

Cooperative Catalyst Effects in Palladium-Mediated Cyanation Reactions of Aryl Halides and Triflates

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Substoichiometric quantities of copper or zinc species dramatically improve both conversion rate and efficiency of Pd(0)-catalyzed cyanation reactions. The optimum reaction conditions involve the use of a nitrile solvent, NaCN, and a catalyst system employing the combination of cuprous iodide with tetrakis(triphenylphosphine)palladium(0), [Pd(PPh₃)₄]. Beneficial effects were observed for the conversion of aryl halides, aryl triflates, and a vinyl bromide to the corresponding nitriles. The process was demonstrated on preparative scale with a broad range of aromatic and heteroaromatic substrates containing diverse functionality. A dual catalytic cycle is proposed to explain the profound influences of the cocatalyst system.

Introduction

The palladium-catalyzed displacement of aryl halides and triflates with cyanide ion to afford the corresponding aryl nitrile has been reported.^{2,3} The transition-metal-catalyzed process offers practical improvements to the Rosemund–von Braun reaction for which the same overall transformation necessitates both stoichiometric quantities of copper cyanide and high reaction temperatures. Product isolations are also complicated by separation of the resulting copper halide.⁴ Tetrakis(triphenylphosphine)palladium(0) [Pd(PPh₃)₄], a reactive and readily available Pd(0) source,⁵ has been used most extensively in the catalyzed reaction. However, the Pd(PPh₃)₄-mediated process is recognized as being notoriously unreliable, thus prompting reports of several modifications to the original protocol. These variations are categorized generally by the application of either modified ligand sets,^{2f,6} the use of covalent^{5,7,8} and alumina impregnated cyanide sources,⁹ or the inclusion of crown ether additives.¹⁰ Additionally, conducting the reaction in the presence of electrochemical reducing potential has been shown to minimize the persistent problem of catalyst deactivation.¹¹ Although these modifications

have proven beneficial in the specific examples for which they were developed, an expedient procedure which yields the palladium-catalyzed cyanation reaction generally applicable to a wide variety of substrates has not been demonstrated. In this paper, we report a solution to this troublesome but important synthetic problem.

Our synthesis of a tricyclic partial ergot alkaloid drug candidate required the preparation of the aryl nitrile derivative **2** from **1a** which was accomplished through the use of a transition metal-catalyzed process (eq 1).¹² Standard Pd(PPh₃)₄-catalyzed cyanation protocols involving KCN and aryl iodide **1a** in THF at reflux were ineffective.^{2b} Ultimately, our discovery that the Pd(0)-mediated reaction could be dramatically accelerated by addition of a catalytic amount of copper(I) iodide allowed efficient production of **2**.¹² We detail herein a systematic study of this reaction and apply the new and experimentally expedient method to a wide range of structurally diverse substrates. The convenient process affords a dependable catalyst system which allows the facile conversion of aryl iodides, bromides and triflates to the corresponding nitrile derivatives.

Results and Discussion

Cyanation of iodide **1a** to **2** required the presence of both Pd(PPh₃)₄ and CuI. The cocatalyzed cyanation reaction of **1a** was complete within 2.5 h in deoxygenated THF at reflux (Table 1). *Without CuI, similar conditions provided only 10% conversion to 2 after 18 h.* The use of catalytic CuI without a Pd(0) catalyst did not generate any detectable amounts of aryl nitrile.¹³

Evaluation of several reaction parameters furnished an improved protocol. The relative reaction rates for the Pd/Cu-catalyzed cyanation of **1a** conducted in varied

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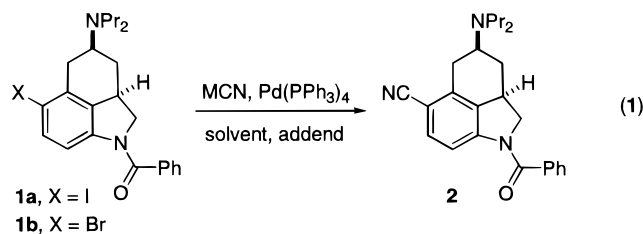
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Table 1. Pd(PPh₃)₄-Catalyzed Cyanation of **1**^a

entry	substrate	solvent	M	mol % CuI	time, h	%, conv ^b
1	1a	THF	K	0	18	10
2	1a	THF	K	10	3	100
3	1a	THF	K	10 ^c	3	100
4	1a	THF	Na	10	0.5	100
5	1a	THF	Bu ₄ N	10	72	3
6	1a	MeCN	K	10	1.5	99
7	1a	MeCN	Na	10	0.5	99
8	1a	EtOAc	K	10	4	96
9	1a	EtOAc	Na	10	0.5	98
10	1a	DMF	Na	10	24	25 ^d
11	1a	MeOH	Na	10	19	3 ^d
12	1b	EtCN	Na	10	4	99 ^d

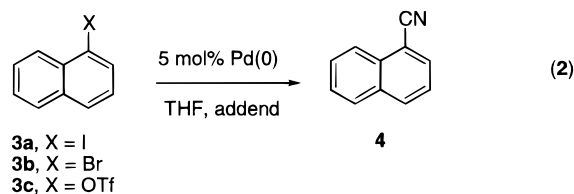
^a Conditions: 2 equiv of MCN, 5 mol% Pd(PPh₃)₄, 0.4 M **1** in deoxygenated solvent under N₂, 65 °C. ^b Conversion determined by HPLC. ^c 10 mol % PPh₃ added. ^d Reaction conducted at reflux.

media at a constant temperature (65 °C) increased in the order: EtOAc < THF < MeCN (Table 1, entries 2, 6, and 8). Both DMF and methanol were poor solvents for the reaction and provided only modest conversion to the desired product (entries 10, 11). Deoxygenating solvents by subsurface nitrogen sparge enhanced reproducibility and conversion yields.^{12,14} NaCN consistently afforded more rapid conversions than KCN; however, both were suitable reagents. Use of high quality, finely powdered dry cyanide sources also improved reliability.¹⁵ Tetra-*n*-butylammonium cyanide (Bu₄N⁺CN⁻) was ineffective and led to only 3% conversion of **1a** to **2** after 72 h (entry 5). The optimal reaction conditions involve the combination of a nitrile solvent with NaCN.

A study of reactions involving naphthalene derivatives **3** established the requisite characteristics of the catalyst system (eq 2, Table 2). As observed for **1**, the cyanation of **3a** employing KCN (2 equiv) in deoxygenated THF and Pd(PPh₃)₄ (5 mol %) provided negligible production of **4** (7%, 6 h). Conversely, the presence of copper salts resulted in efficient conversion of **3** to **4** (entry 2). Copper(I) iodide effected the most pronounced acceleration. A 2:1 Cu:Pd ratio was most often employed. Although a 1:1 metal ratio was sufficient to accomplish the desired conversion, the reaction proceeded at a proportionately slower rate (entry 4). CuI, CuOTf·0.5 C₆H₆ and CuBr were also competent addends. CuCl, however, did not impact the Pd(0)-catalyzed reaction (entry 10).

The reaction proved sensitive to the oxidation state of the copper species. Although Cu(OTf)₂ (entry 7) and CuBr₂ (entry 9) were effective cocatalysts, reactions employing the corresponding copper(I) species provided more rapid conversion.

The accelerating effect was not limited to copper cocatalysts. Zinc iodide (10 mol %) in THF also facilitated the palladium-catalyzed cyanation of **3a** (entry 11).¹⁶ Other transition metal addends, including MgBr₂, Fe(CN)₃, and Cr(CO)₆, did not accelerate or improve the Pd(PPh₃)₄-catalyzed conversion of **3a** to **4** under the conditions studied.

Table 2. Additive Effects on the Pd(PPh₃)₄-Catalyzed Cyanation of **3a**^a

entry	addend	time, h	%, conv ^b
1	none	0	7
2	10 mol % CuI	1	100
3	10 mol % CuI ^c	1	100
4	5 mol % CuI	2	100
5	10 mol % CuCN	2	100
6	10 mol % CuOTf	4	94
7	10 mol % Cu(OTf) ₂	3	57
8	10 mol % CuBr	3	100
9	10 mol % CuBr ₂	6	100
10	10 mol % CuCl	1	4
11	10 mol % ZnI ₂	2.5	100
12	10 mol % KI	1	1
13	10 mol % TMSCN	3.5	>98
14	10 mol % B(Ph) ₃	2	100

^a Conditions: 2 equiv of KCN, 5 mol % Pd(PPh₃)₄, 0.4 M **3a** in THF. ^b Conversion determined by HPLC. ^c 10 mol % PPh₃ added.

Table 3. Pd(0)-Catalyzed Cyanation Reactions of Aryl Bromide **3b**^a

entry	Pd source	mol %, CuI	solvent	time, h	%, conv ^b
1	Pd ₂ (dba) ₃ 4 DPPF	0	NMP	7	61 ^c
2	Pd ₂ (dba) ₃ 4 DPPF	10	NMP	7	69 ^c
3	Pd ₂ (dba) ₃ 4 DPPF	0	EtCN	20	22
4	Pd ₂ (dba) ₃ 4 DPPF	10	EtCN	6	97
5	Pd(PPh ₃) ₄	0	EtCN	8	12
6	Pd(PPh ₃) ₄	10	EtCN	4	97
7	Pd(PPh ₃) ₄	10	MeCN	7	97

^a Conditions: 5 mol % Pd, 2 equiv of NaCN, 1 M solution of **3b** at reflux temperature. ^b Conversion determined by HPLC. ^c 60 °C.

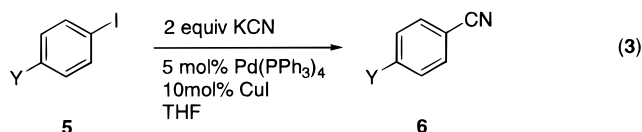
Importantly, the accelerating effect was not limited to cyanation reactions catalyzed by Pd(PPh₃)₄ as a similar influence was demonstrated for a Pd₂(dba)₃-mediated process. [Pd₂(dba)₃]·CHCl₃ in the presence of chelating phosphines (1,1'-bis(diphenylphosphino)ferrocene, DPPF) in NMP has been reported to be a useful system for catalysis of cyanide addition to aryl iodides and triflates.^{2f} However, like other palladium-catalyzed cyanation protocols, aryl bromides were shown to be far less reactive substrates, and minimal conversion of bromobenzene to benzonitrile was reported after extended reaction time (12%, 12 h, 60 °C).^{2f} While no beneficial effects of added copper(I) iodide was observed for the cyanation reaction of **3b** conducted in NMP (Table 3, entries 1 and 2), CuI (10 mol %) efficiently promoted the conversion of **3b** in

(13) For a high-temperature copper-mediated cyanation reaction, see: Carr, R. M.; Cable, K. M.; Wells, G. N.; Sutherland, D. R. *J. Labeled Compd. Radiopharm.* **1994**, *34*, 887.

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(15) Commercially available NaCN (99.40%) routinely provided excellent results whereas a lower purity source (95%) has resulted in poor conversion.

(16) A failed attempt to effect Pd(PPh₃)₄-catalyzed cyanation of an aryl bromide employing KCN and catalytic Zn(CN)₂ has been reported; see ref 7a. We have found that DMF is a poor reaction medium for the cocatalyzed process (Table 1).

Table 4. Substituent Effects on Pd(0)-Catalyzed Cyanation of 5

entry	substrate	Y	addend	time	%, conv ^a
1	5a	OCH ₃	10 mol % CuI	4	97
2	5a		none	4	14
3	5b	H	10 mol % CuI	1	100 ^b
4	5b		none	5	8 ^b
5	5c	COCH ₃	10 mol % CuI	1	100
6	5c		none	4	47
7	5d	NO ₂	10 mol % CuI	5	48
8	5d		none	1	98

^a Conversion determined by GC. ^b Conversion determined by HPLC.

propionitrile with [Pd₂(dba)₃]·CHCl₃-(4 DPPF) (5 mol %) (entry 4). Complete conversion of the bromide **3b** to **4** was observed after 6 h in propionitrile while only 22% conversion occurred after 20 h in the absence of the CuI additive.

Consistent with kinetic studies which have documented the relative reactivity of the two Pd(0) catalysts,⁵ the Pd(PPh₃)₄ and CuI-catalyzed reaction proved more rapid than the analogous Pd₂(dba)₃-mediated process, and conversion of **3b** was complete within 4 h (Table 3, entry 6). The corresponding reaction conducted at lower temperature in acetonitrile at reflux provided 97% conversion after 7 h (Table 3, entry 7). Furthermore, the cyanation reaction of aryl bromide **1b** in EtCN was also efficiently accomplished within 4 h (Table 1, entry 12). Although several favorable catalyst systems were identified, the application of CuI and Pd(PPh₃)₄ provided the optimal catalyst combination studied.

Application of the new methodology to a broad range of substrates was an important focus of this study. A preliminary evaluation of electronic effects confirmed that the cocatalyst system positively influenced the conversion for a variety of simple aromatic iodides **5** to the corresponding nitriles **6** (eq 3). Copper-induced acceleration was most pronounced for the electron-rich substrates (Table 4). The impact was moderated for electron-poor substrates which are typically more reactive substrates for the palladium-catalyzed processes. For example, **5d** was an exceptionally reactive substrate and complete conversion to **6** in the absence of CuI was accomplished within 1 h. Interestingly, conversion in the presence of 10 mol % CuI stalled after only 48% conversion.

Evaluation of the process employing substrates containing diverse functionality was conducted in a series of preparative experiments (Table 5). In addition to simple substituted aryl halides, several iodo- and bromo-substituted heterocycles were successfully converted to the corresponding nitriles. The facile cyanation method illustrated in Tables 3 and 5 for the conversion of aryl bromides has particular practical significance since the substrates are often more readily available than the corresponding aryl iodides.

Analogous to the corresponding halide derivatives **3a** and **3b**, the Pd(PPh₃)₄-catalyzed conversion of aryl triflate **3c** to **4** failed to go to completion. The standard Pd/Cu-catalyzed protocol established above provided complete conversion within 1 h. In general, the scope of the

Table 5. CuI/Pd(PPh₃)₄-Catalyzed Cyanation Reactions of Aryl and Vinyl Halides and Triflates^a

entry	substrate	product	time, h	%, yield ^b
1		7	1	90
2		X = I 8	1	92
3		Br 8	6	91
4	3c	4	1	90
5		9	1	87
6		10	2	83
7		11	4	71
8		12	2	76 ^c
9		13	2	90 ^d

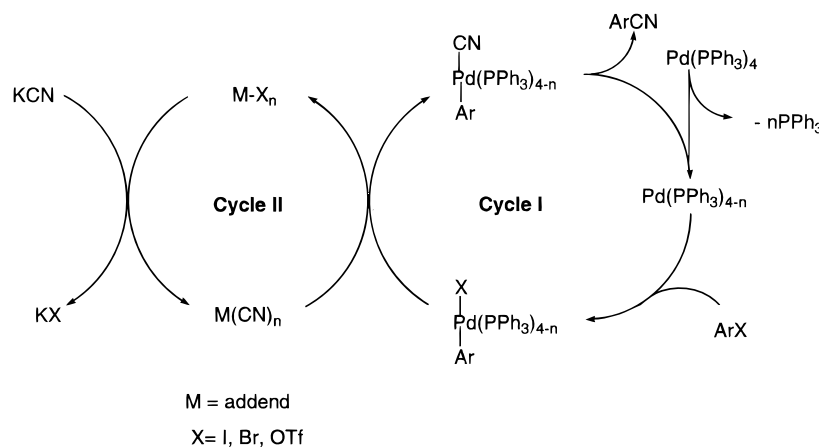
^a Conditions: 2 equiv of NaCN, 5 mol % Pd(PPh₃)₄, 10 mol % CuI, nitrile solvent at reflux, MeCN (ArI, ArOTf); EtCN (ArBr). ^b Isolated yield. ^c Reaction conducted in valeronitrile, 115 °C. ^d 10 mol % Pd(PPh₃)₄, 20 mol % CuI, MeCN, 50 °C.

process proved broad and accommodated a wide range of substrates including species containing Lewis basic functionality.

Modification of the standard protocol was required in some special cases. Only trace levels of conversion of 5-bromoindole were observed when the reaction was conducted in propionitrile (97 °C, 16 h). The use of valeronitrile as solvent allowed a higher reaction temperature (110 °C) and resulted in the production of useful yields of the desired nitrile (entry 8). The successful cyanation of a vinyl halide was also enabled by the addition of CuI (entry 9). Addition of up to 50 mol % Pd(PPh₃)₄ failed to efficiently catalyze the conversion of this substrate in the absence of the cocatalyst (<20% yield). The sensitivity of the vinyl bromide required a reduction of the standard reaction temperature to 50 °C. An increased catalyst loading of 10 mol % Pd(PPh₃)₄ and 20 mol % CuI offset the rate-retarding effect of the lower reaction temperature.

The operative mechanism of the bimetallic catalyst system has not been established. However, several observations provide insight. Combinations of catalytic quantities of Pd(PPh₃)₄ and KI (Table 2, entry 12) or LiI (not shown) failed to promote the cyanation reaction, and only

Scheme 1



trace conversion of either **3a** or **3b** was observed after 6 h. These results discount the possibility that the metal addends serve as halide sources which might in turn be responsible for the observed effects.^{2c,17}

Interestingly, the addition of PPh_3 had minimal effect on the rate of the copper/palladium-catalyzed cyanation reaction. Conducting the cocatalyzed cyanation reaction of **3a** in the presence of up to 40 mol % triphenylphosphine afforded complete conversion to the nitrile at a rate nearly indistinguishable from that achieved with the bimetallic catalyst system. Similarly, the CuI-promoted cyanation reaction of **1a** remained operational when conducted in the presence of 10 mol % PPh_3 and catalytic $\text{Pd}(\text{PPh}_3)_4$ (entries 2 and 3, Table 1). In contrast, addition of PPh_3 completely suppresses the copper-accelerating effect associated with the palladium-catalyzed Stille cross-coupling reaction.^{18,19}

A two-cycle process is proposed to explain the role of the addend.²⁰ The transition metal additive might serve as a vehicle which transfers the cyanide ion between the poorly soluble stoichiometric source (KCN or NaCN) and the Pd(II) intermediate (Scheme 1). This second cycle (II) could act in concert with the primary process which involves activation of the substrate through the Pd(0)-mediated oxidative addition reaction followed by transmetalation and reductive elimination.

Two pathways in which the proposed $\text{M}(\text{CN})_n$ intermediate might influence the reaction are considered. High concentration of alkali metal cyanide (KCN or NaCN) is known to inhibit the palladium-catalyzed cyanation reaction.^{2c,d} Catalyst inhibition might be minimized by conversion of cyanide ion to the more covalent transition metal species (i.e. $\text{M}(\text{CN})_n$). Limited solubility of KCN and NaCN allows application of only a catalytic amount of added copper or zinc salts.²¹ Reaction conditions which allow ionic cyanide concentrations to overwhelm the intercepting catalytic addend are therefore ineffective. For example, no benefit of a cocatalyst was realized when a soluble cyanide species (e.g. *n*- Bu_4NCN) was employed (Table 1, entry 5) or when the reaction medium significantly improved the solubility of the alkali cyanide (Table 1, entries 10, 11).

Alternatively, the proposed $\text{M}(\text{CN})_n$ intermediate might facilitate the reaction by providing a species which functions more efficiently in the transmetalation step with the Pd(II) complex than does either NaCN or KCN.²² A reaction was initiated in the absence of a copper cocatalyst in which **3a** was treated with 2 equiv KCN and 5 mol % $\text{Pd}(\text{PPh}_3)_4$ (THF). As expected, production of the nitrile peaked at only 10% conversion in 1 h. Addition of 10 mol % CuI to this reaction mixture led to 89% conversion after 3.5 h. The rate at which **4** was produced following addition of the cocatalyst was much slower when compared to reactions in which CuI was present at the outset (complete, 1 h). This suggests that some degree of catalyst poisoning had occurred, and although facilitating the transmetalation step may be a contributing factor, it is not the exclusive role of CuI.

While the exact nature of the proposed catalytically active metal cyanide species has not been determined, the feasibility of such an entity to be involved in the transmetalation step was demonstrated. Both CuCN and $\text{KCu}(\text{CN})_2$ (1 equiv) proved to be efficient agents for the cyanation of **1a** in the presence of Pd(0) (5 mol %). High yields of the cyanoindoline **2** were obtained after reaction in THF at reflux with rates similar to the CuI-catalyzed process (3–4 h). The Pd(0) catalyst was required in both of these examples to produce **2**.

The proposed mechanism requires that an effective cocatalyst must have the capacity to react with NaCN or KCN to form a covalently bound cyanide species which can be regenerated upon transmetalation with the Pd(II) intermediate. Additive candidates are therefore not limited to transition metals. This analysis prompted our evaluation of trimethylsilyl cyanide (TMSCN)^{23,24} and triphenylborane as cocatalysts.²⁵ Indeed, the $\text{Pd}(\text{Ph}_3)_4$ -catalyzed conversion of **3a** to **4** was accomplished in 3.5 h when conducted in the presence of 10 mol % TMSCN (Table 2, entry 13) and within 2 h with added $\text{B}(\text{Ph})_3$ (Table 2, entry 14). These results are consistent with

(21) The solubilities of sodium and potassium cyanide in several solvents at 60 °C are: DMF, 15.0 mmol dm^{-3} ; THF, 2.4 mmol dm^{-3} ; acetonitrile, 1.9 mmol dm^{-3} . Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776.

(22) $\text{L}_2\text{Pd}(\text{CN})_2$ complexes have been prepared from NaCN and the corresponding L_2PdCl_2 species, see Vertuyft, A. W.; Cary, L. W.; Nelson, J. H. *Inorg. Chem.* **1976**, *15*, 3161.

(23) Trimethylsilyl cyanide is an effective stoichiometric cyanide source for Pd(0)-catalyzed processes when the reaction is conducted in triethylamine as solvent; see ref 8.

(24) For leading references describing the conversion of TMS-X to TMS-CN, see Sukata, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2257.

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(20) A related mechanism was proposed to interpret kinetic data derived from Pd(II)-catalyzed cyanation reactions; see ref 2d.

the proposed mechanism albeit the reactions were markedly slower when compared to the more optimal Pd(PPh₃)₄/CuI catalyst system.

Although these experiments establish the proposed mechanism to have predictive value, other possibilities remain viable. For example, Lewis acids are known to accelerate the nickel-catalyzed diene hydrocyanation reaction.²⁶ If operative in the present case, a Lewis acid effect is not general nor does it correlate with the acidity of the addends. For example, copper(I) iodide is a more effective adjutant than copper(II) triflate. Moreover, the presence of other Lewis acids such as MgBr₂ does not afford appreciable acceleration of the Pd(0)-catalyzed conversion of **3a** to **4** (5% conv, 3 h, THF).

Conclusion

A novel cocatalyzed cyanation reaction involving Pd(0) catalysts has been developed that provides efficient and reproducible access to aryl nitriles. The process, studied in greatest detail for a CuI/Pd(PPh₃)₄ catalyst system, appears to be mechanistically distinct from the copper effect involved in the palladium-catalyzed cross-coupling reaction.¹⁸ The new process allows efficient conversion of aryl and vinyl halides as well as aryl triflates to the corresponding nitrile derivatives utilizing potassium or sodium cyanide. Palladium-catalyzed cyanation reactions were demonstrated to be uniformly sluggish or to stall completely in the absence of the cocatalyst. Several different copper sources and zinc(II) iodide were shown to accelerate the palladium(0)-catalyzed reaction. The copper cocatalyst extended the effectiveness of both Pd(PPh₃)₄ and [Pd₂(dba)₃]·CHCl₃-DPPF mediated processes. This convenient and reliable protocol eliminates the harsh reaction conditions and excessive metal waste which are characteristic of previous existing methods.

Experimental Section

All solvents were deoxygenated by a subsurface N₂ purge for 30–45 min immediately prior to use. High-pressure liquid chromatography (HPLC) was performed using a Zorbax RX-C₈ column (4.6 mm i.d. × 25 cm) with diode array UV detection. Similar absorption coefficients (>95%) were established for the starting material and product at the monitored wavelength. Gas chromatography (GC) was performed using a Fisher Scientific DB-1 capillary column (30 m; film thickness 0.25 mm). Products were compared to authentic samples obtained commercially for compounds **4**, **6a–c**, **11**, and **12**. Spectral data for **7**²⁷ and **8**²⁸ were compared with reported values. Pd(PPh₃)₄ was prepared as previously described.²⁹

Commercially available CuI (Aldrich, 99.999%) was typically purified;³⁰ however, experiments in which the reagent was used directly provided similar results. All other catalysts were purchased and used without further purification. NaCN (Mallinckrodt, 99.40%) and KCN (Fisher, ≥98%) were finely ground and stored in a vacuum oven (100–150 °C) prior to use.

Representative Procedure. The substrate (3.94 mmol), KCN (0.51 g, 7.88 mmol), Pd(PPh₃)₄ (0.228 g, 0.197 mmol), and CuI (0.394 mmol) were placed in a flask which was flushed with N₂. Solvent (5 mL) was added via syringe. The resulting mixture was heated to reflux under N₂ with vigorous agitation by a magnetic stirrer and sampled at 15 min intervals. The mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), and then filtered through Celite. The filtrate was washed with water and brine, dried over anhydrous MgSO₄, and concentrated by rotary evaporation. Purification was accomplished by silica gel chromatography.

8-Quinolinecarbonitrile (9). 8-Quinolinyl trifluoromethanesulfonate (0.50 g, 1.8 mmol), CuI (0.034 g, 0.18 mmol), NaCN (0.18 g, 3.6 mmol), and Pd(PPh₃)₄ (0.10 g, 0.087 mmol) were charged to a round-bottom flask. Acetonitrile (5 mL) was added, and the mixture was heated to reflux for 1 h. Reaction workup was accomplished employing the standard method. The product was purified by silica gel chromatography (30% ethyl acetate in hexanes) to give 0.24 g of the desired product (87%). Mp 87.5–88.3 °C; TLC *R*_f = 0.3 (30% ethyl acetate in hexanes); IR (CHCl₃) 2232 cm⁻¹; ¹H NMR (CDCl₃) δ 8.94 (dd, 1H, *J* = 1.2, 4.2 Hz), 8.15 (dd, 1H, *J* = 1.0, 8.5 Hz), 8.0–7.96 (m, 2H), 7.52–7.42 (m, 2H); ¹³C NMR (CDCl₃) δ 152.0, 146.9, 136.2, 135.1, 132.6, 127.6, 125.5, 122.4, 116.9, 112.5; mass spectrum, *m/z* (FIA, *M* + 1) 155. Anal. Calcd for C₁₀H₆N₂: C, 77.91; H, 3.92; N, 18.17. Found: C, 77.94; H, 4.08; N, 18.06.

8-Cyano-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolin-3-one (10). The aryl bromide³¹ (1.07 g, 3.47 mmol), CuI (0.07 g, 0.4 mmol), NaCN (0.36 g, 7.3 mmol), and Pd(PPh₃)₄ (0.21 g, 0.18 mmol) were charged to a round-bottom flask. Propionitrile (5 mL) was added, and the mixture was heated to reflux for 2 h. Reaction workup was accomplished employing the standard method. The product was purified by silica gel chromatography (ethyl acetate) to give 0.73 g of the desired product (83%). Mp 146–147.4 °C; TLC *R*_f = 0.38 (ethyl acetate); IR (CHCl₃) 2231, 1630 cm⁻¹; ¹H NMR (CDCl₃) δ 7.33–7.28 (m, 3H), 3.40 (dd, 1H, *J* = 3, 13 Hz), 2.95–2.88 (m, 5H), 2.53–2.48 (m, 2H), 2.29–2.22 (m, 2H), 1.81–1.71 (m, 2H), 1.04 (s, 3H); ¹³C NMR (CDCl₃) δ 170.4, 149.4, 135.3, 132.7, 129.7, 126.0, 118.8, 110.2, 61.1, 37.8, 32.0, 29.5, 29.1, 27.9, 21.9; mass spectrum, *m/z* (FIA, *M* + 1) 255. Anal. Calcd for C₁₆H₁₈N₂O: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.89; H, 7.21; N, 10.97.

(Z)-6-[2-Cyano-1-(3-fluorophenyl)ethenyl]-1-[(1-methylethyl)sulfonyl]-1*H*-benzimidazol-2-amine (13). The corresponding vinyl bromide³² (2.00 g, 46 mmole), CuI (0.16 g, 0.84 mmol), KCN (0.60 g, 9.2 mmol), and Pd(PPh₃)₄ (0.52 g, 0.45 mmol) were charged into the reaction flask. Acetonitrile (40 mL) was added, and the resulting mixture was heated to 50 °C for 90 min. The reaction mixture was cooled to room temperature. The mixture was filtered through a plug of silica gel, and the solid cake was washed with ethyl acetate followed by a wash with methylene chloride until the eluting solution was colorless. The filtrate was concentrated to a solid. The solid was stirred in ethyl acetate and washed with water followed by a wash with brine. The organic phase was dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to 1.5 g of an amorphous white solid (85% yield). ¹H NMR (DMSO) δ 7.9 (s, 1H), 7.7–7.0 (m, 6H), 5.9 (s, 2H), 5.5 (s, 1H), 3.8 (m, 1H), 1.4 (d, 6H); IR (CHCl₃) 2215, 1640, 1608 cm⁻¹, MS *m/z* (FID) 384. Anal. Calcd for C₁₉H₁₇N₄O₂SF: C, 59.36; H, 4.46; N, 14.57. Found: C 59.41; H 4.57; N 14.03.

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