Priority Communication

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Palladium-Catalyzed Carbonylative Transformation of Phenols *via* In-Situ Triflyl Exchangement

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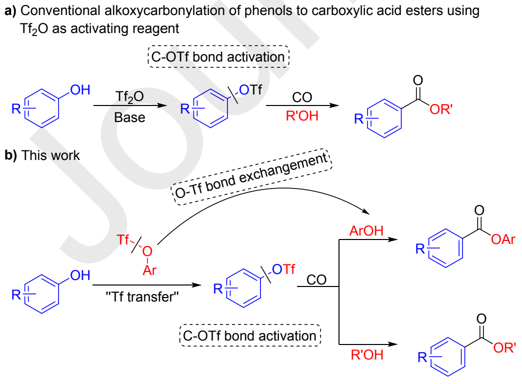
ABSTRACT: Phenols are attractive starting materials due to their ready availability. Herein, we developed a novel method on palladium-catalyzed alkoxycarbonylation of phenols. By using commercially available $Pd(OAc)_2$ and P*t*Bu_3•HBF_4 as the catalyst system and aryl triflates as triflyl source to activate the other phenol, various carboxylic acid esters were prepared in moderate to good yields via Tf exchange and then O-Tf bond cleavage. Notably, phenols generated from aryl triflates after Tf transfer or other additional aliphatic alcohols can all be employed as nucleophiles to synthesize the corresponding esters.

Keywords: aryl triflates • carbonylation • palladium catalyst • Tf transfer • carboxylic acid esters

Esters are present in a range of pharmaceuticals, polymers, agrochemicals, natural products, and biological systems and they have also been applied as versatile building blocks in organic synthesis.[1] Due to their important applications, many efficient methodologies have been developed for the construction of carboxylic acid esters, such as esterification of carboxylic acids or activated analogues with alcohols.[2] On the other hand, carbonylation is one of the most powerful and straightforward method for the direct synthesis of carbonyl-containing compounds from the point of view of atom and step economy. Since the seminal work by Heck and co-workers in 1974,[3,4] palladium-catalyzed carbonylation of aryl halides with alcohols by using carbon monoxide (CO) as an inexpensive and readily available C1 source has become an efficient and straightforward method for the synthesis of carboxylic acid esters.

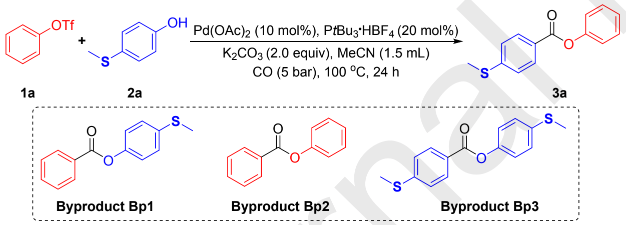


Scheme 1. Methods for alkoxycarbonylation of phenols.

Phenols are widely present in numerous compounds. Additionally, as an important industrial commodity, phenols are produced on the scale of millions of tons per year from fuel and biomass.[5] Concerning the synthetic applications, one of the most popular pathway is reacting phenols with trifluoromethanesulfonic anhydride (Tf_2O) to give aryl triflates (ArOTf) which are outstanding electrophiles in various organic transformations.[6] In comparation, aryl triflates are also good alternatives to aryl halides in alkoxycarbonylation for the synthesize of esters (Scheme 1a).[7] The advantages are obvious, including 1) readily and wide availabilities of phenols; 2) aryl triflates are stable and easy to storage; 3) aryl triflates are easy to be activated in reactions and so on. However, the aryl triflates used usually need to be pre-prepared from trifluoromethanesulfonic anhydride (Tf_2O) and phenols which certainly increased the number of manipulation steps and costs and also limited certain functional groups. Herein, we developed a novel method for the palladium-catalyzed alkoxycarbonylation of phenols to esters with in-situ triflate exchanging as one of the key steps (Scheme 1b).[8] More specifically, triflate (Tf^-) is transferred from aryl triflates to other phenols to form a new aryl triflates, which undergo palladium-catalyzed carbonylation to produce the desired products. The features of this new procedure including: 1) using commercially available $Pd(OAc)_2$ and P*t*Bu_3•HBF_4 as a convenient catalyst system; 2) stable aryl triflates severing as Tf sources to activate the other phenols which avoid preparation steps; 3) phenols generated after aryl triflates after Tf transfer or other additional added alcohols can be employed as nucleophiles to synthesize the corresponding carboxylic acid esters.

We started our studies by using phenyl triflate (**1a**) and 4-(methylthio)phenol (**2a**) as the substrates, in the presence of commercially available $Pd(OAc)_2$ as the catalyst and P*t*Bu_3•HBF_4 as the ligand, the alkoxycarbonylation reaction was carried out under 5 bar of CO using 2.0 equiv of K_2CO_3 as the base in 1.5 mL of MeCN at 100°C for 24 h. To our delight, the desired product phenyl 4-(methylthio)benzoate **3a** was formed in 24% yield (Table 1, entry1). Meanwhile, byproducts **Bp1**, **Bp2** and **Bp3** were produced as well and 20% yield of byproduct 4-(methylthio)phenyl 4-(methylthio)benzoate **Bp3** was detected. As we expected, no desired product was determined in the absence of palladium catalyst and phosphine ligand (Table 1, entry 2). To further improve the yield of the desired product **3a**, a series of optimizations were performed, and the results are summarized in Table 1. Several bases (Na_2CO_3, $NaHCO_3$, Cs_2CO_3, DBU and CsF) and ligands (PPh_3 and PCy_3) were screened, no better yields were obtained (Table 1, entries 3-6). A series of solvents were also screened subsequently, no desired product was detected when toluene, THF, 1,4-dioxane, DMSO or NMP was used as the solvent (Table 1, entries 7-10). When toluene or THT was employed as the solvent, phenyl triflate **1a** is easier to be directly carbonylated with 4-(methylthio)phenol **2a** without undergoing Tf transfer process and produced a large amount of byproduct **1** 4-(methylthio)phenyl benzoate (Table 1, entries 8 and 9). By employing DMAc as the solvent, the yield of **3a** was improved slightly and no or traces of the other byproducts were detected (Table 1, entry 11). The effects of the reaction temperature and CO gas pressure were also tested (Table 1, entries 12-15). By using DMAc as the solvent, 53% yield of the target product was obtained when the reaction was performed under 3 bar of CO at 90 °C (Table 1, entry 15). By extending the reaction time, the yield of **3a** can be further improved. The reaction can give the best yield (68%) of **3a** and a 60% isolated yield when the reaction was carried out for 48 hours (Table 1, entry 16). Furthermore, the loading of palladium catalyst and ligand were studied as well, no better yields were obtained. (Table 1, entries 17 and 18). After systematic studies, the optimal conditions were established as $Pd(OAc)_2$ (10 mol %), $PtBu_3$•HBF_4 (20 mol %), K_2CO_3 (2.0 equiv), CO (3 bar) in DMAc (1.5 mL) at 90 °C for 48 h (Table 1, entry 16).

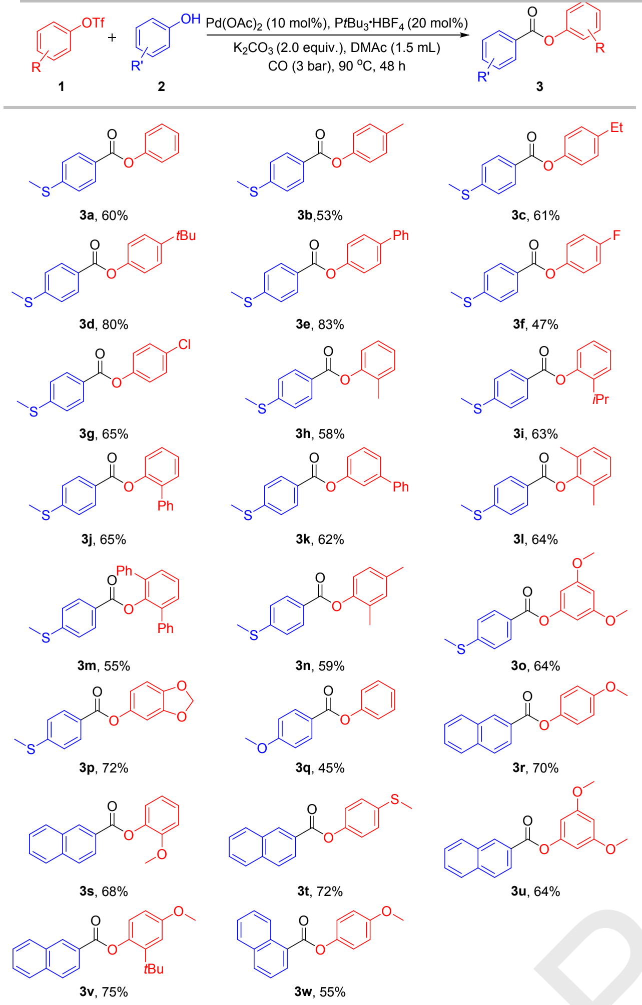
Table 1. Optimization of reaction conditions.[a]



Entry	Variations from the standard conditions	Yield[b] (%)
1	----	**3a**: 24%; **Bp3**: 20%
2	without catalyst/ligand	**3a**: n.d
3	Na_2CO_3, $NaHCO_3$ or Cs_2CO_3 instead of K_2CO_3	**3a**: trace
4	DBU instead of K_2CO_3	**3a**: 12%
5	CsF instead of K_2CO_3	**3a**: 22%
6	PPh_3 or PCy_3 instead of $PtBu_3$·HBF_4	**3a**: trace
7	DMF instead of MeCN	**3a**: 19%
8	Toluene instead of MeCN	**3a**: n.d; **Bp1**: 36%
9	THF instead of MeCN	**3a**: n.d; **Bp1**: 48%
10	1,4-Dioxane, DMSO or NMP instead of MeCN	**3a**: n.d
11	DMAc instead of MeCN	**3a**: 29%
12	DMAc instead of MeCN, 3 bar CO	**3a**: 40%; **Bp3**: 12%
13	DMAc instead of MeCN, 1 bar CO	**3a**: 12%
14	DMAc instead of MeCN, 3 bar CO, 80 °C	**3a**: 35%
15	DMAc instead of MeCN, 3 bar CO, 90 °C	**3a**: 53%
16	DMAc instead of MeCN, 3 bar CO, 90 °C, 48 h	**3a**: 68% (60%)
17	5 mol% of $Pd(OAc)_2$, 10 mol% of $PtBu_3$·HBF_4, DMAc instead of MeCN	**3a**: trace
18	15 mol% of $Pd(OAc)_2$, 30 mol% of $PtBu_3$·HBF_4, DMAc instead of MeCN	**3a**: 40%

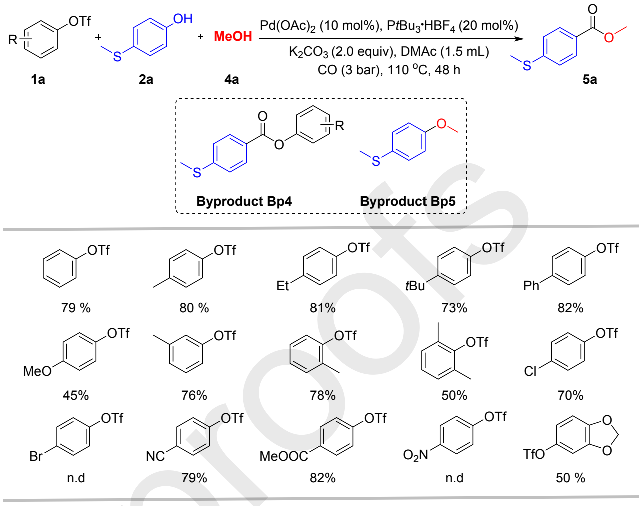
[a] Reaction conditions: phenyl triflate **1a** (0.3 mmol), 4-(methylthio)phenol **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $PtBu_3$·HBF_4 (20 mol %), K_2CO_3 (0.4 mmol), CO (5 bar), MeCN (1.5 mL), 100 °C, 24 h. Abbreviations used in this table: n.d. = not detected, Byproduct = Bp, DMAc = *N*,*N*-Dimethylacetamide. [b] As determined by gas chromatography (GC), using hexadecane as the internal standard.

With the optimized reaction conditions in hand, the scope of various aryl triflates **1** with different phenols **2** were examined (Scheme 2). The *para*-position of aryl triflates with electron-rich groups such as Me, Et, *t*Bu, Ph can deliver the corresponding products (**3b-3e**) in moderate to good yields (53-83%). Aryl triflates containing electron-deficient groups such as F, Cl at the *para* position can also afford corresponding products (**3f, 3g**) in 47 and 65% yields, respectively. The *para*-position of aryl triflates with CHO, Ac, COOMe were also tested, but unfortunately no desired product was detected. The possible reason may be that the strong electron-deficient phenols generated from aryl triflates after Tf transfer have low nucleophilic activity, which is not conducive for the carbonylation process. Aryl triflates with *ortho*/*meta*-substitution can be successfully applied in this reaction as well and gave the corresponding products in 58-65% yields (**3h-3k**). We also tested disubstituted aryl triflates as the substrates and resulting 55-85% yields of the corresponding esters (**3l-3o**). Notably, benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate was also successfully transformed into the product **3p** in 72 % yield. Subsequently, the scope of phenols was considered, *p*-methoxyphenol and naphthol can participate in the desired alkoxycarbonylation reaction and 45%-75% yields of the corresponding esters (**3q-3w**) were obtained. Some other phenols such as phenol, *p*-cresol, *p*-chlorophenol were tested as well, but unfortunately low yields of the desired products were detected, and a large amount of byproducts were produced. Hence, in this system, the Tf transfer step is the most important step and driven by relatively basic phenol derivative.

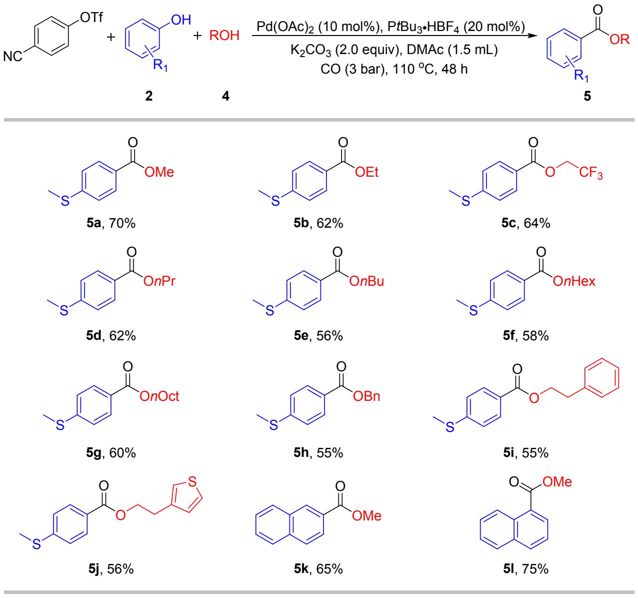


Scheme 2. Substrate scope of aryl triflates and phenols. Reaction conditions: all reactions were carried out with 0.2 mmol of phenyl triflates **1** (1.5 equiv), phenols **2** (1.0 equiv), $Pd(OAc)_2$ (10 mol %), P*t*Bu_3·HBF_4 (20 mol %), K_2CO_3 (2.0 equiv), CO (3 bar), DMAc (1.5 mL), 90 °C, 48 h.

Delightfully, we find this method was also applicable to the synthesis of carboxylic acid esters when other additional aliphatic alcohol was added as a new nucleophile. Under the condition of $Pd(OAc)_2$ (10 mol %), P*t*Bu_3·HBF_4 (20 mol %), K_2CO_3 (2.0 equiv), CO (3 bar), DMAc (1.5 mL), 110 °C, 48 h, the alkoxycarbonylation reaction of 4-(methylthio)phenol **1a** with methanol (MeOH) using phenyl triflate as Tf source proceeded well and the corresponding carboxylic acid ester methyl 4-(methylthio)benzoate **5a** was detected in 79 % GC yield; meanwhile, byproduct **Bp4** and **Bp5** were detected as well. Under these reaction conditions, the testing of various aryl triflates as the triflate exchanging reagents were examined subsequently (Scheme 3). It shows that both electron-rich (Me, Et, *t*Bu, Ph, OMe) and electron-deficient (Cl, CN, COOMe) substituted aryl triflates can be applied successfully and gave the desired product **5a** in moderate to good yields (45-82%). It is worth mentioning that we also tested 4-bromophenyl trifluoromethanesulfonate and 4-nitrophenyl trifluoromethanesulfonate as triflate exchanging reagents, but unfortunately no desired product was detected besides byproduct **Bp5**. It is worth mentioning that it is quite a challenge to purify the desired product due to the similar polarity of the desired product and byproduct **Bp4** when aryl triflates with R-substituted (R = Me, Et, *t*Bu, Ph, OMe, Cl, COOMe) were employed as the Tf source.

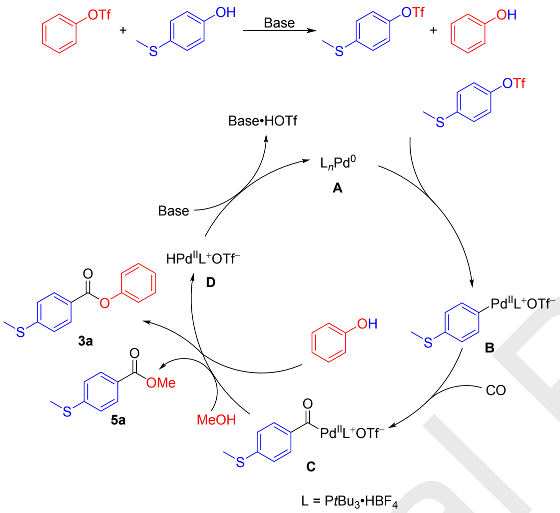


Scheme 3. Substrate scope of aryl triflate. Reaction conditions: all reactions were carried out with 0.2 mmol of phenyl triflates **1** (2.0 equiv), phenols **2** (1.0 equiv), MeOH (2.0 equiv), $Pd(OAc)_2$ (10 mol %), P*t*Bu_3·HBF_4 (20 mol %), K_2CO_3 (2.0 equiv), CO (3 bar), DMAc (1.5 mL), 110 °C, 48 h. The yield of 5a was determined by GC using hexadecane as an internal standard.



Scheme 4. Substrate scope of phenols and aliphatic alcohols. Reaction conditions: all reactions were carried out with 0.2 mmol of 4-cyanophenyl trifluoromethanesulfonate (2.0 equiv), phenols **2** (1.0 equiv), alcohols **4** (2.0 equiv), $Pd(OAc)_2$ (10 mol %), P*t*Bu_3·HBF_4 (20 mol %), K_2CO_3 (0.4 mmol), CO (3 bar), DMAc (1.5 mL), 110 °C, 48 h.

In order to overcome the challenge mentioned, 4-cyanophenyl trifluoromethanesulfonate was selected as the Tf source to active phenols. The alkoxycarbonylation reaction of 4-(methylthio)phenol **1a** or naphthol with different aliphatic alcohols were performed (Scheme 4). The tested alcohols, including ethanol, trifluoroethanol, propanol, butanol, hexanol, octanol, benzyl alcohol and 2-phenylethanol were all able to give the corresponding esters (**5b**-**5i**) in moderate yields (55-64%). Moreover, when 3-thiopheneethanol was used as a nucleophilic reagent, the reaction gave the corresponding product **5j** in 56% yield. Using 1-naphthol or 2-naphthol as the substrate instead of 4-(methylthio)phenol were also successfully employed in this alkoxycarbonylation reaction, and the corresponding products (**5k**, **5l**) were obtained in 75% and 55% yield, respectively. It is worth to mention that no desired product could be detected when isopropanol or *tert*-butanol was tested as the substrate.



Scheme 5. Proposed reaction mechanism.

On the basis of our experimental results and literatures,[4] a plausible reaction pathway is proposed for this alkoxycarbonylation of phenols (Scheme 5). Firstly, in the presence of K_2CO_3, phenyl triflate reacted with 4-(methylthio)phenol to produce 4-(methylthio)phenyl triflate and phenol via Tf transfer. Then, the newly formed 4-(methylthio)phenyl triflate reacts with L_nPd^0 species A to generate the oxidative addition complex $MeSPhLPd^{II}OTf$ B. Subsequently, coordination and insertion of CO with intermediate B forms the key intermediate acyl-palladium complex C. Nucleophilic attack of phenol or methanol on intermediate C will provide the target carboxylic acid ester 3a or 5a, together with the simultaneous formation of intermediate D. Under the assistance of base, intermediate D undergoes reductive elimination to regenerate the active Pd^0L_n species A for the next catalytic cycle.

In conclusion, a novel methodology for the palladium-catalyzed alkoxycarbonylation of phenols with aryl triflates as triflyl source has been developed. By using commercially available $Pd(OAc)_2$ and P*t*Bu$_3$•HBF$_4$ as the catalyst system, various aryl triflates and alcohols were tested and the corresponding esters were isolated in moderate to good yields. Notably, not only phenols generated from aryl triflates after Tf transfer, but also other additional aliphatic alcohols could be employed as nucleophiles to synthesize the corresponding carboxylic acid esters under these reaction conditions.

Notes

The authors declare no competing financial interest.

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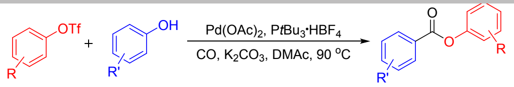
Graphic abstract:



Highlights

1. A novel methodology for the palladium-catalyzed alkoxycarbonylation of phenols with aryl triflates as triflate source has been developed.

2. Commercially available $Pd(OAc)_2$ and $PtBu_3 \cdot HBF_4$ has been used as the catalyst system.

3. Aryl triflates were explored as Tf transfer reagents and applied in carbonylation.