JOC Article

Carbopalladation of Nitriles: Synthesis of 3,4-Disubstituted 2-Aminonaphthalenes and 1,3-Benzoxazine Derivatives by the Palladium-Catalyzed Annulation of Alkynes by (2-Iodophenyl)acetonitrile

Qingping Tian, Alexandre A. Pletnev, and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

larock@iastate.edu

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Intramolecular carbopalladation of the cyano group has been employed for the synthesis of 3,4-disubstituted 2-aminonaphthalenes. (2-Iodophenyl)acetonitrile reacts with a variety of internal alkynes to afford 2-aminonaphthalenes in high yields with good regioselectivity. The scope and limitations of this process, which proceeds by the intramolecular addition of a vinylpalladium species to the triple bond of the cyano group, have been studied. The annulation of certain hindered propargylic alcohols affords 1,3-benzoxazine derivatives, rather than the expected 2-aminonaphthalenes. The involvement of trialkylamine bases in the formation of these heterocyclic compounds has been established. A proposed mechanism for the synthesis of 1,3-benzoxazine derivatives involves the formation of the expected 2-amino-3-(1-hydroxyalkyl)naphthalenes, followed by their condensation with an iminium ion species formed from the trialkylamine base used in the reaction.

Introduction

Aminonaphthalenes are useful precursors to a variety of substances that have interesting industrial and pharmaceutical uses. For example, complex heterocyclic systems such as benzo[*c*]phenothiazines,[1] benzo[*f*]quinazolines,[2] benzindoles,[3] benz[*a*]- and benz[*c*]acridines,[4] naphtho[1,2-*d*]imidazoles,[5] and others have been synthesized from naphthylamines. For over a century, aminonaphthalenes have been a staple of the dyestuffs industry, serving as diazo and coupling components in the preparation of azo dyes.[6] Despite the significant carcinogenic and mutagenic activity of 1- and 2-naphthylamines,[6b,7] their derivatives have been explored as spasmolytic, emetic, and antitumor agents.[8]

With the emergence of asymmetric synthesis, 2-aminonaphthalenes have found new uses as starting materials for the synthesis of binaphthyl C_2-symmetric chiral ligands.[9] In particular, 1,1′-binaphthyl-2,2′-diamine chiral auxiliaries have been used for enantioselective reduction of ketones, asymmetric synthesis of lactones, asymmetric hydrogenation of α-acylaminoacrylic acids, and asymmetric alkylation of aromatic aldehydes.[10] Additional substituents at positions 3 and 3′ of binaphthyl systems have been recognized to impose further steric interactions, which often results in a remarkable increase in asymmetric induction.[9] This underscores the importance of developing effective and practical routes to 3-substituted 2-aminonaphthalenes. In another asymmetric application, 2-naphthylamines have been used for the synthesis of naphthyl-Troger's base, a representative of a class of chiral structures that have both theoretical and practical interest as molecular receptors, chiral solvating agents (e.g., in host−guest complexes) and chiral modifiers in enantioselective reactions.[11]

Naphthylamines can be prepared from naphthalene and its derivatives by a number of traditional synthetic organic methods available for the synthesis of aromatic amines.[12] Classical routes to aminonaphthalenes include the treatment of naphthols with bisulfites and ammonia

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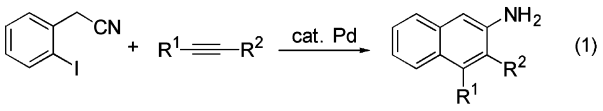
(Bucherer reaction)[13] and the acid-catalyzed transformation of tetralone oximes (Semmler−Wolff reaction).[14] Very specific aminonaphthalene systems, such as substituted *o*-aminonaphthols, 2-cyano-1-aminonaphthalenes, and others, have been prepared with various success by a variety of aminobenzannulation approaches.[15] To the best of our knowledge, there is no general and efficient methodology for the synthesis of aminonaphthalenes by alkyne annulation. Yet, such an approach could be extremely valuable, as it would allow for rapid construction of a fairly complex functionalized cyclic system from two independent components.

Recently, useful palladium−alkyne annulation methodology has been developed in this group, which offers convenient routes to various carbo- and heterocyclic compounds.[16] These reactions involve the insertion of an internal alkyne into an arylpalladium intermediate and subsequent cyclization onto a functional group present in the ortho position. In continuation of our work, we have investigated the possibility that a cyanomethyl group might serve as the neighboring functional group and that the vinylpalladium intermediate might add across the carbon−nitrogen triple bond to produce 2-aminonaphthalenes (eq 1). Here, we wish to report full details of our work on developing the Pd-catalyzed alkyne annulation of internal alkynes by (2-iodophenyl)acetonitrile into general methodology for the synthesis of 3,4-disubstituted 2-aminonaphthalenes.[17,18]



(1)

Results and Discussion

We chose the reaction of diphenylacetylene and (2-iodophenyl)acetonitrile as a model system for our initial investigation (eq 1; R^1, R^2 = Ph). First of all, the standard reaction conditions used in much of our previous palladium annulation chemistry[16] were employed in the reaction. As hoped for, the carbon−nitrogen triple bond of the cyano group participated in the reaction and 2-amino-3,4-diphenylnaphthalene was obtained in a 34% yield (Table 1, entry 1).

Since the yield of the reaction was low, considerable effort has been carried out to optimize the reaction conditions so as to improve the yields. First, different reaction times and palladium catalysts were examined in the reaction (Table 1, entries 1−7). Using $Pd(OAc)_2$, GC-MS analysis indicated that the reaction had not reached completion even after 11 h (entries 1 and 2). Thus, longer reaction times were employed. According to GC-MS analysis, the reaction was complete after 48 h and higher yields were observed (entries 3 and 4). Other palladium catalysts, such as $Pd(dba)_2$ and $Pd(PPh_3)_4$, did not afford good yields (entries 5−7). $Pd(OAc)_2$ appears to be the best catalyst. Somewhat surprising was the observation that 5 mol % $Pd(OAc)_2$ is as effective as 20 mol % of the catalyst (compare entries 1 and 2, 3 and 4).

The next variable examined was the solvent (entries 8−12). The use of dimethylformamide (DMF) as the solvent is crucial to the success of this reaction (entry 3). The reaction was also carried out in 9:1 DMF/H_2O, although the yield was considerably lower (entry 8). Other solvents, including dimethyl sulfoxide (DMSO), $MeNO_2$, dimethylacetamide (DMA), and MeCN were inefficient, and none of the desired product was observed (entries 9−12). The failure of DMA is particularly striking, since it usually behaves very similar to DMF as one might expect with such similar structures.

The next task was to find the best base for the reaction. A series of inorganic bases were examined first (entries 3 and 13−18), and NaOAc was observed to furnish the highest yield (entry 3). After careful consideration of the possible mechanism of the annulation (vide infra), we realized that a hydrogen source is required for the reaction. With this in mind, NaH and HCOONa were examined as bases (entries 17 and 18). However, neither reaction afforded the desired product. It is known that tertiary amines containing an α-hydrogen can provide a hydride to palladium through insertion of the palladium into the C−H bond adjacent to nitrogen.[19] Therefore, Et_3N was examined in the reaction, and the yield of annulation product was significantly improved (entry 19). It was also noticed that employing *n*-Bu_4NCl as the chloride source afforded better yields than LiCl (compare entries 3 and 20, 19 and 21). Another tertiary amine, *i*-Pr_2NEt, was also examined in the reaction, and a high yield was obtained (entry 22). However, the corresponding secondary amines did not furnish good yields (entries 23 and 24). We also confirmed again that a reaction time of 48 h is enough for the reaction, since no improvement in yield was observed after 48 h (compare entries 21, 25, and 26).

In a continued effort to optimize the reaction conditions, the effects of phosphines and Lewis acids were explored (entries 27−32). It was observed that the addition of the Lewis acids $Zn(OAc)_2$ and $ZnCl_2$ only made the reaction worse (compare entries 27−29). The addition of catalytic amounts of phosphines, such as PPh_3, P(*o*-tolyl)$_3$, and tris(2,6-dimethoxyphenyl)phosphine, did not improve the yield, and longer reaction times were required for the reaction to reach completion (entries 30−32).

Having established the optimal solvent, reaction time, catalyst, and base, we turned our attention toward the amount of the base Et_3N. Varying amounts of Et_3N, from 1 to 5 molar equiv, were examined (entries 21 and 33−35). The results indicate that 2 equiv of Et_3N afforded the best yield of naphthylamine (entry 34).

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TABLE 1. Optimization of the Reaction Conditions for Palladium-Catalyzed Annulation of Diphenylacetylene by (2-Iodophenyl)acetonitrile (eq 1, R^1, R^2 = Ph)[a]

entry	catalyst	solvent	base (equiv)	additive (equiv)	chloride (equiv)	time (h)	% isolated yield
1	5% $Pd(OAc)_2$	DMF	NaOAc (2)		LiCl (1)	11	34
2	20% $Pd(OAc)_2$	DMF	NaOAc (2)		LiCl (1)	11	40
3	5% $Pd(OAc)_2$	DMF	NaOAc (2)		LiCl (1)	48	52
4	20% $Pd(OAc)_2$	DMF	NaOAc (2)		LiCl (1)	48	51
5	5% $Pd(dba)_2$	DMF	NaOAc (2)		LiCl (1)	11	19
6	5% $Pd(dba)_2$	DMF	NaOAc (2)		LiCl (1)	72	30
7	5% $Pd(PPh_3)_4$	DMF	NaOAc (2)		LiCl (1)	32	32
8	5% $Pd(OAc)_2$	9:1 DMF/H_2O	NaOAc (2)		LiCl (1)	24	37
9	5% $Pd(OAc)_2$	DMSO	NaOAc (2)		LiCl (1)	21	—[b]
10	5% $Pd(OAc)_2$	$MeNO_2$	NaOAc (2)		LiCl (1)	21	—[b]
11	5% $Pd(OAc)_2$	DMA	NaOAc (2)		LiCl (1)	21	—[b]
12	5% $Pd(OAc)_2$	MeCN	NaOAc (2)		LiCl (1)	96	—[c]
13	5% $Pd(OAc)_2$	DMF	Na_2CO_3 (2)		LiCl (1)	48	41
14	5% $Pd(OAc)_2$	DMF	K_2CO_3 (2)		LiCl (1)	48	35
15	5% $Pd(OAc)_2$	DMF	KOAc (2)		LiCl (1)	48	42
16	5% $Pd(OAc)_2$	DMF	$NaHCO_3$ (2)		LiCl (1)	48	32
17	5% $Pd(OAc)_2$	DMF	NaH (2)		LiCl (1)	48	—[d]
18	5% $Pd(OAc)_2$	DMF	HCOONa (2)		LiCl (1)	48	—[d]
19	5% $Pd(OAc)_2$	DMF	Et_3N (3)		LiCl (1)	48	73
20	5% $Pd(OAc)_2$	DMF	NaOAc (2)		*n*-Bu_4NCl (1)	48	63
21	5% $Pd(OAc)_2$	DMF	Et_3N (3)		*n*-Bu_4NCl (1)	48	76
22	5% $Pd(OAc)_2$	DMF	*i*-Pr_2NEt (3)		*n*-Bu_4NCl (1)	48	75
23	5% $Pd(OAc)_2$	DMF	Et_2NH (3)		*n*-Bu_4NCl (1)	48	—[d]
24	5% $Pd(OAc)_2$	DMF	*i*-Pr_2NH (3)		*n*-Bu_4NCl (1)	48	51
25	5% $Pd(OAc)_2$	DMF	Et_3N (3)		*n*-Bu_4NCl (1)	72	76
26	5% $Pd(OAc)_2$	DMF	Et_3N (3)		*n*-Bu_4NCl (1)	120	77
27	5% $Pd(OAc)_2$	DMF	NaOAc (2)		*n*-Bu_4NCl (3)	24	35
28	5% $Pd(OAc)_2$	DMF	NaOAc (2)	$Zn(OAc)_2$ (1)	*n*-Bu_4NCl (3)	21	23
29	5% $Pd(OAc)_2$	DMF	NaOAc (2)	$ZnCl_2$ (1)	*n*-Bu_4NCl (3)	21	24
30	5% $Pd(OAc)_2$	DMF	Et_3N (3)	PPh_3 (0.1)	*n*-Bu_4NCl (1)	72	77
31	5% $Pd(OAc)_2$	DMF	Et_3N (3)	P(*o*-tolyl)$_3$ (0.1)	*n*-Bu_4NCl (1)	72	78
32	5% $Pd(OAc)_2$	DMF	Et_3N (3)	PAr_3[e] (0.1)	*n*-Bu_4NCl (1)	96	66
33	5% $Pd(OAc)_2$	DMF	Et_3N (1)		*n*-Bu_4NCl (1)	48	63
34	5% $Pd(OAc)_2$	DMF	Et_3N (2)		*n*-Bu_4NCl (1)	48	78
35	5% $Pd(OAc)_2$	DMF	Et_3N (5)		*n*-Bu_4NCl (1)	48	71
36	5% $Pd(OAc)_2$	DMF	Et_3N (2)		*n*-Bu_4NCl (1)	48	74[f]
37	5% $Pd(OAc)_2$	DMF	Et_3N (2)		*n*-Bu_4NCl (1)	48	83[g]
38	5% $Pd(OAc)_2$	DMF	Et_3N (2)		*n*-Bu_4NCl (1)	48	74[h]

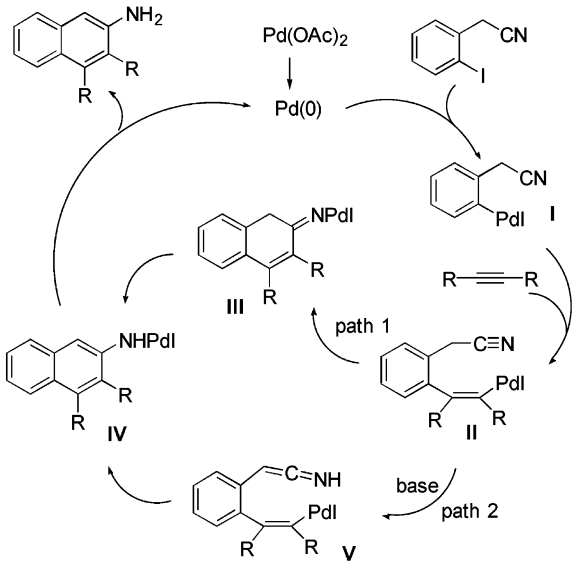
[a] All reactions were run in the presence of 2 equiv of diphenylacetylene (unless indicated otherwise) at 100 °C. [b] (2-Iodophenyl)acetonitrile disappeared, but none of the desired product was obtained. [c] (2-Iodophenyl)acetonitrile did not react completely, and only a trace of the desired product was observed. [d] Only a trace of the desired product was observed. [e] Ar = 2,6-dimethoxyphenyl. [f] A 1 equiv amount of diphenylacetylene was employed. [g] A 3 equiv amount of diphenylacetylene was employed. [h] A 5 equiv amount of diphenylacetylene was employed.

The final variable examined was the stoichiometry of the diphenylacetylene. Different amounts of diphenylacetylene were employed in the reaction (entries 34 and 36−38). The highest yield was obtained when 3 equiv of diphenylacetylene was utilized (entry 37).

On the basis of the above investigation, the optimal conditions for this reaction are as follows: 5 mol % $Pd(OAc)_2$, 3 equiv of diphenylacetylene, 2 equiv of Et_3N, and 1 equiv of *n*-Bu_4NCl in DMF are heated at 100 °C for 48 h. *i*-Pr_2NEt is also a suitable choice of base.

The proposed mechanism of 2-aminonaphthalene formation is shown in Scheme 1. This process presumably starts with reduction of the $Pd(OAc)_2$ to the actual catalyst Pd(0). The oxidative addition of (2-iodophenyl)-acetonitrile to Pd(0) produces an arylpalladium intermediate **I**, which rapidly adds across the triple bond of the alkyne to afford a vinylic palladium species **II**. A priori, two different paths for intramolecular carbopalladation of the cyano group in **II** appear plausible. The vinylic palladium moiety **II** may undergo addition to the neighboring CN triple bond to generate the iminopalladium intermediate **III**, which undergoes rapid tautomerization to the aminopalladium species **IV** (path 1). An alternative

SCHEME 1



path might involve base-induced formation of ketenimine **V**[20] and subsequent syn addition of the vinylpalladium

TABLE 2. Pd-Catalyzed Annulation of Internal Alkynes by (2-Iodoaryl)acetonitriles (eq 1)[a]

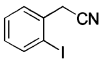
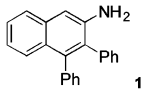
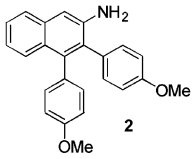
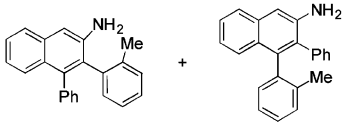
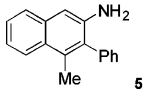
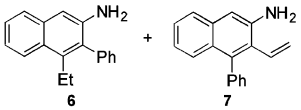
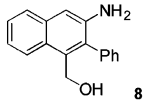
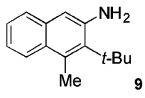
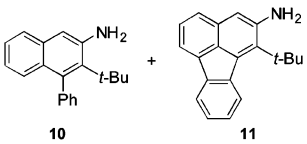
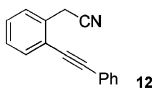
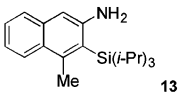
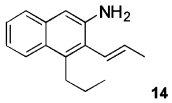
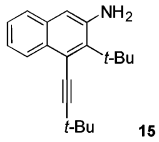
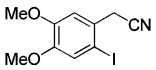
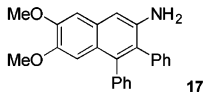
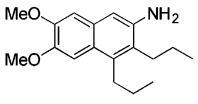
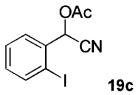
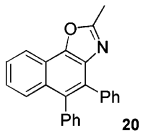
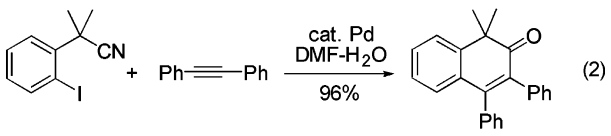
entry	nitrile	alkyne R^1	alkyne R^2	product(s)	% isolated yield
1		Ph	Ph	 **1**	83
2		*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	 **2**	80
3		Ph	*o*-MeC_6H_4	 **3** **4**	44 + 45
4		Me	Ph	 **5**	65
5		Et	Ph	 **6** **7**	37 + 17
6		CH_2OH	Ph	 **8**	29
7		CH_2OH	CH_2OH	-	-
8		CMe_2OH	CMe_2OH	-	-
9		CH_2OMe	CH_2OMe	-	-
10		Me	*t*-Bu	 **9**	75[b]
11		Ph	*t*-Bu	 **10** **11**	27 + 15
12		Ph	$SiMe_3$	 **12**	58
13		Ph	H		51
14		Me	Si(*i*-Pr)$_3$	 **13**	54

Table 2 (Continued)

entry	nitrile	alkyne R^1	alkyne R^2	product(s)	% isolated yield
15		*n*-Pr	*n*-Pr	 **14**	30
16		Ph	C(O)Me	-	-
17		Me	$CH(OEt)_2$	-	-
18		Ph-C≡C	Ph	-	-
19		*t*-Bu-C≡C	*t*-Bu	 **15**	91[c]
20	 **16**	Ph	Ph	 **17**	81
21		*n*-Pr	*n*-Pr	 **18**	62
22	 **19c**	Ph	Ph	 **20**	53

[a] See the Experimental Section for the reaction conditions. [b] A 2 equiv amount of H_2O was employed in the reaction; without water, the yield was 61%. [c] Isolated as an inseparable mixture with about 6% of the other regioisomer as determined by ^1H NMR spectral analysis.

moiety to the C−N double bond to generate **IV** (path 2). On the basis of the success of our previous annulation of diphenylacetylene with 2-(2-iodophenyl)-2-methylpropanenitrile (eq 2),[17] which presumably proceeds via a very similar mechanism, we favor path 1. In the next step, aminopalladium complex **IV** is reduced to the final product, accompanied by regeneration of the Pd(0) catalyst. Although we have evidence indicating that the Pd(II) moiety in **IV** is reduced by Et_3N (vide infra), we cannot exclude some involvement of DMF, since the yield of the annulation product was sharply reduced when other solvents, such as DMSO and DMA, were used in the reaction (entries 9 and 11, Table 1). Also, traces of water inadvertently present in DMF or *n*-Bu_4NCl may be the hydrogen source in the reduction[21] or simple protonation of **IV** to generate Pd(II), which is subsequently reduced to Pd(0) by other species.

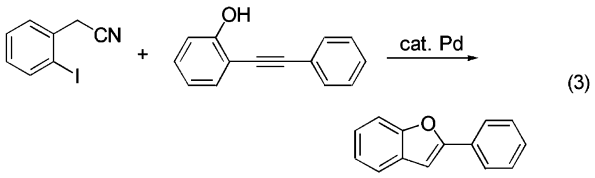


(2)

To study the scope of this annulation, a variety of internal alkynes have been introduced into the reaction (Table 2). 2-Amino-3,4-diarylnaphthalenes **1** and **2** were obtained in very good yields from annulation of the corresponding diarylacetylenes (entries 1 and 2). The current methodology is expected to be readily applicable to the synthesis of various 2-amino-3,4-diarylnaphthalenes from symmetrical diarylacetylenes. An excellent overall yield of the annulation product was also obtained in the reaction of an unsymmetrical alkyne, 2-(phenylethynyl)toluene (entry 3). However, both possible regioisomers **3** and **4** were isolated in approximately equal amounts. Apparently, the difference between the steric demands of the two aryl substituents in this diarylacetylene is not large enough to command better regioselectivity in arylpalladium addition across the triple bond of the alkyne (see below). The attempted annulation of 2-(phenylethynyl)phenol afforded 2-phenylbenzofuran

(20) Whittaker, D. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons: New York, 1994; p 513.
(21) Coperet, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 3422.

instead of the target aminonaphthalene (eq 3). Examples of this Pd-catalyzed cyclization are well-known in the literature.[22]



(3)

The annulation works reasonably well for internal alkynes other than diarylacetylenes. Thus, 2-amino-4-methyl-3-phenylnaphthalene (**5**) was isolated in a 65% yield as a single isomer from the reaction of (2-iodophenyl)acetonitrile and 1-phenyl-1-propyne (entry 4). The regioselectivity of this reaction can be nicely explained by addition of the aryl group of the arylpalladium intermediate **I** (Scheme 1) to the less hindered end of the alkyne, placing the palladium moiety on the more hindered end of the original triple bond. Such regioselectivity for the addition has been frequently observed in our previous research.[23,24] As a result, the more sterically hindered group present in the alkyne ends up in the 3 position of the naphthalene product and the less hindered group in the 4 position, which is indeed observed. However, for this regioselectivity to be pronounced, the two groups must be significantly different sterically (entries 4, 10, 11, 14, and 19). In other cases, formation of both possible regioisomers may be expected (entries 3 and 5). When 1-phenyl-1-butyne was employed as the alkyne, the anticipated aminonaphthalene **6** was isolated in a 37% yield along with an unexpected product **7**, which obviously arose from the second regioisomer (entry 5). While we observed only a single isomer **8** in the annulation of 3-phenyl-2-propyn-1-ol (entry 6), we cannot rule out the possibility that an aldehyde or carboxylic acid product similar to **7** was formed in the reaction, but was subsequently lost to side reactions, such as oxidation or condensation.

Surprisingly, symmetrical propargylic diols failed to afford annulation products (entries 7 and 8). Protecting the hydroxy groups in 2-butyne-1,4-diol did not rectify the problem, as the corresponding dimethoxy derivative did not undergo annulation either (entry 9). The reasons behind these results are unclear and may include coordination of these electron-rich functionalized alkynes to the palladium catalyst prior to the oxidative addition step, which diverts the catalyst from the annulation process.

Internal alkynes bearing a bulky *tert*-butyl group led to the expected 2-aminonaphthalenes **9** and **10** with good regioselectivity (entries 10 and 11). The regiochemistry of these and other products in Table 1 could be determined by 1D and 2D ^{1}H NMR spectral analysis. We also observed the formation of the tetracyclic amine **11**, which presumably arises from the in situ cyclization of **10** by a mechanism that is unclear (entry 11). The reaction of 1-phenyl-2-(trimethylsilyl)acetylene afforded the simple coupling product **12** in a 58% yield (entry 12). None of the desired aminonaphthalene product was observed. This reaction presumably proceeds by desilylation of the alkyne to produce phenylacetylene, which undergoes coupling with (2-iodophenyl)acetonitrile to give **12**. The same product **12** was also obtained in a similar yield when phenylacetylene was used as the alkyne (entry 13). A significant amount of 1,4-diphenylbutadiyne was also detected by GC-MS in this reaction mixture. The more hindered silyl group in 1-triisopropylsilyl-1-propyne was stable to desilylation, and this alkyne afforded a 54% yield of the aminonaphthalene **13** (entry 14).

The unusual product **14** was formed as the sole product in the reaction of 4-octyne (entry 15). The (*E*)-stereochemistry of **14** was established from ^{1}H NMR coupling constants between the olefinic hydrogens (J = 16.2 Hz) and fully confirmed by 2D NOESY spectroscopy. Internal alkynes bearing electron-withdrawing groups did not undergo annulation, possibly because of competing Michael addition-like processes (entries 16 and 17). Also unsuccessful was the annulation of 1,4-diphenylbutadiyne (entry 18). It has been reported, however, that diarylbutadiynes may easily undergo Pd-catalyzed formation of 1,2,3-butatriene derivatives under conditions similar to ours.[25] Another 1,3-diyne, 2,2,7,7-tetramethyl-3,5-octadiyne, afforded the expected annulation product **15** in excellent yield and with very good regioselectivity (entry 19).

An electron-rich (2-iodophenyl)acetonitrile derivative **16** was prepared and used in the annulation of diphenylacetylene and 4-octyne (entries 20 and 21). In both cases, the corresponding 2-aminonaphthalenes **17** and **18** were obtained in good yields. Interestingly, we did not observe any unsaturated product similar to **14** in the reaction of 4-octyne (entry 21). No electron-poor derivatives of (2-iodophenyl)acetonitrile were examined in the annulation, since our previous research on nitrile carbopalladation indicated that arylpalladium and vinylpalladium intermediates (**I** and **II**, Scheme 1) formed from electron-deficient substrates are usually not nucleophilic enough for successful attack on the cyano group.[18,19d]

We have also prepared a number of protected cyanohydrins **19** (Scheme 2) in order to investigate the possibility of synthesizing 3,4-disubstituted 2-amino-1-naphthols by this methodology. Unfortunately, only 2-acetoxy-2-(2-iodophenyl)acetonitrile (**19c**) proved stable enough to survive our reaction conditions, cleanly affording the oxazole derivative **20** in a 53% yield (entry 22). An almost identical yield (52%) of **20** was achieved when the reaction was run at 130 °C. Silyl-protected cyanohydrins **19a**,**b** underwent a retroreaction to produce 2-iodobenzaldehyde as the major product. Even the piperidine derivative **19d** was hydrolyzed to 2-iodobenzaldehyde,

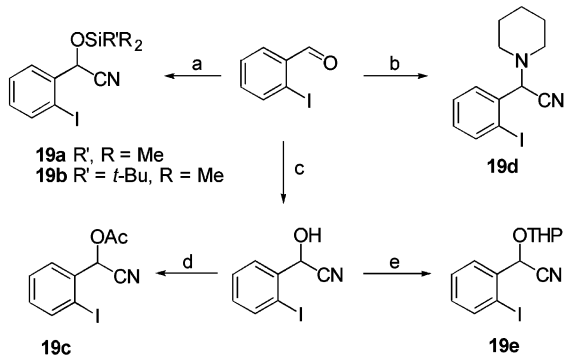
(22) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017, and references therein.

(23) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579. (c) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.

(24) Interestingly, the regiochemistry of the Pd-catalyzed hydrostannylation of unsymmetrical *o*-substituted diphenylacetylenes appears to be controlled by the electronic polarization of the carbon−carbon triple bond, see: Alami, M.; Liron, F.; Garvais, M.; Peyrat, J.-F.; Brion, J.-D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1578. In that report, the palladium moiety of H−PdSnR$_3$ adds to the more electron-rich end of the triple bond, which also happens to be the more sterically hindered end.

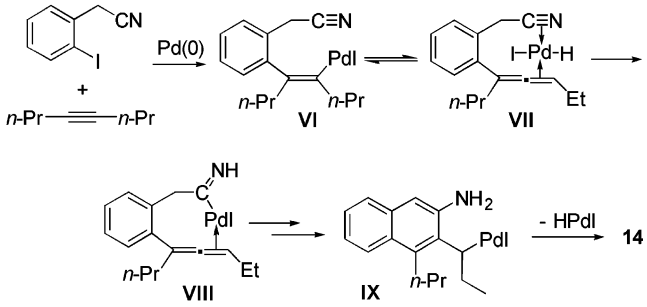
(25) Dyker, G.; Borowski, S.; Henkel, G.; Kellner, A.; Dix, I.; Jones, P. G. *Tetrahedron Lett.* **2000**, *41*, 8259.

SCHEME 2[a]



[a] (a) $R'R_2SiCN$, cat. KCN, cat. 18-crown-6, CH_2Cl_2, r.t.; (b) NaCN, piperidine, aq $NaHSO_3$, 0 °C to r.t.; (c) KCN, aq $NaHSO_3$, 0 °C to r.t.; (d) Ac_2O, pyridine, r.t.; (e) 3,4-dihydropyran, cat. *p*-TsOH, CH_2Cl_2, r.t.

SCHEME 3

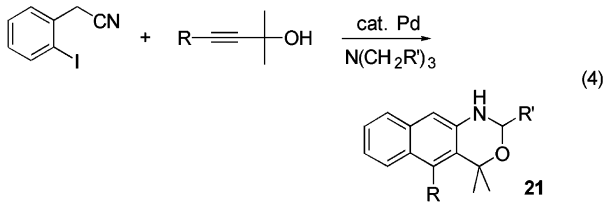


presumably by traces of water present in the DMF or n-Bu_4NCl. Attempted annulation of the THP-protected cyanohydrin **19e** afforded a messy reaction mixture containing numerous products that could not be identified.

A possible mechanism for the formation of unsaturated products **7** and **14** is depicted in Scheme 3. Oxidative addition of (2-iodophenyl)acetonitrile to Pd(0) and subsequent insertion of 4-octyne furnishes intermediate **VI**. This species may undergo β-hydrogen elimination to produce an allene intermediate **VII**. Addition of the Pd−H to the cyano group will generate an acyl-like organopalladium intermediate **VIII**, which in turn can add to the allene to furnish (after imine tautomerization) a σ- or π-benzylic intermediate **IX**, which might be expected to eliminate HPdX to generate the new carbon−carbon double bond and eventually regenerate the Pd(0) catalyst. When electron-rich acetonitrile **16** is used (entry 21, Table 2), none of the similar unsaturated product is observed presumably because the vinylic palladium intermediate corresponding to **VI** is more nucleophilic and attacks the C−N triple bond faster then it undergoes β-hydrogen elimination.

We also propose an alternative mechanism shown in Scheme 4. Upon formation of the aminopalladium intermediate **X** during the normal annulation cycle (Scheme 1), the palladium moiety may insert into a benzylic C−H bond of the alkyl substituent in the 3 position of the naphthalene and eventually migrate to the alkyl chain to furnish an alkylpalladium intermediate **IX** by a mechanism that differs from the one in Scheme 3. After a palladium β-hydrogen elimination, **IX** can produce the product **14**. We have no evidence that allows us to choose between these two mechanisms. The absence of the side chain elimination product in entry 21 (Table 2) may probably be explained by the assumption that the benzylic C−H bond in the more electron-rich analogue of **X** is much less activated toward oxidative addition to the aminopalladium species, thereby precluding its migration to the alkyl chain.

Using hindered propargylic alcohols for the annulation with (2-iodophenyl)acetonitrile, we have made an unusual observation that 1,3-benzoxazine derivatives **21** are produced instead of the anticipated 2-aminonaphthalenes (eq 4, R = Ph or Me). Thus, annulation of (2-iodophenyl)-

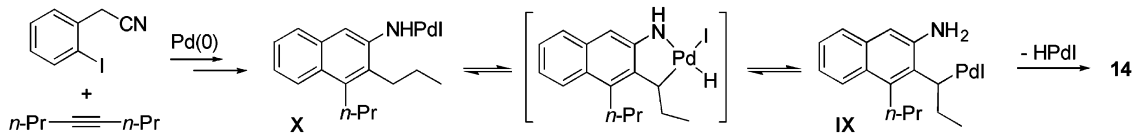


(4)

acetonitrile onto 2-methyl-3-pentyn-2-ol afforded 2,4,4,5-tetramethyl-1,4-dihydro-2*H*-naphtho[2,3-*d*][1,3]oxazine (**21a**) in a 25% isolated yield (entry 1, Table 3). Analogous 1,3-benzoxazine derivative **21b** was obtained from 2-methyl-4-phenyl-3-butyn-2-ol in a 35% yield under our original annulation conditions. When the reaction was run at 130 °C, the yield of **21b** increased to 50% (entry 2). Substituting tri-*n*-butylamine for triethylamine led to the formation of 4,4-dimethyl-5-phenyl-2-propyl-1,4-dihydro-2*H*-naphtho[2,3-*d*][1,3]oxazine (**21c**) in a 38% yield (entry 3). This result provides clear and unambiguous evidence that the C2-carbon of the 1,3-oxazine ring comes from the trialkylamine base, one of the alkyl groups of which is incorporated into the structure of the final product. It has also been established that primary alkyl groups are transferred preferentially from the trialkylamine because no incorporation of the isopropyl unit was found when *i*-Pr_2NEt was employed (entry 4).

The following mechanism accounts for the Pd-catalyzed synthesis of 1,3-benzoxazine derivatives from (2-iodophenyl)acetonitrile, hindered propargylic alcohols, and trialkylamines (Scheme 5). The marked difference in steric bulk between the two substituents on the triple bond of the alkyne causes regioselective formation of the vinylpalladium intermediate **XI** shown in Scheme 5, which proceeds to add to the cyano group and eventually form the aminopalladium species **XII**. It is possible that the Pd(II) in **XII** is reduced at this point by the trialkyl-

SCHEME 4



SCHEME 5

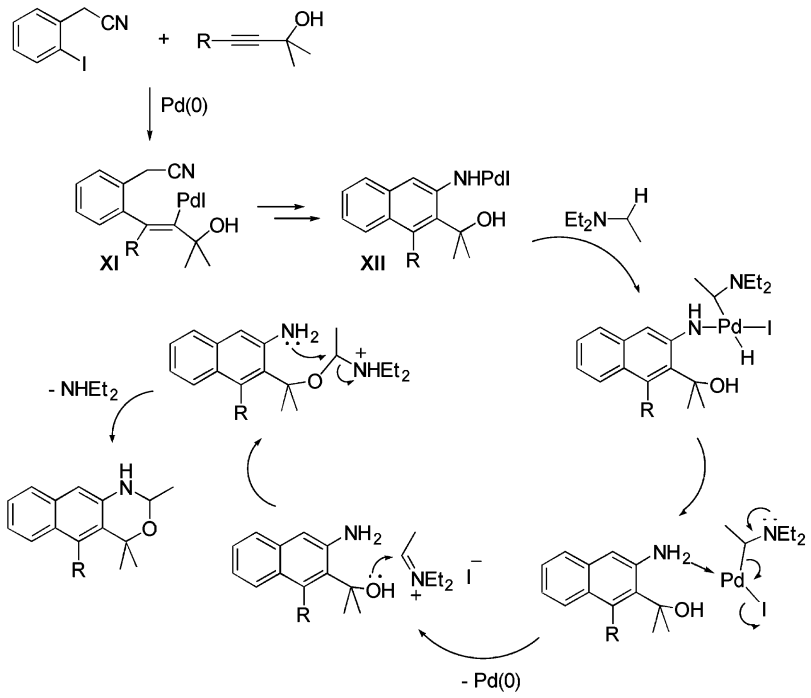
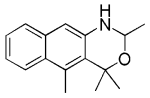
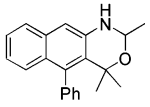
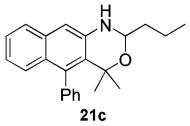


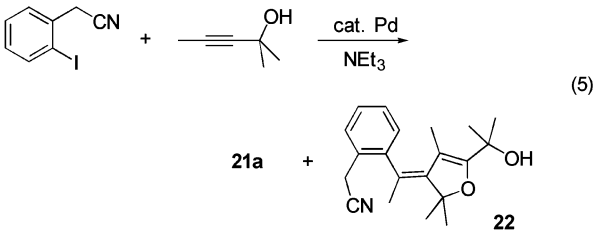
TABLE 3. Synthesis of 1,3-Benzoxazine Derivatives (eq 4)[a]

entry	R	amine (2 equiv)	product	% isolated yield
1	Me	Et_3N	 **21a**	25
2	Ph	Et_3N	 **21b**	50[b]
3	Ph	*n*-Bu_3N	 **21c**	38
4	Ph	*i*-Pr_2NEt	**21b**	16[c]

[a] See the Experimental Section for the reaction conditions. [b] This reaction was run at 130 °C; the yield at 100 °C was 35%. [c] 96% conversion of the starting material after 48 h.

amine. This reduction may involve Pd(II) insertion into the activated α-C−H bond of the amine, reductive elimination, and fragmentation of the resulting (α-aminoalkyl)palladium species, which leads to regeneration of Pd(0) and formation of the anticipated 2-aminonaphthalene product and an iminium moiety (Scheme 5). It is also possible that this iminium intermediate, which has been proposed in other Pd-catalyzed transformations of triethylamine,[19a,26] may be formed from triethylamine and a Pd(II) species at some other point in the reaction. The iminium intermediate then undergoes nucleophilic attack by the two nucleophilic groups present in the hydroxyl-substituted aminonaphthalene, which results in formation of the 1,3-oxazine ring. This mechanism may explain the exclusive transfer of primary alkyl groups from the amine (entry 4, Table 3), as the iminium ion species formed from a secondary alkylamine may be too hindered for facile condensation with the bulky alcohol moiety.

The reaction between (2-iodophenyl)acetonitrile and 2-methyl-3-pentyn-2-ol afforded another unusual product besides **21a** (eq 5). A complex furan derivative **22** was isolated in a 26% yield. This compound is clearly a product of a double alkyne insertion, which presumably proceeds by the mechanism shown in Scheme 6. Instead of adding to the C−N triple bond of the cyano group, the vinylpalladium intermediate **XIII** apparently inserts a second molecule of the alkyne to furnish dienylpalladium species **XIV**. Intramolecular attack of an OH group then leads to the final product **22**.



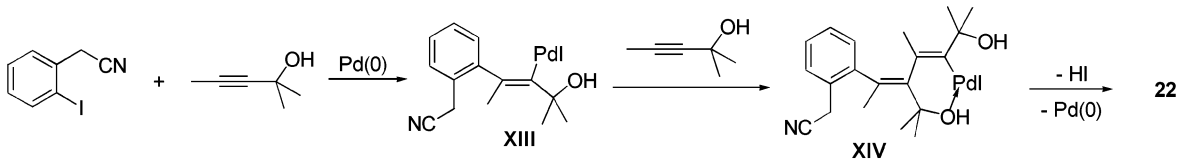
(5)

Conclusions

The palladium-catalyzed annulation of alkynes by (2-iodophenyl)acetonitrile provides a general route to 3,4-disubstituted 2-aminonaphthalenes, which are formed in moderate to very good yields from a variety of internal alkynes. In many cases, the annulation exhibits excellent

(26) Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429.

SCHEME 6



regioselectivity. The unusual formation of 1,3-benzoxazine derivatives from certain hindered propargylic alcohols has also been observed. This reaction apparently proceeds with involvement of the trialkylamine base present in the reaction, which transfers one of its alkyl groups to the final product.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short-wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. $Pd(OAc)_2$ was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd.

General Procedure for the Palladium-Catalyzed Reaction of (2-Iodophenyl)acetonitrile and Internal Alkynes. Palladium acetate (0.0028 g, 0.0125 mmol), Et_3N (0.070 mL, 0.5 mmol), *n*-Bu_4NCl (0.070 g, 0.25 mmol), (2-iodophenyl)acetonitrile (0.061 g, 0.25 mmol), the alkyne (0.75 mmol), and 5 mL of DMF were placed in a 4 dram vial, which was heated in an oil bath at 100 °C for 48 h unless indicated otherwise. The reaction mixture was cooled, diluted with ether, washed with saturated aqueous NH_4Cl, dried over Na_2SO_4 or $MgSO_4$, and filtered. The solvent was removed on a rotary evaporator, and the product was isolated by column chromatography on silica gel. The following compounds, prepared by the above procedure, have been previously described by us:[17] 2-amino-3,4-diphenylnaphthalene (**1**), 2-amino-4-methyl-3-phenylnaphthalene (**5**), 2-amino-3-*tert*-butyl-4-methylnaphthalene (**9**), and 2-amino-3-((*E*)-1-propenyl)-4-*n*-propylnaphthalene (**14**).

The following new compounds were prepared by the above procedure.

2-Amino-3,4-bis(4-methoxyphenyl)naphthalene (2). Obtained as a yellow solid in an 80% yield from the reaction of (2-iodophenyl)acetonitrile and bis(4-methoxyphenyl)acetylene after purification by column chromatography using 2:1 hexanes/ethyl acetate: mp 194−196 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 3.77 (br s, 2H), 3.78 (s, 3H), 6.73−6.79 (m, 4H), 7.00−7.05 (m, 4H), 7.10−7.12 (m, 2H), 7.35−7.41 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.1, 108.0, 112.9, 113.8, 122.3, 125.5, 126.0, 126.9, 127.6, 129.8, 131.5, 131.6, 131.9, 134.3, 139.7, 142.7, 157.9, 158.2 (1 sp^3 carbon missing due to overlap); IR (neat) 3465, 3365, 3052, 3012, 2957, 2837 1613, 1240 cm^{-1}; HRMS *m*/*z* 355.15795 (calcd for $C_{24}H_{21}NO_2$, 355.15723).

2-Amino-6,7-dimethoxy-3,4-di-n-propylnaphthalene (18). Obtained as an amber oil in a 62% yield from the reaction of **16** and 4-octyne after purification by column chromatography using 1:1 hexanes/ethyl acetate: ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.6 Hz, 3H), 1.11 (t, J = 7.6 Hz, 3H), 1.57−1.70 (m, 4H), 2.64−2.69 (m, 2H), 2.93−2.97 (m, 2H), 3.70 (br s, 2H), 3.96 (s, 3H), 3.97 (s, 3H), 6.84 (s, 1H), 6.88 (s, 1H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.8, 14.9, 22.9, 24.0, 30.2, 31.3, 55.7, 55.8, 104.0, 105.2, 108.1, 122.1, 125.7, 129.4, 135.7, 141.7, 146.9, 148.9; IR (neat) 3457, 3370, 3004, 2956, 2869, 2826, 1627 cm^{-1}; HRMS *m*/*z* 287.18906 (calcd for $C_{18}H_{25}NO_2$, 287.18853).

2,4,4-Trimethyl-5-phenyl-1,4-dihydro-2*H*-naphtho[2,3-*d*][1,3]oxazine (21b). Obtained as a white solid in a 50% yield from the reaction (conducted at 130 °C) of (2-iodophenyl)-acetonitrile and 2-methyl-4-phenyl-3-butyn-2-ol after purification by column chromatography using 4:1 hexanes/ethyl acetate: mp 179−180 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3H), 1.44 (d, J = 5.4 Hz, 3H), 1.54 (s, 3H), 4.43 (br s, 1H), 5.07 (q, J = 5.4 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.97−7.02 (m, 2H), 7.25−7.32 (m, 3H), 7.43−7.46 (m, 3H), 7.55 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.4, 22.2, 29.6, 30.4, 73.5, 110.4, 122.3, 125.1, 125.8, 126.9, 127.3, 127.4, 127.6, 130.9, 132.4, 132.9, 137.2, 140.2, 140.3; IR (neat) 3398, 3062, 3026, 2982, 2931, 1618 cm^{-1}; HRMS *m*/*z* 303.16293 (calcd for $C_{21}H_{21}NO$, 303.16231).

Characterization of all other new annulation products prepared in this study can be found in the Supporting Information.

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Supporting Information Available: Preparation and characterization of the starting materials **16** and **19c** and characterization data for all new compounds (including copies of ^{1}H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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