ORGANIC
LETTERS

2006
Vol. 8, No. 22
5161−5164

An Efficient Catalyst for Pd-Catalyzed Carbonylation of Aryl Arenesulfonates

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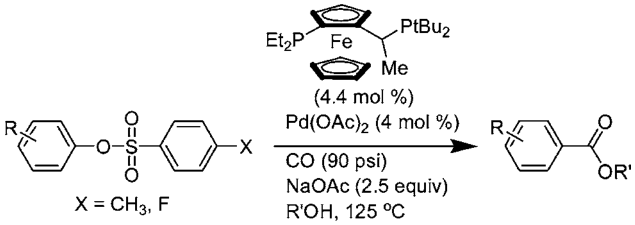
Received September 6, 2006

ABSTRACT



Aryl carboxylic esters were synthesized by Pd-catalyzed carbonylation of aryl *p*-fluorobenzenesulfonates or -tosylates. A unique Josiphos ligand was discovered through high-throughput catalyst screening, which was the key for the successful carbonylation of various substrates. This catalyst is effective and works well for both electron-rich and electron-poor aryl arenesulfonates. Isolated yields of up to 90% were obtained for aryl *p*-fluorobenzenesulfonates and -tosylates.

Palladium-catalyzed carbonylation of aryl and benzyl halides was pioneered by Heck and co-workers in the 1970s and is an important organometallic reaction to make aryl carboxylic acid derivatives.[1] Over the last three decades, remarkable progress has been made in this area.[2] The carbonylation substrates have been extended from the original aryl bromides, iodides, and benzyl chlorides to less reactive aryl chlorides and more reactive but less stable aryl triflates.[3] Generally, aryl chlorides are air-stable and cost-effective starting materials and therefore are preferred over the corresponding bromides, iodides, and triflates in industrial manufacturing processes. However, the carbonylation of aryl chlorides often requires harsh reaction conditions with reaction temperatures of 150 °C or above. The carbonylation of aryl triflates can proceed at milder temperatures such as 60∼120 °C, but they are much more expensive starting materials and are also prone to decomposition over a long period. Aryl arenesulfonates, such as aryl tosylates, are another family of synthetic equivalents that are cost effective and air stable and can be easily accessed from phenols and arenesulfonyl chlorides. Nevertheless, like aryl chlorides, they are difficult substrates to carbonylate. To the best of our knowledge, only one precedent was reported by Kubota et al.[4] where 4-acetylphenyl tosylate was satisfactorily converted to 4-acetylbenzoate in 81% yield catalyzed by $PdCl_2$ and 1,3-bis(diphenylphosphino)propane (dppp). However, no or very low conversions were observed for phenyl tosylates with electron-rich or neutral substituents. Hence, a catalyst system with a general scope of effective carbonylation of aryl arenesulfonates has not been established. It is

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(1) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318−3326. (b) Heck, R. F. *Adv. Catal.* **1977**, *26*, 323−349.

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10.1021/ol062208g CCC: $33.50

of great importance to discover a catalyst system such that aryl arenesulfonates can be used as synthetically useful inexpensive starting materials to make aryl carboxylic acid derivatives. Herein, we report such a general and efficient catalyst system that can satisfactorily effect the carbonylation of diverse aryl arenesulfonates.

Aryl arenesulfonates have been a difficult class of substrates toward transition-metal-catalyzed C−C bond formation. Successful examples of such reactions have not been reported until recently. Buchwald's group has reported Suzuki−Miyaura and carbonyl enolate coupling of aryl arenesulfonates catalyzed by $Pd(OAc)_2$ and 2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl.[5] Hu et al. also reported Suzuki−Miyaura coupling of aryl arenesulfonates by employing a $Ni(COD)_2$/tricyclohexylphosphine catalyst.[6] These precedents indicate a strong ligand dependency for the activation of a $C(sp^2)-O$ bond and thus have prompted us to conduct broad ligand screens for the carbonylation of aryl arenesulfonates. It has been reported that bidentate phosphine ligands were superior to monodentate phosphine ligands in the Pd-catalyzed carbonylation of aryl or pyridinyl chlorides due to their chelating effects on Pd(0) and therefore stabilize the active catalyst species.[3a,b] Hence, our initial screens have been focused on bidentate ligands, including ferrocenyl phosphines, biaryl diphosphines, and phospholanes, together with those well-established monodentate ligands, such as N-heterocyclic carbenes (NHC) and Buchwald's monodentate phosphines, which have proved to be good supporting ligands for Pd-catalyzed cross-coupling chemistry.

As the model substrate for our study, we chose *p*-tolyl *p*-fluorobenzenesulfonate, which bears a fluoro group and therefore is more reactive than *p*-tolyl tosylate. Some selected screening results are summarized in Figure 1 with the corresponding ligand structures depicted at the bottom. Of approximately 100 ligands screened, only a handful of ligands showed some carbonylation activity (Figure 1). The Josiphos ligand **1** was discovered to be the most active one that afforded the carbonyl product in 74% yield after 12 h at 135 °C. The next best ligand is binapine, **7**, which gave 28% yield under the same conditions. The Josiphos ligand **2**, which was reported by Beller et al. to be an excellent supporting ligand for Pd-catalyzed carbonylation of aryl chlorides,[3b] only afforded 13% yield. Ligand **14** (dppp), which is effective for the carbonylation of 4-acetylphenyl tosylate,[4] showed no reaction for our model substrate. A few monodentate ligands also showed some levels of carbonylation activity. Among them, the phosphoramidite ligand **8** is the most effective, affording the product in 23% yield, whereas the Buchwald ligand **9** and NHC **11** gave ∼6% yields. It is generally believed that the catalytic cycle for carbonylation of an aryl halide first involves oxidative addition of the aryl halide, followed by CO insertion and alcoholysis of the acyl palladium complex.[1] The characteristics of bulky and electron-rich structures of the best ligands in Figure 1 indicate that electron richness and bulkiness are two favorable properties to facilitate the carbonylation process. However, ligands having these two properties are not all effective, as demonstrated by the Josiphos ligand family; analogues **2**−**5** did not perform as well as ligand **1**.

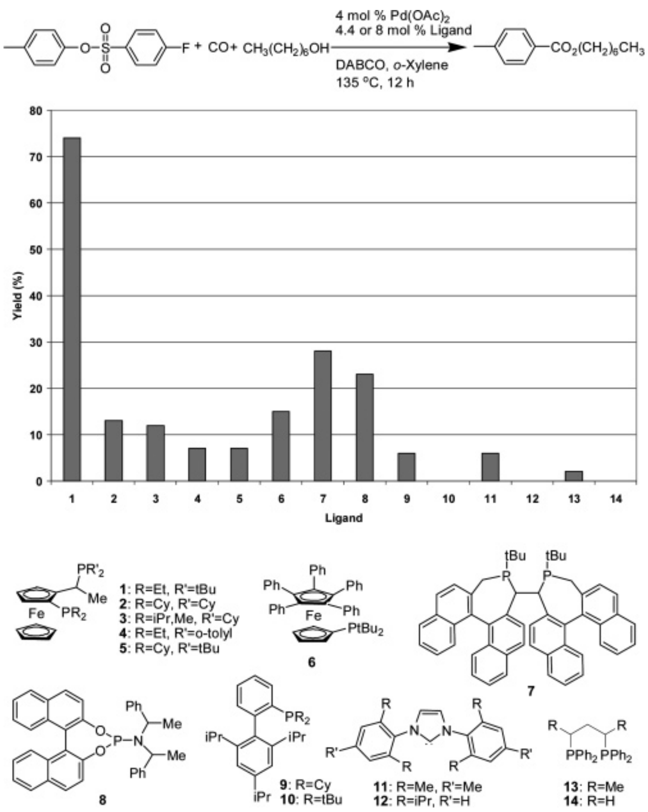

Figure 1. Ligand screening for Pd-catalyzed carbonylation of *p*-tolyl *p*-fluorobenzenesulfonate. Either 4.4 mol % of bidentate ligands or 8 mol % of monodentate ligands were used. HPLC yield.

In our initial screens, we tested a variety of solvents and bases with *n*-heptanol as the nucleophile for a broad range of ligands. For ligand **1**, the solvent and base effects are summarized in Table 1. Polyethylene glycol (PEG) 400, diphenyl ether, and *o*-xylene were all effective for the reaction, but the use of PEG 400 resulted in the highest yield (entries 1−5). In contrast, aprotic solvents such as DMAc and NMP were less effective (entries 2 and 3). A number of organic or inorganic bases, for example, DABCO, $EtN(^iPr)_2$, $NaOAc·3H_2O$, NaOAc, KF, and KO^tBu, were effective for the reaction. With PEG 400 as solvent, $NaOAc·3H_2O$ was found to be the most effective one (entry 13). After identifying these improved conditions, we switched the solvent to ethanol, which also acted as the nucleophile and is more commonly used to make carboxylic esters. Ethanol proved very effective; with $NaOAc·3H_2O$ or NaOAc as the base, yields of >90% were obtained (entries 14 and 15).

Next, more reaction parameters, such as the ligand−palladium (L/Pd) ratio, temperature, and CO pressure, were further investigated (Table 2). Although the reaction has not been completely optimized, it can be accomplished with

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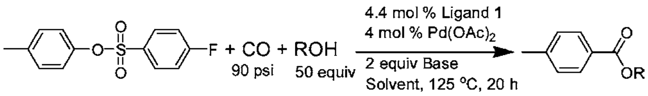
[5] Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818−11819.

[6] Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058−3059.

Table 1. Solvent and Base Effects[a]

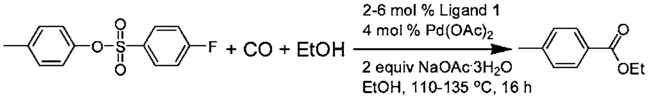


entry	solvent	base	yield (%)[b]
1	*o*-xylene	DABCO	51
2	DMAc	DABCO	30
3	NMP	DABCO	25
4	diphenyl ether	DABCO	56
5	PEG 400	DABCO	65
6	PEG 400	KF	79
7	PEG 400	K_3PO_4	58
8	PEG 400	K_2CO_3	53
9	PEG 400	Cs_2CO_3	47
10	PEG 400	KO^tBu	66
11	PEG 400	Cy_2NMe	60
12	PEG 400	$EtN(^iPr)_2$	75
13	PEG 400	$NaOAc{\cdot}3H_2O$	82
14	EtOH	$NaOAc{\cdot}3H_2O$	93[c]
15	EtOH	NaOAc	95

[a] Reactions of entries 1−13 were performed at 0.05 M substrate; R = *n*-heptyl. Reactions of entries 14 and 15 were performed at 0.2 M substrate; R = ethyl. [b] HPLC yield. [c] Isolated yield.

>90% yields to the carbonyl product under the following conditions: CO pressure ranging from 50 to 150 psi, L/Pd ratio ranging from 1.0 to 1.5, and reaction temperature above 125 °C (entries 1, 2, 4, and 6). Meanwhile, lower conversion was observed under higher CO pressure (entry 3), suggesting that CO, as a ligand, competed with aryl arenesulfonate for the active Pd centers and thus inhibited the reaction progress. The reaction was found not to be very sensitive to the L/Pd ratio, and 84% yield was obtained even with the L/Pd ratio as low as 0.5. Because of the inert nature of the C(sp^2)−O bond toward oxidative addition, elevated temperatures are required even with the best performing ligand. The reaction was conducted in a continuously stirred tank reactor with the capability of in situ monitoring of reaction progress by IR spectroscopy. The carbonyl product has a characteristic absorbance at 1722 cm^{-1}. The kinetic profiles (see Supporting Information) by IR indicated that the reaction did not proceed at an appreciable rate at temperatures less than 120 °C. The reaction went to completion within 20 h at 125 °C, which is considerably lower than the temperature (150 °C) required by the carbonylation process of aryl chlorides.

Table 2. L/Pd Ratio, Temperature, and CO Pressure Effects[a]

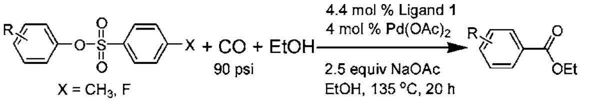


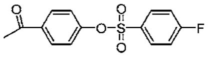
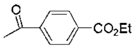
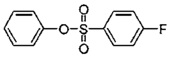
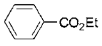
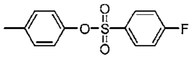
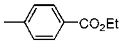
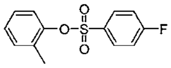
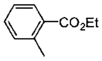
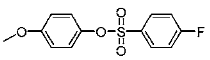
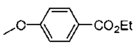
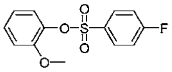
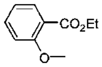
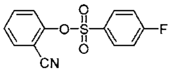
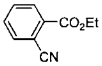
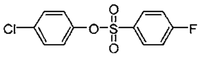
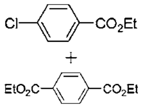
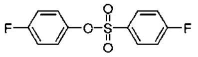
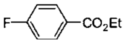
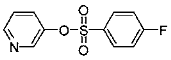
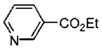
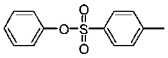
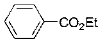
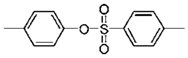
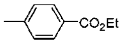
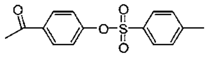
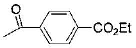
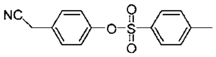
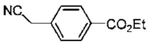
entry	L/Pd ratio	temp (°C)	*P* (psi)	yield (%)[b]
1	1.0	125	50	93
2	1.0	125	150	93
3	1.0	125	300	81
4	1.0	135	90	95
5	1.0	110	90	17
6	1.5	135	50	96
7	0.5	135	50	84

[a] All reactions were performed at 0.2 M substrate. [b] HPLC yield.

Finally, the scope of this catalyst system was examined with respect to aryl arenesulfonates bearing varied functional groups (Table 3). The catalyst afforded the carbonyl products in 80−96% yields at 135 °C for most *p*-fluorobenzenesulfonates as well as the -tosylates without electron-donating groups (entries 1−8, 11, 13, and 14). Slightly lower yields were obtained for the tolyl tosylate and pyridinyl sulfonate under the same conditions (entries 10 and 12). Functional groups such as alkoxy, cyano, fluoro, and ketone were well tolerated. Ortho-substituted substrates were also effectively converted (entries 4, 6, and 7). The catalyst works better

Table 3. Carbonylation of Aryl *p*-Fluorobenzenesulfonates and Tosylates[a]



entry	substrate	product (%)	yield (%)[b]
1			96
2			96
3			93
4			90
5			92
6			92
7			83
8			94[c]
9			79
10			70
11			92
12			61
13			96
14			93

[a] All reactions were performed at 0.2 M substrate. [b] Isolated yields. [c] 24% $ClPhCO_2Et$ + 70% $Ph(CO_2Et)_2$.

with substrates bearing electron-withdrawing groups (entry 12 vs 13); however, high yields (92−96%) were obtained for *p*-fluorobenzenesulfonates bearing either electron-donating or neutral groups (entries 2−6). It is noteworthy that for the chloro-substituted aryl arenesulfonate, carbonylation at both C−Cl and C−O bonds occurred, resulting in diethyl terephthalate as the predominant product (entry 8). We are pleased to find that this catalyst system has good generality and is the most active and efficient catalyst for the carbonylation of aryl arenesulfonates to date.

In summary, we have discovered an efficient catalyst system for effective carbonylation of aryl *p*-fluorobenzenesulfonates and -tosylates with a general functional group tolerance under less severe reaction conditions than those of aryl chlorides. This catalyst system provides an alternative route to make aryl carboxylic acid derivatives from readily available and air-stable starting materials and therefore is useful in an industrial manufacturing process. The catalyst was also found to be effective for the carbonylation of aryl chlorides, and further investigations are ongoing.

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

OL062208G