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Aminocarbonylation of Aryl Tosylates to Carboxamides

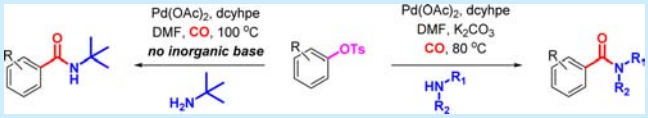
Seungwon Chung,*[,†] Neal Sach,[‡] Chulho Choi,[†] Xiaojing Yang,[†] Susan E. Drozda,[†] Robert A. Singer,[§] and Stephen W. Wright*[,†]

[†]Biotherapeutics Chemistry and [§]Chemical Research and Development, Pfizer Global Research and Development, Pfizer Global Research and Development, 445 Eastern Point Road, Groton, Connecticut 06340, United States

[‡]Oncology Chemistry, Pfizer Global Research and Development, 10770 Science Center Drive, La Jolla, California 92121, United States

Supporting Information

ABSTRACT: The palladium - catalyzed aminocarbonylation of aryl tosylates with amines is reported. Suitable conditions were identified by high throughput reaction screening and then further optimized. The substrate scope of the reaction with respect to the aryl tosylate component and the amine component are reported. Competitive aminolysis of the aryl tosylates to afford the amine toluenesulfonamides and the phenol was not observed.



The synthesis of aryl and heteroaryl esters and amides from the corresponding aryl halides or triflates via palladium catalyzed carbonylation with carbon monoxide is a useful procedure that is widely employed in organic synthesis, and particularly in the synthesis of compounds pharmaceutical and agricultural importance.[1] The carbonylation of aryl and heteroaryl triflates provides a synthetic transformation of phenols and hydroxy-heteroaryl compounds into carboxylic acid derivatives that makes use of a readily available and well-populated starting material set, and frequently provides reliable access to product regioisomers that are orthogonal to those derived from readily available aryl and heteroaryl halides.[2]

During the course of a recent synthetic program, we found an opportunity to convert readily available phenol starting materials to carboxamide products by palladium catalyzed carbonylation. While the use of the aryl triflates worked well, we considered the eventual need to conduct this chemistry on significantly larger scales and therefore the need to reduce the costs and environmental impact of this transformation. While triflates are useful, the trifluoromethanesulfonic anhydride from which they are prepared is relatively expensive, and the triflate ion may not necessarily be benign.[3] We therefore considered the possibility of palladium catalyzed carbonylation of aryl tosylates to provide the desired amide products. Tosylates are often crystalline, exceptionally inexpensive, reasonably stable and simple to isolate, and the tosylate ion has long been recognized as nontoxic. Aryl and heteroaryl tosylates would also be desirable starting materials as they would be expected to be less sensitive to moisture and nucleophiles than the corresponding triflates. However, we recognized that the carbonylation of tosylates to amides could also be quite difficult. The tosylates would be expected to undergo oxidative addition to palladium(0) much less easily than the similar triflates,[4] and the rapid aminolysis of the aryl tosylate in the reaction mixture to provide the starting phenol and the amine toluenesulfonamide had to be considered as a potentially serious side reaction.[5]

We were encouraged by the recent successful development of conditions to effect the alkoxycarbonylation of aryl and heteroaryl tosylates to afford esters.[6] Recently, the palladium catalyzed alkoxy- and aminocarbonylation of vinyl tosylates under high pressure (100 psig) was reported; these reactions performed best with the Skewphos ligand.[7] There is only one literature example of aminocarbonylation with an aryl tosylate.[8] This reaction was performed under rather forcing conditions of temperature and pressure (dioxane at 180 °C) using microwave heating and molybdenum hexacarbonyl as the source of carbon monoxide. Nevertheless, this single example offered encouragement that more generally useful conditions for the aminocarbonylation of aryl and heteroaryl tosylates might be identified.

A high throughput screen was conducted in a CAT-96 gas handling device to identify possible conditions that might be of promise.[9] This screen examined 60 possible combinations of five solvents and 12 phosphine ligands in combination with carbon monoxide, palladium acetate, *tert*-butylamine, and Hunig's base to effect the transformation of **1** to **2** (see Supporting Information). The selection of *tert*-butylamine was motivated by its compatibility with the high throughput screening technique, as well as by our ability to transform the resulting *tert*-butyl amide **2** efficiently to either a primary amide or a nitrile.[10,11] A large excess (25 equiv) of *tert*-butylamine was selected for initial screening to maximize the potential for product formation as well as the potential for unwanted tosylate aminolysis in any particular screening reaction. The initial reaction screen was performed at a low concentration of **1** (0.01 M) and relatively high temperature (120 °C) and pressure (130 psig). Product yields were estimated after an arbitrary 18 h

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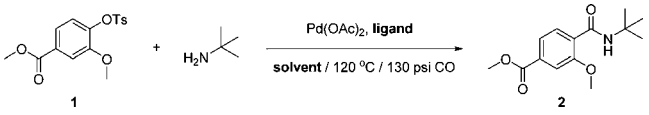
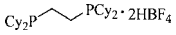
reaction time by the product UV area percent of a UPLC analysis of each reaction. Three conditions were identified which showed some promise; the remaining experiments failed to provide significant amounts of the desired product **2**. These conditions are excerpted in Table 1. Full results of this screen are given in the Supporting Information.

Table 1. Summary of Screening of Ligands and Solvents[a]



entry	solvent	ligand	yield[b] (%)
11	DMF	dcyhpe·2HBF$_4$[c]	30
21	MeCN	dcyppp·2HBF$_4$	21
22	MeCN	dcyppb·2HBF$_4$	15

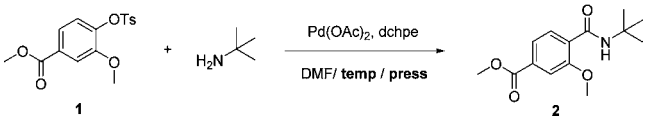
[a]For experimental details, see the Supporting Information. [b]As UV area percent of UPLC analysis of the reaction mixture. [c]dcyhpe·2HBF$_4$ =



Notably, the successful ligands were from the recently described, very electron rich bis(dicyclohexylphosphino)alkane family.[12] More well established bisphosphines such as dppp, dppf and BINAP, as well as monophosphines such as triphenylphosphine and tri(*tert*-butyl)phosphine, failed to return significant amounts of **2** under these conditions. Having identified the dcyhpe·2HBF$_4$/DMF conditions as the screening hit with the highest apparent conversion, we studied this reaction further, in particular to understand the effects of temperature and pressure on the reaction, with the goals of improving the reaction profile and yield of desired product, as well as of reducing the temperature and pressure to levels readily accommodated by the laboratory equipment most commonly available in organic chemistry laboratories. For this second round of reaction screening experiments, the reactions were conducted in an Endeavor reactor at 0.1 M concentration. Catalyst loading was maintained at 6 mol percent while *tert*-butylamine was reduced to 20 equiv. As in the initial screen, product yields were estimated after an arbitrary 18 h reaction time by the product area percent of a GCMS analysis of each reaction (Table 2).

This work showed that the carbon monoxide pressure could be reduced to 60 psi without detriment, allowing the reaction to be run without need for specialized autoclave equipment. Notably, a reduction in the reaction temperature appeared to be beneficial

Table 2. Screen of Temperature and Pressure



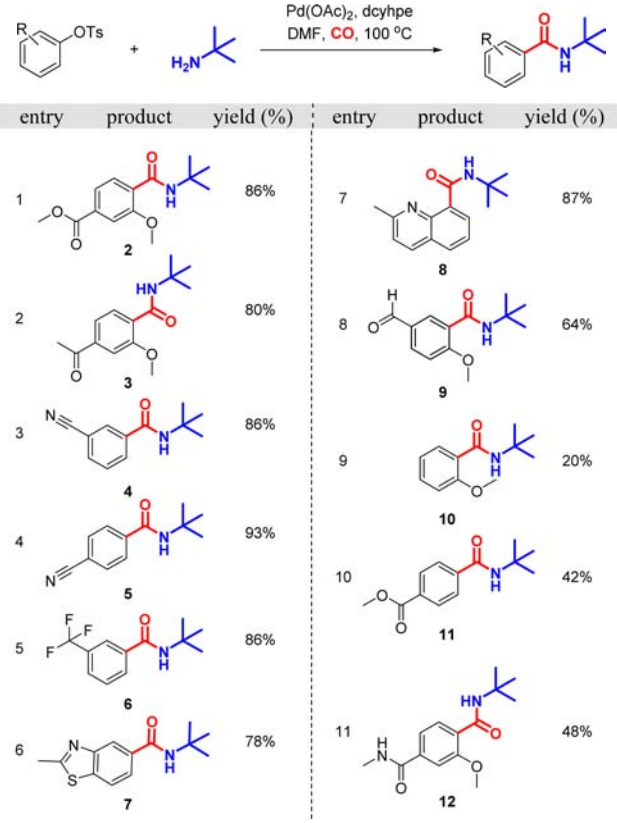
entry	temp (°C)	pressure (psi)	yield[a] (%)
1	120	100	74
2	120	60	65
3	100	60	>90
4	80	15	49
5[b]	100	60	>90
6[c]	100	60	47

[a]As area percent of GCMS analysis of the reaction mixture. [b]3% catalyst. [c]1% catalyst.

(entry 3), resulting in the complete consumption of the starting material and a cleaner overall reaction profile. Further simultaneous reduction of the reaction temperature and pressure resulted in diminished conversion of the starting material (entry 4). Remarkably, no aminolysis of the phenol tosylate was observed, indicating that this potentially serious side reaction failed to proceed at a significant rate. The catalyst loading was reduced to 3% without change in the reaction profile (entry 5). Further reduction of the catalyst loading to 1% resulted in diminished conversion of the starting material (entry 6). As expected, a negative control experiment performed under a nitrogen atmosphere returned only starting material. Following this second round of reaction screening, we conducted a preparative experiment on a 5 mmol scale at 0.2 M concentration, keeping the other parameters (solvent, temperature, pressure, catalyst loading) the same as entry 3 of Table 2. Under these conditions, compound **2** was returned in 86% purified yield. Having found efficient conditions for the preparation of **2** from the readily available aryl tosylate **1**, we examined the extension of this method to other aryl tosylate substrates (Table 3), including several that had previously been included in reports dealing with palladium−catalyzed alkoxycarbonylation.[13]

We found that aryl tosylates substituted with electron withdrawing groups were converted to the corresponding amides in good yields (entries 1−5). Heterobicyclic substrates likewise worked well (entries 6, 7). An aldehyde was well tolerated despite the use of a large excess of primary amine, and

Table 3. Evaluation of Aryl Tosylate Substrate Scope[a]



[a]All reactions were conducted with Pd(OAc)$_2$ (6%), dcyhpe·2HBF$_4$ (6%), and 20 equiv of *tert*-BuNH$_2$ in DMF at 100 °C under 60 psig of CO. [b]Isolated yields of purified products.

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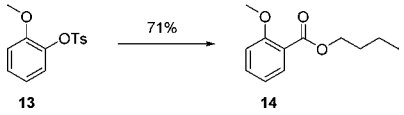
no byproducts resulting from imine formation were observed (entry 8). Aryl tosylates lacking electron withdrawing groups or an *ortho*-directing methoxy group were not fully converted to corresponding amides (entries 9−11).[14] In these cases the reactions appeared to be stalled after 18 h and extension of the reaction time up to 48 h did not result in further progression. In no case were the products of aryl tosylate aminolysis (the parent phenol or N-*tert*-butyl 4-toluenesulfonamide) observed. Further work was carried out using 2-methoxyphenyl tosylate (**13**) to understand why those substrates lacking electron withdrawing groups failed to proceed to completion. The substitution of DMA for DMF in the reaction mixture resulted in no substantial improvement in yield of the carbonylation product, suggesting that reduction of **13** to anisole was not the problem.[15] However, the substitution of 1-butanol for *tert*-butylamine resulted in a 71% isolated yield of the expected butyl ester.[16] (Scheme 1)

Scheme 1. Carbonylation of 2-Methoxyphenyl Tosylate to *n*-Butyl Ester



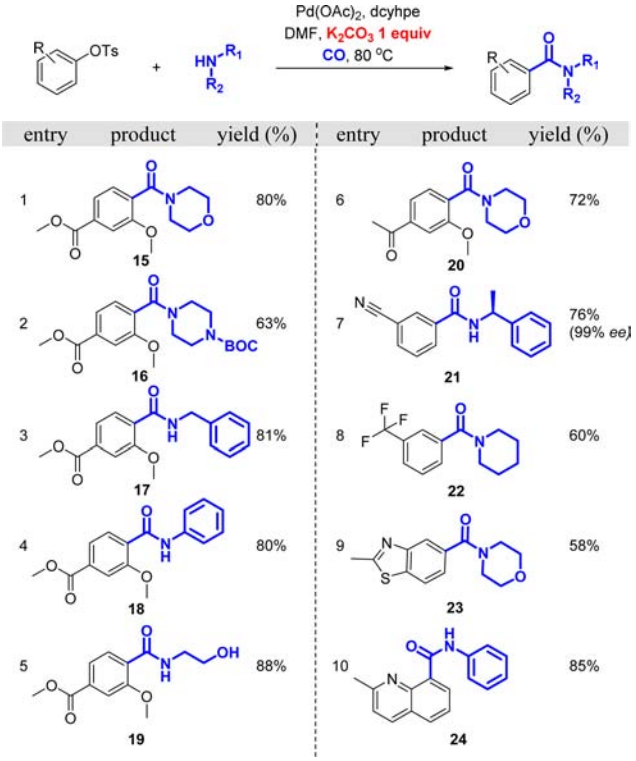
This result showed that the catalyst was competent to undergo oxidative addition to 2-methoxyphenyl tosylate (**13**), and the subsequent carbonylation and reductive elimination steps proceeded as expected. We postulate that the poor conversion of substrates such as **13** is likely due to deactivation of the catalyst by the amine present in the mixture, through formation of a palladium(II) amine complex that is not catalytically competent. For those substrates that undergo oxidative addition rapidly, such as **1**, significant formation of the amide product can occur before the catalyst is consumed. To test this hypothesis, tosylate **13** was subjected to carbonylation in the presence of aniline, which would be expected to coordinate palladium at a slower rate than *tert*-butylamine. The expected anilide was obtained in 40% isolated yield, as opposed to the 20% yield obtained with *tert*-butylamine. The addition of LiBr as a supporting ligand to stabilize the palladium[17] was deleterious and resulted in the failure of **13** to afford any carbonylation product.

Additionally, we sought to modify the reactions conditions to permit the use of more structurally diverse amines (Table 4). For these transformations, we decreased the amine component to two equivalents and incorporated one equivalent of potassium carbonate. The addition of potassium carbonate increased reaction yields relative to the same reactions conducted without potassium carbonate, and the reaction temperature could be reduced to 80 °C. The transformation under these conditions worked well to provide good yields of the expected amide products with a variety of amines, including relatively weakly basic amines such as morpholine, aniline, and ethanolamine (entries 1−6).

The reaction with ethanolamine showed no evidence of formation of the ester or bis-acylated products. A chiral amine worked well, and the product was obtained without epimerization (entry 7), showing that palladium(II) oxidation of the amine to an imine was not a competing side reaction.

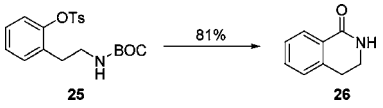
Lastly, an intramolecular reaction (Scheme 2) showed that the expected cyclization occurred with concomitant cleavage of the BOC group following cyclization.[18,19]

Table 4. Evaluation of Amine Substrate Scope[a]



[a]All reactions were conducted with $Pd(OAc)_2$ (3%), dcyhpe·2HBF$_4$ (4%) with 2 equiv of amine and 1 equiv of K_2CO_3 in DMF at 80 °C under 60 psig of CO. [b]Isolated yields of purified products.

Scheme 2. Intramolecular Aminocarbonylation



In this case, there was no additional free amine present in the reaction mixture. This result also supports our postulate that the catalyst is entirely competent to effect carbonylation of substrates lacking electron withdrawing groups, and that the low conversion observed with substrates such as **13** is likely due to deactivation of the catalyst by the amine in the reaction mixture.

In summary, we report for the first time the aminocarbonylation of aryl tosylates to afford amides. Competitive aminolysis of the aryl tosylates was not observed. The reaction proceeded well with aryl tosylates bearing electron withdrawing substituents, presumably due to rapid oxidative addition of Pd(0) under the reaction conditions. Aryl tosylates lacking electron withdrawing groups and/or an *ortho*-directing alkoxy group were not fully converted to the corresponding amides. In these cases it appears that the rate of oxidative addition of Pd(0) to the aryl tosylate proceeded more slowly, permitting a competitive pathway involving catalyst deactivation by the amine to become more significant. A variety of amines were tolerated and performed well, including less basic amines such as aniline and morpholine.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds. The Supporting Information is available free of

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: seungwon.chung@pfizer.com.
*E-mail: stephen.w.wright@pfizer.com.

Notes

The authors declare no competing financial interest.

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(12) These ligands are commercially available as their HBF_4 salts. We found that these ligands purchased as the free phosphines were of unreliable purity.

(13) See ref 6a.

(14) The following substrates failed to afford significant amounts (>10% by UPLC) of the desired carbonylation product under these conditions: 4-methoxyphenyl tosylate, 2,4-dimethylphenyl tosylate, and pyridin-3-yl tosylate.

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