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Arylalkene Synthesis via Decarboxylative Cross-Coupling of Alkenyl Halides

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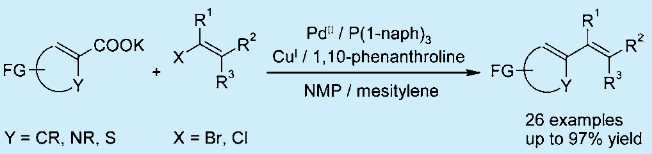
Ⓢ *Supporting Information*

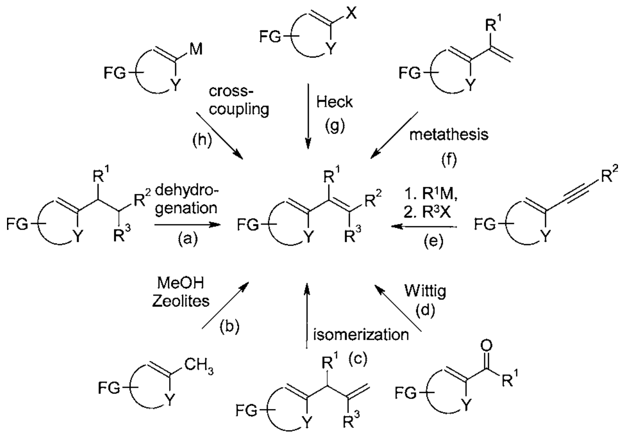
ABSTRACT: A bimetallic catalyst system generated from readily available palladium(II) and copper(I) salts, 1,10-phenanthroline and tri-1-naphthylphosphine was found to efficiently mediate the decarboxylative cross-coupling of alkenyl bromides and chlorides with aromatic carboxylates. It allows the regiospecific synthesis of a broad range of aryl- and heteroarylalkenes in high yields.



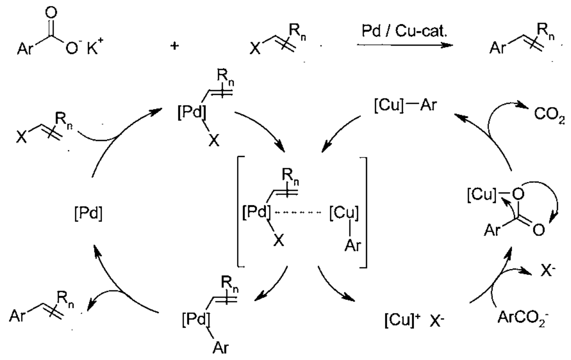
Aryl- and heteroarylalkenes are common structural subunits of natural products,[1] bioactive substances[2] and functional materials,[3] and efficient synthetic entries to this important moiety are constantly sought (Scheme 1).[4] Industrially, aryl- and heteroarylalkenes are prepared, for example, via dehydrogenation reactions (a),[5] condensations (b),[6] or isomerizations (c).[7] Further established methods for the stereoselective synthesis of arylalkenes include Wittig[8] or Peterson olefinations (d),[9] carbometalations of alkynes (e),[10] olefin metatheses (f),[11] Heck reactions of aryl halides[12] or carboxylates (g),[13] and transition metal-catalyzed cross-coupling reactions (h).[14] Since alkenyl halides are substrates easily accessible in defined stereochemistries,[15] their catalytic cross-coupling with organometallic reagents has found widespread application, in particular for the regiospecific arylation of alkenes.[14] However, the organometallic reagents, e.g., (hetero)arylzinc, -boron, or -tin compounds, are often costly, hard to access, or sensitive to air and moisture.

Within recent years, decarboxylative coupling reactions have emerged as a powerful new strategy for C−C and C−heteroatom bond formation.[16] Their key advantage over couplings of organometallic reagents is that the carbon nucleophiles are generated in situ from widely available carboxylate salts by extrusion of CO_2. In the presence of a suitable catalyst, usually a bimetallic copper/palladium or silver/palladium system, various aromatic carboxylic acids have successfully been coupled with a broad range of (hetero)aryl halides[17] and pseudohalides.[18]

Scheme 1. Synthetic Approaches to (Hetero)Arylalkenes



Scheme 2. Mechanistic Blueprint for a Decarboxylative Alkenylation



However, the substrate range of known catalyst systems does not seem to extend to alkenyl halides. Cinnamyl bromides, which must viewed as vinylogous aryl halides, are the sole substrates for which successful decarboxylative cross-couplings have been reported, namely, with cinnamic acids (Miura et al.)[19] and pentafluorobenzoic acid (Liu et al.).[20] Myers' decarboxylative Heck reaction was the first to give access to vinylarene products from benzoic acids,[13] but the regiochemistry of the arylation step depends on the steric and electronic properties of the alkene, rather than being definable by a leaving group.

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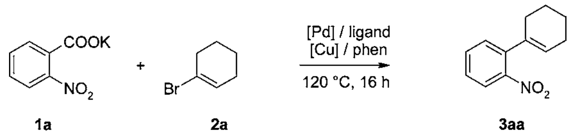
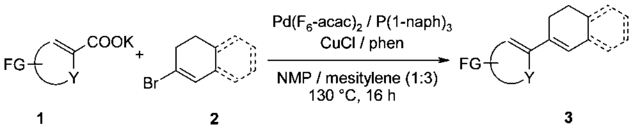
Table 1. Optimization of the Reaction Conditions[a]

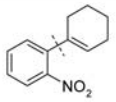
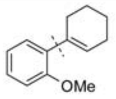
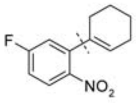
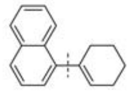
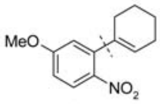
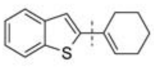
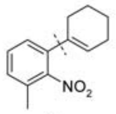
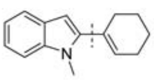
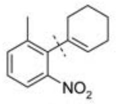
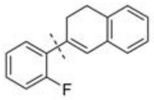
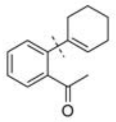
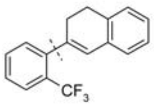
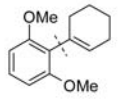
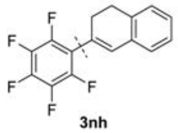


entry	Cu-source	Pd-source	ligand	**3aa** (%)
1[b]	CuBr	Pd(acac)$_2$	–	19
2	"	"	–	48
3	"	"	dppm	71
4	Cu$_2$O	"	"	44
5	CuOAc	"	"	63
6	CuI	"	"	46
7	"	"	"	73
8	"	Pd(dba)$_2$	"	69
9	"	PdI$_2$	"	63
10	"	PdBr$_2$	"	67
11	"	PdCl$_2$	"	68
12	"	Pd(OAc)$_2$	"	71
13	"	Pd(F$_6$-acac)$_2$	"	75
14	"	"	PPh$_3$	83
15	"	"	PCy$_3$	87
16	"	"	P(*t*-Bu)$_3$	79
17	"	"	P(*p*-Tol)$_3$	81
18	"	"	P(*o*-Tol)$_3$	92
19	"	"	P(1-naph)$_3$	97
20[c]	"	"	"	99
21[d,e]	"	"	"	74
22[e,f]	"	"	"	83

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), Pd-source (1.0 mol %), phosphine ligand (2.0 mol %), Cu-source (10 mol %), 1,10-phen (10 mol %), 4 mL of mesitylene/NMP 3:1, 120 °C, 16 h. Yields determined by GC analysis using *n*-tetradecane as the internal standard. phen =1,10-phenanthroline; dppm = bis(diphenylphosphino)methane. [b] In NMP/quinoline 3:1. [c] 130 °C. [d] In situ generation of **1a** from the benzoic acid and K$_3$PO$_4$. [e] With 200 mg of 4 Å molecular sieves. [f] Without drying and degassing.

Table 2. Scope with Regard to the Aromatic Carboxylates[a]



product	yield (%)	product	yield (%)
 **3aa**	92	 **3ha**	51[c,d]
 **3ba**	82	 **3ia**	47[c,d]
 **3ca**	94	 **3ja**	75
 **3da**	86	 **3ka**	59
 **3ea**	78[b]	 **3lh**	63[c,e]
 **3fa**	71[c]	 **3mh**	46[c]
 **3ga**	43[c,d]	 **3nh**	87[c]

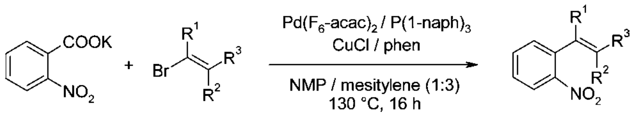
[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), Pd(F$_6$-acac)$_2$ (1.0 mol %), P(1-naph)$_3$ (2.0 mol %), CuCl (10. mol %), 1,10-phen (10 mol %), 4 mL of solvent, 130 °C, 16 h. Isolated yields. [b] 24 h. [c] 150 °C. [d] CuI/PdBr$_2$ as the catalyst. [e] NMP/mesitylene 2:1.

An efficient and generally applicable protocol for the decarboxylative cross-coupling of alkenyl halides would be highly desirable, since it would allow the regiospecific synthesis of arylalkenes starting from simple (hetero)aromatic carboxylates. We believed that such a process should, in principle, be possible if the decarboxylation step is mediated by copper and the cross-coupling step by palladium (Scheme 2). The key to success would be to synchronize the decarboxylation and cross-coupling cycles.

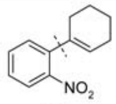
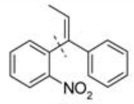
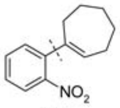
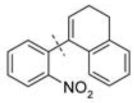
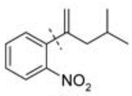
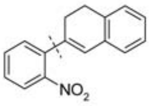
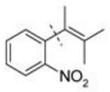
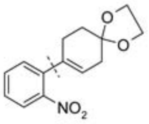
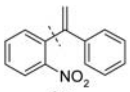
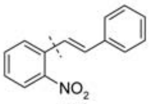
In our search for a suitable catalyst system, we chose the reaction of potassium 2-nitrobenzoate (**1a**) with 1-bromocyclohexene (**2a**) as a model and investigated various catalysts that had proven to give excellent yields in analogous couplings of **1a** with aryl bromides.[17a,21] However, as anticipated, they displayed poor activity in the arylation of the cyclic alkenyl bromide **2a**. Using a combination of CuBr/1,10-phenanthroline and Pd(acac)$_2$ in a mixture of *N*-methylpyrrolidone (NMP) and quinoline,[21] only 19% yield were obtained at 120 °C (Table 1, entry 1). A step-up in the yields was achieved by reducing the solvent polarity and, thus, slowing down the decarboxylation in relation to the cross-coupling step (Table 1, entry 2). The addition of certain phosphine ligands such as the bidentate bis(diphenylphosphino)methane (dppm) further improved the yield to 71% (Table 1, entry 3). Copper sources containing halide ions were found to be particularly effective, and copper chloride provided the best yields (Table 1, entry 7). Among the palladium precursors, Pd(F$_6$-acac)$_2$ proved to be the optimal choice (Table 1, entries 8–13). An extensive ligand screening revealed that the moderately electron-donating, sterically demanding ligand tri-1-naphthylphosphine gave higher yields than all phosphines previously employed in the coupling of aryl halides (Table 1, entries 14–19). This suggests that the oxidative addition, which is facilitated by particularly electron-rich ligands, is not rate determining for alkenyl bromides.

With the optimal catalyst system, 10 mol % copper chloride 1 mol % Pd(F$_6$-acac)$_2$ in NMP/mesitylene (1:3), full conversion of **2a** and near-quantitative yield of the desired 1-cyclohexenyl-2-nitrobenzene (**3aa**) was reached within 16 h at 130 °C (Table 1, entry 20). Remarkably, considerable yields were obtained

Table 3. Scope with Regard to the Alkenyl Bromides[a]

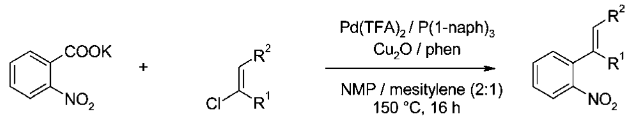


1a **2** **3**

product	yield(%)	product	yield(%)
 **3aa**	92	 **3af**	74
 **3ab**	74	 **3ag**	68
 **3ac**	92 (80)[b]	 **3ah**	97
 **3ad**	70	 **3ai**	97
 **3ae**	39	 **3aj**	92

[a]Reaction conditions: **1a** (0.6 mmol), **2** (0.5 mmol), Pd(F$_6$-acac)$_2$ (1.0 mol %), P(1-naph)$_3$ (2.0 mol %), CuCl (10 mol %), 1,10-phen (10 mol %), 4 mL of solvent, 130 °C, 16 h. Isolated yields. [b]10 mmol scale.

Scheme 3. Decarboxylative Couplings of Alkenyl Chlorides



1a

4c: R^1 = i-Bu, R^2 = H
4j: R^1 = H, R^2 = Ph
4a: R^1, R^2 = (CH$_2$)$_4$

3ac (89%)
3aj (92%)
3aa (38%)

already at 100 °C, which is an extremely low temperature for a decarboxylative cross-coupling reaction (for more details, see the Supporting Information). The reaction was also successfully performed starting directly from the carboxylic acid and without drying or degassing, which underlines its robustness (Table 1, entries 21−22).

Having thus found an effective protocol for the decarboxylative arylation of alkenyl bromides, we next investigated its scope. As can be seen from the examples in Table 2, *ortho*-substituted aromatic and heteroaromatic carboxylic acids smoothly reacted with 1-bromocyclohex-1-ene (**2a**) or the less volatile 3-bromo-1,2-dihydronaphthalene (**2h**) to give the corresponding (hetero)arylalkenes. Ether, ketone, fluoro and trifluoromethyl groups were tolerated, and the reaction proceeds well even for sterically hindered *o*,*o*-disubstituted benzoic acids. Non-*ortho* substituted benzoic acids could not yet be converted, which was expected since the presence of bromide salts has been reported to impede their decarboxylation.[17a,22]

The reaction is also widely applicable with regard to the alkenyl bromides. As can be seen from the examples in Table 3, mono-, di-, and even trisubstituted alkyl bromides gave similarly high yields. Unwanted double bond isomerization, a common side reaction in the alternative Heck reactions, did not take place in significant amounts. The reaction proved to be high yielding even for products that are inaccessible via decarboxylative Heck reactions, e.g., cyclic arylalkenes or 2-arylalkenes, thus demonstrating the complementarity of both approaches. Only for highly volatile substrates, the isolated yields remained unsatisfactory at 0.5 mmol scale, since the product partly evaporated during work-up. The synthesis of **3ac** in 80% yield on a gram scale demonstrates that the reaction can easily be scaled up.

Further studies revealed that only minor adjustments were necessary to extend this reaction from alkenyl bromides to the less costly, but also less reactive alkenyl chlorides. Thus, representative alkenyl chlorides (**4**) were coupled with 2-nitrobenzoic acid (**1a**) to give the products up to 92% yield in the presence of 1 mol % Pd(TFA)$_2$, 3 mol % tri-1-naphthylphosphine, 3 mol % Cu$_2$O and 5 mol % 1,10-phenanthroline in NMP/mesitylene (2:1) at 150 °C (Scheme 3).

In conclusion, an efficient and broadly applicable protocol for the decarboxylative cross-coupling of alkenyl bromides with aromatic carboxylates has been developed. This reaction provides an efficient, regiospecific entry to arylalkenes from easily accessible aromatic carboxylates and alkenyl bromides or chlorides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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