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Rhodium-catalyzed *ortho*-Arylation of (Hetero)aromatic Acids

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Abstract: Rhodium acetate effectively promotes the carboxylate-directed *ortho*-arylation of (hetero)aromatic carboxylates with aryl bromides. The main advantage of this phosphine-free, redox-neutral method arises from its efficiency in assembling biologically meaningful electron-rich arylpyridines, which are problematic substrates in known C–H arylations using Pd, Ru, and Ir catalysts.

Keywords: rhodium • aryl bromides • benzoic acids • biaryls • heteroarenes • C-H arylation

Arylated pyridines represent a key motif in various pharmaceutically active substances,[1–3] and expedient synthetic entries to this substructure are constantly sought.

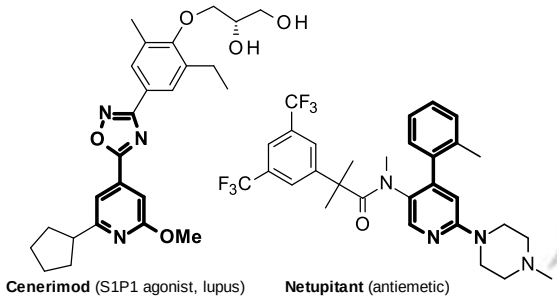
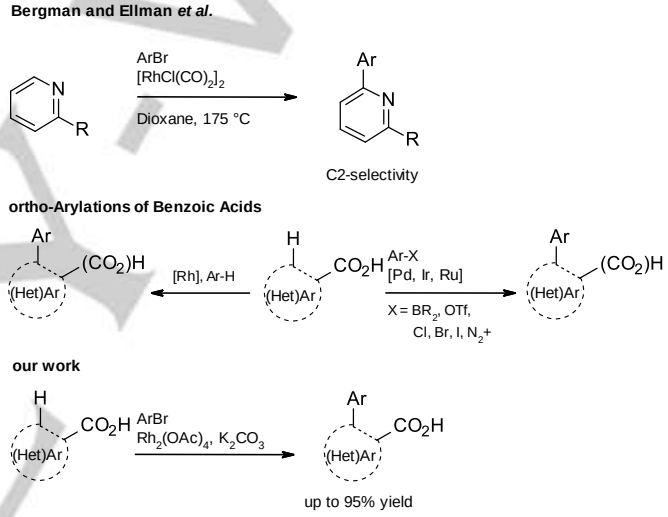


Figure 1. Pharmaceuticals containing heteroaromatic biaryl motifs.[4,5]

Known methods for the arylation of (hetero)arenes include cross-couplings of organometallic reagents with aryl (pseudo)halides, Ullmann reactions, or decarboxylative couplings.[6–11] In the case of pyridines, most preformed organometallic reagents are unstable, C–H arylations are particular advantageous for the construction of heteroaryl skeletons.[12] The arylation can be directed into specific positions by various donor groups, and even by the heteroatom of heteroarenes. In this context, Bergman and Ellmann demonstrated that pyridines can be arylated selectively at the C-2 position of the pyridine ring.[13–16] This directing effect of the heterocyclic nitrogen can be overridden by other ring substituents, for example by carboxylates. Larrosa showed that in the presence of a sophisticated Pd catalyst, nicotinic acid derivatives are arylated in the position *ortho* to the carboxylate rather than the nitrogen atom.[17]

The use of carboxylates as directing groups is particularly advantageous for heterocyclic substrates, because they are often present as leftovers from the construction of the heterocycle skeleton.[18] Following the arylation step, they can either be removed tracelessly, or reused as leaving groups in decarboxylative couplings.[19,20] Carboxylate-directed C–H arylations are effectively promoted by Pd[21–29], Ir,[30] or Ru[31–34] systems. Rh systems, and Cp*Rh in particular, are at the heart of modern C–H functionalization chemistry.[35–40] Su and You have used Rh in carboxylate-directed oxidative (decarboxylative) arylation processes, e.g. thiophenes.[41–43]



Scheme 1. C–H Arylations directed by neighboring atoms and *o*-carboxylates.

In the context of a planned synthesis of 2-alkoxy-4-arylpyridines, we identified 2-alkoxynicotinic acids as the optimal starting materials. Based on the work by Larrosa, one would expect it to undergo selective arylation at the 4-position. Thereafter, the carboxylate group could subsequently be removed by protodecarboxylation or converted to halides, alkoxides, amines, etc. However, the known Pd and Ru systems gave unsatisfactory yields for our model reaction, the coupling of 2-alkoxynicotinic acid with 4-bromotoluene (Table 1, entries 1, 2), and all our attempts to develop effective protocols based on the above catalysts failed.

In search for alternative catalysts, we identified dirhodium tetraacetate as a promising candidate. Aryl phosphines have been reported to react with this dinuclear Rh^{II} complex, liberating acetic acid and forming a carbometalated dinuclear aryl–Rh species in which the phosphine coordinates to one of the Rh nuclei, and the C-2 carbon binds to the other Rh.[44,45] Considering the proverbial affinity of Rh^{II} to carboxylates, we reasoned that a similar base-assisted cyclometallation deprotonation (CMD)

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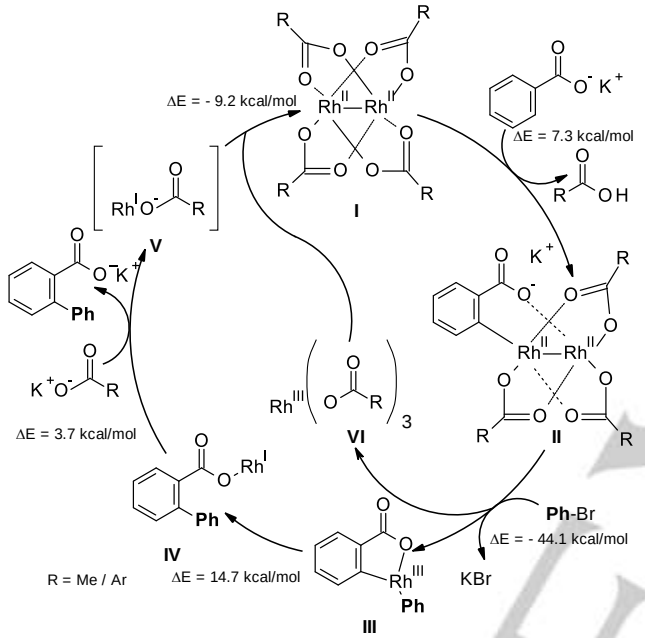
mechanism might be possible with a carboxylate rather than a phosphine as ortho-directing group. This would open up the catalytic cycle sketched out in Scheme 2. It starts with a directed CMD reaction furnishing cyclometallated Rh^{II} carboxylate **II**, which has a structure analogous to that observed in the reaction with aryl phoshines. It reacts with an aryl bromide to give the diaryl Rh^{III} complex **III**, along with stable Rh^{III} carboxylate **VI**. The intermediacy of **III** seems in line with literature reports on Rh-catalyzed arylations.[41,43] The desired biaryl product is then formed by reductive elimination and released by salt metathesis with fresh carboxylate substrate. The coordinatively unsaturated Rh^{I} species **V** could be stabilized by conproportionation with **VI** regenerating Rh^{II} carboxylate **I**.



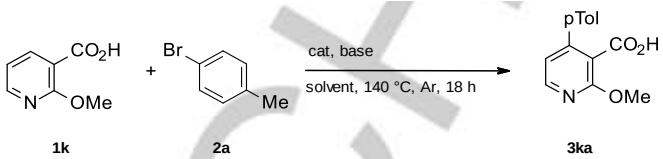
Scheme 2. Mechanistic blueprint for a Rh^{II} catalysed arylation.

When probing $Rh_2(OAc)_2$ in our model reaction, it gave good results in combination with the simple base K_2CO_3 (Table 1, Entry 3). The C-H arylation was directed exclusively *ortho* to the carboxylate group rather than the pyridine nitrogen.

Systematic studies revealed that aprotic polar solvents are beneficial with best results obtained in DMF. The catalyst loading can be reduced to 0,5 mol% Rh (Table 1, Entry 12), and only a slight excess of the base is required. A temperature of 140°C is optimal, below that, the yields drop markedly (Table 1, Entry 11). Further studies revealed that many rhodium(III) salts showed similar activity in this transformation (Supporting Information), which can be rationalized with their swift conversion to Rh^{II} carboxyates when heated in the presence of carboxylates.[46]

In order to probe the general applicability of our new protocol, we investigated its scope with regard to both coupling partners (Tables 2, 3, and S10). As can be seen in Table 2, benzoic acids bearing electron-donating or -withdrawing substituents were smoothly coupled with 4-bromotoluene (**2a**), among them even unprotected anthranilic acid (**1h**). Various heterocyclic acids gave good results, including our targeted nicotinates bearing *ortho*-amino or *ortho*-methoxy groups. Similarly to other directed *ortho*-arylations, competing diarylation was observed when two *ortho*-positions were accessible, e.g. for **1p**. While most acids were converted with a low Rh-loading of 0.5 mol%, a few examples like 2-fluorobenzoic acid **1c** or 2-cyanobenzoic acid **1e** need larger amounts of Rh.

Table 1. Screening of the reaction conditions.[a]



1k **2a** **3ka**

Entry	mol% cat	equiv Base	Solvent	Yield 3[b] [%]
1	5.0 cataCXium A-Pd-G3	2.2 Cs_2CO_3	DMF	14
2	4.0 [(*p*-cym)$RuCl_2$]$_2$ + 8 PEt_3·HBF_4	1.1 K_2CO_3	NMP	0
3	4.0 $Rh_2(OAc)_4$	1.0 K_2CO_3	"	77
4	"	"	DMF	79
5	"	"	DMSO	23
6	"	"	mes	5
7	"	–	DMF	1
8	"	0.5 K_2CO_3	"	24
9	"	1.5 K_2CO_3	"	87
10	"	2.0 K_2CO_3	"	33
11[b]	"	1.5 K_2CO_3	"	7
12[c]	0.25 $Rh_2(OAc)_4$	"	"	91

[a] Reactions conditions: **1k** (0.5 mmol), **2a** (0.75 mmol), cat, base, solvent (2 mL), 140 °C, 18 h. Yields of the corresponding methyl esters determined by GC analysis after esterification with K_2CO_3 (2 equiv) and MeI (5 equiv) in NMP using *n*-tetradecane as internal standard. [b] 130 °C. [c] 6 h. DMF: dimethylformamide, NMP: *N*-methylpyrrolidone, mes: mesitylene, DMSO: dimethylsulfoxide.

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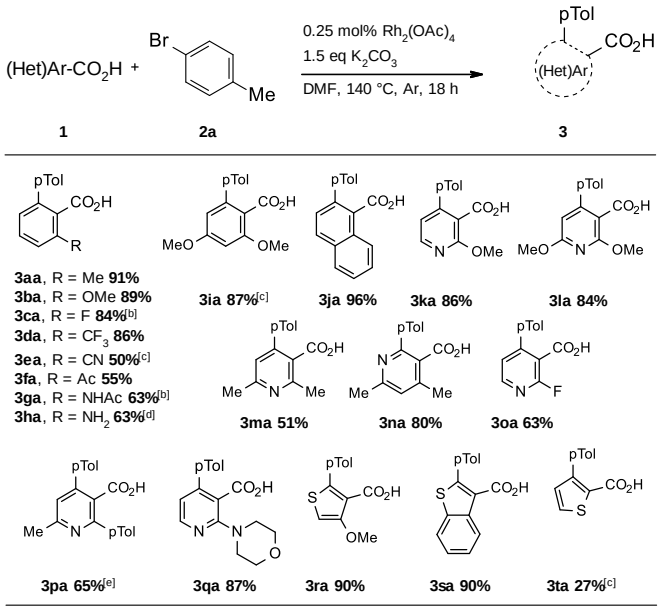
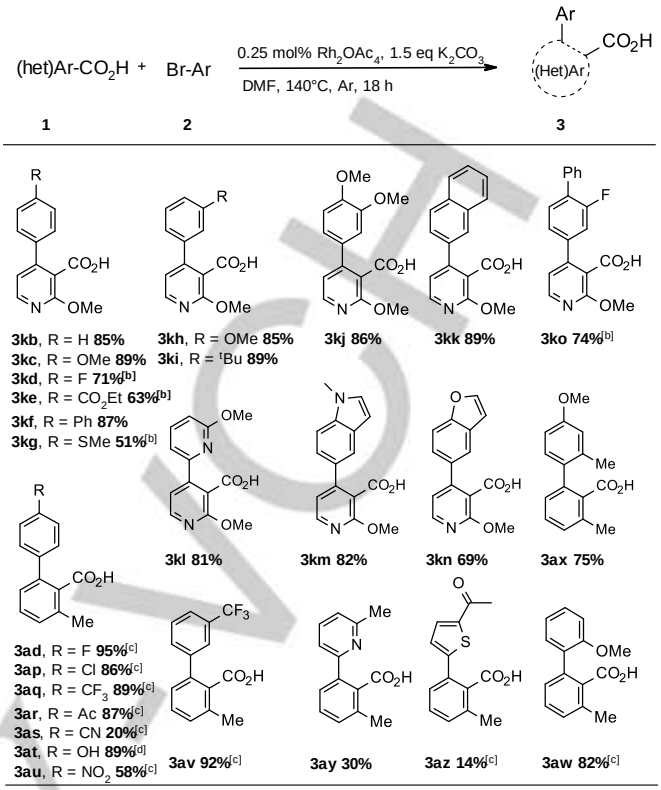
Table 2. Substrate scope with regard to the carboxylate component.[a]



[a] Reactions conditions: **1** (0.5 mmol), **2a** (0.75 mmol), 0.25 mol% $Rh_2(OAc)_4$, K_2CO_3 (1.5 equiv), DMF (2 mL), 140 °C, 18 h. Yields of the corresponding methyl esters after esterification with K_2CO_3 (2 equiv) and MeI (5 equiv) in NMP. [b] 1 mol% $Rh_2(OAc)_4$. [c] 4 mol% $Rh_2(OAc)_4$. [d] Isolated as the corresponding dimethyl amine. [e] **2a** (1.25 mmol).

The coupling is broadly applicable with regard to the aryl bromide (Table 3). Various functional groups including esters, ketones were tolerated, and even 4-bromophenol **2t** was coupled in excellent yield. Arylated phenols are structural components of several drug precursors.[47]

Table 3. Substrate scope with regard to aryl bromides.



[a] Reactions conditions: **1** (0.5 mmol), **2** (0.75 mmol), 4 mol% $Rh_2(OAc)_4$, K_2CO_3 (1.5 equiv), DMF (2 mL), 140 °C, 18 h. Yields of the corresponding methyl esters after esterification with K_2CO_3 (2 equiv) and MeI (5 equiv) in NMP. [b] 1 mol% $Rh_2(OAc)_4$. [c] 4 mol% $Rh_2(OAc)_4$. [d] 1 mol% $Rh_2(OAc)_4$, Isolated as the free carboxylic acid.

Removal of the carboxylate group by protodecarboxylation was possible in situ by heating the reaction mixture in the presence of Cu^{II}/tetramethylphenanthroline and quinoline (see the supporting information).[48]

To probe the validity of our mechanistic blueprint, a series of control experiments, kinetic investigations and DFT calculations were performed (see the supporting information). Heating o-toluic acid in deuterated methanol in the presence of rhodium acetate led to selective *ortho*-deuteration.[49] In contrast, rhodium acetate did not promote halogen exchange between aryl iodide and potassium bromide.[50] The findings support our hypothesis that the reaction is initiated by a reversible *ortho*-metallation step. A competition experiment of deuterated and non-deuterated *ortho*-toluic acid with 4-bromotoluene showed only a moderate kinetic isotope effect, suggesting that this step is not alone rate-determining (Scheme 3, top). ESI-MS analysis of reaction mixtures of *ortho*-toluic acid under catalytic conditions, both in the presence and absence of 4-bromotoluene, display several dinuclear Rh fragments carrying the 2-methylbenzoate fragments, suggesting that the reaction is indeed initiated by carboxylate coordination. We additionally synthesized dirhodium tetra-*ortho*-toluate (**5**) and found it to effectively catalyse the reaction and quantitatively form the product if coupled with 4-bromotoluene and without $Rh_2(OAc)_4$ (Table S9).

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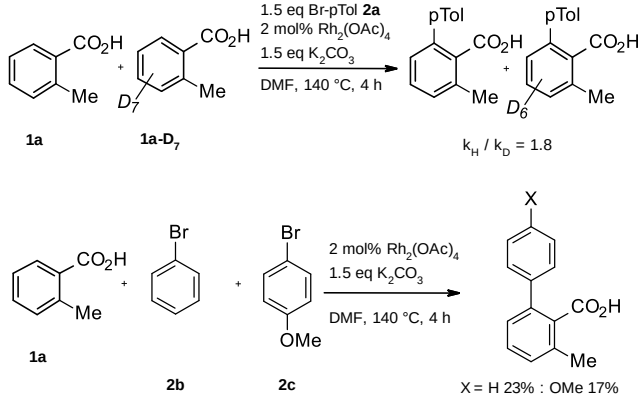

Scheme 3. Selected mechanistic experiments (see SI for conditions).

In a competition experiment, *ortho*-toluic acid was allowed to react with a mixture of bromobenzene and electron-rich 4-methoxyaryl bromide, furnishing similar quantities of both arylation products. This indicates that oxidative addition is not rate-determining, either (Scheme 3, bottom), so that the overall rate seems to be mostly limited by the C-C bond-forming step.

The initial reaction rates for the arylation of **1k** with **2a** were determined after 1 h for catalyst loadings between 0.5 and 2.0 mol%. The results point to almost first-order kinetics (1.2±0.2) with regard to Rh dimer. This is in agreement with our mechanism in which the rate-determining steps involve a mononuclear Rh complex. For these experiments we chose **1k** over *ortho*-toluic acid **1a**, because **1a** has an induction period over several hours before the product formation quickly increases. The addition of strongly coordinating pyridine helps breaking up the dirhodium tetracarboxylate structure and strongly reduces the induction period. Further kinetic studies conducted at a 0.5 mol% Rh dimer loading revealed that the reaction follows almost zero-order kinetics with regard to 4-bromotoluene, which is in line with the findings of the competition experiment. Interestingly, the initial kinetic order of the carboxylate **1k** is negative (-2.6 ± 0.2) indicating a poisoning effect, possibly through a competing pyridyl-rhodium coordination.

The DFT-calculations of the reaction steps support the proposed mechanism. All intermediates have been verified to be stable minima on the potential energy surface. The calculated energies (ΔE_r) of all steps of the catalytic cycles are within a feasible range. Notably, the disproportionation of intermediate **II** to **III** and **VI** was calculated to be a favorable process. In a dilute solution, species **V** is likely to enter a new catalytic cycle directly. However, its alternative recombination with $Rh^{(III)}$ carboxylate (**VI**) with formation of the $Rh^{(II)}$ dimer (**I**) is clearly exothermic. This is consistent with the proposed role of the $Rh^{(II)}$-carboxylate dimer as a catalyst reservoir. For a more detailed scheme with the calculated structures including solvent molecules see the supporting information (Scheme S5).

The In conclusion, low loadings of simple rhodium acetate catalyse the *ortho*-C-H arylation of various aromatic and heteroaromatic carboxylic acids with a broad range of aryl bromides. The new protocol is well-suited to the synthesis of functionalised aryl pyridines, which are of special interest in pharmaceutical research. Dinuclear $Rh_2(OAc)_2$ was found to be particularly suited for *ortho*-C-H bond activation of benzoic acids opening up further opportunities for directed functionalizations.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

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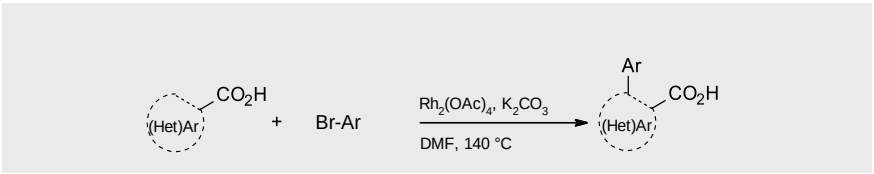

Rhodium acetate effectively promotes the carboxylate-directed *ortho*-arylation of aromatic carboxylates with aryl bromides. It is particularly effective in the synthesis of biologically meaningful electron-rich aryl pyridines. 56 examples demonstrate the efficiency and broad application of this straightforward arylation protocol.

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