Palladium-Catalyzed Carbonylation of Aryl Bromides with N-Substituted Cyanamides

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Abstract: The palladium(0)-catalyzed three-component coupling reaction of aryl bromides, carbon monoxide, and *N*-alkyl cyanamides has been developed employing a two-chamber system with ex situ generation of carbon monoxide from a silacarboxylic acid. The reactions proceeded well and were complete with a reaction time of only five hours leading to the corresponding *N*-alkyl cyanamides in good yields. The methodology was further extended to ^{13}C isotope labeling of the carbonyl group through the use of a ^{13}CO produced from the corresponding ^{13}C-labeled version of the silacarboxylic acid.

Key words: *N*-alkyl cyanamides, transition-metal catalysis, isotope labeling, aminocarbonylation, multicomponent reaction, palladium

Cyanamides occupy a special place in organic chemistry as they are present attractive N–C–N building blocks, the reactivity of which can be further enhanced by installing an acyl group next to the amine nitrogen.[1] Cyanamides are widely used in the synthesis of amidines, quinazolinones, and some *N*-acyl cyclic guanidines.[2] In addition, there is an increased attention to cyanamides because of their applications as potent inhibitors of aldehyde dehydrogenase (A1DH)[3a–c] and their occurrence in biologically interesting molecules (Figure 1).[3d,e] As a consequence of this, there is a continued interest in the development of new methodologies for their synthesis.

Since the first example reported by Heck and co-workers in 1974,[4] the three-component carbonylative coupling of an aryl halide, carbon monoxide, and a nucleophile has been expanded to the synthesis of a series of aromatic acyl derivatives including ketones,[5] esters,[6] amides,[7] aldehydes,[8] anhydrides,[9] acid chlorides,[10] and so on.[11] Despite the considerable attention for the application of nitrogen nucleophiles in carbonylative reactions, there are no examples for the employment of N-substituted cyanamides. In 2012, the group of Louie developed a palladium(0)-catalyzed cross-coupling of *N*-alkyl cyanamides with aryl halides.[12] And just recently, while our work was in progress, Larhed and co-workers disclosed that the parent cyanamide is also a competent nucleophile for the carbonylative coupling leading to synthesis of nonsubstituted *N*-acyl cyanamides.[13] Besides providing access to a larger functional diversity, N-alkylation blocks deprotonation of the base-labile cyanamide functionality. Correctly chosen, this would in turn allow the N-alkyl substituent to act as a cyanamide-protecting group.

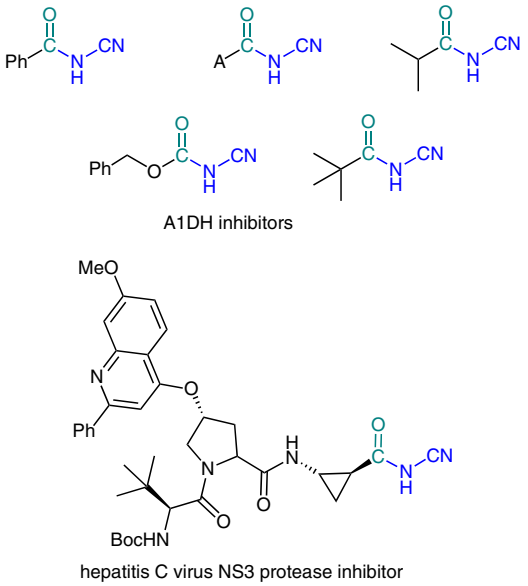

Figure 1 *N*-Acyl cyanamides utilized as A1DH or hepatitis C virus NS3 inhibitors

Over the last three years, our group has developed and explored a connected two-chamber system for a number of palladium-catalyzed carbonylative reactions[14] of aryl halides and triflates using ex situ generation of CO gas from solid CO precursors, such as COgen and SilaCOgen.[15] During this work we became interested in applying alkylated cyanamides as nucleophiles in carbonylation reactions with stoichiometric CO. In this manuscript we wish to report on the development of the multicomponent reaction for performing a palladium-catalyzed carbonylative reaction providing direct access to N-substituted acyl cyanamides from aryl bromides (Scheme 1). The developed method tolerates different N-alkylated cyanamides and performs with the inherent high functional-group tolerance of palladium catalysis. Finally, the method was extrapolated to include ^{13}C labeling using ^{13}CO obtained by simple exchange of the CO precurser for the ^{13}C-labeled silacarboxylic acid derivative in the two-chamber system.

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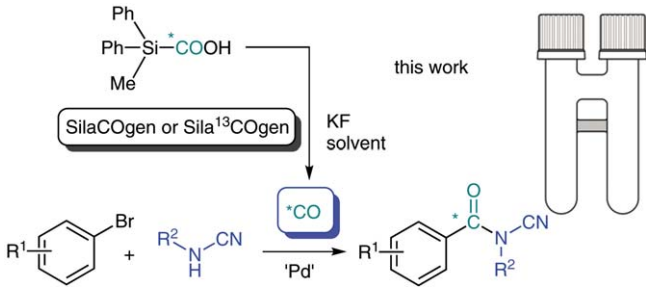


Scheme 1 Pd(0)-catalyzed carbonylative coupling of N-substituted cyanamides with aryl bromides in a two-chamber reactor

The initial investigation focused on the reaction of 2-bromonaphthalene (**1a**, 1.0 equiv) and *N*-benzyl cyanamide (**2a**, 1.2 equiv) in the presence of $[Pd(cinnamyl)Cl]_2$ (5 mol%), Ph_3P (10 mol%), K_3PO_4 (1.5 equiv), and CO (2.5 equiv) generated from methyldiphenylsilacarboxylic acid (SilaCOgen) in butyronitrile (0.1 M) as shown in Table 1.[16] We found that the desired product **3a** was obtained in a 33% yield after five hours at 90 °C (Table 1, entry 1).

Applying the more electron-rich and sterically demanding monodentate phosphine ligand, CataCXium A (**L1**, Figure 2), improved the yield of **3a** significantly to 83% (Table 1, entry 2). On the other hand, employing bidentate phosphine ligands such as dppp, DPEPhos (**L2**), and XantPhos (**L3**) led to a reduced efficiency of the coupling reaction (Table 1, entries 3–5). Varying the amount of CataCXium A did not improve the yield of **3a** (Table 1, entries 6 and 7), while exchange of K_3PO_4 as the base for K_2CO_3, Cy_2NMe, or DIPEA only led to a slight reduction of the coupling yield (Table 1, entries 8–10). Replacement of the solvent butyronitrile with toluene or dioxane also led to a deterioration of the coupling yield to **3a** (Table 1, entries 11 and 12).

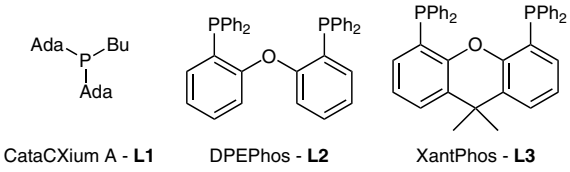
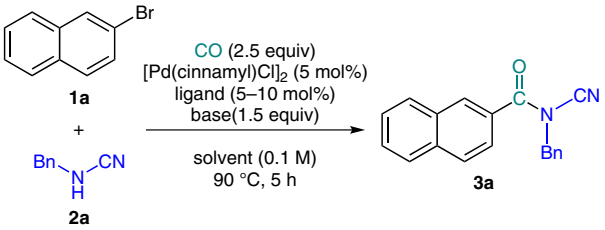


Figure 2 Ligands used

Having identified optimal reaction conditions for the preparation of an N-substituted acyl cyanamide, we next set out to examine the substrate scope of this palladium-catalyzed carbonylative reaction with various aryl bromides (Scheme 2). All reactions proceeded smoothly with *N*-benzyl cyanamide and were complete in five hours generating the corresponding acyl cyanamides in yields ranging from 42–86%. Both aryl bromides with electron-withdrawing and electron-donating substituents proved to be compatible with the coupling conditions. Substrates displaying an *ortho* substituent proved reactive, albeit providing reduced yields as exemplified with acyl cyanamide **3g**. On the other hand, substituents in the *para* or *meta* position did not have a significant influence on the coupling efficiency. It is interesting to note that the thioester containing product **3n** could be prepared although with some deterioration of the yield most likely due to competing amination at the thioester bond. For successful coupling with the more electron-deficient aryl bromides containing a 4-nitro or a 4-cyano substituent as in **3q** and **3r**, it was necessary to reduce the reaction temperature to 80 °C, as well as increasing the loading of the catalytic system in order to promote a reasonable conversion.

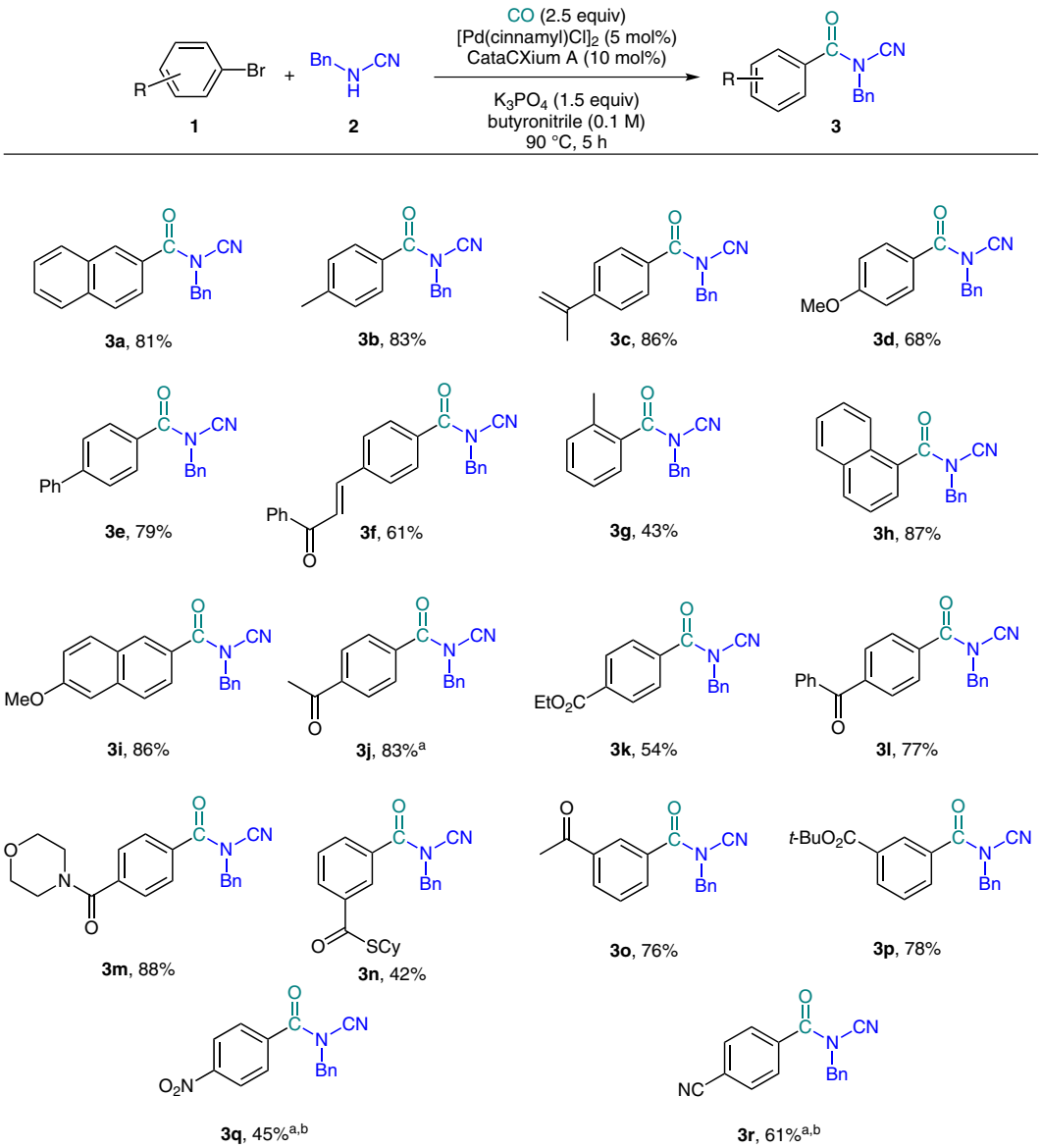
Next, a few other *N*-alkyl-substituted cyanamides were evaluated as coupling partners with 2-naphthyl bromide (**1a**, Scheme 3). Not too surprisingly, the alkyl substituent on the cyanamide did indeed influence the reactivity of this particular nucleophile, however, the three examples **3s**–**u** could all be secured in acceptable yields after column chromatography.

Table 1 Selected Entries for the Optimization of the Carbonylative Coupling of 2-Bromonaphthalene (**1a**) with *N*-Benzyl Cyanamide (**2a**)[a]



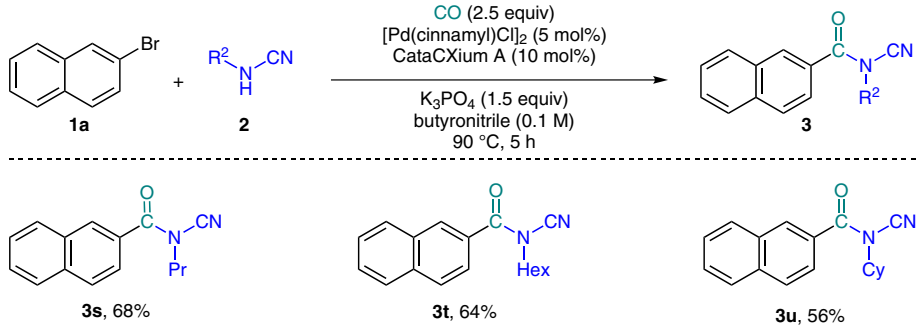
Entry	Ligand	Base	Solvent	Yield (%)[b]
1	Ph_3P	K_3PO_4	butyronitrile	33
2	**L1**	K_3PO_4	butyronitrile	83 (81)
3	DPPP	K_3PO_4	butyronitrile	75
4	**L2**	K_3PO_4	butyronitrile	11
5	**L3**	K_3PO_4	butyronitrile	35
6[c]	**L1**	K_3PO_4	butyronitrile	37
7[d]	**L1**	K_3PO_4	butyronitrile	80
8	**L1**	K_2CO_3	butyronitrile	74
9	**L1**	Cy_2NMe	butyronitrile	77
10	**L1**	DIPEA	butyronitrile	74
11	**L1**	K_3PO_4	dioxane	65
12	**L1**	K_3PO_4	toluene	42

[a] Chamber 1: ArBr (0.20 mmol), *N*-benzyl cyanamide (0.24 mmol), $[Pd(cinnamyl)Cl]_2$ (5 mol%), ligands (monodentate ligands 10 mol%, bidentate ligands 5 mol%), K_3PO_4 (1.5 equiv), and solvent (2.0 mL); chamber 2: methyldiphenylsilacarboxylic acid (0.50 mmol), KF (0.50 mmol), and butyronitrile (2.0 mL).
[b] Yield was determined by ^1H NMR spectroscopic data of crude products using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield is given in parenthesis.
[c] Conditions: 5 mol% CataCXium A (**L1**) was employed.
[d] Conditions: 20 mol% CataCXium A (**L1**) was employed.

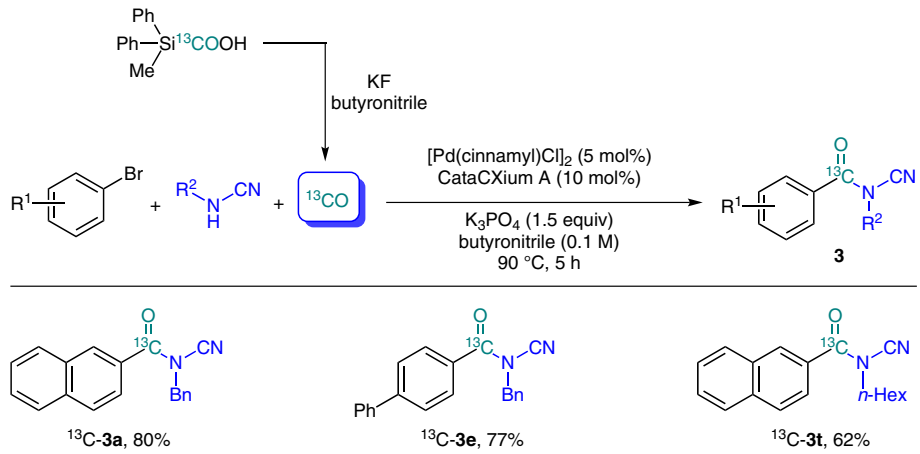


Scheme 2 Scope of the Pd(0)-catalyzed carbonylative coupling of *N*-benzyl cyanamide with aryl bromides. (a) 80 °C. (b) [Pd(cinnamyl)Cl_2] (7.5 mol%), CataCXium A (15 mol%)

Finally, we examined the possibility for ^{13}C isotope labeling applying ^{13}CO generated from ^{13}C-labeled methyldiphenylsilacarboxylic acid (Scheme 1). As illustrated in Scheme 4, starting from 2-bromonaphthalene, the corresponding *N*-acyl cyanamide ^{13}C-**3a** was obtained in an 80% yield (Scheme 4).[16] Repeating the sequence in the coupling with 4-bromobiphenyl afforded ^{13}C-**3e** in the yield of 77%, whereas with the *n*-hexyl-substituted cyanamide ^{13}C-**3t** was generated in a yield of 62%.



Scheme 3 Examination of other *N*-alkyl cyanamides in the Pd(0)-catalyzed carbonylative coupling with aryl bromides



Scheme 4 Synthesis of various ^{13}C-labeled *N*-acyl cyanamides

In summary, a protocol for the direct transformation of a variety of aryl bromides into *N*-acyl cyanamides via a palladium-catalyzed carbonylative protocol has been developed using our previously described two-chamber system with a slight excess of ex situ generated carbon monoxide. Both electron-deficient and electron-rich aryl bromides could be transformed into the desired product, and furthermore, the process tolerates a wide variety of functional groups while an example with an *ortho* substituent provide slightly reduced yields. Lastly, isotope labeling with ^{13}CO proved the corresponding ^{13}C-labeled *N*-acyl cyanamides.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are general methods, an experimental section and copies of ^{1}H and ^{13}C NMR spectra for all products.

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(16) **General Procedure for the Synthesis of *N*-Benzyl-*N*-cyano-2-naphthamide (3a)**

In an argon-filled glovebox to chamber 1 of the two-chamber system was added 2-bromonaphthalene (42 mg, 0.20 mmol), $[Pd(cinnamyl)Cl]_2$ (5.0 mg, 0.01 mmol), CataCXium A (8.0 mg, 0.02 mmol), K_3PO_4 (65 mg, 0.3 mmol), and butyronitrile (1.0 mL) in that order. The chamber was closed with a screwcap fitted with a Teflon seal. To chamber 2 of the two-chamber system was added methyldiphenylsilacarboxylic acid (122 mg, 0.50 mmol) and KF (30 mg, 0.50 mmol). The chamber was closed with a screwcap fitted with a Teflon seal. The loaded two-chamber system was removed from the glovebox and heated to 30 °C for 15 min. Then *N*-benzyl cyanamide (31 mg, 0.24 mmol) in butyronitrile (1.0 mL) was added to chamber 1. Lastly butyronitrile (2.0 mL) was added to chamber 2. This reaction was stirred at 90 °C for 5 h and was then cooled to r.t. The solids were filtrated off, and the reaction was concentrated under vacuum. The crude residue was subjected to flash chromatography using pentane–EtOAc (10:1) as eluent. This resulted in 46 mg (81%) of **3a** as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 7.94–7.98 (m, 2 H), 7.91 (d, *J* = 8.4 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.44–7.84 (m, 7 H), 4.98 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 135.3, 133.8, 131.9, 130.0, 129.2, 129.1 (2 C), 129.0 (2 C), 128.8, 128.7, 128.6, 127.9, 127.8, 127.2, 124.3, 111.1, 51.4. HRMS: *m/z* calcd for $C_{19}H_{15}N_2O$ $[M + H]^+$: 287.1184; found: 287.1178.

^{13}C-Labeled *N*-Benzyl-*N*-cyano-2-naphthamide (^{13}C-3a)

According to the general procedure. Flash chromatography using pentane–EtOAc (10:1) as eluent resulted in 46 mg (80% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 4.4 Hz, 1 H), 7.81–7.96 (m, 4 H), 7.41–7.64 (m, 7 H), 4.96 (d, *J* = 2.8 Hz, 2 H). ^{13}C NMR (0100 MHz, $CDCl_3$): δ = 168.1 (^{13}C-enriched), 135.4, 133.9, 132.0 (d, *J* = 5.1 Hz), 130.1 (d, *J* = 2.2 Hz), 129.3 (2 C), 129.1 (d, *J* = 2.9 Hz, 2 C), 128.8, 128.7, 128.6, 128.4, 127.9, 127.7, 127.3, 124.3 (d, *J* = 2.2 Hz), 111.1 (d, *J* = 3.6 Hz), 51.5. HRMS: *m/z* calcd for $C_{18}{}^{13}CH_{15}N_2O$ $[M + H]^+$: 288.1218; found: 288.1213.