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Efficient Synthesis of Phenanthridinone Derivatives via a Palladium-Catalyzed Coupling Process†

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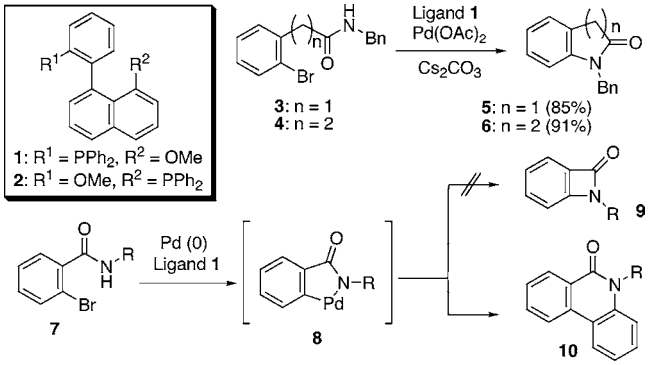
ABSTRACT

A palladium-mediated domino reaction was developed to conveniently synthesize phenanthridinone derivatives. Phosphine ligand 1 strongly promotes the domino process, which includes aryl–aryl coupling and C–N bond formations concomitant with a deamidation reaction. The versatility and applicability to a broad range of substrates make this reaction useful for the development of bioactive derivatives.

Palladium-mediated reactions are powerful synthetic tools for constructing highly complex molecules. Among these reactions, C−N bond formations[1] have been recently employed as the key step for the total synthesis of nitrogen-containing natural products as well as for the construction of heterocycles in drug discovery due to their high efficiency and compatibility with numerous functional groups.

We have recently developed novel phenylnaphthyl phosphine ligands **1** and **2** and have demonstrated their excellent functions in Pd-catalyzed intramolecular amidations.[2] Utilizing **1** and **2**, we have efficiently prepared indoline **5** and quinoline derivative **6** from **3** and **4**, respectively. As part of our continuing investigation on these C−N bond forming reactions by virtue of ligands **1** and **2**, we have explored *β*-lactam formation from 2-bromobenzamide derivative **7**. Initially, we expected that five-membered palladacycle **8**, which is readily afforded by oxidative addition of Pd(0), would yield desired product **9** via a reductive elimination of Pd(II) species (Scheme 1). However, the reaction unexpectedly afforded phenanthridinone derivative **10** as the sole

Scheme 1. Pd-Mediated Lactam Ring Formations Using Ligand **1**



† This paper is dedicated to the memory of the late Prof. Kiyoshi Tanaka, who passed away December 8, 2004.

(1) For reviews on Pd-catalyzed C−N bond formations, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (d) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041−2075.

(2) (a) Yoshikawa, S.; Odaira, J.; Kitamura, Y.; Bedekar, A. V.; Furuta, T.; Tanaka, K. *Tetrahedron* **2004**, *60*, 2225−2234. (b) Kitamura, Y.; Hashimoto, A.; Yoshikawa, S.; Odaira, J.; Furuta, T.; Kan, T.; Tanaka, K. *Synlett* **2006**, 115−117.

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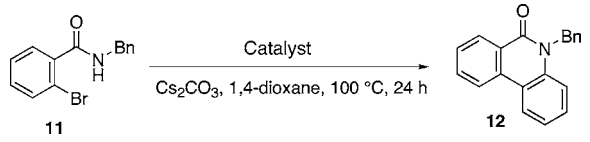
product by a homocoupling reaction of **7**. This coupling reaction should proceed through a domino process concomitant with C−C and C−N bond forming reactions.

Because we are interested in ligand efficacy and because of the importance of phenanthridinone derivatives,[3] we further investigated this reaction. Herein, we report the details of this domino reaction in the presence of ligand **1**.

First, we explored the appropriate synthetic conditions with **11** (Table 1).[4] Ligand **1** afforded **12** in an excellent yield of

Table 1. Ligand Effect on the Coupling Reaction of **11**[a]



11 **12**

entry	catalyst	yield (%)[b]
1	$Pd(OAc)_2$/**1**	77
2	$Pd(OAc)_2$/**2**	29
3	$Pd(OAc)_2$/BINAP	44
4	$Pd(OAc)_2$/MOP	48
5	$Pd(PPh_3)_4$	–
6	$Pd(OAc)_2$	49

[a] The reaction was conducted using a Pd catalyst (6.0 mol %), a ligand (5.0 mol %), and Cs_2CO_3 (1.0 equiv) in dioxane for 24 h at 100 °C. [b]Yields of the isolated products.

77% (Table 1, entry 1); however, ligand **2**, BINAP, and MOP did not show prominent effects (Table 1, entries 2−4), and $Pd(PPh_3)_4$ completely inhibited the reaction (Table 1, entry 5). This coupling also proceeded under ligand-free conditions (Table 1, entry 6). Hence, these results indicate that novel phosphine **1** is a powerful ligand for this reaction.

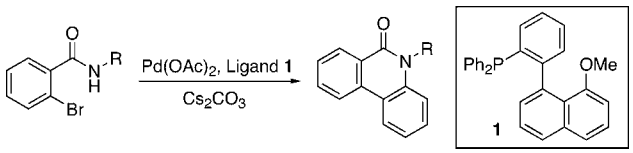
As shown in Table 2, the outcome of the reaction strongly depends on the amide substituents. The reaction of substrates containing methyl, allyl, and phenyl substituents resulted in low yields (Table 2, entries 1−3).[5] However, substrates with *p*-methoxy- and 2,4-dimethoxybenzyl moieties provided

(3) Phenanthridinone derivatives are often found in bioactive compounds and have received much attention as valuable intermediates for nitrogen-containing natural products. See: (a) Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc. Perkin Trans. 1* **2001**, 523−528. (b) Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K.; Akamatsu, H.; Hori, A.; Abe, H.; Takeuchi, Y. *Synthesis* **2002**, 237−241. (c) Bellocchi, D.; Macchiarulo, A.; Costantino, G.; Pellicciari, R. *Bioorg. Med. Chem.* **2005**, *13*, 1151-1157. (d) Ishida, J.; Hattori, K.; Yamamoto, H.; Iwashita, A.; Mihara, K.; Matsuoka, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4221-4225.

(4) **Typical procedure for a domino coupling:** $Pd(OAc)_2$ (2.5 mg, 0.010 mmol) was added to a solution of ligand **1** (3.6 mg, 0.0086 mmol) in 1,4-dioxane (1.2 mL) under an argon atmosphere. After sonicating the solution, **11** (50 mg, 0.17 mmol) and Cs_2CO_3 (56 mg, 0.17 mmol) were added to the solution at room temperature and the mixture was stirred for 24 h at 100 °C. After stirring, H_2O was added and then extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 7:3) to afford **12** (19 mg, 77%) as a colorless solid. The structure of **12** was unambiguously determined by X-ray analysis. (See Supporting Information.)

(5) The reaction did not proceed unless the amide nitrogen group was protected. Only the starting material was recovered. The same observation is depicted in ref 6.

Table 2. Effects of the Amide Substituents[a]



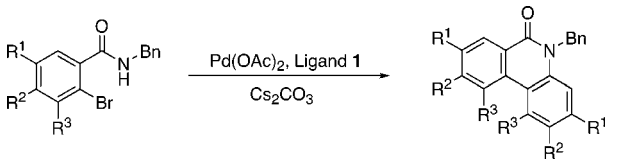
entry	substrate	product	yield (%)[b]
1	**13a**: R = Me	**14a**	28
2	**13b**: R = allyl	**14b**	32
3	**13c**: R = Ph	**14c**	23
4	**13d**: R = *p*-methoxybenzyl	**14d**	64
5	**13e**: R = 2,4-dimethoxybenzyl	**14e**	72

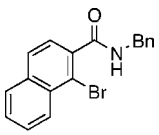
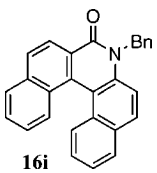
[a] The reaction was conducted with $Pd(OAc)_2$ (6.0 mol %), ligand **1** (5.0 mol %), and Cs_2CO_3 (1.0 equiv) in dioxane for 24 h at 100 °C. [b]Yields of the isolated products.

corresponding products **14d** and **14e** in 64% and 72% yields, respectively. These results along with the satisfactory result from *N*-benzyl-protected **11** (Table 1, entry 1) revealed that benzyl related protecting groups are appropriate for this coupling reaction.

To further test the scope and limitations of the reaction, we examined a variety of substituted 2-bromobenzamides (Table 3). Interestingly, this reaction depends on the elec-

Table 3. Effects of the Electronic Property of the Substituents[a]



entry	substrate	product	yield (%)[b]
1	**15a**: $R^1 = R^2 = H$, $R^3 = NO_2$	**16a**	–
2	**15b**: $R^1 = NO_2$, $R^2 = R^3 = H$	**16b**	–
3	**15c**: $R^1 = R^3 = H$, $R^2 = F$	**16c**	45
4	**15d**: $R^1 = Cl$, $R^2 = R^3 = H$	**16d**	37
5	**15e**: $R^1 = R^2 = H$, $R^3 = Me$	**16e**	81
6	**15f**: $R^1 = R^3 = H$, $R^2 = Me$	**16f**	67
7	**15g**: $R^1 = OMe$, $R^2 = R^3 = H$	**16g**	41
8	**15h**: $R^1 = R^2 = OMe$, $R^3 = H$	**16h**	92
9	 **15i**	 **16i**	59

[a] The same conditions as those in Table 2 were used. [b]Yields of the isolated products.

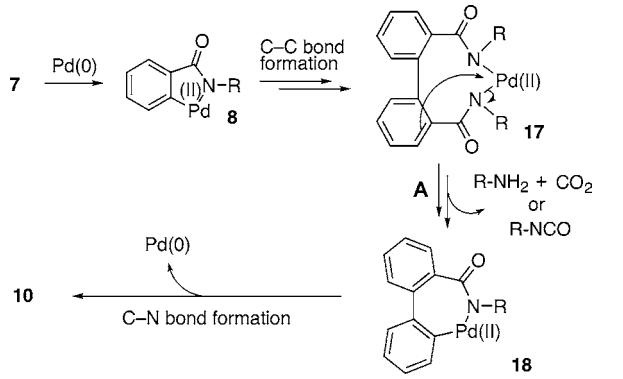
tronic nature of the aromatic ring. The reaction with aryl halides **15a**−**d**, which possess electron-withdrawing groups, did not proceed smoothly (Table 3, entries 1−4). On the

other hand, substrates **15e** and **15f**, which possess electron-donating methyl substituents, afforded the coupling products in 81% and 67% yield, respectively. It is noteworthy that the reaction of **15h**, which possesses an electron-rich phenyl moiety due to electron donation from two methoxy groups, afforded **16h** in excellent yield (Table 3, entry 8). These results clearly demonstrate that an electron-rich aryl moiety makes the domino reaction efficient.

Another promising property of this coupling is the compatibility with sterically hindered 3-substituted bromobenzamides such as **15e** (Table 3, entry 5). An extension of this observation is demonstrated in the coupling of naphthyl derivative **15i** to binaphthyl **16i** (Table 3, entry 9). Because products **16e** and **16i** are axially chiral, further applications of this protocol on asymmetric synthesis should provide optically active compounds.

During the course of our investigation, Ferraccioli and Catellani reported the same type of coupling reactions using a different catalytic system.[6,7] Taking both their proposed mechanism and our results into account, the reaction possibly proceeds through domino C−C and C−N bond formations involving an *ipso* substitution as shown in Scheme 2. The

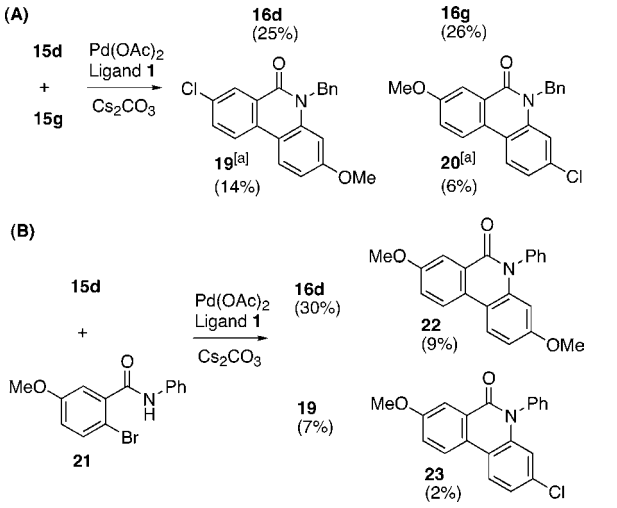
Scheme 2. Outline of the Catalytic Cycle



high reactivity of substrates with electron-donating substituents on the aromatic ring (Table 3, entries 5−8) could support a nucleophilic attack of the aromatic electron to Pd(II) (step A). After the deamidation reaction by the elimination of amine and CO_2[8] or the isocyanate derivative[9] to **18**, the C−N bond is formed by the reductive elimination of Pd(II) to yield phenanthridinone derivative **10**.

Next, we expanded this coupling reaction to the cross-coupling process. To examine the feasibility of this approach, we conducted the reaction using an equimolar amount of substrates **15d** and **15g**, which have nearly the same reactivities (Table 3, entries 4 and 7). However, the reaction gave a mixture of all the theoretically predicted coupling products, including homocoupled products **16d** (25%) and **16g** (26%) and cross-coupled **19** (14%) and **20** (6%) (Scheme 3A).[10]

Scheme 3. Extension of the Cross-Coupling Reaction



[a] The yields were calculated by ^{1}H NMR.

Another coupling reaction with **15d** and **21**, which have different N-protecting groups, also gave a mixture of coupling products (Scheme 3B).[11] Although selective cross-coupling would be difficult, the convenience of this protocol should be applicable to combinatorial chemistry as well as to diversity oriented synthesis. Furthermore, the removal of the PMB group proceeded under acidic conditions to give **24** as shown in Scheme 4. Therefore, various compounds, which are diversified at the amide substituent, should be readily prepared by the deprotection−alkylation sequence at the resulting amide nitrogen group.

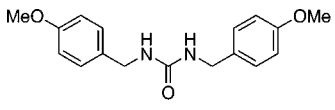
In summary, we have clarified that our ligand **1** works well toward the C−C and C−N bond forming domino reaction and have developed an efficient method for phenanthridinone synthesis. This reaction is a promising method

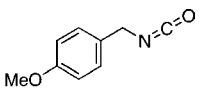
(6) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2006**, *128*, 722−723.

(7) A similar reaction was originally discovered by Caddick et al. during their investigations of an intramolecular Heck reaction of **13b** in the presence of an N-heterocyclic carbene (NHC) ligand. Phenanthridinone **14b** was obtained in 32% yield. See: Caddick, S.; Kofie, W. *Tetrahedron Lett.* **2002**, *43*, 9347−9350.

(8) Ref 6 has proposed a mechanism for the decomposition of the amide substituent by a nucleophilic attack of the palladium-bonded bicarbonate anion to yield an amine derivative and CO_2.

(9) During the reaction of **11** to **12** (Table 1, entry 1), we observed a peak that corresponds to benzyl isocyanate (*m*/*z* 313) using GC-MS analysis. For details of the GC-MS analysis, see Supporting Information. Moreover, symmetrical urea derivative **25** was isolated in 40% yield from the experiment of entry 4 in Table 2. Urea **25** could be derived from the dimerization and subsequent decarboxylation of corresponding isocyanate derivative **26**.

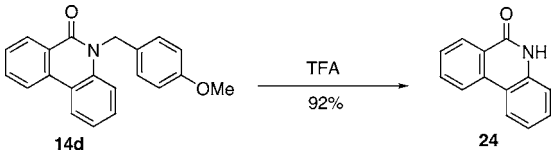




(10) The reason for the predominant yield of homocoupling products **16d** and **16g** might be explained by the reactivity order of the substrates.

(11) The predominant formation of *N*-benzyl-substituted phenanthridinone derivative **16d** could be explained by the high reactivity of *N*-benzyl-protected substrate **15d**.

Scheme 4. Deprotection of the PMB Protecting Group



14d **24**

for developing a variety of phenanthridinone derivatives and should be applicable to a broad range of substrates.[12]

Further mechanistic studies and applications to prepare axially chiral biaryls as well as to develop alternative bioactive heterocycles using this catalytic system are currently underway.

Acknowledgment. We thank Prof. Yasuhiro Uozumi (Institute for Molecular Science) and Prof. Kyoko Nozaki (The University of Tokyo) for their valuable discussions on the mechanistic consideration of the reaction. Financial support from the Uehara Memorial Foundation is also gratefully acknowledged.

Supporting Information Available: Spectral data for all new compounds and details for experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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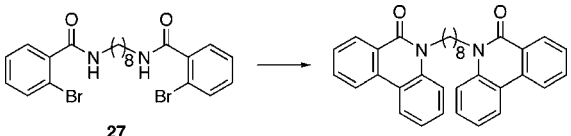
(12) The reaction with N-tethered 2-bromobenzamide **27** gave phenanthridinone dimer **28** as the major product. For the details of this reaction, see Supporting Information.



27 **28** (31%)