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A decarboxylative approach for regioselective hydroarylation of alkynes

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Regioselective activation of aromatic C–H bonds is a long-standing challenge for arene functionalization reactions such as the hydroarylation of alkynes. One possible solution is to employ a removable directing group that activates one of several aromatic C–H bonds. Here we report a new catalytic method for regioselective alkyne hydroarylation with benzoic acid derivatives during which the carboxylate functionality directs the alkyne to the *ortho*-C–H bond with elimination *in situ* to form a vinylarene product. The decarboxylation stage of this tandem sequence is envisioned to proceed with the assistance of an *ortho*-alkenyl moiety, which is formed by the initial alkyne coupling. This ruthenium-catalysed decarboxylative alkyne hydroarylation eliminates the common need for pre-existing *ortho*-substitution on benzoic acids for substrate activation, proceeds under redox-neutral and relatively mild conditions, and tolerates a broad range of synthetically useful aromatic functionality. Thus, it significantly increases the synthetic utility of benzoic acids as easily accessible aromatic building blocks.

Aryl-substituted alkenes are prevalent structures in biologically active compounds and important synthetic intermediates for fine chemicals and materials. The addition of an arene to an alkyne is one attractive route to these structures because of the commercial and synthetic availability of both reagents[1–5]. Such alkyne hydroarylations are more atom efficient and produce less salt waste than catalytic coupling of alkynes with pre-functionalized aromatic compounds (Fig. 1a)[2,3,6–8]. However, a long-standing challenge that faces practical alkyne hydroarylations is to control the regioselectivity for reaction at one of multiple arene C–H bonds. For example, alkyne hydroarylations by Friedel–Crafts processes require electron-donating arene substituents for satisfactory reactivities (Fig. 1b), and the directing effects of these substituents often lead to mixtures of *ortho*- and *para*-alkenylarene isomers[9,10].

In recent years, various transition-metal catalysts have been developed for alkyne hydroarylation via the formal activation of arene C–H bonds to form metal–aryl intermediates[4,5]. A number of these reported catalysts are Lewis acidic and cleave the C–H bond by electrophilic aromatic substitution, which is mechanistically analogous to the Friedel–Crafts reaction and leads to similar limitations on regioselectivity (Fig. 1b)[1,11,12]. An alternative approach is the direct cleavage of a C–H bond at the position *ortho* to a coordinating functionality via cyclometallation (Fig. 1c)[13], which was first demonstrated in Lewis and Smith's report on cyclometallated ruthenium(II) complexes that catalysed the *ortho*-alkylation of phenol with ethylene[14]. This chelation-assisted C–H functionalization strategy was explored further by Murai and co-workers for the ruthenium-catalysed hydroarylations of alkenes and alkynes with aromatic ketones[15,16]. Since these pioneering studies, chelation-assisted alkyne hydroarylation has been explored with various transition-metal catalysts and a wide range of heteroatom-based directing groups[4,6,17–20]. However, removal of these *ortho*-directing groups from the hydroarylation products requires additional chemical transformations and is not always achievable[21–23]. Thus, access to *ortho*-substituted alkenylarenes by alkyne hydroarylation is limited by the nature of the *ortho*-directing groups, and access to *meta*- or *para*-substituted alkenylarenes has not been achieved selectively by existing methods for alkyne hydroarylation[24,25].

We hypothesized that the reactions of arenecarboxylic acids could address the problem of controlling the regioselectivity of alkyne hydroarylation. The carboxyl functionality could serve as an *ortho*-directing group that would be removed by metal-mediated decarboxylation after C–H alkenylation and give products with the vinyl group *meta* or *para* to the remaining substituents (Fig. 1d)[26–30]. This decarboxylative approach to alkyne hydroarylation would use ubiquitous benzoic acids as easily accessible aromatic building blocks, with CO_2 as the only by-product and no salt waste. However, catalytic decarboxylation of benzoic acid derivatives is typically slow and generally requires *ortho*-substitution of σ-electron-withdrawing or sterically hindered groups for substrate activation[31]. The vast majority of such decarboxylative transformations also require high reaction temperatures, often above 140 °C, which thus significantly limits the substrate scope[27–31]. To achieve satisfactory reactivity, many decarboxylation processes also utilize stoichiometric silver(I) or copper(II) salts that further limit the compatibility with oxidation-sensitive functional groups, although significant progress has been made by Gooßen and co-workers to reduce the amounts of these salt additives[27,32–34].

We considered that the hydroarylation reaction would bypass these issues because the alkene unit attached to the initial intermediate formed after C–C bond formation could serve as an activating unit for decarboxylation and would eliminate the need for such a group in the benzoic acid reactant. Although the strategy of utilizing carboxyl functionality as a removable *ortho*-directing group has been reported as part of a tandem sequence or in a separate step[35–47], the decarboxylative C–H alkenylation with alkynes has not been reported. The dominant majority of the reported decarboxylative C–H functionalization processes require high reaction temperatures (130–170 °C) and stoichiometric Ag(I) or Cu(II) salts to promote decarboxylation. Moreover, most of the benzoic acids that undergo these reactions must contain *ortho*-substituents for activation, with just a few exceptions that still needed high reaction temperatures of over 120 °C (refs 35,40,46,47). Thus, we sought a new strategy for regioselective alkyne hydroarylations that involves site selectivity directed by a carboxylate group that is eliminated *in situ* under mild conditions.

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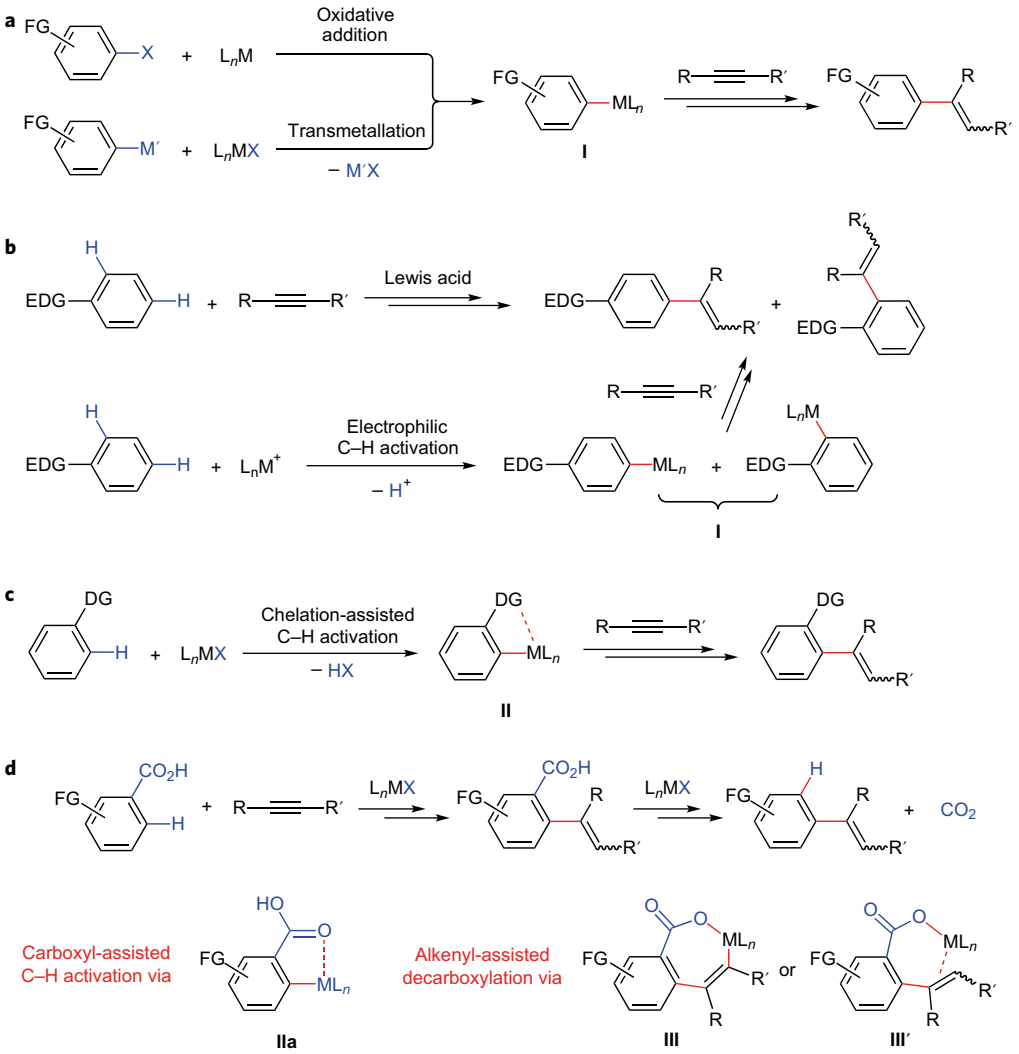


Figure 1 | Strategies for catalytic alkyne hydroarylation and the resulting regiochemistry. a, Transition-metal-catalysed alkyne hydroarylation with aryl halides or main-group metal aryl complexes as sources for transition-metal aryl nucleophiles (**I**). FG, functional group (aromatic substituent); X, halogen atoms; M, transition metals; L_n, coordinated ligands; M′, main group metals. **b**, Friedel–Crafts alkyne hydroarylation with electron-rich arenes by Lewis acid catalysis or by transition-metal-catalysed electrophilic C–H bond activation. EDG, electron-donating and *ortho/para*-directing group. **c**, Transition-metal-catalysed alkyne hydroarylation via chelation-assisted C–H bond activation to form cyclometallated transition-metal aryl nucleophiles (**II**). DG, σ-donating functional group to direct C–H activation at the *ortho*-position. **d**, A catalytic decarboxylative alkyne hydroarylation with benzoic acids by a proposed tandem sequence that involves cyclometallated intermediates of *ortho*-carboxyl metal aryls (**IIa**) and *ortho*-alkenyl metal carboxylates (**III** or **III′**).

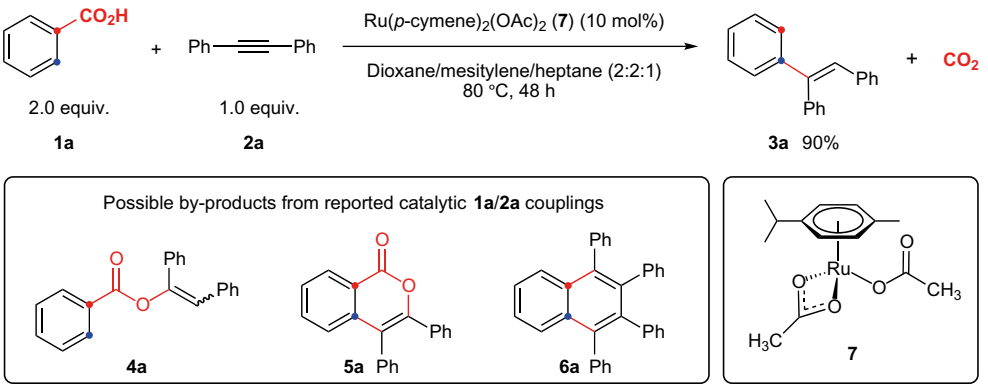
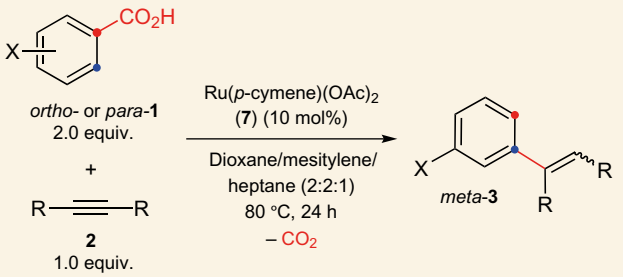


Figure 2 | Model reaction for the catalyst development of decarboxylative alkyne hydroarylation. Blue and red dots indicate the original *ipso* and *ortho* positions, respectively, of the benzoic acid substrate. Benzoic acid (**1a**, 2.0 equiv.) reacts with diphenylacetylene (**2a**, 1.0 equiv.) using 10 mol% Ru(*p*-cymene)$(OAc)_2$ (**7**), 2:2:1 mixed solvent of 1,4-dioxane/mesitylene/heptane and magnetic stirring at 80 °C for 48 hours under N_2 atmosphere. The desired hydroarylation product **3a** was formed in 90% yield by GC analysis. The possible by-products **4a** (from alkyne hydrocarboxylation), **5a** (from oxidative [4+2] annulation) and **6a** (from decarboxylative [2+2+2] annulation) were detected in only trace amounts.

Table 1 | Decarboxylative alkyne hydroarylation with *ortho*- and *para*-benzoic acids.



Entry	Starting material	Product	Yield (%)	*E*:*Z* ratio
1	*para*-**1**	**3a**: X = H, R = Ph	80*	>20:1
2	*para*-**1**	**3ba**: X = OMe, R = Ph	90	60:1
3	*para*-**1**	**3c**: X = Me, R = Ph	85	30:1
4	*para*-**1**	**3d**: X = NMe_2, R = Ph	88	20:1
5	*para*-**1**	**3e**: X = SMe, R = Ph	69†	35:1
6	*para*-**1**	**3f**: X = OH, R = Ph	85	>20:1
7	*para*-**1**	**3g**: X = NH_2, R = Ph	63	>20:1
8	*para*-**1**	**3h**: X = OAc, R = Ph	70	40:1
9	*para*-**1**	**3i**: X = NHAc, R = Ph	85	42:1
10	*para*-**1**	**3j**: X = Ac, R = Ph	32	20:1
11	*para*-**1**	**3k**: X = $CONMe_2$, R = Ph	60‡	18:1
12	*para*-**1**	**3l**: X = F, R = Ph	9	>20:1
13	*para*-**1**	**3m**: X = Cl, R = Ph	30	>20:1
14	*para*-**1**	**3n**: X = Br, R = Ph	35	>20:1
15	*para*-**1**	**3o**: X = I, R = Ph	42†	75:1
16	*para*-**1**	**3p**: X = CF_3, R = Ph	42†	10:1
17	*para*-**1**	**3pa**: X = NO_2, R = Ph	<10§	ND
18	*para*-**1**	**3pb**: X = CHO, R = Ph	<10§	ND
19	*para*-**1**	**3pc**: X = CO_2Me, R = Ph	<10§	ND
20	*para*-**1**	**3bg**: X = OMe, R = ^{n}Pr	65	40:1
21	*para*-**1**	**3bh**: X = OMe, R = ^{n}Bu	55	40:1
22	*para*-**1**	**3bi**: X = OMe, R = CH_2OMe	80	1:30
23	*para*-**1**	**3bj**: X = OMe, R = 2-(MeO)Ph	93	<1:20
24	*para*-**1**	**3bk**: X = OMe, R = 3-(MeO)Ph	81	ND
25	*para*-**1**	**3bl**: X = OMe, R = 4-(MeO)Ph	63	50:1
26	*para*-**1**	**3bm**: X = OMe, R = 2-(F)Ph	84	<1:20
27	*para*-**1**	**3bn**: X = OMe, R = 4-(F)Ph	71	50:1
28	*para*-**1**	**3bo**: X = OMe, R = 4-(CF_3)Ph	66	50:1
29	*ortho*-**1**	**3c**: X = Me, R = Ph	63	20:1
30	*ortho*-**1**	**3ba**: X = OMe, R = Ph	88	60:1
31	*ortho*-**1**	**3f**: X = OH, R = Ph	90	22:1
32	*ortho*-**1**	**3q**: X = Ph, R = Ph	70	30:1
33	*ortho*-**1**	**3l**: X = F, R = Ph	84‖	60:1

Conditions: **1** (0.4 mmol), **2** (0.2 mmol), **7** (0.02 mmol), 2:2:1 dioxane/mesitylene/*n*-heptane (10 ml in total), 80 °C, 24 hours; average isolated yields of two runs; stereoselectivity and regioselectivity determined by ^{1}H NMR spectroscopy. *Reaction time 48 hours. †Reaction temperature 100 °C. ‡Reaction temperature 100 °C and 1,4-dioxane solvent. §Estimated yield by GC analysis. ‖Dichloromethane solvent. ND, not determined.

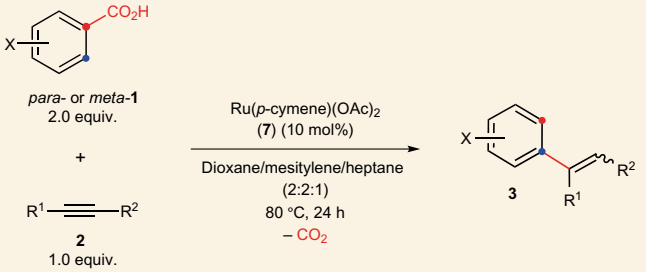
We report the discovery of a new catalyst for decarboxylative alkyne hydroarylation with various benzoic acids that overcomes the limitation on the scope of decarboxylation, generates alkenylarenes with a broad scope of aromatic substituents in *ortho*-, *meta*- and *para*-positions and proceeds under sufficiently mild conditions to tolerate a synthetically useful range of functional groups (Fig. 1d). This catalytic process operates by a tandem sequence that involves an initial C–H activation stage during which the carboxyl group causes a specific C–H bond to add to the metal and an alkyne subsequently inserts into the metal–aryl bond to form an *ortho*-alkenylbenzoic acid intermediate (**IIa**)[27,48]. This coupling of the arene with the alkyne is followed by a decarboxylation stage in which the newly installed alkenyl moiety coordinates to the metal centre of a carboxylate intermediate to facilitate CO_2 release either as an alkenyl σ-donor ligand (**III**) or as a π-olefin ligand (**III′**). The low-energy decarboxylation process from alkenyl coordination effectively eliminates the prior prerequisite of *ortho*-substitution on benzoic acids and occurs at a significantly lower temperature than those of typical decarboxylation processes. The broad substrate scope of this decarboxylative alkyne hydroarylation is demonstrated by the regioselective formation of alkenylarenes from benzoic acids with various *ortho*-, *meta*- and *para*-substituents, as well as the parent benzoic acid. The mild and redox-neutral reaction conditions allow remarkable compatibility with unprotected, oxidation-sensitive functionality, such as anilines and phenols. Thus, our catalyst system enables decarboxylative alkyne hydroarylation with biomass-derived phenolic acids, such as vanillic acid, a degradation product from lignin.

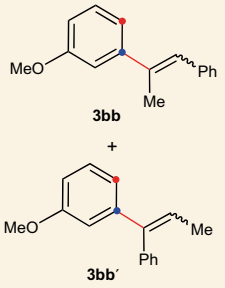
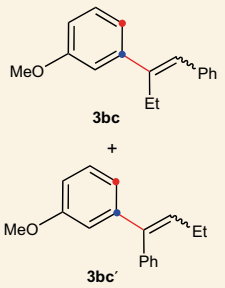
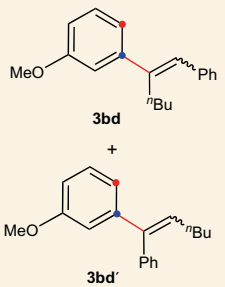
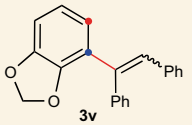
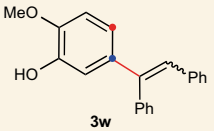
Results and discussion

We began our catalyst development with the model reaction between benzoic acid (**1a** in Fig. 2) and diphenylacetylene (**2a**). We focused our attention on ruthenium(II)-based catalyst precursors, which have been explored extensively for chelation-assisted C–H bond functionalizations, including alkyne hydroarylation[49]. Ruthenium catalysts have been explored rarely as promoters of the decarboxylation of benzoic acids[47]. A major challenge was to achieve high chemoselectivity to promote hydroarylation product **3a** over multiple by-products from reported coupling reactions, which include alkyne hydrocarboxylation (**4a**)[29], oxidative [4+2] heterocyclization (**5a**)[48] and oxidative [2+2+2] carbocyclization via decarboxylation (**6a**)[35]. To this end, we evaluated a wide range of reaction parameters, such as ruthenium catalyst precursor, ligand, salt additive, solvent and reaction temperature. As benzoic acid and its substituted analogues are generally commercially available and inexpensive, we conducted the reactions with 2 equiv. benzoic acid to maximize the conversion of alkyne. In all the reactions we monitored during this study, the excess benzoic acid remained unreacted after full conversion of the alkyne; no direct protodecarboxylation of benzoic acids was observed. Selected results from these experiments are summarized in Supplementary Table 1. We found that coupling between **1a** and **2a** was promoted by 10 mol% Ru(*p*-cymene)$(OAc)_2$ (**7**) at 80 °C and in a mixed solvent of 2:2:1 dioxane/mesitylene/heptane. Under these conditions, **3a** formed selectively in 90% yield over 48 hours; the combined yield of by-products detected was less than 5%. Reactions conducted with a single solvent of the mixed-solvent system occurred with a similarly high level of high chemoselectivity for **3a** as those with the mixed solvent, but in a much lower yield (Supplementary Table 1 gives details).

With conditions for the catalytic process identified, we investigated the decarboxylative hydroarylation of **2a** with various substituted benzoic acids (Table 1, entries 1–19 and 29–33). All the reactions occurred with a high stereoselectivity for *syn*-hydroarylation. The observed regioselectivity was consistent with the envisioned tandem sequence of *ortho*-C–H alkenylation and subsequent decarboxylation[40]. Thus, reactions with *para*-substituted benzoic acids proceeded with exclusive regioselectivity to give *meta*-substituted alkenylarenes **3ba** and **3c–3p**. High yields were achieved with

Table 2 | Product selectivity when using *meta*-benzoic acids and differentially substituted alkynes.



Entry	Starting material	Product(s)	Product ratio	Yield (%)	*E*:*Z* ratio
1	*para*-**1**	 **3bb** + **3bb′**	**3bb** + **3bb′** 16:1	60*	>20:1 (**3bb**)
2	*para*-**1**	 **3bc** + **3bc′**	**3bc** + **3bc′** 10:1	73*	>20:1 (**3bc**)
3	*para*-**1**	 **3bd** + **3bd′**	**3bd** + **3bd′** 9:1	77*	>20:1 (**3bd**)
4	*para*-**1**	*meta*-**3be**: X = OMe, R^1 = CH_2OMe, R^2 = Ph	**3be** Exclusively	77	1:25
5	*para*-**1**	*meta*-**3bf**: X = OMe, R^1 = CH_2OMe, R^2 = 4-BrPh	**3bf** Exclusively	66	1:25
6	*meta*-**1**	**3r**: X = OMe, R^1 = R^2 = Ph	**3r** + **3r′** Mixture of four isomers, 10:7:2:1	50†	NA
7	*meta*-**1**	**3s**: X = NMe_2, R^1 = R^2 = Ph	*para*-**3s** Exclusively	50†	2:1
8	*meta*-**1**	**3t**: X = ^{i}Pr, R^1 = R^2 = Ph	*para*-**3t** Exclusively	70†	60:1
9	*meta*-**1**	**3u**: X = ^{t}Bu, R^1 = R^2 = Ph	*para*-**3u** Exclusively	74†	100:1
10	*meta*-**1**	 **3v**	**3v** Exclusively	75	40:1
11	*meta*-**1**	 **3w**	**3w** Exclusively	66	12:1

Conditions: **1** (0.4 mmol), **2** (0.2 mmol), **7** (0.02 mmol), 2:2:1 dioxane/mesitylene/heptanes (10 ml in total), 80 °C, 24 hours; average isolated yields of two runs; stereo- and regioselectivity determined by ^{1}H NMR spectroscopy. *Dichloromethane solvent. †Reaction time 48 hours.

strongly electron-donating *para*-substituents, which included methyl, methoxy and dimethylamino groups (products **3ba**, **3c** and **3d**). With the weakly electron-donating *para*-methylthio group, the reaction required a higher temperature of 100 °C to give product **3e** in 69% yield. The redox-neutral property of the current process tolerated not only acyl-protected but also unprotected phenol and aniline functionality to form *meta*-O- or N-functionalized products **3f**–**3i** in good yields. In contrast, significantly lower reactivity was observed with arenes containing *para*-substituents that are deactivating groups for electrophilic aromatic substitution. For example, benzoic acids with *para* halogen, acetyl, carboxamido and CF_3 groups led to products **3j**–**3p** in low-to-modest yields, even at a higher reaction temperature of 100 °C. Similarly, benzoic acids with *para*-nitro, -formyl and -methoxycarbonyl groups led to low yields of the desired hydroarylation products (**3pa**–**3pc**, less than 10% by gas chromatography (GC) analysis) and the competitive formation of by-product **6a** by [2+2+2] decarboxylative carbocyclization[35].

With *ortho*-substituted benzoic acids, the same *meta*-substituted alkenylarenes should form as are formed from the *para*-substituted analogues. This envisioned regioselectivity was observed from the reactions of several benzoic acids that contained *ortho*-substituents, including methyl, methoxy, hydroxy, phenyl and fluoro groups (Table 1, entries 29–33). These *ortho*-substituted benzoic acids led to the exclusive formation of *meta*-substituted alkenylarenes without the detectable formation of *ortho*-substituted alkenylarenes or the corresponding arenes from protodecarboxylation. This lack of *ipso*-selective decarboxylative transformations with *ortho*-substituted benzoic acids supported our proposed decarboxylation pathways that involve coordination with the *in situ* attached *ortho*-alkenyl moiety, rather than decarboxylation facilitated by the steric properties of pre-existing *ortho*-substituents.

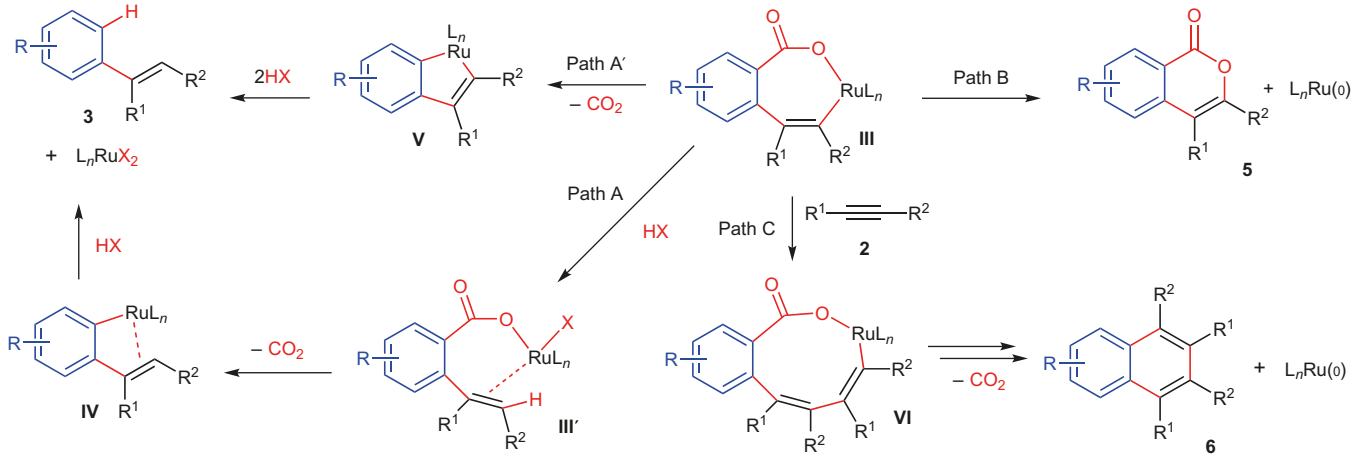


Figure 3 | Proposed divergent reactivity of a cyclometallated alkenylruthenium(II) carboxylate intermediate. The catalytic process occurs by a tandem decarboxylation process from *ortho*-alkenyl benzoate intermediates. A cyclometallated alkenylruthenium(II) carboxylate complex forms by carboxylate-directed C–H activation and the insertion of the alkyne into the Ru–C bond. Protonation of the Ru–alkenyl bond in **III** generates the alkenyl-chelated Ru(II) carboxylate intermediate **III′** (Path A), which forms the hydroarylation product **3** and, after protonation, the Ru(II) aryl intermediate **IV**. An alternative decarboxylation process can occur from intermediate **III** (Path A′). The ruthenacycle **V** is doubly protonated at the Ru–aryl and Ru–alkenyl bonds to form **3**. The competing process, C–O bond-forming reductive elimination, would generate **5** via oxidative [4+2] annulation (Path B). A third possible reaction involves the insertion of a second alkyne **2** into the Ru–alkenyl bond (Path C), which leads to by-product **6** via sequential decarboxylation and C–C reductive elimination. HX, acidic proton sources such as HOAc, benzoic acid substrate or PivOH additive.

Meta-substituted benzoic acids were expected to undergo competitive C–H functionalization at two different *ortho*-sites of the carboxyl group. Indeed, 3-methoxybenzoic acid reacted with **2a** to give an inseparable mixture of four regio- and stereoisomers of hydroarylation products in 50% overall yields and low selectivities (products **3r**/**r′** (Table 2)). We hypothesized that both electronic and steric properties of *meta*-substituents could affect the regioselectivity. The more sterically demanding *meta*-substituents should inhibit *ortho*-alkenylation and promote *para*-alkenylation. Consistent with this assertion, sterically demanding *meta*-dimethylamino, isopropyl and *tert*-butyl substituents led to the exclusive formation of *para*-alkenylation products **3s**–**3u** in 50–74% yields. This control over regioselectivity by aromatic substituents was also observed with two protocatechuic acid derivatives that contained both *meta*- and *para*-substituents. The exclusive formation of *ortho*-alkenylation product **3v** suggested a dominant electronic effect and negligible steric effect from the acetal-protected 3,4-dihydroxy moiety. In contrast, the reaction with vanillic acid led to the exclusive formation of product **3w** via regioselective C–H activation and alkenylation at the aromatic site that is *para* to the methoxy group and *meta* to the hydroxy group.

The scope of the alkyne that undergoes this hydroarylation was investigated with 4-methoxybenzoic acid as the reaction partner (Table 1, entries 20–28, and Table 2, entries 1–5). No coupled products were detected from reactions with terminal alkynes, such as phenylacetylene; the absence of such products possibly resulted from the formation of unproductive Ru(II) alkynyl or vinylidenyl complexes. Unsymmetrical aryl–alkyl alkynes reacted with exclusive regioselectivity to form 1-alkyl-1-*meta*-anisyl alkene products (**3bb**–**3bf**). Methyl-, ethyl- and *n*-butyl-substituted phenylacetylenes were less reactive than diphenylacetylene (**2a**) and required 20 mol% $Cu(OAc)_2$ additive to give products **3bb**–**3bd** in 60–77% yields as well as small amounts of the isocoumarin by-product **5** and the naphthalene by-product **6a** from oxidative annulation reactions[35,48]. The observed higher overall yields and lower chemoselectivity with added $Cu(OAc)_2$ probably results from its well-known role as an oxidizing reagent for ruthenium-catalysed oxidative C–H functionalization processes[26,49]. We propose that $Cu(OAc)_2$ helps to regenerate the active catalyst from a deactivated catalyst created from the side reactions that form by-products **5** and **6a**. The active catalyst is regenerated by oxidizing Ru(0) to Ru(II) carboxylate complexes, which are needed to initiate the C–H activation that leads to the formation of the desired hydroarylation product **3**. Compared with alkynes that contain simple alkyl groups, methoxymethyl-substituted arylacetylenes reacted faster and no $Cu(OAc)_2$ additive was required to achieve good yields (products **3be** and **3bf**). This enhancement in reactivity by a methoxymethyl substituent was also observed for symmetrical dialkylacetylenes (products **3bg**–**3bi**). Results from reactions with several symmetrical diarylacetylenes provided additional information on steric effects on alkyne reactivity (products **3bj**–**3bo**). In particular, higher yields were observed with alkynes that contained *ortho*-substituted aryl groups (products **3bj** and **3bm**) than with those that contained *meta*- or *para*-substituted aryl groups.

We propose that the overall catalytic process occurs by a tandem sequence that involves decarboxylation from *ortho*-alkenyl benzoate intermediates (Fig. 1d). A cyclometallated alkenylruthenium(II) carboxylate complex (**III** in Fig. 3) probably forms by carboxylate-directed C–H activation and subsequent insertion of the alkyne into the Ru–aryl linkage (Supplementary Fig. 1 gives details of the proposed catalytic cycle). Protonation of the Ru–alkenyl bond in **III** would generate the alkenyl-chelated Ru(II) carboxylate intermediate **III′** (Path A in Fig. 3), which would form the hydroarylation product **3** via decarboxylation and subsequent protonation of the resulting alkenyl-chelated Ru(II) aryl intermediate **IV**. An alternative decarboxylation process is the direct decarboxylation from intermediate **III**, which is the microscopic reverse of Ru–aryl addition across a C=O double bond in CO_2 (Path A′). The resulting ruthenacycle **V** undergoes double protonation of the Ru–aryl and Ru–alkenyl bonds to release hydroarylation product **3**. Both Path A and Path A′ feature decarboxylation assisted by coordination of the *ortho*-alkenyl moiety, which occurs through π-alkene complexation in Path A and σ-alkenyl ligation in Path A′. As a competing process, C–O bond-forming reductive elimination from **III** would generate an isocoumarin **5** as the by-product of oxidative [4+2] annulation (Path B)[48]. As a third possible reaction of **III**, the insertion of a second equivalent of alkyne **2** into the Ru–alkenyl bond (Path C) would lead to the formation of an oxidative [2+2+2] by-product **6** via sequential decarboxylation and C–C reductive elimination to close the ring[35]. If alkenyl-assisted

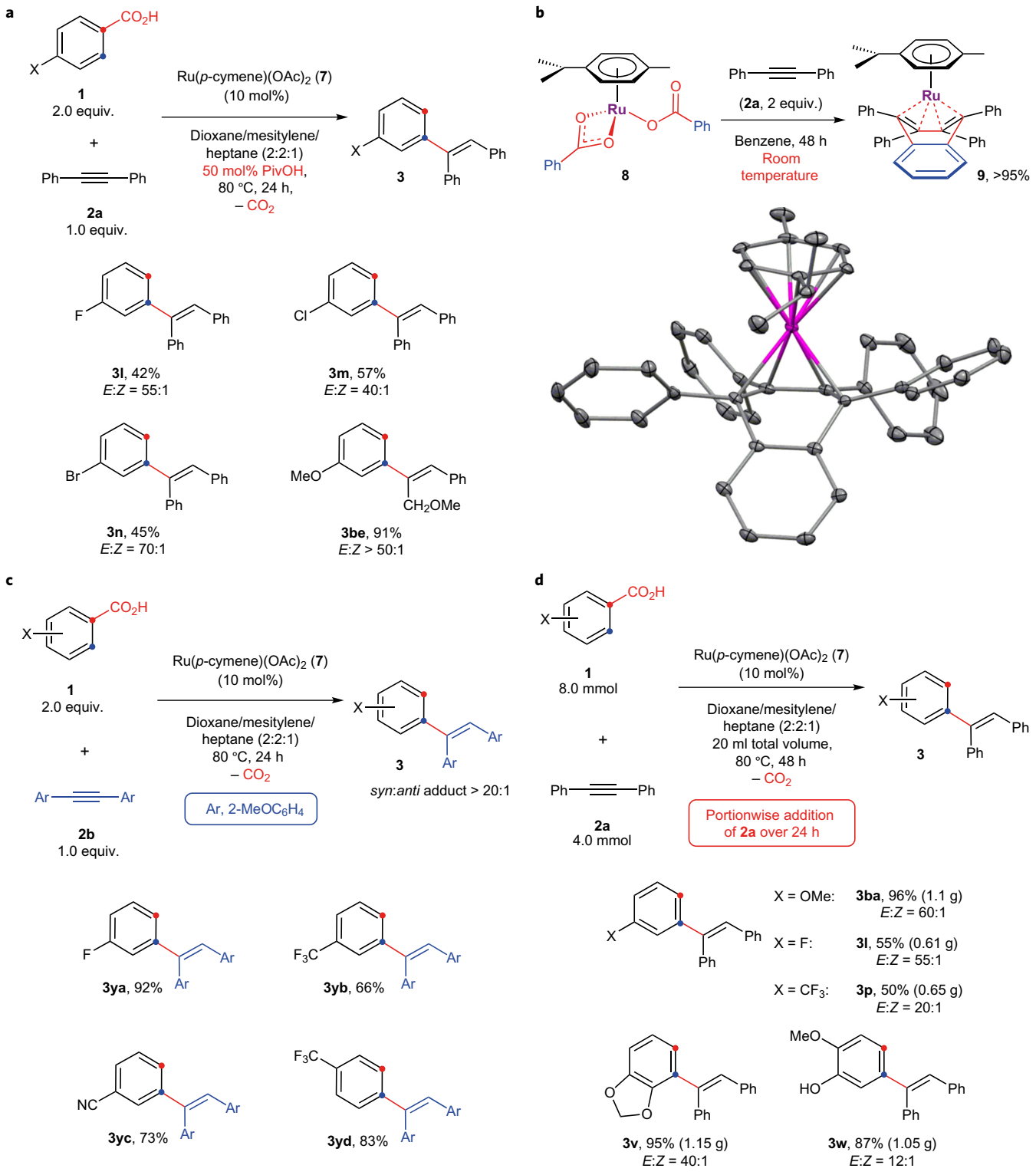


Figure 4 | Mechanism-guided efforts towards catalyst improvement. a, Improved yields of hydroarylation products with the additive of 50 mol% PivOH. **b**, Stoichiometric formation of a Ru(η^6-*p*-cymene)(η^4-tetraphenylnaphthalene) complex **9** and the ORTEP diagram of its X-ray structure. Thermal ellipsoids are set at 30% probability level, and all hydrogen atoms are omitted for clarity. **c**, Improved yields of hydroarylation products with a sterically bulky alkyne substrate **2b**. **d**, Results of scale-up reactions under the modified catalytic conditions of slow addition for alkyne substrate **2a**.

decarboxylation proceeds via Path A′, then intermediate **V** could undergo further alkyne insertion and subsequent ring closure by C–C reductive elimination to generate by-product **6**.

The proposed diverse reactivity of intermediate **III** was supported by several experimental results and guided further improvement of the catalyst. First, acid additives favoured formation of the hydroarylation product **3** over by-products, presumably by facilitating the protonation steps in Path A. The coupling between **2a** and various *para*-substituted benzoic acids conducted with 50 mol% pivalic acid (PivOH)[28] led to hydroarylation products **3l**,

3m and **3be** in higher yields than produced in the absence of the acid (Fig. 4a). Second, a 2:1 reaction between **2a** and a Ru(II) benzoate complex, Ru(*p*-cymene)$(OBz)_2$ (**8**), at room temperature over 48 hours led to the quantitative formation of the Ru(0) complex **9** (Fig. 4b). The solid-state structure of complex **9** was established by single-crystal X-ray diffraction (Supplementary Fig. 2 and Supplementary Tables 2 and 3 give more details). This complex contains an η^4-1,2,3,4-tetraphenylnaphthalene ligand, in addition to the η^6-*p*-cymene ligand, and displayed no catalytic reactivity for decarboxylative alkyne hydroarylation. The naphthalene ligand was presumably generated by [2+2+2] annulation in Path C[35,38]. The mild temperature for the stoichiometric formation of complex **9** and its complete lack of catalytic activity suggest that Path C is detrimental to the hydroarylation process and leads to catalyst deactivation. Consistent with this assertion, 1,2,3,4-tetrasubstituted naphthalenes (**6**) were the major by-products of the reactions of electron-poor benzoic acids that were less reactive towards decarboxylative hydroarylation (products **3l**–**3p** in Table 1). However, more-hindered alkynes, which would be less prone to undergo two consecutive insertion reactions, formed the hydroarylation products in high yields (products **3bj** and **3bm** in Table 1).

The higher chemoselectivity towards hydroarylation with 1,2-di(*ortho*-anisyl)acetylene (**2b**) was evident from reactions with electron-deficient benzoic acids (Fig. 4c). 4-Fluorobenzoic acid and 4-trifluoromethylbenzoic acid both reacted with **2b** to give significantly higher yields (products **3ya** and **3yb**) than those with diphenylacetylene (**2a**) (**3l** and **3p** in Table 1) and without the need for added PivOH or a higher reaction temperature. 4-Cyanobenzoic acid, which did not react with **2a** at 80–100 °C, also reacted with **2b** to form **3yc** in 73% yield. The chemoselectivity for hydroarylation was also higher for reactions with higher ratios of benzoic acid to alkyne or for reactions in which the alkyne was added slowly to the reaction system. With this modified procedure that involved the slow addition of the alkyne (Fig. 4d), couplings between **2a** and several substituted benzoic acids occurred in higher yield on scales up to 4.0 mmol than they did on a small scale (0.1 mmol), which allowed isolation of gram quantities of hydroarylation products.

Most of the benzoic acids employed in the current procedure are commercially available and less expensive than other aromatic building blocks used in regioselective catalytic coupling with alkynes[7–9]. In particular, the reactions of the benzoic acids provide new opportunities for phenolic acids derived from biomass to serve as renewable aromatic building blocks in chemical synthesis (products **3ba**–**3bo**, **3f**, **3s/s′**, **3w** and **3x**). As a leading example, 4-hydroxybenzoic acid can be separated from biomass sources, including lignin, and is now (2016) commercially available at ~60US$ per kilogram (8.3US$ mol^{-1}) from Sigma-Aldrich. Decarboxylative hydroarylation with 4-hydroxybenzoic acid gave *meta*-alkenylphenol **3f** in high yield and dominant (*E*)-stereoselectivity (Table 1, entry 6). In comparison, other reported alkyne hydroarylation procedures with various arenes or aryl nucleophiles were either incompatible with unprotected phenol functionality, gave inseparable mixtures of *ortho*/*para*-alkenylation products with phenol ether substrates[10] or used more-expensive halophenols (for example, 3-iodophenol at ~780US$ mol^{-1} from Sigma-Aldrich) and generated stoichiometric halide salt waste[50].

In summary, we have developed a decarboxylative approach to the hydroarylations of alkynes to synthesize alkenylarene products with controlled and versatile regioselectivity. Compared with existing catalytic methods for the decarboxylative coupling of benzoic acids, this process occurs at a much lower temperature because the decarboxylation is facilitated by the *ortho*-alkenyl moiety after sequential C–H activation and alkyne insertion. The mild, redox-neutral conditions make the reaction compatible with various aromatic substituents at the *para*-, *meta*- and *ortho*-positions. This new decarboxylation strategy eliminates the prerequisite of *ortho*-substituents in the arene that induce decarboxylation and thereby allows a broad scope of substituted benzoic acids to serve as aromatic components of the alkyne hydroarylation. A series of *meta*- and *para*-substituted alkenylarenes, as well as alkenylarenes that possess unprotected phenol and aniline functionality, can be prepared conveniently by this method. We expect that the alkenyl assistance demonstrated in this study can be exploited further to facilitate decarboxylative transformations.

Methods

The general procedure for decarboxylative alkyne hydroarylation is as follows. In a nitrogen-atmosphere glovebox, [Ru(*p*-cymene)$(OAc)_2$] (**7**, 71 mg, 0.2 mmol) and 10.0 ml of mixed solvent (4.0 ml dioxane, 4.0 ml mesitylene and 2.0 ml heptanes) were added into a 20 ml scintillation vial equipped with a magnetic stir bar. The mixture was stirred for ten minutes to be used as a homogeneous stock solution of catalyst precursor. A 4 ml scintillation vial equipped with a magnetic stir bar was charged with the alkyne substrate (0.2 mmol, 1.0 equiv.), arenecarboxylic acid substrate (0.4 mmol) and 1.0 ml of the stock solution of catalyst precursor (containing 0.02 mmol of complex **7**). The vial was then sealed with a Teflon-lined cap, transferred out of the glovebox and stirred in an 80 °C oil bath for 24 hours. The reaction mixture was cooled to room temperature and then all volatile materials were removed under reduced pressure. Further purification was achieved by flash column chromatography using dichloromethane, ethyl acetate and hexanes as the eluent. The *E*/*Z* alkene stereo- and regioselectivity for aromatic substitution was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. Yields of the isolated products are based on the average of two runs under identical conditions. Supplementary Figs 3–92 and Supplementary Methods give full experimental details and analytical data for the characterization of new compounds.

Data availability. The X-ray crystallographic coordinates for the structure reported in this study are deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 1483081 (**9** at 100 K, high-temperature phase). These data can be obtained free of charge.

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References

1. Jia, C. *et al.* Efficient activation of aromatic C–H bonds for addition to C–C multiple bonds. *Science* **287,** 1992–1995 (2000).
2. Nevado, C. & Echavarren, A. M. Transition metal-catalyzed hydroarylation of alkynes. *Synthesis*, 167–182 (2005).
3. Mitchell, D. & Yu, H. Synthetic applications of palladium-catalyzed hydroarylation and related systems. *Curr. Opin. Drug Discov. Dev.* **6,** 876–883 (2003).
4. Kitamura, T. Transition-metal-catalyzed hydroarylation reactions of alkynes through direct functionalization of C–H bonds. A convenient tool for organic synthesis. *Eur. J. Org. Chem.* 1111–1125 (2009).
5. Bandini, M. Gold-catalyzed decorations of arenes and heteroarenes with C–C multiple bonds. *Chem. Soc. Rev.* **40,** 1358–1367 (2011).
6. Cacchi, S. The palladium-catalyzed hydroarylation and hydrovinylation of carbon–carbon multiple bonds: new perspectives in organic synthesis. *Pure Appl. Chem.* **62,** 713–722 (1990).
7. Cacchi, S., Fabrizi, G., Goggiamani, A. & Persiani, D. Palladium-catalyzed hydroarylation of alkynes with arenediazonium salts. *Org. Lett.* **10,** 1597–1600 (2008).
8. Xu, X. *et al.* Palladium-catalyzed hydroarylation of alkynes with arylboronic acids. *Tetrahedron* **66,** 2433–2438 (2010).
9. Song, C. E., Jun, D.-U., Choung, S.-Y., Roh, E. J. & Lee, S.-G. Dramatic enhancement of catalytic activity in an ionic liquid: highly practical Friedel–Crafts alkenylation of arenes with alkynes catalyzed by metal triflates. *Angew. Chem. Int. Ed.* **43,** 6183–6185 (2004).
10. Li, R., Wang, S. R. & Lu, W. $FeCl_3$-catalyzed alkenylation of simple arenes with aryl-substituted alkynes. *Org. Lett.* **9,** 2219–2222 (2007).
11. Reetz, M. T. & Sommer, K. Gold-catalyzed hydroarylation of alkynes. *Eur. J. Org. Chem.* 3485–3496 (2003).
12. Shi, Z. & He, C. Efficient functionalization of aromatic C–H bonds catalyzed by gold(III) under mild and solvent-free conditions. *J. Org. Chem.* **69,** 3669–3671 (2004).
13. Albrecht, M. Cyclometalation using *d*-block transition metals: fundamental aspects and recent trends. *Chem. Rev.* **110,** 576–623 (2010).
14. Lewis, L. N. & Smith, J. F. Catalytic C–C bond formation via *ortho*-metalated complexes. *J. Am. Chem. Soc.* **108,** 2728–2735 (1986).
15. Murai, S. *et al.* Efficient catalytic addition of aromatic carbon–hydrogen bonds to olefins. *Nature* **366,** 529–531 (1993).
16. Kakiuchi, F., Yamamoto, Y., Chatani, N. & Murai, S. Catalytic addition of aromatic C–H bonds to acetylenes. *Chem. Lett.* 681–682 (1995).

17. Schipper, D. J., Hutchinson, M. & Fagnou, K. Rhodium(III)-catalyzed intermolecular hydroarylation of alkynes. *J. Am. Chem. Soc.* **132,** 6910–6911 (2010).
18. Hashimoto, Y., Hirano, K., Satoh, T., Kakiuchi, F. & Miura, M. Ruthenium(II)-catalyzed regio- and stereoselective hydroarylation of alkynes via directed C–H functionalization. *Org. Lett.* **14,** 2058–2061 (2012).
19. Hashimoto, Y., Hirano, K., Satoh, T., Kakiuchi, F. & Miura, M. Regioselective C–H bond cleavage/alkyne insertion under ruthenium catalysis. *J. Org. Chem.* **78,** 638–646 (2013).
20. Min, M., Kim, D. & Hong, S. $AgSbF_6$-controlled diastereodivergence in alkyne hydroarylation: facile access to *Z*- and *E*-alkenyl arenes. *Chem. Commun.* **50,** 8028–8031 (2014).
21. Zhang, F. & Spring, D. R. Arene C–H functionalisation using a removable/modifiable or a traceless directing group strategy. *Chem. Soc. Rev.* **43,** 6906–6919 (2014).
22. Rousseau, G. & Breit, B. Removable directing groups in organic synthesis and catalysis. *Angew. Chem. Int. Ed.* **50,** 2450–2494 (2011).
23. Liu, G., Shen, Y., Zhou, Z. & Lu, X. Rhodium(III)-catalyzed redox-neutral coupling of *N*-phenoxyacetamides and alkynes with tunable selectivity. *Angew. Chem. Int. Ed.* **52,** 6033–6037 (2013).
24. Wang, C., Chen, H., Wang, Z., Chen, J. & Huang, Y. Rhodium(III)-catalyzed C–H activation of arenes using a versatile and removable triazene directing group. *Angew. Chem. Int. Ed.* **51,** 7242–7245 (2012).
25. Tang, R.-Y., Li, G. & Yu, J.-Q. Conformation-induced remote *meta*-C–H activation of amines. *Nature* **507,** 215–220 (2014).
26. Ackermann, L. Carboxylate-assisted transition-metal-catalyzed C–H bond functionalizations: mechanism and scope. *Chem. Rev.* **111,** 1315–1345 (2011).
27. Shepard, A. F., Winslow, N. R. & Johnson, J. R. The simple halogen derivative of furan. *J. Am. Chem. Soc.* **52,** 2083–2090 (1930).
28. Gooβen, L. J., Rodriguez, N. & Gooβen, K. Carboxylic acids as substrates in homogeneous catalysis. *Angew. Chem. Int. Ed.* **47,** 3100–3120 (2008).
29. Rodriguez, N. & Gooβen, L. J. Decarboxylative coupling reactions: a modern strategy for C–C-bond formation. *Chem. Soc. Rev.* **40,** 5030–5048 (2011).
30. Cornella, J. & Larrosa, I. Decarboxylative carbon–carbon bond-forming transformations of (hetero)aromatic carboxylic acids. *Synthesis* **44,** 653–676 (2012).
31. Tang, J., Biafora, A. & Goossen, L. J. Catalytic decarboxylative cross-coupling of aryl chlorides and benzoates without activating *ortho* substituents. *Angew. Chem. Int. Ed.* **44,** 13130–13133 (2015).
32. Myers, A. G., Tanaka, D. & Mannion, M. R. Development of a decarboxylative palladation reaction and its use in a Heck-type olefination of arene carboxylates. *J. Am. Chem. Soc.* **124,** 11250–11251 (2002).
33. Gooβen, L. J., Deng, G. & Levy, L. M. Decarboxylation: synthesis of biaryls via catalytic decarboxylative coupling. *Science* **313,** 662–664 (2006).
34. Gooβen, L. J., Thiel, W. R., Rodriguez, N., Linder, C. & Melzer, B. Copper-catalyzed protodecarboxylation of aromatic carboxylic acids. *Adv. Synth. Catal.* **349,** 2241–2246 (2007).
35. Ueura, K., Satoh, T. & Miura, M. Rhodium- and iridium-catalyzed oxidative coupling of benzoic acids with alkynes via regioselective C–H bond cleavage. *J. Org. Chem.* **72,** 5362–5367 (2007).
36. Maehara, A., Tsurugi, H., Satoh, T. & Miura, M. Regioselective C–H functionalization directed by a removable carboxyl group: palladium-catalyzed vinylation at the unusual position of indole and related heteroaromatic rings. *Org. Lett.* **10,** 1159–1162 (2008).
37. Mochida, S., Hirano, K., Satoh, T. & Miura, M. Synthesis of stilbene and distyrylbenzene derivatives through rhodium-catalyzed *ortho*-olefination and decarboxylation of benzoic acids. *Org. Lett.* **12,** 5776–5779 (2010).
38. Wang, C., Rakshit, S. & Glorius, F. Palladium-catalyzed intermolecular decarboxylative coupling of 2-phenylbenzoic acids with alkynes via C–H and C–C bond activation. *J. Am. Chem. Soc.* **132,** 14006–14008 (2010).
39. Cornella, J., Righi, M. & Larrosa, I. Carboxylic acids as traceless directing groups for formal *meta*-selective direct arylation. *Angew. Chem. Int. Ed.* **50,** 9429–9432 (2011).
40. Bhadra, S., Dzik, W. I. & Gooβen, L. J. Synthesis of aryl ethers from benzoates through carboxylate-directed C–H-activating alkoxylation with concomitant protodecarboxylation. *Angew. Chem. Int. Ed.* **52,** 2959–2962 (2013).
41. Mamone, P., Danoun, G. & Gooβen, L. J. Rhodium-catalyzed *ortho* acylation of aromatic carboxylic acids. *Angew. Chem. Int. Ed.* **52,** 6704–6708 (2013).
42. Luo, J., Preciado, S. & Larrosa, I. Overriding *ortho–para* selectivity via a traceless directing group relay strategy: the *meta*-selective arylation of phenols. *J. Am. Chem. Soc.* **136,** 4109–4112 (2014).
43. Quan, Y. & Xie, Z. Iridium catalyzed regioselective cage boron alkenylation of *o*-carboranes via direct cage B–H activation. *J. Am. Chem. Soc.* **136,** 15513–15516 (2014).
44. Qin, X., Sun, D., You, Q., Cheng, Y. & You, J. Rh(III)-catalyzed decarboxylative *ortho*-heteroarylation of aromatic carboxylic acids by using the carboxylic acid as a traceless directing group. *Org. Lett.* **17,** 1762–1765 (2015).
45. Zhang, Y., Zhao, H., Zhang, M. & Su, W. Carboxylic acids as traceless directing groups for the rhodium(III)-catalyzed decarboxylative C–H arylation of thiophenes. *Angew. Chem. Int. Ed.* **54,** 3817–3821 (2015).
46. Shi, X.-Y. *et al.* A convenient synthesis of *N*-aryl benzamides by rhodium-catalyzed *ortho*-amidation and decarboxylation of benzoic acids. *Chem. Eur. J.* **21,** 1900–1903 (2015).
47. Shi, X.-Y. *et al.* Ru(II)-catalyzed *ortho*-amidation and decarboxylation of aromatic acids: a versatile route to *meta*-substituted *N*-aryl benzamides. *Sci. China Chem.* **58,** 1286–1291 (2015).
48. Ackermann, L., Pospech, J., Graczyk, K. & Rauch, K. Versatile synthesis of isocoumarins and α-pyrones by ruthenium-catalyzed oxidative C–H/O–H bond cleavages. *Org. Lett.* **14,** 930–933 (2012).
49. Arockiam, P. B., Bruneau, C. & Dixneuf, P. H. Ruthenium(II)-catalyzed C–H bond activation and functionalization. *Chem. Rev.* **112,** 5879–5919 (2012).
50. Cacchi, S., Felici, M. & Pietroni, B. The palladium-catalyzed reaction of aryl iodides with mono- and disubstituted acetylenes: a new synthesis of trisubstituted alkenes. *Tetrahedron Lett.* **25,** 3137–3140 (1984).

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Author contributions

J.Z. performed the experiments and data analysis. R.S. participated in the high-throughput screening experiments for catalyst development. J.Z., J.F.H. and P.Z. designed the catalytic sequence and developed the reaction conditions. P.Z. and J.F.H. prepared this manuscript with feedback from J.Z. and R.S.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to P.Z.

Competing financial interests

The authors declare no competing financial interests.