JOC*Note*

Pd-Catalyzed Amidation of 2-Chloro- and 2,7-Dichloro-1,8-naphthyridines

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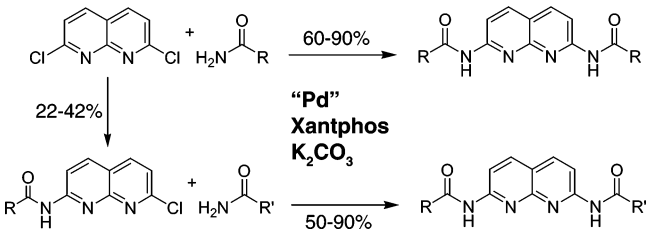
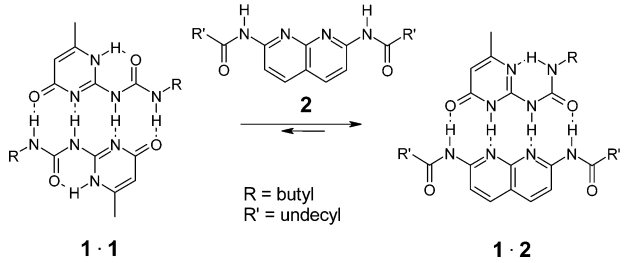


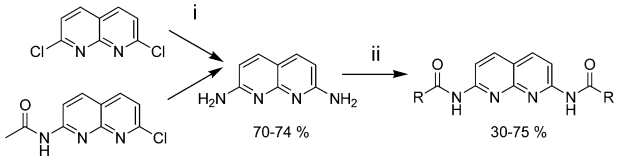
The catalytic amidation between 2-chloro- and 2,7-dichloro-1,8-naphthyridines and primary amides bearing functional groups is reported. When $Pd(OAc)_2$, xantphos, and K_2CO_3 are used, it is possible to obtain symmetric as well as nonsymmetric 2,7-diamido-1,8-naphthyridines in 50−90% yield with good functional-group tolerance. Monoamidation of 2,7-dichloro-1,8-naphthyridine using 0.9 equiv of the amide proceeded with good selectivity compared to the formation of the diamide, but as a result of the difficult isolation of the product, isolated yields were poor to moderate (22−42%).

The use of intermolecular interactions to organize two- or three-dimensional structures from synthetic molecules through a spontaneous and reversible process is termed self-assembly.[1] Among several noncovalent interactions, multiple hydrogen-bond arrays have received much attention for their use in self-assembly processes.[2] Specifically, quadruple hydrogen-bonding units[3] have been demonstrated to be very useful in supramolecular polymer chemistry as a result of their strength and directionality.[4] Although self-complementary quadruple hydrogen-bonding motifs have been available since 1997, developing complementary quadruple hydrogen-bonding units has been much more challenging.[5] Zimmerman et al. were the first to report a complementary quadruple hydrogen bond with a 2,7-diamido-1,8-naphthyridine derivative.[3c,6] Recently, Li and co-workers[7] reported the strong and selective complementary complexation of the 6[1*H*] tautomeric form of a ureido-pyrimidinone **1** (UPy) with 2,7-diamido-1,8-naphthyridines **2** (Napy) via quadruple hydrogen bonds between acceptor−donor−donor−acceptor (ADDA) and donor−acceptor−acceptor−donor (DAAD) arrays (Scheme 1). Subsequently, we showed that this heterocomplex formation exhibits a concentration-dependent selectivity with K_a(UPy−Napy) = $>10^6$ M^{-1}.[8] The high selectivity and strength render the UPy−Napy heterodimer very attractive for constructing supramolecular architectures. The literature procedure to synthesize these diamidonaphthyridines **2** uses 2,7-diamino-1,8-naphthyridine[9] obtained by aminolysis of either the nonsymmetric 7-acetamido-2-chloro-1,8-naphthyridine[9] or the symmetric 2,7-chloro-1,8-naphthyridine[10] (Scheme 2).

SCHEME 1. UPy (1)−Napy (2) Heterocomplexation



SCHEME 2. Traditional 2,7-Diamido-1,8-naphthyridine Synthesis[a]



[a] i: NH_4OH, 180 °C, 24 h. ii: Acid chloride, Et_3N, $CHCl_3$.

The aminolysis reaction requires high pressures and temperatures, thus creating a potential safety hazard. Furthermore, the isolated diamino product is often of low purity. A subsequent reaction with an acid chloride yields the diamido derivatives in low to moderate yields (Scheme 2).[7c,9] Therefore, improving the synthetic route toward functionalized Napy derivatives is a key issue in the development of complementary quadruple hydrogen bonding for self-assembly.

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(6) For a more recent example of the use of Napy in supramolecular systems, see: Park, T.; Zimmerman, S. C.; Nakashima, S. *J. Am. Chem. Soc.* **2005**, *127*, 6520.
(7) (a) Wang, X.-W.; Li, X.-Q.; Shao, X.-B.; Zhao, X.; Deng, P.; Jiang, X.-K.; Li, Z.-T.; Chen, G.-J. *Chem.−Eur. J.* **2003**, *9*, 2904. (b) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128. (c) Li, X.-Q.; Jiang, X.-K.; Wang, X.-Z.; Li, Z.-T. *Tetrahedron* **2004**, *60*, 2063. (d) Li, X.-Q.; Feng, D.-J.; Jiang, X.-K.; Li, Z.-T. *Tetrahedron* **2004**, *60*, 8275.
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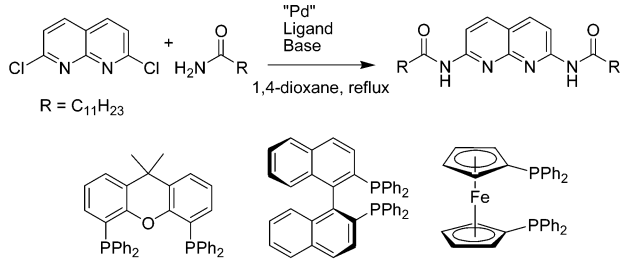
TABLE 1. Optimization of Conditions[a]



entry	% Pd[b]	ligand	base	conv[c] (%)	yield[d] (%)
1	8	xantphos	Cs_2CO_3	>99	82
2	8	xantphos	KO-*t*-Bu	<25	0
3	8	BINAP	Cs_2CO_3	56	25
4	8	DPPF	Cs_2CO_3	36	15
5	4	xantphos	Cs_2CO_3	>99	78
6	4[e]	xantphos	K_2CO_3	>99[f]	85
7	4[e,g]	xantphos	K_2CO_3	>99[f]	80

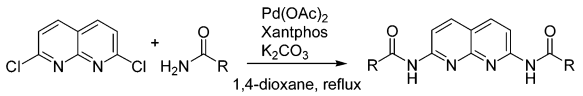
[a] Reaction conditions: 0.5 mmol of 2,7-dichloro-1,8-naphthyridine, 1.0 mmol of dodecanamide, L/Pd = 2.0, 2.1 equiv of base, 3−5 mL of 1,4-dioxane, 100 °C, 24 h. [b] One molar percent Pd refers to 0.5 mol % $Pd_2(dba)_3$ (dba = dibenzylideneacetone). [c] As determined by ^1H NMR. [d] Isolated yields. [e] $Pd(OAc)_2$ was used. [f] Reaction time 5 h. [g] A total of 0.05 mmol of $PhB(OH)_2$ was added.

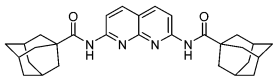
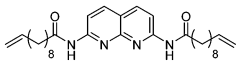
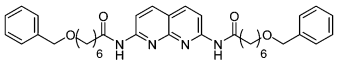
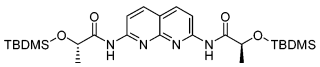
Over the past decade, palladium-catalyzed C−N bond-forming reactions by the cross-coupling of aryl halides and amines have been extensively studied by the groups of Hartwig and Buchwald.[11] Although a wide range of aryl halides could be aminated with various amines, attempts to perform the analogous coupling reactions using primary amides as the nitrogen nucleophile were less successful. Recently, Buchwald and Yin reported the successful Pd-catalyzed amidation of various aryl halides, tosylates, and triflates,[12] as well as a Cu-catalyzed cross-coupling of aryl bromides and iodides with primary amides.[13] These results prompted us to explore the application of these catalytic amidations on chloronaphthyridines. In this note, we describe a general Pd-catalyzed amidation of mono- and dichloro-1,8-naphthyridines with primary amides to obtain a DAAD quadruple hydrogen-bond motif.

The reaction between 2,7-dichloro-1,8-naphthyridine and dodecanamide was examined first to establish the most effective conditions (Table 1). With xantphos[14] as the ligand and Cs_2CO_3 as a base, the reaction went smoothly (Table 1, entry 1). In contrast, replacing Cs_2CO_3 by the strong base KO-*t*-Bu decreased the yield significantly (entry 2). This can be rationalized by the hydrolysis of the weak Napy amide bond to a primary amine[7c,15] upon workup of the basic reaction mixture.

In addition to xantphos, bidentate phosphine ligands 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) and 1,1′-bis-(diphenylphosphino)ferrocene (DPPF) were also tested (entries 3 and 4). However, conversions as well as isolated yields were lower. Near-quantitative conversion was observed when the amount of palladium(0) was reduced or replaced by a palladium(II) source, $Pd(OAc)_2$ (entries 5 and 6). It was reported earlier by Buchwald et al. that $Pd(OAc)_2$ is the Pd source of choice in reactions involving electron-deficient aryl halides. Because 2,7-dichloro-1,8-naphthyridine is an electron-deficient aryl dihalide, the reaction was complete within 5 h. The addition of a catalytic amount of phenyl boronic acid to decrease the reaction time of the Pd(II) precatalyst to Pd(0) did not improve the yield further (entry 7).[13c] From an industrial point of view, 1,4-dioxane has often been replaced by toluene as a solvent; however, as a result of the poor solubility of the dichloro compound, 1,4-dioxane was selected.

TABLE 2. Pd-Catalyzed Amidation of 2,7-Dichloro-1,8-naphthyridine[a]



entry	product	mol% Pd	time(h)	yld(%)
1		10	20	82
2		4.5	4	90
3		8.6[b]	10	60
4		4.7	10	82

[a] Reaction conditions: 2,7-dichloro-1,8-naphthyridine (1 equiv), amide (2 equiv), L/Pd = 2.5−3.0, and K_2CO_3 (2.0−2.1 equiv) in refluxing 1,4-dioxane (0.15−0.25 M). [b] $Pd_2(dba)_3$ was used as the palladium source.

When the optimized conditions were used, that is, xantphos as the ligand, K_2CO_3 as the base, and dioxane as the solvent, several primary amides were reacted with 2,7-dichloro-1,8-naphthyridine (Table 2). As demonstrated in Table 2, symmetric Napy derivatives were obtained in high yields in 4−10 h. A bulky primary amide like adamantyl-1-carboxylic amide (entry 1) required a longer reaction time. It was previously reported that the use of a base such as Cs_2CO_3 or K_2CO_3 is compatible with the presence of functional groups.[16] Amidation with 10-undecenamide went very rapidly, and the product was isolated in high yield (entry 2). A small amount of the terminal double bond of the amide was isomerized to an internal double bond during the reaction when 4 mol % $Pd(OAc)_2$ was used. Increasing the amount of palladium to 10 mol % also increased the amount of isomerized product, which is difficult to separate from the desired compound (see Supporting Information).

Bis-hydroxy-terminated naphthyridines are useful derivatives for polymer structures. However, 6-hydroxy-hexanamide did not react under the aforementioned conditions to yield the desired product. When the reaction was performed with 6-benzyloxy-protected hexanamide, the symmetric product was obtained in moderate yield (entry 3). A second protected hydroxy amide, which was readily synthesized from commercially available

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SCHEME 3. Two Approaches to Nonsymmetric 7-Amido-2-chloro-1,8-naphthyridines

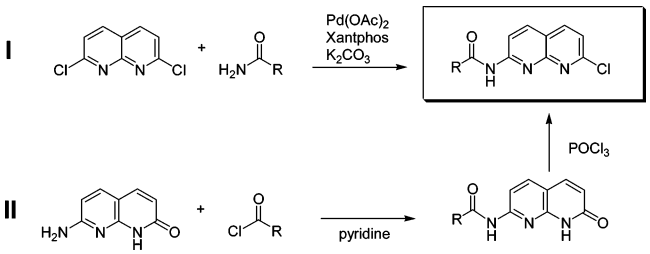
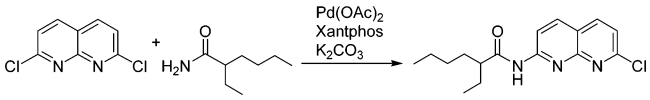


TABLE 3. Nonsymmetric Pd-Catalyzed Amidation of 2,7-Dichloro-1,8-naphthyridine[a]



entry	*T* (°C)	solvent	time (h)	conv[b] (%)	m/d ratio[c]
1	100	1,4-dioxane	6	>99	3.3
2	80	1,4-dioxane	20	>99	3.8
3	60	1,4-dioxane	20	20	>20
4	60	THF	16	55	7.1
5	60	DMF	16	65	18
6[d]	80	1,4-dioxane	8	>92	6.8

[a] Reaction conditions: 0.25 mmol of 2,7-dichloro-1,8-naphthyridine, 2 mol % $Pd(OAc)_2$, 4 mol % xantphos, 0.7 mmol of K_2CO_3, 1.0 equiv of 2-ethylhexanamide, and 1.0 mL of solvent. [b] Based on amide consumption, as determined by ^{1}H NMR. [c] Monoamido/diamido ratio. [d] A total of 0.9 equiv of 2-ethylhexanamide was used.

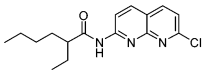
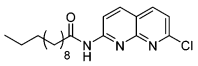
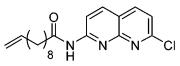
ethyl-*S*-lactate, also reacted with dichloronaphthyridine in high yield (entry 4). A strong advantage of the catalytic route, next to the high yield of amidation, is that purification by column chromatography of the crystallizable products (entries 2 and 4) is not necessary.

Next, we examined the synthesis of nonsymmetric naphthyridines. The introduction of functional groups on one side of the compound would open up the possibility to functionalize various other organic compounds with Napy groups. Nonsymmetric naphthyridines have been prepared previously by the nonsymmetric hydrolysis of Napy to a 7-amino-2-amido-1,8-naphthyridine derivative.[7c] A subsequent reaction with an acid chloride yields a nonsymmetric diamide derivative in moderate yield.[7d] We decided to pursue two alternative approaches using the catalytic amidation mentioned before (Scheme 3).

The first strategy, requiring the least number of synthetic steps, is the monoamidation of 2,7-dichloro-1,8-naphthyridine. It is reasonable to assume that the second amidation of dichloronaphthyridine is slower than the first amidation because, after the substitution of the first chloro substituent, the reactivity is lowered by the weaker electron-withdrawing amide substituent. Therefore, the catalytic amidation of the dichloro derivative with 1 equiv of 2-ethylhexanamide was examined (Table 3).

Although conversion is quantitative within 6 h when 1.0 equiv of amide is used, it is evident that the second amidation competes with the first. This is expressed in the mono- to diamido- ratio being quite small (entry 1). A decrease in temperature results in an increase of this ratio; however, it also results in a decrease in conversion (entries 2 and 3). Although the conversion increased slightly by using THF and DMF at 60 °C (entries 4 and 5), the difficulty of removing DMF from the reaction mixture makes 1,4-dioxane at 80 °C the preferred solvent. Finally, a good product to side-product ratio was obtained by reducing the amount of the primary amide to 0.9 equiv and reducing the reaction time to 8 h.

TABLE 4. Nonsymmetric Pd-Catalyzed Amidation of 2,7-Dichloro-1,8-naphthyridine[a]

entry	product	conv (%)[b]	m/d ratio[c]	yld (%)[d]
1		92	6.8	42
2		94	7,0	25
3		91	6,2	22

[a] Reaction conditions: 0.25 mmol of 2,7-dichloro-1,8-naphthyridine, 2 mol % $Pd(OAc)_2$, 4 mol % xantphos, 0.7 mmol of K_2CO_3, 0.9 equiv of amide, 1.0 mL of 1,4-dioxane, 8 h, 80 °C. [b] Based on amide consumption, as determined by ^{1}H NMR. [c] Monoamido/diamido ratio. [d] Isolated in >99% purity after UPy-assisted column chromatography.

When the optimized conditions were used, three nonsymmetric chloronaphthyridines were synthesized and isolated (Table 4, entries 1−3). In contrast to the synthesis of symmetric diamidonaphthyridines, these nonsymmetric compounds are very difficult to purify. However, we could use supramolecular chemistry to achieve the isolation of the nonsymmetric product. As a result of the formation of strong heterocomplexes of **1** with Napy, the R_f factor of the latter compounds was reduced, allowing their separation from the nonbinding monoamides. Although the Ullmann−Goldberg type catalytic monoamidations have been reported before for aryl bromides with secondary amides,[17] to our knowledge this is the first time a Buchwald−Hartwig monoamidation with primary amides is reported.

In the second strategy of Scheme 3, the amide is introduced by the reaction of 7-amino-[1*H*]-2-oxo-1,8-naphthyridine[10] with an acid chloride of choice, followed by the conversion of the oxo group to the chloride using $POCl_3$. By this strategy, moderate overall reaction yields of 50−60% were reported.[8,9] We used this strategy to obtain the starting material with one acetylamido side chain to synthesize a series of nonsymmetric diamidonaphthyridines (Table 5).

Although the nonsymmetric products required purification by column chromatography, isolated yields were moderate to good. The introduction of bulky side groups, however, led to a decrease in yield, and more catalyst had to be used (entries 1−3). As found previously, functional groups could be introduced in good yields (entries 4−6). Furthermore, no olefin isomerization was detected at catalyst loadings lower than 2 mol % (entry 4).

All of these compounds are quite prone to acidic or basic hydrolysis as a result of the electron-poor character of the naphthyridine core, which makes the carbon in the amide carbonyl more electrophilic.[18] Therefore, a 2-ethylpentyl[7] or a *tert*-butyl side chain was introduced to decrease the sensitivity to hydrolysis. In addition, these side chains also enhanced the

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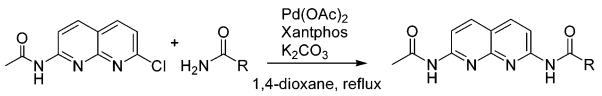
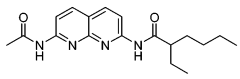
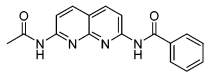
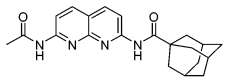
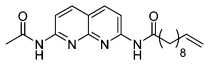
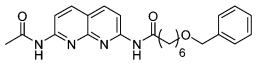
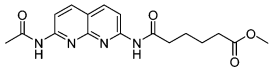
(18) A full study on this subject will be reported elsewhere.

TABLE 5. Pd-Catalyzed Amidation of 7-Acetamido-2-chloro-1,8-naphthyridine[a]



entry	product	mol% Pd	time(h)	yld(%)
1		1.4	18	66
2		4.0[b]	20	51
3		10	20	35
4		1.0	20	88
5		4.0[b]	18	80
6		4.0[b]	24	76

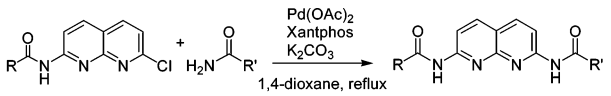
[a] Reaction conditions: 7-acetamido-2-chloro-1,8-naphthyridine (1 equiv), amide (1.2 equiv), L/Pd = 2.0, and K_2CO_3 (1.4 equiv) in refluxing 1,4-dioxane (0.20−0.25 M). [b] $Pd_2(dba)_3$ was used in combination with Cs_2CO_3 (1.4 equiv).

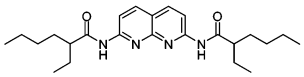
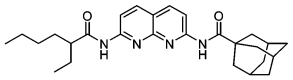
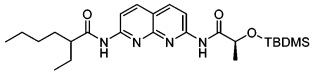
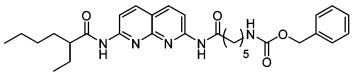
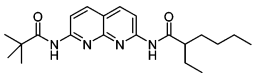
solubility of the derivatives. Pd-catalyzed amidation reactions on these 2-chloro-1,8-naphthyridine derivatives are summarized in Table 6.

Slightly higher yields were obtained when 7-(2-ethyl)-hexanamido-2-chloro-1,8-naphthyridine was used as the halide instead of the acetamido derivative (entries 1 and 2). This can be rationalized either by its greater solubility or by the decomposition of the acetamido derivatives on silica gel. The asymmetric TBDMS-protected alcohol-containing naphthyridine was obtained in good yield, and in contrast to its symmetric analogue, it was readily soluble in apolar solvents such as toluene and pentane (entry 3). In contrast to all previously isolated compounds, the benzyl-carbamate-protected 6-amino-hexanamido-naphthyridine was isolated as an oil (entry 4). Finally, a moderate yield was obtained when 2-ethylhexanamide was reacted with 7-*tert*-butyl-2-chloro-1,8-naphthyridine (entry 5).

In conclusion, a general palladium-catalyzed amidation of 2-chloro- and 2,7-dichloro-1,8-naphthyridines was developed using $Pd(OAc)_2$ as the catalyst, xantphos as the ligand, K_2CO_3 as the base, and 1,4-dioxane as the solvent. Because a weak base is used in this procedure, functional groups are incorporated easily. Furthermore, introducing branched side chains not only increases stability toward hydrolysis but also enhances solubility of the naphthyridine derivatives. The simplicity and functional-group tolerance make this an attractive method for synthesizing Napy-functionalized molecules that can be used in many aspects of the self-assembly of discrete structures as well as supramolecular copolymers. Significant differences in reactivity between 2-chloro-7-amido and 2,7-dichloro-1,8-naphthyridines allow the synthesis of monoamidonaphthyridines with good selectivity, but as a result of the similar chromatographic behavior of the monoamido and diamidonaphthyridines, isolated yields of the monoamidonaphthyridines are poor to moderate.

TABLE 6. Pd-Catalyzed Amidation of 7-Amido-2-chloro-1,8-naphthyridine[a]



entry	product	mol% Pd	time(h)	yld(%)
1		4.0	16	89
2		10	20	47
3		1.1	10	85
4		1.1	20	65
5		1.3	20	54

[a] Reaction conditions: 7-amido-2-chloro-1,8-naphthyridine (1 equiv), amide (1.2 equiv). L/Pd = 2.0, and K_2CO_3 (1.4 equiv) in refluxing 1,4-dioxane (0.20−0.25 M).

Experimental Section

General Procedure for the Symmetric Pd-Catalyzed Amidation of 2,7-Dichloro-1,8-naphthyridine with Primary Amides (Tables 1 and 2). A Schlenck tube was charged with Pd catalyst, ligand (L/Pd = 2.0−3.0), inorganic base (2 equiv), 2,7-dichloro-1,8-naphthyridine (1 equiv), primary amide (2 equiv), and 1,4-dioxane. The Schlenck tube was capped, evacuated, and back-filled with Ar three times. While still under Ar, it was immersed into a 100 °C oil bath. After stirring for 4−24 h, the mixture was cooled, filtered over diatomaceous earth, and evaporated in vacuo.

General Procedure for the Nonsymmetric Pd-Catalyzed Amidation of 2,7-Dichloro-1,8-naphthyridine with Primary Amides (Table 4). A Schlenck tube was charged with Pd catalyst, ligand (L/Pd = 2.0−3.0), inorganic base (1.4 equiv), 2,7-dichloro-1,8-naphthyridine (1 equiv), primary amide (0.9 equiv), and 1,4-dioxane. The Schlenck tube was capped, evacuated, and back-filled with Ar three times. While still under Ar, it was immersed into an 80 °C oil bath. After stirring for 8 h, the mixture was cooled, filtered over diatomaceous earth, and evaporated in vacuo.

General Procedure for the Pd-Catalyzed Amidation of 7-Amido-2-chloro-1,8-naphthyridine with Primary Amides (Tables 5 and 6). A Schlenck tube was charged with Pd catalyst, ligand (L/Pd = 2.0), K_2CO_3 (1.4 equiv), corresponding 7-amido-2-chloro-1,8-naphthyridine (1 equiv), primary amide (1.2 equiv), and 1,4-dioxane (0.20−0.25 M). The Schlenck tube was capped, evacuated, and back-filled with Ar three times. While still under Ar, it was immersed into a 100 °C oil bath. After stirring for 10−24 h, the mixture was cooled, filtered over diatomaceous earth, and evaporated in vacuo.

Acknowledgment. We thank Dr. Xiaohua Huang and Prof. Stephen L. Buchwald for helpful suggestions and STW and CW/NWO for financial support.

Supporting Information Available: Detailed experimental procedures and the characterization of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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