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Cross-Coupling

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# Aryl Formate as Bifunctional Reagent: Applications in Palladium-Catalyzed Carbonylative Coupling Reactions Using In Situ Generated CO**

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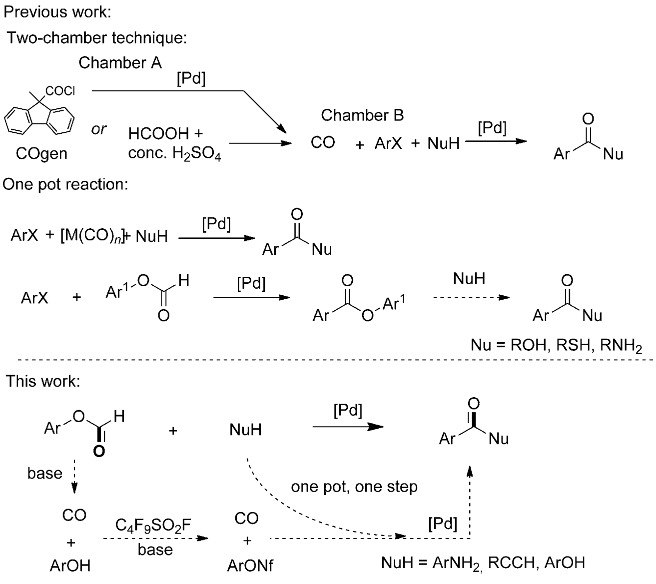
***Abstract:*** *After decades of development, carbonylation reactions have become one of the most powerful tools in modern organic synthesis. However, the requirement of CO gas limits the applications of such reactions. Reported herein is a versatile and practical protocol for carbonylative reactions which rely on the cooperation of phenyl formate and nonaflate, and the generation of CO in situ. This protocol has a high functional-group tolerance and could be applied in carbonylations with C, N, and, O nucleophiles. The corresponding amides, alkynones, furanones, and aryl benzoates were synthesized in good yields.*



***Scheme 1.*** Comparison of the prior work to the current work.

Ever since the pioneering work of Heck and Schoenberg in 1974, palladium-catalyzed carbonylative transformations of aryl halides have undergone impressive developments.[1] It has now constituted one of the most efficient and widely used methodologies for constructing carbonyl-containing compounds, such as aldehydes, amides, esters, etc.[2] However, the high toxicity, and odorless and flammable character of CO gas means that transformations using CO gas must be operated with special care. Usually, autoclaves and well-ventilated fume hoods, equipped with special CO detectors and alarms, are required for these reactions, and has actually hindered the applications of such reactions.

Given the disadvantages of using gaseous CO "CO-free" carbonylation reactions have attracted a lot of attention over the last three decades.[2b,3] To generate CO and consume CO in a closed system, a two-chamber technique was recently developed by Skrydstrup and co-workers. By using this technique, 9-methylfluorene-9-carbonyl chloride (COgen) was developed to generate CO gas with the assistance of a palladium catalyst (Scheme 1). And it was also reported to be suitable for $^{13}$C-isotope labeling.[4] Notably, formic acid was also developed to generate CO through a dehydration reaction in sulfuric acid at elevated temperatures (Morgan reaction).[4b] In contrast, the in situ generation of CO from metal carbonyl complexes was proven to be compatible with a number of carbonylation reactions, both for one-pot transformations and the two-chamber technique.[5] Remarkably, alkyl formate was developed for the alkoxycarbonylation of olefins and aryl halides as well. Compared to alkyl formate, aryl formate was reported to generate CO in the presence of base under much milder reaction conditions.[6] The groups of Manabe[7] and Tsuji[8] independently reported the esterification of aryl halides using aryl formates. Also, the synthesis of amides, alkyl esters, amides, and thioesters can be achieved by a two-step process using 2,4,6-trichlorophenyl formate[7c] as a reactive intermediate. However, because of the fact that phenol could also acts as a strong nucleophile in the reaction, the choice of direct carbonylative coupling partners, such as amines, alkynes, alkenes, was limited.

Hydroxy groups are very useful functional groups and they are frequently converted into sulfonates, such as trifluorosulfonate (OTf), and subjected to a variety of additional transformations because of their leaving ability.[9] More recently, nonafluorobutanesulfonyl fluoride (NfF), has become a more attractive sulfonylating reagent because of its stability, reactivity, and availability.[10] Actually, it is now produced on the industrial scale by anodic fluorination of a cyclic sulfolene precursor.[11] In 2012, our group reported the palladium carbonylative synthesis of esters and amides starting from the in situ generated nonaflate under low pressure of carbon monoxide (1 bar).[12] With our continuous interest in developing carbonylation reactions, our initial idea

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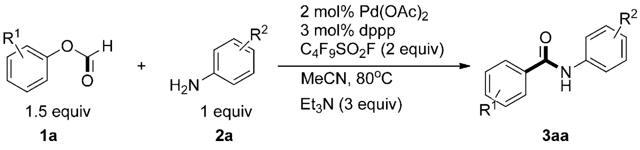
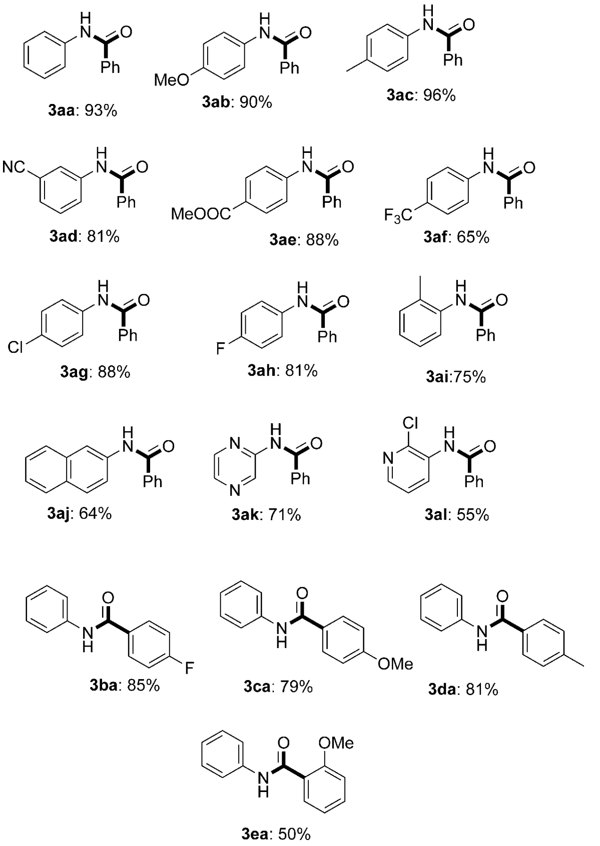
was to transform the in situ generated phenol into the aryl nonaflate, which could further act as a pseudohalide. The in situ generated CO accompanied by a nucleophile, thus furnishes carbonylation reactions without the need for external CO (Scheme 1).

We started our investigations using the following reaction conditions: aniline (0.5 mmol, 1 equiv), phenyl formate (0.5 mmol, 1 equiv), FNf (0.5 mmol, 1 equiv), with 2 mol% of $Pd(OAc)_2$, 6 mol% of $BuPAd_2$, and with 3 equivalents of $Et_3N$ as a base in MeCN at 80°C for 24 hours. Surprisingly, 22% of benzanilide was observed and phenyl benzoate and phenylnonaflate were observed as by products. Subsequently, we tested various ligands (dppe, dppp, dppb, $PPh_3$, etc.) and bases, and also varied the amounts of phenyl formate and nonafluorosulfonyl fluoride used (see the Supporting Information). We identified the optimized reaction conditions to be include dppp (3 mol%) as the ligand, $Pd(OAc)_2$ (2 mol%) as the catalyst, with 1.5 equivalents of phenyl formate and 2 equivalents of FNf, which acts as the pseudohalide and as well as the CO source, and the desired benzanilide was formed in 93% yield in the presence of 1 equivalent of aniline.

With the best reaction conditions, different anilines were subjected to the reaction (Table 1). Anilines bearing electron-donating groups, such as anisidine and toluidine, resulted in excellent yields (90% and 96%, respectively). Also, many anilines bearing electron-withdrawing groups, such as the cyano, carboxylate group, chloro, and fluoro group, gave good yields of the corresponding amides (81–88%). Even the trifluoromethyl group, which is a strong electron-withdrawing group, led to moderate yield of the desired amide upon isolation (65%). Additionally, to learn about the steric effect of aniline derivatives, *ortho*-toluidine was tested, and although the conversion was lower, 75% of the product was obtained upon isolation. Naphthyl amine was then tested and moderate yield was obtained (64%). More interestingly, the reaction works well with a heteroaromatic amine such as 2-aminopyrazine, and good yield was obtained (71%). Notably, in the case of 3-amino-2-chloropyridine, the corresponding amide was isolated in 55% yield and the chloro substituent on the pyridine ring remained intact, even though it is considered to be highly reactive under palladium catalysis. However, the use of aliphatic amines such as morpholine and octylamine was not successful and afforded only the formylation product of the corresponding amines. Moreover, to learn about the electronic effects as well as the steric effect of the phenyl formate on this reaction, different formates were tested in addition. Although *ortho*-methoxy-substituted phenyl formate gave lower yield (50%), the other aryl formates showed good reactivity towards the corresponding benzanilides.

***Table 1:*** Carbonylative synthesis of amides.[a,b]





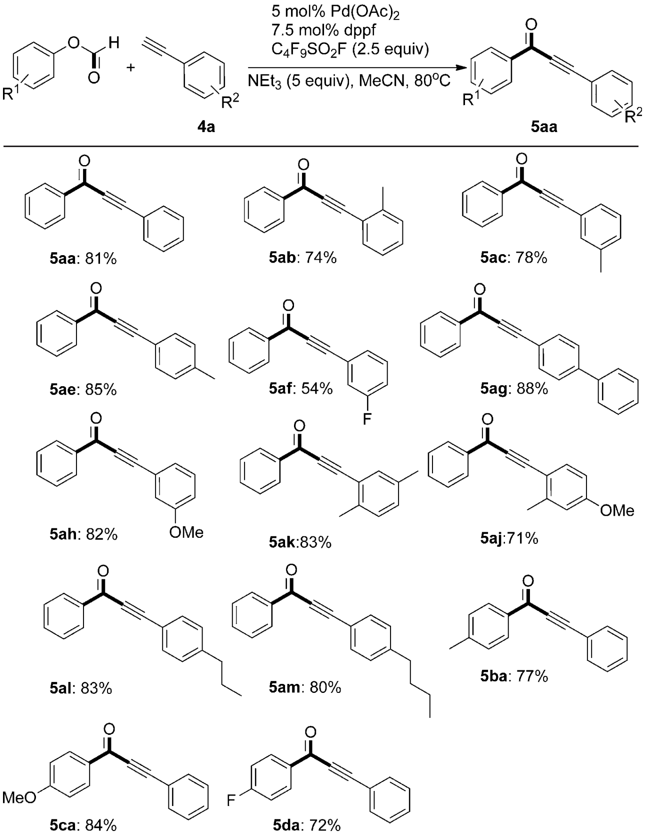
**3aa**: 93%
**3ab**: 90%
**3ac**: 96%
**3ad**: 81%
**3ae**: 88%
**3af**: 65%
**3ag**: 88%
**3ah**: 81%
**3ai**:75%
**3aj**: 64%
**3ak**: 71%
**3al**: 55%
**3ba**: 85%
**3ca**: 79%
**3da**: 81%
**3ea**: 50%

[a] Reaction conditions: Aniline (0.5 mmol), phenyl formate (0.75 mmol), $C_4F_9SO_2F$ (2 equiv), $Pd(OAc)_2$ (2 mol%), dppp (3 mol%), $Et_3N$ (3 equiv), $CH_3CN$ (2 mL) in a 12 mL sealed vial, 80°C, 16 h.
[b] Yields of isolated products. dppp = 1,3-bis(diphenylphosphanyl)propane.

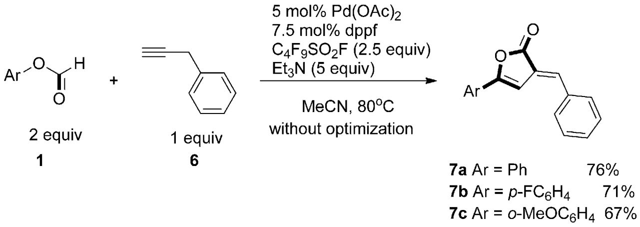
1,3-Ynones moieties are known as versatile substrates for natural product synthesis.[13] With this in mind, it would be interesting to synthesize these molecules under CO-free conditions. During the course of our reaction optimization (see Table S2 in the Supporting Information), we found that when the scale of the reaction was increased to 1 mmol, a higher pressure of generated CO was necessary to facilitate the reaction. After optimization [$Pd(OAc)_2$ (5 mol%), dppf (7.5 mol%), $Et_3N$ (5 equiv), phenyl formate (2 equiv), NfF (2.5 equiv), phenylacetylene (1 equiv, 1 mmol) at 80°C for 16 h] good yield of the desired alkynone was obtained (81%; Table 2). The the scope of this transformation was then investigated, and moderate to good yields were obtained with different substituted phenylacetylenes and aryl formats under identical reaction conditions (54–88%).

Furanones represent an important family of organic compounds in natural products and bioactive derivatives. Our previous work has shown that by using a carbonylative reaction, furanones can be synthesized under palladium-catalyzed coupling reactions.[14] Surprisingly, when prop-2-yn-1-ylbenzene (**6**) was subjected to the reaction conditions, the furanone **7a** was obtained selectively with a moderate yield (76%; Scheme 2). Other phenyl formates, such as *para*-fluorophenyl formate and even the sterically hindered *ortho*-methoxy phenyl formate, were tested without further optimization and gave the desired furanones in 67–71% yields upon isolation. This reaction represents the first carbonylative synthesis of furanones in a CO-free manner.

***Table 2:*** Carbonylative synthesis of alkynone without external CO.[a,b]

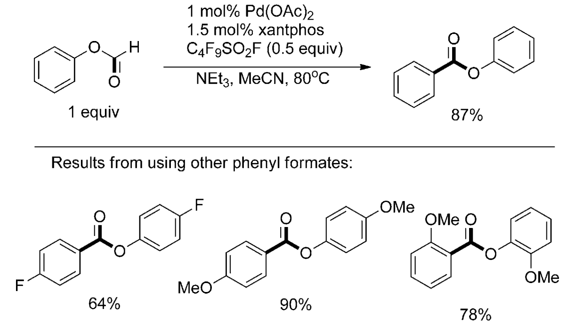


[a] Reaction conditions: Phenylacetylene (1 mmol), phenyl formate (2 mmol), $C_4F_9SO_2F$ (2.5 equiv), $Pd(OAc)_2$ (5 mol%), dppf (7.5 mol%), $Et_3N$ (5 equiv), $CH_3CN$ (5 mL) in a 12 mL sealed vial, 80 °C, 16 h.
[b] Yields of isolated products. dppf = 1,1′-bis(diphenylphosphino)ferrocene.



***Scheme 2.*** Palladium-catalyzed carbonylative synthesis of furanone without external CO.

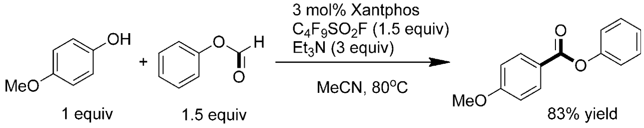
Based on our previous experience with the alkoxycarbonylation of phenols to give esters using in situ formed aryl nonaflates with 1 bar of external CO gas, we further extended our methodology to ester synthesis in the absence of external CO gas and using phenyl formate as the only substrate (Scheme 3). By using $Pd(OAc)_2$ (1 mol%), Xantphos (1.5 mol%), NfF (0.5 equiv), and phenyl formate (1 equiv) in acetonitrile at 80 °C, phenyl benzoate was produced in 87% yield. With other phenyl formates ($p$-F, $p$-OMe, and $o$-OMe), yields from 64 to 90% were obtained.



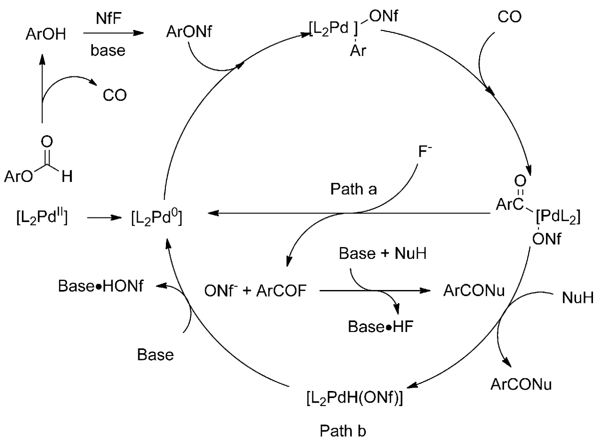
***Scheme 3.*** Palladium-catalyzed synthesis of symmetrical phenyl benzoate derivatives without external CO. Reaction conditions: Phenyl formate (1 mmol), $C_4F_9SO_2F$ (0.5 equiv), $Pd(OAc)_2$ (1 mol%), Xantphos (1.5 mol%), $Et_3N$ (1.5 equiv), $CH_3CN$ (2 mL) in a 12 mL sealed vial, 80 °C, 16 h. Yields are those of the isolated products. Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

Notably, in addition to the above-mentioned symmetrical aryl benzoates, unsymmetrical phenyl benzoates can be produced by our procedure as well. Phenyl 4-methoxybenzoate was isolated in 83% yield from phenyl formate and $p$-methoxyphenol in a one-pot manner without further optimization (Scheme 4).

With respect to the reaction mechanism, as shown in Scheme 5, the aryl formate decomposes to generate one molecule of CO and phenol which will further react with perfluorobutanesulfonyl fluoride to generate aryl nonaflate (ArONf). Palladium acetate is reduced to $Pd^0$ and starts the catalytic cycle.[15] Subsequently, nonaflate will act as a pseudohalide and undergo oxidative addition with $Pd^0$. After the



***Scheme 4.*** Palladium-catalyzed synthesis of unsymmetrical phenyl benzoates without external CO. Reaction conditions: $p$-methoxyphenol (0.5 mmol, 1 equiv), phenylformate (0.75 mmol), $C_4F_9SO_2F$ (1.5 equiv), $Pd(OAc)_2$ (2 mol%), Xantphos (3 mol%), $Et_3N$ (3 equiv), $CH_3CN$ (2 mL) in a 12 mL sealed vial, 80 °C, 16 h. Yields are those of isolated products.



***Scheme 5.*** Proposed reaction mechanism.

coordination and insertion of the in situ generated CO, an acyl palladium complex is generated as the key intermediate. Subsequently, two possible pathways to generate the target molecule could be considered. According to our analysis of the final reaction mixture, benzoyl fluoride derivatives were observed by GC-MS. A significant amount of benzoyl fluoride was observed especially when the benzene ring was bearing donating substituents. The generation of benzoyl fluoride can be explained by the nucleophilic attack of the fluoride ion on the electron poor carbonyl on the acyl palladium intermediate.[16] In this case $Pd^0$ can be regenerated by the decoordination of nonaflate on the palladium center (Path a). The generated benzoyl fluoride can further react with nucleophiles and produce the final product with the help of a base.[7a] Another possible pathway is go through the traditional carbonylative coupling pathway which proceeds by the nucleophilic attack of the nucleophile onto the acyl palladium intermediate and regeneration of $Pd^0$ with a base (Path b).

In summary, carbonylative coupling reactions using aryl formates as the CO source and pseudohalide precursors have been developed. No external carbon monoxide gas was required. The corresponding amides, alkynones, furanones, and phenyl benzoates were synthesized in good yields upon reaction with amines, alkynes and phenols, respectively. The development of this protocol with other nucleophiles and detailed mechanistic studies are underway in our group.

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**Keywords:** carbon monoxide · carbonylation · cross-coupling · homogeneous catalysis · palladium

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