Pd-Catalyzed Decarbonylative Heck Olefination of Aromatic Carboxylic Acids Activated in situ with Di-*tert*-butyl Dicarbonate

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Abstract: The first protocol for a direct Heck olefination of aromatic carboxylic acids has been developed. By treatment with commercially available di-*tert*-butyl dicarbonate, the carboxylic acids are converted in situ into the mixed anhydrides, which in the presence of a palladium catalyst react with olefins to give styrene derivatives. As by-products, only volatile CO and CO_2 along with *tert*-butanol are formed, making the work-up of the reaction products particularly easy. A mixture of $PdCl_2$, LiCl and γ-picoline was identified to be the most effective catalyst system.

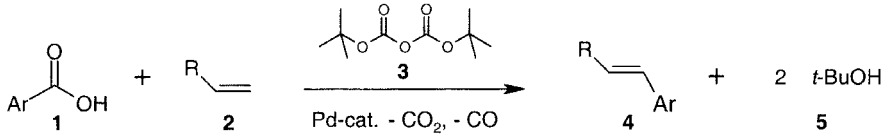
Key words: carboxylic acids, catalysis, palladium, Heck reaction, di-*tert*-butyl dicarbonate

The Heck olefination is a powerful transformation that has found many applications in organic chemistry. Due to its high tolerance for functional groups, it is often used in the synthesis of natural products and synthetic drugs.[1] Over the last decade, several highly active catalyst systems have been developed.[2] Usually, aryl halides are employed as starting materials, but other aryl sources such as aryl triflates,[3] diazonium salts,[4] sulfonyl halides[5] and aroyl chlorides[6] have been used as well. However, all these substrates require stoichiometric amounts of base and thus, equivalent amounts of waste salts are produced. The first base- and salt-free Heck olefination was developed by de Vries et al. using carboxylic anhydrides as aryl sources.[7] In this reaction variant, one equivalent of carboxylic acid is released which can, in principle, be converted back into the starting anhydride. We recently disclosed the first decarbonylative Heck olefination of phenol esters, which are more conveniently accessible than carboxylic anhydrides.[8] However, the necessity to generate the starting materials in an extra reaction step and separate the olefin products from the carboxylic acids or phenols are practical disadvantages of these processes for small-scale applications.

Our new strategy to make use of the widely available aromatic carboxylic acids as aryl sources for Heck olefinations was to utilize the mixed anhydrides of carbonic and aromatic carboxylic acids as reactive intermediates (Scheme 1). Such anhydrides are easily formed just by mixing carboxylic acids **1** with dialkyl dicarbonates such as di-*tert*-butyl dicarbonate (Boc_2O) **3**, a popular protecting agent for amines.[9,10] During this activation process, CO_2 and one equivalent of the alcohol are released. It has previously been reported that certain Pd-complexes selectively insert into the acyl-oxygen-bond of such compounds.[11] Thus, a catalytic cycle consisting of the oxidative addition of the mixed anhydride to give an acyl Pd monoalkylcarbonate complex, exchange of the alkylcarbonate e.g. for a halide, extrusion of CO to give an aryl complex, insertion of an olefin into the aryl-Pd-bond, and finally release of the product via β-hydride elimination appeared to be feasible. In the overall process, only CO, CO_2 and an alcohol are formed as byproducts.

We chose the reaction of benzoic acid **1a**/Boc_2O **3** with styrene **2a** as our model system (Scheme; R, Ar = Ph) and screened various Pd-complexes under different conditions in order to identify a suitable catalyst system for the desired conversion. Selected results are displayed in Table 1.

In analogy to the Pd-catalyzed olefination of carboxylic anhydrides or phenol esters, the presence of halide ions is crucial for the activity of the Pd catalyst (entries 1–8).[7,8] This is probably due to the fact that halide ligands facilitate the decarbonylation of the acyl groups on the palladium. In this respect, LiCl proved to be the most effective halide source.[12] Stabilizing ligands such as phosphines or amines avoid agglomeration of the palladium and, thus, increase the catalyst lifetime. However, they significantly reduce the activity of the catalyst (entries 9–11). The best



Scheme 1 Heck olefination of carboxylic acids.

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balance between these two effects is observed for γ-picoline, which sufficiently stabilizes the palladium to avoid precipitation and loss of catalytic activity while still permitting reasonable reaction rates.

Table 1 Effects of the Conditions on the Product Distribution[a]

Entry	Pd source	Additive	Ligand	Conv. (%)	Sel.[f] (%)
1	$Pd(OAc)_2$	-	-	0	
2	$Pd(acac)_2$	-	-	0	
3	$PdCl_2$	-	-	0	
4	$PdCl_2$	KBr	-	0	
5	$PdCl_2$	NaBr	-	10	95
6	$PdCl_2$	LiBr	-	25	95
7	$PdCl_2$	NaCl	-	0	
8	$PdCl_2$	LiCl	-	40	95
9	$PdCl_2$	LiCl	PPh_3	45	10
10	$PdCl_2$	LiCl	γ-picoline	55	95
11	$PdCl_2$	LiCl	isoquinoline	46	85
12[b]	$PdCl_2$	LiCl	γ-picoline	20	50
13[c]	$PdCl_2$	LiCl	γ-picoline	35	90
14[d]	$PdCl_2$	LiCl	γ-picoline	90	95
15[e]	$PdCl_2$	LiCl	γ-picoline	53	95

[a] *Conditions*: 1.00 mmol benzoic acid, 1.20 mmol styrene, 1.00 mmol BOC_2O, 0.03 mmol catalyst, 5 mL *N*-methylpyrrolidone, 0.10 mmol ligand, 0.10 mmol additive, 120 °C, 16 h.
[b] DMF as the solvent.
[c] DMPU as the solvent.
[d] Slow addition of 2.00 mmol BOC_2O.
[e] 160 °C, 2 h, slow addition of BOC_2O.
[f] Sideproducts: homoanhydride and *tert*-butylester.

Amides such as DMF or NMP proved to be the optimal solvents, probably due to their ability to stabilize Pd-complexes in solution (entries 10 and 12). The optimal reaction temperature was 120 °C: at lower temperatures, the reaction is rather slow and at higher temperatures, the mixed anhydrides are not stable enough, so that side products such as homoanhydrides are formed. Especially for electron defficient carboxylic acids decarboxylation of the mixed anhydrides under formation of *tert*-butyl esters is observed. Due to the thermal instability of the carbonic acid derivatives, it is beneficial to add Boc_2O in excess. Slow addition of Boc_2O over the entire reaction time further improved the yield of the desired stilbene (entries 14 and 15).

We next investigated the reaction of a range of carboxylic acids with various olefins under the optimized reaction conditions. Many functionalized aromatic and heteroaromatic carboxylic acids can be converted with different olefins in good yields (Table 2). Even electron-rich carboxylic acids, which are less reactive in the alternative reaction protocols via anhydrides or phenol esters,[7,8] gave high yields in this new transformation (e.g. **4h–l).** A strong preference for the formation of the *trans* 1,2-olefins is observed, in analogy to conventional Heck reactions. The reaction was also successfully performed on larger scale (**4a**).

In summary, our new protocol allows the first in situ activation and direct Heck olefination of aromatic carboxylic acids. Therefore, one reaction step is saved in comparison to previously reported procedures. The reaction protocol involves only commercially available, air-stable chemicals and produces only volatile by-products. It is, therefore, particularly useful for small-scale applications in research and drug discovery.

Representative Experimental Procedure

Preparation of stilbene **4a**: A 20 mL flask was charged with palladium chloride (0.03 mmol, 5.30 mg), lithium chloride (0.10 mmol, 4.30 mg), benzoic acid (1.00 mmol, 122 mg), di-*tert*-butyl dicarbonate (1.00 mmol, 218 mg), styrene (1.20 mmol, 150 μL), γ-picoline (0.30 mmol, 27.0 μL) and dry NMP (5 mL). The reaction mixture was briefly purged with argon and heated to 120 °C. An excess of di-*tert*-butyl dicarbonate (436 mg, 2.00 mmol) in NMP (1 mL) was slowly added via syringe pump over several hours. After 16 hours, the crude reaction mixture was diluted with toluene (30 mL) and washed with 2 N HCl (15 mL), water (15 mL), and saturated aqueous $NaHCO_3$ (15 mL). The organic layer was dried over $MgSO_4$, the volatiles were removed in vacuo and the residue was filtered through a small plug of SiO_2 using hexane as eluent yielding **4a** (145 mg, 80%) and small quantities of its regioisomers. The product was characterized via ^1H-, ^{13}C NMR and HRMS. The analytical data was identical with that reported in literature.

Acknowledgement

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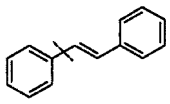
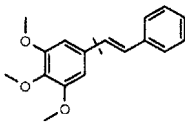
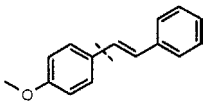
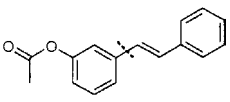
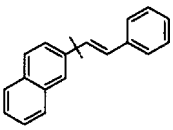
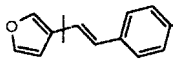
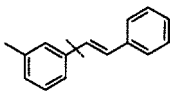
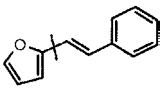
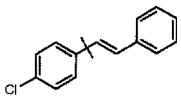
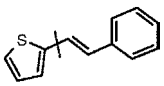
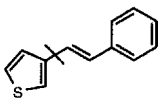
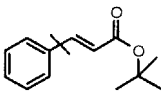
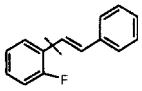
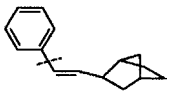
Table 2 Heck Olefination of Carboxylic Acids

Comp.	Structure	Yield (%)[b]	Sel.[c]	Comp.	Structure	Yield (%)[b]	Sel.[c]
4a		80 (78)[d]	18:1	**4h**		65	11:1
4b		48	10:1	**4i**		45	19:1
4c		87	13:1	**4j**		45	14:1
4d		66	16:1	**4k**		71	20:1
4e		72	20:1	**4l**		81	19:1
4f		78	14:1	**4m**		51	23:1
4g		88	28:1	**4n**		80	5:1[e]

[a] *Conditions*: 1.00 mmol carboxylic acid, 1.20 mmol olefin, 3.00 mmol BOC_2O, 0.03 mmol $PdCl_2$, 0.10 mmol LiCl, 0.10 mmol γ-picoline, 5 mL *N*-methylpyrrolidone, 120 °C, 16 h.
[b] Isolated yields.
[c] Ratio of 1,2-:1,1-substituted olefins.
[d] On 25 mmol scale.
[e] Mixture of isomers

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