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Cobalt-Catalyzed Coupling of Benzoic Acid C–H Bonds with Alkynes, Styrenes, and 1,3-Dienes

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Abstract

A method for cobalt-catalyzed, carboxylate-directed functionalization of arene C–H bonds is reported. Alkynes, styrenes, and 1,3-dienes can be coupled with benzoic acids to provide cyclic products in good yields. The reactions proceed in the presence of a cobalt(II) hexafluoroacetylacetonate catalyst, (TMS)₂NH base, Ce(SO₄)₂ cooxidant, and oxygen oxidant.

A step in the right direction

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Keywords

alkenylation; benzoic acid; C–H activation; cobalt; olefin

Transition-metal-catalyzed C–H functionalization has been extensively used in the syntheses of bioactive molecules and functional materials.^[1] Most methods involve the use of directing groups to ensure regioselective conversion of a specific C–H bond to give the desired product. In contrast, non-directed C–H functionalization is often limited to symmetric substrates owing to potential formation of isomer mixtures. The functionalization can be directed by a number of common groups, including amines, carboxylates, and aldehydes.^[2] Alternatively, more efficient directing groups can be installed in one or more synthetic transformations, since most common functionalities are relatively inefficient in promoting C–H activation/functionalization. For example, we and other groups have shown that upon converting carboxylates to aminoquinoline amides, functionalization of sp² and sp³ C–H

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Conflict of interest

The authors declare no conflict of interest.

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bonds can be accomplished under palladium, rhodium, ruthenium, iron, cobalt, nickel, and copper catalysis (Scheme 1, **1**→**3**→**4**→**2**).^[1j,3] Very general reactivity is observed, thereby enabling arylation, alkylation, fluorination, sulfonylation, amination, etherification, carbonylation, and alkenylation of carbon–hydrogen bonds. In contrast, more weakly coordinating carboxylate groups can direct C–H functionalization of sp² C–H bonds under palladium, iridium, ruthenium, platinum, and rhodium catalysis (**1**→**2**).^[4] More challenging unactivated sp³ C–H bonds in carboxylic acids can be functionalized under palladium catalysis, with the first arylation reported by the Yu group in 2007.^[4b] It would be beneficial to employ first-row transition-metal catalysis in carboxylic acid C–H bond functionalization for the following reasons. First, a large variety of starting materials possessing carboxylate functionality are commercially available or can be easily prepared, thus shortening the synthetic schemes since installation and removal (often under harsh conditions) of the directing group is not required. Second, base metals are substantially more available than second- and third-row transition metals. Only two catalytic methods for carboxylate-directed sp² C–H bond functionalization mediated by first-row transition metals have been reported.^[5] These examples present a very significant breakthrough in catalysis. However, this method requires the use of highly pyrophoric AlMe₃ in combination with a designer ligand for Fe catalysis,^[5a] and a limited range of internal alkynes can be employed in cobalt-catalyzed couplings to afford regioisomeric product mixtures.^[5b]

Several research groups have reported examples of both low- and high-valent-cobalt catalysis for coupling sp² C–H bonds with alkenes and alkynes.^[3d–g,6] Specifically, an early report by Matsunaga and Kanai describes a pentamethylcyclopentadienyl (Cp*) cobalt (III) complex as a catalyst for the alkenylation of N-protected indoles to yield pyrrolodindolones.^[6e] Coupling of alkynes with sp² C–H bonds in anilides, esters, and oximes is feasible.^[6e–i] Our group has disclosed cobalt-catalyzed, aminoquinoline-directed coupling of alkenes, alkynes, and carbon monoxide with sp² C–H bonds by employing oxygen as a terminal oxidant.^[3d–f] We report here a general method for cobalt-catalyzed, carboxylate-directed functionalization of *ortho*-C–H bonds in benzoic acids. Alkynes, styrenes, and 1,3-dienes react to afford cyclic products with excellent regioselectivity.

Reaction optimization was carried out by coupling 1-hexyne with *p*-toluic acid (Table 1). The best results were obtained when (TMS)₂NH base, Ce(SO₄)₂ cooxidant, and pivalic acid additive were used in trifluoroethanol, affording 78% yield of the cyclic product (entry 1). The pivalic acid additive is important to increase conversion (entry 2). Other hindered carboxylic acid additives gave lower yields of product (entries 3–4). Reaction in hexafluoroisopropanol is less efficient (entry 5). When a *p*-toluic acid sodium salt was used, a lower yield of **6** was obtained (entry 6). Other silyl- containing bases are inferior compared to (TMS)₂NH.^[7] Notably, the coupling product was obtained in 42% yield when oxygen was used as the sole oxidant (entry 7). The reaction is slower under inert atmosphere, thus showing that both Ce^{IV} and oxygen are required for high yields of the product (entry 8). No conversion was observed when Co-(hfacac)₂ was omitted (entry 9).

The reaction scope with respect to alkynes is presented in Table 2. Functionalities such as cyano groups, phthalimide, and olefins are tolerated (**7**–**9**). Alkenylation of a THP-protected propargylic alcohol in combination with in situ deprotection furnished coupling product **10**

in 76% yield. Silyl and aryl acetylenes are competent substrates (**11** and **12**). Internal alkynes are also compatible with the reaction conditions (**13–15**). 1-Phenyl-1-propyne selectively produced a single regioisomer of product in 65% yield (**15**). Internal alkynes possessing *n*-butyl, cyclohexyl, and cyanopropyl substituents are reactive as well (**16–18**). The reactions proceed with selectivity values comparable to those observed in aminoquinoline benzamide couplings.^[3d]

The reaction scope with respect to carboxylic acids is presented in Table 3. Both electron-rich (**19**) and electron-poor (**21–23**) aromatic acids are successfully coupled with alkynes. Similar to other transition-metal-catalyzed arene C–H bond functionalizations,^[1] the carboxylic acid directed alkenylation favors reactions at less hindered C–H bonds, resulting in good to excellent regioselectivity (**23–25**). Methoxy, chloro, fluoro, vinyl, and propenyl functionalities are all compatible with the reaction conditions (**21–24**, **28**, and **29**). An isocoumarin derived from 1-naphthoic acid was obtained in 72% yield (**27**). Heterocycle-containing carboxylic acids are also competent substrates (**30**, **31**).

We previously reported that the conditions for aminoquinoline benzamide reactions with alkenes and alkynes are quite similar.^[3d,e] Gratifyingly, coupling of benzoic acid C–H bonds with olefins is also feasible without any modification of the standard conditions (Table 4). Reaction of *p*-toluic acid with styrene gives product **32** in 67% yield. Coupling of the same acid with *m*-bromo- and *o*-chlorostyrenes affords **33** and **34** in 71 and 48% yields, respectively. Unsubstituted benzoic acid, methoxy-, and chloro-substituted derivatives couple with styrene as well, giving products **35–37** in good yields. Furthermore, terminal 1,3-dienes can be coupled with benzoic acids. Use of 1,3-dienes in directed C–H functionalization catalyzed by first-row transition metals is not known.^[8] Alkylation using a 1,2-disubstituted 1,3-butadiene afforded coupling product **38** in a 63% yield. (+)-Nopadiene reacted with *p*-toluic acid to afford the product as a 1:1 mixture of diastereoisomers in 28% yield (**39**). Alkyl-substituted olefins are unreactive.

Based on previous work by us and others, it is likely that the reaction proceeds via Co^{III} intermediate **40a**, formed through oxidation of Co(hfacac)₂ in the presence of the benzoic acid ligand (Scheme 2). Insertion of an alkyne into the cobalt–aryl bond would provide **41**. Compound **41** could undergo direct reductive elimination to **42**, or Co^{III} vinyl could be protonated to give **44**, which could undergo oxidative cyclization to give **42**. Additionally, an alternative mechanism with a cobalt acetylide intermediate as proposed by Ribas in a different system^[9] [**40a** (X = OCOR or other anion) → **40b** (X = alkynyl) → **43** → **42**] is feasible, despite the fact that internal alkynes are reactive. We note that the timing of Co–aryl versus Co–alkynyl bond formation is not clear at this point for our system. To distinguish between those pathways, **44** and **45** were reacted under standard conditions. For reaction with **44**, product **42** was not formed, while **45** gave **20** in good yield. Distinguishing between cobalt acetylide and migratory insertion mechanisms should be possible by employing deuterated acetylene such as **46-d₁**, provided that there is no H/D scrambling under the reaction conditions. Unfortunately, extensive scrambling was observed, as shown in Scheme 2. Thus, it is likely that the reaction proceeds via a cobalt acetylide intermediate, but a migratory insertion mechanism (**40** → **41**) cannot be excluded.

In conclusion, we have developed a method for cobalt-catalyzed coupling of alkynes, styrenes, and 1,3-dienes with sp^2 C–H bonds in benzoic acids. The reaction proceeds in trifluoroethanol solvent with a $Co(hfacac)_2$ catalyst, oxygen oxidant, $Ce(SO_4)_2$ cooxidant, and $(TMS)_2NH$ base. Both terminal and internal alkynes are reactive, and excellent regioselectivity is observed. The utilization of a commercially available cobalt salt and simple carboxylate directing group to achieve sp^2 C–H functionalization are major advantages of this method. Future work will involve expansion of reaction scope with respect to alkenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Carboxylic acid C-H bond functionalization. **1**→**2**: Pd for sp^3 C-H; Pd, Ir, Rh, Ru for sp^2 C-H bonds, many examples; Fe, Co, two examples, limited scope. **1**→**3**→**4**→**2**: sp^2 and sp^3 C-H; Cu, Fe, Co, Ni, Ru, Rh, Pd; many examples.

Scheme 2.
Mechanistic considerations.

Table 1

Optimization of reaction conditions.^[a]

Entry	Variation from standard conditions	Yield of 2 [%]
1	none	78
2	No PivOH	61
3	1-AdCOOH instead of PivOH	71
4	MesCOOH instead of PivOH	67
5	(CF ₃) ₂ CHOH instead of CF ₃ CH ₂ OH, no PivOH	45
6 ^[b]	4-MeC ₆ H ₄ COONa instead of 5 , no PivOH	24
7 ^[c]	No Ce(SO ₄) ₂	42
8 ^[d]	No O ₂	51
9	No Co(hfacac) ₂	0

^[a] Toluic acid (0.2 mmol), solvent (2 mL), under N₂ for 24 h then under O₂ for 24 h. Yields are ¹H NMR yields using 1,1,2-trichloroethane internal standard.

^[b] (CF₃)₂CHOH solvent.

^[c] Toluic acid (0.75 mmol), CF₃CH₂OH (7.5 mL), isolated yield.

^[d] Reaction was kept under N₂ for 48 h. PivOH = pivalic acid, 1-AdCOOH = adamantane 1-carboxylic acid, MesCOOH = 2,4,6-trimethylphenylbenzoic acid, hfacac = hexafluoroacetylacetonate.

Table 2

Reaction scope with respect to alkynes.^[a]

^[a] Toluic acid (0.75 mmol), CF_3CH_2OH (7.5 mL), under N_2 for 24 h then O_2 for 24 h. Yields are yields of isolated product. See the Supporting Information for details.

^[b] Isolated as a 7:1 mixture of isomers.

^[c] Tetrahydropyranyl-protected alcohol was used. Nphth = phthalimide, TIPS = triisopropylsilyl, Cy = cyclohexyl, Ar^1 = 3,5-Me₂C₆H₃, Ar^2 = 4-CF₃C₆H₄, Ar^3 = 4-CF₃OC₆H₄.

Table 3

Reaction scope with respect to benzoic acids.

^[a] Acid (0.75 mmol), CF₃CH₂OH (7.5 mL), under N₂ for 24 h then O₂ for 24 h. Yields are yields of isolated product. See the Supporting Information for details.

^[b] N₂ for 24 h then O₂ for 48 h.

^[c] Isolated as a 7:1 mixture of isomers.

^[d] Isolated as a 97:3 mixture of isomers.

^[e] Isolated as a 98:2 mixture of isomers.

^[f] Isolated as a 10:1 mixture of isomers.

Table 4

Alkylation of benzoic acids.

^[a] Acid (0.75 mmol), olefin (1.5 equiv), CF₃CH₂OH (7.5 mL), N₂ for 24 h then O₂ for 24 h. Yields are those of isolated products. See the Supporting Information for details.

^[b] Isolated as a 10:1 regioisomer mixture.

^[c] Isolated as 1:1 diastereoisomer mixture.