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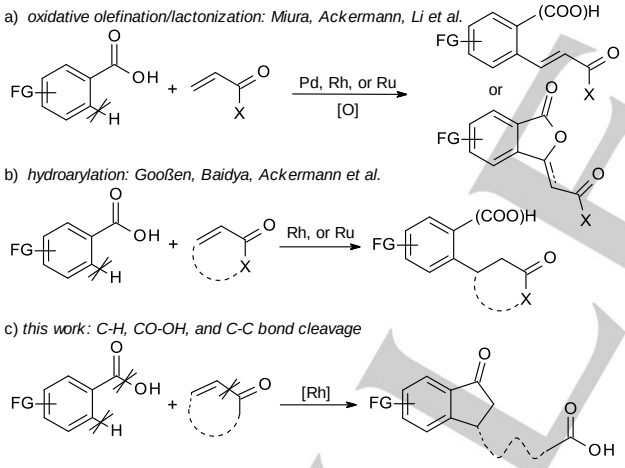
COMMUNICATION

Rh-Catalyzed Annelation of Benzoic Acids with α,β-Unsaturated Ketones with Cleavage of C–H, CO–OH, and C–C Bonds

Guodong Zhang, Zhiyong Hu, Florian Belitz, Yang Ou, Nico Pirkl and Lukas J. Gooßen*

Abstract: In the presence of a $[Cp^*RhCl_2]_2$ catalyst, the Lewis acid $In(OTf)_3$ and the mild base Na_2CO_3, aromatic carboxylates and α,β-unsaturated ketones undergo a unique hydroarylation/Claisen/retro-Claisen process to give the corresponding indanones. In this carboxylate-directed *ortho*-C–H annelation, the C–COR bond of the ketone and the CO–OH group of the aromatic carboxylate are cleaved, and the hydroxy group is transferred from the aromatic to the aliphatic acyl residue. This reactivity is synthetically useful particularly when starting from cyclic ketones, which are converted into indanones bearing aliphatic carboxylate side-chains, thus greatly increasing the molecular complexity of aromatic carboxylates in a single step.

Over the past two decades, transition metal-catalyzed directed C–H functionalizations have undergone tremendous development, evolving from pioneering examples into robust and versatile tools for modern organic synthesis.[1] Initially, this approach was often limited by the use of complex directing groups[2] which needed to be installed and later removed, thus adding steps to the overall process. In state-of-the-art methods, the selectivity can be enforced even by ubiquitous functionalities, including ketones,[3] hydroxy,[4] or carboxylate groups.[5]



Scheme 1. Carboxylate-directed C−H coupling with α,β-unsaturated carbonyls.

The key advantages of carboxylate directing groups are their broad availability and the fact that they can be removed tracelessly or used as anchor points for further regiospecific C–C or C–heteroatom bond-forming reactions via decarboxylative coupling.[6] Inspired by pioneering work by Miura,[7] a huge variety of carboxylate-directed sp^2 C−H *ortho*-functionalizations have been developed e.g. by Yu,[8] Li,[9] Daugulis,[10] Larrosa,[11] Ackermann,[12] Su,[13] Baidya,[14] our group,[15] and others.[16]

The predominant pathways for *ortho*-C–H functionalizations of carboxylates with α,β-unsaturated carbonyl compounds are oxidative Heck-type couplings (Scheme 1a), which lead either to *ortho*-vinylated carboxylates, or to alkyl or alkenyl lactones.[17] For some heteroarenes, e.g. thiophenes or furans, this reaction proceeds with concomitant decarboxylation.[18] Hydroarylation pathways give rise to *ortho*-alkylated benzoates (Scheme 1b).[15a,16a] For maleimides, a decarboxylative variant is also known.[14c,19] Still, we believed that many exciting synthetic opportunities would open up, if the carboxylate group could be funneled into new reaction pathways after the hydroarylation step. We, thus, investigated the reaction of methyl vinyl ketone with o-toluic acid in the presence of various Ru and Rh catalysts aiming at the discovery of a reaction, in which the carboxylate acts as a deciduous directing group.[15a,b] However, to our surprise, we detected 7-methyl-1-indanone and acetic acid rather than the targeted methyl *o*-tolylethyl ketone, when using $[Cp^*RhCl_2]_2$ as the catalyst (Scheme 1c).

This was an exciting finding, not only because 1-indanones are a privileged substructure in various bioactive molecules,[20] but also because this product could have formed only with cleavage of a CO–OH group under basic conditions. Such reactivity is highly desirable but rare. In sharp contrast to its derivatives, free carboxylic acids do not easily undergo nucleophilic addition/elimination reactions.[21] Whereas esters react with enolates to form β-keto ester enolates and alcohols, carboxylic acids would be deprotonated by such nucleophiles, disrupting the C–C bond-forming process.[22] However, our mechanistic analysis of the above experimental findings seemed to imply that C–C bond formation via a Claisen-type condensation starting directly from the free carboxylic acid must have been involved (Scheme 2). It suggests that such reactions are possible without prior preparation of esters and consumption of stoichiometric strong base.

Based on the well-documented ability of $[Cp^*RhCl_2]_2$ to promote *ortho*-C–H functionalizations,[23] it is safe to assume that the reaction is initiated by base-assisted, concerted metalation-deprotonation (CMD). There is also ample literature evidence that unsaturated compounds insert into aryl–rhodium bonds, pointing towards **III** as a subsequent catalytic intermediate.[24] A conceivable route to the indanone product involves the intramolecular substitution of the hydroxy group by the rhodium enolate, followed by reductive elimination of an acyl indanone. Such compounds are known to undergo retro-Claisen deacylations in the presence of various Lewis acids.[25] This step must occur rapidly, because if the diketone **V** accumulates, it will undergo Michael additions leading to unwanted aggregates. In the overall process, the hydroxy group is transferred from an aromatic to an aliphatic acyl group, which can be expected to

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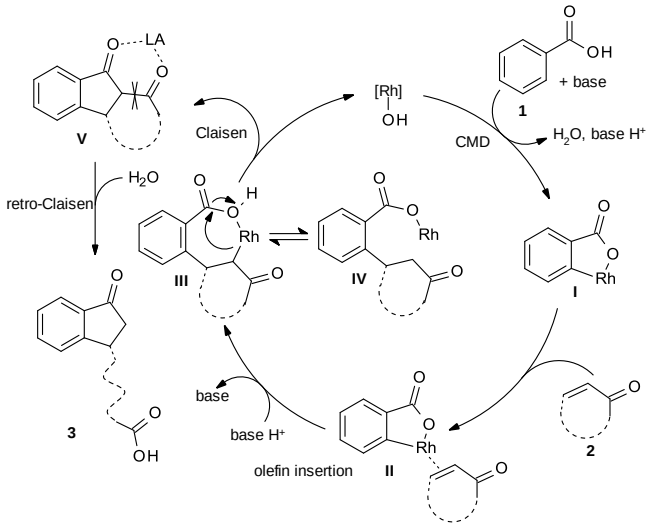
have only minimal influence on the thermodynamics of the reaction.



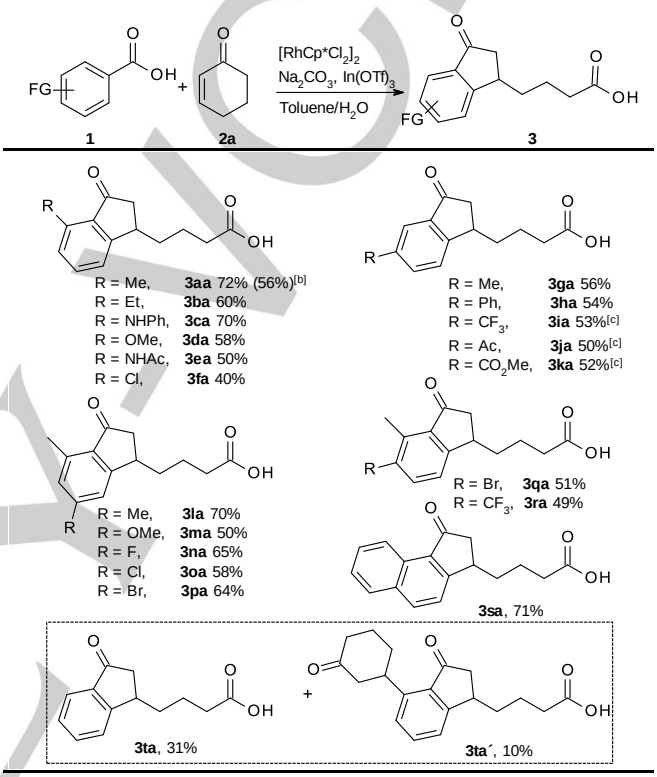
Scheme 2. Mechanistic blueprint.

This reaction pathway could open up an interesting access to indanone moieties that would compare favorably with established syntheses, e.g. via Friedel-Crafts cyclization of cinnamic acid or cinnamoyl chloride derivatives,[26] or via hydroacylation of unsaturated benzaldehyde derivatives.[27] In the case of cyclic alkenone starting materials, the acyl leaving group would remain tethered to the indanone ring, thus further increasing product complexity.

Motivated by these synthetic opportunities, we performed a holistic optimization of the catalyst system and the reaction conditions using the model reaction of 2-methylbenzoic acid (**1a**) and 2-cyclohexen-1-one (**2a**) in order to turn this idea into an effective chemical process (Table S1). Among all catalysts tested, $[Cp^*RhCl_2]_2$ gave the best yield of **3a**. A Lewis acid was required to promote the desired reaction. The best results were obtained with $In(OTf)_3$. A protic solvent was found to be essential. 79% yield was achieved at 120 °C using a slight excess of **2a**, 5 mol% $[Cp^*RhCl_2]_2$, and 15 mol% $In(OTf)_3$ in a biphasic toluene/water mixture buffered with 0.6 equivalents of Na_2CO_3. The identity of the indanone product was unambiguously determined by single crystal X-ray diffraction (Supporting information).

The substrate scope was investigated using the coupling of various arenecarboxylic acids with 2-cyclohexen-1-one (**2a**) (Table 1). Electron-poor and electron-rich benzoic acids reacted equally well, and wide variety of functional groups are tolerated, including keto-, ester, bromo, amide, and even N–H groups. For *meta*-substituted benzoic acids, the reaction proceeded with high regioselectivity in favor of the less hindered *ortho*-position. Benzoic acids bearing strongly electron-withdrawing groups gave only moderate yields even at an increased catalyst loading. The tolerance of acetamido, methoxycarbonyl, and acetyl groups opens up opportunities for follow-up directed C–H functionalizations.[2a,b] When starting with unsubstituted benzoic acid (**1t**), the product **3ta'** forms. Since the carbonyl group of indanones is ineffective as DG in Rh-catalyzed C–H activation,[3a] the second hydroarlyation must have taken place while the carboxylate group was still intact. Hence, the Rh enolate formation must be reversible (see Scheme 2, **III**, **IV**), and the Claisen condensation slower than the hydroarylation step. After double hydroarylation of **1t**, only one of the two ketone side chains can undergo the follow-up Claisen steps leading to **3ta'**.

Table 1. Coupling of arenecarboxylic acids with 2-cyclohexen-1-one.[a]



[a] Reaction conditions: 0.5 mmol of **1a-t**, 0.6 mmol of **2a**, 5 mol% of $[Cp^*RhCl_2]_2$, 15 mol% of $In(OTf)_3$, 0.6 equiv. of Na_2CO_3, 0.15 mL of toluene/H_2O (3:2), 120 °C, 16 h, argon; isolated yields. [b] 10 mmol scale. [c] 0.75 mmol of **2a**, 6 mol% of $[Cp^*RhCl_2]_2$, 0.12 mL of toluene/H_2O (3:1).

We next investigated the scope with regard to α,β-unsaturated ketones in the coupling of 2-methylbenzoic acid (**1a**) (Table 2).

Non-cyclic methyl alkenyl ketones yielded the corresponding indanones in moderate yields along with sodium acetate as the byproduct (**3ab**-**3af**). If one considers how easily and sustainably these substrates are accessible from acetone, this may well be one of the most attractive synthetic entries to substituted indanones.

We placed special emphasis on cyclic enone substrates, since these give uniquely efficient access to indanones bearing aliphatic carboxylate side chains. The carboxylate group can then be utilized as a leaving group in various decarboxylative couplings including Hunsdiecker-Borodin reactions, photochemical couplings, decarboxylative elimination, and many others.[28] 2-Cyclohexen-1-ones bearing alkyl or aryl side chains in various positions were successfully converted into the alkylcarboxlate-functionalized indanones, demonstrating the robustness of this

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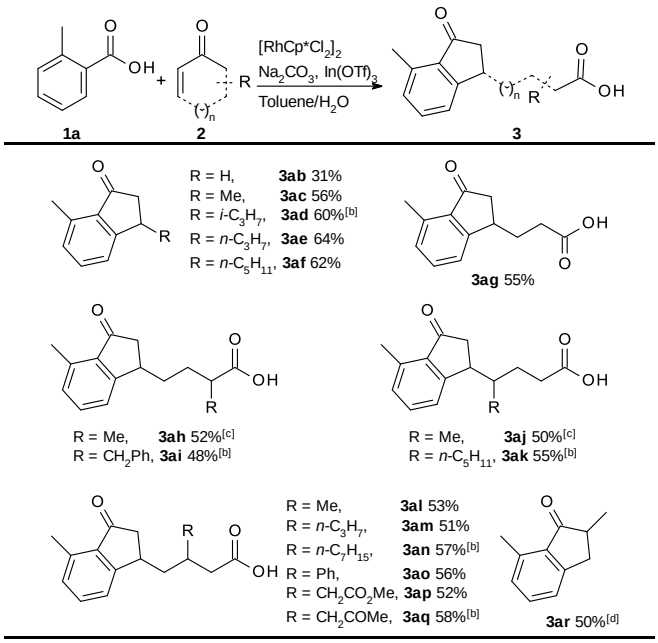
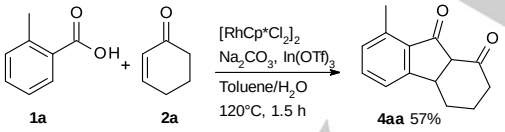
reaction variant (**3ah**-**3aq**). 2-Cyclopenten-1-one also reacted well (**3ag**), whereas smaller rings did not give satisfactory yields.

Table 2. Coupling of 2-methylbenzoic acid with α,β-unsaturated ketones.[a]



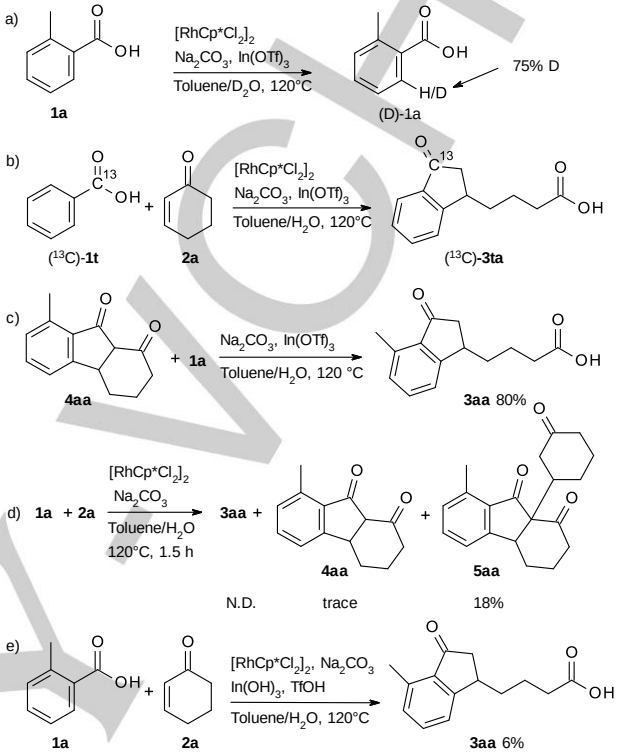
[a] Reaction conditions: 0.5 mmol of **1a**, 0.6 mmol of **2b-r**, 5 mol% of $[Cp^*RhCl_2]_2$, 15 mol% of $In(OTf)_3$, 0.6 equiv. of Na_2CO_3, 0.15 mL of toluene/H_2O (3:2), 120 °C, 16 h, argon; isolated yields. [b] 0.75 mmol of **2**, 6 mol% of $[Cp^*RhCl_2]_2$, 0.12 mL of toluene/H_2O (3:1), 140 °C. [c] 140 °C. [d] 1.0 mmol of **2**, 150 °C.

The reaction was successfully scaled up to 10 mmol for product **3aa** as an example (Table 1). If the reaction is stopped after 1.5 h, the diketone **4aa** can be isolated in good selectivity, opening up further synthetic opportunities (Scheme 3).



Scheme 3. Preferential formation of diketones at incomplete conversion.

Several control experiments were conducted to shed some light on the reaction mechanism. When heating *o*-tolyl carboxylate in the presence of $[Cp^*RhCl_2]_2$ in ^{t}AmylOH/D_2O, selective *ortho*-deuteration was observed, indicating reversible C−H bond cleavage (Scheme 4a). A ^{13}C-labeling experiment confirmed that the carbonyl group of the indanone originates from the benzoate (Scheme 4b). Upon treatment with $In(OTf)_3$, the bicyclic diketone **4aa**, which is the main product at incomplete conversion of **1a**, is smoothly converted into **3aa**, supporting the proposed reaction pathway via Claisen and retro-Claisen condensation steps (Scheme 4c). In the absence of a Lewis acid, the Claisen condensation is sluggish, and deacylation is even slower, so that intermediate **4aa** directly enters Michael addition pathways leading to complex product mixtures (Scheme 4d). The hydrolysis products of $In(OTf)_3$, namely InOx(OH)y and TfOH are inactive (Scheme 4e), demonstrating that the reaction takes place faster than the hydrolysis of the Lewis acid. All these findings confirm that the cooperative action of $[Cp^*RhCl_2]_2$ and $In(OTf)_3$ is required to facilitate this regioselective annelation of benzoic acids via C–H activation and cleavage of C–C and CO–OH bonds



Scheme 4. Mechanistic investigations.

In conclusion, the reaction of aromatic carboxylic acids with α,β-unsaturated ketones in the presence of a bimetallic Rh/In catalyst system opens up a versatile synthetic entry to the important substance class of indanones. It also demonstrates that the long-standing challenge of substituting the hydroxy groups in carboxylic acids with carbon nucleophiles can be achieved within the coordination sphere of rhodium. If this reaction mode can be extended to intermolecular Claisen couplings of carboxylic acids with enolizable carbonyl compounds, it might open up many opportunities for sustainable C–C bond-forming reactions that work without either prior esterification or strong bases.

Experimental Section

An oven-dried 10 mL vessel was charged with $[Cp^*RhCl_2]_2$ (16.3 mg, 0.025 mmol), Na_2CO_3 (32 mg, 0.30 mmol), $In(OTf)_3$ (57.9 mg, 0.075 mmol), and the corresponding benzoic acid (0.50 mmol). Under an argon atmosphere, toluene (90 µL), H_2O (60 µL), and the corresponding cyclic α,β-unsaturated ketone (0.60 mmol) were added via syringe. The resulting mixture was stirred at 120 °C for 16 h, then acidified with 0.1 M HCl (pH = 2-3) and extracted with ethyl acetate (5 × 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, 2.5% formic acid and 2.5% methanol in ethyl acetate/cyclohexane) yielding the corresponding alkylcarboxylic acid.

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Keywords: rhodium • C−H activation • aromatic carboxylates • aliphatic carboxylates • annelation

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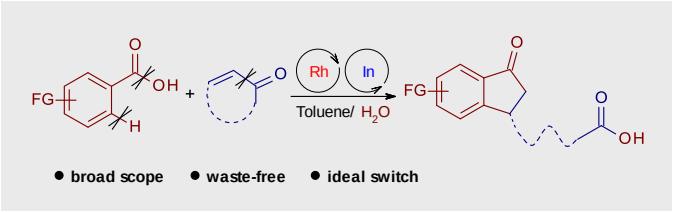

In the presence of a bimetallic Rh/In catalyst, aromatic carboxylic acids react with α,β-unsaturated ketones with formation of two new C-C bonds along with the selective cleavage of non-activated C–H, CO–OH and C–COR bonds. The resulting annelation opens up a versatile synthetic entry to functionalized indanones.

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Rh-Catalyzed Annelation of Benzoic Acids with α,β-Unsaturated Ketones with Cleavage of C–H, CO–OH, and C–C Bonds