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Mild Pd-Catalyzed Aminocarbonylation of (Hetero)Aryl Bromides with a Palladacycle Precatalyst

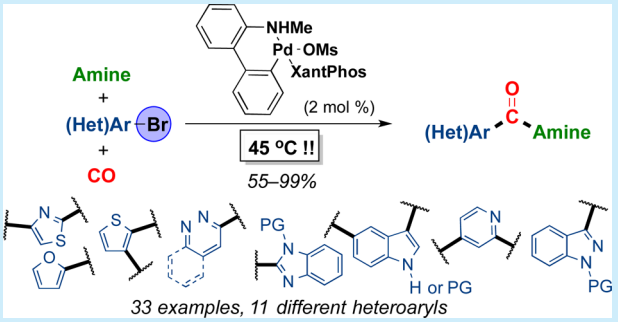
Stig D. Friis,[†,‡] Troels Skrydstrup,*[,†] and Stephen L. Buchwald*[,‡]

[†]Center for Insoluble Protein Structures (inSPIN), Interdisciplinary Nanoscience Center (iNANO) and Department of Chemistry, Aarhus University, Gustav Wieds Vej 14, 8000 Aarhus C, Denmark

[‡]Department of Chemistry, Massachusetts Institute of Technology, Room 18-490, Cambridge, Massachusetts 02139, United States

Supporting Information

ABSTRACT: A palladacyclic precatalyst is employed to cleanly generate a highly active XantPhos-ligated Pd-catalyst. Its use in low temperature aminocarbonylations of (hetero)aryl bromides provides access to a range of challenging products in good to excellent yields with low catalyst loading and only a slight excess of CO. Some products are unattainable by traditional carbonylative coupling.



Heterocycles are an important constituent in many pharmaceuticals.[1] Transition metal catalysis plays a key role in the selective functionalization of heteroaromatic systems. Yet, many metal-catalyzed transformations suffer from the metal coordinating ability of heterocycles, resulting either in byproduct formation or inhibition of catalytic turnover.[2] In many instances, specialized reaction conditions or catalyst systems are needed in order to provide reasonable yields of the desired products.[3]

Amides represent a ubiquitous functional group in pharmaceutically relevant compounds and are frequently attached to a heteroaryl core (Figure 1). Although many routes rely on the use of carboxylic acid starting materials,[4] an appealing approach to amides relies on a three-component Pd-catalyzed coupling of a (hetero)aryl halide with an amine and CO.[5] While this transformation has been widely used, limitations remain with substrates bearing sensitive functional groups, as the coupling of (hetero)aryl bromides usually must be conducted at elevated temperatures.[6] The more reactive (hetero)aryl iodides can in some cases be utilized, but only a narrow selection of such iodides are available due to their limited stability.[7] The literature also reveals a lack of good procedures for the conversion of more difficult (hetero)aryl bromides, including 3-bromoindole, 3-bromopyridazine, 2-bromothiazole, or 2-bromobenzimidazole, into the corresponding amides.

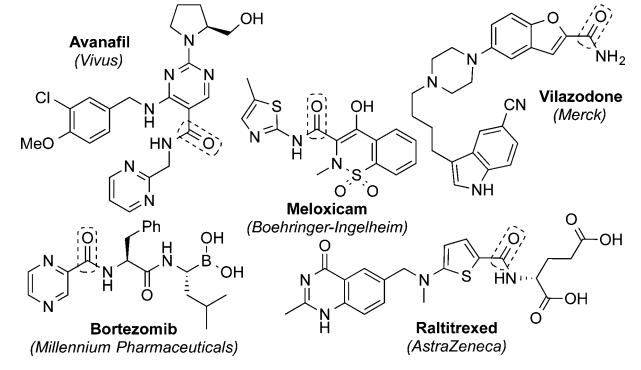


Figure 1. Selection of FDA-approved drugs containing heteroaryl amides.

Herein, we describe the low temperature conversion of aryl and heteroaryl bromides to their corresponding secondary and tertiary amides enabled by the use of a palladacycle precatalyst. The increased activity of the catalyst generated from this precatalyst provides easy access to products, which are otherwise inaccessible via Pd-catalyzed aminocarbonylation or provide low yields due to significant unproductive side reactions such as S_NAr or addition to/substitution of other functional groups in the molecule.

In recent years, palladium precatalysts have received significant attention because of their ability to selectively generate the ligated Pd(0)-complex with only minimal coordinating byproducts.[8] The employment of these precatalysts, with their ease of use, significantly enhances the catalytic activity, compared to catalysts generated from, e.g., $Pd(dba)_2$ or $Pd(OAc)_2$.[9] We therefore envisioned that a catalyst generated from the palladacycle precatalyst **1** (Figure 2) could provide the additional activity needed, in order to carbonylate more difficult heteroaryl bromides, as well as substrates susceptible to S_NAr-type reactions. The *N*-methyl-2-aminobiphenyl based precatalyst **1** was chosen over the simpler 2-aminobiphenyl based precatalyst

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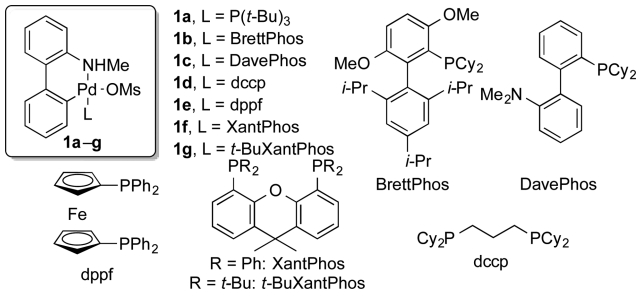


Figure 2. Palladacycle precatalyst and phosphine ligands examined for low temperature aminocarbonylations.

to eliminate the potential reaction of the carbazole byproduct, which would cause reduced yields and possibly complicate purification of the products.[8f]

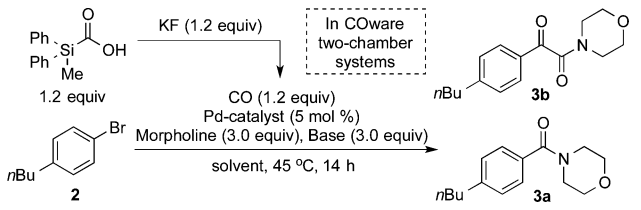
Applying our COware two-chamber system and a solid silacarboxylic acid CO precursor, to avoid the handling of the toxic gas, we set out to develop conditions for this transformation.[10] As illustrated in Table 1, the unactivated aryl bromide **2** was selected for the optimization studies. Poor catalyst stability was observed when starting with the precatalysts **1a–d** bearing monodentate ligands or dccp [1,3-bis(dicyclohexylphosphino)propane], and only trace conversion of **2** was observed. With precatalyst **1e** based on the ligand dppf [1,1′-bis(diphenylphosphino)ferrocene], conversion to product was observed, but in low yield. In contrast, with the precatalyst based on XantPhos **1f**,[5d,11] full conversion of **2** was seen and amide **3a** was isolated in a 92% yield, when the reaction was carried out at a temperature of only 45 °C. Decreasing the temperature further resulted in incomplete conversion of **2**.

The nature of the base included in the reaction was also crucial. Employing **1f** with the stronger base DBU (Table 1, entry 5) reduced the yield of the desired product significantly and instead provided the double carbonylated product **3b** in a 19% GC yield.[12] Triethylamine proved to be the ideal base and was chosen for further optimization as it gave a slightly higher isolated yield and is easily removed under vacuum (Table 1, entry 7); dioxane is the solvent of choice (Table 1, entries 8–10). Increasing the concentration to 0.50 M while lowering the catalyst loading to 2.0 mol % with 2.0 equiv of nucleophile and base did not significantly affect the isolated yield (Table 1, entry 11).

With conditions for a low temperature aminocarbonylation at hand enabled by the use of **1f**, we set out to probe the scope of this protocol as shown in Scheme 1. The excellent yields of **4a** and **4b** demonstrate that electron-poor and electron-rich aryl bromides can undergo efficient coupling using this catalytic system. Turning to the heteroaromatic bromides, 5-bromoisoquinoline was first coupled to afford **4c** in a 99% isolated yield. Having the bromide situated on a heteroaryl ring did not affect the yield, as **4d** was isolated in 98% yield, while 87% of the 2,6-difunctionalized pyridine **4e** was realized. The presence of an additional nitrogen in the ring was also inconsequential as 5-bromopyrimidine could be converted to **4g** in 93% yield.[13]

The indole ring system represents a privileged structure in drug discovery, and it is well-known that reaction of substrates in which the nitrogen is unprotected can be problematic.[2b,3b,14]

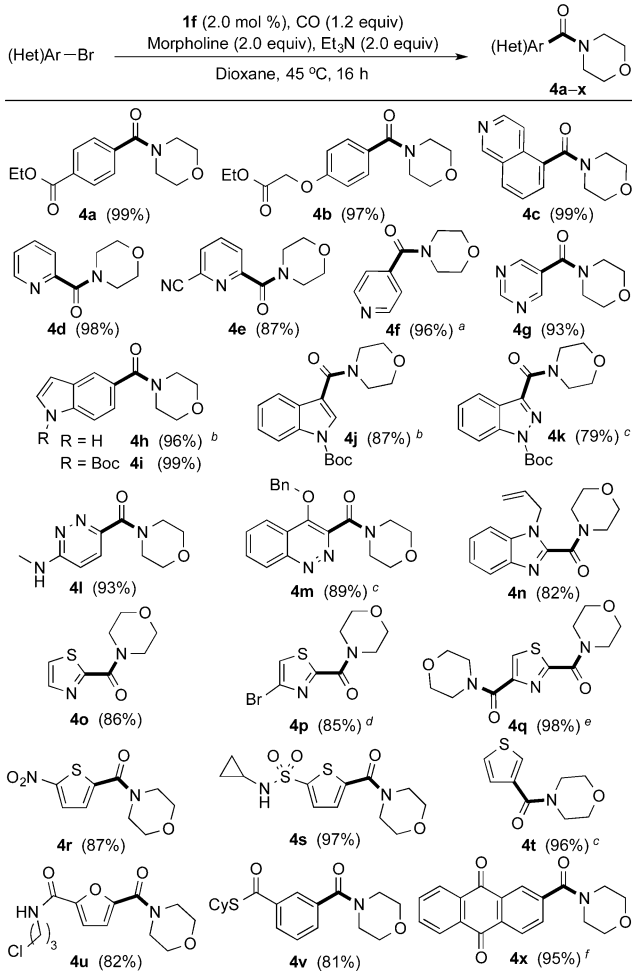
Table 1. Optimization of Low Temperature Aminocarbonylation Employing a Palladacycle Precatalyst[a]



entry	catalyst	solvent	base	yield of **3a** [%][b]
1	**1a–d**	dioxane	Cy_2NMe	trace
2	**1e**	dioxane	Cy_2NMe	16
3	**1f**	dioxane	Cy_2NMe	99 (92)
4	**1g**	dioxane	Cy_2NMe	0
5[c]	**1f**	dioxane	DBU	6
6	**1f**	dioxane	K_2CO_3	97
7	**1f**	dioxane	Et_3N	99 (97)
8	**1f**	MeCN	Et_3N	24
9	**1f**	PhMe	Et_3N	trace
10	**1f**	CPME	Et_3N	21
11[d]	**1f**	dioxane	Et_3N	99 (93)

[a]**2** (0.25 mmol), 0.25 M. [b]GC yield, isolated yield in parentheses. [c]Yield of **3b**: 19% [d]**2** (1.0 mmol), **1f** (2 mol %), Et_3N (2.0 mmol), and morpholine (2.0 mmol) in dioxane (2.0 mL).

Scheme 1. Low Temperature Aminocarbonylation of (Hetero)Aryl Bromides with Morpholine; Isolated Yields and Average of Two Runs, (Het)Ar–Br (1.0 mmol), 0.50 M



[a]Used as HCl salt, Et_3N (3.0 mmol). [b]80 °C. [c]65 °C. [d]$MePh_2SiCO_2H$ (1.0 mmol), KF (1.0 mmol). [e]2,4-Dibromothiazole (0.5 mmol). [f]0.25 M.

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This tendency was also observed in this transformation as the carbonylation of unprotected 5-bromoindole must be conducted at 80 °C to provide **4h** in a satisfactory yield. On the other hand, the corresponding *N*-Boc substrate was carbonylated to provide an excellent yield of **4i** at 45 °C. While no observable conversion of 3-bromo-*N*-Boc-indole was seen at this temperature, at 80 °C the desired heteroaryl amide **4j** was produced in a 87% isolated yield. The more activated *N*-Boc-3-bromoindazole coupled well to afford a 79% yield of amide **4k**.

The aminocarbonylation of a bromopyridazine and a bromocinnoline also proceeded efficiently, leading to products **4l** and **4m** in good yields, although a slightly higher reaction temperature was necessary to realize a good yield of **4m**, possibly due to the presence of an *ortho* substituent in the substrate. The allyl-protected 2-bromobenzimidazole also coupled nicely at low temperature to give **4n** in an 82% isolated yield.

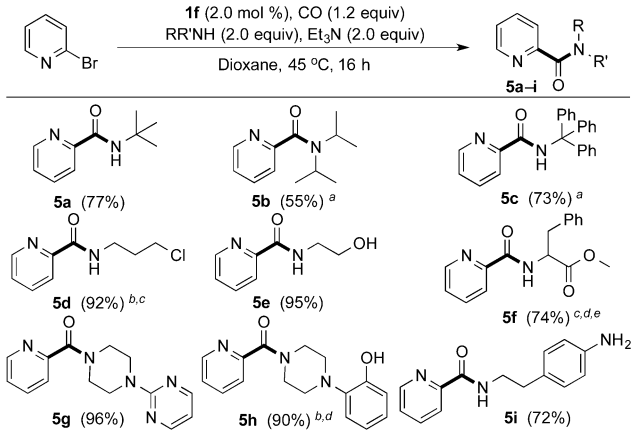
The use of bromothiazoles as substrates was next examined. In particular, these substrates are susceptible to S_NAr with the amine nucleophile.[15] Subjecting 2-bromothiazole to the optimized reaction conditions furnished an 86% yield of product **4o**, with no observation of product arising from S_NAr. Applying identical conditions on the 2,4-dibromothiazole resulted in only a 73% yield of the desired product **4p**. The slightly lower yield was due to a second carbonylation at C4 with the slight excess of CO. Nevertheless, the yield was improved to 85% by lowering the amount of the silacarboxylic acid to 1.0 equiv, thereby preventing the coupling at the more electron-rich 4-position. On the other hand, employing 2.4 equiv of CO provided smoothly the difunctionalized thiazole **4q** in excellent yield, emphasizing the importance of being able to accurately control the quantity of CO utilized in the reaction.

Three different thiophenes were tested, providing both amide **4r** and **4s** in excellent yields. However, when moving the bromide to the more electron-rich C3-position, a slight increase in temperature was required for the reaction to go to completion, providing **4t** in 96% yield. The products **4u** and **4v** both contain functional groups that allow for easy postcoupling modification via S_N2 substitution of the primary alkyl chloride in **4u** or acyl substitution of the thioester displayed by **4v**. These functional groups, however, also make them sensitive substrates, which may not be tolerated under traditional aminocarbonylation conditions at elevated temperatures. However, applying this more active catalytic system at 45 °C provided the desired products in good yield.

Next, variations of the amine nucleophile were examined in the aminocarbonylation of 2-bromopyridine. Using a volatile, sterically hindered primary amine, *tert*-butylamine, did not have a profound effect on the efficiency of the reaction, as the product **5a** was isolated in 77% yield (Scheme 2). On the other hand, coupling with the more sterically hindered diisopropylamine proved to be slightly more sluggish, furnishing 55% of the desired amide **5b** at 65 °C. This increased temperature was also necessary to achieve full conversion with tritylamine as the nucleophile, giving **5c**, which can easily be converted into the primary amide.[16] 3-Chloropropylamine is commercially available as the corresponding hydrochloride, possibly due to potential polymerization or intramolecular cyclization. Additional base was consequently added for its reaction, and after 16 h at 45 °C, product **5d** could be isolated in a 92% yield, with no signs of S_N2 substitution on the alkyl chloride.

Amines carrying an additional nucleophile were also examined. For example, ethanolamine was used for the synthesis of **5e** in 95% yield. The presence of a free phenol is also tolerated as seen by the high yield formation of **5h**. However, introducing a free aniline did have a slightly detrimental effect as **5i** could only be isolated in a 72% yield.

Scheme 2. Low Temperature Aminocarbonylation of 2-Bromopyridine and a Selection of Amines; Isolated Yields and Average of Two Runs, 2-Bromopyridine (1.0 mmol), 0.50 M



[a]65 °C. [b]Et_3N (4.0 mmol). [c]Used as HCl ammonium salt. [d]0.25 M. [e]RR′NH (1.2 mmol), Et_3N (3.2 mmol).

In order to demonstrate the superiority of the palladacycle precatalyst, it was compared to a selection of traditional Pd(0) and Pd(II) sources reported in the literature (Figure 3).[5e,17] The

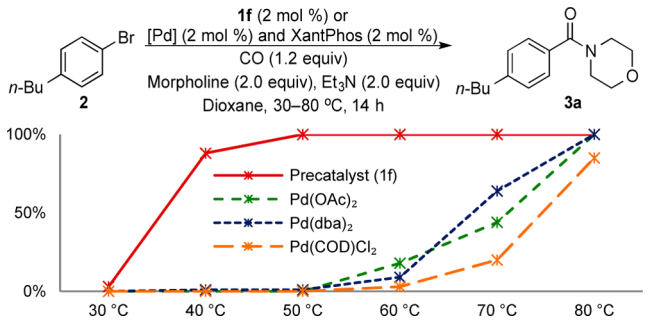


Figure 3. Comparison of palladacycle precatalyst **1f** with traditional Pd sources at different temperatures. GC yields, **2** (1.0 mmol), 0.50 M.

conversion of aryl bromide **2** into amide **3a** was examined at six temperatures ranging from 30 to 80 °C, applying either precatalyst **1f** or $Pd(OAc)_2$, $Pd(dba)_2$, or $Pd(COD)Cl_2$ in combination with an equimolar amount of XantPhos. Whereas the traditional Pd sources did not show any catalytic turnover at temperatures lower than 60 °C and produced synthetically useful yields only at 80 °C, precatalyst **1f** furnished amide **3a** in good yield at 40 °C, while providing the amide quantitatively at 50 °C, emphasizing that a more active catalyst for the aminocarbonylation is generated from this palladacycle precatalyst.

In conclusion, the use of a palladacycle precatalyst has been shown to have a significant rate-enhancing effect on the aminocarbonylation relative to traditional catalytic systems. The low temperature at which this carbonylative coupling is conducted provides access to a range of products that are otherwise not easily accessible. An array of electron-rich and electron-poor aryl and heteroaryl bromides has, despite their sensitive nature, been coupled in good to excellent yields. Moreover, both tertiary and secondary amides have been synthesized, while formal access to primary amides has been

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shown using tritylamine as the nucleophile. Due to the generality of the method and its ease of use, it should see wide utilization in both academic and industrial, particularly pharmaceutical, settings.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ts@chem.au.dk.
*E-mail: sbuchwal@mit.edu.

Notes

The authors declare the following competing financial interest(s): MIT holds or has filed patents on some of the ligands and precatalysts used in this work, for which S.L.B. receives royalty payments. T.S. is a co-owner of SyTracks a/s.

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