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Pd-Catalyzed decarboxylative cross-coupling reactions of epoxides with α,β-unsaturated carboxylic acids†

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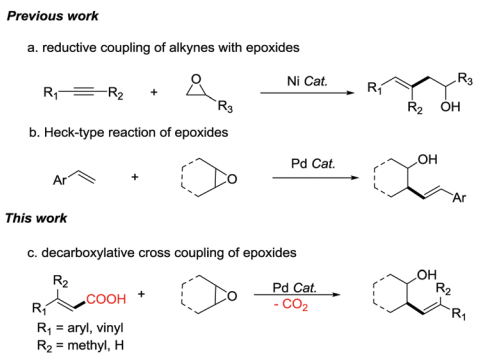
A Pd-catalyzed decarboxylative cross-coupling of α,β-unsaturated carboxylic acids with cyclic and acyclic epoxides has been developed. Both β-monosubstituted and β-disubstituted unsaturated carboxylic acids, as well as conjugated diene unsaturated carboxylic acids are suitable reaction substrates. Substituted homoallylic alcohols were obtained in moderate to good yields. The product was obtained as a mixture of diastereomers favoring the anti diastereomer of the cyclic epoxides. This work provides a method for the modification of complex organic molecules containing α,β-unsaturated carboxylic acids.

Transition metal-catalyzed cross-couplings are among the most vital C–C bond-forming reactions in modern organic synthesis.[1] Alcohols are valuable compounds that play vital roles in organic synthesis. One synthesis method for alcohols is through ring-opening reactions of epoxides where C–C bonds are constructed.[2] In the past few decades, various epoxide ring-opening reactions have been realized,[3] including transition-metal-catalyzed Negishi-type[4] and Suzuki-type[5] ring-opening/cross-coupling reactions. In addition, reductive ring-opening/coupling reactions of epoxides have been reported.[6] For example, reductive coupling of alkynes and epoxides does not break the C–C bond to form an alcohol as implied in Scheme 1a but rather forms the same types of homoallylic alcohols made in this publication.[6c] Furthermore, Heck-type reaction[7] and C–H activation reaction[8] of epoxides have also been reported. For example, palladium-catalyzed Heck-type reaction of epoxides is shown in Scheme 1b.[7a] Carboxylic acids are one of the most important classes of organic structures, and are found in many active molecules.[9] Recently, decarboxylative cross-coupling has emerged as a powerful tool for the construction of C–C bonds.[10] We hypothesized that decarboxylative cross-couplings could be used with epoxide ring-opening reactions to synthesize alcohols. To the best of our knowledge, there have been no reports on decarboxylative cross-coupling of carboxylic acids with epoxides.[11]



Scheme 1 Decarboxylative cross-coupling reactions of epoxides with α,β-unsaturated carboxylic acids.

Herein, we report the first example of Pd-catalyzed decarboxylative cross-coupling reactions of α,β-unsaturated carboxylic acids with epoxides. The product was obtained as a mixture of diastereomers favoring the anti diastereomer of the cyclic epoxides (Scheme 1c). In addition to β-monosubstituted unsaturated carboxylic acids, β-disubstituted unsaturated carboxylic acids and conjugated diene unsaturated carboxylic acids also give products with moderate to good reaction yields. This methodology provides access to a diverse array of synthetically valuable substituted homoallylic alcohols.[12] It also provides a method for the modification of complex organic molecules containing α,β-unsaturated carboxylic acids.

We began our study by selecting cinnamic acid (**1a**) and cyclohexene oxide (**2a**) as model reaction substrates (Table 1). When using $Pd(PPh_3)_4$ as a catalyst, dppf as a ligand, Cy_2NMe as a base and $PhCF_3$ as a solvent, the desired product was observed in a low yield (entry 1). First, we assessed the reaction by modifying the ligand and solvent in the presence of $Pd(PPh_3)_4$ as the catalyst. Using dioxane instead of $PhCF_3$ as the solvent resulted in almost no increase in reaction yield (entry 2). Switching the ligand to Xantphos decreased the reaction yield (entries 3 and 4).

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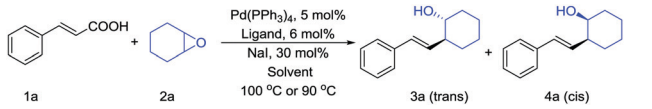
Table 1 Optimization of the reaction conditions



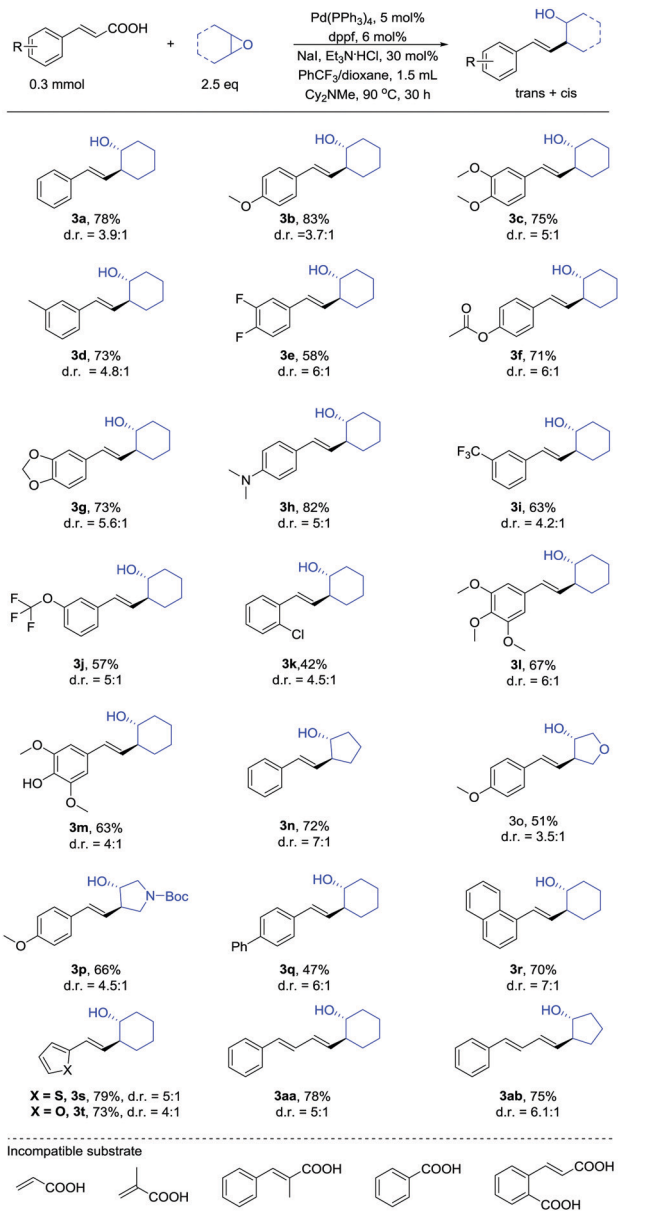
Entry	Catalyst	Ligand	Base	Solvent	Yield% **3a : 4a** (d.r.)
1[a]	$Pd(PPh_3)_4$	dppf	Cy_2NMe	$PhCF_3$	28(4.5 : 1)
2[a]	$Pd(PPh_3)_4$	dppf	Cy_2NMe	Dioxane	31(3.5 : 1)
3[a]	$Pd(PPh_3)_4$	Xantphos	Cy_2NMe	$PhCF_3$	10(4.2 : 1)
4[a]	$Pd(PPh_3)_4$	Xantphos	Cy_2NMe	Dioxane	15(3.2 : 1)
5[b]	$Pd(PPh_3)_4$	dppf	Cy_2NMe	$PhCF_3$	50(4 : 1)
6[b]	$Pd(PPh_3)_4$	dppe	Cy_2NMe	$PhCF_3$	10(4.2 : 1)
7[b]	$Pd(PPh_3)_4$	dppp	Cy_2NMe	$PhCF_3$	2
8[b]	$Pd(PPh_3)_4$	PCy_3	Cy_2NMe	$PhCF_3$	Trace
9[b]	$Pd(PPh_3)_4$	dppf	K_3PO_4	$PhCF_3$	8(4 : 1)
10[b]	$Pd(PPh_3)_4$	dppf	Cs_2CO_3	$PhCF_3$	5(4 : 1)
11[b]	$Pd(PPh_3)_4$	dppf	$(iPr)_2NEt$	$PhCF_3$	10(4.1 : 1)
12[c]	$Pd(PPh_3)_4$	dppf	Cy_2NMe	$PhCF_3$	62(5 : 1)
13[c]	$Pd(PPh_3)_4$	dppf	Cy_2NMe	Toluene	46(5.5 : 1)
14[c]	$Pd(PPh_3)_4$	dppf	Cy_2NMe	DMA	21(4.2 : 1)
15[c]	$Pd(PPh_3)_4$	dppf	Cy_2NMe	$PhCF_3$/DMA	28(4.3 : 1)
16[d]	**$Pd(PPh_3)_4$**	**dppf**	**Cy_2NMe**	**$PhCF_3$/Diox**	**81(3.9 : 1)**
17	—	dppf	Cy_2NMe	$PhCF_3$/Diox	0
18	$Pd(PPh_3)_4$	—	Cy_2NMe	$PhCF_3$/Diox	(3.1 : 1)
19[e]	$Pd(PPh_3)_4$	dppf	Cy_2NMe	$PhCF_3$/Diox	Trace

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.3 mmol), base (1.5 equiv.) in 2 mL solvent at 100 °C for 24 h. [b] **1a** (0.3 mmol), **2a** (0.6 mmol), base (1.5 equiv.) in 2 mL solvent at 100 °C for 24 h. [c] **1a** (0.3 mmol), **2a** (0.6 mmol) in 2 mL solvent (10 : 1) at 90 °C for 24 h. [d] 1.5 mL solvent (5 : 1), **1a** (0.3 mmol), **2a** (2.5 equiv.) and NaI/Et_3N·HCl at 90 °C for 30 h. [e] No NaI. The yield was determined by GC using benzophenone as internal standard. Diox = dioxane.

We then adjusted the substrate proportions under the initial reaction conditions (entry 5) and the reaction yield was significantly improved. Using the new substrate proportions, we screened a series of ligands, such as dppe, dppp and PCy_3, but they gave reaction yields of less than 10% (entries 6–8). These results indicate that dppf is a relatively good ligand for the targeted reaction. Under the condition of dppf as a ligand, we examined other bases, but saw no improvement in the reaction yield (entries 9–11). Lowering the reaction temperature has certain benefits for improving the reaction yield (entry 12). Finally, we obtained the optimal reaction conditions by using a mixed solvent system of $PhCF_3$ and dioxane (81% GC yield, d.r. = 3.9 : 1, entry 16). We confirmed the presence of two isomers by NMR (see ESI†). Reactions performed without $Pd(PPh_3)_4$ did not result in product formation (entry 17). On removal of dppf, the yield will be significantly reduced (entry 18). A control experiment indicated that the reaction completely failed without the addition of NaI (entry 19). Using other catalysts, such as $Pd(OAc)_2$, significantly reduced the reaction yield (see ESI†).

We next examined the substrate scope using the optimized conditions described above (Table 2). Many of the substituted unsaturated carboxylic acids coupled with cyclic epoxides in moderate to good yields and preferential anti-selectivity on the cyclic ring. Both electron-rich and electron-poor unsaturated carboxylic acids afforded the products. The functional groups ether (**3b**, **3c**), halogen (**3e**), trifluoromethoxy (**3j**), amino (**3h**) and trifluoromethyl (**3i**) were well tolerated and afforded good yields. In particular, the ester (**3f**), alcohol (**3m**), ketal (**3g**) and amide (**3p**) substitutions were compatible with the reaction conditions. Moreover, carboxylic acids bearing *ortho*-chlorine (**3k**), bicyclic naphthyl (**3r**), thiophene (**3s**) and furan (**3t**) groups also participated in the reaction.

Table 2 Scope of β-monosubstituted unsaturated carboxylic acids



Conjugated dienes are found in many complex active molecules and pharmaceuticals and play vital roles in organic synthesis and materials science.[13] We found that conjugated diene unsaturated carboxylic acids furnished the corresponding products in good yields (**3aa** and **3ab**). In particular, sorbic acid showed satisfactory reactivity towards product formation (Scheme 2), which is notable because it is difficult to synthesize diene substituted homoallylic alcohols by other methods.[14]

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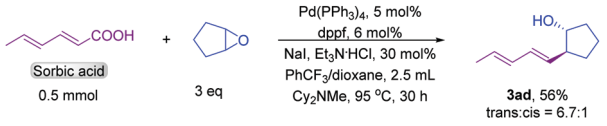


Scheme 2 Decarboxylation of sorbic acids.

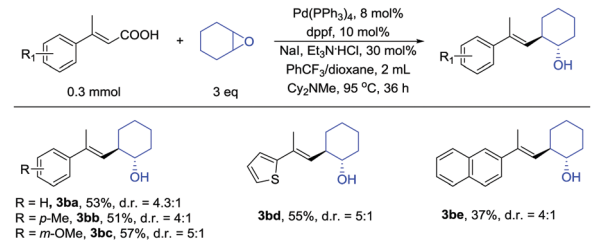
In addition to β-monosubstituted unsaturated carboxylic acids, β-disubstituted unsaturated carboxylic acids also give the products. Many β-disubstituted unsaturated carboxylic acids coupled with epoxides in moderate yields (Table 3). Some substituent groups, such as methyl (**3bb**) and methoxy (**3bc**), were tolerated and afforded moderate yields. Thiophene (**3bd**) and naphthalene (**3be**) can also be present in the reaction.

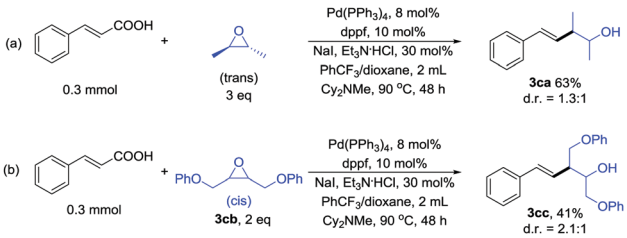
For monosubstituted and 1,1-disubstituted acyclic epoxides the products formed in these reactions are the ester that would result from direct nucleophilic attack of the carboxylic acid on the epoxide (see ESI†). So we tested 1,2-disubstituted acyclic epoxide as the reaction substrate. The *trans*-2,3-epoxybutane couples with cinnamic acid to form the product in 63% yield (Scheme 3a). The treatment of cis **3cb** with cinnamic acid afforded the product in 41% yield (Scheme 3b). These results indicated that the yield of acyclic epoxide was worse than cyclic epoxide. Unfortunately, for styrene epoxides, such as *trans*-stilbene oxide, we almost got 1,2-diphenylethan-1-one (see ESI†).

An unsymmetrical epoxy (Scheme 4) substrate was investigated and two regioselective products, tertiary alcohol (**3da**) and secondary alcohol (**3db**) were obtained. The regioselectivity at the less-substituted positions was superior (**3da** : **3db** = 2.5 : 1). Therefore, the selectivity of the asymmetric epoxy mainly depends on steric hindrance (the configuration of the isomers was assigned by ^{1}H NMR and H–H COSY spectra).

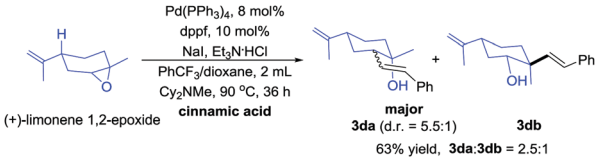
We next demonstrated the decarboxylative cross-coupling reactions of epoxides for late-stage modification of biologically active molecules containing α,β-unsaturated carboxylic acids. The treatment of retinoic acid with cyclohexene oxide afforded the product (**3ea**) in good yield (Scheme 5a). Modification of acitretin with cyclohexene oxide resulted in the formation of **3eb** in high yield (Scheme 5b). The treatment of abscisic acid with cyclohexene oxide obtained the product in 38% yield (Scheme 5c). The treatment of estrone derivative with cyclohexene oxide afforded the product (**3ed**) in 72% yield (Scheme 5d). These results fully demonstrate the value of this decarboxylative reaction in the modification of complex active molecules.

Table 3 Scope of β-disubstituted unsaturated carboxylic acids

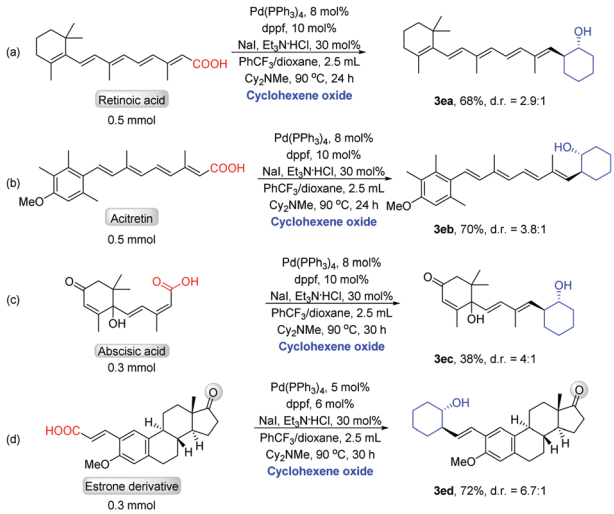




Scheme 3 Examples of acyclic epoxides.



Scheme 4 Example of asymmetric epoxide.



Scheme 5 The modification of complex molecules.

The mechanism of the reaction was investigated through several experiments. Reactions using 0.5 equiv. of radical trapping agent 2,2,6,6-tetramethylpiperidineoxy (TEMPO) were largely inhibited. Then, we performed a reaction of an *in situ* formed palladium(0) complex of dppf with iodohydrin. It formed cyclohexanone and cyclohexanol (ESI†). Another reaction of the palladium(0) complex with cyclohexene oxide gave similar results in the presence of 1 equiv. of NaI and $Et_3N{\cdot}HCl$ (ESI†). On removal of NaI, no production of cyclohexanone and cyclohexanol was observed. We observed the product with 16% yield when using iodohydrin instead of the epoxide and in the absence of sodium iodide (see ESI†). These results are similar to previous reports.[7a] The cyclooctadiene monoxide couples with cinnamic acid to form primarily [3.3.0]-bicyclooctanols (ESI†).[6b] Moreover, (*Z*)-cinnamic acid also afforded the same *trans*-alkene product, and the stereoconvergent reaction was considered to be carried out by a radical pathway (ESI†).[15]

On the basis of the above results and previous reports,[11,16] a possible reaction mechanism is depicted in ESI.† Initially, the

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β-iodohydrin, which is *in situ* produced from the epoxide and NaI, reacts with (dppf)palladium(0) species to give a β-hydroxyalkyl radical (**I**) and an L_nPdI complex. Addition of the hydroxyalkyl radical (**I**) at the α-position of the C—C double bond in cinnamic acid would give the benzylic radical **II**. Next, the radical **II** combines with $(L_n)PdI$ to form alkylpalladium(II) species **III**. Finally, decarboxylation of the Pd(II) species occurs to generate the product while regenerating the Pd(0) species.

In summary, we have developed the first Pd-catalyzed decarboxylative cross-coupling of α,β-unsaturated carboxylic acids with epoxides. The products were obtained as a mixture of diastereomers favoring the anti diastereomer of the cyclic epoxides. Reactions with β-monosubstituted and β-disubstituted unsaturated carboxylic acids proceed with moderate to good yields and conjugated diene unsaturated carboxylic acids showed moderate reactivity. This methodology also provides access to a diverse array of substituted homoallylic alcohols, which are valuable structural fragments in organic synthesis. It also provides a route for the modification of complex organic molecules containing α,β-unsaturated carboxylic acids.

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Conflicts of interest

There are no conflicts to declare.

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