Novel Synthesis of Naphthobenzazepines from *N*-Bromobenzylnaphthylamines by Regioselective C-H Activation Utilizing the Intramolecular Coordination of an Amine to Pd

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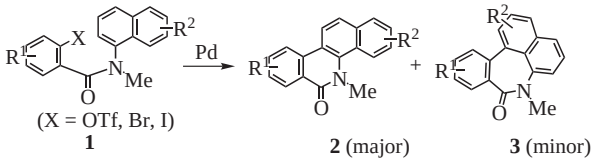
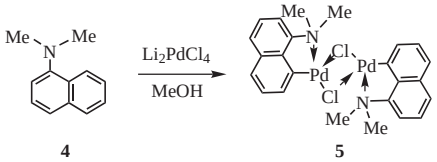
Abstract: In a biaryl coupling reaction of *N*-bromobenzylnaphthylamine using Pd reagent, the intramolecular coordination of the benzylamino group to Pd causes the regioselective C-H activation at the *peri*-position to the amine group on the naphthalene ring to produce a new skeletal compound, naphthobenzazepine, in good to excellent yield.

Key words: C-H activation, heterocycles, palladium, regioselectivity, synthetic methods

Palladium-assisted aryl-aryl coupling reactions have been used to synthesize many condensed aromatic compounds.[1] Recently, we reported that intramolecular biaryl coupling reactions of *N*-arylbenzamides using palladium reagents were a very versatile way to synthesize condensed aromatic lactams, some of which are transformed into several alkaloids.[2–5] In the intramolecular biaryl coupling reaction of *N*-naphthylbenzamide (**1**) using a Pd reagent, a small amount of naphthobenzazepinone (**3**) is obtained along with the expected benzo[*c*]phenanthridone (**2**), as shown in Scheme 1.[2,4–6]

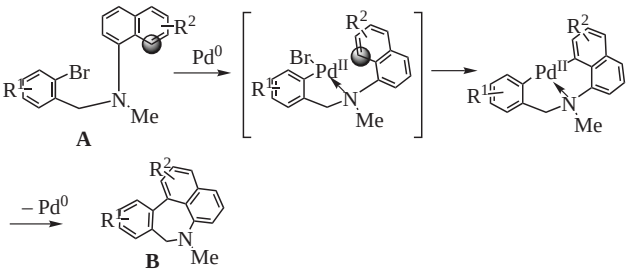


Scheme 1 Pd-assisted biaryl coupling reaction of *N*-naphthylbenzamide (**1**)

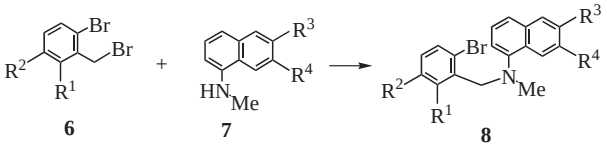


Scheme 2 Palladacycle of naphthylamine (**4**)

In 1967, Cope et al. reported that cyclopalladation reactions of naphthylamine (**4**) with palladium (II) chlorides gave palladacycle (**5**) selectively, indicating that regioselective C-H bond activation occurs at the *peri*-position to the amino group of **4** (Scheme 2).[7] Therefore, we envisioned that the intramolecular biaryl coupling reaction of *N*-bromobenzylnaphthylamine (**A**) using Pd reagent would afford a new skeletal compound, naphthobenzazepine (**B**), via an oxidative addition to Pd(0) and coordination of the amine to Pd(II), followed by the regioselective electrophilic substitution of Pd(II) at the *peri*-position and reductive elimination of Pd(0), as shown in Scheme 3 (phosphine ligands are omitted for clarity).[8,9]



Scheme 3 Synthetic strategy of naphthylbenzazepine (**B**) from *N*-benzylnaphthylamine (**A**) using regioselective C-H activation by Pd



Scheme 4 Synthesis of *N*-(6′-bromobenzyl)-1-naphthylamine (**8**). *Reagents and conditions*: Method A: K_2CO_3, Bu_4NI, DMF, 100 °C, 1–2 h; Method B: *i*-Pr_2NEt, DMF, 100 °C, 1 h

First, the biaryl coupling reaction of *N*-(bromobenzyl)naphthylamine (**8a**) was examined in relation to synthetic studies of fagaridine and decarine.[5] A compound (**8a**) was synthesized from 6-bromo-3-isopropoxy-2-methoxybenzyl bromide (**6a**)[10] and *N*-methyl-6,7-methylenedioxy-1-naphthylamine (**7a**)[4] by applying Method A (see Scheme 4 and run 1, Table 1). Then, the coupling reaction using Pd reagents was investigated. After many experiments, the biaryl coupling reaction using $Pd(OAc)_2$ (0.2 equiv), (*o*-tol)$_3$P (0.4 equiv), and K_2CO_3 (2 equiv) in DMF proceeded smoothly to provide naphthobenzazepine (**9a**), a new skeletal compound, in 71% yield. The structures of the products (**9a** and **11a**) were elucidated from elemental analyses and ^{1}H NMR data, in which **9a** showed

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Table 1 Results of Reaction of Benzylbromide (**6**) and Naphthylamines (**7**)

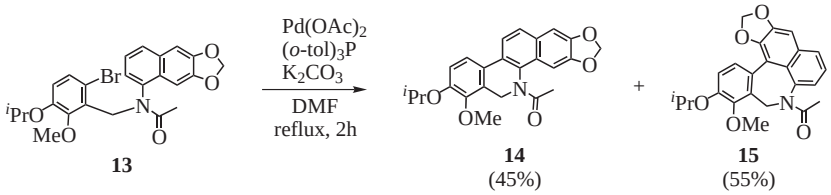
Substituent	Method	Product	Yield (%)
R^1 = OMe, R^2 = *i*-PrO, $R^3 + R^4 = OCH_2O$	A	**8a**	71
$R^1 = R^2 = R^3 = R^4$ = H	A	**8b**	98
$R^1 = R^2$ = H, $R^3 + R^4 = OCH_2O$	A	**8c**	70
$R^1 = R^2$ = OMe, $R^3 = R^4$ = H	A	**8d**	63
$R^1 = R^2$ = OMe, $R^3 + R^4 = OCH_2O$	A	**8e**	98
$R^1 = R^2$ = H, $R^3 = R^4$ = OMe	B	**8f**	95
$R^1 = R^2 = R^3 = R^4$ = OMe	B	**8g**	74
$R^1 = R^2$ = H, R^3 = OMe, R^4 = *i*-PrO	B	**8h**	quant.
$R^1 = R^2 = R^3$ = OMe, R^4 = *i*-PrO	B	**8i**	96

only one singlet signal (δ = 7.02 ppm) due to the aromatic proton in addition to the signals due to five aromatic protons and *N*-methyl signal (δ = 3.01 ppm).[12]

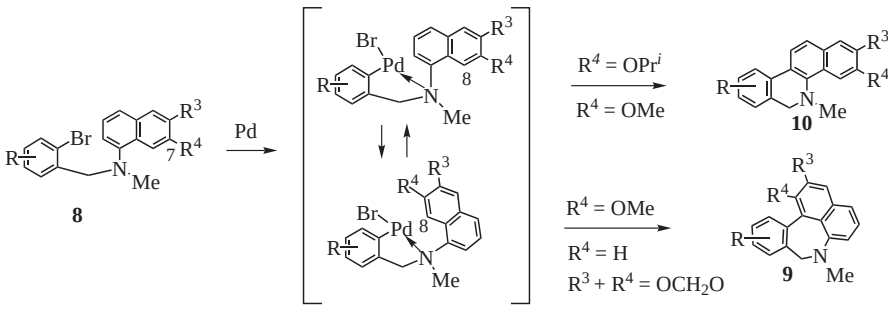
By contrast, the biaryl coupling reaction of *N*-naphthylbenzamide (**1**, X = Br) with Pd gave mainly **2**, as shown in Scheme 2 and furthermore, the reaction of *N*-acetyl amide (**13**)[13] afforded *N*-acetyl benzo[*c*]phenanthridine (**14**)[15] and *N*-acetyl naphthobenzazepine (**15**)[15] in 45% and 55% yields, respectively (Scheme 5). These prove the contribution of the benzylamino group to the production of **9a**, as shown in Scheme 3.

Next, the coupling reaction of *N*-(6′-bromobenzyl)-1-naphthylamines (**8**) using the system combining $Pd(OAc)_2$, $(o\text{-tol})_3P$, and K_2CO_3 was investigated. The starting materials (**8**) for the coupling reaction were synthesized from dibromides (**6**) and *N*-methyl-1-naphthylamines (**7**)[16] using Method A or B in high yields, as shown in Scheme 4 and Table 1. The results of the coupling reaction of **8** using Pd reagent are summarized in Table 2. *N*-Bromobenzylnaphthylamines (**8b**–**e**), which possess a methylenedioxy group or no substituent group on the naphthalene ring, produced only naphthobenzazepines (**9b**–**e**)[18] in moderate to high yields (see runs 2–5, Table 2). Interestingly, *N*-bromobenzylnaphthylamines (**8f** and **g**), which possess a methoxy group at C_7 on the naphthalene ring, produced naphthobenzazepines (**9f** and **g**)[18] and benzo[*c*]phenanthridines (**10f**[19] and **g**[20]) along with debromo-products (**11f** and **g**)[21] (see runs 6 and 7, Table 2). The methoxy group at C_7 on the naphthalene ring might hinder the coupling reaction at the *peri*-position (C_8 position) to the amino group on the naphthalene ring.[22]

N-Bromobenzylnaphthylamines (**8h** and **i**) possessing a bulky isopropoxy group relative to a methoxy group at C_7 on the naphthalene ring produced only benzo[*c*]phenanthridines (**10h** and **10i**) along with debromo- and demethylated-products (**11** and **12**)[21] (see runs 8 and 9, Table 2). These results strongly indicate that a relatively bulky substituent at the C_7 position makes the *peri*-palladation unfavorable, as shown in Scheme 6. The structures of the products were elucidated from elemental analyses, MS data, and ^{1}H NMR data. Some selected data are given in the References and Notes. Compounds (**9c**,**e**,**f**,**g**) showed only one singlet signal due to the aromatic proton and compounds (**10f**,**h**,**i**) showed two singlet signals due to the aromatic protons, in addition to the signals due to other aromatic protons. Especially, the δ values of the *N*-methyl signals were very diagnostic for structure elucidation. *N*-Methyl signals appeared at δ = 2.97–3.08 ppm for the naphthobenzazepines (**9**), δ = 2.62–2.65 for the benzo[*c*]phenanthridines (**10**), and δ = 2.75–2.84 ppm for the amides (**11**).

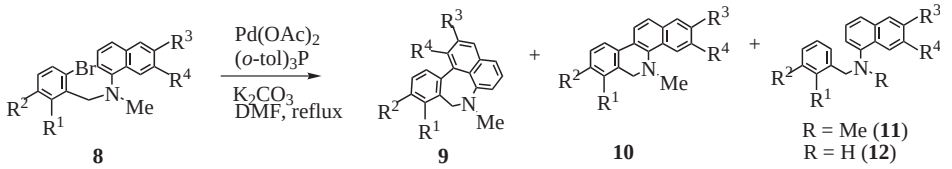


Scheme 5 Biaryl coupling reaction of amide (**13**)



Scheme 6 Proposed mechanism for biaryl coupling reaction of *N*-(bromobenzyl)naphthylamine (**8**) by Pd

Table 2 Results of Coupling Reaction of Substituted *N*-(6-bromobenzyl)-*N*-methyl-1-naphthylamines (**8**) in DMF under Reflux[a]



8 **9** **10**

Run		Substrate	Yield (%)			
			9	**10**	**11**	**12**
1	**8a**	R^1 = OMe, R^2 = *i*-PrO, $R^3 + R^4 = OCH_2O$	71	–	trace	–
2	**8b**	$R^1 = R^2 = R^3 = R^4$ = H	81	–	–	–
3	**8c**	$R^1 = R^2$ = H, $R^3 + R^4 = OCH_2O$	86	–	–	–
4	**8d**	$R^1 = R^2$ = OMe, $R^3 = R^4$ = H	44	–	–	–
5	**8e**	$R^1 = R^2$ = OMe, $R^3 + R^4 = OCH_2O$	60	–	–	–
6	**8f**	$R^1 = R^2$ = H, $R^3 = R^4$ = OMe	22	33	12	–
7	**8g**	$R^1 = R^2 = R^3 = R^4$ = OMe	18	34	10	10
8	**8h**	$R^1 = R^2$ = H, R^3 = OMe, R^4 = *i*-PrO	–	44	11	20
9	**8i**	$R^1 = R^2 = R^3$ = OMe, R^4 = *i*-PrO	–	53	11	26

[a] All reactions were carried out using 0.2 equiv of $Pd(OAc)_2$, 0.4 equiv of $(o\text{-Tol})_3P$, and 2 equiv of K_2CO_3 under Ar atmosphere for 2 h.

Note that in a biaryl coupling reaction of *N*-bromobenzylnaphthylamine using Pd reagent, the intramolecular coordination of the benzylamino group to Pd causes regioselective C-H activation to produce a new skeletal compound, naphthobenzazepine, and the bulkiness of the substituent at C_7 on the naphthalene ring affects the regioselectivity of the biaryl coupling reaction.

Acknowledgment

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(10) 6-Bromo-3-isopropoxy-2-methoxybenzyl bromide (**6a**) was prepared from 3-isopropoxy-2-methoxybenzaldehyde[11] in 54% yield via reduction with $NaBH_4$ and bromination with Br_2.

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(12) Selected ^{1}H NMR data (200 MHz, $CDCl_3$): Compound **9a**: δ = 3.01 (3 H, s, N-Me), 6.57 (1 H, br. d, *J* = 7.0 Hz), 6.86 (1 H, d, *J* = 8.5 Hz), 7.02 (1 H, s), 7.08 (1 H, br. d, *J* = 7.0 Hz), 7.14 (1 H, t, *J* = 7.0 Hz), 7.41 (1 H, d, *J* = 8.5 Hz). Compound **11a**: δ = 2.75 (3 H, s, N-Me), 7.11 (1 H, s), 7.75 (1 H, s).

(13) Compound **13** was prepared from 6-bromo-3-hydroxy-2-methoxybenzaldehyde[14] in 48% yield via etherification with isopropyl bromide, reductive alkylation with 6,7-methylenedioxy-1-naphthylamine and $NaBH_4$, and N-acetylation.

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(15) Selected ^{1}H NMR data (200 MHz, $CDCl_3$): Compound **14**: δ = 3.80 (1 H, d, *J* = 15.4 Hz, $ArCH_AH_BN$), 6.25 (1 H, d, *J* = 15.4 Hz, $ArCH_AH_BN$), 6.93 (1 H, d, *J* = 8.6 Hz), 7.13 (1 H, s), 7.28 (1 H, s), 7.52 (1 H, d, *J* = 8.6 Hz), 7.62 (1 H, d, *J* = 8.6 Hz), 7.69 (1 H, d, *J* = 8.6 Hz).Compound **15**: δ = 3.93 (1 H, d, *J* = 15.8 Hz, $ArCH_AH_BN$), 5.97 (1 H, d,

J = 15.8 Hz, $ArCH_AH_BN$), 6.84 (1 H, d, J = 8.8 Hz), 7.10 (1 H, dd, J = 7.6, 1.4 Hz), 7.17 (1 H, s), 7.29 (1 H, t, J = 7.8 Hz), 7.59 (1 H, d, J = 8.8 Hz), 7.61 (1 H, dd, J = 7.8, 1.4 Hz).

(16) 6,7-Dimethoxy-*N*-methyl-1-naphthylamine (**7f**) and 7-isopropoxy-6-methoxy-*N*-methyl-1-naphthylamine (**7h**) were prepared from 6,7-dimethoxy-1-naphthylamine[13] and 7-isopropoxy-6-methoxy-1-naphthylamine[17] in 86% and 76% yields, respectively, via trifluoroacetylation, methylation with MeI and hydrolysis with alkaline aqueous EtOH.

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(18) Selected ^{1}H NMR data (200 MHz, $CDCl_3$): Compound **9b**: δ = 3.05 (3 H, s, N-Me). Compound **9c**: δ = 2.97 (3 H, s, N-Me), 7.06 (1 H, s). Compound **9d**: δ = 3.08 (3 H, s, N-Me), 6.92 (1 H, d, J = 8.6 Hz), 7.14 (1 H, d, J = 8.6 Hz). Compound **9e**: δ = 3.00 (3 H, s, N-Me), 6.88 (1 H, d, J = 8.6 Hz), 7.03 (1 H, s), 7.45 (1 H, d, J = 8.6 Hz). Compound **9f**: δ = 2.98 (3 H, s, N-Me), 3.48 (3 H, s, OMe), 7.07 (1 H, s). Compound **9g**: δ = 3.03 (3 H, s, N-Me), 3.48 (3 H, s, OMe), 6.85 (1 H, d, J = 8.8 Hz), 7.03 (1 H, s), 7.27 (1 H, d, J = 8.8 Hz).

(19) Selected ^{1}H NMR data (200 MHz, $CDCl_3$): Compound **10f**: δ = 2.65 (3 H, s, N-Me), 7.14 (1 H, s), 7.54 (1 H, d, J = 8.6 Hz), 7.66 (1 H, s), 7.79 (1 H, d, J = 8.6 Hz). Compound **10g**: Mp 180–183 °C (lit.[20] 186–188 °C). Compound **10h**: δ = 2.63 (3 H, s, N-Me), 7.14 (1 H, s), 7.53 (1 H, d, J = 8.6 Hz), 7.69 (1 H, s), 7.78 (1 H, d, J = 8.6 Hz). Compound **10i**: δ = 2.62 (3 H, s, N-Me), 6.94 (1 H, d, J = 8.4 Hz), 7.13 (1 H, s), 7.50 (1 H, d, J = 8.4 Hz), 7.51 (1 H, d, J = 8.6 Hz), 7.69 (1 H, s), 7.71 (1 H, d, J = 8.6 Hz).

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(21) Selected ^{1}H NMR data (200 MHz, $CDCl_3$): Compound **11f**: δ = 2.82 (3 H, s, N-Me), 7.04 (1 H, dd, J = 7.4, 1.2 Hz), 7.13 (1 H, s), 7.63 (1 H, s). Compound **11g**: δ = 2.84 (3 H, s, N-Me), 6.86 (1 H, dd, J = 8.0, 1.4 Hz), 7.12 (1 H, s), 7.59 (1 H, s). Compound **11h**: δ = 2.81 (3 H, s, N-Me), 7.02 (1 H, dd, J = 7.6, 1.2 Hz), 7.13 (1 H, s), 7.62 (1 H, s). Compound **11i**: δ = 2.84 (3 H, s, N-Me), 6.87 (1 H, dd, J = 8.0, 1.2 Hz), 7.11 (1 H, s), 7.56 (1 H, s). Compound **12g**: δ = 6.56 (1 H, br d, J = 7.2 Hz), 7.02 (1 H, s), 7.10 (1 H, s). Compound **12h**: δ = 6.55 (1 H, dd, J = 7.0, 1.4 Hz), 7.12 (1 H, s), 7.18 (1 H, s). Compound **12i**: δ = 6.60 (1 H, dd, J = 7.4, 1.2 Hz), 7.01 (1 H, s), 7.11 (1 H, s).

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