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Pd-Catalyzed Dearboxylative Heck Coupling with Dioxygen as the Terminal Oxidant

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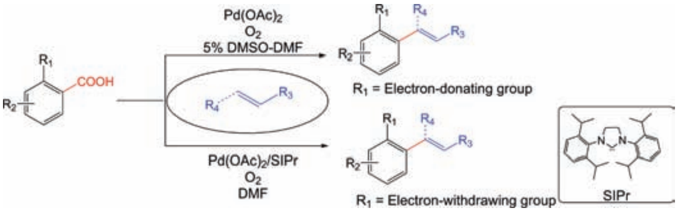
ABSTRACT



Pd-catalyzed decarboxylative Heck coupling of aromatic carboxylic acids with various olefins is developed using O_2 as the terminal oxidant. Enhancement of O_2 pressure leads to improving reaction turnover in this transformation and allows significantly reducing catalyst loading for efficient conversion of electron-rich benzoic acids. A Pd catalyst supported by a carbene ligand enables using electron-deficient benzoic acids as coupling partners.

Of contemporary interest is the transition-metal-catalyzed decarboxylative cross-coupling for C−C bond formation. Work along this line has been motivated by the concept that decarboxylative cross-coupling reactions open up new opportunities to employ a large pool of readily available aromatic carboxylic acids as arylating reagents.[1−5] In 2002, Myers and co-workers reported the first example of Pd-catalyzed decarboxylative Heck coupling of benzoic acids with styrene or α,β-unsaturated carbonyls, providing an attractive alternative to traditional Heck coupling.[2a] In view of the requirement for high loadings of palladium catalyst and silver salt in Myers' protocol, there is still significant room for improvement for the decarboxylative Heck reaction. To address the issue associated with the use of excessively expensive silver salt, we have established a Pd-catalyzed method for decarboxylative Heck coupling in which 1.2 equiv of BQ (BQ = *p*-benzoquinone) was used as a replacement for a silver salt.[2f] Unfortunately, this method is

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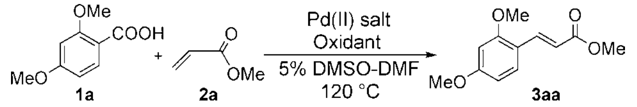
limited to electron-rich aromatic carboxylic acids. Goossen and Larrosa have independently disclosed that Ag salts were effective catalysts for protodecarboxylation of a wide range of benzoic acids,[4] pointing out the possibility that a silver salt is responsible for the decarboxylative process in the Pd/Ag-promoted decarboxylative Heck reaction. In our investigation on decarboxylative coupling of benzoic acids with indoles, we observed that Pd-catalyzed decarboxylation occurred for electron-rich aromatic carboxylic acids including heteroaromatic ones, whereas decarboxylation of electron-deficient aromatic carboxylic acids resulted from the contribution of the silver salt.[2j] Herein, we demonstrate that the Pd catalyst itself can effect decarboxylative Heck coupling of both electron-rich and electron-deficient aromatic carboxylic acids without the need for any Ag salt when dioxygen is used as the terminal oxidant and show that due to the difference in reactivity between electron-rich aromatic carboxylic acids and electron-deficient ones different Pd catalysts are required for decarboxylative Heck coupling to occur: $Pd(OAc)_2$ efficiently works for electron-rich aromatic carboxylic acids, while the $Pd(OAc)_2$/SIPr system (SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) enables the use of electron-deficient aromatic carboxylic acids as coupling partners.

For economical and environmental reasons, there is an increasing demand for the use of dioxygen as an oxidant for metal-catalyzed selective oxidation reactions. In this field, remarkable progress has been made,[6] including oxidation of alcohols to carbonyl compounds,[7] oxygenation of olefins,[8] and oxidative cross-coupling reactions.[9] To the best of our knowledge, however, the catalytic decarboxylative coupling of aromatic carboxylic acids with dioxygen as an oxidant has not been reported previously. Since Pd-catalyzed aerobic oxidative reactions generally involve direct aerobic oxidation of Pd(0) species that compete with aggregation of the catalyst into inactive palladium black, the rapid oxidation of the Pd(0) intermediate is a key to achieving efficient conversion for these reactions.[9c] In this report, we observed that in many cases a slight increase in dioxygen pressure significantly improved the yields due to acceleration of oxidation of the Pd(0) intermediate.

We initiated our investigation by examining the decarboxylative coupling of 2,4-dimethoxybenzoic acid **1a** with 2 equiv of methyl acrylate **2a**. Gratifyingly, the reaction conducted in 5% DMSO/DMF (v/v) mixed solvents at 120 °C in the presence of 10 mol % of $Pd(TFA)_2$ (TFA = trifluoroacetate) under 1 atm of dioxygen provided the desired product **3aa** in 85% yield (Table 1, entry 1). Using $Pd(OAc)_2$ in place of $Pd(TFA)_2$ furnished 90% isolated yield under otherwise identical conditions (entry 2). An amount of 5 mol % of $Pd(OAc)_2$ furnished a decreased yield under 1 atm of dioxygen (entry 3); however, a slight increase in dioxygen pressure (1.8 atm) allowed reducing palladium loading to 5 mol % without compromising the yield (entry 4). However, the reaction gave poor yields under both 1 and 1.8 atm of air (Table 1, entries 5 and 6).

Table 1. Decarboxylative Heck Coupling of 2,4-Dimethoxybenzoic Acid **1a** with Methyl Acrylate **2a** under Different Conditions[a]



entry	Pd (mol %)	oxidant (1 atm)	isolated yield (%)[b,c]
1	$Pd(TFA)_2$ (10)	O_2	85
2	$Pd(OAc)_2$ (10)	O_2	90
3	$Pd(OAc)_2$ (5)	O_2	73
4[d]	$Pd(OAc)_2$ (5)	O_2	89
5	$Pd(OAc)_2$ (10)	air	34
6[e]	$Pd(OAc)_2$ (10)	air	36

[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), 5% DMSO−DMF (2 mL), 120 °C, 10 h. [b] Average of two runs. [c] The *E*/*Z* ratio of product is >20:1, as determined by ^1H NMR. [d] The reaction was carried out under 1.8 atm of O_2. [e] The reaction was carried out under 1.8 atm of air.

We next evaluated the substrate scope of this protocol with respect to aromatic carboxylic acids. As shown in Table 2, this protocol was applicable to the coupling of a broad array of aromatic carboxylic acids with methyl acrylate **2a**. An amount of 5 mol % of $Pd(OAc)_2$ with 1.8 atm of O_2 furnished good to excellent yields with many electron-rich aromatic carboxylic acids. Compared with 2,4-dimethoxybenzoic acid, 2-methoxy-4-methylbenzoic acid is less electron-rich and thereby less reactive, providing the corresponding product in 75% yield with 10 mol % of $Pd(OAc)_2$ under 1 atm of dioxygen and 34% yield with 5 mol % of $Pd(OAc)_2$ under 1.8 atm of dioxygen (Table 2, entry 3). Compared with its isomer 2,4,5-trimethoxybenzoic acid, 2,4,6-trimethoxybenzoic acid was a less effective substrate to afford 70% yield in the presence of 10 mol % of $Pd(OAc)_2$ under 1 atm of dioxygen, which reflected the effect of substitution pattern on the reactivity of benzoic acids toward decarboxylative coupling (Table 2, entries 4 and 5). In the reaction of benzoic acid bearing an amino group, 2 mol % of $Pd(OAc)_2$ gave rise to a yield comparable to that obtained with 5 mol % of $Pd(OAc)_2$ under 1.8 atm of dioxygen, presumably because coordination of the amino-containing substrate to the Pd center stabilized the Pd catalyst (Table 2, entry 6). An elevated dioxygen pressure (3.2 atm) was required to deliver an excellent yield for benzoic acid bearing a bromo substituent, which could be explained by rapid aerobic oxidation of a Pd(0) intermediate under a higher dioxygen pressure that should

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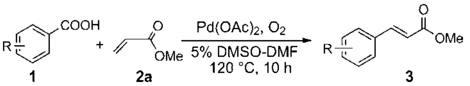
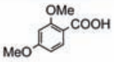
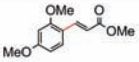
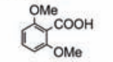
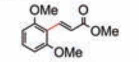
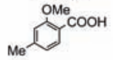
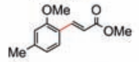
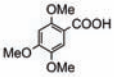
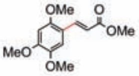
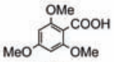
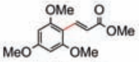
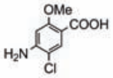
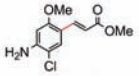
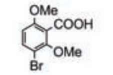
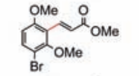
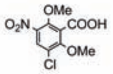
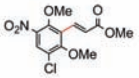
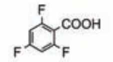
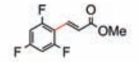
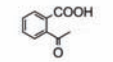
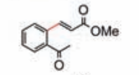
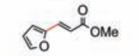
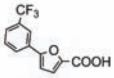
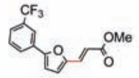
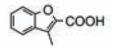
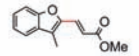
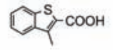
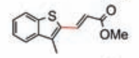
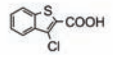
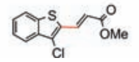
Table 2. Decarboxylative Heck Coupling of Aromatic Carboxylic Acids with Methyl Acrylate **2a**[a]



1 + **2a** → **3**

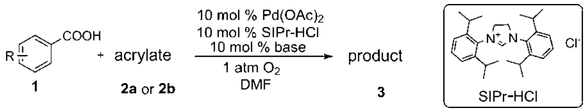
entry	Ar-COOH		product[b]		yield (%)[c]
1		**1a**		**3aa**	90 (89)[d]
2		**1b**		**3ba**	88 (96)[d]
3		**1c**		**3ca**	75 (34)[d]
4		**1d**		**3da**	91 (94)[d]
5		**1e**		**3ea**	70 (55)[d]
6		**1f**		**3fa**	64 (60)[e]
7		**1g**		**3ga**	36 (85)[f]
8		**1h**		**3ha**	23 (43)[g]
9		**1i**		**3ia**	52 (64)[g]
10		**1j**		**3ja**	30 (26)[d]
11		**1k**		**3ka**	44 (30)[d]
12		**1l**		**3la**	61 (67)[d]
13		**1m**		**3ma**	53 (85)[d]
14		**1n**		**3na**	40 (72)[g]
15		**1o**		**3oa**	40 (75)[g]

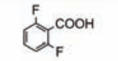
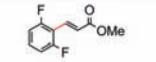
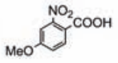
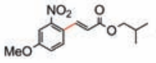
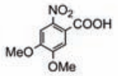
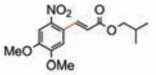
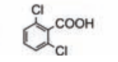
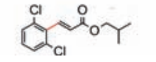
[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), Pd(OAc)$_2$ (10 mol %), O$_2$ (1 atm), 5% DMSO−DMF (2 mL), 120 °C, 10 h. [b] The ratio of *E*/*Z* > 20:1, as determined by ^{1}H NMR. [c] Isolated yield by an average of two runs. [d] Yield in parentheses based on Pd(OAc)$_2$ (5 mol %) with O$_2$ (1.8 atm). [e] Yield in parentheses based on Pd(OAc)$_2$ (2 mol %) with O$_2$ (1.8 atm). [f] Yield in parentheses based on Pd(OAc)$_2$ (10 mol %) with O$_2$ (3.2 atm). [g] Yield in parentheses based on Pd(OAc)$_2$ (10 mol %) with O$_2$ (1.8 atm).

reduce the concentration of Pd(0) species and therefore efficiently inhibit oxidative addition of the C−Br bond by the Pd(0) complex (Table 2, entry 7). As exemplified by 3-chloro-2,6-dimethoxy-5-nitrobenzoic acid, the addition of an electron-withdrawing group to the aromatic ring of benzoic acid led to a decrease in yield due to concomitant formation of a protodecarboxylation product (Table 2, entry 8). However, electron-deficient trifluorobenzoic acid formed the hoped-for product in a good yield (Table 2, entry 9). *Ortho*-substituted acetobenzoic acid, a substrate that is unreactive in Pd/Ag-catalyzed decarboxylative Heck reaction,[2a] was observed for the first time to undergo decarboxylative coupling with methyl acrylate **2a**, albeit in a low yield (Table 2, entry 10). Heteroaromatic carboxylic acids proved to be suitable substrates, regardless of the presence or absence of a substituent on the position *ortho* to the carboxyl (Table 2, entries 11−15). This reaction can be scaled up. For example, the reaction of **1a** with **2a** on a 1 mmol scale gave a yield (85%) comparable to that on a 0.2 mmol scale.

When this reaction was expanded to electron-deficient benzoic acids, very low yields of the desired products were obtained due to the poor reactivity of the Pd(II) catalyst toward decarboxylation of electron-deficient benzoic acids. The previous studies by Goossen, Larrosa, and us have established that silver salts efficiently promote decarboxylation of electron-deficient benzoic acids.[2j,k,4] The difference in the ability to promote decarboxylation between Ag(I) and Pd(II) likely results from the fact that Ag(I) is more electron rich than Pd(II). Thus, we speculated that a combination of Pd(II) with a strong electron-donating ligand such as an N-heterocyclic carbene would improve the activity of the Pd catalyst in decarboxylative coupling of electron-deficient benzoic acids by enhancing the electron density at the Pd(II) center. We were pleased to find that the Pd(OAc)$_2$/SIPr system effected decarboxylative Heck coupling of electron-deficient benzoic acids in moderate to good yields (Table 3).

Table 3. Decarboxylative Heck Coupling of Electron-Deficient Benzoic Acids with SIPr as Ligand[a]

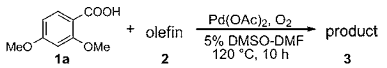


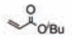
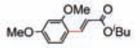
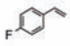
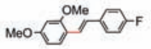
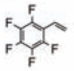
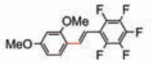
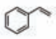
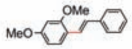
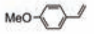
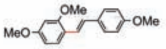
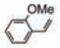
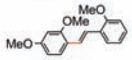
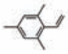
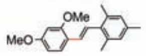
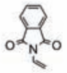
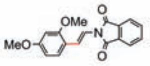
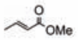
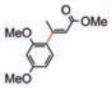
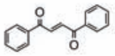
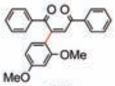
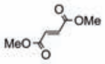
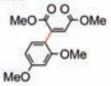
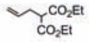
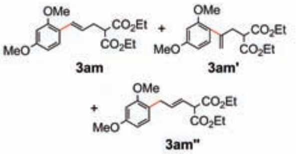
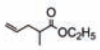
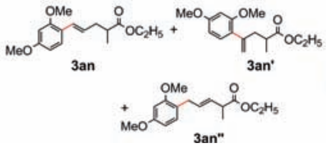
entry	Ar-COOH		base	°C	product[b]		yield (%)[c]
1		**1p**	KOAc	120		**3pa**	72
2		**1q**	K$_3$PO$_4$	150		**3qb**	41
3		**1r**	K$_3$PO$_4$	150		**3rb**	58
4		**1s**	K$_3$PO$_4$	150		**3sb**	53

[a] Conditions: **1** (0.2 mmol), **2** (0.6 mmol), Pd(OAc)$_2$ (10 mol %), SIPr−HCl (10 mol %), base (10 mol %), O$_2$ (1 atm), DMF (2 mL), 10 h. [b] The ratio of *E*/*Z* > 20:1, as determined by ^{1}H NMR. [c] Isolated yield by an average of two runs.

Using 10 mol % of Pd(OAc)$_2$ as catalyst, the decarboxylative Heck coupling of a variety of olefins with 2,4-dimethoxybenzoic acid **1a** was also investigated under 1 atm of dioxygen; it is also revealed that an increase in dioxygen pressure efficiently improved the reaction turnover between the yields obtained with 5 mol % of Pd(OAc)$_2$ under 1.8 atm of dioxygen and the yields obtained with 10 mol % of Pd(OAc)$_2$ under 1 atm of dioxygen (Table 4). A sterically

Table 4. Decarboxylative Heck Coupling of 2,4-Dimethoxybenzoic Acid **1a** with Various Olefins[a]



entry	olefin		product[b]		yield (%)[c]
1		2b		3ab	93 (83)[e]
2		2c		3ac	61 (74)[e]
3		2d		3ad	90 (76)[e]
4		2e		3ae	84 (65)[e]
5		2f		3af	56 (69)[e]
6		2g		3ag	85 (52)[e]
7		2h		3ah	94 (51)[e]
8		2i		3ai	48 (57)[f]
9		2j		3aj	58 (67)[e]
10[d]		2k		3ak	81 (81)[e]
11[d]		2l		3al	61 (58)[f]
12		2m			62 (61)[e] (8.7:1:1)[g]
13		2n			80 (71)[e] (6.6:1:1)[g]

[a] Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Pd(OAc)$_2$ (10 mol %), O$_2$ (1 atm), 5% DMSO−DMF (2 mL), 120 °C, 10 h. [b] The ratio of *E*/*Z* > 20:1 unless otherwise noted, as determined by ^{1}H NMR. [c] Isolated yield by average of two runs. [d] The ratio of *Z*/*E* > 20:1, as determined by NOESY experiment and ^{1}H NMR. [e] Yield in parentheses based on Pd(OAc)$_2$ (5 mol %) with O$_2$ (1.8 atm). [f] Yield in parentheses based on Pd(OAc)$_2$ (10 mol %) with O$_2$ (1.8 atm). [g] The ratio of desired product to minor product.

and electronically diverse array of styrene derivatives smoothly underwent reactions to form (*E*)-stilbenes exclusively in good yields with an *E*/*Z* ratio >20 (Table 4, entries 2−7). *N*-Vinyl phthalimide, a heteroatom-substituted olefin, participated in this reaction to provide the corresponding product in 57% yield with 10 mol % of Pd(OAc)$_2$ under 1.8 atm of dioxygen (Table 4, entry 8). 1,2-Disubstituted olefins can also be arylated with a high level of stereoselectivity in good yields to furnish trisubstituted olefins of which structures were unequivocally confirmed by NOESY experiments (Table 4, entries 9−11). For example, (*E*)-methyl crotonate produced trisubstituted *E* isomer in 67% yield with an *E*/*Z* ratio >20 (Table 4, entry 9), and both (*E*)-1,2-dibenzoylethylene and dimethyl fumarate stereoselectively generated the *Z* isomer in 81% and 58% yields, respectively (Table 4, entries 10 and 11). It is noteworthy that the Heck coupling of 1,2-disubstituted olefins for synthesis of trisubstituted olefins is not common because of the lower reactivity of this kind of olefin.[9g,10] The reaction of unactivated alkyl-substituted olefins preferentially formed *trans*-styrenyl olefins with terminal olefins and allylic olefins as minor products (Table 4, entries 12 and 13). Thus, a broad range of both mono- and disubstituted olefins can be used as coupling partners in this decarboxylative Heck reaction.

In summary, we have developed a new Pd-catalyzed method for decarboxylative Heck coupling of various aromatic carboxylic acids with a wide range of olefins by using dioxygen as the terminal oxidant. Increasing dioxygen pressure resulted in a raised reaction turnover for this transformation, and as for electron-rich benzoic acid, increasing dioxygen pressure enabled a lowering of the catalyst loading. Furthermore, enhancing electron density of Pd(II) via coordination of the electron-donating N-heterocyclic carbene ligand to the Pd(II) center efficiently improved the yield for electron-deficient benzoic acids. Efforts are currently underway to improve the efficiency of this reaction further and use dioxygen as a terminal oxidant for other decarboxylative coupling reactions.

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Supporting Information Available: Detailed experimental procedures and characterization for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (c) García-Rubia, A.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511.