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Carboxyl-Directed Conjugate Addition of C–H Bonds to α , β -Unsaturated Ketones in Air and Water

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Abstract: A simple ruthenium-catalyzed conjugate addition of C-H bonds to α,β -unsaturated ketones directed by a removable carboxyl group was developed as an effective protocol to synthesize ortho-alkylated benzoic acids in a greener manner. Without any additives, satisfactory to excellent yields of the targeted products were achieved in neat water, and the process characterizes in mild reaction conditions (in air and water), simple operations, and broad substrate scope. Noteworthy features of this method include mild reaction conditions (in air and water), operational simplicity and broad substrate scope. The versatility and utility of the addition products were demonstrated through further transformation into commonly inaccessible but highly useful motifs of metaalkylbenzenes 3-substituted substituted and isochromanones.

Keywords: conjugate addition; C–H activation; ruthenium catalysis; carboxyl-directing; organic reaction in water

As an alternative to the conjugate addition of organometallic reagents to α . β -unsaturated carbonvl compounds, the direct addition of C-H bonds to unsaturated carbon-carbon bonds has been intensively investigated because it offers a more straightforward and economical route to form C-C bonds.^[1] Such processes proceed through aromatic C-H activation and subsequent unsaturated bond insertion, thus avoiding the generation of stoichiometric amounts of byproducts. After the pioneering work of Murai's group,^[2] the chelation-assisted strategy is widely applied to the direct addition of C–H bonds to α,β unsaturated carbonyl compounds catalyzed by Pd, Rh, Ir, Ru, Co or Mo complexes, and improved selectivity has been achieved with the assistance of a directing group such as carbonyl,^[3] imine,^[4] nitrogen heterocycle,^[5] and bidentate 8-aminoquinoline.^[6] Despite these remarkable advances, the addition reactions were commonly carried out in organic solvents. Moreover, additives and inert atmosphere are often required. Therefore, the development of a simple catalytic system to accomplish these transformations in a non-toxic solvent under aerobic conditions is still highly desirable in terms of both green chemistry and practicality.

The carboxyl group has been regarded as a fascinating directing group due to its advantages of being installed and removed easily and convenient for further transformation to other functional groups. In addition, carboxylic acids are commercially availabl easy to store, and simple to handle.^[7] However, to the best of our knowledge, ortho-C-H alkylation of aromatic acids with carbonyl compounds has not been reported so far. In 2016, Li's group reported a tandem dehydrogenative cyzclization of benzoic acids and ethyl vinyl ketone utilizing $Cu(OAc)_2 \cdot H_2O$ as an oxidant, and the seven-membered cyclic intermediate shown in Scheme 1 was proposed as the likely intermediate.^[8] Combining the structure of the cyclic intermediate and our understanding on the direct addition of C-H bonds to α,β -unsaturated ketones, we envisioned that ortho-alkylated benzoic acids could be generated if the cyclic intermediate was protonated. However, the high reactivity of carboxyl, annulation cyclization, self e.g. decarboxylation or decarboxylative cross-coupling,^{[9-} ^{11]} makes the step of protonation particularly challenging.



Scheme 1. Ruthenium-catalyzed direct addition of C–H bonds to α,β -unsaturated ketones in air and water

As part of our continuous interest in carboxyldirected C-H functionalizations,^[12] we demonstrate herein an efficient ruthenium-catalyzed conjugate addition of C-H bonds to α,β -unsaturated ketones directed by carboxyl to afford a variety of orthoalkylated benzoic acids in neat water (Scheme 1), which complements conventional alkylation reactions such as the Friedel-Crafts reaction and cross-coupling between aryl (or alkyl) halides and alkyl (or aryl) metal reagents. Noteworthy features of the proposed method include commercially available and cheap substrates, additive-free catalytic system, benign solvent, mild aerobic atmospheric conditions, operational simplicity, and broad substrate scope. The facile manipulation of the ortho-alkylated benzoic acids as an additional synthetic opportunity was demonstrated to synthesize commonly inaccessible but highly valuable motifs of meta-substituted alkylbenzenes and 3-substituted isochromanones.

To validate our hypothesis, *o*-toluic acid (1a) and ethyl vinyl ketone (2a) were chosen as representative starting materials. In accordance with our previous work,^[12c] the reaction was firstly performed in 1,4dioxane with a $[RuCl_2(p-cymene)]_2$ catalyst under an atmosphere of N₂. Unfortunately, neither the cyclized nor the alkylated product was detected (Table 1, entry 1). Given the proton-transfer as an important step to initiate the addition reaction, NaOAc (0.5 equiv) was added as a basic additive. Delightfully, 3a in a yield of 50% was obtained accompanied by 16% yield of 3a' (Table 1, entry 2). The basic NaOAc may neutralize the generated proton in the step of C-H activation and facilitate the arene metalation. A further experiment showed surprisingly that this transformation could be easily performed under air without the protection of an inert atmosphere (Table 1, entry 3). However, when NaOAc was replaced by acidic additives such as acetic acid, pivalic acid, and 2,4,6-trimethylbenzoic acid, no conjugation addition product was detected. Under similar conditions, commonly used catalysts such as $Cp*RuCl(PPh_3)_2$, RuCl₂(COD), RuCl₂(PPh₃)₃, [Cp*RhCl₂]₂, Pd(TFA)₂, $Pd(OAc)_2$, were all found to be ineffective for this reaction (Table 1, entries 4-9). Moderate to good yields of **3a** were observed when the reaction was run in toluene, DCE, DME, THF, CH₃CN, PhCl, or H₂O (entries 10-16).

Further optimization showed that this transformation could successfully proceed in neat water, giving a 52% yield of **3a** without any additives (Table 1, entry 17). Subsequently, the amount of the catalyst and reaction time were examined to optimize the reaction conditions with H₂O as a solvent. The yield of **3a** could be enhanced to 79% by reducing the amount of the catalyst loading to 1.5 mol%, shortening the reaction time to 12 h, and lowering the temperature to 95 °C (Table 1, entry 18).

After investigating the model reaction, the scope of this new protocol in/on water with various aromatic acids was studied in detail. As shown in Table 2, the substituents on the phenyl ring had less influence on the yields of the desired product. For example,

Table 1. Selected results for optimizing reaction conditions.[a]

Entry	Catalyst	Solvent -	$Yield(\%)^b$	
			3a	3a'
1 ^[c,d]	$[RuCl_2(p-cymene)]_2$	dioxane		
2 ^[c]	$[RuCl_2(p-cymene)]_2$	dioxane	50	16
3	$[RuCl_2(p-cymene)]_2$	dioxane	55	21
4	Cp*RuCl(PPh ₃) ₂	dioxane	3	10
5	RuCl ₂ (COD)	dioxane	ND^{e}	3
6	RuCl ₂ (PPh ₃) ₃	dioxane	ND	ND
7	[Cp*RhCl ₂] ₂	dioxane	ND	81
8	$Pd(TFA)_2$	dioxane	ND	4
9	$Pd(OAc)_2$	dioxane	ND	ND
10	$[RuCl_2(p-cymene)]_2$	toluene	50	13
11	$[RuCl_2(p-cymene)]_2$	DCE	47	ND
12	$[RuCl_2(p-cymene)]_2$	DME	50	26
13	$[RuCl_2(p-cymene)]_2$	THF	66	13
14	$[RuCl_2(p-cymene)]_2$	CH ₃ CN	40	8
15	$[RuCl_2(p-cymene)]_2$	PhCl	42	11
16	$[RuCl_2(p-cymene)]_2$	H_2O	54	4
17^{d}	$[RuCl_2(p-cymene)]_2$	H_2O	52	5
18^{f}	$[RuCl_2(p-cymene)]_2$	H_2O	79	ND

^[a] Reactions were carried out with **1a** (0.1 mmol), **2a** (0.2 mmol), [RuCl₂(p-cymene)]₂ (5 mol%), NaOAc (0.5 equiv), solvent (0.6 mL) at 130 °C for 24 h, under air in pressure tubes.

- ^[b] Determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.
- $^{[c]}$ Protected by N₂.
- ^[d] Without NaOAc.
- ^[e] ND = not detected.
- ^[f] [RuCl₂(*p*-cymene)]₂ (1.5 mol%), run at 95 °C without NaOAc for 12 h under air.

aromatic acids bearing ortho-substituted electrondonating groups reacted efficiently with good yields of the desired products (**3b-3g**, 42%-69%). Halogens (Cl, Br, and I) were also compatible with the catalytic conditions and afforded 57-78% yields (3h-3j), which further demonstrates the synthetic potential to highly functionalized targets by a stepwise coupling. The reactions of di-substituted aromatic acids bearing one substituent at the ortho position of carboxyl gave the desired products in good to excellent yields (3k-3u, 51%-83%) and 3-methoxy-2-methylbenzoic acid delivered the highest yield of the addition product (31, 83%). Importantly, 1 mmol and 5 mmol scale transformations of 3-methoxy-2-methylbenzoic acid by the Ru-catalyzed protocol afforded **31** in 80% and 74% isolated yields, respectively (see Supporting Information).

Aromatic acids with two possible sites for the C–H bond activation, such as meta- or para-substituted benzoic acids, were also easily converted into alkylated products under the optimal conditions.

Table 2. Substrate scope for the conjugate addition of aromatic acids with α,β -unsaturated ketones.^[a]



^[a] Reactions were carried out with acids (0.2 mmol), α,β unsaturated ketones (0.4 mmol), [RuCl₂(*p*-cymene)]₂ (1.5 mol%), H₂O (1.0 mL) at 95 °C for 12 h, under air in pressure tubes, isolated yield.

Meta-substituted benzoic acids could undergo selective alkylation at less sterically hindered position (3v-3y), suggesting that the reaction is mainly under steric control rather than electronic control. Noteworthy, the *meta*-nitrobenzoic acid bearing a strongly electron-withdrawing group reacted smoothly with an ethyl vinyl ketone to give the alkylation product in a 40% yield. This result was different from previous reports using the carboxyl as a directing group,^[8,12] where nitrobenzoic acid is inactive. However, employing *meta*-isophthalic acid as a substrate, no targeted product was detected.

Benzoic acid, *para*-substituted benzoic acids and piperonylic acid affored a mixture of dialkylated and monoalkylated products, and dialkylated compounds were isolated as the main products even if excessive acids were used (See supporting information, Table S1). The reaction was also extendable to heteroaromatic carboxylic acids such as 1-methyl-1H-indole-2-carboxylic acid and thiophene-2**Table 3.** Conjugate addition of benzoic acids and para-substituted benzoic acids with ethyl vinyl ketone.



^[a] Reactions were carried out with acids (0.2 mmol), ethyl vinyl ketone (0.4 mmol), [RuCl₂(*p*-cymene)]₂ (1.5mol%), H₂O (1.0 mL) at 95 °C for 12 h, under air in pressure tubes, isolated yield.

carboxylic acid (3z and 3aa).

To further explore the substrate scope and limitations of this process, the reactions between 3methoxy-2-methylbenzoic acid and various α,β unsaturated ketones were tested (Table 2, 3ab- 3af). Under the optimized reaction conditions, aliphatic α,β -unsaturated ketones could be converted into the desired products smoothly. The long chain aliphatic ketones showed slightly lower reactivity compared to that of the short chain aliphatic ketones (3ae and 3af). However, no targeted product was detected using (E)hex-4-en-3-one as a substrate probably due to the steric hindrance. Moreover, aryl substituted α,β unsaturated ketones displayed poor activity in this transformation. For example, 1-phenylprop-2-en-1one failed to afford the desired product, and 5phenylpent-1-en-3-one generated much lower yield of the addition product (18% ¹H NMR yield).

To understand the reaction mechanism, different experiments were conducted. The H/D exchange experiment with isotopically labeled solvent was firstly carried out (Scheme 2). When the benzoic acid was treated with D₂O in the absence of ketone, 87% deuterium incorporation was observed at the two *ortho* positions of the carboxyl (Scheme 2a). If the reaction was performed in D₂O, the desired product with 18% deuterium incorporation was obtained at the *ortho* of the carboxyl and carbonyl, respectively, (Scheme 2b). The formation of D_5 -3ag underwent the



Scheme 2. Probing the reversibility of the C–H activation step.

deuterolysis of ruthenacycle intermediate and H/D exchange with D_2O through a keto-enol tautomerization at a high temperature (see Supporting Information).^[13] These results imply that a reversible cyclometalation mode exist in the reaction.^[14]

The kinetics isotope effects (KIE) were determined within 10 min at a low conversion. Parallel experiments utilizing equimolar D_5 -benzoic acid and benzoic acid were conducted independently to assess the reaction rates for *ortho*-C–H *vs* C–D (Scheme 3**a**), and a $K_{\rm H}/K_{\rm D}$ ratio of 3.7 was obtained. The competing reaction of D_5 -benzoic acid and benzoic acid with the ethyl vinyl ketone (**2a**) were carried out in the same reaction tube giving a $K_{\rm H}/K_{\rm D}$ ratio of 6.0 (Scheme 3**b**). The KIE observed under these conditions indicate that the C–H bond cleavage is likely the rate-limiting step.^[15]

(a) through two parallel reactions



(b) through competing reactions



Scheme 3. The experiments to determine the kinetics isotopic effects.

To confirm whether the catalyst is intact after the reaction, the additional experiment using o-toluic acid and ethyl vinyl ketone as substrates was performed (see Supporting Information). By comparing the HRMS spectra of the fresh and used catalysts, the pcymene was very probably linked to the ruthenium after the reaction. Based on our mechanistic studies and the understanding on the carboxyl-assisted C-H bond activation reactions catalyzed by ruthenium,^[16] a plausible alkylation process was proposed in Scheme 4. The catalytic addition reaction was initiated by the dissociation of the dimeric precatalyst [RuCl₂(*p*-cymene)]₂, affording a coordinatively unsaturated monomer A. Then, the species A would experience a cyclometalation reaction with the aromatic acids via a Ru(II)-catalyzed C-H activation under the assistance of the carboxyl to generate the intermediate **B**, releasing two equivalents of protons simultaneously. The coordination of Ru with the double bond of α , β -unsaturated ketones produced the



Scheme 4. Proposed mechanism.

complex C. Subsequently, the insertion of the C=C bond into the C-Ru bond afforded the sevenmembered ruthenacycle **D**. The protonation of **D** by the HCl afforded the final product and regenerated the active ruthenium catalyst to continue the catalytic cycle.

Facile manipulation of the alkyl aromatic acids offers an additional synthetic opportunity. For example, the carboxyl can be removed by Ag₂CO₃-promoted decarboxylation protocol in a traceless fashion to furnish *meta*-substituted alkylbenzene,^[17] which is difficult to prepare via the traditional Friedel–Crafts reaction (Scheme 5). Moreover, the intramolecular oxidative cyclization of the obtained *ortho*-alkylated benzoic acid **3a** delivered avaluable 3-substituted isochromanone (Scheme 6), which not only appears in a number of natural products with therapeutic potentials, but also serves as a useful and significant precursor for synthesizing pharmaceutical and agrochemical products.^[18]



Scheme 5. Decarboxylation of 3i.



Scheme 6. Synthesis of 3-substituted isochromanone.

In summary, an efficient ruthenium-catalyzed conjugate addition of C–H bonds to α , β -unsaturated ketones directed by carboxyl group was developed for the synthesis of a wide range of *ortho*-alkylated

benzoic acids in good to excellent yields. Employing water as a singular solvent, this protocol was successfully realized free of any additives under air atmospheres, which makes it a greener synthesis and easier practical operation. Additional notable features of the new method were commercially available and cheap starting materials, broad substrate scope, relatively cheaper ruthenium catalysts, and easy scale up. Moreover, the simple and efficient transformation of the addition products into highly valuable motifs makes this method more important in practical syntheses. This finding provides useful insights for an environmentally friendly direct addition of C-H bonds to unsaturated double bonds. Further studies on the applications of this methodology are currently under way in our laboratory.

Experimental Section

A typical experimental procedure: An oven-dried reaction vessel was charged with [RuCl₂(*p*-cymene)]₂ (Ru*,1.8 mg, 1.5 mol%, 0.003 mmol), aromatic acids (0.2 mmol), $\alpha_{,\beta}\beta_{-}$ unsaturated ketones (0.4 mmol), and deionized water (1.0 mL).The vial was sealed under air and heated at 95 °C (oil bath temperature) for 12 h. When the reaction was complete, the resulting mixture was cooled to room temperature, and filtered through a short silica gel pad. Then, the mixture was concentrated *in vacuo* to give a residue, which is purified by the preparative thin-layer chromatography (TLC) on silica gel to afford the corresponding products.

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COMMUNICATION

Carboxyl-Directed Conjugate Addition of C-H Bonds to α,β -Unsaturated Ketones in Air and Water



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Wen-Jing Han, Fan Pu, Chao-Jun Li, Zhong-Wen Liu, Juan Fan, and Xian-Ying Shi*

✓ H₂O as a sole solvent ✓ Unnecessary inert atomosphere ✓ Broad substrate scope

