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Development of a Decarboxylative Palladation Reaction and Its Use in a Heck-type Olefination of Arene Carboxylates

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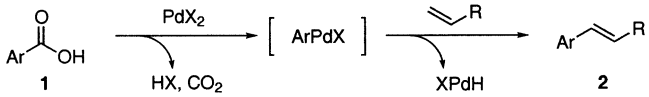
We describe the development of a palladium-catalyzed decarboxylative coupling reaction of arene carboxylates with olefinic substrates. The process can be viewed as proceeding by an initial Ar-S_E reaction, depicted in Scheme 1, involving ipso attack of an electrophilic Pd(II) intermediate on an arene carboxylate to form an arylpalladium(II) species with loss of carbon dioxide. This intermediate is then proposed to react with an olefinic substrate by steps common to the Heck coupling process.[1]

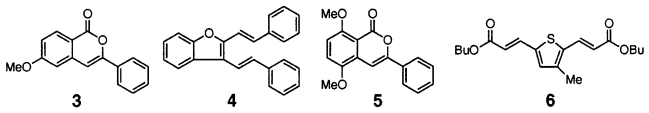
Scheme 1



A large number of palladium sources, as well as other metals, were screened for their ability to promote the decarboxylative coupling of 2,4,5-trimethoxybenzoic acid (**1a**) with styrene. After many unsuccessful experiments, we discovered that warming of **1a** and styrene (1.2 equiv) in the presence of potassium carbonate (5 equiv), palladium(II) trifluoroacetate (0.15 equiv), and copper(II) trifluoroacetate (hydrate, 2 equiv) in DMSO (85 °C, 12 h) led to the formation of the coupling product *trans*-2,4,5-trimethoxystilbene (**2a**) in 82% yield. These conditions did not translate well with other, less electron-rich carboxylic acid substrates, which could be recovered unchanged from the reaction mixture, pointing toward a problem in the decarboxylation step. Two critical reaction parameters were identified whose modification led to a more general and efficient method. First, the use of the additive silver(I) carbonate (3 equiv), in lieu of K_2CO_3 and $Cu(O_2CCF_3)_2$, was found to dramatically improve the efficiency of the decarboxylation reaction. This additive presumably functions as both a base and a stoichiometric oxidant and is believed to prolong the lifetime of the active catalyst. The second critical parameter proved to be the reaction solvent. The optimum reaction medium was found to be 5% DMSO in DMF. Use of either solvent alone led to dramatically reduced yields of coupling products (vide infra).

Under these presently optimal reaction conditions (0.2 equiv of $Pd(O_2CCF_3)_2$, 3 equiv of Ag_2CO_3, 5% DMSO-DMF), a wide range of arene carboxylates was found to undergo efficient Heck-type decarboxylative coupling with olefinic substrates between 80 and 120 °C (0.5−3 h reaction time, Table 1). Reactions could be conducted in the air (all entries, Table 1), under nitrogen, or under pure oxygen without discernible differences and were unaffected by small amounts of water. Good coupling yields were obtained with many electron-rich carboxylic acid substrates (entries 1−6), as well as substrates with electron-withdrawing substituents such as fluoro, chloro, bromo, and nitro (entries 9−14). Certain heterocyclic carboxylic acids were also effective substrates (entries 15−18). Our experiments suggest that at least one *ortho* substituent is necessary for successful decarboxylative palladation to occur (vide infra). Many *o,o*-disubstituted benzoic acids were effective substrates; the coupling reactions of the sterically hindered mesitylene carboxylic acid (entries 7 and 8) are particularly noteworthy. Several alkenes were used successfully as Heck reaction partners, including styrene, acrylates, (*E*)-ethyl crotonate (entry 4), and, notably, cyclohexenone (entries 5, 8).[2]

The primary pathway mitigating decarboxylative palladation in those cases where this was not the major course of reaction was an apparent C−H insertion or *ortho*-palladation reaction, a pathway that was especially prevalent among substrates lacking *ortho* substituents, those with a single *ortho* substituent, and in certain heteroaromatic systems. For example, *p*-anisic acid was observed to form the isocoumarin derivative **3**,[3] while 2-benzofurancarboxylic acid reacted by a slightly different sequence to form *trans*,*trans*-2,3-distyrylbenzofuran (**4**) (see also Table 1, entry 18 and Supporting Information). Use of 5% DMSO-DMF as solvent was found to maximize the decarboxylative coupling pathway relative to C−H insertion (e.g., **1b** → **2b**, 70% yield, whereas in DMF alone the isocoumarin **5** was the major product).



Evidence supporting the proposed mechanism for the decarboxylative coupling process was gained from ^{1}H NMR studies of the reaction of **1a** with $Pd(O_2CCF_3)_2$ (1.2 equiv) in pure DMSO-d_6 (eq 1). Heating these reactants at 80 °C for 1 h led to the evolution of CO_2 (precipitate formed in lime water) and the disappearance of resonances associated with **1a**. Peaks for a new intermediate, with arene resonances upfield of those of **1a**, were identified (72% yield based on an internal standard). This intermediate was assigned as the arylpalladium(II) species **7**, a proposal supported by the finding that addition of styrene (1.5 equiv, 23 °C) led to rapid (<3 min) formation of the coupling product **2a** (73%; quantitative based on **7**) with simultaneous precipitation of a solid presumed to be Pd(0). Further evidence for the assignment of the observed intermediate as the arylpalladium(II) species was obtained by treating **7** with excess trifluoroacetic acid (10 equiv) followed by heating (70 °C, 12 h), leading to quantitative protonolysis to give 1,2,4-trimethoxybenzene. ^{1}H NMR analysis confirmed that the rate of decarboxylation of **1a** was much faster in DMF-d_7 containing small amounts of DMSO-d_6 than it was in either solvent alone. These observations, coupled with those concerning the competing *ortho*-palladation reaction discussed above, point toward the unique effectiveness of low concentrations of DMSO in DMF in the decarboxylative coupling process. Although speculative at this point,

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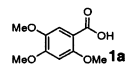
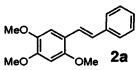
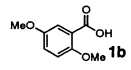
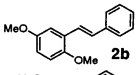
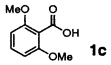
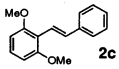
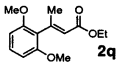
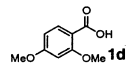
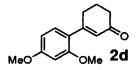
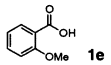
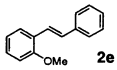
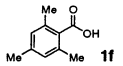
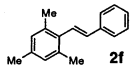
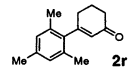
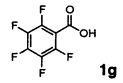
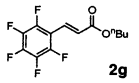
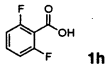
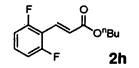
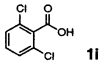
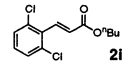
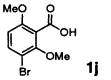
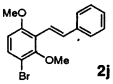
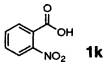
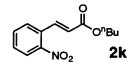
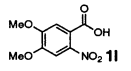
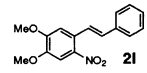
Table 1. Decarboxylative Olefination Reactions[a]

Entry	Acid	Alkene	Product	Reaction Time (h)	Isolated Yield (%)
1[b]	 **1a**		 **2a**	1	91
2	 **1b**		 **2b**	3	71
3	 **1c**		 **2c**	1	92
4	**1c**		 **2q**	3	66
5[b]	 **1d**		 **2d**	0.5	90
6	 **1e**		 **2e**	3	72
7	 **1f**		 **2f**	1.5	99
8	**1f**		 **2r**	0.5	61
9	 **1g**		 **2g**	0.5	66
10	 **1h**		 **2h**	3	76
11	 **1i**		 **2i**	3	47
12	 **1j**		 **2j**	0.5	82
13	 **1k**		 **2k**	3	42
14	 **1l**		 **2l**	3	85
15	**1m**		**2m**	1	78
16[b]	**1n**		**2n**	1	88
17	**1o**		**2o**	3	90
18[b]	**1p**		**2p**	1	57[c]

[a] Conditions: acid (1 equiv), alkene (1.5 equiv), $Pd(O_2CCF_3)_2$ (0.2 equiv), Ag_2CO_3 (3 equiv), 5% DMSO-DMF, 120 °C, except as noted. [b] Reaction conducted at 80 °C. [c] The bis-olefinated product **6** was also formed in 35% yield.

the data are consistent with the idea that a palladium(II)-sulfoxide (or possibly sulfide) complex mediates the decarboxylation step (but not *ortho*-palladation) and that this reaction is attenuated in the presence of high concentrations of the sulfoxide ligand.[4]

(1)

Although the transformation we describe is new, there are many important precedents which must be cited to appropriately reference our findings. Among these is the electrophilic decarboxylation of electron-rich acids to form organomercurials by Hg(II) salts,[5] the Pesci reaction, a hemidecarboxylation of phthalic acids by mercury salts,[6] the decarboxylative substitution of unsaturated acids by Br_2,[7] NBS,[8] NO_2^+,[9] and H^+,[10] and palladium-catalyzed Heck-type couplings of aromatic acid chlorides,[11] anhydrides,[12] and *p*-nitrophenyl esters[13] with various olefinic substrates. An important distinction between our work and earlier palladium-catalyzed processes is that the latter are proposed to evolve carbon monoxide, not carbon dioxide as in our work, a proposal which we have validated experimentally in the case of coupling of acid chlorides and olefins (Supporting Information). The primary novelty of the discovery we report is the decarboxylative palladation reaction, a step which might be productively utilized in ways beyond the coupling described, for example, in a palladium-catalyzed protiodecarboxylation reaction of aromatic carboxylic acids or in alternative C−C bond-forming processes.[14]

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Supporting Information Available: Experimental procedures, spectral data for new compounds (**2d**, **2g**−**r**, and **4**−**6**), and additional experimental results (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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