Synthetic Methods

DOI: 10.1002/anie.201301328

Rhodium-Catalyzed *ortho* Acylation of Aromatic Carboxylic Acids**

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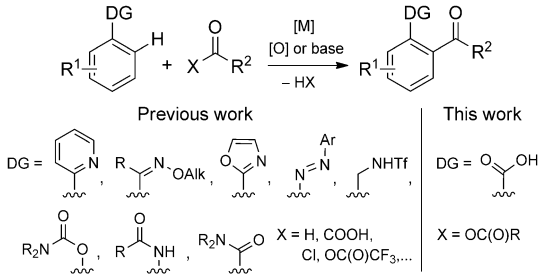
Transition-metal-catalyzed directed *ortho* functionalizations of arenes constitute modern and sustainable tools for the regiospecific formation of carbon–carbon and carbon–heteroatom bonds.[1] In such reactions, coordinating groups direct metal catalysts into their *ortho* position, thus enabling site-selective C–H functionalizations. In most cases, strongly coordinating nitrogen-, sulfur-, or phosphorus-based directing groups are employed. Only recently, catalysts have been discovered that permit the use of more weakly coordinating carboxylate directing groups,[2] for example, in *ortho* arylations,[3] olefinations,[4] carbonylations,[5] allylations,[6] hydroxylations,[7] alkoxylations,[8] amidations,[9] halogenations,[10] and lactone syntheses.[11] Their key advantage is that the carboxylate group can subsequently be utilized as a leaving group in further functionalization steps, or tracelessly removed by protodecarboxylation.[3c,8,12]

While for example, *ortho* arylations have already reached an impressive performance level,[1] *ortho* acylations are less developed (Scheme 1).[13] Effective ways of directing acyl



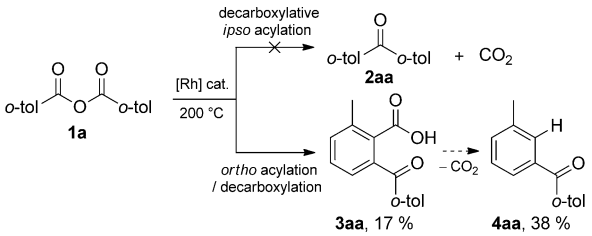
Scheme 1. Previous work on C–H bond acylation. DG = directing group, Tf = trifluoromethanesulfonyl.

substitutents to the position *ortho* to a functional group are oxidative couplings of aldehydes[14] or alcohols,[15] decarboxylative couplings of α-oxoacids,[16] or carbonylative processes.[17]

We are aware of only two examples of catalytic *ortho* acylations in which broadly available carboxylic acid derivatives serve as acylating agents, namely the ruthenium-catalyzed reaction of phenyl pyridines with acid chlorides by Kakiuchi et al.[18] and the analogous palladium-catalyzed reaction with mixed trifluoroacetic anhydrides by Fu et al.[19] The *ortho* acylations of benzoic acids with carboxylic acid derivatives are without literature precedent. Such transformations would be of considerable interest because they would open up an expedient synthetic pathway to an important substrate class.[20] For example, the 2-acylbenzoic acid balanol is a protein kinase C inhibitor.[20a] Other examples are synthetic intermediates en route to 2-[2-(imidazolyl)alkyl]-1(2*H*)-phthalazinones, which have antiasthma activity,[20b] or anxiolytic isoindolinone derivatives.[20c]

A selective *ortho* acylation of benzoic acids would compare favorably with established acylation methods because their Friedel–Crafts acylation gives mostly the *meta*-acylated products,[21] whereas ring openings of phthalic anhydrides are either unselective[22] or require costly and sensitive organometallic reagents.[23]

In the course of our work on decarboxylative couplings[24] targeting aryl ketones,[25] we heated 2-toluic anhydride (**1a**) with a rhodium catalyst with the intention of generating the symmetrical ketone **2aa** by extrusion of CO_2 (Scheme 2).



Scheme 2. Discovery of an *ortho* acylation/decarboxylation reaction.

However, instead of the desired decarboxylative coupling product **2aa**, a mixture of the unsymmetrical ketone **4aa** and 6-(2-toluoyl)-2-toluic acid (**3aa**) was formed.

This seminal experiment pointed to the principal feasibility of an *ortho* acylation, which in this case proceeded with a subsequent partial protodecarboxylation. Our mechanistic rationale is outlined in Scheme 3. The anhydride **1** had presumably undergone oxidative insertion of the rhodium catalyst into its acyl–O bond leading to the benzoate **B**, which has structural precedent,[26] and has been proposed as intermediate also in rhodium-catalyzed cross-couplings of anhydrides.[27] Assisted by the added base, the rhodium would then have inserted intramolecularly into the *ortho*-C–H bond to give **C**. The formation of *ortho*-metalated Rh^{III} carbox-

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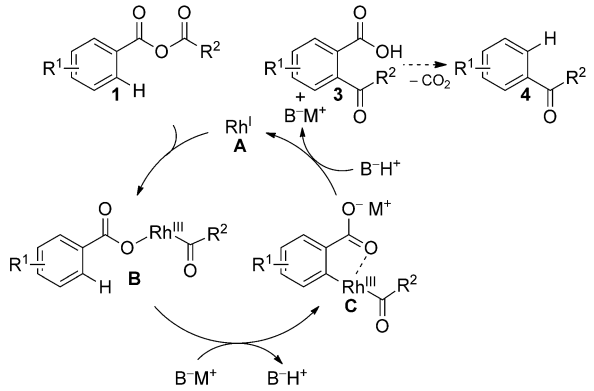
[**] We thank Saltigo GmbH and NanoKat for funding, and Umicore for donating chemicals. We acknowledge T. Knauber and G. Deng for pioneering experiments, and thank J.-Y. Chung, W. Eichmann, B. Exner, B. Frensch, K. Messemer, and A. Marxen for technical assistance.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301328.



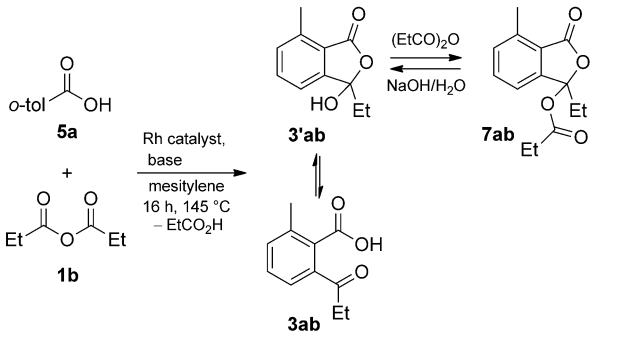
Scheme 3. Proposed mechanism of the *ortho* acylation.

ylates is well documented.[28] Reductive elimination would have furnished the *ortho*-acylbenzoic acid **3** and regenerated the rhodium catalyst **A**. *ortho*-Acylbenzoates such as **3** are known to decarboxylate readily above 160 °C in the presence of various metal mediators, thus explaining the formation of **4**.[29]

After the initial serendipitous discovery, we investigated whether this reaction concept could be transformed into a general method for the *ortho* acylation of benzoic acids with carboxylic anhydrides. We were particularly interested in selectively coupling two different carboxylic acid residues with each other, and thus chose the coupling of 2-toluic acid (**5a**) with propionic anhydride (**1b**) as a test reaction (Table 1). We screened various metal complexes and found rhodium to be a uniquely active catalyst metal. [{Rh(cod)Cl}$_2$] provided the desired product **3ab** in 29% yield after basic hydrolysis (entries 1–4). In situ analysis of the reaction mixture provided an explanation for the incomplete turnover: The primary reaction product **3ab** exists in equilibrium with its cyclized tautomer **3′ab**,[30] which uses up an anhydride equivalent in an esterification step. As a minor side product, the aromatic anhydride self-coupling product 6-(2-toluoyl)-2-toluic acid (**3aa**; 10–15%) is also observed. Use of **1b** in excess should make up for losses in the parasitic equilibrium reaction and ensure better conversion of **5a**. Indeed, when using 4 equivalents of **1b**, the product **3ab** was obtained in 68% yield, and the amount of **3aa** was reduced to below 5% (entry 5). Almost quantitative conversion was obtained when switching to Cs_2CO_3 as the base (entry 9), whereas a range of other inorganic and organic bases were less effective. Control experiments confirmed that no reaction takes place without rhodium or without base (entries 10 and 11).

We next investigated the generality of the optimized protocol using various benzoic acids (**5**) in combination with aliphatic anhydrides (**1**). As can be seen from the examples in Table 2, both electron-rich and electron-deficient aromatic and heteroaromatic carboxylic acids (**5**) were selectively *ortho*-acylated with **1b**. A variety of functionalities including alkoxy, trifluoromethyl, bromo, chloro, fluoro, hydroxy, amino, and keto groups were tolerated. The double acylation products were observed in trace amounts at most. The *meta*-substituted carboxylates were acylated selectively in the less hindered *ortho* position and *para*-substituted compounds

Table 1: Development of the catalyst system.



Entry	[Rh]	Equivalents **1b**	Base	**3ab** Yield [%]
1	[{Rh(Cp*)Cl$_2$}$_2$]	1	KF	18
2	[{Rh(OAc)$_2$}$_2$]	1	KF	23
3	[{Rh(coe)Cl}$_2$]	1	KF	27
4	[{Rh(cod)Cl}$_2$]	1	KF	29
5	[{Rh(cod)Cl}$_2$]	4	KF	68
6	[{Rh(cod)Cl}$_2$]	4	CsF	82
7	[{Rh(cod)Cl}$_2$]	4	K_3PO_4	69
8	[{Rh(cod)Cl}$_2$]	4	K_2CO_3	71
9	[{Rh(cod)Cl}$_2$]	4	Cs_2CO_3	93
10	–	4	Cs_2CO_3	0
11	[{Rh(cod)Cl}$_2$]	4	–	0

Reaction conditions: 0.50 mmol of **5a**, 0.50–2.00 mmol of **1b**, 1.5 mol% of Rh catalyst, 0.50 mmol of base, 0.50 mL of mesitylene, 16 h, 145 °C. Work-up: 12.5 mmol of NaOH, 2 mL of H_2O, 1 h, 100 °C. Yields were determined by HPLC analysis using anisole as an internal standard. cod = cyclo-1,5-octadiene, coe = cyclooctene, Cp* = pentamethylcyclopentadiene.

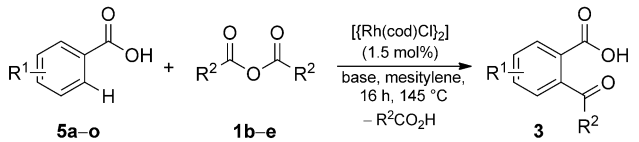
were monoacylated with high selectivity. In the reaction of a range of linear and branched aliphatic anhydrides with **5a**, the corresponding *ortho*-acylbenzoic acids **3ac**–**3ae** were also formed with high selectivity (Table 2).

In contrast, use of the sterically crowded pivalic anhydride (**1f**) as the acylation agent led to the exclusive formation of the aromatic anhydride self-coupling product, while the *ortho*-pivaloylbenzoic acids were not observed. This result opened up an additional synthetic opportunity, namely a selective desymmetrizing self-condensation of benzoic acids. Upon treating benzoic acids (**5**) with **1f** in the presence of the rhodium catalyst, *ortho*-aroylbenzoic acids (**3**) are produced in high yields and selectivities. The products were isolated as *n*-propyl esters after in situ alkylation (Scheme 4).

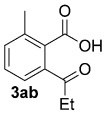
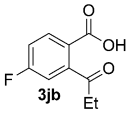
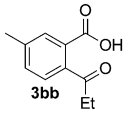
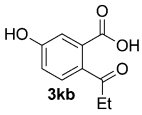
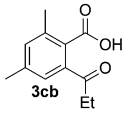
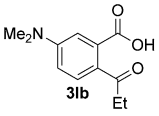
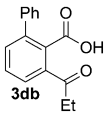
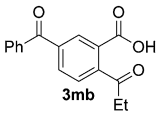
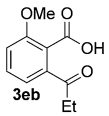
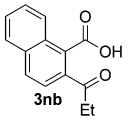
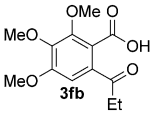
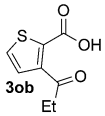
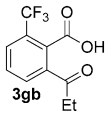
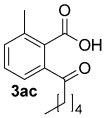
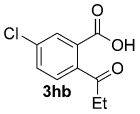
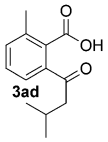
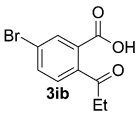
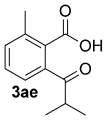
The alternative in situ conversion of a mixture of the benzoic acid **5** and its acid chloride to the symmetrical anhydride and then on to the *ortho*-aroylbenzoic acid **3** was less effective under identical conditions (33% yield for **3aa**).

After *ortho* acylation, the carboxylate group can optionally be removed by in situ protodecarboxylation. However, it turned out that the rhodium complex mediates this step only at temperatures above 200 °C. Higher yields were obtained when the *ortho* acylation was combined with hydrolysis and subsequent copper-mediated protodecarboxylation[29] in a sequential one-pot procedure (Scheme 5). The overall aryl ketone synthesis is a rare example of an aromatic substitution in which the substitution pattern is changed in a defined way.

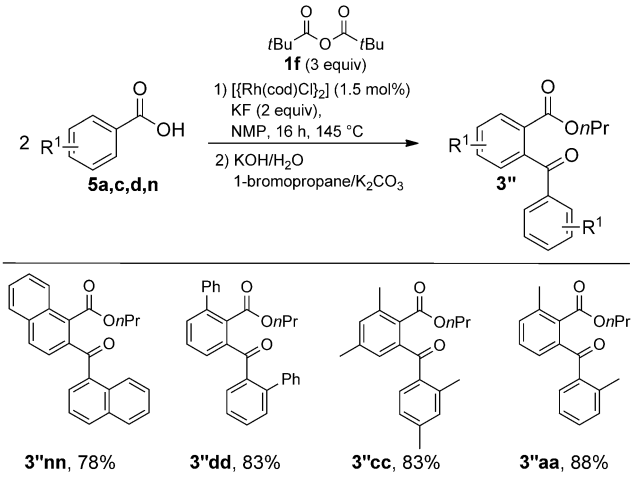
Table 2: Scope of the *ortho* acylation of carboxylic acids.



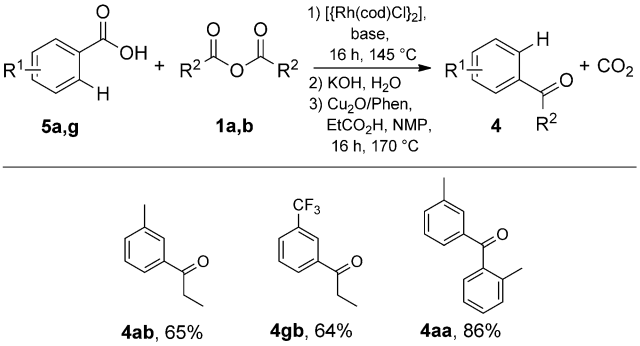
5a–o **1b–e** **3**

Product	Yield [%]	Product	Yield [%]
 **3ab**	86	 **3jb**	45[b,c]
 **3bb**	69	 **3kb**	46[b]
 **3cb**	75	 **3lb**	74[b,d]
 **3db**	87[a]	 **3mb**	88[b]
 **3eb**	92[a]	 **3nb**	60
 **3fb**	92[a]	 **3ob**	20[d]
 **3gb**	87	 **3ac**	82
 **3hb**	70[b]	 **3ad**	68[a]
 **3ib**	52[b]	 **3ae**	73[a]

Reaction conditions: 0.5 mmol of **5**, 2 mmol of **1**, 1.5 mol% of $[\{Rh(cod)Cl\}_2]$, 125 μmol of Cs_2CO_3, 0.5 mL of mesitylene, 16 h, 145 °C. Work-up: 12.5 mmol of NaOH, 2 mL of H_2O, 1 h, 100 °C. Yields of isolated products are given. [a] 1 mmol of KF. [b] 1 mmol of CsF, 155 °C. [c] 2 mL of mesitylene. [d] Isolated as the propyl ester following in situ alkylation with 1-bromopropane.



Scheme 4. Self-acylation of aromatic benzoic acids. NMP = *N*-methylpyrrolidone.



Scheme 5. One-pot synthesis of *meta*-substituted ketones. Phen = 1,10-phenanthroline.

As demonstrated by the examples **4aa** and **4ab**, it can be used to convert **5** into *meta*-alkyl aryl ketones, which are the disfavored regioisomers in Friedel–Crafts acylations of the corresponding alkyl arenes.

A series of mechanistic studies were performed to shed some light on the reaction mechanism. The addition of a stoichiometric amount of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) as a radical scavenger had only a little influence on the reaction outcome, and thus excludes single-electron transfer processes. When mixed anhydrides were generated in the absence of free carboxylate groups, that is, by mixing 2-toluic anhydride (**1a**) with an excess of **1b**, **3ab** was also obtained in high yields. This result indicates that the anhydride group is capable of directing the acylation to its *ortho* position.

Although an alternative catalytic cycle with the C–H activation and oxidative addition steps in reverse order cannot be excluded at that stage, there is some evidence that the reaction starts with a slow oxidative insertion step and formation of an acyl rhodium(III) species. When heating $[\{Rh(cod)Cl\}_2]$ with a stoichiometric amount of 2-toluic anhydride (**1a**) to 145 °C in the absence of base, no conversion of the starting material was observed, thus indicating that oxidative addition is either base-assisted or not the initiating catalytic step. Upon addition of CsF, the formation of cesium toluate and toluyl fluoride was observed above 100 °C. At 145 °C, the product was formed without detection of any rhodium-containing intermediates. The initial reaction step must thus be slow. However, in the reaction of a 1:1 mixture of perdeuterated and undeuterated benzoic acid (**5p** and $[D_5]$-**5p**) with **1b**, a kinetic isotope effect of only 1.5 was measured.

This value is rather low, and indicates that C–H bond cleavage is not rate determining and is unlikely to be the initial reaction step.

In conclusion, [{Rh(cod)Cl}$_2$] was found to direct the acylation of benzoic acids with anhydrides into the *ortho* position, a selectivity that is complementary to the *meta* selectivity of Friedel–Crafts catalysts. In combination with an optional protodecarboxylation, this strategy opens up new opportunities for selective arene functionalization.

Experimental Section

Synthesis of **3ab**: Under a nitrogen atmosphere, a vessel was charged with 2-toluic acid (1.36 g, 10.0 mmol), cesium carbonate (815 mg, 2.50 mmol), and chloro(1,5-cyclooctadiene)rhodium(I) dimer (74.0 mg, 0.15 mmol). Degassed mesitylene (10 mL) and propionic anhydride (5.13 mL, 5.21 g, 40.0 mmol) were then injected, and the mixture was stirred at 145 °C for 16 h. After cooling, 6.25 M NaOH solution (40 mL) was added and the solution was heated to 100 °C for 1 h. The reaction mixture was then acidified with conc. HCl (pH < 4) and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane gradient) to give **3ab** (1.37 g, 7.12 mmol, 71 %) as a colorless solid.

Received: February 14, 2013
Published online: ■■ ■■, ■■■■

Keywords: acylation · anhydrides · C–H functionalization · ketones · rhodium

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Communications

Synthetic Methods

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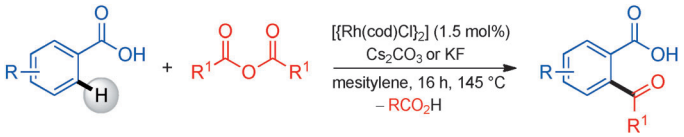

Rhodium-Catalyzed *ortho* Acylation of Aromatic Carboxylic Acids

New directions: The carboxylic acid functional group directs the *ortho* acylation of benzoic acids with carboxylic anhydrides in the presence of a rhodium catalyst (see scheme; cod = cyclo-1,5-octadiene). The acylation at the *ortho* position is complementary to the *meta* selectivity of Friedel–Crafts reactions. The resulting products can undergo protodecarboxylation to deliver an aryl ketone.