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Palladium-Catalyzed Norbornene-Mediated Tandem *ortho*-C−H-Amination/*ipso*-C−I-Cyanation of Iodoarenes: Regiospecific Synthesis of 2-Aminobenzonitrile

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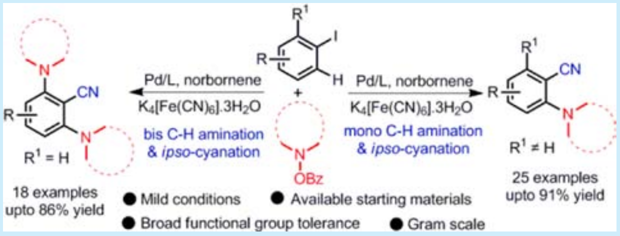
Ⓢ *Supporting Information*

ABSTRACT: Efficient tandem *ortho*-C−H-amination/*ipso*-cyanation of iodoarenes was accomplished under a norbornene-mediated Pd-catalyzed process. A series of functionalized 2-aminobenzonitriles with much potential in the pharmaceutical industry were obtained by this protocol. This strategy was successfully employed for substitution with two cyano and four amino functionalities in an arene unit in one step under specified conditions.

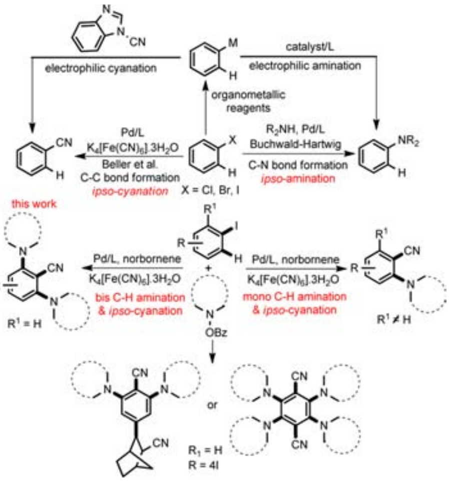


Bis/polyfunctionalization of a substituted arene is important in organic synthesis and a challenging task.[1] Directed transition-metal-catalyzed activation and subsequent functionalization provides a feasible route.[2] It involves more than one step, and removal of the directing group is not always easy. A combination of C−H activation and simultaneous cross-coupling leads to formation of two new bonds in one step.

The Catellani reaction by Pd-catalyzed norbornene-mediated *ortho*-C−H substitution of iodoarenes followed by terminal cross-coupling provides an effective route to tandem formation of two C−C bonds.[3] This process was subsequently extended to different useful functionalizations.[4−7] Useful applications of this protocol using amine-OBz were demonstrated in *ortho*-C−H-amination/*ipso*-hydrogenation of aryl halides,[8] *ortho*-amination/*ipso*-alkynation,[1a] *ortho*-amination/*ipso*-arylation,[1d] and *ortho*-amination/*ipso*-borylation.[9] Due to our interest in transition-metal-mediated C−H functionalization,[10] we report a Pd/norbornene-catalyzed *ortho*-C−H-amination/*ipso*-cyanation of aryl iodide using electrophilic *N*-benzoyloxyamine and a benign cyanating agent, $K_4Fe(CN)_6{\cdot}3H_2O$, leading to synthesis of 2-aminobenzonitrile (Scheme 1). We also demonstrated bis-*ortho*-amination of iodoarenes and tetra-*ortho*-amination/bis-*ipso*-cyanation of 1,4-diiodoarenes at selected conditions (Scheme 1). This is the first report of formation of two C−C and four C−N bonds producing 1,4-dicyano-2,3,5,6-aminoarenes in one step by this Pd-catalyzed norbornene-mediated strategy.

Aryl nitriles are very important because they are useful agrochemicals, pharmaceutically active compounds, natural products, herbicides, and dyes.[11] They have wide applications as synthetic intermediates.[12] Introduction of a cyano group with another useful functionality will be very useful in organic synthesis due to potential for further manipulation.[13] Several molecules containing an aminobenzonitrile moiety have important biological activities (Figure 1).[14]

Scheme 1. Pd-Catalyzed Cross-Coupling Reactions on Aryl Halides



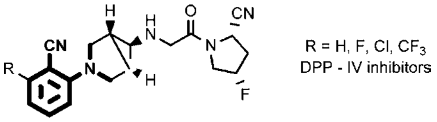


Figure 1. Biologically active molecules containing 2-aminobenzonitrile moiety.

To optimize the reaction conditions, a series of experiments were performed with variation of reaction parameters, such as catalyst, solvent, ligand, temperature, and time for a representative reaction of 1-iodo-2-methylbenzene (**1a**), morpholinobenzoate (**2a**), and potassium ferrocyanide. Results are summarized in Table 1. In this reaction, toluene was found to be more effective compared to CH_3CN, DMF, 1,4-dioxane, DCE, and

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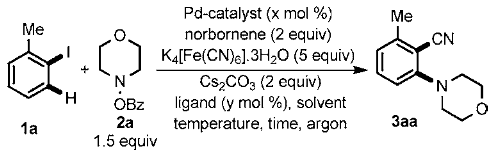
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	ligand (mol %)	solvent	yield (%)[b]
1	$Pd(OAc)_2$ (5)	PPh_3 (10)	CH_3CN	28
2	$Pd(OAc)_2$ (5)	PPh_3 (10)	DMF	41
3	$Pd(OAc)_2$ (5)	PPh_3 (10)	toluene	61
4	$Pd(OAc)_2$ (5)	PPh_3 (10)	1,4-dioxane	7
5	$Pd(OAc)_2$ (5)	PPh_3 (10)	DCE	18
6	$Pd(OAc)_2$ (5)	PPh_3 (10)	NMP	3
7	$Pd(OAc)_2$ (5)	(2-furyl)$_3$P (10)	toluene	23
8	$Pd(OAc)_2$ (5)	Cy_3P (10)	toluene	18
9	$Pd(OAc)_2$ (5)	$(4\text{-}MeOC_6H_4)_3P$ (10)	toluene	27
10	$Pd(OAc)_2$ (5)	$(3\text{-}ClC_6H_4)_3P$ (10)	toluene	12
11	$PdCl_2$ (5)	PPh_3 (10)	toluene	31
12	$Pd(CH_3CN)_2Cl_2$ (5)	PPh_3 (10)	toluene	48
13	$Pd(PPh_3)_4$ (5)	PPh_3 (10)	toluene	19
14	$Pd(PPh_3)_2Cl_2$ (5)	PPh_3 (10)	toluene	50
15	$Pd_2(dba)_3$ (5)	PPh_3 (10)	toluene	23
16	$Pd(OAc)_2$ (10)	PPh_3 (20)	toluene	91
17[c]	$Pd(OAc)_2$ (10)	PPh_3 (20)	toluene	73
18[d]	$Pd(OAc)_2$ (10)	PPh_3 (20)	toluene	90
19[e]	$Pd(OAc)_2$ (10)	PPh_3 (20)	toluene	83
20	$Pd(OAc)_2$ (10)		toluene	trace
21		PPh_3 (20)	toluene	0
22[f]	$Pd(OAc)_2$ (10)	PPh_3 (20)	toluene	0
23[g,h]	$Pd(OAc)_2$ (10)	PPh_3 (20)	toluene	81, 90

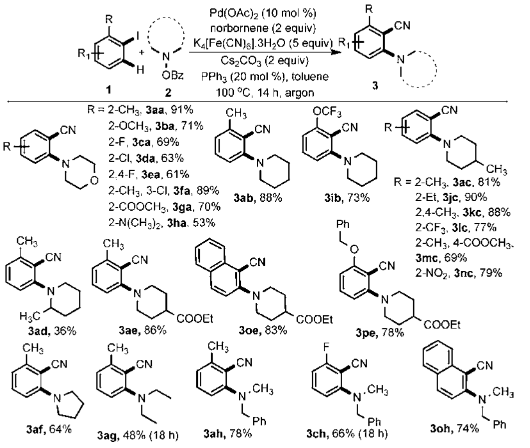
[a]Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2a** (0.75 mmol, 1.5 equiv), $K_4[Fe(CN)_6].3H_2O$ (2.5 mmol, 5 equiv), catalyst, ligand, norbornene (1.0 mmol, 2.0 equiv), Cs_2CO_3 (1.0 mmol, 2 equiv), 100 °C. [b]Isolated yield. [c]90 °C. [d]110 °C. [e]4 equiv of $K_4[Fe(CN)_6]\cdot 3H_2O$. [f]Reaction was carried out in the absence of norbornene. [g]13 h. [h]15 h.

NMP (entries 1–6). A variety of ligands were tested to determine if the yield improved further. The best yield was obtained using PPh_3 as ligand (entries 3 and 7–10). During the optimization, we observed that $Pd(OAc)_2$ showed better catalytic activity compared to $PdCl_2$, $Pd(PPh_3)_4$, and $Pd_2(dba)_3$ (entries 3, 11, 13, and 15), although $Pd(CH_3CN)_2Cl_2$ and $Pd(PPh_3)_2Cl_2$ provided comparable yields (entries 3, 12, and 14). The efficiency of the reaction became maximum when $Pd(OAc)_2$ and PPh_3 were increased to 10 and 20 mol %, respectively (entry 16). Reaction at 90 °C furnished a lower yield (entry 17), and a higher temperature (110 °C) did not affect the outcome of the reaction (entry 18). Potassium ferrocyanide (4 equiv) led to a lower yield (entry 19). The reaction did not proceed at all in the absence of Pd catalyst and norbornene separately (entries 21 and 22), and trace product was detected in the absence of ligand (entry 20). The reaction was complete in 14 h (TLC) (entry 23).

In a general experimental procedure, a mixture of aryl iodide, *N*-benzoyloxyamine, potassium ferrocyanide, norbornene, palladium acetate, triphenyl phosphine, and cesium carbonate in toluene was heated at 100 °C (bath temperature) for 14 h. Standard workup and purification by column chromatography provided the pure product.

Next, we explored the substrate scope with a series of *ortho*-substituted aryl iodides and *N*-benzoyloxyamines. The results are summarized in Scheme 2. Both electron-donating ($-CH_3$, $-Et$, $-OCH_3$, $-N(CH_3)_2$, $-OCH_2Ph$) and electron-withdrawing groups ($-F$, $-Cl$, $-COOCH_3$, $-OCF_3$, $-CF_3$) on the aromatic ring of iodoarenes were compatible under the reaction conditions. 2-Chloro- and 2-fluoroiodobenzenes underwent reaction cleanly to give the corresponding products (**3da**, **3ca**) in good yields. Reaction of 1-iodonaphthalene also proceeded smoothly to provide the corresponding products (**3oe**, **3oh**) in high yields. For 2-iodo-*N*,*N*-dimethylaniline, moderate yield was observed (**3ha**). Remarkably, $-COOMe$, $-NO_2$, $-CF_3$, and $-OCH_2Ph$ groups on the iodoarenes (**1g**, **1m**, **1n**, **1l**, **1p**) were also acceptable under these conditions to provide the corresponding products (**3ga**, **3mc**, **3nc**, **3lc**, **3pe**) in good yields.

Scheme 2. *ortho*-Mono-C–H Amination and *ipso*-C–I-Cyanation of 2-Substituted Iodoarenes



Substituted *N*-benzoyloxyamines such as piperidine-1-yl benzoate (**2b**), 4-methylpiperidine-1-yl benzoate (**2c**) ethyl-1-(benzoyloxy)piperidine-4-carboxylate (**2e**) and *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine (**2h**) underwent the reaction without any difficulty to provide the corresponding products under the same reaction conditions. However, reactions with pyrrolidine-1-yl benzoate (**2f**), *O*-benzoyl-*N*,*N*-diethylhydroxyl amine (**2g**), and 2-methylpiperidine-1-yl benzoate (**2d**) were not very satisfactory, giving the respective products in relatively low yield.

When *ortho*-unsubstituted iodoarenes **4** were used, double *ortho*-C–H-amination and *ipso*-C–I-cyanation occurs, giving 1,3-diamino benzonitriles **5**. The best yield was obtained when 3.0 equiv each of norbornene and Cs_2CO_3 was employed in dry toluene at 100 °C (Scheme 3). Various iodoarenes containing electron-donating ($-CH_3$, $-{}^tBu$, $-OCH_3$, $-Ph$, $-OCH_2Ph$) and electron-withdrawing ($-OCF_3$, $-COCH_3$, $-COOEt$, $-CHO$, $-NO_2$) substituents attached at the *para*-position participated in this reaction, giving moderate to good yields. The $-CHO$, $-CF_3$, $-O$-allyl, and $-COOEt$ groups remained inert under the reaction conditions. **2a**, **2b**, **2c**, **2e**, and **2h** were subjected to this reaction to provide the corresponding products in good yields.

When 1,4-diiodobenzene was employed in the reaction, interesting results were obtained (Scheme 4). Reaction with 5 equiv of *N*-OBz-amine (**2h**) under the same reaction conditions produced 1,4-dicyano-2,3,5,6-tetraaminobenzene. This is a remarkable example of 2 C–C and 4 C–N bond formations in

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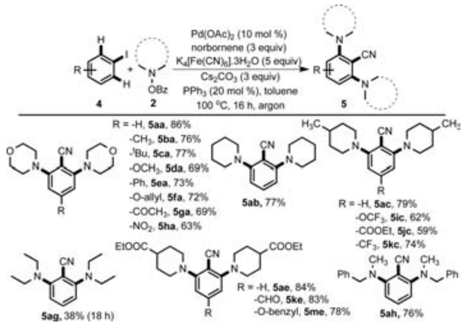
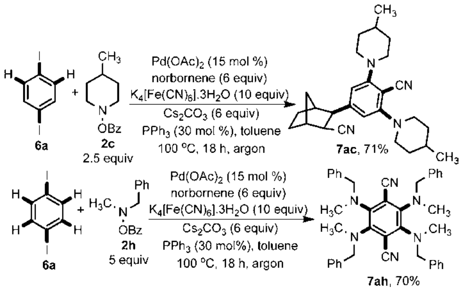
Scheme 3. *ortho*-Bis-C−H-Amination and *ipso*-C−I-Cyanation of Iodoarenes



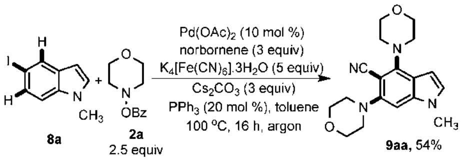
Scheme 4. Reaction for 1,4-Diiodoarene



one step. There is no such observation reported in earlier reactions of similar type.[3−9] However, with 2.5 equiv of *N*-OBz-amine, **7ac** with expected bis-amination at two *ortho*-positions and *ipso*-cyanation with cyanonorbornene tagged at the 4-position was formed (Scheme 4). The compounds were properly characterized by spectroscopic analysis.

We checked this protocol of *ortho*-bis−C-H-amination and *ipso*-C−I-cyanation with iodoheteroarene (Scheme 5). 5-Iodo-1-methyl-1*H*-indole (**8a**) was found to react under the optimized reaction conditions, producing moderate yield of the corresponding product 1-methyl-4,6-dimorpholino-1*H*-indole-5-carbonitrile (**9aa**). We did not observe any C_3-cyanation of indole under the reaction conditions, which is usually encountered in Pd-catalyzed cyanation.[15]

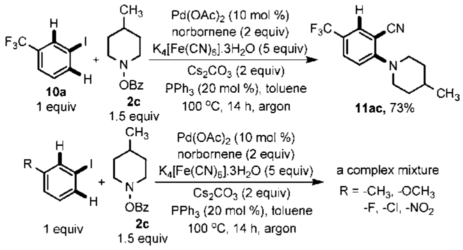
Scheme 5. *ortho*-Bis-C−H-Amination and *ipso*-C−I-Cyanation of Heteroiodoarenes



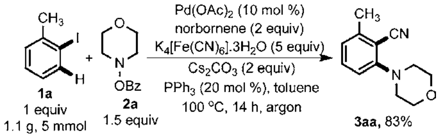
Interestingly, *meta*-CF$_3$-substituted iodoarene showed excellent regioselectivity toward C−H-amination/C−I-cyanation under the reaction conditions (Scheme 6). Here, amination occurred exclusively at the position *para* to the −CF$_3$ group. However, with other substitutions (−CH$_3$, −OCH$_3$, −F, −Cl, −NO$_2$) on the *meta*-position of iodoarenes, a complex mixture of products was obtained. We do not have any logical explanation at this moment.

This protocol is also useful when operated on a gram scale, and product yield is comparable with that in the milligram scale (Scheme 7). Notably, a majority of the products are synthesized for the first time.

Scheme 6. Reaction for *meta*-Substituted Iodoarenes

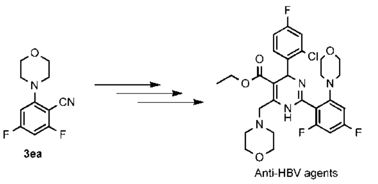


Scheme 7. Gram Scale Experiment



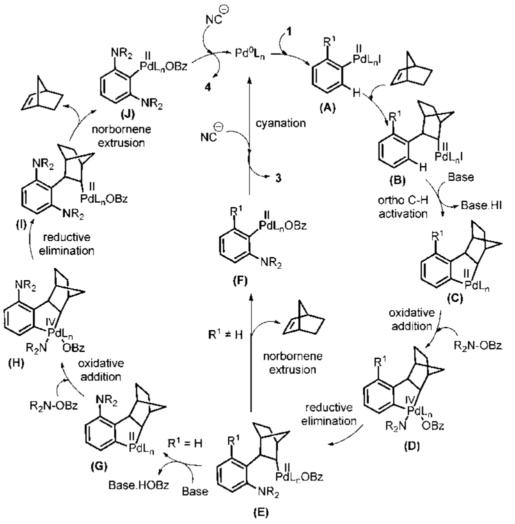
Compound **3ea** (Scheme 2) is an important precursor to the synthesis of anti-HBV agents Mo10 (Scheme 8).[16]

Scheme 8. Synthetic Potential of Aminobenzonitrile Product



A speculative catalytic cycle of the reaction is proposed in Scheme 9 in accordance with previous reports.[3−9] The first step involves oxidative addition of iodoarene **1** with Pd(0) followed by a subsequent insertion of norbornene to produce intermediate **B**. *ortho*-C−H-activation then occurs and subsequent elimination of HI in the presence of a base gives a five-membered palladacycle **C**. In the next step, further oxidative addition of *N*-benzoyloxyamine to **C** results, leading to intermediate **D** with the oxidation of Pd(II) to Pd(IV),[5,6] which undergoes a reductive elimination with the formation of *ortho*-aminated arene species **E**. Next, *ortho*-substituted iodoarenes **E** lead to intermediate **F** by

Scheme 9. Proposed Reaction Mechanism



deinsertion of norbornene via β-carbon elimination. **F** can be trapped by a cyanide ion through *ipso*-functionalization to produce **3** with regeneration of Pd(0) catalyst to start the next cycle. For *ortho*-free iodoarenes, diaminated intermediate **I** can be generated from **E** through subsequent C−H activation of a second *ortho*-position, oxidative addition of *N*-benzoyloxyamine of intermediate **G**, and reductive elimination of **H**. **I** undergoes deinsertion of norbornene via β-carbon elimination and is trapped by cyanide ion to produce **4**.

In conclusion, we developed an efficient protocol for tandem *ortho*-C−H-amination and *ipso*-cyanation of iodoarenes under norbornene-mediated Pd-catalyzed process, leading to the synthesis of a series of functionalized 2-aminobenzonitriles that have potential in the pharmaceutical industry. This reaction was also used for substitution of two cyano- and four amino-functionalities in an arene unit under specified conditions. To the best of our knowledge, we are not aware of any report of such observation in similar reactions. The other notable features of this procedure are tolerance to a wide spectrum of functional groups, relatively mild conditions, applicability to heteroarenes, and reproduction in gram scale. We believe this will find wide applications in organic synthesis and in the pharmaceutical industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02113.

> Experimental procedure, characterization data, and ^{1}H, ^{13}C NMR and ^{19}F spectra (PDF)

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Notes

The authors declare no competing financial interest.

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