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Palladium-Catalyzed Decarbonylative Heck Coupling of Aromatic Carboxylic Acids with Terminal Alkenes

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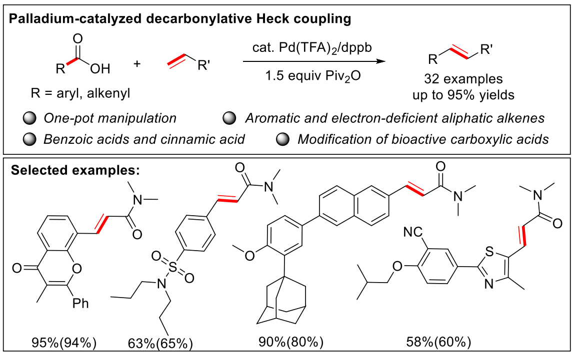
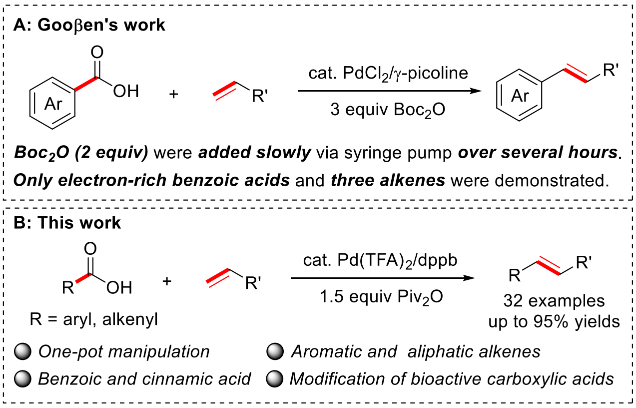
ABSTRACT: A palladium-catalyzed decarbonylative alkenylation of aromatic carboxylic acids was developed. Under the reaction conditions, various benzoic acids including those bearing functional groups coupled to terminal alkenes, producing the corresponding internal alkenes in good to high yields. Cinnamic acids and bioactive benzoic acids such as 3-methylflavone-8-carboxylic acid, probenecid, adapalin, and febuxostat were also applicable to this reaction, demonstrating the potential synthetic value of this new reaction in organic synthesis.



Heck coupling is one of the most powerful methods for preparing alkenes and has been widely used in the synthesis of some natural products, synthetic drugs, and functional material molecules.[1] Usually, aryl halides,[2] aryl triflates,[3] aryl diazonium salts,[4] and so on[5] are used as the aryl source. For comparison, aromatic carboxylic acids are more abundant and readily available. Their transformation for constructing functional molecules has attracted chemists' attention.[6] Their utilization in Heck couplings as the aryl source instead would greatly promote the synthesis of alkenes with high synthetic efficiency. Chemists have converted carboxylic acids into active derivatives such as aroyl chlorides,[7] anhydrides,[8] esters,[9] and amides[10] and then allowed these derivatives to couple to alkenes. Despite the fact that the corresponding internal alkenes could be produced by this strategy, the prepreparation of these derivatives has decreased their synthetic efficiency to some extent. The direct coupling of aromatic carboxylic acids with alkenes through decarboxylation has also been achieved; however, overstoichiometric oxidants are required, which also lead to some oxidative side reactions and the tolerance issue of functional groups prone to oxidants.[11] In 2002, Gooβen and coauthors reported a palladium-catalyzed decarbonylation Heck reaction from carboxylic acid using di-*tert*-butyl dicarbonate (Boc_2O) as an in situ activating reagent (Scheme 1A).[12] This reaction avoided the use of oxidants and the prepreparation of carboxylic derivatives, well overcoming the issues described above. However, because of the thermal instability, 3 equiv of Boc_2O was required. Moreover, most of the Boc_2O (2.0 equiv) should be slowly added via a syringe pump over several hours for a better yield, limiting its practical application in organic synthesis. In addition, only electron-rich benzoic acids and three alkenes were demonstrated.

Scheme 1. Decarbonylative Heck Coupling of Carboxylic Acids with Alkenes



Herein we report a new palladium-catalyzed decarbonylative Heck coupling reaction (Scheme 1B). This reaction used Piv_2O as the in situ activating reagent of carboxylic acids and was conducted in one pot,[13,14] well overcoming the manipulation shortcoming of Gooβen's work in which the

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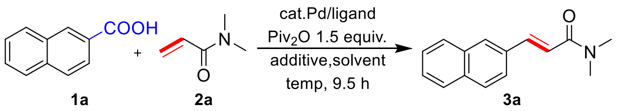
activating reagent should be added slowly. This substrate scope is also relatively general. Both electron-rich and electron-deficient benzoic acids readily coupled with various aromatic and electron-deficient aliphatic alkenes. This reaction was also applicable to cinnamic acid and bioactive benzoic acids. These results showed the potential application value of this new reaction in organic synthesis.

Heating a mixture of $Pd(TFA)_2$/dppb (5 mol %), 2-naphthoic acid **1a**, *N*,*N*-dimethylacrylamide **2a** (2.0 equiv), and Piv_2O (1.5 equiv) in dioxane to 150 °C for 10 h, the corresponding decarbonylative coupling product **3a** was produced in 60% yield (Table 1, entry 1). By the addition of 50 mol % NaCl, the yield of **3a** increased to 90% (Table 1, entry 2).[15] A similar result was obtained with KCl (Table 1, entry 3); however, NaBr and NaF could not enhance the reaction (Table 1, entries 4 and 5). Other selected palladium catalysts such as $Pd(OAc)_2$ and $Pd(AcAc)_2$ were tried, but relatively low yields were given (Table 1, entries 6–9).[16] Without the addition of palladium catalysts, no reaction took place (Table 1, entry 10). The phosphine ligands were subsequently screened, with dppb being the best choice (Table 1, entries 11–16). Increasing the ratio of Pd/P to 1:4 led to a slight decrease in yield, whereas no reaction was observed in the absence of phosphine ligands (Table 1, entries 17 and 18). This reaction also took place in THF, toluene, PhOMe, and NMP but was sluggish in DMF and DCE (Table 1, entries 19–24). Elevating the reaction temperature could not enhance the yield; whereas the reaction was conducted at 140 °C, only a 58% yield of **3a** was produced (Table 1, entries 25 and 26).

Table 1. Optimization of Reaction Conditions[a]



entry	cat. Pd	additive	ligand	solvent	yield (%)[b]
1	$Pd(TFA)_2$	-	dppb	dioxane	60
2	$Pd(TFA)_2$	NaCl	dppb	dioxane	90
3	$Pd(TFA)_2$	KCl	dppb	dioxane	89
4	$Pd(TFA)_2$	NaBr	dppb	dioxane	22
5	$Pd(TFA)_2$	NaF	dppb	dioxane	58
6	$Pd(OAc)_2$	NaCl	dppb	dioxane	40
7	$Pd(AcAc)_2$	NaCl	dppb	dioxane	41
8	$PdCl_2$	NaCl	dppb	dioxane	19
9	$Pd_2(dba)_3$	NaCl	dppb	dioxane	75
10	-	NaCl	dppb	dioxane	N.D.
11	$Pd(TFA)_2$	NaCl	dppp	dioxane	15
12	$Pd(TFA)_2$	NaCl	dpppe	dioxane	48
13	$Pd(TFA)_2$	NaCl	dppf	dioxane	70
14	$Pd(TFA)_2$	NaCl	DPE-phos	dioxane	79
15	$Pd(TFA)_2$	NaCl	PPh_3	dioxane	73
16	$Pd(TFA)_2$	NaCl	PPh_2Cy	dioxane	65
17[c]	$Pd(TFA)_2$	NaCl	dppb	dioxane	81
18	$Pd(TFA)_2$	NaCl	-	dioxane	N.D.
19	$Pd(TFA)_2$	NaCl	dppb	THF	61
20	$Pd(TFA)_2$	NaCl	dppb	toluene	39
21	$Pd(TFA)_2$	NaCl	dppb	PhOMe	22
22	$Pd(TFA)_2$	NaCl	dppb	NMP	12
23	$Pd(TFA)_2$	NaCl	dppb	DMF	trace
24	$Pd(TFA)_2$	NaCl	dppb	DCE	trace
25[d]	$Pd(TFA)_2$	NaCl	dppb	dioxane	58
26[e]	$Pd(TFA)_2$	NaCl	dppb	dioxane	92

[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Piv_2O (0.3 mmol), catalyst (5 mol % Pd), ligand (Pd/P = 1:2), additive (50 mol %), N_2, 150 °C, 10 h, solvent (2 mL). dppb (1,4-bis(diphenylphos phanyl)butane); dppp (1,3-bis(diphosp-hino)propane); dpppe (1,5-bis(diphenylphosphanyl)petane); dppf (1,1′-bis(diphenylphosphino)-ferrocene); DPE-phos ((oxybis(2,1-phenylene))bis(diphenylphosph-ane)). [b] GC yield using tridecane as an internal standard. [c] dppb (10 mol %). [d] 140 °C. [e] 160 °C.

With the optimized reaction conditions in hand, the substrate scope was subsequently investigated. As shown in Table 2, this reaction was relatively general. Various carboxylic acids coupled to terminal alkenes to produce the corresponding products in good to high yields. In addition to 2-naphthoic acid **1a**, 1-naphthoic acid also worked well to give the product **3b** in 97% yield. The π-extended anthracene-9-carboxylic acid also proved to be a good substrate (**3c**). Under the reaction conditions, both electron-rich and electron-deficient benzoic acids were applicable, furnishing the expected coupling products in good to high yields. The steric hindrance did not seem to affect the reaction because benzoic acids bearing 4-Ph, 3-Ph, and 2-Ph were all decarbonylatively alkenylated, and the coupling products **3g**, **3h**, and **3i** were generated in 74, 89, and 86% yields, respectively. Halo groups (F and Cl) also survived well. Heteroaromatic internal alkenes were also efficiently prepared through a similar decarbonylative alkenylation (**3n**–**p**). Notably, cinnamic acid was also workable, providing an efficient method for the synthesis of dienes (**3q** and **3r**).

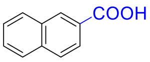
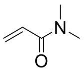
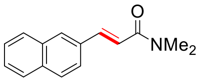
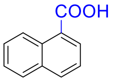
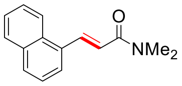
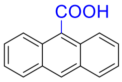
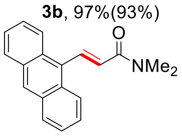
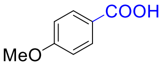
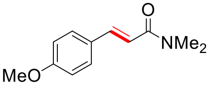
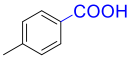
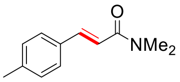
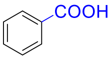
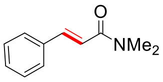
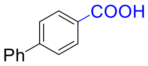
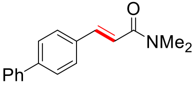
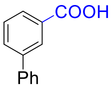
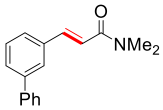
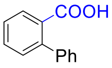
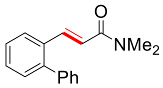
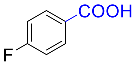
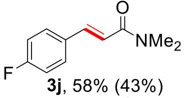
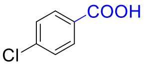
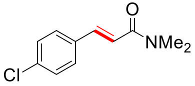
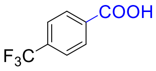
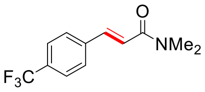
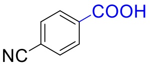
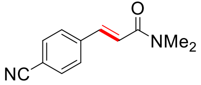
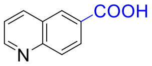
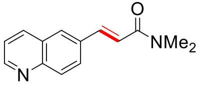
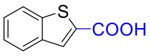
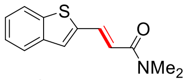
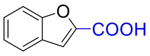
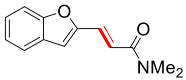
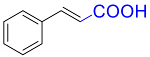
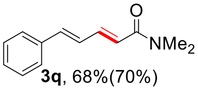
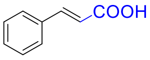
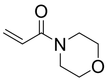
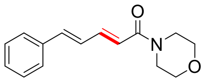
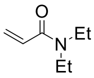
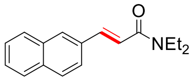
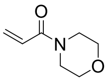
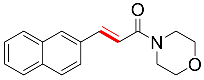
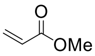
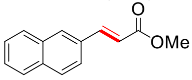
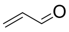
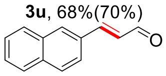
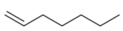
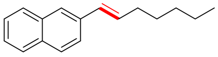
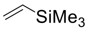
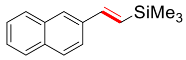
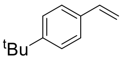
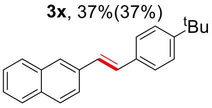
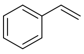
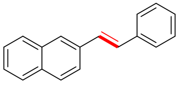
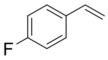
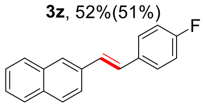
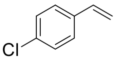
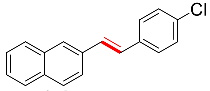
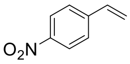
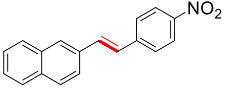
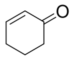
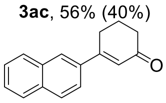
Other selected electron-deficient terminal alkenes such as *N*,*N*-diethylacrylamide, 1-morpholinoprop-2-en-1-one, and methyl acrylate were transformed into the corresponding internal alkenes in the present catalytic system (**3s**–**u**). However, only a trace amount of product was given with acrylaldehyde (**3v**). The reaction also progressed sluggishly with hept-1-ene (**3w**). To our delight, trimethyl(vinyl)silane could couple to **1a** to give **3x** in 37% yield. Aromatic terminal alkenes including those bearing functional groups also worked well under the reaction conditions (**3y**–**ac**). The internal alkenes exemplified by **2m** were not applicable to this reaction.

Interestingly, this reaction was applicable to the modification of bioactive carboxylic acids (Scheme 2). For example, 3-methylflavone-8-carboxylic acid, a clinical drug for coronary heart disease, was alkenylated to produce **3ae** in 95% yield. Probenecid is a clinical drug for hyperuricemia with chronic gouty arthritis and gouty stones. It also reacted smoothly with **2a**, producing the expected product **3af** in 63% yield. The clinic drugs adapalin and febuxostat were also proved to be the right substrates, furnishing the coupling products in high yields.

On the basis of previous literature,[12,14] a plausible mechanism was proposed. As shown in Scheme 3, the carboxylic acid was first in situ activated by Piv_2O to produce a mixing anhydride **A**, followed by oxidative addition with the active Pd(0) complex generated in situ to give an intermediate **B**. The resulting **B** further underwent decarbonylation,[17] transfer insertion, and β-elimination to yield the desired product and complex **E**. Complex **E** was subsequently transformed into the active Pd(0) catalyst to complete the catalytic cycle.

In summary, we have developed a decarbonylative alkenylation of carboxylic acids with terminal alkenes. This reaction used Piv_2O as the in situ activating reagent for carboxylic acids, avoided the use of overstoichiometric

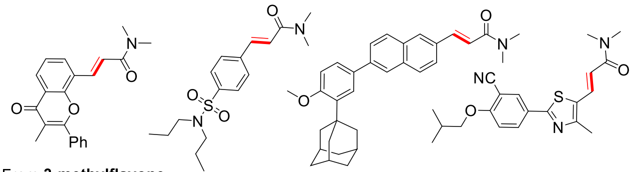
Table 2. Scope of Decarbonylative Heck-Type Coupling of Carboxylic Acids with Alkenes^{a}

Entry	Carboxylic acid	Alkene	Product, yield^{b}
1	 **1a**	 **2a**	 **3a**, 90%(87%)
2	 **1b**	**2a**	 **3b**, 97%(93%)
3^{c,h}	 **1c**	**2a**	 **3c**, 78%(75%)
4^{c,e}	 **1d**	**2a**	 **3d**, 62%(61%)
5^{c}	 **1e**	**2a**	 **3e**, 74%(70%)
6^{c,e}	 **1f**	**2a**	 **3f**, 77%(69%)
7^{c,e}	 **1g**	**2a**	 **3g**, 74%(76%)
8	 **1h**	**2a**	 **3h**, 89%(86%)
9^{c,e}	 **1i**	**2a**	 **3i**, 86%(85%)
10^{c,e,h}	 **1j**	**2a**	 **3j**, 58% (43%)
11^{c,e}	 **1k**	**2a**	 **3k**, 80%(80%)
12^{d,e}	 **1l**	**2a**	 **3l**,76%(75%)
13	 **1m**	**2a**	 **3m**, 71%(70%)
14	 **1n**	**2a**	 **3n**, 79%(76%)
15^{d}	 **1o**	**2a**	 **3o**, 63%(62%)
16^{d}	 **1p**	**2a**	 **3p**, 72%(73%)
17^{d,e}	 **1q**	**2a**	 **3q**, 68%(70%)
18^{c,e}	 **1q**	 **2b**	 **3r**, 55%(53%)
19	**1a**	 **2c**	 **3s**, 82%(76%)
20	**1a**	 **2b**	 **3t**, 86%(80%)
21^{d}	**1a**	 **2d**	 **3u**, 68%(70%)
22	**1a**	 **2e**	 **3v**, trace
23	**1a**	 **2f**	 **3w**, trace
24^{c,e}	**1a**	 **2g**	 **3x**, 37%(37%)
25^{d,e,g}	**1a**	 **2h**	 **3y**, 62%(57%)
26$^{d.e.g}$	**1a**	 **2i**	 **3z**, 52%(51%)
27^{d,f}	**1a**	 **2j**	 **3aa**, 56%(50%)
28^{d,f}	**1a**	 **2k**	 **3ab**, 62%(55%)
29^{d}	**1a**	 **2l**	 **3ac**, 56% (40%)
30	**1a**	 **2m**	 **3ad**, N.D

^{a}Conditions: carboxylic acid (0.2 mmol), alkene (0.4 mmol), Piv$_2$O (1.5 equiv), NaCl (50 mol %), Pd(TFA)$_2$ (5 mol %), dppb (5 mol %), N$_2$, 150 °C, dioxane (2 mL), 10 h. ^{b}GC yield using tridecane as the internal standard. The data in parentheses are isolated yields obtained by PTLC. For **3j** and **3ac**, recrystallization was additionally performed. trans/cis was generally more than 30:1. Two isomers were detected by GC and GC-MS for **3q** (trans/cis = 15/1) and **3r** (trans/cis = 5:1). ^{c}dppb (10 mol %). ^{d}DPE-phos (10 mol %). ^{e}THF. ^{f}12 h. ^{g}20 h ^{h}NMR yield using tridecane as an internal standard.

https://dx.doi.org/10.1021/acs.orglett.0c02462

Scheme 2. Modification of Bioactive Carboxylic Acids through Decarbonylative Heck Coupling[a,b]



From **3-methylflavone -8-carboxylic acid**
3ae[c], 95%(94%)

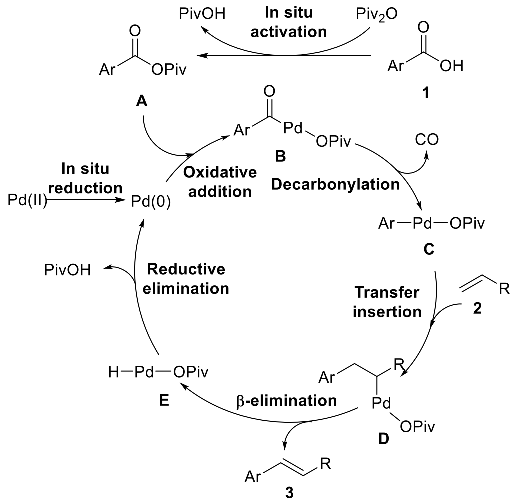
From **probenecid**
3af[c], 63%(65%)

From **adapalin**
3ag[c,d,e], 90%(80%)

From **febuxostat**
3ah[c], 58%(60%)

[a]Conditions: carboxylic acid (0.2 mmol), alkene (0.4 mmol), Piv_2O (1.5 equiv), NaCl (50 mol %), $Pd(TFA)_2$ (5 mol %), dppb (5 mol %), N_2, 150 °C, 10 h, dioxane (2 mL). [b]GC yield using tridecane as an internal standard; The data in parentheses are isolated yields obtained by PTLC. [c]DPE-phos (10 mol %). [d]THF. [e]NMR yield using tridecane as an internal standard.

Scheme 3. Proposed Mechanism for the Decarbonylative Heck Coupling of Carboxylic Acids



oxidants, and was conducted in one pot. A relatively wide substrate scope was demonstrated. Bioactive carboxylic acids were also successfully modified by the strategy. These results showed the potential synthetic value of this new reaction in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02462.

General information, experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectroscopies (PDF)

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Notes

The authors declare no competing financial interest.

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(16) We noticed that a very low yield was given with $PdCl_2$. The result might be ascribed to the relative difficulty for the in situ reduction of $PdCl_2$ in comparison with $Pd(OAc)_2$ under the reaction conditions. First, the Pd(0) complex worked well (Table 1, entry 9). Second, several control experiments with $PdCl_2$ were conducted. By the addition of 20% NaOAc, the yield was increased to 50%. It was deduced that the phosphine ligand might act as the reductant of $PdCl_2$. With 7.5 mol % dppb, the yield was increased to 27%, whereas the yield was increased to 46% with 10 mol % dppb.

(17) In this reaction, CO rather than CO_2 was detected; see the SI.