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Palladium-Catalyzed Arylation of Cyanamides

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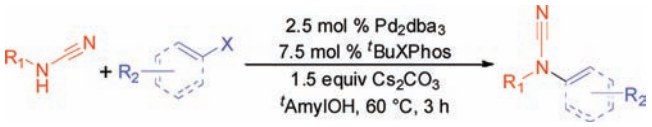
ABSTRACT



The cross-coupling of alkyl cyanamides with a number of aryl, heteroaryl, and vinyl halide and pseudohalide coupling partners has been developed via a modification of Pd-catalyzed amidation methods. The reactions proceed selectively under mild conditions with reasonable reaction times in moderate to excellent yields.

Incredible progress has been made in metal-catalyzed cross-coupling methods culminating with the recent awarding of a Nobel Prize.[1] In addition to C−C bond forming reactions, the progress in carbon−heteroatom cross-coupling has become a potent synthetic tool.[2] As such, we were surprised to find that, to the best of our knowledge, cyanamides have never been the subject of a cross-coupling study.

Cyanamides are highly versatile N−C−N building blocks for a number of organic transformations, primarily in the synthesis of a number of guanidine-containing molecules, in the synthesis of amidines, and in the synthesis of a number of heterocycles.[3] These products are found in innumerable applications: from antiviral[4] and anticancer compounds[5] to organometallic ligands[6] and to central nervous system antagonists.[7] Apart from cyanamide derived compounds, cyanamide moieties themselves can be found in a number of biologically active compounds. Cyanamides have been utilized as "warheads" in a number of drug leads for covalent enzyme inhibition.[8] Simple cyanamide (H_2NCN) itself is under investigation as an alcohol deterrent agent, and as such, pro-drugs for its application are also being investigated.[9]

While a number of methods to synthesize cyanamides exist, methods for the formation of unsymmetrical aryl/alkyl and aryl/aryl cyanamides are sparse, particularly with electron-deficient aryl substituents. Common methods for the preparation of cyanamides include simple

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substitution of cyanogen bromide or more exotic cyanating agents.[10] However, the reduced nucleophilicity of aryl or diaryl amines (particularly with electron-withdrawing groups) can lead to poor yields. A common alternative, the Von Braun reaction,[11] while effective, requires extraneous formation of a trisubstituted amine, thereby potentially leading to moderate to low yields. As an alternative, more-direct approach, we believed a mild and efficient cross-coupling method might be utilized to greatly expand the inventory of available cyanamides.

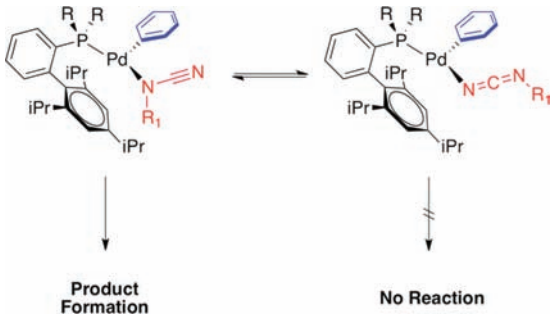


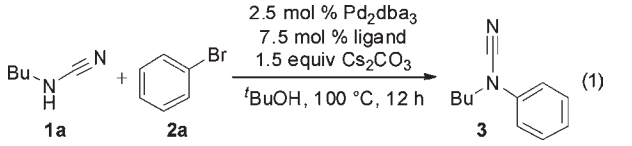
Figure 1. Promixal and terminal cyanamide coordination equilibrium.

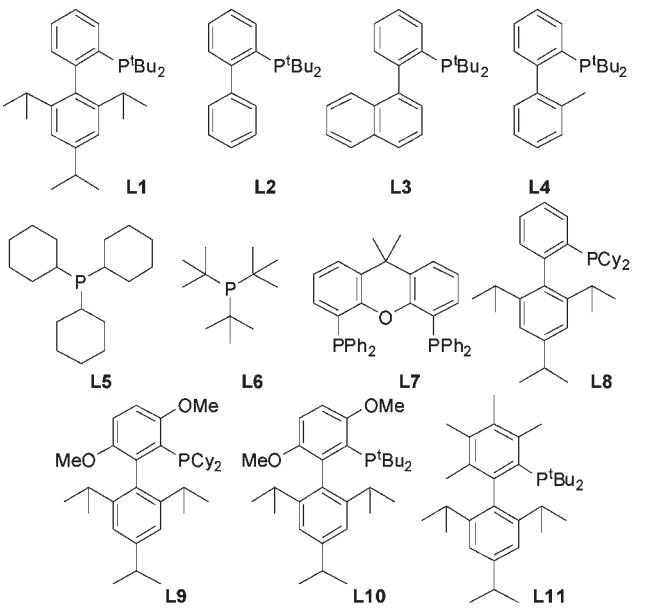
Containing both nucleophilic and electrophilic sites within the same molecule, cyanamides have a somewhat unique reactivity. The basicity of the amino nitrogen is strongly reduced due to the conjugation of its lone pair with the C−N triple bond. As such cyanamides exist as both an *N*-cyanoamine and diimide tautomers (Figure 1), while the *N*-cyanoamine form dominates; in a few reactions (e.g., silylation, protonation, metal coordination, etc.) the diimide form appears to dominate.[3,6] Furthermore, monsubstituted cyanamides are prone to thermal trimerization. In addition, trimerization occurs in both Lewis acidic and basic conditions to form melamine and isomelamine derivatives.[12] Even as much, we hypothesized that Pd-catalyzed aryl amidation conditions may be mild enough to facilitate coupling. Herein, we report a general Pd-catalyzed method for the cross-coupling of alkyl cyanamides with a number of aryl, heteroaryl, and vinyl halides as well as pseudohalides.

Initial investigations focused on the Pd-catalyzed cross-coupling of butyl cyanamide (**1a**) and bromobenzene (**2a**, eq 1, Table 1). Our survey of phosphine ligands revealed that the use of ^{t}BuXPhos resulted in full conversion of bromobenzene and formation of the desired product (**3**) in 55% yield.

Interestingly, XPhos, BrettPhos, and XantPhos ligands, which are more effective than ^{t}BuXPhos in analogous Pd-catalyzed amidation reactions,[14] not only gave incomplete

Table 1. Ligand Screen for the Pd-Catalyzed Arylation of Butyl Cyanamide (**1a**)[a]





ligand	L1	L2	L3	L4	L5[c]	L6[c]	L7	L8	L9	L10	L11	no L
conv[b] (%)	**100**	27	24	27	3	29	74	35	59	70	92	12
yield[b] (%)	**55**[d]	*e*	*e*	*e*	0	0	24	*e*	*e*	0	*e*	0

[a] Reaction conditions: **1a** (0.25 M in ^{t}BuOH), **2a** (1 equiv), Cs_2CO_3 (1.5 equiv), Pd_2dba_3 (2.5 mol %), Ligand (7.5 mol %), 100 °C, 12 h. [b] Determined via GC using naphthalene as an internal standard. [c] 10 mol % ligand used. [d] Isolated yield. [e] Trace.

conversion of starting material but also afforded only trace amounts of the desired cross-coupling product (**3**). Further evaluation of the reaction conditions led to the following optimized conditions: cyanamide (1.1 equiv), aryl halide (1 equiv), Cs_2CO_3 (1.5 equiv), Pd_2dba_3 (2.5 mol %), and ^{t}BuXPhos (7.5 mol %) in ^{t}AmylOH at 60 °C for 3 h. $Pd(OAc)_2$ (5 mol %), instead of Pd_2dba_3, is not a competent precatalyst. However, when $PhB(OH)_2$ (5 mol %) is added as a sacrificial reductant, cross-coupling does occur, although yields are slightly lower than when Pd_2dba_3 is employed.

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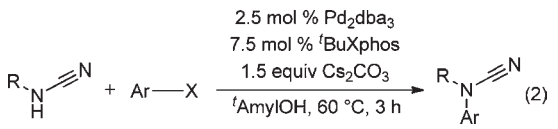
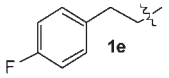
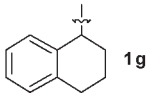
(13) Where general XPhos motif = 2-*disubstituted*-phosphino-R_x-substituted-2′,4′,6′-triisopropylbiphenyl. (a) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576. (b) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001.

(14) Where XantPhos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. (a) Hicks, J. D.; Hyde, A. M.; Martinez-Cueza, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720–16734. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048. (c) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104.

(15) Where BrettPhos = 2-(dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl. See also ref 13.

Table 2. Cross-Coupling Substrate Scope[a]



entry	R	Ar	X	yield %[b]
1	**1a**	C_6H_4, **2a**	Br	**3** (76)
2	**1a**	C_6H_4, **2a**	I	**3** (67)
3	**1a**	C_6H_4, **2a**	Cl	**3** (NR)
4	**1a**	*p*-Cl-C_6H_4, **2b**	Br	**4** (NR)
5	**1a**	*p*-Me-C_6H_4, **2c**	Br	**5** (77)
6	**1a**	*p*-Me-C_6H_4, **2c**	I	**5** (63)
7	**1a**	*p*-Me-C_6H_4, **2c**	OTf	**5** (74)
8	**1a**	*p*-^{t}Bu-C_6H_4, **2d**	Br	**6** (77)
9	**1a**	*p*-F-C_6H_4, **2e**	Br	**7** (65)
10	**1a**	*p*-CF_3-C_6H_4, **2f**	Br	**8** (92)
11	**1a**	*p*-CN-C_6H_4, **2g**	Br	**9** (82)
12	**1a**	*m*-Ac-C_6H_4, **2h**	Br	**10** (79)
13	**1a**	*p*-OMe-C_6H_4, **2i**	Br	**11** (63)[c]
14	**1a**	*p*-Me_2N-C_6H_4, **2j**	Br	**12** (66)[c]
15	**1a**	*o*-Me-C_6H_4, **2k**	Br	**13** (NR)
16	**1a**	2,4,6-Me-C_6H_4, **2l**	Br	**14** (NR)
17	^{t}Bu, **1b**	**2f**	Br	**15** (49)
18	Bn, **1c**	**2f**	Br	**16** (89)
19	 **1e**	**2f**	Br	**17** (84)
20	 **1f**	2-pyridyl, **2m**	Br	**18** (96)
21	 **1g**	**2f**	Br	**19** (NR)

[a] Reaction conditions: cyanamide (1.1 equiv), aryl halide (1 equiv), Cs_2CO_3 (1.5 equiv), Pd_2dba_3 (2.5 mol %), ^{t}BuXPhos (7.5 mol %), 60 °C, 3 h. [b] All yields are average isolated yields from experiments run in at least duplicate. [c] Pd_2dba_3 (3.5 mol %), ^{t}BuXPhos (10.5 mol %), 60 °C, 6 h.

Our cross-coupling conditions are amenable with a number substituted aryl bromides, triflates, and iodides (eq 2, Table 2). Furthermore, the order of reactivity follows ArBr > ArOTf > ArI (entries 1–2, 5–8). However, reactions with aryl chlorides led to catalyst poisoning (by an, as of yet, undetermined mechanism) and resulted in minimal (< 10%) conversion (entries 3–4). Selective coupling can be obtained as seen in the reaction of butyl cyanamide (**1a**) with 1-bromo-4-fluoro-benzene, which leads to formation of *N*-butyl-*N*-(4-fluorophenyl)cyanamide (**7**, entry 9). While the conditions are effective with most aryl halides screened, yields are generally higher with activated (i.e., electron-deficient) aryl halides (entries 10–12). For reactions with electron-rich aryl halides, yields are generally depressed, and extended reaction times and higher catalyst loadings are required (entries 13–14). Other alkyl cyanamides, such as benzyl and cyclohexyl cyanamide, are also excellent substrates (entries 18 and 20, respectively). However, bulky *tert*-butyl cyanamide leads to decreased yields (entry 17). Negative steric effects are further observed in the lack of reaction between both *o*-bromotoluene and mesityl bromide with **1a** (entries 15–16) as well as tetrahydronaphthylcyanamide **1g** and previously productive **2f** (entry 21). Bulky coupling substrates in combination with the large ^{t}BuXPhos ligand may force unproductive diimide coordination, effectively killing the catalyst (Figure 1).

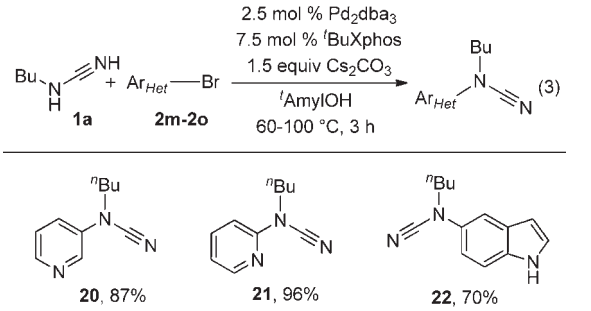
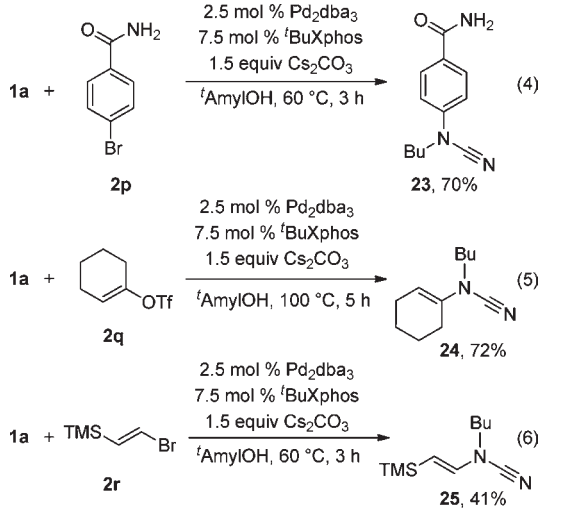


Figure 2. Cross-coupling of **1a** with heteroaryl bromides.

Heterocycles were also found to be viable substrates. Coupling of 3-bromopyridine occurred smoothly, leading to **20** in excellent yield (eq 3, Figure 2). Previous attempts to achieve cyanate 2-aminopyridines with cyanogen bromide or *N*-cyanoimidazole led to presumed cyanation at the pyridine nitrogen, followed by rapid decomposition. As such, we were delighted to find coupling of 2-bromopyridine with butyl cyanamide proceeded to afford **21** in excellent yield. Free amines are amenable to reaction conditions if conformationally restrained from nucleophilic addition into the nitrile as seen in the coupling of 5-bromoindole (**22**).

In addition, cyanamides react preferentially in the presence of amides as seen in the coupling between the exclusive coupling of 4-bromobenzamide and butyl cyanamide (eq 4). The coupling of vinyl bromides and vinyl triflates afforded rare vinyl cyanamides, albeit in decreased yields (eqs 5–6).



In conclusion, we have developed a mild and efficient method for the Pd-catalyzed arylation of alkyl

cyanamides. The reaction is amenable to electron-donating and-withdrawing aryl halides as well as heteroaryl halides and pseudohalides. In addition, vinyl halides are also able to be cross-coupled with cyanamides to yield vinyl cyanamides in moderate yields. Mechanistic investigations are ongoing in our laboratories.

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Supporting Information Available. Experimental details, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.