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Pd(II)-catalyzed decarboxylative allylation and Heck-coupling of arene carboxylates with allylic halides and esters†

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This work demonstrates an alternative method to prepare allylated arenes and aryl-substituted allylic esters *via* catalytic decarboxylative C–C bond formation using aromatic carboxylic acids and allylic halides and esters.
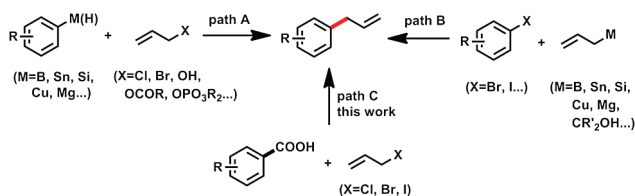
The development of more efficient protocols for C–C bond formation that use low-cost, safe and environmentally benign starting materials remains a critical challenge for organic chemists. Recently, metal-catalyzed decarboxylative couplings show that simple carboxylic acids seem to be efficient surrogates for both halides and organometallics.[1] Many efficient protocols to construct C–C bonds *via* palladium-catalyzed decarboxylative couplings have been developed by Myers,[2] Gooßen,[3] Tunge,[4] Miura,[5] and others.[6] Although most of these systems suffer from limited substrate scope, relatively high temperature and/or overloading additives, catalytic decarboxylative C–C bond formation remains very attractive since carboxylic acids are stable, easily available and relatively environmentally benign. We wish to report herein a palladium-catalyzed decarboxylative allylation of arenes by using arene carboxylates and allylic halides.

Allylic aromatic compounds show versatile biological activities in natural products.[7] Additionally, they also represent an important class of organic intermediates in complex molecule synthesis due to the versatility of olefin transformations. In the past decades, two fundamental methods have been explored to construct the allylic arenes (Scheme 1).[8] In path A, an aromatic nucleophile attacks an allyl electrophile to give the allylated arene. Traditional acid/Lewis acid catalyzed Friedel–Crafts aromatic

Scheme 1 Synthesis of allylic aromatic compounds.

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allylation could be also involved in this path. In path B, a polarity reversing attack gives the desired allylic arenes which might involve a transmetallation between an aryl metal intermediate formed by electrophilic aromatic substitution and an allylic partner. Although these methods are usually practical to prepare allylated arenes, most of them suffer from complex mixture of products (Friedel–Crafts aromatic allylation) and usage of organometallic reagents which might be relatively high-cost and low stability. Taking advantage of high stability, low-cost and commercial availability of arene carboxylates, we successfully accomplished a palladium-catalyzed decarboxylative arene allylation by using simple aryl carboxylic acids and allylic halides (Scheme 1, path C).[4]

As the initial research, we chose 2,4,5-trimethoxybenzoic acid and allylic bromide as standard substrates to optimize suitable conditions for this reaction (Table 1). It was found that the solvent, catalysts, and additives affect the reaction efficiency critically. The desired allylic arene was obtained in 62% yield under the conditions: 20 mol% Pd(OAc)$_2$, 3 eq. Ag$_2$CO$_3$, 5% DMSO/toluene (v/v), 110 °C, 2 h (entry 1). The investigation of solvent effect showed that toluene was a more effective solvent (entries 2–6). However, increase of the dosage of DMSO to 20% v/v of solvent gave only 49% yield of the product (entry 7). No products were detected without DMSO in this system (entry 8). Other silver salts as additives gave relatively low yields (entries 9–11). Addition of 20 mol% Cu$_2$O used as a co-catalyst gave a slightly higher yield of the product (entry 12). Reduction of the amount of Ag$_2$CO$_3$ gave relatively lower yields (entries 13). The yields of the desired product decreased to 45%, 55% and 55% by using 20 mol% of Pd(TFA)$_2$, 20 mol% of PdCl$_2$ and 10 mol% of Pd(OAc)$_2$ respectively (entries 14–16). A 46% yield of allylated arene was formed when the reaction was carried out at 80 °C (entry 17). Interestingly, the yields increased appreciably to 75% and 89% by reducing the dosage of Cu$_2$O to 5 mol% and 1 mol% respectively (entries 18 and 19). An 80% yield of the product was obtained by using 10 mol% Pd(OAc)$_2$ (entry 20). However, reducing the amount of Pd(OAc)$_2$ to 5 mol% resulted only 54% yield of the desired product (entry 21).

As depicted in Table 2, various arene carboxylates and allylic halides were tested as substrates for the coupling reaction under the typical conditions. The corresponding (E)-α-coupled allylic arenes were obtained as major products. Reaction of allylic iodide with 2,4,6-trimethoxylbenzoic acid gave a very low yield of the product (entry 1). Electron-rich arene carboxylates gave high to excellent yields of the corresponding products except for
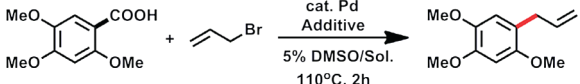
Table 1 Optimization of the typical reaction conditions[a]

Entry	Catalyst (mol%)	Additive (eq.)	Solvent	Yield (%)[b]
1	Pd(OAc)$_2$ (20)	Ag$_2$CO$_3$ (3)	Toluene	62
2	Pd(OAc)$_2$ (20)	Ag$_2$CO$_3$ (3)	Benzene	36
3	Pd(OAc)$_2$ (20)	Ag$_2$CO$_3$ (3)	DCE	54
4	Pd(OAc)$_2$ (20)	Ag$_2$CO$_3$ (3)	Dioxane	56
5	Pd(OAc)$_2$ (20)	Ag$_2$CO$_3$ (3)	DMF	trace
6	Pd(OAc)$_2$ (20)	Ag$_2$CO$_3$ (3)	DMSO	0
7	Pd(OAc)$_2$ (20)	Ag$_2$CO$_3$ (3)	Toluene (20% DMSO)	49
8	Pd(OAc)$_2$ (20)	Ag$_2$CO$_3$ (3)	Toluene (0% DMSO)	15
9	Pd(OAc)$_2$ (20)	Ag$_2$SO$_4$ (3)	Toluene	31
10	Pd(OAc)$_2$ (20)	Ag$_2$O (3)	Toluene	39
11	Pd(OAc)$_2$ (20)	AgOAc (6)	Toluene	47
12	Pd(OAc)$_2$ (20)/Cu$_2$O (20)	Ag$_2$CO$_3$ (3)	Toluene	67
13	Pd(OAc)$_2$ (20)/Cu$_2$O (20)	Ag$_2$CO$_3$ (1)	Toluene	49
14	Pd(TFA)$_2$ (20)/Cu$_2$O (20)	Ag$_2$CO$_3$ (3)	Toluene	45
15	PdCl$_2$ (20)/Cu$_2$O (20)	Ag$_2$CO$_3$ (3)	Toluene	55
16	Pd(OAc)$_2$ (10)/Cu$_2$O (20)	Ag$_2$CO$_3$ (3)	Toluene	55
17[c]	Pd(OAc)$_2$ (20)/Cu$_2$O (20)	Ag$_2$CO$_3$ (3)	Toluene	46
18	Pd(OAc)$_2$ (20)/Cu$_2$O (5)	Ag$_2$CO$_3$ (3)	Toluene	75
19	**Pd(OAc)$_2$(20)/Cu$_2$O (1)**	**Ag$_2$CO$_3$(3)**	**Toluene**	**89**
20	**Pd(OAc)$_2$(10)/Cu$_2$O (1)**	**Ag$_2$CO$_3$(3)**	**Toluene**	**80**
21	Pd(OAc)$_2$ (5)/Cu$_2$O (1)	Ag$_2$CO$_3$ (3)	Toluene	54

[a] Reaction conditions: 2,4,5-trimethoxybenzoic acid (0.1 mmol), allylic bromide (0.2 mmol), 5% DMSO/solvent (v/v), 110 °C, 2 h, unless otherwise noted. [b] Yield determined by GC with nitrobenzene as internal standard. [c] The reaction was carried out at 80 °C.
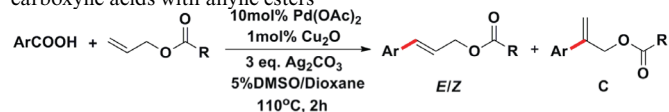
2,4-dimethoxylbenzoic acid (entries 2–5). The desired allylated arene was also obtained in good yield using halogen-substituted benzoic acid (entry 6). Although the yield was low, heterocyclic carboxylic acid was also an effective substrate (entry 7). Various alkyl-substituted allylic chlorides were proved to be effective coupling partners (entries 8–11). 1-Bromo-2-butene and aryl-substituted allylic halide gave low yields of the product (entries 12 and 13). A 33% yield of the desired product was obtained by using halide branched allylic halide such as 1, 2-dibromo-2-propene (entry 14). Although only electron-rich aromatic carboxylic acids bearing at least one *ortho* substituted group are effective substrates, the features of direct decarboxylative arene allylation using carboxylic acids and allylic halides, relatively few side products and short reaction time make this procedure very attractive.

In the Tsuji–Trost reaction, allylic halides and allylic esters act as effective coupling partners. However, the direct decarboxylative Heck-type coupling products were formed by using aromatic carboxylic acids and allylic carboxylic esters under similar conditions (Table 3). Various arene carboxylates and allylic carboxylic esters were investigated as substrates for the direct decarboxylative Heck-type coupling. Our experiments show that aromatic carboxylic acids with at least one *ortho* substituent are effective substrates (entries 1–6). It is noteworthy that polyfluorobenzoic acids give relatively low yields of the desired products (entries 7–9). Various allylic carboxylic esters have been proved to be effective coupling partners (entries 10–13). A competing Heck coupling would occur between the allylic and the acrylic double bonds (entries 12 and 13). However, the C–C bond formation only took place at the
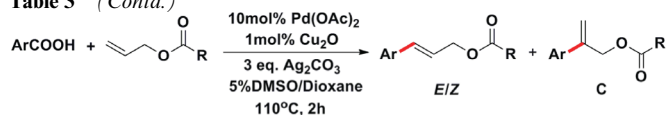
Table 2 Palladium-catalyzed decarboxylative allylation of arenes[a]

Entry	Allylic halide	Product	Yield (%)[b]
1	(allyl iodide)	(2,4,5-trimethoxy allyl arene)	12
2	(allyl bromide)	(2,4,5-trimethoxy allyl arene)	90
3	(allyl bromide)	(2,6-dimethoxy allyl arene)	88
4	(allyl chloride)	(2,4,5-trimethoxy allyl arene)	70
5[c]	(allyl chloride)	(2,6-dimethoxy allyl arene)	28
6	(allyl bromide)	(bromo dimethoxy allyl arene)	60
7	(allyl bromide)	(methylbenzofuran allyl)	27
8	(methallyl chloride)	(dimethoxy methallyl arene)	48
9[c]	(methallyl chloride)	(dimethoxy methallyl arene)	30
10	(crotyl chloride)	(2,4,5-trimethoxy crotyl arene)	90 (E/Z = 1.8/1)[d]
11	(crotyl chloride)	(2,6-dimethoxy crotyl arene)	82 (E/Z = 1.6/1)[d]
12[c]	(crotyl bromide)	(2,4,5-trimethoxy crotyl arene)	17
13[c]	Ph (cinnamyl bromide)	(2,4,5-trimethoxy cinnamyl arene)	27
14[c]	(2,3-dibromopropene)	(bromo allyl arene)	33

[a] Reaction conditions: acid (0.3 mmol), allylic halide (0.6 mmol), 10 mol% Pd(OAc)$_2$, 1 mol% Cu$_2$O, 3 eq. Ag$_2$CO$_3$, 5% DMSO/toluene (v/v), 110 °C, 2 h. [b] Isolated yields. [c] 20 mol% Pd(OAc)$_2$. [d] The E- and Z-isomers are confirmed by NOE experiments.

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Table 3 Palladium-catalyzed decarboxylative Heck coupling of aromatic carboxylic acids with allylic esters[a]

ArCOOH + [allylic ester] → [conditions: 10 mol% Pd(OAc)₂, 1 mol% Cu₂O, 3 eq. Ag₂CO₃, 5% DMSO/Dioxane, 110 °C, 2h] → E/Z product + C product

Entry	Allylic ester	Product	Yield (%)[b]
1	allyl acetate	aryl (2,4,6-trimethoxy) E/Z allyl acetate	70 (16/8/1)
2	allyl acetate	aryl (2,4,5-trimethoxy) allyl acetate	95 (10/2/1)
3	allyl acetate	aryl (2,4-dimethoxy) allyl acetate	90 (8/2/1)
4	allyl acetate	aryl (2,4-dimethoxy-Br) allyl acetate	80 (20/4/1)
5	allyl acetate	aryl (2-methoxy) allyl acetate	42 (14/2/1)
6	allyl acetate	aryl (2,4,6-trimethyl) allyl acetate	52[c]
7	allyl acetate	aryl (2,6-difluoro) allyl acetate	26 (16/2/1)
8	allyl acetate	aryl (2,4,6-trifluoro) allyl acetate	41 (15/3/1)
9	allyl acetate	aryl (pentafluoro) allyl acetate	33 (20/3/1)
10	methallyl acetate	aryl (2,4,5-trimethoxy) methallyl acetate	62 (5/1/4)
11	allyl benzoate	aryl (2,4,5-trimethoxy) allyl benzoate	90 (8/2/1)
12	allyl cinnamate	aryl (2,4,5-trimethoxy) allyl cinnamate	95 (6/1/1)
13	allyl methacrylate	aryl (2,4,5-trimethoxy) allyl methacrylate	80 (6/1/1)

Table 3 *(Contd.)*

ArCOOH + [allyl Ph ether] → [conditions: 10 mol% Pd(OAc)₂, 1 mol% Cu₂O, 3 eq. Ag₂CO₃, 5% DMSO/Dioxane, 110 °C, 2h] → E/Z product + C product

Entry	Allylic ester	Product	Yield (%)[b]
14	allyl phenyl ether	aryl (2,4,5-trimethoxy) allyl phenyl ether	86 (8/1/1)

[a] Reaction conditions: acid (0.5 mmol), allylic ester (1.0 mmol), 10 mol% Pd(OAc)₂, 1 mol% Cu₂O, 3 eq. Ag₂CO₃, 5% DMSO/dioxane (v/v), 110 °C, 2 h. [b] Isolated yields, the isomers are confirmed by GC-MS, the ratios of the isomers are determined by ^{1}H NMR, and the *E*- and *Z*-isomers are confirmed by NOE experiments. [c] Only one compound was obtained.

position of the terminal allylic C=C bond alternative to the other one. This suggests that another C=C bond could be tolerated in the allylic substrate. In addition, an allylic ether is also an effective coupling partner in this system (entry 14). A very low yield (21%) of the product was obtained without Cu₂O in the reaction of 2,4,6-trimethoxybenzoic acid with allylic acetic ester under the typical conditions. This suggests that catalytic Cu₂O in this system is very important to form the desired product smoothly.

It is very interesting that a γ-coupled product was formed in moderate yield using (*Z*)-1,3-dichloro-2-butene as allylic coupling partner (Scheme 2). A possible mechanism was demonstrated as following. Decarboxylation of aromatic acid and Pd would generate intermediate **1**, then proceed *via* a Heck-like addition to form intermediate **2** followed by elimination of PdL₂(OAc)Cl as an alternative to PdL₂(OAc)H to give product **3** rather than **4**. Therefore, the mechanism for the decarboxylative allylation might be similar to that proposed by Myers.[2] Carboxyl exchange between palladium acetate and arene carboxylic acid followed by decarboxylation forms an arylpalladium intermediate which should be the rate-determining step, then olefin insertion followed by β-halide elimination to give the corresponding allylic arene. This procedure might be present as a potentially interesting topic that draws further attention. While in the decarboxylative Heck-type coupling with allylic ester and ether, a β-hydride elimination would occur to give aryl-branched allylic esters and/or ether. Further studies on the mechanism in details involving the role of Cu₂O are ongoing.
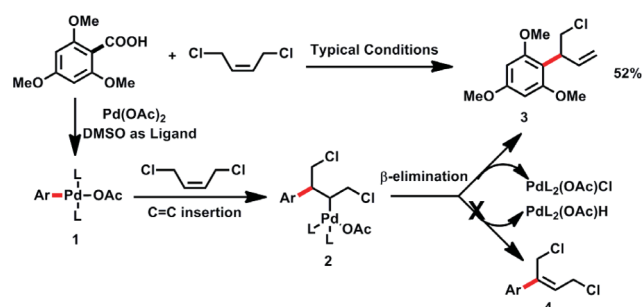
Scheme 2 An insight into the possible mechanism.

In summary, this work demonstrates an alternative method to prepare allylated arenes and aryl-substituted allylic esters *via* catalytic decarboxylative C–C bond formation using aromatic

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carboxylic acids and allylic halides and esters. The mechanism for the decarboxylative allylation might involve a Heck-like addition of Ar-PdL$_2$(OAc) to the double bond followed by elimination of PdL$_2$(OAc)Cl or PdL$_2$(OAc)Br. Although one *ortho* substituent in the electron-rich arene carboxylic acid is necessary, the organometallic-reagent free, short reaction time, and relatively high chemoselectivity features make this system attractive. Further investigation of this procedure is underway in our laboratory.

Notes and references

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