Pd-Catalyzed Couplings

Decarbonylative Heck Olefination of Enol Esters: Salt-Free and Environmentally Friendly Access to Vinyl Arenes[**]

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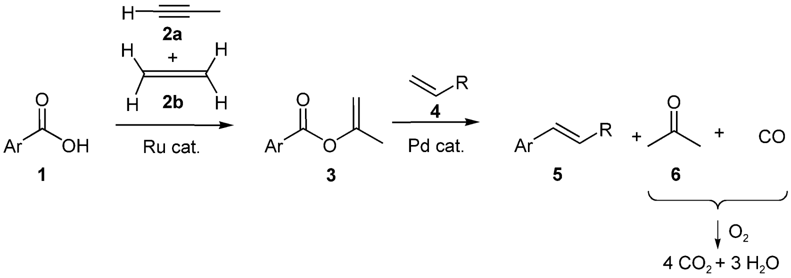
Dedicated to Prof. Dr. Manfred Reetz
on the occasion of his 60th birthday

The Mizoroki–Heck reaction, one of the most elegant methods for the attachment of carbon chains onto aromatic rings, has found many applications in both academic and industrial laboratories.[1] The standard process starting from aryl halides,[2] triflates,[3] diazonium salts,[4] aroyl-[5] and arylsulfonyl halides[6] suffers from the requirement of stoichiometric amounts of base to neutralize the acid released in the reaction. The large quantities of salts inevitably formed must then be separated and disposed of in an environmentally acceptable way—a complex procedure, particularly on an industrial scale.

The reduction of the salt load of Heck reactions has previously been approached in two ways: In the first, nonfunctionalized arenes are used for the oxidative coupling with olefins.[7] In analogy to the Friedel–Crafts reaction, this reaction is regioselective for very few substrates; usually product mixtures are obtained that can be hard to separate. The second, more generally applicable approach makes use of carboxylic acids as the source of the aryl residue.[8–10] These are first converted into the corresponding anhydrides or *p*-nitrophenyl esters, which are then used in a palladium-catalyzed decarbonylative olefination step. The substitution pattern on the aromatic ring is determined by the position of the carboxylate group. Along with the desired vinyl arenes, the corresponding carboxylic acid or *p*-nitrophenol is produced as the by-product, which can be converted back into the starting material with fresh carboxylic acid. In the overall process, the only by-products eliminated are hence CO and water. However, the technical realization of such a cyclic process would be rather difficult, and the ecological advantage of a salt-free reaction might not balance the energy required for the separation and recycling of the by-products. Based on both economical and ecological considerations, there is still a high demand for alternative processes that start from environmentally benign compounds, produce no waste salts, and require no energetically demanding material streams.

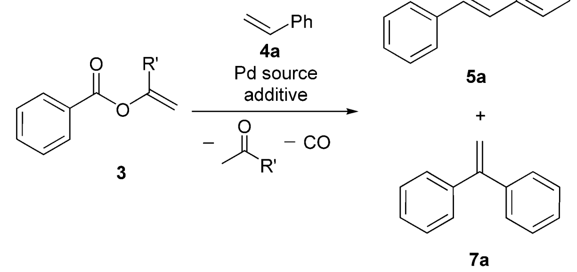
Herein, we report on a novel strategy for the introduction of carbon chains to arenes that fulfills these requirements in an excellent way (Scheme 1). Aromatic carboxylic acids **1** are initially converted into the isopropenyl esters **3** in a waste-free and atom-economical fashion by coupling to propyne (**2a**) or allene (**2b**), which are available from the C_3 fraction from the steam cracker.[11a] These intermediates **3** then react further to give the vinyl arenes **5** in a newly developed decarbonylative Heck olefination. The only by-products, CO and acetone (**6**), can be burned in an environmentally neutral way, potentially providing some of the energy required for the reaction.



Scheme 1. Salt-free synthesis of vinyl arenes from carboxylic acids.

While a number of active catalyst systems are available for the first reaction step,[11] metal-catalyzed coupling reactions of enol esters are still unknown. This second step in the process would require metal complexes with enough activity to insert into the C–O bond of the poorly reactive enol esters. Such catalysts could undergo a cycle consisting of the oxidative addition of the enol ester to give an acyl–metal enolate, decarbonylation to give the aryl complex, insertion of the olefin into the metal–aryl bond, β-hydride elimination, and protonation of the enolate with formation of the corresponding ketone.[12]

Using the model reaction depicted in Scheme 2, a conversion of isopropenyl benzoate (**3a**, R′ = Me) with styrene (**4a**) to yield *trans*-stilbene (**5a**), we investigated the catalytic activity of various combinations of palladium precursors, additives, and ligands (Table 1). While barely any conversion was observed for palladium acetate or $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) modest catalytic activity for the desired reaction was displayed by palladium(II)



Scheme 2. Decarbonylative Heck olefination of vinyl benzoates.

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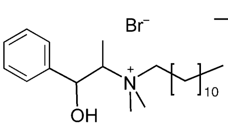
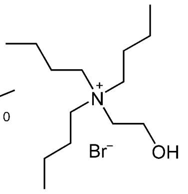
Table 1: Optimization of the catalyst system for the reaction in Scheme 2.[a]

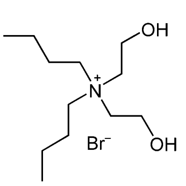
No.	Pd source	Additive	R′	Solvent	Conv.	Sel.[b]
1	$Pd(OAc)_2$	–	Me	NMP	0	n.d.[c]
2	$(dba)_3Pd_2$	–	Me	NMP	0	n.d.[c]
3	$PdCl_2$	–	Me	NMP	45	80
4	$PdBr_2$	–	Me	NMP	50	90
5	$PdCl_2$	LiCl	Me	NMP	60	>95
6[d]	$PdCl_2$	LiCl	Me	NMP	38	95
7[e]	$PdCl_2$	LiCl	Me	NMP	10	n.d.[c]
8	$PdCl_2$	LiBr	Me	NMP	70	>95
9	$PdBr_2$	NaBr	Me	NMP	75	70
10	$PdBr_2$	KBr	Me	NMP	80	>95
11	$PdBr_2$	LiBr	Me	NMP	70	>95
12	$PdBr_2$	$(n\mathrm{Bu})_4N^+Br^-$	Me	NMP	100	90
13	$PdBr_2$	$(n\mathrm{Oct})_4P^+Br^-$	Me	NMP	95	90
14	$PdBr_2$	**8a**	Me	NMP	100	>95
15	$PdBr_2$	**8b**	Me	NMP	100	>95
16	$PdBr_2$	**8c**	Me	NMP	100	75
17[f]	$PdBr_2$	**8b**	Me	NMP	100	95
18	$PdBr_2$/celite	**8b**	Me	NMP	100	95
19[g]	$PdBr_2$/celite	**8b**	Me	NMP	100	95
20	$PdBr_2$	**8b**	Me	DMF	35	50[h]
21	$PdBr_2$	**8b**	Me	o-$C_6H_4Cl_2$	40	55
22	$PdBr_2$	**8b**	Me	sulfolane	90	50
23	$PdBr_2$	**8b**	Me	–	90	80
24	$PdBr_2$	**8b**	H	NMP	40	80
25	$PdBr_2$	**8b**	*t*Bu	NMP	80	90
26	$PdBr_2$	**8b**	Ph	NMP	90	90
27	$PdBr_2$	**8b**	*n*Bu	NMP	100	<10[i]

[a] Reaction conditions: 1.00 mmol vinyl benzoate (**3**), 2.00 mmol styrene (**4a**), 0.03 mmol Pd source, 0.03 mmol additive, 0.03 mmol ligand, 4 mL solvent, 16 h, 160 °C. Conversions and selectivities (both in %) were determined by GC analysis with *n*-tetradecane as the internal standard. The ratio **5a**/**7a** was around 10:1 in all conversions. [b] Main side products: benzoic acid and benzoic anhydride. [c] n.d.: not determined. [d] With isoquinoline as a ligand. [e] With PPh_3 as a ligand. [f] 0.5 mL solvent, 0.005 mmol $PdBr_2$, and additive. [g] Experiment conducted with regenerated catalyst. [h] Side product: *N*,*N*-dimethylbenzamide. [i] Isomerization to the product with the internal C=C bond.

halides (entries 1–4). In analogy to decarbonylative olefinations of anhydrides and *p*-nitrophenyl esters, the conversion could be improved by adding metal halides (entries 5, 8–11); however, early precipitation of metallic palladium could not totally be prevented by these additives. Coordinating ligands, such as amines or phosphanes, succeeded in stabilizing the palladium in solution, but at the same time decreased its catalytic activity (entries 6, 7). Hence, only unsatisfactory yields could be obtained when the catalytic systems optimal for anhydrides[8d] or *p*-nitrophenyl esters[8b] were applied to isopropenyl esters (entries 5, 6).


8a


8b


8c

A combination of palladium bromide and tetraalkylammonium or tetraalkylphosphonium bromides proved to be active and selective catalysts for these substrates (entries 12, 13). Finally, the hydroxy-substituted ammonium salts *N*-dodecyl-*N*-methylephedrinium bromide (**8a**) and tri-*n*-butyl(2-hydroxyethyl)ammonium bromide (**8b**) were found to stabilize the palladium in solution for sufficient time to give quantitative conversion along with high selectivity (entries 14–16).[13] With this additive, the catalyst load could be reduced to 0.5 mol% without losses in the yield (entry 17).

The catalyst was recycled successfully following the method of de Vries (entries 18, 19).[14] Thus, celite was added to the reaction mixture, and palladium in reduced form precipitated on it over the course of the reaction. After complete conversion, the solid was removed by centrifugation and treated with the corresponding amount of Br_2 and **8b** as solutions in *N*-methylpyrrolidone (NMP). The resulting mixture displayed the same catalytic activity as the original catalyst.

N-Methylpyrrolidone proved to be a particularly suitable solvent (entries 15, 20–22). In contrast to traditional Heck reactions, the dilution can be significantly reduced since there is no longer a necessity to dissolve stoichiometric amounts of inorganic salts (entry 17). Notable product yields are obtained even in the absence of a solvent—a major advantage of the new protocol from an ecological perspective (entry 23).

Besides isopropenyl esters, other enol esters with terminal double bonds, for example, vinyl benzoate (**3b**, R′ = H), 1-(*tert*-butyl)vinylbenzoate (**3c**, R′ = *t*Bu), and 1-phenylvinyl benzoate (**3d**, R′ = Ph) were successfully olefinated (entries 24–26). In the reaction of 2-hex-1-enyl benzoate (**3e**, R′ = *n*Bu), however, mainly isomerization to a mixture of (*E*)- and (*Z*)-2-hex-2-enyl benzoate was observed (entry 27).

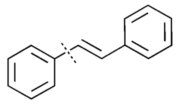
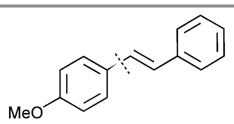
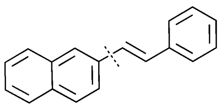
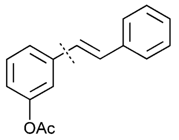
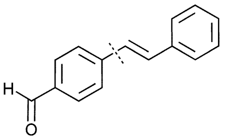
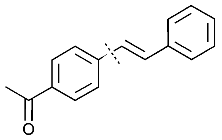
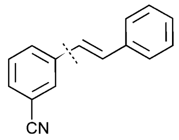
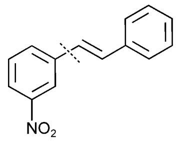
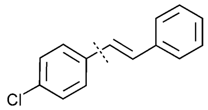
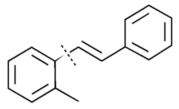
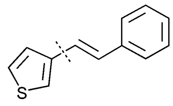
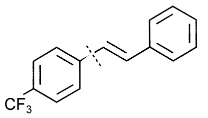
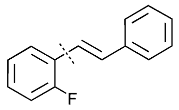
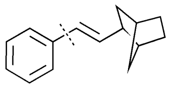
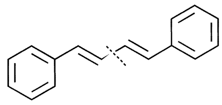
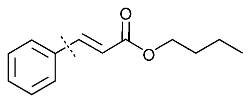
In the model reaction of the relatively unreactive styrene, the principal product was *trans*-stilbene (**5a**); under optimized conditions, 1,1-diphenylethylene (**7a**) was formed in less than 10% yield. The only side-product observed was triphenylethylene, at levels of around 2%. In analogy to the traditional Heck olefination, yet higher selectivities were obtained with activated olefins such as acrylates (Table 2, **5p**).

The general applicability of the new reaction was investigated with a series of isopropenyl carboxylates **3a**,**f**–**r**, previously prepared from the corresponding carboxylic acids and propyne gas,[11c] and with the olefins **4a**–**c** following Scheme 3. Table 2 shows the broad applicability of the new Heck reaction variant. Electron-rich and electron-deficient aryl, heteroaryl, and vinyl carboxylic acid esters were coupled to various olefins in good yields. The reaction tolerates many functionalities, including esters, ethers, nitro, keto, trifluoromethyl, and even formyl groups.

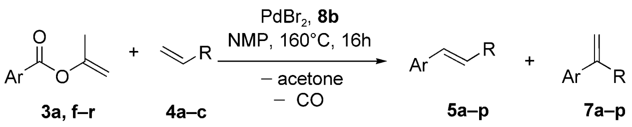
The workup is particularly easy since only volatile side products are formed: the celite is removed by filtration or centrifugation together with the precipitated palladium(0), the solvent is evaporated under high vacuum along with excess olefin, then the vinyl arene is purified by distillation.

Overall, for the first time an efficient and selective catalyst system for the decarbonylative Heck olefination of enol esters

Table 2: Conversion of various isopropenyl carboxylates with olefins (Scheme 3).[a]

Cmpd.	Structure	Yield [%][b]	**5**:**7**[c]	Cmpd.	Structure	Yield [%][b]	**5**:**7**[c]
5a		95	10:1	**5i**		92	8:1
5b		85	9:1	**5j**		75	9:1
5c		78	13:1	**5k**		98	9:1
5d		92	13:1	**5l**		77	9:1
5e		96	10:1	**5m**		95	15:1
5f		75	10:1	**5n**		87	15:1
5g		99	15:1	**5o**		67	5:1[d]
5h		63	9:1	**5p**		98	>50:1

[a] Reaction conditions: 1.00 mmol isopropenyl benzoate, 2.00 mmol olefin, 0.03 mmol $PdBr_2$, 0.03 mmol **8b**, 4 mL NMP, 16 h, 160 °C. [b] Overall yield [%] of vinyl arenas as isolated products. [c] The relative amounts of 1,2- and 1,1-substituted vinyl arenes were determined by gas chromatography. [d] Mixture of double-bond isomers.



Scheme 3. Decarbonylative Heck olefination of isopropenyl carboxylates.

has been developed. In contrast to traditional Heck reactions, the addition of both base and solvent can be avoided, and instead of waste salts, only volatile, flammable by-products are formed. This reaction combined with a waste-free synthesis of the isopropenyl ester substrates by addition of a carboxylic acid onto propyne results in a salt-free, environmentally benign overall process. This is the first example of a palladium-catalyzed coupling reaction of the poorly reactive enol esters and could open up new perspectives for related reactions, such as ketone syntheses or reductions.[15]

Experimental Section

5p: A 20-mL flask was charged with $PdBr_2$ (8.00 mg, 0.03 mmol), **8b** (9.30 mg, 0.03 mmol), and celite (200 mg). The flask was then heated to 140 °C under vacuum for 15 min and flushed with argon. Subsequently, **3a** (162 mg, 1.00 mmol), **4c** (175 μL, 1.20 mmol), and NMP (4.00 mL) were added by syringe. The resulting mixture was then stirred for 16 h at 160 °C. After filtration of Pd^0/celite and removal of the volatiles under high vacuum, the residue was fractionally distilled to give **5p** (195 mg, 95%) as a colorless liquid. The spectroscopic data of the product correspond to those of (*E*)-3-phenyl-2-propenoic acid 1-butylester, CAS registry number [538-65-8]. The Pd^0/celite mixture was dried under vacuum then treated with Br_2 (2.00 μL, 0.037 mmol) in NMP (1 mL) and stirred for 15 min. Following addition of **8b** (9.30 mg, 0.03 mmol), the mixture can be reused as the catalyst.

The experiments in Table 2 were carried out analogously. The products were purified by column chromatography and characterized by NMR, MS, and HRMS.

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