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# Access to 2-(Het)aryl and 2-Styryl Benzoxazoles via Palladium-Catalyzed Aminocarbonylation of Aryl and Vinyl Bromides

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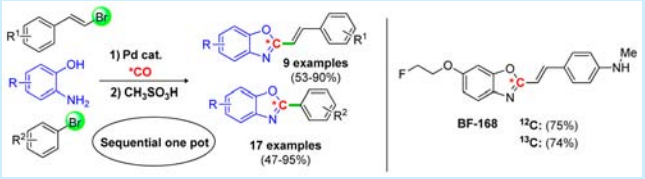
Supporting Information

**ABSTRACT:** A sequential one-pot procedure for the synthesis of either 2-(hetero)aryl or 2-styryl benzoxazoles is reported, starting from aryl and vinyl bromides, respectively, involving an initial aminocarbonylation with 2-aminophenols as nucleophiles followed by an acid mediated ring closure to generate the heterocycle. The methodology displays a broad substrate scope in moderate to excellent yields and can be exploited for $^{13}$C-isotope labeling. Finally, this carbonylative protocol was applied to the synthesis of a potential Alzheimer's plaque binder and a selective PPAR antagonist including site-specific labeling with $^{13}$C-carbon monoxide.




2-(Hetero)aryl and 2-styryl benzoxazoles are important structural motifs, as they appear in several natural products and pharmaceutical agents (Figure 1).[1] Because of the inherent ability of 2-styryl benzoxazoles to bind to both senile plaques and neurofibrillary tangles (NFTs), they draw interest as potential molecular probes for Alzheimer's disease (AD) diagnostics.[2] From a systematic screening study, Okamura and co-workers demonstrated that 2-styryl benzoxazole (compound BF-168, Figure 1) shows high binding affinity to NFTs.[3] The ability to visually detect signs of AD in a noninvasive manner is of key importance both in preclinical AD detection and for clinical drug development programs focused on methods for AD-treatment.[4,5] Hence, methods for the expedient synthesis of isotopically labeled 2-(hetero)aryl and 2-styryl benzoxazoles is of high relevance.

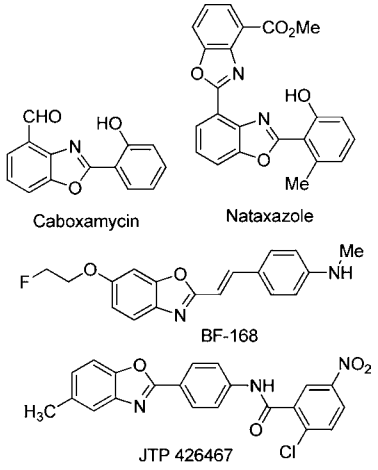



**Figure 1.** Relevant 2-aryl- and 2-styryl benzoxazoles.

Traditional approaches to 2-(hetero)aryl and 2-styryl benzoxazoles rely on the coupling of 2-aminophenols with either aldehydes under oxidative conditions[6] or by the coupling to carboxylic acid derivatives.[7] There are also several reports based on the Cu-catalyzed coupling of primary amides and *o*-dihaloaromatic compounds to yield 2-aryl benzoxazoles.[8] More recently, Pd- or Cu-mediated couplings of aryl halides with benzoxazoles via C−H functionalization have been developed.[9] Nevertheless, all these methods are limited by high reaction temperatures or inaccessible starting materials.

Our group recently developed a safe procedure for performing small scale carbonylations applying two-chamber reactors (COware) and CO generated *ex situ* from stable precursors such as COgen.[10,11] With such technology at hand, we embarked on a two-step synthesis of 2-aryl and 2-styryl benzoxazoles via a one-pot sequence involving a Pd-catalyzed aminocarbonylation, followed by acid mediated cyclization. The development of such a methodology would also allow for the introduction of a $^{13}$C-label in the 5-membered ring heterocycle, which would be highly relevant for the isotope labeling of bioactive compounds.[2,3]

As a starting point, the aminocarbonylation between (*E*)-1-(2-bromovinyl)-4-methoxybenzene and 2-aminophenol was optimized to ensure full conversion to the amide of interest (Table 1). A small screening of ligands, reaction temperature, bases, and solvents was performed, applying Pd(cod)Cl$_2$ as the metal source in the presence of 1.5 equiv of CO. First, a small

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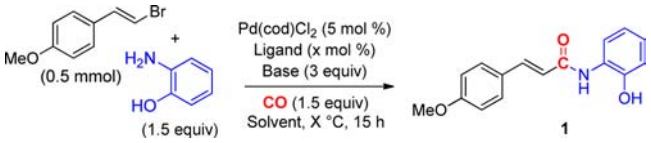
**Table 1. Optimization of the Aminocarbonylation**[a]




| entry | ligand (mol %) | base | solvent | temp | conv[b] (%) |
|---|---|---|---|---|---|
| 1 | Xantphos (5) | DBU | dioxane | 80 | >95 (80)[c] |
| 2 | $HBF_4P(t\text{-}Bu)_3$ (5) | DBU | dioxane | 80 | >95 (92)[c] |
| 3 | $HBF_4PCy_3$ (10) | DBU | dioxane | 80 | >95 (81)[c] |
| 4 | $PPh_3$ (10) | DBU | dioxane | 80 | 80 |
| 5 | $HBF_4P(t\text{-}Bu)_3$ (5) | DBU | dioxane | 60 | >95 (90)[c] |
| 6 | $HBF_4P(t\text{-}Bu)_3$ (5) | DBU | dioxane | 40 | 80 |
| 7 | $HBF_4P(t\text{-}Bu)_3$ (5) | DBU | dioxane | rt | 40 |
| 8[d] | $HBF_4P(t\text{-}Bu)_3$ (3) | DBU | dioxane | 60 | 80 |
| 9[e] | $HBF_4P(t\text{-}Bu)_3$ (1) | DBU | dioxane | 60 | 60 |
| 10 | $HBF_4P(t\text{-}Bu)_3$ (5) | DABCO | dioxane | 60 | 75 |
| 11 | $HBF_4P(t\text{-}Bu)_3$ (5) | TEA | dioxane | 60 | 64 |
| 12 | $HBF_4P(t\text{-}Bu)_3$ (5) | $K_2CO_3$ | dioxane | 60 | 55 |
| 13 | $HBF_4P(t\text{-}Bu)_3$ (5) | $K_3PO_4$ | dioxane | 60 | 47 |
| 14 | $HBF_4P(t\text{-}Bu)_3$ (5) | $Cs_2CO_3$ | dioxane | 60 | 50 |
| 15 | $HBF_4P(t\text{-}Bu)_3$ (5) | DBU | THF | 60 | >95 (92)[c] |
| 16 | $HBF_4P(t\text{-}Bu)_3$ (5) | DBU | toluene | 60 | 40 |
| 17 | $HBF_4P(t\text{-}Bu)_3$ (5) | DBU | MeCN | 60 | >95 (90)[c] |
| 18 | $HBF_4P(t\text{-}Bu)_3$ (5) | DBU | CPME | 60 | 70 |
| 19[f] | $HBF_4P(t\text{-}Bu)_3$ (5) | DBU | THF | 60 | 40 |

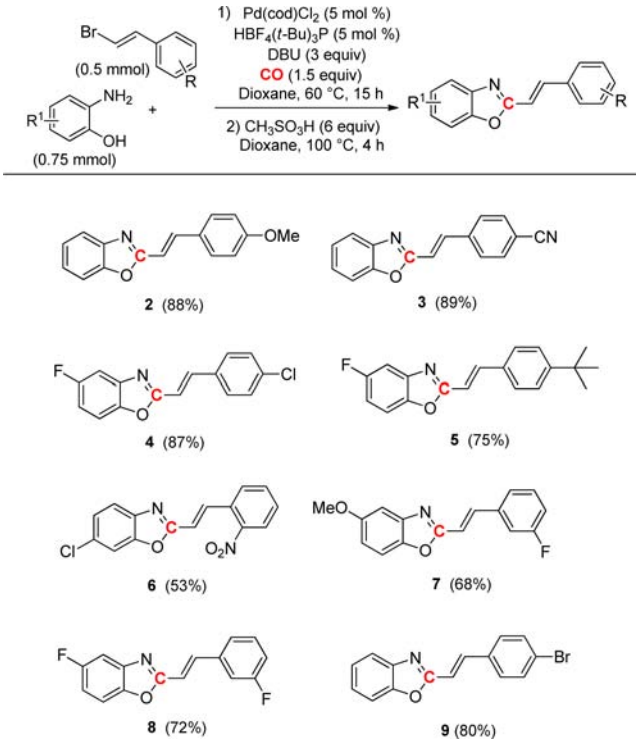
[a]Chamber A: COgen (0.75 mmol), $HBF_4P(t\text{-}Bu)_3$ (1 mol %), $Pd(cod)Cl_2$ (1 mol %), $Cy_2NMe$ (1.5 mmol) in dioxane (3 mL). Chamber B: (*E*)-1-(2-bromovinyl)-4-methoxybenzene (0.5 mmol), 2-aminophenol (0.75 mmol), $Pd(cod)Cl_2$ (5 mol %), ligand (*x* mol %), base (1.5 mmol) in solvent (3 mL). [b]Determined by $^1H$ NMR. [c]Isolated yield. [d]3 mol % of $Pd(cod)Cl_2$ used. [e]1 mol % of $Pd(cod)Cl_2$ used. [f]1.0 mmol of DBU used.

ligand screening was performed, indicating that both the mono- and bidentate ligands are effective in the carbonylation (Table 1, entries 1−4) The best isolated yield was accomplished using $P(t\text{-}Bu)_3$ as the ligand administered as its $HBF_4$ salt (Table 1, entry 2).[13] The reaction temperature could be lowered to 60 °C without affecting the conversion (Table 1, entries 5−7). Attempts to lower the catalytic loading led to unsatisfactory conversion rates (Table 1, entries 8 and 9). Next, different bases were tested (Table 1, entries 10−14), and as can be seen in Table 1, DBU was the only base of those tested capable of ensuring high conversion rates and isolated yields. Finally, different solvents were examined, where full conversion was also obtained for THF and MeCN (Table 1, entries 15−18). Decreasing the amount of DBU resulted in a dramatic drop in conversion (Table 1, entry 19).

With the optimal reaction conditions at hand for the aminocarbonylation, we then proceeded to investigate the cyclization step. Previous work by Chakraborti and co-workers had shown that methanesulfonic acid in dioxane was able to promote 2-aryl benzoxazole formation, starting from acid chlorides and 2-aminophenols.[14] The same was also observed by us with full conversion to the 2-styryl benzoxazole by reaction with 3 equiv of methanesulfonic acid in dioxane at 100 °C for 4 h. The reaction temperature for the cyclization could not be lowered, and dioxane was found to be the solvent of choice.

With conditions for the cyclization established, the one-pot reaction was tested next. The aminocarbonylation between (*E*)-1-(2-bromovinyl)-4-methoxybenzene and 2-aminophenol was performed in dioxane at 60 °C. After 15 h, 6 equiv (to quench DBU prior to cyclization) of methanesulfonic acid were added to the reaction mixture and the temperature was raised to 100 °C for an additional 4 h of reaction time. This setup provided the desired 2-styryl benzoxazole **2** in an 88% isolated yield (Scheme 1). Next, this sequence was repeated on a variety of

**Scheme 1. Synthesis of 2-Styryl Benzoxazoles from Vinyl Bromides**[a,b]




[a]Chamber A: COgen (0.75 mmol), $HBF_4P(t\text{-}Bu)_3$ (1 mol %), $Pd(cod)Cl_2$ (1 mol %), $Cy_2NMe$ (1.5 mmol) in dioxane (3 mL). Chamber B: Vinyl bromide (0.5 mmol), 2-aminophenol (0.75 mmol), $Pd(cod)Cl_2$ (5 mol %), $HBF_4P(t\text{-}Bu)_3$ (5 mol %), DBU (1.5 mmol) in dioxane (3 mL). [b]Isolated yields.

different vinyl bromides and 2-aminophenol derivatives, the results of which are illustrated in Scheme 1. Electron-rich vinyl bromides were successfully transformed into the 2-styryl benzoxazoles in good overall yields (compounds **2** and **5**). Also electron-deficient vinyl bromides yielded the desired 2-styryl benzoxazoles (compounds **3**, **4**, **7**, and **8**), including (*E*)-1-(2-bromovinyl)-2-nitrobenzene, which provided the benzoxazole **6** in a 53% yield. Gratifyingly, also (*E*)-1-bromo-4-(2-bromovinyl)-benzene could be transformed into the 2-styryl benzoxazole **9**, leaving the aromatic bromide untouched. Finally, the vinyl chloride, (*E*)-1-(2-chlorovinyl)-4-methoxybenzene, was tested as the electrophilic coupling partner, but no product formation was observed.

Next, attention was turned toward aryl bromides as electrophiles. Oxidative addition to aryl bromides is generally more difficult; however, a small increase in the reaction temperature to 80 °C of the aminocarbonylation restored the reactivity for these substrates (Scheme 2). Electron-deficient aryl bromides displayed good reactivity, and the 2-aryl benzoxazoles were isolated in yields ranging from 85% to 95% (compounds **10**, **12**, **19**, and **21**−**23**). Electron-rich aryl



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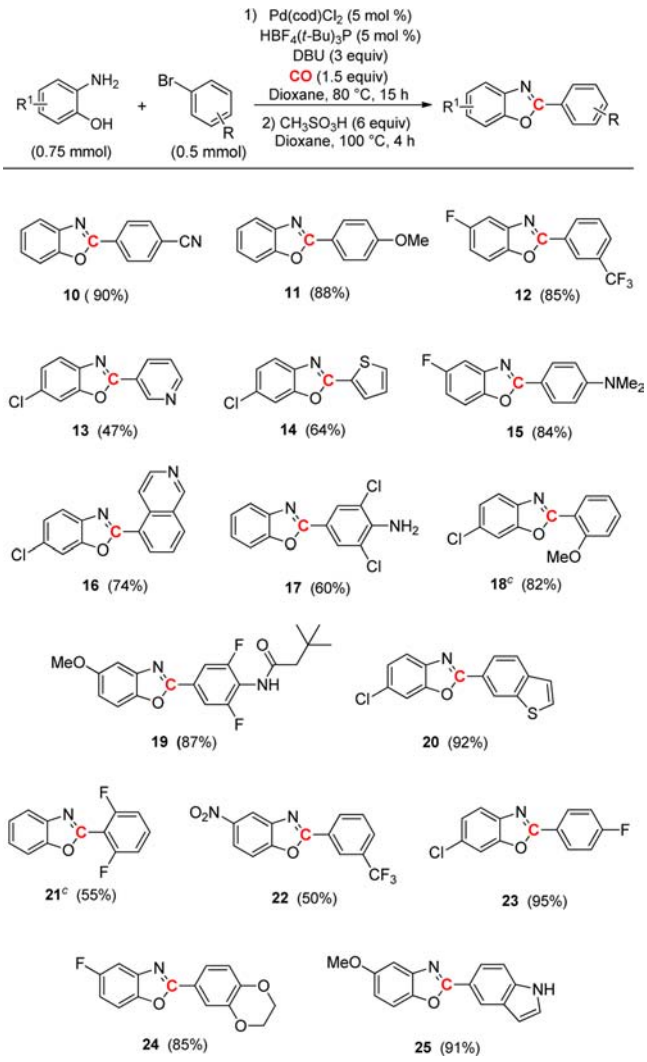
**Scheme 2. Synthesis of 2-Aryl Benzoxazoles from Aryl Bromides**[a,b]

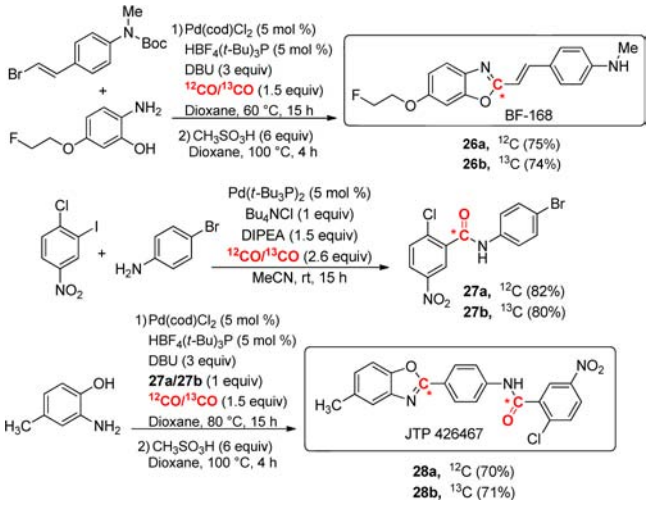



[a]Chamber A: COgen (0.75 mmol), $HBF_4P(t\text{-}Bu)_3$ (1 mol %), $Pd(cod)Cl_2$ (1 mol %), $Cy_2NMe$ (1.5 mmol) in dioxane (3 mL). Chamber B: Aryl bromide (0.5 mmol), 2-aminophenol (0.75 mmol), $Pd(cod)Cl_2$ (5 mol %), $HBF_4P(t\text{-}Bu)_3$ (5 mol %), DBU (1.5 mmol) in dioxane (3 mL). [b]Isolated yields. [c]Reaction conducted at 100 °C.

bromides were also successfully converted into the corresponding 2-aryl benzoxazoles in good overall yields (compounds **11**, **15**, **18**, and **24**). *ortho*-Substituted aryl bromides turned out to be more challenging under the given reaction conditions. However, by raising the temperature of the aminocarbonylation to 100 °C, reactivity was restored, and the desired benzoxazoles could be secured in 82% and 55% isolated yield, respectively (compounds **18** and **21**). Finally, heteroaryl bromides were successfully applied as electrophiles affording the desired cyclic compounds in isolated yields ranging from 47% from 92% (compounds **13**, **14**, **16**, **20**, and **25**). Again different 2-aminophenols were tolerated under the developed conditions, but unfortunately there was no reaction when 2-amino-3-hydroxypyridine was tested as the nucleophile. Finally, when 1,1′-biphenyl triflate was examined as the electrophile for the aminocarbonylation, no conversion was observed.

With a variety of 2-aryl and 2-styryl benzoxazoles synthesized, demonstrating the generality of the developed conditions, we turned to exploit our reaction conditions for the synthesis and isotope labeling of two bioactive compounds. As targets, the potential senile plaque binder BF-168 and the selective PPAR antagonist JTP 426467 were chosen (Scheme 3). For the synthesis of BF-168, the aminocarbonylation was

**Scheme 3. Synthesis of BF-168 and JTP 426467**




performed applying 2-amino-5-(2-fluoroethoxy)phenol and (*E*)-*tert*-butyl (4-(2-bromovinyl)phenyl)(methyl)carbamate, followed by addition of methanesulfonic acid. Due to the acidic conditions applied for the cyclization, Boc-deprotection was achieved simultaneously, affording the senile plaque binder BF-168 **26a** in a satisfactory 75% yield for the two steps. The $^{13}C$-labeled version of BF-168 **26b** was successfully synthesized in an analogous manner using $^{13}C$-labeled carbon monoxide generated from $^{13}COgen$.

In order to synthesize JTP 426467, two consecutive aminocarbonylations were required. Applying conditions developed by Arndtsen and co-workers, in which acid chlorides are generated *in situ* from aryl iodides with CO and $Bu_4NCl$, allowing efficient reactions with poor nucleophiles such as anilines, afforded amide **27a** in a satisfactory 82% isolated yield (Scheme 3).[15] Having formed **27a**, construction of the 2-aryl benzoxazole could be performed employing our general conditions using 2-amino-4-methylphenol as the nucleophile. Gratifyingly, the selective PPAR antagonist JTP 426467 **28a** was generated in a 70% isolated yield. Finally, the synthesis was repeated using $^{13}COgen$ as the carbon monoxide source in both carbonylations affording double $^{13}C$-labeled JTP 426467 **28b** in a comparable 71% yield (Scheme 3).

In conclusion, an effective one-pot procedure for the synthesis of 2-aryl and 2-styryl benzoxazoles has been developed. As the reaction proceeds via a Pd-catalyzed aminocarbonylation, this protocol is highly suitable for $^{13}C$-labeling of the oxazole ring. Noteworthy is the broad substrate scope allowing both aryl and vinyl bromides to be used as electrophiles and thereby illustrating the generality of the developed conditions. Finally, we succeeded in synthesizing the senile plaque binder BF-168 and the selective PPAR antagonist JTP 426467 along with their $^{13}C$-labeled analogs in good overall yields applying the developed reaction conditions.



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## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details and copies of all the $^{1}H$ and $^{13}C$ NMR spectra for all the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare the following competing financial interest(s): Anders Lindhardt and Troels Skrydstrup are co-owners of SyTracks a/s, which commercializes the two-chamber technology.

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