and 4 in Table 3), although the reaction using PPh$_3$ was sluggish. Oxynitidine (**17**) had previously been converted to nitidine (**2**) by reduction with LiAlH$_4$ and oxidation with DDQ.[10]



Scheme 3 Synthesis of oxynitidine (**17**)
Reagents and Conditions : (a) (i) (COCl)$_2$, CH$_2$Cl$_2$, DMF, reflux, (ii) 6,7-methylenedioxy-1-naphthylamine (**11**), CH$_2$Cl$_2$, Et$_3$N; (b) MeI, NaH, DMF, rt, 79% from **15**; (c) Pd reagent, see Table 3.

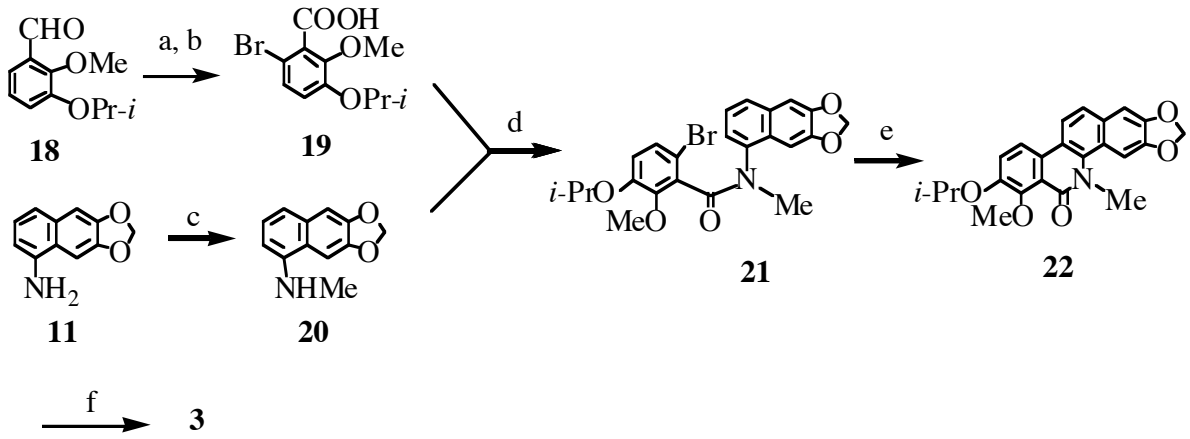
Table 3. Coupling reaction of 2-iodo-4,5-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (**16**) to oxynitidine (**17**) in DMF under reflux[a)]

run	Pd(OAc)$_2$ (eq.)	ligand	(L/Pd)[b)]	base	time(h)	yield(%)	
						17	S.M.
1	0.2	PPh$_3$	(2)	Ag$_2$CO$_3$	5	30	54
2	1.0	PPh$_3$	(2)	Ag$_2$CO$_3$	43	88	10
3	0.2	(*o*-tol)$_3$P	(2)	Ag$_2$CO$_3$	5	64	16
4	1.0	(*o*-tol)$_3$P	(2)	Ag$_2$CO$_3$	2	89	10

a) All reactions were carried out using Pd(OAc)$_2$ and ligand in the ratio indicated in the Table and 2 mol equivalents of base. b) Molar ratio between ligand and Pd.

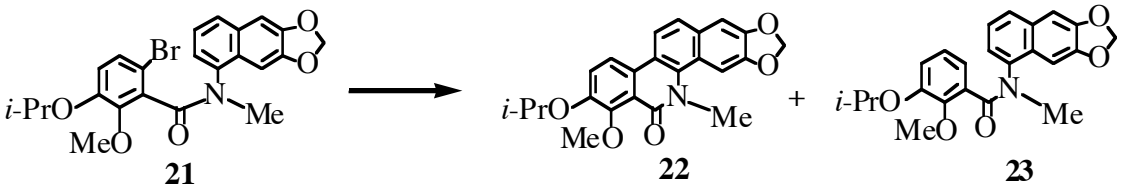
4) Synthesis of fagaridine (3)[4h]

For the synthesis of the phenolic alkaloid fagaridine (**3**), an isopropyl group was chosen as the protective group for the phenol, following the work of Ishii *et al.*[11] Bromo amide (**21**), the starting material for the coupling reaction, was synthesized from bromo acid (**19**) and *N*-methylnaphthylamine (**20**), which were prepared from 3-isopropoxy-2-methoxybenzaldehyde (**18**) and **11**, respectively, as shown in Scheme 4. The results of the aryl-aryl coupling reaction of **21** using the palladium reagent are summarized in Table 4. The coupling reactions proceeded smoothly to provide **22** in excellent yield, accompanied by a small amount of debromo amide (**23**) (run 5 in Table 4). The reduction of the coupling products (**22**) with LiAlH$_4$ followed by treatment with conc. HCl gave fagaridine (**3**).



Scheme 4 Synthesis of fagaridine (**3**)
Reagents and Conditions : (a) $NaClO_2$, 31%H_2O_2, NaH_2PO_4, aq. MeCN, 10°C, 89%; (b) 0.7N aq. NaOH, dibromodimethylhydantoin, rt, 80%; (c) (i) $(CF_3CO)_2O$, pyridine, 0°C, (ii) MeI, KOH, acetone, reflux, (iii) 5% NaOH, EtOH, reflux, 76% from **11**; (d) (i) $(COCl)_2$, CH_2Cl_2, DMF, rt, (ii) **20**, CH_2Cl_2, Et_3N, rt, 64% from **19**; (e) Pd reagent, see Table 4; (f) (i) $LiAlH_4$, THF, rt, (ii) conc-HCl, reflux, 86%.

Table 4. Coupling reaction of 6-bromo-3-isopropoxy-2-methoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (**21**) in DMF under reflux[a)]

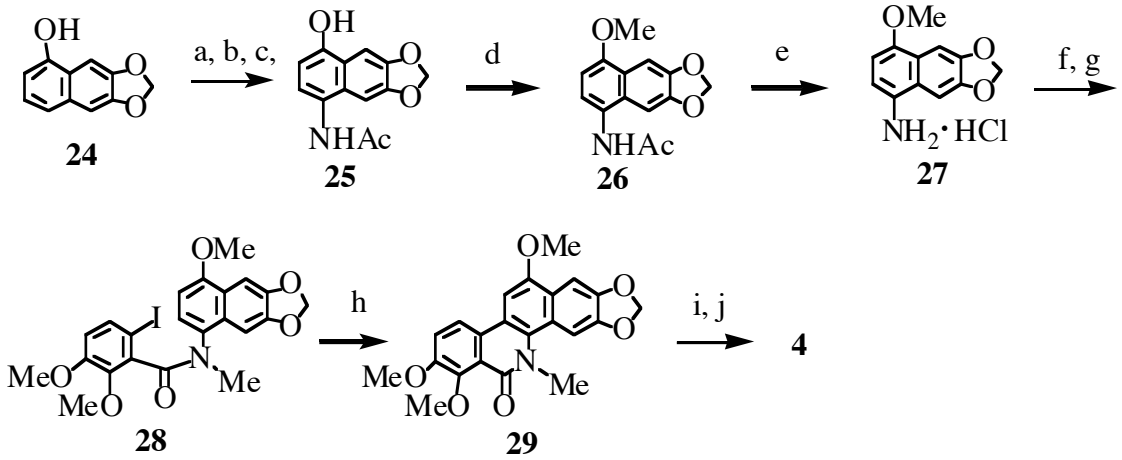


run	$Pd(OAc)_2$	ligand	L/Pd[b)]	base	time(h)	yield(%)		
						22	**23**	S.M.
1	1.0	Ph_3P	(2)	Ag_2CO_3	4	50	-	26
2	1.0	$(o\text{-tol})_3P$	(2)	Ag_2CO_3	2	93	-	5
3	0.2	$n\text{-Bu}_3P$	(3)	K_2CO_3	4	68	6	-
4	0.2	$(o\text{-tol})_3P$	(2)	Ag_2CO_3	4	87	-	13
5	0.2	$(o\text{-tol})_3P$	(2)	K_2CO_3	4	89	7	-

a) All reactions were carried out using 2 mol equivalents of base.
b) Molar ratio between ligand and $Pd(OAc)_2$.

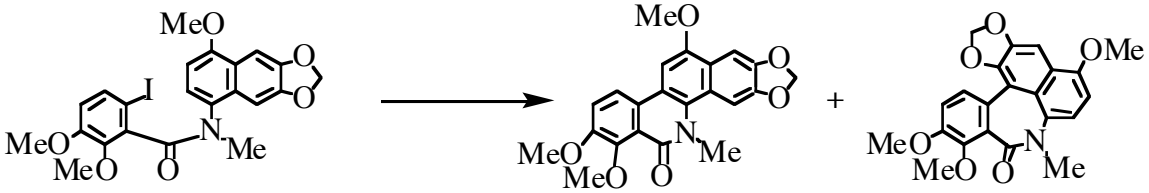
5) Synthesis of 12-Methoxydihydrochelerythrine (4)[4c]

The key compound (**28**) for the synthesis of 12-methoxydihydrochelerythrine (**4**) was prepared by condensation of the carboxylic acid (**10a**) with the naphthylamine (**27**), which was derived from 6,7-methylenedioxy-1-naphthol (**24**) *via* several steps, as shown in Scheme 5. The coupling reaction of **28** in the presence of $Pd(OAc)_2$, a phosphine ligand, and Ag_2CO_3 in DMF under reflux afforded 12-methoxyoxychelerythrine (**29**) in excellent yield along with a small amount of naphthobenzoazepinone (**30**) as shown in Table 5 (see runs 2 and 3). The reduction of **29** with $LiAlH_4$ followed by treatment with HCl and $NaBH_4$ gave 12-methoxydihydrochelerythrine (**4**).



Scheme 5. Synthesis of 12-methoxydihydrochelerythrine (**4**)
Reagents and Conditions : (a) *i*-AmONO, K_2CO_3, DMF, 0°C; (b) 10% Pd/C-H_2, THF; (c) AcCl, pyridine, rt, 63% from **24**; (d) MeI, K_2CO_3, DMF, rt, 86%; (e) 1N HCl, MeOH, 72%; (f) (i) 2-iodo-5,6-dimethoxybenzoic acid (**10a**), $(COCl)_2$, CH_2Cl_2, DMF, reflux, (ii) CH_2Cl_2, Et_3N, 84%; (g) MeI, NaH, DMF, rt, 91% (h) Pd reagent, see Table 5; (i) $LiAlH_4$, 10% HCl, rt, 82%; (j) $NaBH_4$, MeOH, rt, 77%.

Table 5. Coupling reaction of 6-iodo-2,3-dimethoxy-*N*-(4-methoxy-6,7-methylenedioxy-1-naphthyl)-*N*-methylbenzamide (**28**) in DMF under reflux[a)]



28 **29** **30**

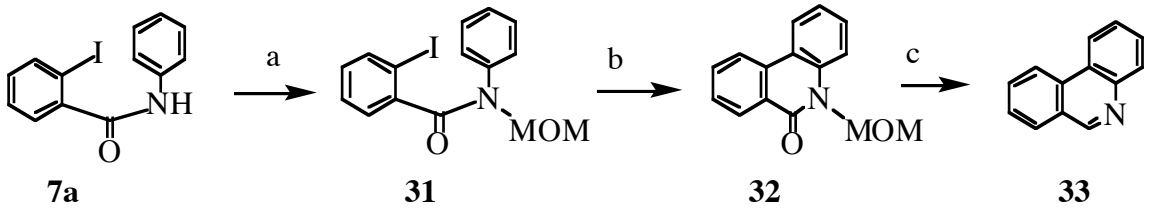
run	$Pd(OAc)_2$ (eq)	ligand	base	time (min)	yield (%)	
					29	**30**
1	0.2	P(*o*-tol)$_3$	Na_2CO_3	180	51	-
2	0.2	PPh_3	Ag_2CO_3	30	91	9
3	0.2	P(*o*-tol)$_3$	Ag_2CO_3	30	95	5
4	0.2	P(*o*-tol)$_3$	NaOAc	120	20	-

a) All reactions were carried out using $Pd(OAc)_2$ and ligand in a ratio of 1 : 2 and 2 mol equivalents of base.

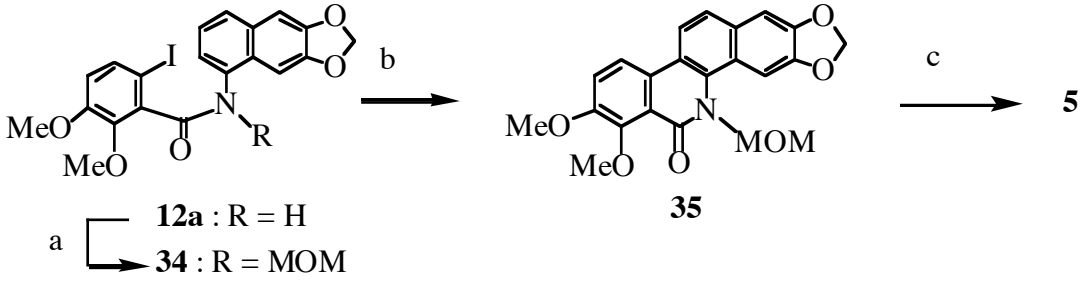
6) Synthesis of norchelerythrine (5)[4d] and decarine (6)[4h]

To examine the general applicability of this method using an aryl-aryl coupling reaction assisted by palladium, we intended to synthesize two tertiary benzo[*c*]phenanthridine alkaloids, norchelerythrine (**5**) and decarine (**6**). As a model study for the synthesis of these tertiary alkaloids, we planned that the tertiary amide (**31**), which was protected by the methoxymethyl (MOM) group, would be converted to *N*-MOM lactam (**32**) with the assistance of a palladium reagent; subsequently, **32** could be transformed to phenanthridine (**33**) *via* reduction with $LiAlH_4$ and treatment with HCl.

The starting material (**31**) for the coupling reaction by palladium was prepared by methoxymethylation of **7a** (Scheme 6). Subsequently, the coupling reaction of **31** using Pd(OAc) (0.1 eq.) in the presence of P(*o*-Tol)$_3$ (0.2 eq.) and Na_2CO_3 (2 eq.) gave phenanthridone (**32**) in excellent yield. The reduction of **32** with $LiAlH_4$ followed by treatment with HCl gave the expected phenanthridine (**33**).

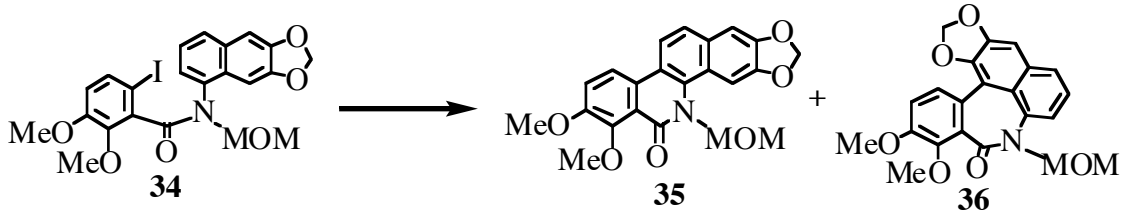


Scheme 6 Synthesis of phenanthridine (**33**)
Reagents and Conditions : (a) dimethoxyethane, CH_2Cl_2, P_2O_5, rt, 62%; (b) $Pd(OAc)_2$, (0.1 eq.), P(*o*-tol)$_3$ (0.2 eq.), Na_2CO_3 (2 eq.), DMF, reflux, 90 min, 97%; (c) (i) $LiAlH_4$, THF, rt, (ii) 6N-HCl, THF, reflux, 54%.



Scheme 7 Synthesis of norchelerythrine (**5**)
Reagents and Conditions: (a) $MeOCH_2Cl$, NaH, DMF, rt, 87%; (b) Pd reagent, see Table 6; (c) (i) $LiAlH_4$, THF, rt, (ii)10%HCl, THF, rt, 92%.

Table 6. Coupling reaction of 6–iodo–2,3–dimethoxy–*N*–methoxymethyl–*N*–(6,7–methylenedioxy–1–naphthyl)benzamide (**34**) in DMF under reflux[a)]

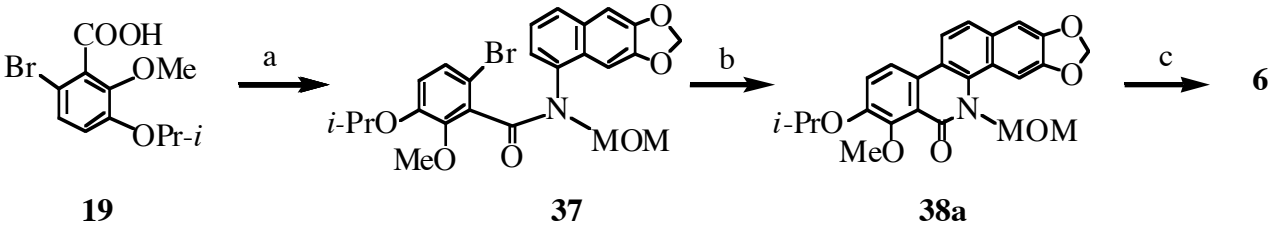


run	$Pd(OAc)_2$ (eq.)	ligand	base	time (min)	yield (%)	
					35	**36**
1	0.2	PPh_3	Na_2CO_3	40	51	13
2	1.0	PPh_3	Na_2CO_3	30	76	20
3	0.2	PPh_3	Ag_2CO_3	30	70	18
4	0.2	P(*o*-tol)$_3$	Na_2CO_3	60	74	16
5	0.2	P(*o*-tol)$_3$	Ag_2CO_3	40	96	1

a) All reactions were carried out using $Pd(OAc)_2$ and ligand in a ratio of 1 : 2 and 2 mol equivalents of base.

By applying this synthetic strategy, a total syntheses of norchelerythrine (**5**) and decarine (**6**) were investigated. We designed a route for the synthesis of **5** through *N*-MOM lactam (**35**). The synthesis of **35** from **12a**, which was the synthetic intermediate for chelerythrine (**1**), is shown in Scheme 7. The coupling reaction of **34** in the presence of $Pd(OAc)_2$, a phosphine ligand, and a base in DMF under reflux afforded **35** in good to excellent yield accompanied by a small amount of naphthobenzoazepinone (**36**) as shown in Table 6. The reduction of **35** with $LiAlH_4$ and subsequent treatment with HCl provided **5**.

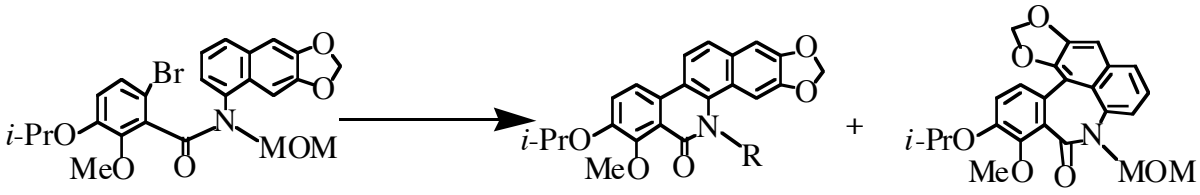
Next, a synthesis of the phenolic alkaloid decarine (**6**) was investigated. The bromo amide (**37**) was prepared from **19** and naphthylamine (**11**) *via* methoxymethylation (Scheme 8). The results of the biaryl coupling reaction of **37** using the palladium reagent are summarized in Table 7. The coupling reactions proceeded in good yield, especially when using equimolar $Pd(OAc)_2$, $(o\text{-tol})_3P$, and Ag_2CO_3 (run 2 in Table 7). A small amount of de-MOM compound (**38b**) and naphthobenzoazepinone (**39**) were always obtained. The reduction of **38a** with $LiAlH_4$ followed by treatment with conc. HCl gave decarine (**6**).



19 **37** **38a**

Scheme 8 Synthesis of decarine (**6**)
Reagents and Conditions : (a) (i) $(COCl)_2$, CH_2Cl_2, reflux, (ii) 6,7-methylenedioxy-1-naphthylamine (**11**), CH_2Cl_2, Et_3N, rt, 78%; (ii) $MeOCH_2Cl$, NaH, DMF, rt, 75%; (b) Pd reagent, see Table 7; (c) (i) $LiAlH_4$, THF, rt, (ii) conc-HCl, reflux, 84%.

Table 7. Coupling reaction of 6-bromo-3-isopropoxy-2-methoxy-*N*-methoxymethyl-*N*-(6,7- methylenedioxy-1-naphthyl)benzamide (**37**) in DMF under reflux[a)]



37 **38a** : R=MOM **38b** : R=H **39**

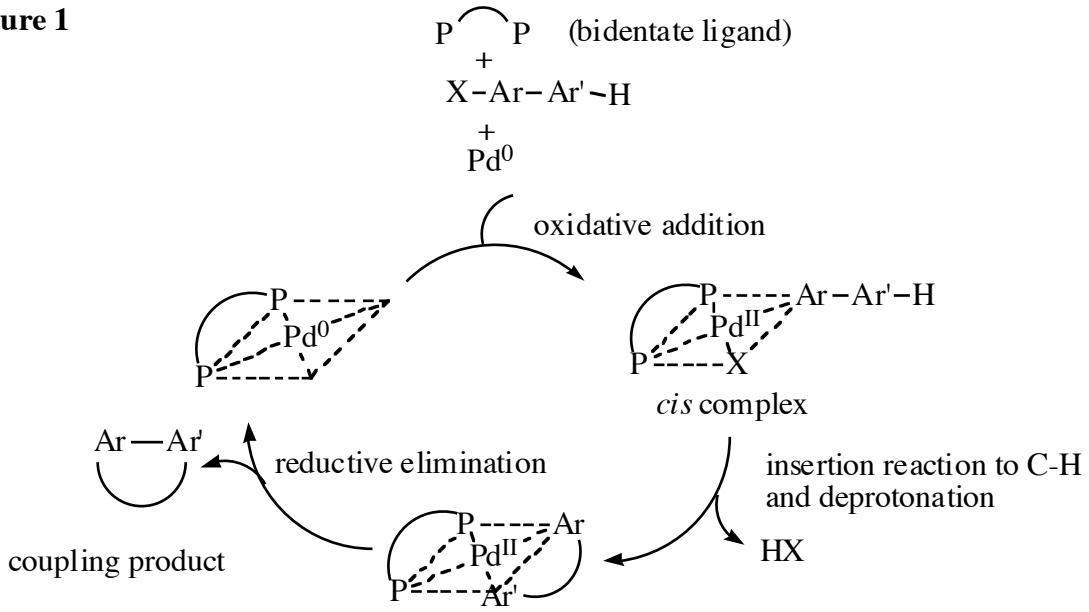
run	$Pd(OAc)_2$ (eq.)	ligand	base	time (h)	yield(%)		
					38a	**38b**	**39**
1	1.0	*n*-Bu_3P	K_2CO_3	5	58	13	22
2	1.0	$(o\text{-tol})_3P$	Ag_2CO_3	5	91	3	6
3	0.2	$(o\text{-tol})_3P$	K_2CO_3	5	55	16	12
4	0.1[b)]	-	K_2CO_3	5	65	16	17

a) All reactions were carried out using $Pd(OAc)_2$ and ligand in a ratio of 1 : 2 and 2 mol equivalents of base. b) Herrmann's catalyst was used.

7) A new palladium reagent for an intramolecular coupling reaction between aryltriflate and arene[4e, 4f]

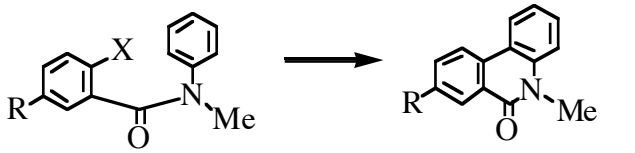
In order to examine the diversity of possible leaving groups for biaryl coupling reactions, we investigated the biaryl coupling reaction of amides (**C**, X = OTf in Scheme 1) bearing a triflate group instead of a halogen. The biaryl coupling reaction of triflate amide (**40a**)[12] with $Pd(OAc)_2$, PPh_3, and Ag_2CO_3, (effective conditions for a halo amide) was examined under several reaction conditions. As shown in Table 8, the coupling reaction did not proceed, even with equimolar palladium reagent (runs 2 and 3 in Table 8).[13] We therefore tried to develop a new method.

Figure 1



Bidentate ligands such as 1,3-bis(diphenylphosphino)propane (DPPP) have lower cone angles[15a] and P-Pd-P angles[15b] than do monodentate ligands such as PPh_3 and P(*o*-tol)$_3$, and they coordinate to the metal in the square-planar Pd complex in an obligatory *cis* arrangement, in contrast to the *trans* arrangement of monodentate ligands.[16] We considered that DPPP would be less bulky than the monodentate ligands and thus more suitable for a biaryl coupling process (the insertion of palladium(II) to the C-H bond on the aryl ring, deprotonation, and reductive elimination of palladium) for steric reasons.[17] (See Figure 1.) Another candidate was the palladium reagent prepared from $Pd(OAc)_2$-Bu_3P. This was known to be highly active,[18] and we assumed that the zero-valent palladium complex prepared from Bu_3P would have a powerful oxidative addition ability. We examined the coupling reaction of **40a** using DPPP (runs 5 and 6 in Table 8), but the desired product (**9b**) was obtained only in low yield. Similarly, using Bu_3P, **9b** was obtained in low yield (run 7 in Table 8). Surprisingly, however, the combination of DPPP and Bu_3P afforded **9b** in excellent yield (run 8 in Table 8). Although the coupling reaction proceeded even in the presence of 0.3 eq. of $Pd(OAc)_2$, a few equivalents of Bu_3P were necessary to obtain coupling products

Table 8. Coupling reaction of *N*-methyl-*N*-phenyl-2-substituted benzamides (**40** and **7**) to *N*-methylphenanthridones (**9**)[a)]



40a X = OTf R = H
40b X = OTf R = OMe
7b X = I R = H
7c X = Br R = H

9b R = H
9c R = OMe

	run	Pd (eq.)	ligand (L/Pd)[b)]	Bu_3P	base	solvent	time	yield (%) **9**	yield (%) S.M.
40a	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	benzene	3 h		NR
	3	$Pd(OAc)_2$ (1.0)	PPh_3 (2)	-	Ag_2CO_3	DMF	5 h		NR
	4	$Pd(PPh_3)_4$ (0.05)	-	-	Ag_2CO_3	benzene	11 h		NR
	5	$Pd(OAc)_2$ (1.0)	DPPP (1)	-	Ag_2CO_3	DMF	190 h	21	24
	6	$Pd(OAc)_2$ (1.0)	DPPP (1)	-	$^iPr_2NEt$	DMF	4 h	15	59
	7	$Pd(OAc)_2$ (1.0)	-	1.0	Ag_2CO_3	DMF	96 h	27	62
	8	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	DMF	5 h	93	-
	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	$^iPr_2NEt$	DMF	30 min	92	-
	13	$Pd(OAc)_2$ (0.3)	DPPP (1)	0.3	$^iPr_2NEt$	DMF	5 h	17	63[d)]
	14	$Pd(OAc)_2$ (0.5)	DPPP (1)	0.5	$^iPr_2NEt$	DMF	3 h	72	6
	15	$Pd(OAc)_2$ (0.3)	DPPP (1)	0.3	Cy_2NMe	DMF	5 h	16	45[e)]
	16	$Pd(OAc)_2$ (0.1)	DPPP (1)	0.1	DBU	DMF	30 min	87	-
40b	17	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	DMF	3.5 h	76	-
	18	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	$^iPr_2NEt$	DMF	30 min	88	-
	19	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	DBU	DMF	30 min	93	-
7b	20	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	DMF	15 min	93	-
	21	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	$^iPr_2NEt$	DMF	15 h	98	-
	22	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	DBU	DMF	1.5 h	84	-
7c	23	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	Ag_2CO_3	DMF	20 min	93	-
	24	$Pd(OAc)_2$ (1.0)	DPPP (1)	1.0	$^iPr_2NEt$	DMF	15 h	90	-

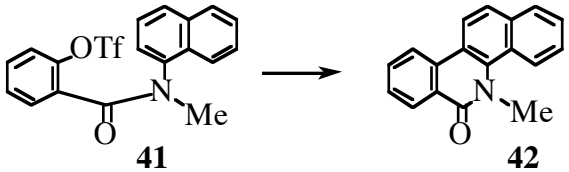
a) All reactions were carried out under an argon atmosphere using $Pd(OAc)_2$, ligand, and Bu_3P in the ratio indicated in the Table and 2 mol equivalents of base under reflux. b) Molar ratio between ligand and $Pd(OAc)_2$. c) No reaction occurred and starting material was recovered in a yield of more than 80%. d) *N*-Methylbenzanilide was obtained in 17% yield. e) *N*-Methylbenzanilide was obtained in 37% yield.
DPPP : 1,3-Bis(diphenylphosphino)propane

(**9a** and **42**) in good yield (runs 9-11 in Table 8 and run 2 in Table 9). Using equimolar $Pd(OAc)_2$, DPPP, Bu_3P, and $^iPr_2NEt$ base in DMF, the reaction proceeded quickly, and **9b** was obtained in excellent yield (run 12 in Table 8). However, using less than equimolar palladium reagent, the coupling reaction did not proceed in satisfactory yield, even in the presence of organic bases (runs 13-15 in Table 8).

This new procedure was then applied to the coupling reactions of triflates (**40b**[19] and **41**[19]). The results of

the coupling reactions of **40b** shown in Table 8 (runs 17 and 18 in Table 8) and **41** shown in Table 9 indicate that our method is very useful for coupling reactions between aryl triflates and arenes, although equimolar palladium reagent was required.

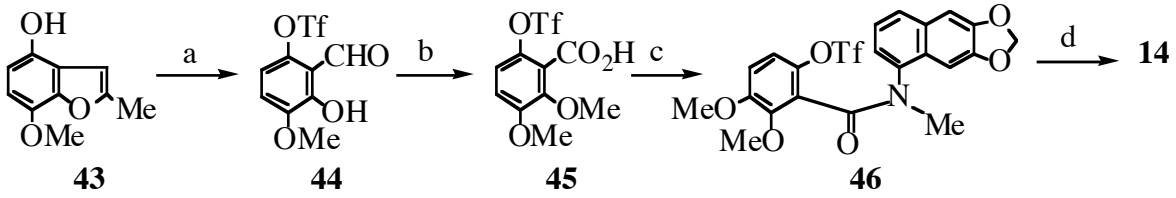
Table 9. Coupling reaction of 2-(trifluoromethanesulfonyloxy)-*N*-methyl-*N*-(1-naphthyl)benzamide (**41**) in DMF under reflux[a)]



41 **42**

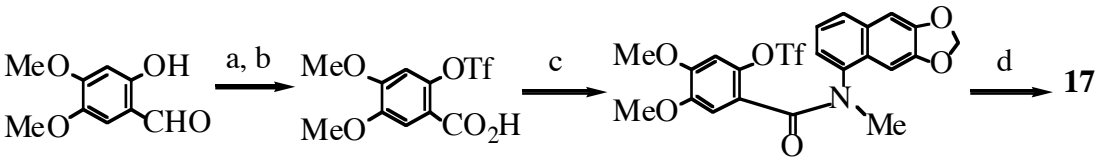
run	$Pd(OAc)_2$ (eq.)	ligand (L/Pd)[b)]	Bu_3P	base	time	yield (%)
1	1.0	DPPP (1)	1.0	Ag_2CO_3	20 min	97
2	0.3	DPPP (1)	3.0	Ag_2CO_3	3 h	70
3	1.0	DPPP (1)	1.0	$^iPr_2NEt$	20 min	96

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 $Pd(OAc)_2$.



43 **44** **45** **46**

Scheme 9 Synthesis of triflate amide (**46**)
Reagents and Conditions : (a) Tf_2O, CH_2Cl_2, NEt_3, 0°C , 99%; (b) (i) O_3, CH_2Cl_2, -78°C, then Me_2S, rt,(ii) conc-HCl, EtOH, reflux, 45%; (b) (i) MeI, DMF, K_2CO_3, rt, 87%, (ii) $NaClO_2$, 31%H_2O_2, NaH_2PO_4, aq. MeCN, 10°C, 87%; (c) (i) $(COCl)_2$, CH_2Cl_2, DMF, reflux, (ii) **20**, CH_2Cl_2, Et_3N, rt, 91%; d) Pd reagent, see runs 1 and 2 in Table 10.



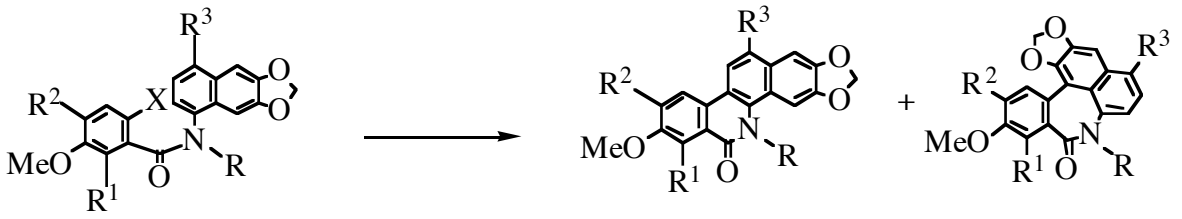
47 **48** **49**

Scheme 10 Synthesis of triflate amide (**49**)
Reagents and Conditions : (a) Tf_2O, CH_2Cl_2, NEt_3, 0°C ,75%; (b) $NaClO_2$, 31%H_2O_2, NaH_2PO_4, aq. MeCN, 10°C, 97%; (c) (i) $(COCl)_2$, CH_2Cl_2, DMF, reflux, (ii) **20**, CH_2Cl_2, Et_3N, rt, 88%; d) Pd reagent, see run 8 in Table 10.

The application of our novel method to halo amides (**7b** and **7c**) gave **9b** in excellent yield (runs 20-23 in Table 8). We then applied this procedure to the OTf amides (**46** and **49**), which were synthesized from acids (**45** and **48**) and **20** as shown in Schemes 9 and 10. The biaryl coupling reaction of **46** and **49** by our new palladium-phosphine combination system was examined. As seen in Table 10, a small amount of

benzonaphthazepinones was obtained with phenanthridones in each reaction. Upon using $^{i}Pr_2NEt$ as the base, the coupling reaction of **46** proceeded quickly and in higher yield to give oxychelerythrine (**14**) (runs 1 and 2 in Table 10). The application of this method to halo amides (**13a** and **13b**) gave **14** in excellent yield (runs 4-7 in Table 10). Using this procedure, the coupling reaction of **49** provided oxynitidine (**17**) in excellent yield (run 8 in Table 10). Iodo amides (**16**, **34**, and **28**) provided benzo[*c*]phenanthridones (**17**, **35**, and **29**) in high yield (runs 9-12 in Table 10).

Table 10. Coupling reaction of naphthylamides to benzo[*c*]phenanthridones and naphthobenzazepinones in DMF under reflux[a)]



46 : R=Me, R^1=OMe, R^2=R^3=H, X=OTf
13a : R=Me, R^1=OMe, R^2=R^3=H, X=I
13b : R=Me, R^1=OMe, R^2=R^3=H, X=Br
49 : R=Me, R^1=R^3=H, R^2=OMe, X=OTf
16 : R=Me, R^1=R^3=H, R^2=OMe, X=I
34 : R=CH_2OMe, R^1=OMe, R^2=R^3=H, X=I
28 : R=Me, R^1=R^3=OMe, R^2=H, X=I

14 and **50** : R=Me, R^1=OMe, R^2=R^3=H
17 and **51** : R=Me, R^1=R^3=H, R^2=OMe
35 and **36** : R=CH_2OMe, R^1=OMe, R^2=R^3=H
29 and **30** : R=Me, R^1=R^3=OMe, R^2=H

	run	$Pd(OAc)_2$ (eq.)	ligand	Bu_3P (eq.)	base	time	products (yield, %)
46	1	1.0	DPPP	1.0	$^{i}Pr_2NEt$	30 min	**14** (81) **50** (~ 5)
	2	1.0	DPPP	1.0	Ag_2CO_3	4 h	(62) (~ 3)
	3[b)]	1.0	DPPP	1.0	DBU	1 h	(63)
13a	4	1.0	DPPP	1.0	$^{i}Pr_2NEt$	15 min	(85) (~ 3)
	5	1.0	DPPP	1.0	Ag_2CO_3	15 min	(95) (~ 3)
13b	6	1.0	DPPP	1.0	$^{i}Pr_2NEt$	30 min	(79) (~ 3)
	7	1.0	DPPP	1.0	Ag_2CO_3	30 min	(89) (~ 2)
49	8	1.0	DPPP	1.0	$^{i}Pr_2NEt$	30 min	**17** (93) **51** (~ 5)
16	9	1.0	DPPP	1.0	$^{i}Pr_2NEt$	30 min	(94) (~ 2)
	10	1.0	DPPP	1.0	Ag_2CO_3	30 min	(88) (~ 3)
34	11	1.0	DPPP	1.0	$^{i}Pr_2NEt$	40 min	**35** (83) **36** (16)
28	12	1.0	DPPP	1.0	$^{i}Pr_2NEt$	30 min	**29** (90) **30** (9)

a) All reaction were carried out using $Pd(OAc)_2$ and ligand in a molar ratio of 1 : 1 and 2 equivalents of base. b) Starting material was recovered in 20% yield.

8) Catalytic palladium reagent for coupling reaction between aryltriflate and arene[4i]

The palladium reagent prepared from $Pd(OAc)_2$, together with DPPP, Bu_3P, and $^{i}Pr_2NEt$, was found to be very versatile for coupling reactions between aryl triflates and arenes; however, a stoichiometric amount

of the palladium reagent was usually required to obtain the coupling product in a satisfactorily high yield. Although we reported a catalyzed reaction using $Pd(OAc)_2$ (0.2 eq.) and Bu_3P (0.6 eq.), the procedure was not useful for coupling reactions between aryl triflate and arenes with oxygen functionalities.[4g, 4i] We therefore re-investigated the catalytic ability of our new method.

It has been reported that a palladium reagent catalyzed the intramolecular aryl triflate-arene coupling reaction using DBU as a base, while the addition of LiCl, which was thought necessary for palladium-catalyzed coupling reactions involving triflates, had a deleterious effect on the reaction of highly methoxylated substrates.[20] Thus, we examined the intramolecular coupling reaction of triflyloxybenzanilides (**40**) using $Pd(OAc)_2$ (0.1 eq.), DPPP (0.05 eq.), Bu_3P (0.1 eq.), and DBU (2 eq.) in DMF under reflux and in the absence of LiCl. The reaction of 2-(trifluoromethanesulfonyloxy)-*N*-methyl-*N*-phenylbenzamide (**40a**) under these reaction conditions proceeded smoothly to give *N*-methylphenanthridone (**9a**) in 87% yield (run 16 in Table 8). This procedure was applied to the coupling reaction of triflyloxyphenylbenzamide (**40b**) possessing a methoxy group to produce **9b** in 93% yield (run 19 in Table 8). The application of this method to the synthesis of chelerythrine from naphthylamide (**46**) was then examined. The reaction of **46** for 1 h gave oxychelerythrine (**14**) in 63% yield accompanied by the recovery of **46** in 20% yield (run 3 in Table 10).[4i, 21]

9) Conclusion

We established a convenient method for the synthesis of benzo[*c*]phenanthridine alkaloids (**1-6**), using an intramolecular palladium-assisted aryl-aryl coupling reaction of 2-halo-*N*-arylbenzamides. Subsequently, we developed the novel palladium reagent $Pd(OAc)_2$, which, in combination with DPPP, Bu_3P, and $^{i}Pr_2NEt$ or DBU, was effective for the intramolecular coupling reactions, not only of 2-OTf-*N*-arylbenzamides but also of 2-halo-*N*-arylbenzamides. By these means, we successfully synthesized pyrrophenanthridine and quinazoline alkaloids *via* an intramolecular palladium-assisted aryl-aryl coupling reaction.[22]

ACKNOWLEDGEMENTS

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