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Authors: Yao Fu, Rui Shang, Ming-Chen Fu, and Wan-Min Cheng

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An Efficient Pd-Catalyzed Regio- and Stereoselective Carboxylation of Allylic Alcohols with Formic Acid

Ming-Chen Fu, Rui Shang,*§ Wan-Min Cheng, and Yao Fu*

Abstract: Formic acid is efficiently used as a C1 source to directly carboxylate allylic alcohols in the presence of a low loading of palladium catalyst and acetic anhydride as additive to afford β,γ-unsaturated carboxylic acids with excellent chemo-, regio-, and stereoselectivity. The reaction proceeds through a carbonylation process with in situ-generated carbon monoxide (CO) under mild conditions, avoiding the use of high-pressure gaseous CO. A bisphosphine ligand that has a large bite angle (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) was found to be uniquely effective for this transformation. The regio- and stereoconvergence of this reaction is ascribed to the thermodynamically favored isomerization of the allylic electrophile in the presence of the palladium catalyst.

Direct carboxylation of allylic electrophiles is an efficient pathway to prepare β,γ-unsaturated carboxylic acids, which are valuable building blocks both in laboratory-scale syntheses and in the chemical industry.[1] Among the various allylic electrophiles, unprotected allylic alcohols are considered to be most preferred because they can be directly obtained from renewable resources,[2] and less waste is generated in allylic substitution reactions.[3] The latter is an aspect of significant consideration in large-scale industrial applications. To date, methodologies for directing carboxylation of allylic electrophiles to prepare β,γ-unsaturated carboxylic acids mainly include the following: the transition-metal-catalyzed reductive carboxylation with CO_2 using sacrificial organometallic reagents[4] (e.g., $ZnEt_2$) or metal reductants,[5] and the transition-metal-catalyzed carbonylation process under high-pressure CO gas[6] (typically 40 bar) as reported by Alper,[1c] and recently developed by Beller and coworkers,[7] allowing direct access to various carboxylic acid derivatives. In the interest of utilizing biomass-derived formic acid (FA) as a sustainable C1 source in organic synthesis,[8] we investigated whether a combination of FA and acid anhydride may offer the possibility to generate CO in situ from a mixed acid anhydride to directly carboxylate allylic alcohol under palladium catalysis (Figure 1). Although the combination of FA and acid anhydrides has recently been used in palladium- and nickel-catalyzed reactions to directly carboxylate[9] or formylate[10] aryl halides, as well as for the hydrocarboxylation[11–13,8d] or hydroformylation[14] of unsaturated C–C bonds, its utilization to chemoselectively react with allylic alcohols remains a challenge, probably due to the variety of transformations of FA with unsaturated systems under transition-metal catalysis (e.g., hydrogenation,[15] hydrocarboxylation,[13] hydroformylation[14]).

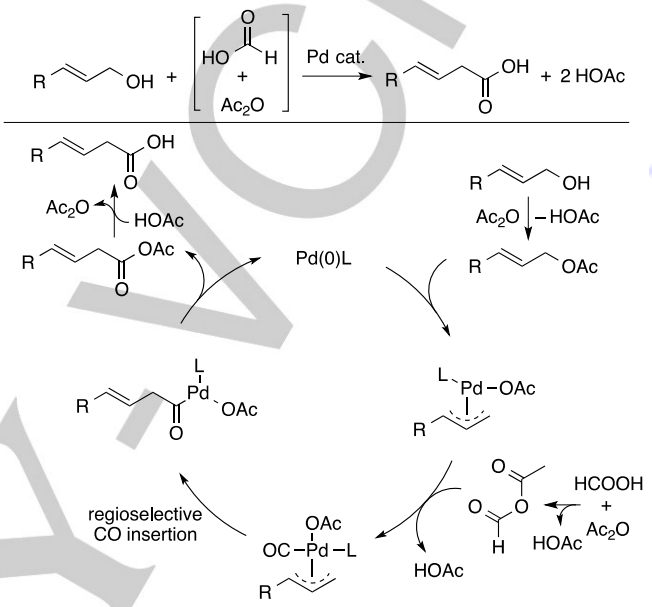

Figure 1. Working hypothesis of direct carboxylation of allylic alcohols with formic acid.

Our working hypothesis is depicted in Figure 1. An acid anhydride may have a dual role: to activate an allylic alcohol and to generate a mixed acid anhydride with FA to generate CO in situ by thermo decomposition.[8d,11-13,16] In the presence of a suitable palladium catalyst, after oxidative addition to form an allyl palladium species, direct regioselective CO insertion, reductive elimination, and acid exchange, β,γ-unsaturated carboxylic acids will be formed, together with acetic acid as the only by-product. This process is of significance for large-scale industrial production because of the environmentally benign nature of the starting materials, FA and alcohols, and no requirement for the use of toxic CO gas under high pressure.

Here we show that the combination of $Pd_2(dba)_3$ and a bisphosphine ligand possessing a large bite angle (Xantphos, bite angle 108°, L10) can catalyze the direct carboxylation of an allylic alcohol with FA in the presence of acetic anhydride. The catalytic system enables this transformation to take place with high chemo-, regio- and stereoselectivity to afford β,γ-unsaturated carboxylic acids in good yields with remarkable functional group compatibility. The reaction reported here presents a new synthetic utility of FA as a C1 source in sustainable organic synthesis and offers an expedient method to prepare β,γ-unsaturated carboxylic acids, as synthetically important building blocks, with the advantages of mild conditions and without having to handle high-pressure toxic CO gas, compared with the currently used industrial carbonylation processes.

[*] M.-C. Fu, Dr. R. Shang,* § W.-M. Cheng, and Prof. Y. Fu*
Hefei National Laboratory for Physical Sciences at the Microscale, iChEM, CAS Key Laboratory of Urban Pollutant Conversion, Anhui Province Key Laboratory of Biomass Clean Energy, Department of Chemistry, University of Science and Technology of China, Hefei 230026, China.
Email: faint123@mail.ustc.edu.cn, fuyao@ustc.edu.cn
[§] R.S.: Department of Chemistry, School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

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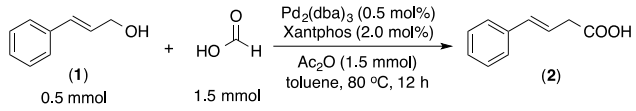
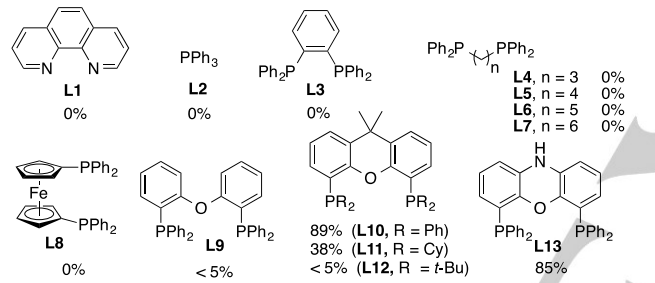
Table 1: Optimization of the reaction conditions



entry[a]	variations from standard condition	yield of **2** (%)[b]
1	none	89 (91[c])
2[d]	$Pd(OAc)_2$ instead of $Pd_2(dba)_3$	76
3[d]	$Pd(acac)_2$ instead of $Pd_2(dba)_3$	<5
4	$Pd(TFA)_2$	<5
5	$PdBr_2$	<5
6	Piv_2O instead of Ac_2O	76
7	TFAA instead of Ac_2O	0
8	HCOOH (1.0 mmol), Ac_2O (1.0 mmol)	72
9[e]	without formic acid	0
10[f]	without Ac_2O	0
11	without $Pd_2(dba)_3$	0
12	using cinnamyl acetate instead of alcohol	81

Ligand Effect:

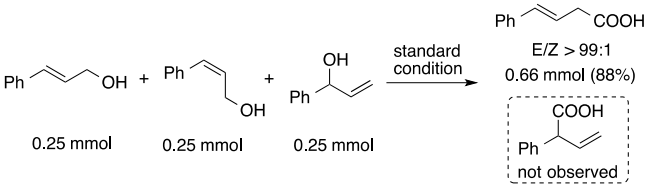


[a] Reaction conditions: cinnamyl alcohol (0.5 mmol), HCOOH (1.5 mmol), $Pd_2(dba)_3$ (0.5 mol%), Xantphos (2.0 mol%), Ac_2O (1.5 mmol), toluene (1.0 mL), 80°C, 12 h. [b] Yield of isolated product, *E*/*Z* > 99:1 determined by ^{1}H-NMR. [c] Isolated yield on gram scale, cinnamyl alcohol (5.0 mol), HCOOH (15 mmol), $Pd_2(dba)_3$ (0.5 mol%), Xantphos (2.0 mol%), Ac_2O (15 mmol), toluene (10 mL), 80°C, 12 h. [d] Catalyst (1.0 mol%). [e] Cinnamyl acetate was isolated in 95%. [f] cinnamyl formate was isolated in 75%.

The optimal reaction conditions, arrived at after considerable experimentation, are shown in Table 1, entry 1. Simply heating a solution of cinnamyl alcohol (0.5 mmol), FA (1.5 mmol), and acetic anhydride (1.5 mmol) in the presence of tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$, 0.5 mol%] and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 2 mol%) in toluene in a sealed Schlenk tube for 12 h afforded (*E*)-4-phenylbut-3-enoic acid in 89% isolated yield, without the detection of any regioisomer or stereoisomer. Although we cannot entirely suppress the dehydrogenation of FA,[17] products of hydrogenation[15] and hydrocarboxylation[11–13] of the unsaturated carbon–carbon bond were not detected. The reaction was scaled up to a 5.0 mmol scale with no loss of yield or selectivity.

After extensive studies of the reaction conditions (see Supporting Information for more details), key factors that significantly affect the reaction outcomes were determined; these are listed in Table 1. The palladium source significantly affected the reaction outcome. As demonstrated in entries 2–5, $Pd(OAc)_2$ gave reduced yields, while $Pd(TFA)_2$ and $Pd(acac)_2$ were totally ineffective. A halide anion, such as a bromide, is totally unsuitable for this transformation, and $PdBr_2$ is totally ineffective (entry 5). The distinct reactivity of different palladium sources may be attributed to their different reactivities, affecting FA decomposition, and thus disturbing the desired carbonylation process. Pivalic anhydride was also effective as an acid anhydride additive, but it gave reduced yields.

Trifluouroacetic anhydride, which reacts with FA to generate CO instantly, was totally ineffective. This indicated that an appropriate rate of CO generation in situ is crucial for the reaction to proceed (entry 7). Reducing the amount of FA and acetic anhydride to 200 mol% resulted in decreased yield (entry 8). Control experiments showed that this reaction does not proceed in the absence of FA or acetic anhydride (entries 9 and 10). Cinnamyl acetate was isolated in 95% yield in the absence of FA, and cinnamyl formate was isolated in 75% in the absence of acetic anhydride. No reaction took place in the absence of palladium catalyst (entry 11). Cinnamyl acetate is also reactive under the optimized reaction conditions (entry 12), but cinnamyl bromide was totally ineffective. Considering the issue of ease of separation, as acetic acid has a low boiling point and is easily removed/collected by distillation, other acid anhydrides generating acid by-products of higher boiling points are not preferred, particularly when the reaction is carried out on the large scale. The ligand plays an essential role in dictating the reaction outcome. The reaction was unsuccessful until we used 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos; L10), a bisphosphine with a large bite angle (108°).[18] Monodentate phosphine and bidentate nitrogen ligands failed as ligands in this transformation. Xantphos (L10) was demonstrated to be an effective ligand in various palladium-catalyzed carbonylation processes, while other biphosphine ligands efficient for palladium-catalyzed carbonylations, such as 1,3-bis(diphenylphosphino)propane (dppp, bite angle 91°), 1,1′-bis(diphenylphosphino)ferrocene (dppf, bite angle 99°), and bis-[2-(diphenylphosphino)phenyl]ether) (DPEphos, bite angle 104°) were totally ineffective. A possible explanation for this is that the bite angle of the palladium bisphosphine ligand is essential to dictate the chemoselectivity of this reaction. The desired product was only detected when a ligand possessing a bite angle similar to that of Xantphos was used (L10–L13). Increasing the steric hindrance on the bisphosphine ligand had an adverse effect on the reaction outcome (L11 and L12).

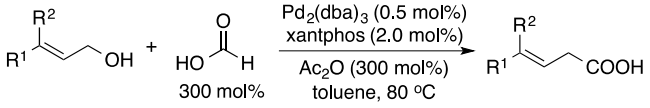


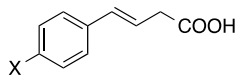
Scheme 1. Regio- and stereoconvergent synthesis using a mixture of cinnamyl alcohol and α-vinylbenzyl alcohol.

After optimization of the reaction conditions, we tested the reaction using a mixture of *Z*/*E*-cinnamyl alcohol and α-vinylbenzyl alcohol. We wondered whether the stereo- and regioisomer of *E*-cinnamyl alcohol would yield products other than (*E*)-4-phenylbut-3-enoic acid. It was interesting to observe that the reaction afforded (*E*)-4-phenylbut-3-enoic acid as the only carboxylation product; no other isomers were detected. Thus, this reaction proceeds in a regio- and stereoconvergent manner, even though a mixture of regio- and stereoisomers was

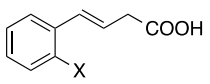
applied. This observation supports the formation of an allyl palladium species as the key intermediate before carbonylation takes place (Scheme 1).

Table 2: Scope with respect to primary allylic alcohols[a]

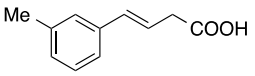




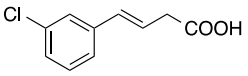
R = -OMe (**3**) 83%
-Cl (**4**) 71%
-F (**5**) 85%



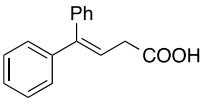
X = -Br (**6**) 55%, *E*/*Z* = 94/6
-Cl (**7**) 91%, *E*/*Z* = 95/5
-OMe (**8**) 73%, *E*/*Z* = 95/5



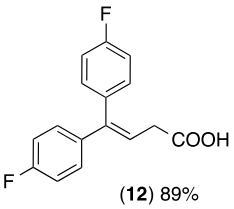
(**9**) 80%



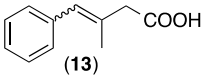
(**10**) 75%



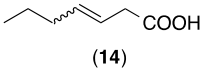
(**11**) 95%



(**12**) 89%



(**13**)
81%[b], *E*/*Z* = 80/20

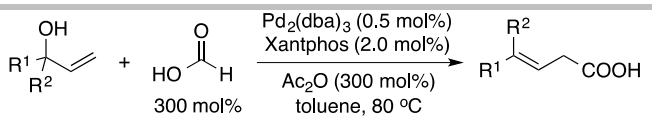


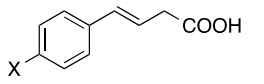
(**14**)
32%[c], *E*/*Z* = 81/19

[a] Reaction conditions: alcohol (0.5 mmol), formic acid (1.5 mmol), $Pd_2(dba)_3$ (0.5 mol%), Xantphos (2.0 mol%), Ac_2O (1.5 mmol), toluene (1.0 mL), 80°C, 12 h. Yield of isolated product. *E*:*Z* > 99:1, unless otherwise noted. *E*:*Z* ratio determined by ^{1}H-NMR. [b] (*E*)-2-methyl-3-phenylprop-2-en-1-ol was used as substrate. [c] (*E*)-hex-2-en-1-ol was used as substrate, HCOOH (2.0 mmol), Ac_2O (2.0 mmol).

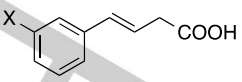
With the understanding of this reaction in hand, we next explored the preparative scope. Table 2 summarizes the scope of the investigation with respect to the primary allylic alcohol. The reactions proceeded well, with high yield and selectivity for both *meta*- and *para*-substituted cinnamyl alcohols (**3**, **9**). For *ortho*-substituted cinnamyl alcohols, the yield and stereoselectivity decreased slightly (**6**, **7**, **8**). The electronic effect on the phenyl ring did not significantly affect the reaction outcome. When (*E*)-3-(2-bromophenyl)prop-2-en-1-ol was used, product was obtained in moderate yield owing to the susceptibility of the Ar–Br bond towards low-valent palladium species. When 3,3-diarylated allylic alcohol was used, the desired product was obtained in high yield and with high selectivity. For a 2,3-disubstituted allylic alcohol, (*E*)-2-methyl-3-phenylprop-2-en-1-ol afforded the desired products in good yields, but with decreased *E*/*Z* selectivity (**13**). The reaction is less effective for a 2-alkyl substituted allyl alcohol; it afforded the desired product in low yield with decreased *E*/*Z* selectivity. It is noteworthy that in the reaction of 2-alkyl substituted allyl alcohols, diene has been detected as a major by-product, indicating the disturbance of β-hydride elimination of a π-allylpalladium species.[19]

Table 3: Scope with respect to secondary and tertiary allylic alcohols[a]

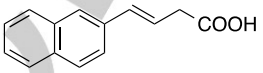




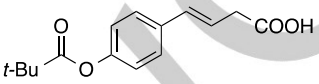
X = -Me (**15**) 81%
= -OMe (**16**) 89%
= -OBn (**17**) 71%
= -CF_3 (**18**) 81%
= -COOMe (**19**) 77%
= -CN (**20**) 70%
= -SMe (**21**) 73%
= -SCF_3 (**22**) 81%
= -OCF_3 (**23**) 66%
= -BPin (**24**) 84%



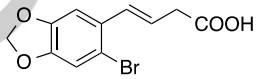
X = -Cl (**25**) 70%
= -F (**26**) 69%
= -OMe (**27**) 90%



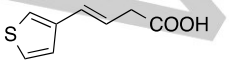
(**28**) 61%



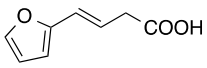
(**29**) 65%



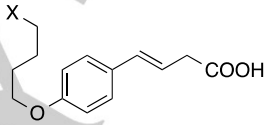
(**30**) 50%, *E*/*Z* = 90/10



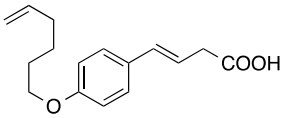
(**31**) 78%



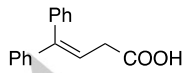
(**32**) 66%[b,c]



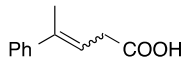
(**33**) X = Cl, 78%
(**34**) X = Br, 30%



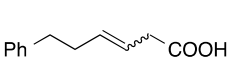
(**35**) 60%



(**36**)
51%[b]



(**37**)
81%, *E*/*Z* = 83/17



(**38**)
42%[d], *E*/*Z* = 80/20

[a] Reaction conditions: alcohol (0.5 mmol), formic acid (1.5 mmol), $Pd_2(dba)_3$ (0.5 mol%), Xantphos (2.0 mol%), Ac_2O (1.5 mmol), toluene (1.0 mL), 80°C, 12 h. Yield of isolated product. *E*:*Z* > 99:1, unless otherwise noted. *E*:*Z* ratio determined by ^{1}H-NMR. [b] Formic acid (2.0 mmol), Ac_2O (2.0 mmol). [c] THF was used as solvent, 100°C. [d] 4,6-bis(diphenylphosphino)-10*H*-phenoxazine was used as ligand.

Next, we evaluated the scope of secondary and tertiary allylic alcohols, as shown in Table 3. A variety of functionalized secondary and tertiary allylic alcohols appear to be amenable substrates. It is noteworthy that in all cases, the double bond was rearranged and the branched product was not observed, indicating that CO insertion selectively takes place at the terminal position. For secondary allylic alcohols, such as 1-aryl allylic alcohol, the yield of the final carboxylation product was comparable with that obtained with corresponding primary alcohol isomers, as shown in Table 2 (**3** and **16**), whereas for tertiary allylic alcohols, a decreased yield was observed (**11, 36**). The decreased catalytic efficiency may partially be ascribed to the steric hindrance on the tertiary carbon center that retards oxidative addition to a bisphosphine ligated palladium center. 1-Phenyl-1-methyl allylic alcohol was an amenable substrate in this transformation and afforded a final carboxylation product in good yield and with a diastereoselectivity of 83/17 (**37**). It should be mentioned here that tertiary allylic alcohol use was found to be unsuccessful in examples in palladium-catalyzed carbonylation reactions under a pressurized CO atmosphere.[1c]

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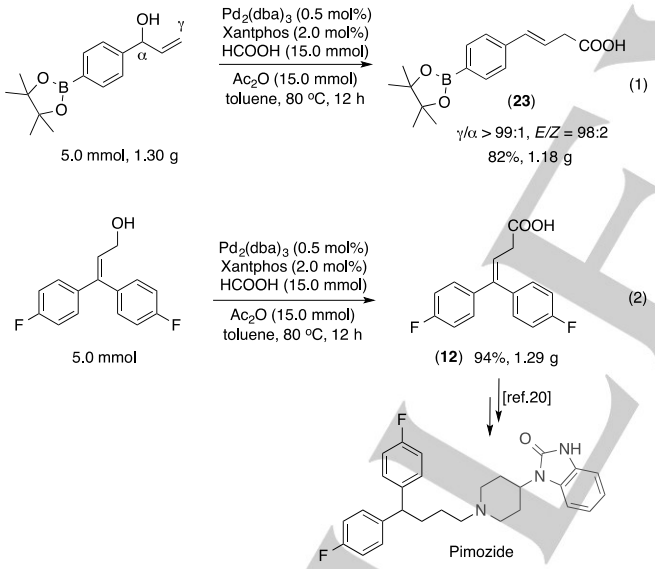
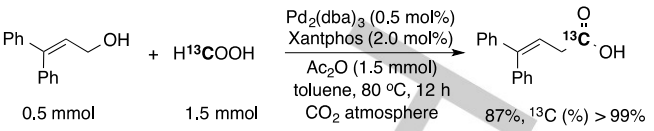
1-Alkyl substituted allylic alcohol afforded the final carboxylation product in moderated yield and with decreased *E*/*Z* selectivity (**38**). Carbonylation cannot take place at a secondary carbon center under the catalytic system here; (*E*)-1-phenylpent-1-en-3-ol failed to give any desired carboxylation product (see Supporting Information for unsuccessful examples).

The functional group compatibility of this reaction is remarkable. Entries in both Table 2 and Table 3 demonstrate that a broad range of functional groups are well tolerated; these groups include ether (**3, 8, 16, 17, 27**), trifluoromethyl (**18**), aryl chloride (**4, 7, 25**), aryl fluoride (**5, 12, 26**), aryl bromide (**6, 30**), trifluoromethyl sulfide (**22**), trifluoromethoxy (**23**), methyl sulfide (**21**), cyano (**20**), ester (**19, 29**), and acetal (**30**). It is also noteworthy that the aryl pinacol boronate (**24**), which is susceptible to transmetallation under palladium catalysis, is well tolerated. Heteroarenes such as thiophene (**31**) and furan (**32**) are also tolerated. Alkyl halides such as alkyl chlorides are well tolerated, with no detection of carboxylation of the halide (**33**). However, when alkyl bromides are used, the yield is low because of SN2 substitution with the acetate anion (**34**). It is interesting to note that Shi and coworkers[13] recently reported that a terminal olefin can be effectively hydrocarboxylated and hydroformylated with FA and acetic anhydride using palladium catalysis, whereas in our reactions, both terminal and interminal olefins remain intact, probably due to the chemoselectivity endowed by the different ligand system (**35**).



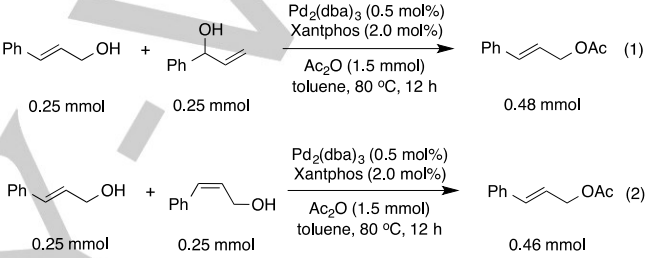
Scheme 2. Gram-scale synthesis. (1) Gram-scale carboxylation with tolerance of easily transmetallated Ar-Bpin functionality. (2) Synthesis of key intermediate of pimozide.

We further performed two gram-scale syntheses to illustrate the synthetic utility of this reaction (Scheme 2). First, a gram-scale reaction regarding orthogonal reactivity with a Suzuki–Miyaura coupling is demonstrated. Transmetallation of aryl boronate does not proceed to allow arylation of an allyl palladium intermediate. Thus, a product possessing useful boronate functionality was obtained in 82% isolated yield on gram scale and with high selectivity. Second, we demonstrate the use of this reaction to prepare an important intermediate of a commercialized medicinal compound,[20] pimozide, an antipsychotic drug for the treatment of Tourette's syndrome.[21]



Scheme 3. ^{13}C-labeling experiment.

We also prepared ^{13}C-labeled β,γ-unsaturated carboxylic acid using ^{13}C-labeled FA by this method. The reaction, performed using H^{13}COOH, under CO_2 atmosphere, afforded the ^{13}C-labeled acid with ^{13}C incorporation > 99%, This confirmed the mechanism of CO generation from FA other than any carboxylation process with CO_2 formed from dehydrogenation of FA (Scheme 3).



Scheme 4. Control experiments regarding regio- and stereoselectivity.

Although the mechanism of this reaction may fit well with our working hypothesis depicted in Figure 1, one intriguing aspect of this reaction is the regio- and stereoconvergence. *E*-cinnamyl alcohol and α-vinylbenzyl alcohol yield the same allyl palladium species after oxidative addition; thus, the selectivity mainly depends on the thermodynamically favorable CO insertion step. According to the literature, a transition-metal or acid catalyst can catalyze the isomerization of an allylic alcohol into a thermodynamically stable isomer (α-vinylbenzyl alcohol to *E*-cinnamyl alcohol).[22] Our control experiment also confirmed that in the absence of FA, both *E*-cinnamyl and α-vinylbenzyl alcohol can smoothly convert into *E*-cinnamyl acetate, catalyzed by the palladium catalyst (Scheme 4, eq. 1). Thus, the regioselectivity could be explained by this thermodynamically favored isomerization. Considering that the diastereomers of allylic alcohol may exhibit different reactivity in transition-metal-catalyzed allylic substitution reactions,[3a] a control experiment was performed to clarify the observed stereoconvergence. The results of this experiment indicated that a reaction using a mixture of *Z*- and *E*-cinnamyl alcohol afforded only *E*-cinnamyl acetate in the absence of FA (Scheme 4, eq. 2). The results of this control experiment further indicated that stereoisomerization of cinnamyl acetate readily takes place in the presence of a palladium catalyst and, furthermore, is independent of the CO insertion step.

In summary, we report here that biomass-derived FA can be used together with acetic anhydride to directly carboxylate allylic alcohols in the presence a low-loading commercially available palladium catalyst to prepare β,γ-unsaturated carboxylic acids with excellent chemo-, regio-, and

stereoselectivity. Regio- and stereoisomers of allylic alcohols react in a convergent manner to afford products with high selectivity. It was found that a bidentate phosphine ligand possessing a large bite angle (Xantphos, L10) plays a crucial role in the success of this transformation. Compared with established carbonylation methods, this reaction avoids the use of high-pressure CO gas and proceeds under mild acidic conditions, generating acetic acid as by-product. We anticipate that the reaction we have developed will find future industrial application as a sustainable and user-friendly process to prepare functionalized β,γ-unsaturated carboxylic acids.

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Keywords: allylic alcohols • β,γ-unsaturated acids • carbonylation • formic acid • palladium-catalyzed

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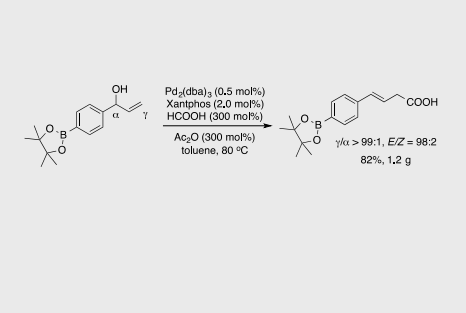
Formic acid is efficiently used as a C1 source to directly carboxylate allylic alcohols using a low loading of palladium catalyst and acetic anhydride as additive to afford β, γ-unsaturated carboxylic acids with good chemo-, regio- and stereoselectivity. A bidentate phosphine ligand possessing a large bite angle (Xantphos) plays a crucial role in the success of this transformation.



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An Efficient Pd-Catalyzed Regio- and Stereoselective Carboxylation of Allylic Alcohols with Formic Acid