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Regioselective C–H Alkylation via Carboxylate-Directed Hydroarylation in Water

Guodong Zhang,[a] Fan Jia,[a] and Lukas J. Gooßen*[a]

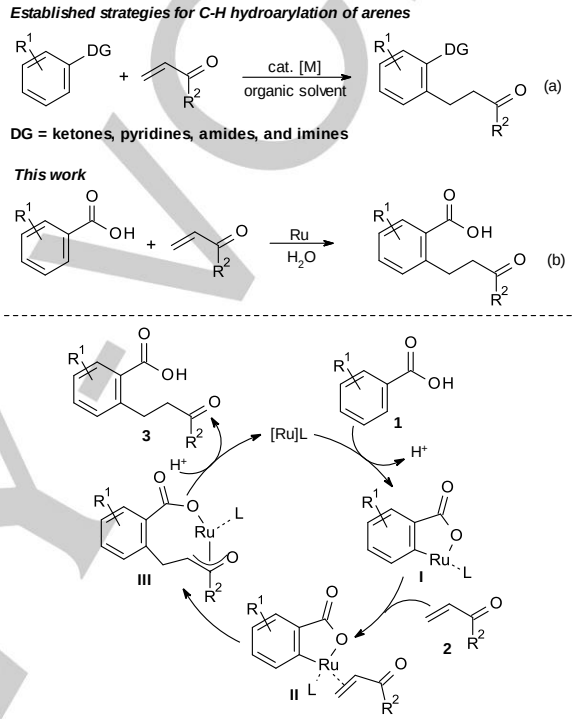
Dedication ((optional))

Abstract: In the presence of catalytic $[Ru(p\text{-cym})Cl_2]_2$ and using Li_3PO_4 as the base, benzoic acids react with olefins in water to afford the corresponding 2-alkylbenzoic acids in moderate to excellent yields. This C–H alkylation process is generally applicable to diversely substituted electron-rich and electron-deficient benzoic acids, along with α,β-unsaturated olefins including unprotected acrylic acid. The widely available carboxylate directing group can be removed tracelessly or utilized for further derivatization. Mechanistic investigations revealed that the transformation proceeds via a ruthenacycle intermediate.

The aryl−alkyl motif is an important substructure in functional materials,[1 1] natural products,[2 2] and pharmaceuticals.[3 3] Strategies for building such structures stand at the forefront of modern organic synthesis.[4] Established methods to access alkylarenes involve organometallic reagents[5] or pre-formed alkylating agents.[6]

Modern reaction development is aiming at the development of catalytic C–H alkylations, ideally based on non-prefunctionalized substrates and without stoichiometric organometallic regents. Among them, directed hydroarylations of alkenes are particularly advantageous due to their ideal atom-economy. In 1993, Murai and co-workers[7] laid the foundation for this area with a Ru-catalyzed C–H hydroarylation of olefins with aromatic ketones. Similar reactions developed since all rely on comparably strong directing groups in combination with Rh, Ir, Ru, Re, Co, Ni, Fe, or other metal catalysts to achieve regioselectivity. These groups, including ketones,[8] pyridines,[9] amides,[10] imines,[11] and others,[12] need to be installed in additional reaction steps and are not easily removed from functionalized substrates (Scheme 1a). Usually, organic solvents are used, but there are a few examples of C-H functionalizations that proceed efficiently in water.[13]

In comparison, carboxylates have many advantages as directing groups such as their wide availability, low cost, low toxicity and broad range of follow-up reactions.[14] Their power as directing groups in *ortho*-C–H functionalizations has been documented by Yu,[15] Daugulis,[16] Larrosa,[17] Ackermann,[18] Su,[19] ourselves,[20] and other groups.[21] The greatest hurdle to the development of new C–H functionalization reactions using this directing group is their intrinsically weak coordinating ability.



Scheme 1. Directed hydroarylations of functionalized (hetero)arenes.

Hitherto, *ortho*-alkylations of benzoic acids remain rare, and alkyl sources are so far limited to dihalogenoalkanes, epoxides, alkyl trifluoroborates, or trimethylaluminium.[15, 22] Considering that olefins are generally cheaper and more readily available than other alkylating agents, the alkylation of benzoic acids with olefins attracts increasing attention. However, undesired β-H elimination of the alkyl–M species that is formed by migratory insertion of the olefin into the C–M bond, results predominately in the alkenylation products.[23] For α,β-unsaturated carbonyl compounds, β-H elimination seems less predominant, which has been attributed to the formation of a stable ruthenium-oxa-π-allyl intermediate that preferentially undergoes protonolysis.[8a, 9a,b] In contrast to the carboxylate directed C-H hydroarylations of maleimides by Baidya and Ackermann, no extrusion of carbon dioxide is observed.[24]

Based on these findings, we envisioned that *ortho*-alkylation of benzoic acids (**1**) with α,β-unsaturated olefins (**2**) would be possible via a carboxylate-directed *ortho*-hydroarylation, leading to 2-alkylbenzoic acids (**3**, Scheme 1b). The proposed mechanism involves a ruthenacycle intermediate **I**, which would coordinate to the olefin (intermediate **II**). 1,4-Conjugate addition of the arylruthenium species to the double bond should then yield

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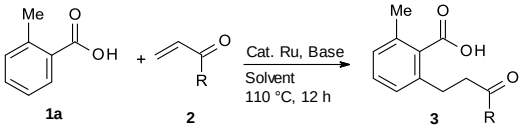
the ruthenium-oxa-π-allyl species **III**. Protonation of **III** would release the alkylarene **3** and regenerate the ruthenium catalyst, closing the catalytic cycle.

Using 2-toluic acid (**1a**) and methyl vinyl ketone (**2a**) as the model reaction, we started our investigations with the catalyst system previously developed for our Ru-catalyzed alkyne hydroarylation (Table 1, see SI for details).[20c]

Table 1. Optimization of the *ortho*-alkylation reactions.[a]

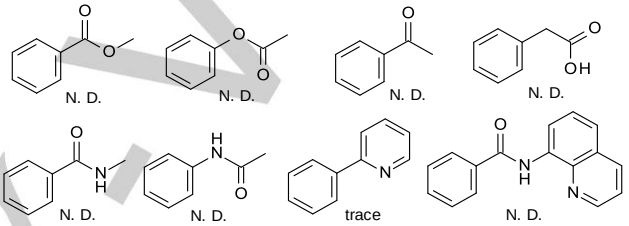


Entry	Catalyst	R	Base (equiv.)	Solvent	Yield (%)[b]
1	$Ru(acac)_2$	Me	K_2CO_3 (0.3)	^{t}AmylOH/H_2O (9/1)	24
2	$Ru(COD)Cl_2$	Me	K_2CO_3 (0.3)	^{t}AmylOH/H_2O (9/1)	21
3	$[RuCl_2(p\text{-cym})]_2$	Me	K_2CO_3 (0.3)	^{t}AmylOH/H_2O (9/1)	79
4	$[RuCl_2(p\text{-cym})]_2$	Me	K_2CO_3 (0.3)	^{t}AmylOH	50
5	$[RuCl_2(p\text{-cym})]_2$	Me	K_2CO_3 (0.3)	toluene	74
6	$[RuCl_2(p\text{-cym})]_2$	Me	K_2CO_3 (0.3)	H_2O	78
7	$[RuCl_2(p\text{-cym})]_2$	Me	$GuanCO_3$ (0.3)	H_2O	69
8	$[RuCl_2(p\text{-cym})]_2$	Me	Na_2CO_3 (0.3)	H_2O	76
9	$[RuCl_2(p\text{-cym})]_2$	Me	K_3PO_4 (0.3)	H_2O	75
10	$[RuCl_2(p\text{-cym})]_2$	Me	Li_3PO_4 (0.3)	H_2O	81
11	$[RuCl_2(p\text{-cym})]_2$	Me	Li_3PO_4 (1.0)	H_2O	85
12[c]	$[RuCl_2(p\text{-cym})]_2$	Me	Li_3PO_4 (1.0)	H_2O	92
13[d]	$[RuCl_2(p\text{-cym})]_2$	Me	Li_3PO_4 (1.0)	H_2O	98
14[e]	$[RuCl_2(p\text{-cym})]_2$	Me	Li_3PO_4 (1.0)	H_2O	14
15[d,f]	$[RuCl_2(p\text{-cym})]_2$	OH	Li_3PO_4 (1.0)	H_2O	47
16[d,f]	$[RuCl_2(p\text{-cym})]_2$	OH	CsF (1.0)	H_2O	54
17[d,f]	$[RuCl_2(p\text{-cym})]_2$	OH	CsF (0.5)	H_2O	58
18[d,g]	$[RuCl_2(p\text{-cym})]_2$	OH	CsF (0.5)	H_2O	88

[a] **1a** (0.5 mmol), **2** (1.0 equiv.), [Ru] (4 mol%), base, degassed solvent (2 mL), 110 °C, 12 h, Ar atmosphere. [b] GC analysis as methyl esters using *n*-tetradecane as the internal standard. [c] **2** (1.2 equiv.). [d] **2** (1.4 equiv.). [e] aerobic conditions. [f] $[RuCl_2(p\text{-cym})]_2$ (5 mol%), 24 h. [g] $[RuCl_2(p\text{-cym})]_2$ (7.5 mol%), 24 h. acac = acetoacetate; COD = 1,5-cyclooctadiene; *p*-cym = *para*-cymene; $GuanCO_3$ = guanidine carbonate.

To our delight, the desired alkylation product was directly detected (entry 1), and a switch to $[RuCl_2(p\text{-cym})]_2$ led to 79% yield (entries 2-3). Several solvents were examined, among which pure water gave an equivalent result to the *tert*-amyl alcohol/water mixture used originally (entries 4-6). A screening of bases showed that the use of 1.0 equiv. of Li_3PO_4 increased the yield to 85% (entries 7-11). The product was obtained quantitatively when using a slight excess of **2a** (entries 12 and 13). In an air atmosphere, the oxidative Heck-type product became predominant (entry 14). Unprotected acrylic acid, which to our knowledge has never before been utilized in C–H alkylations, also gave a good product yield (entry 15). This could further be improved by switching the base to CsF (0.5 equiv.) and increasing the catalyst loading to 7.5 mol% (entries 16-18).

Under optimized conditions, the directing ability of the carboxylate was found to be superior to other typical directing groups, such as ester, ketone, methylene carboxylate, amide, acetamide, and even the strongly coordinating pyridine and Daugulis amide groups, all inefficient for this transformation (Scheme 2).



Scheme 2. Comparison to alternative directing groups for *ortho*-alkylation. *Reaction conditions*: **1'** (0.5 mmol), **2a** (1.4 equiv.), $[RuCl_2(p\text{-cym})]_2$ (2 mol%), Li_3PO_4 (1.0 equiv.), H_2O (2 mL), 110 °C, 12 h, Ar atmosphere. N.D. = not detected.

The scope of the reaction was evaluated using the coupling of a variety of aromatic and heteroaromatic carboxylic acids with methyl vinyl ketone **2a** (Scheme 3). Benzoic acids containing electron-donating or -withdrawing groups in their *ortho* or *meta* positions afforded the desired products in good to excellent yields (**3aa**-**3oa**). For *meta*-substituted benzoic acids, the regioselectivity was high in favor of alkylation at the less hindered *ortho*-position (**3ka**-**3oa**). The tolerance of acetamido, methoxycarbonyl, and acetyl groups opens up opportunities for further functionalization, because these are powerful directing groups in combination with other metals.[25] Polysubstituted benzoic acids and naphthylcarboxylic acids were also suitable (**3pa**-**3va**). Unsubstituted benzoic acid yielded mono- and di-alkylated products in close to 1:1 ratio (**3wa** and **3wa'**). This alkylation was also compatible with heteroaromatic carboxylic acids, such as 2-thiophenecarboxylic acid and 1-methylindole-2-carboxylic acid (**3xa** and **3ya**). For the indole **1y**, both **3ya** and its protodecarboxylated analog **3ya'** could be obtained depending on the reaction temperature.

The scope of α,β-unsaturated carbonyl compounds was further examined in combination with 2-methylbenzoic acid (**1a**). Long-chain alkyl vinyl ketones displayed high reactivity (**3ab** and **3ac**). The hydroarylation of aryl vinyl ketones proceeded well (**3ad**-**3ag**), whereas 3- or 4-substituted vinyl ketones and cyclic enones gave somewhat inferior yields (**3ah**-**3aj**). The hydroarylation of α,β-unsaturated amides was also efficient (**3ak**-**3al**).

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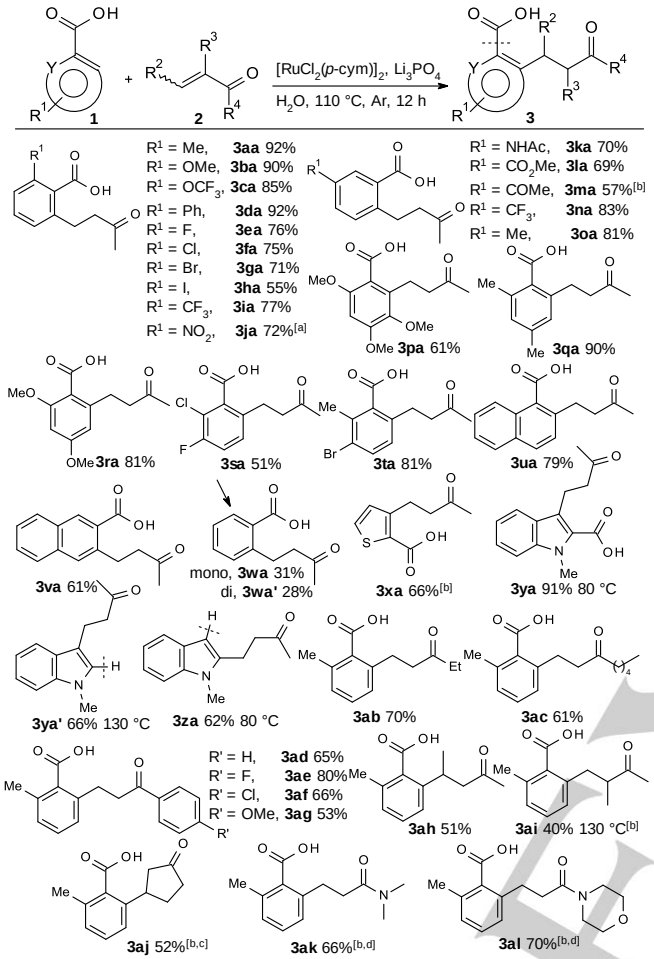
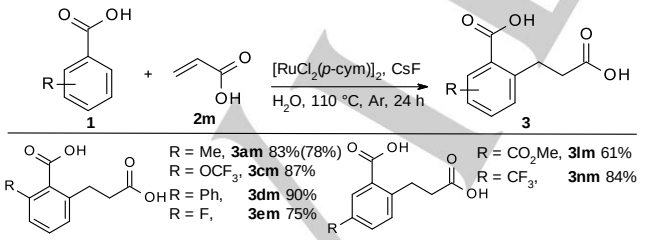
The reaction is also applicable to a range of substituted benzoates in combination with acrylic acid (Scheme 4). Both electron-rich and -deficient substituents were tolerated.

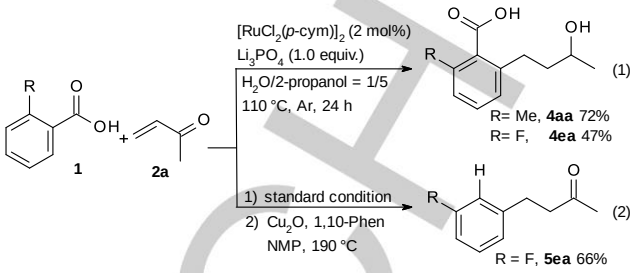


Scheme 3. Substrate scope for benzoic acids combined with α,β-unsaturated ketones / amides. *Reaction conditions*: **1** (0.5 mmol), **2** (1.4 equiv.), $[RuCl_2(p\text{-cym})]_2$ (2 mol%), Li_3PO_4 (1.0 equiv.), H_2O (2 mL), 110 °C, 12 h, Ar atmosphere; isolated yields of the corresponding methyl esters after esterification. [a] Li_3PO_4 (0.5 equiv.). [b] $[RuCl_2(p\text{-cym})]_2$ (5 mol%). [c] **2** (1.0 equiv.). [d] 24 h.

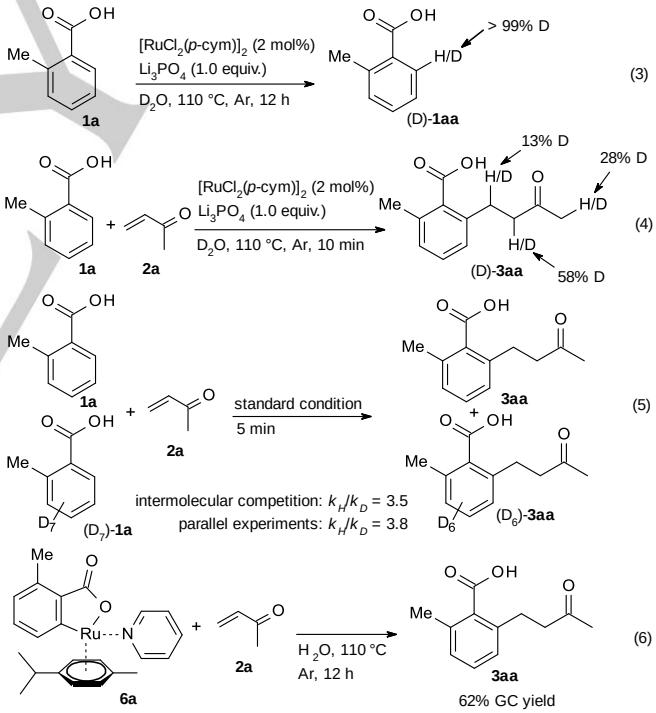


Scheme 4. Substrate scope for benzoic acids combined with acrylic acid. *Reaction conditions*: **1** (0.5 mmol), **2m** (1.4 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (7.5 mol%), CsF (0.5 equiv.), H_2O (2 mL), 110 °C, 24 h, Ar atmosphere; isolated yields of the corresponding methyl esters, and of the free acid in parentheses.

Further investigations revealed that the ketone could be reduced in situ to hydroxyl group using isopropanol as the hydride source [Eq. (1)], and that protodecarboxylation was possible in a one-pot process [Eq. (2)].



The reaction mechanism was investigated by deuteration experiments and kinetic studies. In an H/D exchange experiment in D_2O [Eq. (3)], complete deuteration in the *ortho* position indicated reversible C–H bond cleavage. A deuterium-labelling experiment revealed deuterium incorporation mostly in the α-methylene position of the carbonyl group [Eq. (4)], which is consistent with the proposed mechanism. High kinetic isotope effects (k_H/k_D = 3.5 and 3.8, respectively) were observed in competition and parallel experiments [Eq. (5)], confirming that C−H bond cleavage is rate-determining. The successful conversion of preformed *ortho*-ruthenated toluate **6a** supports the intermediacy of a ruthenacycle [Eq. (6)].



In summary, the carboxylate-directed hydroarylation of olefins in the presence of $[RuCl_2(p\text{-cym})]_2$ provides a convenient and sustainable access to various 2-alkylbenzoic acids. This transformation proceeds smoothly in water. It tolerates various functional groups, including even standard directing groups, which opens up opportunities for further functionalization. The catalyst system is compatible with unprotected acrylic acid. Potential follow-up reactions, including in situ-reduction of the side-chain carbonyl group and ipso-substitution of the carboxylate, further expand the synthetic potential of this transformation.

Experimental Section

An oven-dried 20 mL vessel was charged with $[RuCl_2(p\text{-cym})]_2$ (6.40 mg, 0.01 mmol), lithium phosphate (57.9 mg, 0.50 mmol), and **1** (0.50 mmol). Under exclusion of air, H_2O (2 mL) and **2** (0.70 mmol) were added via syringe. The resulting mixture was stirred at 110 °C for 12 h. After this time period, MeCN (3 mL), K_2CO_3 (138 mg, 1.00 mmol), and MeI (358 mg, 2.50 mmol) were added and the mixture was stirred at 60 °C for 2.5 h. Brine (20 mL) was added and the resulting mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/cyclohexane gradient) yielding the hydroarylation product **3** in the form of its methyl ester.

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Keywords: ruthenium • C–H alkylation • benzoic acids • olefins • hydroarylation

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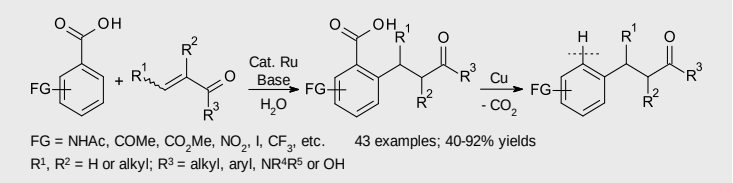

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Regioselective C–H Alkylation of Arenecarboxylates with Olefins in Water

Water serves as the solvent in a regioselective *ortho*-C–H alkylation of arenecarboxylates with α,β-unsaturated olefins catalyzed by ruthenium. A wide range of arene substrates are converted efficiently, and the weakly basic medium allows using even unprotected acrylic acid as an alkyl source.