JOC Article

Carbopalladation of Nitriles: Synthesis of 2,3-Diarylindenones and Polycyclic Aromatic Ketones by the Pd-Catalyzed Annulation of Alkynes and Bicyclic Alkenes by 2-Iodoarenenitriles

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2-Iodobenzonitrile, its derivatives, and various heterocyclic analogues undergo palladium(0)-catalyzed annulation onto diarylacetylenes or bicyclic alkenes to afford 2,3-diarylindenones and polycyclic aromatic ketones in very good to excellent yields. This reaction represents one of the first examples of the addition of an organopalladium moiety to the carbon−nitrogen triple bond of a nitrile. The reaction is compatible with a number of functional groups. A reaction mechanism, as well as a model accounting for the electronic effects of substituents on the aromatic ring of the nitrile, is proposed.

Introduction

The development of new annulation processes is one of the most challenging and important quests in organic synthesis. Annulation is one of the most efficient and economical ways of creating cyclic molecules.[1] Combining two or more independent acyclic moieties to form several bonds in one process potentially provides an opportunity to rapidly synthesize complex molecules without having to spend time and resources on the isolation of intermediates and their reintroduction into subsequent steps. This is especially attractive in this age of high-throughput and combinatorial chemistry.[2] Equally important is the minimization of waste brought about by a decrease in the amounts of reagents and solvents required for a single-step operation as opposed to a multistep endeavor.[3]

Among many transition metals used in organic synthesis, palladium is particularly useful as it offers the most versatile possibilities for carbon−carbon bond formation.[4] Palladium reagents have been used extensively to prepare various carbo- and heterocyclic compounds,[5] by both cyclic carbopalladation and annulation.[6] One of the most important factors contributing to such widespread application of palladium catalysts is their tolerance of most important organic functional groups.[4] However, as more research in palladium-mediated organic methodology is being conducted, new reaction conditions are being discovered that lead to previously unknown palladium-catalyzed reactions with "unreactive" functional groups.[7]

The cyano group has long been considered inert toward organopalladium reagents. Palladium chloride bisacetonitrile and bisbenzonitrile are widely used catalysts, and acetonitrile is one of the most commonly employed solvents in palladium-mediated reactions.[4a,8] In most such reactions, the nitriles are not incorporated into the molecular structure of the products.[9] In many cases, substrates bearing a cyano group can undergo palladium-mediated processes that lead to products in which the cyano group remains intact. In fact, the palladium-catalyzed cyanation of aryl halides is a widely used synthetic approach to arenenitriles, which, once formed in the reaction, are not modified in any way despite the presence of organopalladium intermediates.[10] Other examples of the palladium-catalyzed introduction of a cyano group into a product include the cyanocarbonylation of iodobenzene,[11] cyanosilylation of alkynes,[12] and numerous

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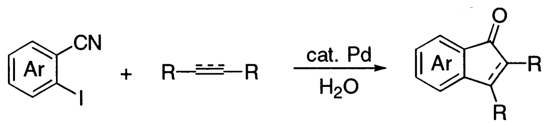
reactions of nitrile-containing organic substrates, e.g., the cross-coupling of aryl halides with terminal acetylenes[13] or organometallic reagents,[14] α-allylation,[15] and decarboxylation of α-cyanoesters.[16]

Palladium-mediated reactions that do modify the nitrile functionality[9,17] usually do not involve carbopalladation of the cyano group. However, there are rare examples of the carbopalladation of nitriles. Thus, Yang et al. have described the palladium-catalyzed arylation of a cyano group in the intramolecular cyclization of 2-bromoarylalkenenitriles,[18] and Cheng has reported the cyano group transfer from solvents to aryl halides mediated by palladium and zinc species.[19]

We have recently reported that the intramolecular carbopalladation of the cyano group in 2-iodobenzonitrile and 2-iodophenylacetonitrile provides a new synthetic route to indenones, 2-aminonaphthalenes, and related compounds.[20] At this time, we report the full details of our investigation of the carboannulation of internal alkynes and bicyclic alkenes by 2-iodoarenenitriles that leads to 2,3-diarylindenones and related polycyclic aromatic ketones (eq 1).



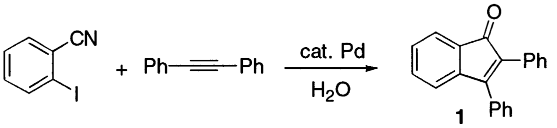
(1)

Indenones and their derivatives have been employed as fungicides and fermentation activators.[21] Their potentially useful biological activity as binding agents for estrogen receptors has been used to study the structure of the receptor's binding site and the orientation of the site's nonsteroidal ligands.[22] Indenones also serve as valuable precursors and intermediates in the synthesis of natural products (e.g., steroids and gibberellins), indanones, indenes, naphthols, and other compounds.[7c,23]

Traditionally, indenones have been synthesized via Friedel−Crafts cyclizations or addition of organometallic reagents to 1,3-indandiones.[22a,24] Many transition-metal reagents and catalysts have been employed in indenone preparations in recent years.[7c,23a] Palladium-catalyzed reactions leading to indenones (including annulation approaches) have also found a place in synthetic organic methodology.[25] One such procedure developed in this laboratory involves the annulation of internal alkynes with 2-halobenzaldehydes.[7c] Although effective and reasonably general, this procedure could still be improved if more stable starting materials could be used in place of easily oxidized aldehydes.

Results and Discussion

Ongoing research in our group on palladium-catalyzed annulation methodology[6a,26] prompted us to examine 2-iodobenzonitrile as a possible substrate for annulation onto diphenylacetylene to produce 2,3-diphenyl-1-indenone (**1**; eq 2). Encouraged by the success of the intramolecular reaction of an aldehyde, a group normally inert toward organopalladium species,[7] we envisioned that a cyano group might serve as a neighboring functional group in this reaction and that the vinylpalladium intermediate might add across the carbon−nitrogen triple bond (see the later mechanistic discussion).



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(2)

Under our standard reaction conditions developed for the synthesis of fluorenes,[27] 2-iodobenzonitrile reacts with diphenylacetylene to afford the fluorene product **2** in 63% yield (eq 3). When PPh_3 was omitted from the reaction conditions shown in eq 3, the reaction furnished **2** in 56% yield. When the solvent was changed from DMF to 9:1 DMF−water, to our delight, the major identifiable product (28%) was found to be the target indenone **1** (eq 2), while none of the fluorene **2** was detected.

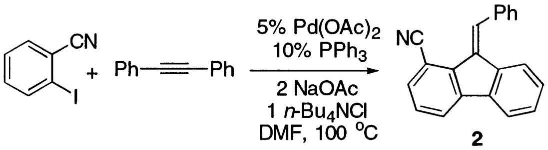

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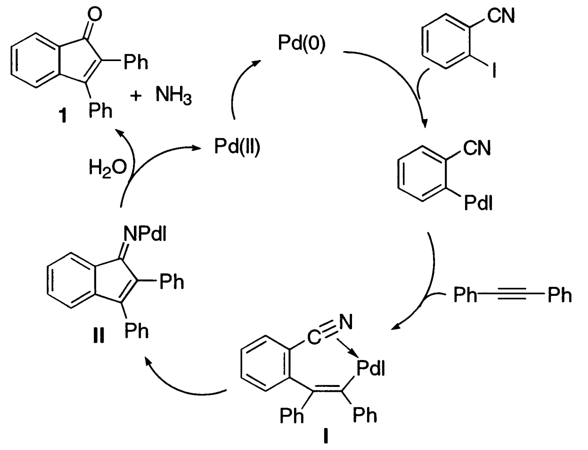
TABLE 1. Optimization of the Pd-Catalyzed Annulation of Diphenylacetylene by 2-Iodobenzonitrile (Eq 2)[a]

entry	catalyst	additive (amt, equiv)	amt of Et_3N (equiv)	solvent	time (h)	isolated yield of **1**[b] (%)
1	5% $Pd(OAc)_2$	n-Bu_4NCl (1)	3	DMF	48	30
2	5% $Pd(OAc)_2$	n-Bu_4NCl (1)	3	DMF	48	25[c]
3	5% $Pd(OAc)_2$	n-Bu_4NCl (1)	2	DMF	48	30
4	5% $Pd(OAc)_2$	n-Bu_4NCl (1)	2	4:1 DMF−H_2O	24	45
5	5% $Pd(OAc)_2$	n-Bu_4NCl (1)	2	9:1 DMF−H_2O	24	42
6	5% $Pd(OAc)_2$	n-Bu_4NCl (1), PPh_3 (0.2)	2	9:1 DMF−H_2O	24	42
7	10% $Pd(dba)_2$	n-Bu_4NCl (1)	2	9:1 DMF−H_2O	24	62
8	10% $Pd(dba)_2$		2	9:1 DMF−H_2O	24	60
9	10% $Pd(dba)_2$			9:1 DMF−H_2O	48	11[d]
10	10% $Pd(dba)_2$		0.5	9:1 DMF−H_2O	24	10
11	10% $Pd(dba)_2$		1	9:1 DMF−H_2O	24	74
12	10% $Pd(dba)_2$		2	9:1 DMF−H_2O	72	59
13	10% $Pd(dba)_2$		3	9:1 DMF−H_2O	24	48
14	10% $Pd(dba)_2$		1	9:1 DMF−H_2O	13	61 (71)[d]
15	10% $Pd(dba)_2$		1	9:1 DMF−H_2O	17	66 (70)[d]
16	10% $Pd(dba)_2$		1	9:1 DMF−H_2O	48	38[e]
17	10% $Pd(dba)_2$	Ag_3PO_4 (0.4)	1	9:1 DMF−H_2O	24	trace
18	10% $Pd(dba)_2$	$AgNO_3$ (1.2)	1	9:1 DMF−H_2O	24	trace
19	10% $Pd(dba)_2$	$TlPF_6$ (1.2)	1	9:1 DMF−H_2O	24	25 (40)[d]
20	10% $Pd(dba)_2$	PPh_3 (0.2)	1	9:1 DMF−H_2O	24	62
21	10% $Pd(dba)_2$	TPPTS (0.2)[f]	1	9:1 DMF−H_2O	24	66

[a] All reactions were run with 3 equiv of diphenylacetylene at 100 °C unless specified otherwise. [b] All yields in parentheses are corrected for unreacted starting material. [c] A 2 equiv sample of water was added to the reaction mixture. [d] Incomplete conversion of 2-iodobenzonitrile. [e] This reaction was run at 80 °C. [f] TPPTS = tris(3-sulfonatophenyl)phosphine, sodium salt.

SCHEME 1



On the basis of our previous research on alkyne annulation chemistry,[6a,26a] we propose the following mechanism for the formation of **1** from 2-iodobenzonitrile and diphenylacetylene (Scheme 1). Oxidative addition of 2-iodobenzonitrile to Pd(0), formed in situ from Pd(II), is followed by diphenylacetylene insertion that leads to the vinylpalladium intermediate **I**. The latter then adds across the carbon−nitrogen triple bond of the neighboring cyano group to produce the iminopalladium intermediate **II**,[28] which hydrolyzes to the indenone **1**. Reduction of the Pd(II) species produced is required to afford a catalytic process and occurs at some point in the reaction.

Since the yield of the reaction was low, substantial optimization efforts were undertaken to improve the yield of this annulation (Table 1). Drawing on the findings of concurrent work on the optimization of a similar annulation of 2-iodophenylacetonitrile,[20] the details of which will be reported in due course, we ran the reaction using catalytic $Pd(OAc)_2$ under conditions described in Table 1, entry 1. This procedure led to a 30% yield of **1**. The yield did not improve upon addition of 2 equiv of water, nor upon reducing the amount of the base (entries 2 and 3, respectively). Using aqueous DMF as a solvent resulted in higher yields of **1** (entries 4 and 5). The addition of triphenylphosphine, intended to facilitate the initial reduction of Pd(II) to Pd(0), as well as to serve as a ligand for palladium, had no effect on the reaction (entry 6). We then decided to use a Pd(0) catalyst. Employing 10% $Pd(dba)_2$ raised the yield of **1** to 62% (entry 7). An almost identical yield was obtained when n-Bu_4NCl was omitted, proving that a chloride source was unnecessary for the annulation (entry 8). Since 1 equiv of ammonia was supposedly formed in the reaction (Scheme 1), we questioned whether using 2 equiv of triethylamine was required, and studied the effect of the amount of base on the reaction yield (entries 9−13). The best results were obtained when we employed only 1 equiv of triethylamine (entry 11), whereas using both lesser and greater amounts was detrimental to the success of the annulation. It was also established that the reaction required a full 24 h, since using shorter reaction times resulted in incomplete consumption of the 2-iodobenzonitrile (entries 14 and 15). Lowering the reaction temperature slowed the annulation considerably and led to only a 38% yield of **1** after 48 h (entry 16). Finally, we studied the effect of some additives on the reaction (entries 17−21). Hoping that a cationic palladium intermediate similar to **I** (Scheme 1) might coordinate to the carbon−nitrogen bond more strongly and thus affect the carbopalladation step favorably, we employed silver and thallium salts known to sequester halide anions from palladium complexes (entries 17−19),[29] only to find that their use decreased the yield of the indenone **1**. Using phosphine ligands resulted in

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(28) The exact opposite process, β-carbon elimination from a strained cyclobutaniminopalladium complex to produce a γ-cyanoalkylpalladium species, has been reported: Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2000**, *122*, 12049.

TABLE 2. Effect of the Solvent and Base on the Annulation (Eq 2)[a]

entry	base	solvent	time (h)	yield of **1** (%)
1	Et_3N	DMF	24	74
2	Et_3N	DMA	24	69
3	collidine	DMF	48	11
4	*i*-Pr_2NEt	DMF	24	57

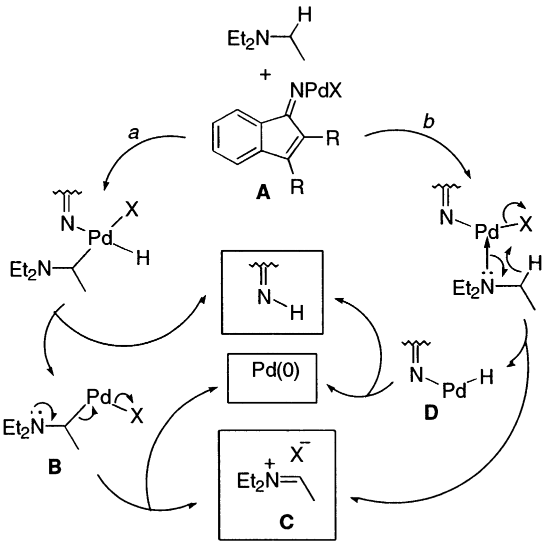
[a] Reactions were run with 3 equiv of diphenylacetylene, 10 mol % $Pd(dba)_2$, and 1 equiv of the base in a 9:1 solvent−water mixture at 100 °C.

lower yields compared to phosphine-free annulation (entries 20 and 21).

We also conducted several experiments designed to elucidate the identity of the reagent responsible for the reduction of Pd(II) back to Pd(0) (Table 2). After analysis of the reaction conditions, we focused on two possibilities. Under our reaction conditions, it seemed plausible that DMF could react with water to produce formic acid, which is known to reduce Pd(II) species.[30] However, when we employed DMA instead of DMF (Table 2, entry 2), the yield of **1** remained virtually unaffected, which strongly discounts the possible role of DMF in the reduction. Alternatively, the reduction could be effected by triethylamine since alkylamines containing α-carbon−hydrogen bonds are also capable of reducing Pd(II) complexes.[31] Substitution of triethylamine by collidine, a nonreducing amine, using our best reaction conditions resulted in a sharply lower yield of the annulation product (entry 3). This suggests that Et_3N may be the reducing agent. Obtaining **1** in a 57% yield in the experiment using *i*-Pr_2NEt, instead of Et_3N (entry 4), seems to support our hypothesis that the alkylamine base may be the reagent actually reducing Pd(II) to Pd(0) in the catalytic cycle in Scheme 1. The lower yield in entry 4 is presumably caused by fewer α-C−H bonds available for the reduction in *i*-Pr_2NEt compared to Et_3N or simply the greater difficulty Pd(II) is going to have in coordinating to this more hindered amine.

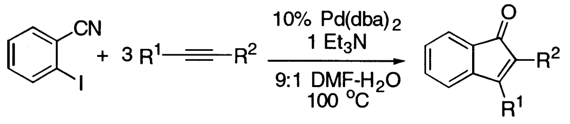
We propose the following two tentative mechanisms for the reduction of Pd(II) by triethylamine (Scheme 2). A palladium(II) species, such as **A**, may undergo insertion into the α-C−H bond activated by the nitrogen in Et_3N (pathway *a*). Examples of such insertion have been reported.[32] Following reductive elimination of the organic product, the (α-aminoalkyl)palladium complex **B** is formed. Fragmentation of **B** leads to a Pd(0) species, which returns to the catalytic cycle, and an iminium salt, **C**, generation of which has also been proposed as the key step in Pd-catalyzed transformations of trialkylamines.[32]

SCHEME 2



Alternatively, **A** could coordinate to the nitrogen in Et_3N and then undergo *pseudo β*-hydride elimination to afford **C** and an organopalladium species, **D**, which produces Pd(0) upon reductive elimination (pathway *b*).[33]

Using our best reaction conditions (Table 1, entry 11), we proceeded to test the applicability of our procedure to the annulation of other alkynes (eq 4). The annulation of 2-iodobenzonitrile onto 1-phenyl-1-propyne resulted in the formation of an inseparable 1:1 mixture of regioisomeric indenones **3** and **4** in a combined 32% yield after a 48 h reaction period (Table 3, entry 1). Only a trace amount of 2,3-di-*n*-propyl-1-indenone (**5**) was detected in the reaction of 4-octyne (entry 2), with about 40% of the starting 2-iodobenzonitrile still present after 48 h. Indenone **6** was formed in low yield when 2-iodobenzonitrile was annulated onto 4,4-dimethyl-2-pentyne (entry 3). The annulation of 2-methyl-4-phenyl-3-butyn-2-ol afforded the expected indenone **7** in an 8% yield along with 3-phenyl-2-(2-propenyl)-1-indenone (**8**), which was apparently derived from **7** (entry 4). This reaction also suffered from low conversion of the starting nitrile. Finally, we were able to obtain 2-*tert*-butyl-3-(*tert*-butylethynyl)-1-indenone (**9**) in a 16% yield from the reaction between 2-iodobenzonitrile and 2,2,7,7-tetramethyl-3,5-octadiyne (entry 5). The reasons behind the poor yields in the annulation of alkynes other than diphenylacetylene are unclear considering that these alkynes have readily participated in many other palladium-mediated annulation reactions.[6a,7c,26a]



(4)

We have also screened a large number of different olefins in an attempt to extend the nitrile annulation

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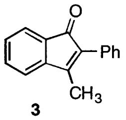
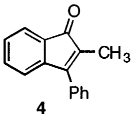
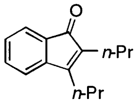
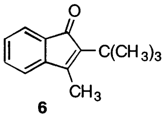
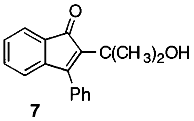
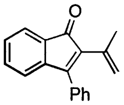
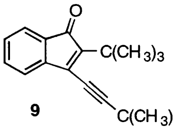
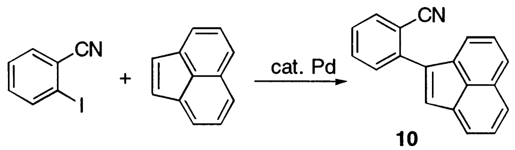
(33) A different mechanism involving insertion of a Pd(II) complex into the *β*- rather than α-C−H bond of the trialkylamine (see ref 31b) seems unlikely, since the former process should be much less favorable than the latter. Reaction between D_2O and our intermediate **C** can explain the formation of deuterium-containing products in ref 31b without involving *β*-C−H bond activation.

TABLE 3. Annulation of 2-Iodobenzonitrile onto Various Alkynes (Eq 4)[a]

entry	alkyne	time (h)	product(s)	% yield
1	$Ph{-}{\equiv}{-}CH_3$	48	 **3** :  **4**	32[b]
2	$n\text{-}Pr{-}{\equiv}{-}n\text{-}Pr$	48	 **5**	trace[c]
3	$H_3C{-}{\equiv}{-}C(CH_3)_3$	48	 **6**	7
4	$Ph{-}{\equiv}{-}C(CH_3)_2OH$	48	 **7** +  **8**	8 + 6[c]
5	$(H_3C)_3C{-}{\equiv}{-}{\equiv}{-}C(CH_3)_3$	24	 **9**	16

[a] All reactions were run with 3 equiv of the alkyne, 10 mol % $Pd(dba)_2$, and 1 equiv of Et_3N in a 9:1 DMF−water mixture at 100 °C. [b] Isolated as a 1:1 inseparable mixture of isomers **3** and **4**. [c] Incomplete conversion of 2-iodobenzonitrile.

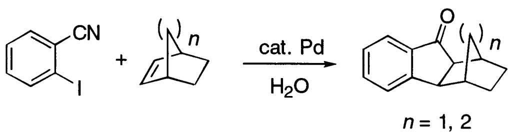
methodology to include alkenes and dienes. No annulation products were observed in the reactions of 2-iodobenzonitrile with *cis*-stilbene, indene, 3,4-dihydronaphthalene, 2,3-dioxene, *N*-phenylmaleimide, undeca-1,2-diene, 1-phenylpropa-1,2-diene, 1,3-cyclohexadiene, and 1,4-cyclohexadiene. However, the reaction of 2-iodobenzonitrile with acenaphthylene afforded a Heck type product, **10**, in 57% yield (eq 5). We believe that the latter reaction follows our proposed annulation mechanism, but the benzylic palladium intermediate formed undergoes solvolysis faster than it can add to the cyano group. The driving force behind this solvolysis is probably the formation of a stable, highly delocalized benzylic cation, which, upon losing a proton, leads to **10**.



10

(5)

During the course of our study of the scope of the nitrile annulation chemistry, we have found that bicyclic alkenes undergo facile annulation by 2-iodobenzonitrile (eq 6). Palladium hydride elimination during annulation, which is likely the major factor in the failure of other olefins and alkylacetylenes, is prevented in bicyclic alkenes by the inability of palladium to align in a *cis* fashion with the bridgehead hydrogen. Such elimination would also produce a very strained bridgehead olefin.



(6)

We have also observed the beneficial effect of increasing the temperature on the yields of this reaction (Table 4). Thus, polycyclic ketone **11** was obtained in 85% yield when the annulation was run at 100 °C. The yield improved to 93% when the temperature was raised to 130 °C (entry 1). The expected *exo* stereochemistry of **11** was confirmed by comparing its ^{1}H NMR spectrum to literature data.[34] A high reaction temperature proved even more beneficial for the annulation of 2-iodobenzonitrile onto bicyclo[2.2.2]octene (entry 2). Not only did it increase the yield of the product ketone **12**, it also enhanced the reaction rate, which was sluggish at 100 °C, presumably because of steric hindrance around the double bond of the olefin. Functionalized polycyclic ketone **13** was obtained from the corresponding norbornene derivative in 89% yield (entry 3), demonstrating the nitrile annulation's tolerance of the ester functionality. The reaction of benzonorbornadiene (prepared from benzyne and cyclopentadiene by a Diels−Alder cycloaddition)[35] at 100 °C was slow, but this problem was rectified by raising the temperature (entry 4). Repeated attempts to carry out a double annulation of 2-iodobenzonitrile onto norbornadiene failed as the nitrile was recovered even at a high temperature and after a prolonged reaction

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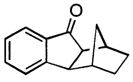
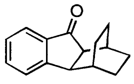
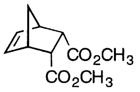
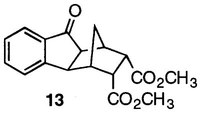
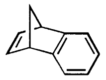
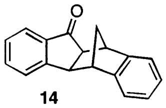
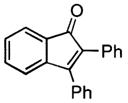
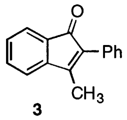
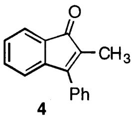
(34) (a) Amrein, W.; Larsson, I.-M.; Schaffer, K. *Helv. Chim. Acta* **1974**, *57*, 2519. (b) Brown, D.; Grigg, R.; Sridharan, V.; Tambyraiah, V.; Thornton-Pett, M. *Tetrahedron* **1998**, *54*, 2595. (c) For ^{1}H NMR spectroscopic methods of assigning the stereochemistry of bicyclic systems, see: Mayo, P.; Tam, W. *Tetrahedron* **2001**, *57*, 5943 and references therein.

(35) Friedman, L.; Logullo, F. M. *J. Org. Chem.* **1969**, *34*, 3089.

TABLE 4. Effect of the Temperature on the Annulation of Bicyclic Alkenes and Alkynes (Eqs 4 and 6)[a]

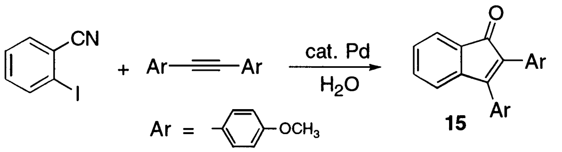
entry	substrate	product(s)	% yield	
			at 100 °C	at 130 °C
1		 **11**	85	93
2		 **12**	55[b]	82
3		 **13**	70	89
4		 **14**	-[c]	59
5	Ph—≡—Ph	 **1**	74	96
6	Ph—≡—CH$_3$	 :  **3** **4**	32[d]	34[d]

[a] See the Experimental Section for the reaction conditions. [b] The reaction time was 72 h. [c] The yield was not determined due to the low conversion of the 2-iodobenzonitrile after 48 h. [d] Isolated as a 1:1 inseparable mixture of isomers **3** and **4**.

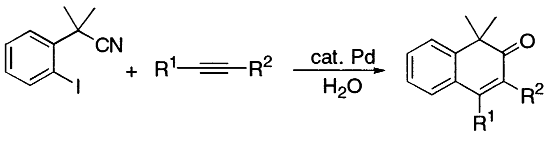
time. We believe that norbornadiene may have formed a strong complex with the palladium catalyst, thus removing the latter from the reaction.[36] This could also explain the low reactivity of benzonorbornadiene (entry 4), which is capable of forming a similar complex with Pd.

Similarly, elevating the reaction temperature improved the yield of 2,3-diphenylindenone (**1**), which was previously obtained in 74% yield using our original reaction conditions (Table 1, entry 11), to almost a quantitative yield (Table 4, entry 5). However, no improvement was observed when 2-iodobenzonitrile was allowed to react with 1-phenyl-1-propyne. The annulation at 130 °C afforded an inseparable 1:1 mixture of the two possible regioisomers **3** and **4** (entry 5) in a yield almost identical to that obtained at a lower temperature (Table 3, entry 1).

On the basis of the aforementioned results, our optimal annulation conditions are as follows: 0.25 mmol of 2-iodobenzonitrile, 3 equiv of diphenylacetylene or bicyclic alkene, 10 mol % Pd(dba)$_2$, 1 equiv of Et$_3$N, and 5 mL of 9:1 DMF−water as the solvent at 130 °C for 24 h. This procedure is expected to be a useful method for the synthesis of various 2,3-diarylindenones other than **1**, as illustrated by the 79% yield of indenone **15** we have obtained (eq 7).



We have also found that the analogous annulation of 2-(2-iodophenyl)-2-methylpropanenitrile onto diphenylacetylene affords a high yield of the expected six-membered ring aromatic ketone **16** (eq 8). Mirroring our observations in the indenone synthesis, regioisomeric naphthenones **17** and **18** are formed in 18% and 11% yields, respectively, when the unsymmetrical alkyne 1-phenyl-1-propyne is used in the annulation.



16 (R^1, R^2 = Ph) 96%
17 (R^1 = Ph, R^2 = CH$_3$) 18%
18 (R^1 = CH$_3$, R^2 = Ph) 11%

Having established the alkyne and olefin limitations of the nitrile annulation methodology, we set out to explore the range of nitrile-containing components

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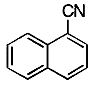
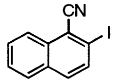
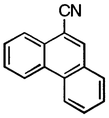
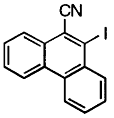
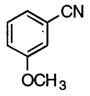
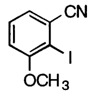
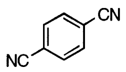
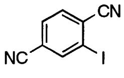
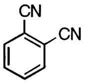
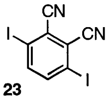
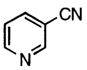
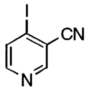
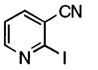
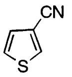
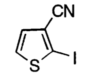
[36] (a) Wertz, D. W.; Moseley, M. A. *Spectrochim. Acta, Part A* **1980**, *36A*, 467. (b) Borsub, N.; Kutal, C. *J. Am. Chem. Soc.* **1984**, *106*, 4826.

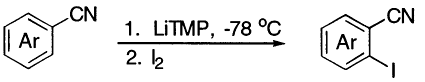
TABLE 5. Preparation of *o*-Iodoarenenitriles by Nitrile-Directed *Ortho*-Lithiation (Eq 9)[a]

entry	substrate	product(s)	% yield
1		 **19**	63
2		 **20**	60
3		 **21**	50
4		 **22**	72
5		 **23**	74[b]
6		 **24** :  **25**	50[c]
7		 **26**	87

[a] See the Experimental Section for the reaction conditions. [b] A two-step reaction sequence was employed here. [c] Isolated as a 1:1 hard-to-separate mixture of isomers **24** and **25**.

we might employ. Several strategies were used to synthesize a series of aromatic *o*-iodoarenenitrile starting materials.

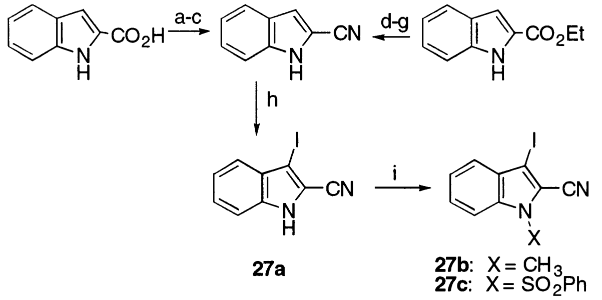
Using the synthetically underutilized ability of the cyano group to direct *ortho*-lithiation,[37] we successfully adopted the procedure of Fraser and Savard for the synthesis of *o*-iodoarenenitriles (eq 9).[38] Nitrile-containing substrates **19**−**23** were prepared in good yields by *ortho*-



(9)

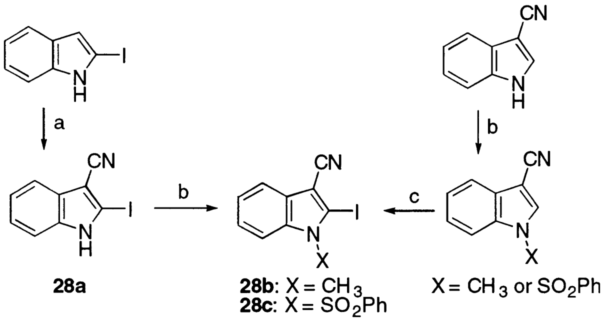
lithiation of the corresponding arenenitriles with lithium tetramethylpiperidide (LiTMP), followed by quenching with iodine (Table 5, entries 1−5). 2,3-Dicyano-1,4-diiodobenzene (**23**) was obtained from sequential introduction of each iodine substituent into the molecule (entry 5). The procedure was also applicable to the synthesis of heterocyclic *o*-iodoarenenitriles **24**−**26** (entries 6 and 7). *Ortho*-lithiation−iodination of 3-cyanopyridine produced a hard-to-separate mixture of regioisomeric **24** and **25** that were partially isolated by column chromatography.

SCHEME 3[a]



[a] Reagents and conditions: (a) $SOCl_2$, ether, rt; (b) NH_3, ether, rt; (c) $POCl_3$, reflux; (d) LAH, ether, rt; (e) MnO_2, ether, rt; (f) H_2NNMe_2, benzene, reflux; then MeI; (g) MeONa, MeOH, reflux; (h) KOH, I_2, DMF, rt; (i) NaH, DMF, 0 °C; then MeI or $PhSO_2Cl$, rt.

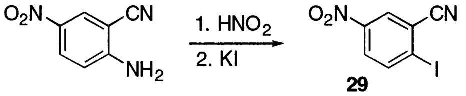
SCHEME 4[a]



[a] Reagents and conditions: (a) $ClSO_2NCO$, MeCN, 0 °C, then Et_3N, rt; (b) NaH, DMF, 0 °C; then MeI or $PhSO_2Cl$, rt; (c) LiTMP, THF, −78 °C; then I_2, −78 °C to rt.

We also prepared two series of regioisomeric heterocyclic substrates designed to probe the effect of steric hindrance and electron density in an indole ring on the nitrile annulation. Substituted iodoindolecarbonitriles **27** and **28** were synthesized as shown in Schemes 3 and 4, respectively. Depending on the immediate availability of the starting materials, 2-cyanoindole was obtained in good yield from either indole-2-carboxylic acid or ethyl indole-2-carboxylate and then iodinated to afford **27a**, which was derivatized at the nitrogen atom to give **27b** and **27c** (Scheme 3). 2-Iodoindole-3-carbonitrile (**28a**) was prepared from 2-iodoindole and was then functionalized to produce indoles **28b** and **28c** (Scheme 4). An alternative method starting with indole-3-carbonitrile worked well for the *N*-methyl compound, but *ortho*-lithiation−iodination of the *N*-sulfonylated precursor to hopefully produce **28c** afforded a mixture of products that had to be separated.

Finally, we synthesized substituted 2-iodobenzonitriles **29** and **30** for a study of the electronic effect of substituents on the benzene ring. 2-Iodo-5-nitrobenzonitrile (**29**) was obtained in 65% yield by iodination of the diazonium salt prepared from 5-nitroanthranilonitrile (eq 10). A



29 (10)

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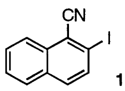
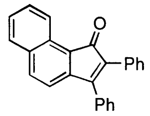
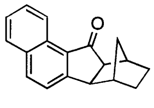
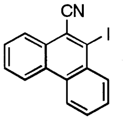
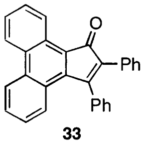
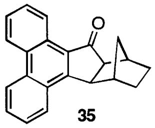
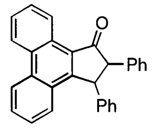
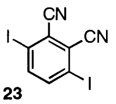
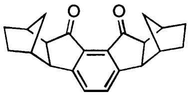
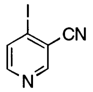
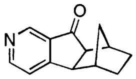
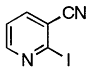
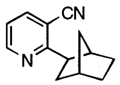
(37) Gawley, R. E.; Rein, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 1, Chapter 2.1, pp 461 and 468.

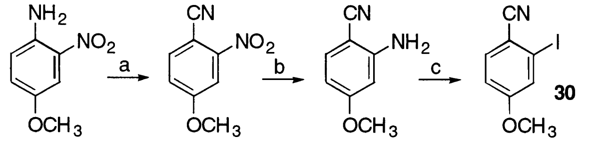
(38) Fraser, R. R.; Savard, S. *Can. J. Chem.* **1986**, *64*, 621.

TABLE 6. Annulation of 2-Iodoarenenitriles (Scheme 6)[a]

entry	nitrile	from diphenylacetylene product(s)	% yield[b]	from norbornene product(s)	% yield[b]
1	 **19**	 **31**	96	 **32**	93
2	 **20**	 **33**	22	 **35**	91
		+  **34**	45		
3	 **23**	-[c]	-	 **36**	33[d]
4	 **24**	-[c]	-	 **37**	52
5	 **25**	-	-	 **38**	40

[a] See the Experimental Section for the reaction conditions. [b] Isolated yield. [c] A complex product mixture is formed. [d] Isolated as a mixture of diastereomers.

SCHEME 5[a]

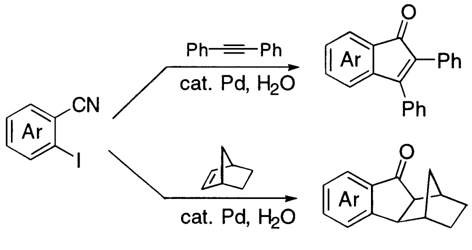


[a] Reagents and conditions: (a) $NaNO_2$, H_2SO_4, 0 °C; then CuCN, NaCN, H_2O; (b) $SnCl_2$, AcOH, DME, 60 °C; (c) $NaNO_2$, H_2SO_4, 0 °C; then KI, H_2O, rt.

three-step synthesis based on variations of the Sandmeyer reaction afforded the electron-rich 2-iodo-4-methoxybenzonitrile (**30**) in 30% overall yield (Scheme 5).

With various *o*-iodoarenenitriles in hand, we proceeded to explore their annulation onto diphenylacetylene and norbornene (Scheme 6). 1-Cyano-2-iodonaphthalene (**19**) readily participated in both reactions, affording polycyclic ketones **31** and **32** in excellent yields identical to those obtained with 2-iodobenzonitrile (Table 6, entry 1). To our surprise, the annulation of 9-cyano-10-iodophenanthrene (**20**) onto diphenylacetylene produced not only the expected fully conjugated ketone **33**, but also its dihydro derivative **34**, which apparently is formed from **33** so as to relieve the former compound's anti-aromaticity (Table 6, entry 2). This phenomenon has been previously observed in an unrelated synthesis of **33**.[39] The reaction of **20** with norbornene proceeded smoothly and led to polycyclic ketone **35** in high yield (entry 2). An attempted double annulation of 2,3-dicyano-1,4-diiodobenzene (**23**) onto diphenylacetylene afforded a complex reaction mixture, in which we were unable to identify any individual annulation products (entry 3). However, the

SCHEME 6



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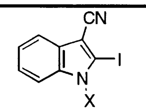
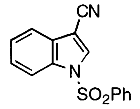
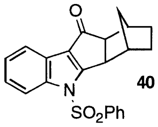
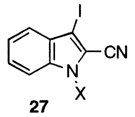
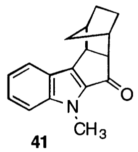
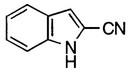
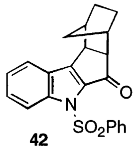
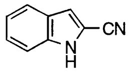
[39] Moritani, I.; Toshima, N.; Nakagawa, S.; Yakushiji, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2129.

TABLE 7. Annulation of Norbornene with Indolecarbonitriles[a]

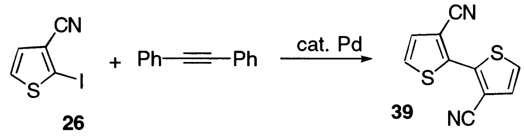
entry	indolecarbonitrile	X	product(s)	% isolated yield
1	 **28**	CH$_3$ (**28b**)	-	-
2		H (**28a**)	-	-
3		SO$_2$Ph (**28c**)		52
			+  **40**	16
4	 **27**	CH$_3$ (**27b**)	 **41**	77
5		H (**27a**)		81
6		SO$_2$Ph (**27c**)	 **42**	69(86)[b]
			+ 	20

[a] See the Experimental Section for the reaction conditions. [b] The yield in parentheses is corrected for the diverted starting material.

double annulation succeeded in the case of norbornene, and polycyclic dione **36** was obtained as a mixture of several diastereomers (entry 3).

Somewhat surprisingly, no annulation products were observed when *o*-iodonicotinonitriles **24** and **25** were allowed to react with diphenylacetylene (entries 4 and 5). The failure may possibly be caused by competing coordination of the pyridines and alkynes with palladium. Yet, no problems were encountered in the annulation of **24** onto norbornene, which produced the heterocyclic ketone **37** in a good yield (entry 4). We found, however, that the reaction between **25** and norbornene did not lead to the expected annulation product, but rather to 2-(2-norbornyl)pyridine-3-carbonitrile (**38**) in 40% yield (entry 5). It seems quite likely that the nitrogen atom of the pyridine ring chelates to the palladium center in the intermediate corresponding to **I** in Scheme 1, thus preventing the norbornylpalladium species from adding to the cyano group and eventually leading to reduction of the C−Pd bond in this intermediate.

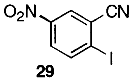
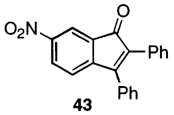
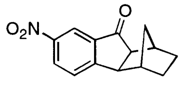
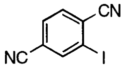
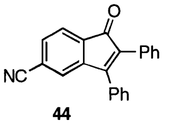
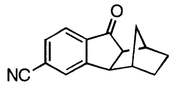
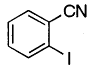
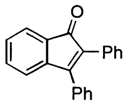
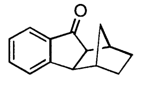
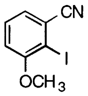
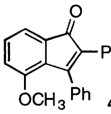
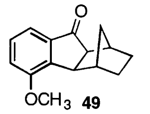
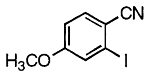
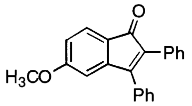
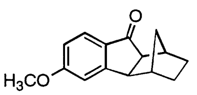
An obstacle of a different kind was encountered in the attempted annulation of 2-iodothiophene-3-carbonitrile (**26**). Instead of incorporating diphenylacetylene into the product structure, this reaction afforded the homo-coupling product **39** in 85% yield (eq 11). Presumably, the palladium catalyst is ligated by the sulfur atom in **26,** making coordination to the alkyne less favorable.



26 **39** (11)

Although no annulation products were observed in the reaction between several indolecarbonitriles (**27a**, **27c**, **28b**) and diphenylacetylene, compounds **27** and **28** were subjected to annulation onto norbornene (Table 7). The more electron-rich *N*-methyl-2-iodo-3-indolecarbonitrile (**28b**) and the parent cyanoindole **28a** furnished no

TABLE 8. Annulation of Substituted 2-Iodobenzonitriles (Scheme 6)[a]

entry	nitrile	from diphenylacetylene		from norbornene	
		product	% yield	product	% yield
1	 **29**	 **43**	53	 **47**	81
2	 **22**	 **44**	47	 **48**	85[b]
3			96	 **11**	93
4	 **21**	 **45**	58	 **49**	75
5	 **30**	 **46**	81[b]	 **50**	84[b,c]

[a] See the Experimental Section for the reaction conditions. [b] The reaction time was 48 h. [c] A byproduct, 4-methoxybenzonitrile, was isolated in 16% yield.

annulation products (entries 1 and 2). Considering the possibility that sluggish oxidative addition of the electron-rich **28a** and **28b** to the palladium catalyst may be responsible for these disappointing results, we examined the reaction of norbornene with the more electron-poor **28c**. This reaction afforded mostly *N*-(benzenesulfonyl)-indole-3-carbonitrile. However, the annulation product **40** was also obtained, albeit only in a modest 16% yield (entry 3). Steric hindrance around the reaction site probably accounts for the large amount of the reduced starting material in this reaction.

To separate sterics from electronic effects, a series of indolecarbonitriles with a different substitution pattern was studied. The electron-rich **27b** furnished a 77% yield of the heterocyclic annulation product **41** (entry 4), whose skeleton is related to that of a key intermediate in the synthesis of a natural product, yuehchukene, and its analogues.[40] The unprotected indolecarbonitrile **27a** afforded 2-cyanoindole in a high yield and no annulation product (entry 5). This result is likely caused by the ease of nitrogen deprotonation in **27a**, which leads to the formation of a negatively charged arylpalladium intermediate and impedes its coordination and subsequent addition to norbornene. The annulation of *N*-(benzenesulfonyl)-3-iodoindole-2-carbonitrile (**27c**) was far more successful, the target product **42** being formed in a 69% isolated yield (entry 6). Desulfonylation and subsequent reduction of the C−I bond in **27c** accounted for 20% of the starting material, which brings the corrected yield of **42** to 86%. Interestingly, no desulfonylated annulation products were detected in the reactions of either **27c** or **28c** (entries 3 and 6).

The steric hindrance around the reaction site appears to have a pronounced effect on the annulation of indolecarbonitriles (compare entries 3 and 6, and 1 and 4), although other factors cannot be excluded. However, the success of the annulation of both the electron-rich **27b** and the electron-poor **27c** suggests that the electronic density of the indole ring does not play a significant role in this reaction.

In contrast, the electronic effects of the substituents in the benzene ring appear to have a major influence on the alkyne annulation with substituted 2-iodobenzonitriles (Table 8). Thus, annulation of electron-deficient benzonitrile derivatives **29** and **22** onto diphenylacetylene afforded only moderate yields of indenones **43** and **44** (entries 1 and 2) compared to the reaction with the parent system (entry 3). The electron-rich 2-iodo-3-methoxybenzonitrile (**21**) also produced indenone **45** in a modest yield (entry 4). On the other hand, the annulation of diphenylacetylene by the less sterically hindered **30** resulted in the formation of indenone **46** in a much higher yield (entry 5).

Both electron-deficient and electron-rich benzonitriles gave equally good results when used in the annulation of norbornene (Table 8). The yields of the polycyclic ketones **47**−**50** were as good as, or better than, the yields of the corresponding indenones. Electron-withdrawing

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(40) Cheng, K. F.; Chan, T. T.; Lai, T. F.; Kong, Y. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3317.

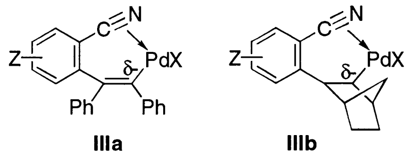

FIGURE 1. Electronic effects of substituent Z on annulations involving 2-iodobenzonitriles.

substituents did not have nearly as big an effect on the annulation of norbornene with **29** and **22** (entries 1 and 2), although the yields of **47** and **48** were still lower than those obtained with 2-iodobenzonitrile itself (entry 3). Annulation of the relatively hindered **21** onto norbornene gave a higher yield compared to the corresponding reaction with diphenylacetylene (entry 4) for reasons that are not obvious. A reduction product, 4-methoxybenzonitrile, was formed in 16% yield from **30**, diverting some starting material from the annulation and lowering the otherwise excellent yield of **50** (entry 5).

We propose the following model to account for the electronic effects of the substituent on the aromatic ring in the annulations onto alkynes and alkenes (Figure 1). For the organopalladium intermediate **III** to successfully add to the cyano group, there has to be a sufficient partial negative charge (δ-) on the carbon atom of the Pd−C bond, as well as reasonable electron density in the carbon−nitrogen triple bond for the nitrile to effectively coordinate to palladium. When the annulation involves an alkyne, intermediate **IIIa** is formed, in which an electron-withdrawing substituent, Z, directly reduces, via conjugation, both the electron density of the cyano group and the partial negative charge on the carbon bearing the palladium moiety, thus inhibiting vinylpalladium attack on the CN and lowering the yield of the annulation.[41] In the case of norbornene, Z has no direct effect on the partial negative charge δ- of the Pd−C bond (intermediate **IIIb)** and only affects the coordinating ability of the cyano group. It is also possible that nitrile carbopalladation in **IIIb** is promoted by steric interactions between the Pd and the bridging methylene unit of the norbornyl system as it relieves the steric congestion. As a result, norbornene annulation by electron-poor substrates furnishes higher yields than the corresponding diphenylacetylene reactions. An electron-donating Z group should not interfere with the annulation, except perhaps by slowing the initial oxidative addition, as observed in the case of **30** (entry 5, Table 8).

Conclusions

The carbon−nitrogen triple bond of aryl and heteroaryl nitriles has been observed to readily participate in organopalladium annulation reactions. An efficient procedure for the synthesis of 2,3-diarylindenones and polycyclic aromatic ketones from readily prepared *o*-iodoarenenitriles has been developed. The reaction is compatible with a variety of functional groups and affords products in good to excellent yields. We have also gained some insights into the mechanism of nitrile carbopalladation through variation of the base and a study of electronic and steric effects in substituted 2-iodobenzonitriles and indolecarbonitriles. This chemistry illustrates that there may be other organopalladium reactions which will occur intramolecularly that normally do not occur by intermolecular processes.

Experimental Section

General Procedures. ^{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, 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. $Pd(OAc)_2$ and PPh_3 were donated by commercial sources. $Pd(dba)_2$ was prepared according to a published procedure.[42] The preparation and characterization of all starting materials can be found in the Supporting Information.

General Procedure for the Palladium-Catalyzed Annulation of Alkynes and Bicyclic Alkenes with 2-Iodoarenenitriles. Palladium bis(dibenzylideneacetone) (14.4 mg, 0.025 mmol), Et_3N (25.3 mg, 0.25 mmol), 2-iodoarenenitrile (0.25 mmol), the alkyne or bicyclic alkene (0.75 mmol), and 5 mL of a 9:1 DMF−water mixture were placed in a 4 dram vial, which was heated in an oil bath at 130 °C for the appropriate period of time. The reaction mixture was cooled, diluted with ether, washed with saturated aq NH_4Cl, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica gel column.

The following compounds, prepared by the above procedure, have been previously reported: indenones **1**, **3**, **4**, **5**, **6**, **7**, and **9**, polycyclic aromatic ketones **11** and **12**, and naphthenone **16**.[7c,20]

7-Aza-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one (37). Compound **37** was obtained in a 52% yield from the reaction of 3-cyano-4-iodopyridine (**24**) and norbornene under the indicated conditions after purification by column chromatography using 1:2 hexanes/EtOAc: light yellow solid, mp 53−54 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.75−0.82 (m, 1H), 0.98−1.05 (m, 1H), 1.33−1.54 (m, 2H), 1.62−1.84 (m, 2H), 2.46 (d, J = 3.9 Hz, 1H), 2.54 (d, J = 6.3 Hz, 1H), 2.65 (d, J = 3.6 Hz, 1H), 3.19 (d, J = 6.3 Hz, 1H), 7.48 (dt, J = 5.1, 0.9 Hz, 1H), 8.74 (d, J = 5.1 Hz, 1H), 8.87 (d, J = 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.7, 29.1, 32.7, 40.8, 41.3, 48.2, 55.9, 121.7, 134.8, 146.3, 154.3, 164.9, 207.8; IR (neat) 1714, 2954 cm^{-1}; HRMS *m/z* 199.09995 (calcd for $C_{13}H_{13}NO$, 199.099714).

***N*-Methyl-6-oxo-6a,7,8,9,10,10a-hexahydro-7,10-methano-6*H*-indeno[2,1-*b*]indole (41).** Compound **41** was obtained in a 77% yield from the reaction of *N*-methyl-3-iodoindole-2-carbonitrile (**27b**) and norbornene under the indicated conditions after purification by column chromatography using 4:1 hexanes/EtOAc: light yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.94−1.03 (m, 2H), 1.33−1.37 (m, 1H), 1.41−1.45 (m, 1H), 1.62−1.77 (m, 2H), 2.46 (d, J = 2.7 Hz, 1H), 2.54 (d, J = 2.7 Hz, 1H), 2.76 (d, J = 3.6 Hz, 1H), 3.11 (d, J = 3.6 Hz, 1H), 3.90 (s, 3H), 7.16−7.20 (m, 1H), 7.34−7.43 (m, 2H), 7.73−7.75 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.7, 28.9, 30.0, 32.0, 38.6, 38.8, 42.3, 62.0, 110.9, 120.1, 121.8, 122.5, 126.6, 140.9, 145.2, 146.2, 196.3; IR (neat)

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[41] This model can also account for the results we have obtained in the attempted annulation of diphenylacetylene by 2-bromobenzonitrile (30% yield of **1** with 80% conversion of the starting material after 72 h) and 2-cyanophenyl triflate (no annulation product). The annulation is probably impeded since the Pd−Br bond in **IIIa** (X = Br) would reduce the partial negative charge on the vinylic carbon due to bromine's relatively high electronegativity, and palladium triflates (**IIIa**, X = OTf) are known to easily dissociate and form cationic palladium complexes, obviously incapable of nucleophilic reactions.

[42] Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.

1682, 2952, 3054 cm^{-1}; HRMS *m*/*z* 251.131315 (calcd for $C_{17}H_{17}NO$, 251.131014).

5-Cyano-2,3-diphenyl-1-indenone (44). Compoud **44** was obtained in a 47% yield from the reaction of 1,4-dicyano-2-iodobenzene (**22**) and diphenylacetylene under the indicated conditions after purification by column chromatography using 1:2 hexanes/EtOAc: red solid, mp 179−181 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 7.25−7.31 (m, 5H), 7.35−7.41 (m, 3H), 7.45−7.47 (m, 3H), 7.63−7.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 116.6, 118.2, 122.9, 123.6, 128.3, 128.4, 128.5, 128.9, 129.2, 129.7, 129.9, 130.0, 131.6, 133.8, 133.9, 146.0, 154.4, 194.6; IR (neat) 1716, 2229, 3053 cm^{-1}; HRMS *m*/*z* 307.100183 (calcd for $C_{22}H_{13}NO$, 307.099714).

Characterization of all other 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, references to the preparation methods and characterization data for all known products, 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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