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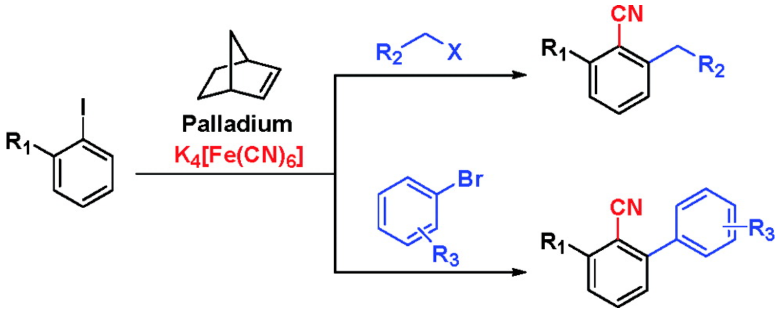

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A Convergent Synthesis of Polysubstituted Aromatic Nitriles via Palladium-Catalyzed C−H Functionalization

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Abstract: A palladium-catalyzed C−H functionalization reaction for the synthesis of highly substituted aromatic nitriles is reported. The modularity of the reaction is demonstrated by the broad range of aryl iodides which can be coupled with metal cyanides and alkyl halides or aryl bromides.

Introduction

We have recently reported a tandem intramolecular ortho alkylation/cyanation reaction for the synthesis of annulated heterocycles via a C−H functionalization manifold.[1] We now show that intermolecular alkylation occurs readily between aryl iodides and alkyl halides, including the much more attractive alkyl chlorides. In addition we find that cross arylation/cyanation can be achieved by combining an aryl iodide with an electron-deficient aryl bromide followed by cyanation. In this way, biaryl compounds with diverse functionality can be prepared in one step. Our approach toward developing a tandem reaction relies on using the inherent reactivity of norbornene to initiate a competitive C−H functionalization pathway, so that C−C and C−CN bond formation can occur sequentially. Catalytic C−H functionalization for the synthesis of carbon−carbon bonds has many advantages over traditional palladium-catalyzed cross-couplings, the greatest being the lack of prefunctionalization of one or both of the coupling partners, which allows for the simple preparation of substrates. Because of its many advantages, palladium-catalyzed C−H functionalization has recently undergone significant advancement within the research community.[2] Many recently reported palladium(IV)-based methods for the functionalization of C−H bonds have relied on oxidative conditions utilizing hypervalent iodine to oxidize palladium(II) to palladium(IV).[3] In the late 1990s, Catellani et al. reported a method that does not use oxidative conditions; rather, it is based upon the formation of palladacycles and their ability to react with electrophiles such as alkyl and aryl halides.[4] Great effort has gone into exploring both the synthetic and mechanistic potential of this reaction,[5] which has led to the elucidation of the reaction mechanism.

Mechanism. The proposed mechanism for the palladium-catalyzed C−H functionalization/cyanation is shown in Figure 1. Initial oxidative addition of palladium(0) into the aryl iodide followed by carbopalladation of norbornene gives product **B**. With no possibility for *syn*-β-hydride elimination to occur, an electrophilic metalation occurs, followed by deprotonation at the ortho position to form palladacycle **C**. This palladium(II) intermediate can then undergo reaction with alkyl or aryl halides to form octahedral palladium(IV) intermediate **D**. This species rapidly undergoes reductive elimination to generate palladium(II) intermediate **E**. If the starting aryl iodide has two unsubstituted ortho positions, a subsequent C−H functionalization will take place at the second ortho position of the aryl iodide. If, however, one of the ortho positions of the aryl iodide is substituted with an appropriate blocking group, only one C−H functionalization will occur. With both ortho positions substituted, extrusion of norbornene via decarbopalladation is favored because of the increased steric strain. This regenerates the aryl palladium species **H**, which can then undergo transmetalation with a metal cyanide, followed by reductive elimination to yield the desired product **J** and regenerate the palladium(0) catalyst. Although norbornene could theoretically be used in catalytic amounts, it is often necessary to utilize stoichiometric amounts to favor the initial carbopalladation and subsequent insertion processes within the reaction. It is also possible that the reaction products could be formed by ortho metalation of an initially formed aryl nitrile; however, when the corresponding

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(1) Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436−14437.

(2) For recent work and review on palladium-catalyzed C−H functionalization, see: (a) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274−7276. (b) Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 8217−8220. (c) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076−15077. (d) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172−1175. (e) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496−16497. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238.

(3) For recent work on Palladium(IV) chemistry, see: (a) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836−5837. (b) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906−4907. (c) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924−1935.

(4) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 119−122.

(5) For recent work on synthesis and mechanistic studies, see: (a) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2006**, *128*, 722−723. (b) Catellani, M.; Motti, E.; Faccini, F.; Ferraccioli, R. *Pure Appl. Chem.* **2005**, *77*, 1243−1248. (c) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485−1488. (d) Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827−4829. (e) Cardenas, D. J.; Martin-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033−5040. (f) Canty, A. J. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; pp 189−211.

10.1021/ja075599i CCC: $37.00

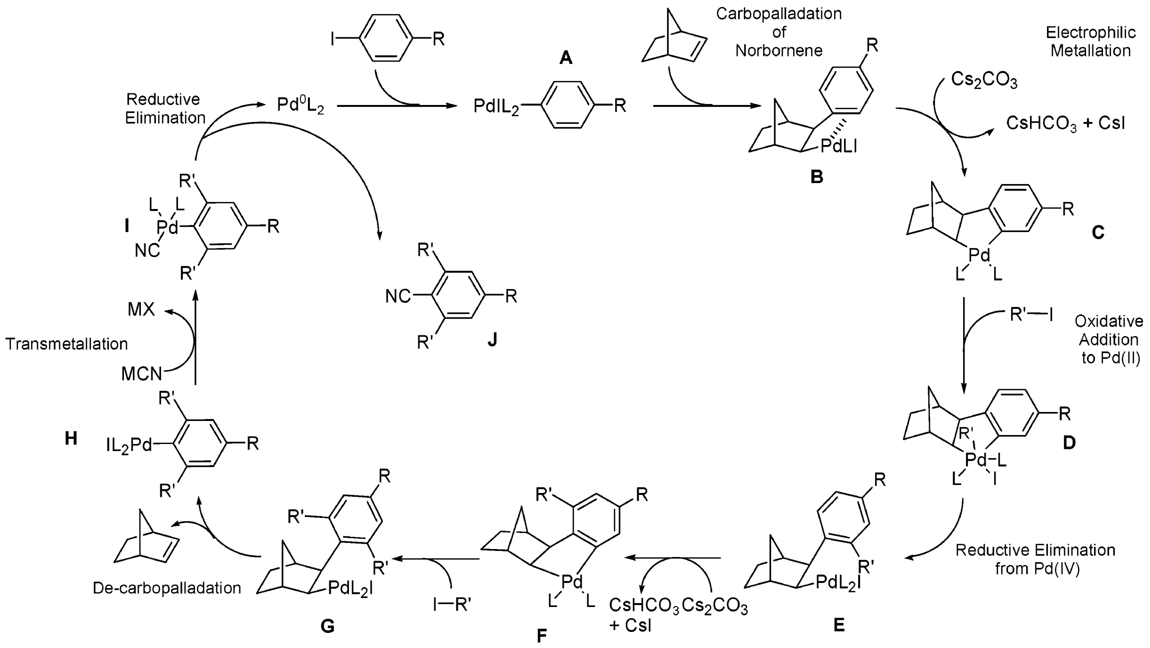


Figure 1. Proposed mechanism of ortho functionalization/cyanation reaction.

aryl nitrile is placed under the reaction conditions no reaction is observed.

Results and Discussion

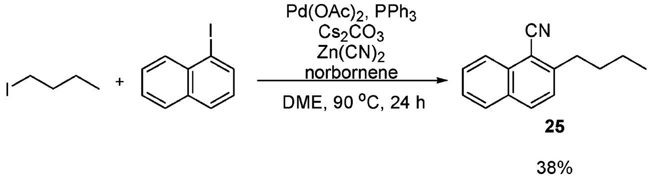
Intramolecular Alkylation/Cyanation. The initial investigation of the tandem alkylation/cyanation reaction focused on using tethered alkyl halides for the ortho functionalization of aryl iodides. While these experiments yielded a mixture of both cyclized and uncyclized benzonitriles, the formation of uncyclized benzonitriles could be suppressed by careful variation of the reaction temperature using microwave irradiation.[6] Under the optimized conditions, substrate **1** was transformed into the five-membered ring oxacycle **2** in 91% yield (Table 1, entry 1). Attempts to lower the catalyst loading from 10 to 5 mol % palladium gave **2** in 63% yield. Extension to larger ring systems was also possible under these conditions, affording the desired six- and seven-membered rings in 78 and 62% yields, respectively (entries 2 and 3). Next, the nitro and methoxy-containing aryl iodides were subjected to the reaction conditions to ascertain the effect of different ortho substituents on the yield of the reaction. Gratifyingly, both substrates furnished the corresponding benzonitriles in good yields (entries 4 and 5), demonstrating that both electron-withdrawing and electron-donating ortho-blocking substituents are tolerated under the reaction conditions. All attempts with substrates lacking an ortho substituent gave complex mixtures.

The synthesis of nitrogen-containing heterocyclic benzonitriles also proved to be very efficient. Five- and six-membered ring products were generated in 78 and 79% yields, respectively (entries 6 and 7), while seven-membered ring formation occurred in 67% yield (entry 8). Aryl bromides were examined under the optimized reaction conditions with **11b** undergoing cyclization in 57% yield (entry 9).

The successful preparation of bicyclic substrates led us to extend the reaction scope to include tricyclic benzonitriles through a double ortho alkylation/cyanation sequence. While the 5,6,5-ring system **17** was prepared in 88% yield (entry 9), larger 6,6,6- and unsymmetrical 5,6,6-ring systems were generated in 75 and 56% yields, respectively (entries 10 and 11). In addition, fully substituted tricyclic benzonitrile **24** was prepared in 74% yield from the corresponding *para*-methoxy aryl iodide **23** (entry 12).

Intermolecular ortho Alkylation/Cyanation. To take advantage of the convergent nature of the reaction sequence and to demonstrate that substituted benzonitriles can be readily prepared, we sought to extend this methodology to the intermolecular alkylation/cyanation of aryl iodides. Initial attempts utilizing 1-iodonaphthalene and bromobutane under the optimized conditions for the intramolecular alkylation/cyanation reaction failed to give any of the desired products. However, when iodobutane was used as the alkylating agent the desired product was isolated in 38% yield (Scheme 1).

Scheme 1. Initial Conditions for Intermolecular Reaction



During the course of the optimization, we observed cyanation of many of the intermediates in the Catellani reaction sequence (Figure 2). These products included direct cyanation of the aryl iodide and cyanation of norbornyl intermediates.

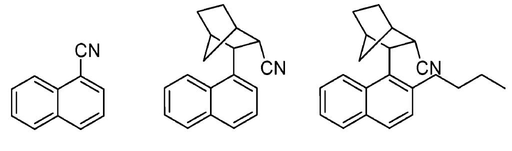


Figure 2. Reaction byproducts observed during optimization.

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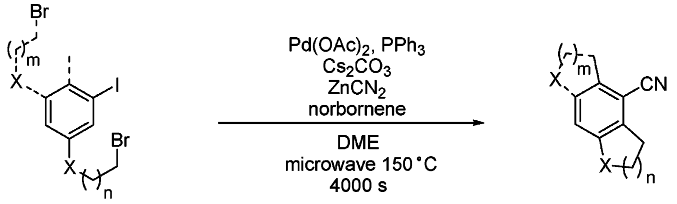
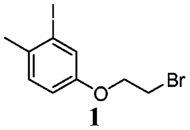
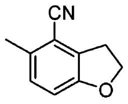
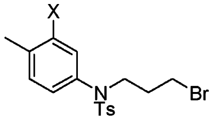
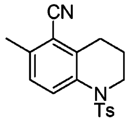
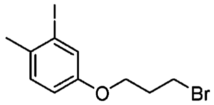
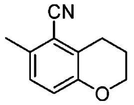
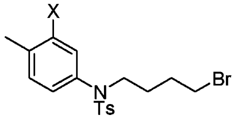
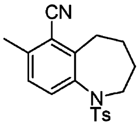
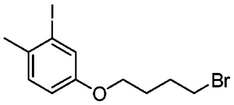
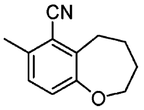
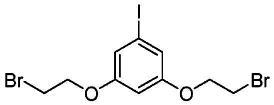
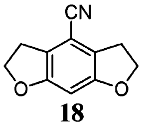
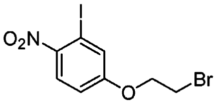
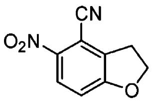
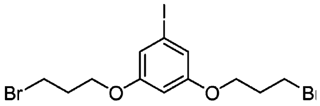
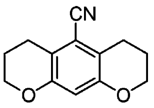
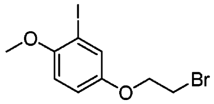
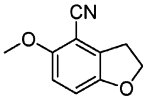
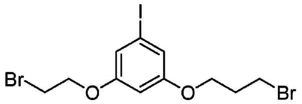
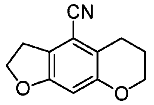
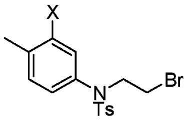
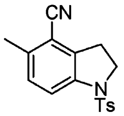
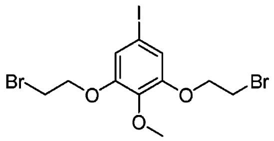
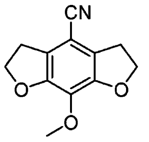
(6) For a review on microwave-assisted organic synthesis, see: Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

Table 1. Synthesis of Annulated Benzonitriles via Palladium-Catalyzed Tandem Intramolecular Alkylation/Cyanation Reaction[a]



Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	 **1**	 **2**	91	7	 **13a, X=I** **13b, X=Br**	 **14**	79 55[c]
2	 **3**	 **4**	78	8	 **15a, X=I** **15b, X=Br**	 **16**	67 47[c]
3	 **5**	 **6**	62	9	 **17**	 **18**	88
4	 **7**	 **8**	73	10	 **19**	 **20**	75
5	 **9**	 **10**	83	11	 **21**	 **22**	56
6	 **11a, X=I** **11b, X=Br**	 **12**	78 57[c]	12	 **23**	 **24**	74

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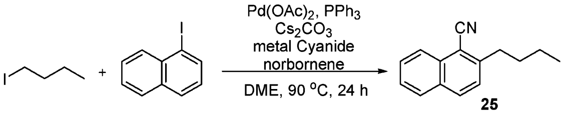
[a] All reactions were run under the following conditions: aryl halide (1.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (22 mol %), Cs_2CO_3 (2.0 equiv), norbornene (3.0 equiv), and $Zn(CN)_2$ (1.0 equiv) in DME (0.05 M) were heated in a sealed tube at 150 °C for 4000 s under microwave irradiation. [b] Isolated yield. [c] Yield from aryl bromide.

To slow the rate of direct cyanation of the aryl iodide, we decided to examine the effect both temperature and metal cyanide have on reaction yield. Reduction of the reaction temperature led to modest improvements in yield. Moving from zinc cyanide to the much less reactive potassium hexacyanoferrate as reported by Beller et al.[7] was more effective (Table

Table 2. Effect of Metal Cyanides on Reaction Yield[a]



Entry	Metal Cyanide (equivalents)	Yield (%)[b]
1	$Zn(CN)_2$ (1)	37
2	$Zn(CN)_2$ (2)	56
3	$Zn(CN)_2$ (3)	13
4	CuCN (1)	63
5	CuCN (2)	31
6	CuCN (3)	3
7	$K_4[Fe(CN)_6]\cdot 3H_2O$ (1)	27
8	$K_4[Fe(CN)_6]\cdot 3H_2O$ (2)	48
9	$K_4[Fe(CN)_6]\cdot 3H_2O$ (3)	67
10	$K_4[Fe(CN)_6]\cdot 3H_2O$ (4)	87
11	$K_4[Fe(CN)_6]\cdot 3H_2O$ (4.5)	93

[a] All reactions were run under the following conditions: 1-iodonaphthalene (1.0 equiv), iodobutane (10.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (22 mol %), Cs_2CO_3 (2.0 equiv), norbornene (3.0 equiv), and metal cyanide in DME (0.05 M) were heated in a sealed tube at 90 °C for 24 h. [b] Yield according to ^1H NMR using mesitylene as an internal standard.

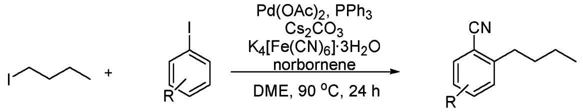
2), presumably because of a slower rate of transmetalation as a result of a stronger iron−cyanide bond in comparison to other metal cyanides.

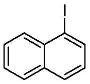
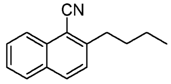
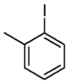
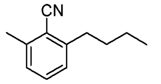
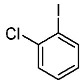
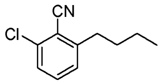
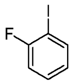
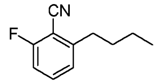
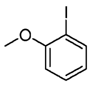
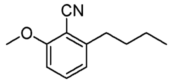
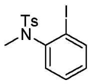
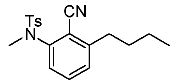
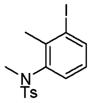
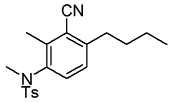
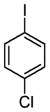
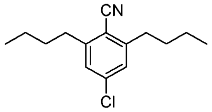
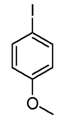
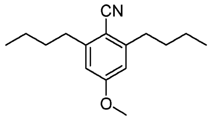
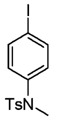
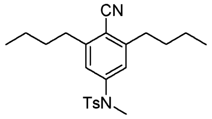
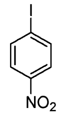
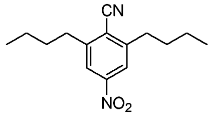
Under the optimized reaction conditions, the scope of the reaction was examined with a variety of aryl iodides (Table 3). A variety of ortho-substituted aryl iodides could be used in the reaction, whereas bisalkylated products were obtained if both ortho positions were unsubstituted. In general, strongly electron-withdrawing groups (entry 11) displayed lower yields, as homocoupling of the parent aryl iodide was observed.

We next turned our attention to examining the various alkyl halides that could be used in the reaction. A range of alkyl iodides was successfully incorporated under the reaction conditions, including methyl iodide. In previous studies, methyl iodide was not compatible with the Catellani reaction conditions because of its high volatility and reactivity (entry 3). However, when the reaction was conducted in a sealed tube the product was isolated in modest yield. Alkylation with dihaloalkanes was also possible, giving the desired products in moderate yield (entries 4 and 5). Attempts to use alkyl bromides under these reaction conditions failed; however, by changing the reaction solvent to acetonitrile under the conditions shown in Table 4, both alkyl bromides and more importantly alkyl chlorides were able to react in good yield (Scheme 2).

The commercial availability and high stability of alkyl chlorides[8] prompted us to optimize the reaction conditions

Table 3. Intermolecular Alkylation/Cyanation Reaction: Scope of Aryl Iodides[a]



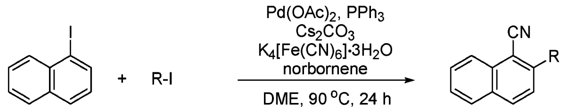
Entry	Aryl Iodide	Product	Yield (%)[b]
1		 **25**	91
2		 **26**	84
3		 **27**	59
4		 **28**	31
5		 **29**	56
6		 **30**	42
7		 **31**	41
8		 **32**	72
9		 **33**	71
10		 **34**	72
11		 **35**	26

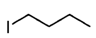
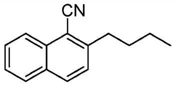
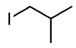
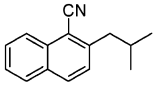
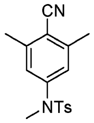
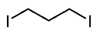
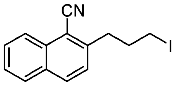
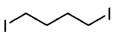
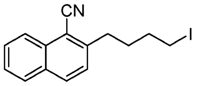
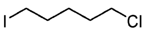
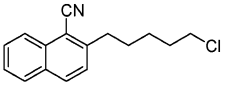
[a] All reactions were run under the following conditions: aryl halide (1.0 equiv), iodobutane (10.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (22 mol %), Cs_2CO_3 (2.0 equiv), norbornene (3.0 equiv), and $K_4[Fe(CN)_6]\cdot 3H_2O$ (4.5 equiv) in DME (0.05 M) were heated in a sealed tube at 90 °C for 24 h. [b] Isolated yield.

---

(7) (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, *12*, 388−1389. (b) Schareina, T.; Zapf, A.; Maegerlein, W.; Mueller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087−1090.

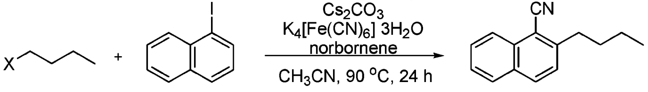
Table 4. Intermolecular Alkylation/Cyanation Reaction: Scope of Alkyl Iodides[a]



Entry	Alkyl Iodide	Product	Yield (%)[b]
1		 **25**	91
2		 **36**	62
3	CH_3I	 **37**	37[c]
4		 **38**	45
5		 **39**	49
6		 **40**	54

[a] All reactions were run under the following conditions: 1-iodonaphthalene (1.0 equiv), alkyl iodide (10.0 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (22 mol %), Cs$_2$CO$_3$ (2.0 equiv), norbornene (3.0 equiv), and K$_4$[Fe(CN)$_6$]·3H$_2$O (4.5 equiv) in DME (0.05 M) were heated in a sealed tube at 90 °C for 24 h. [b] Isolated yield. [c] *N*-(4-Iodophenyl)-4,*N*-dimethylbenzenesulfonamide was used as aryl iodide instead of 1-iodonaphthalene because of volatility of product.

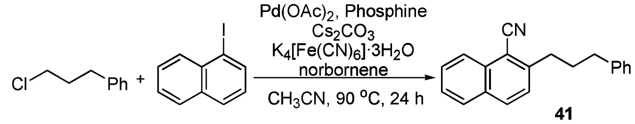
Scheme 2. Reaction of Alkyl Bromides and Chlorides



25

X= Br 87%
X= Cl 65%

Table 5. Variation of Phosphine Ligands[a]



41

Entry	Ligand	Yield (%)[b]
1	PPh_3	57
2	(2-furyl)$_3$P	49
3	Me_3PHBF_4	39
4	Et_3PHBF_4	42
5	$^nBu_3PHBF_4$	68
6	$^tBu_3PHBF_4$	traces
7	Cy_3PHBF_4	28
8	Tri(4-methoxyphenyl) phosphine	56
9	Tri(p-tolyl) phosphine	38

[a] All reactions were run under the following conditions: 1-iodonaphthalene (1.0 equiv), 3-chlorophenylpropane (1.5 equiv), Pd(OAc)$_2$ (10 mol %), ligand (22 mol %), Cs$_2$CO$_3$ (3.0 equiv), norbornene (6.0 equiv), and K$_4$[Fe(CN)$_6$]·3H$_2$O (1.125 equiv) in CH$_3$CN (0.05 M) were heated in a sealed tube at 90 °C for 24 h. [b] Yield according to ^{1}H NMR using mesitylene internal standard.

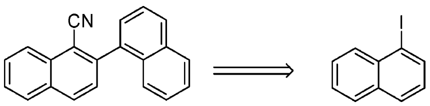


Figure 3. Homocoupled reaction byproduct.

using 1-phenyl-3-chloropropane and 1-iodonaphthalene. It was determined that as little as 1.5 equiv of alkyl chloride could be used in the reaction, while lower amounts led to significant reductions in reaction yield. During a screen of several phosphine ligands, it was found that the $^nBu_3PHBF_4$ ligand precursor developed by Netherton and Fu[9] gave the best yields for the reaction of alkyl chlorides in the Catellani reaction (Table 5).

The scope of the reaction was explored following the completion of the optimization study. It was found that the highly volatile butyl chloride gave a poor reaction yield while higher boiling alkyl chlorides gave better yields; therefore, it is necessary to use the alkyl halide in large excess in some cases. Because of the lower reactivity of alkyl chlorides, we suspected that α-chloroesters and α-chloroamides as well as benzylic chlorides could be used under these reaction conditions. Whereas the corresponding bromo- and iodoalkyls were much too reactive, the desired product was obtained in good yield under the reaction conditions. In those instances where only moderate yields were observed with 1.5 equiv of alkyl chlorides, the major product was the homocoupled iodonaphthalene product (Figure 3). This byproduct is formed by interception of the palladacycle

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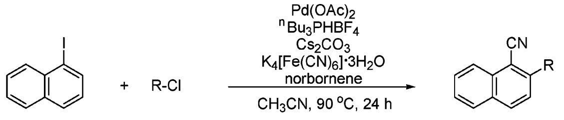
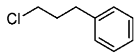
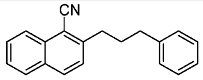
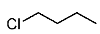
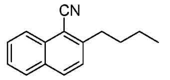
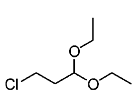
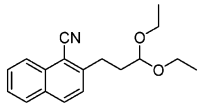
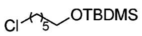
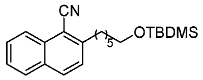
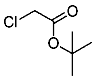
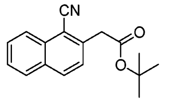
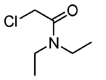
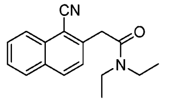
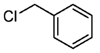
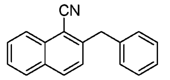
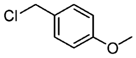
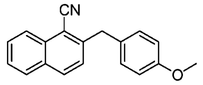
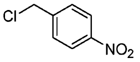
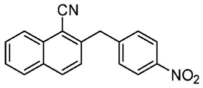
(8) (a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527−12530. (b) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749−5752. (c) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947. (d) Fujii, Y.; Terao, J.; Kuniyasu, H.; Kambe, N. *J. Organomet. Chem.* **2007**, *692*, 375−381.

(9) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.

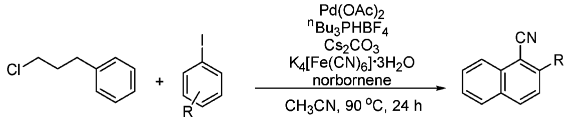
Table 6. Intermolecular Alkylation/Cyanation Reaction Using Alkyl Chlorides: Scope of Alkyl Chlorides[a]

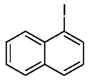
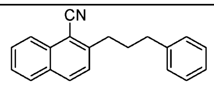
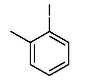
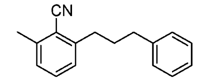
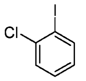
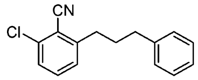
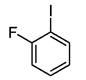
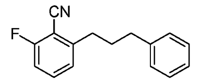
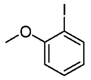
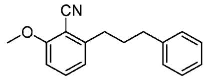
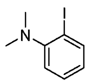
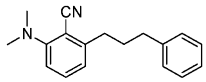
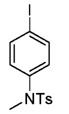
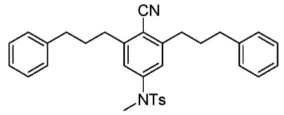


Entry	Alkyl Halide	Product	Yield (%)[b]
1		 **41**	79
2		 **42**	23
3		 **43**	46
4		 **44**	67
5		 **45**	45 62[c]
6		 **46**	61[c]
7		 **47**	85
8		 **48**	33 48[c]
9		 **49**	47

[a] All reactions were run under the following conditions: 1-iodonaphthalene (1.0 equiv), alkyl chloride (1.5 equiv), $Pd(OAc)_2$ (10 mol %), $^nBu_3PHBF_4$ (22 mol %), Cs_2CO_3 (3.0 equiv), norbornene (6.0 equiv), and $K_4[Fe(CN)_6]·3H_2O$ (2.0 equiv) in CH_3CN (0.05 M) were heated in a sealed tube at 90 °C for 24 h. [b] Isolated yield. [c] Three equivalents of alkyl chloride were used.

Table 7. Intermolecular Alkylation/Cyanation Reaction Using Alkyl Chlorides: Scope of Aryl Iodides[a]



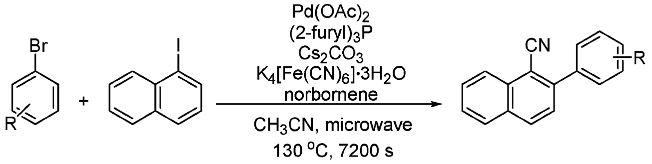
Entry	Aryl Iodide	Product	Yield (%)[b]
1		 **41**	77
2		 **50**	83
3		 **51**	43
4		 **52**	40
5		 **53**	74
6		 **54**	34[d]
7		 **55**	43[e]

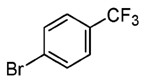
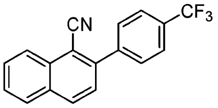
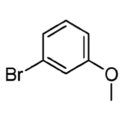
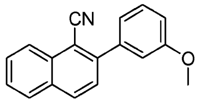
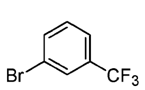
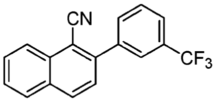
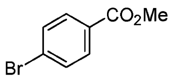
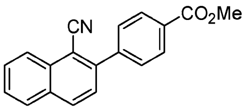
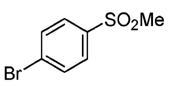
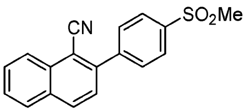
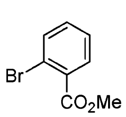
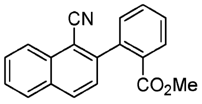
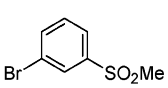
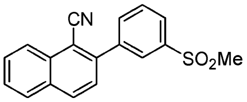
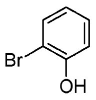
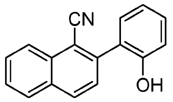
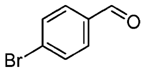
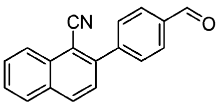
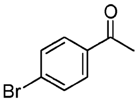
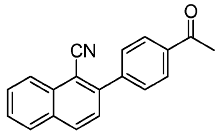
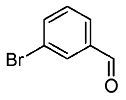
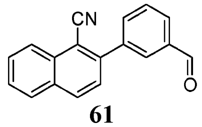
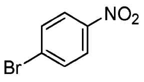
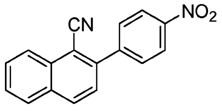
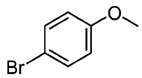
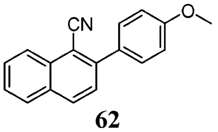
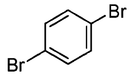
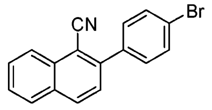
[a] All reactions were run under the following conditions: 1-iodonaphthalene (1.0 equiv), 3-chlorophenylpropane (1.5 equiv), $Pd(OAc)_2$ (10 mol %), $^nBu_3PHBF_4$ (22 mol %), Cs_2CO_3 (3.0 equiv), norbornene (6.0 equiv), and $K_4[Fe(CN)_6]·3H_2O$ (2.0 equiv) in CH_3CN (0.05 M) were heated in a sealed tube at 90 °C for 24 h. [b] Isolated yield. [c] Three equivalents of alkyl chloride were used. [d] Reaction run for 48 h. [e] Six equivalents of alkyl chloride were used.

formed from 1-iodonaphthalene by another molecule of 1-iodonaphthalene. Addition of 3 equiv of alkyl chloride generally improved the yields of the reaction (Table 6). Variation of the aryl iodide was also possible using alkyl chlorides and gave results similar to those from the alkylation using alkyl iodides (Table 7).

Intermolecular ortho Arylation/Cyanation. Although we found that aryl bromides did not react in the intermolecular alkylation, we saw an opportunity to explore the ortho arylation of aryl iodides. Catellani et al. has shown that ortho arylation is possible by coupling electron-deficient aryl bromides with aryl iodides.[10] We undertook an optimization using *para*-bromotrifluoromethylbenzene. Using 1.5 equiv of aryl bromide, we could isolate **56** in 66% yield using only 2.5 mol % of

Table 8. Intermolecular Arylation/Cyanation Reaction: Scope of Aryl Bromides[a]



Entry	Aryl Bromide	Product	Yield (%)[b]	Entry	Aryl Bromide	Product	Yield (%)[b]
1		 **56**	66 94[c]	8		 **63**	56[d]
2		 **57**	30 61[d]	9		 **64**	54
3		 **58**	70	10		 **65**	28 81[e]
4		 **59**	54[c]	11		 **66**	39
5		 **60**	51[c]	12		 **67**	61
6		 **61**	26 47[d]	13		 **68**	91
7		 **62**	traces[d]	14		 **69**	21 56[d]

[a] All reactions were run under the following conditions: 1-iodonaphthalene (1.0 equiv), aryl bromide (1.5 equiv), Pd(OAc)$_2$ (2.5 mol %), tri(2-furyl)phosphine (6 mol %), Cs$_2$CO$_3$ (1.5 equiv), norbornene (1.5 equiv), and K$_4$[Fe(CN)$_6$]·3H$_2$O (5.5 equiv) in CH$_3$CN (0.05 M) were heated in a sealed tube at 130 °C for 7200 s under microwave irradiation. [b] Isolated yield. [c] Three equivalents of aryl bromide were used. [d] Six equivalents of aryl bromide were used. [e] Optimized conditions: 1-iodonaphthalene (1.0 equiv), aryl bromide (1.0 equiv), Pd(OAc)$_2$ (2.5 mol %), triphenylphosphine (6 mol %), Cs$_2$CO$_3$ (1.5 equiv), norbornene (0.5 equiv), and K$_4$[Fe(CN)$_6$] (5.5 equiv) in CH$_3$CN (0.05 M) were heated in a sealed tube at 130 °C for 7200 s under microwave irradiation.

palladium catalyst. The major byproduct was the competitive ortho arylation by another molecule of 1-iodonaphthalene followed by cyanation (Figure 3). Increasing the amount of aryl bromide did improve the yield of desired products. As a general trend, the more electron rich the aryl bromides the greater the quantity of it was needed to favor palladacycle oxidative addition of the aryl bromide over aryl iodide. When very electron-rich aryl bromides were used, such as *para*-bromoanisole, only trace amounts of product (Table 8, entry 7) were observed because of very slow oxidative addition of the aryl bromide. Although slow addition would also seem a likely candidate for minimizing the homocoupled product, all attempts to increase the yield in this manner failed. It should be noted in the case of the *ortho*-bromophenol that the additional coordination site of the phenolate under the reaction conditions most likely favors

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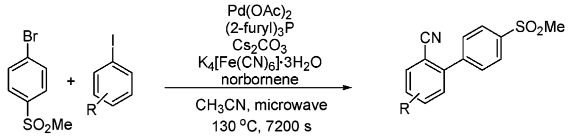
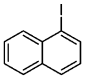
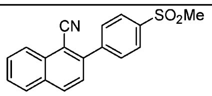
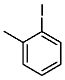
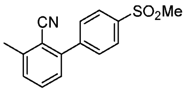
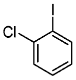
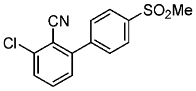
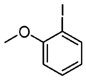
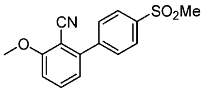
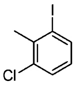
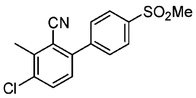
(10) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78−79.

Table 9. Intermolecular Arylation/Cyanation Reaction: Scope of Aryl Iodides[a]



Entry	Aryl Iodide	Product	Yield (%)[b]
1		 **58**	70
2		 **70**	78
3		 **71**	31
4		 **72**	54
5		 **73**	62

[a] All reactions were run under the following conditions: aryl iodide (1.0 equiv), 4-bromophenyl methyl sulfone (1.5 equiv), $Pd(OAc)_2$ (2.5 mol %), tri(2-furyl)phosphine (6 mol %), Cs_2CO_3 (1.5 equiv), norbornene (1.5 equiv), and $K_4[Fe(CN)_6]\cdot 3H_2O$ (5.5 equiv) in CH_3CN (0.05 M) were heated in a sealed tube at 130 °C for 7200 s under microwave irradiation. [b] Isolated yield.

oxidative addition;[11] however, a significant amount of lactone byproduct was observed due to cyclization of the phenol onto the nitrile during column chromatography on silica gel.[12]

Although some of the reaction yields are modest, through careful variation of the reaction parameters to favor the individual coupling partners, good yields may be obtained. To demonstrate this, we undertook a rapid optimization using 1-iodonaphthalene and 2-bromomethyl benzoate, which gave only 28% under the above reaction conditions (entry 10). In a short period of time, we were able to improve the yield to 81% with some minor modifications to the reaction conditions. Subsequent variation of the aryl iodides used in the reaction showed trends similar to those of the ortho alkylation chemistry; however, aryl iodides lacking an ortho-blocking group gave only complex mixtures of products (Table 9).

The wide variety of substituted biaryl compounds, which can be rapidly generated from readily available starting materials, makes this methodology amenable for the generation of large libraries of compounds which can be further functionalized through transformations of the nitrile functionality. Furthermore the ability to utilize compounds containing aryl chlorides and bromides allows for the possibility of further functionalization via palladium catalyzed coupling processes. Extension of this methodlogy to include the use of aryl chlorides and more electron rich aryl bromides is currently in progress.

Summary

In conclusion, we have developed a new methodology for the synthesis of highly substituted benzonitriles. Of particular significance is that this methodology allows for the ortho alkylation of aryl iodides using alkyl chlorides. This has led to the use of alkylating agents that were typically too reactive to withstand the typical Catellani reaction conditions. The ortho arylation, which used a large variety of aryl bromides to synthesize valuable functionalized biaryl building blocks, has also been demonstrated.

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

JA075599I

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(11) Motti, E.; Faccini, F.; Ferrari, I.; Catellani, M.; Ferraccioli, R. *Org. Lett.* **2006**, *8*, 3967−3970.

(12) Previously reported by Beugelmans, R.; Bois-Choussy, M.; Chastanet, J.; Le Gleuher, M.; Zhu, J. *Heterocycles* **1993**, *36*, 2723−2732.