Traceless Directing Groups

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Carboxylic Acids as Traceless Directing Groups for the Rhodium(III)-Catalyzed Decarboxylative C–H Arylation of Thiophenes**

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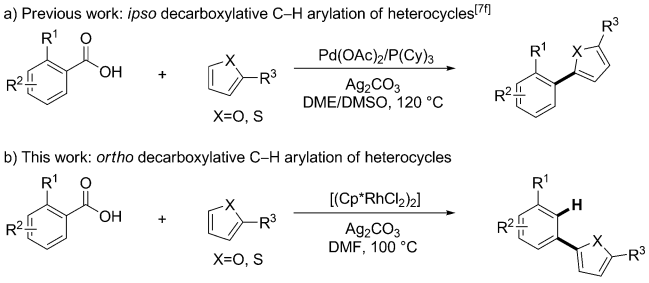
Abstract: *A rhodium(III)-catalyzed carboxylic acid directed decarboxylative C–H/C–H cross-coupling of carboxylic acids with thiophenes has been developed. With a slight adjustment of the reaction conditions based on the nature of the substrates, aryl carboxylic acids with a variety of substituents could serve as suitable coupling partners, and a broad variety of functional groups were tolerated. This method provides straightforward access to biaryl scaffolds with diverse substitution patterns, many of which have conventionally been synthesized through lengthy synthetic sequences. An illustrative example is the one-step gram-scale synthesis of a biologically active 3,5-substituted 2-arylthiophene by way of the current method.*

Transition-metal-catalyzed functional-group-directed C–H functionalization reactions have emerged as a powerful method to construct C–C and C–X (X = heteroatom) bonds and represent state-of-the-art methods for the modification of organic molecules in terms of atom and step economy and regioselectivity.[1] In these reactions, the directing groups are essential for reaction acceleration and regioselectivity control.[1,2] Nevertheless, the strategies using directing groups suffer from limitations when the directing groups or substitution patterns are not present in the target molecules. To overcome these restrictions, the concept of removable directing groups (also termed traceless directing groups) has been put forward and developed for direct C–H functionalization.[2] In this context, the traceless directing group strategy has been applied to the C–H silylation, acyloxylation, halogenation, and borylation of arenes using Ru,[3a] Pd,[3b–c] and Ir[3d] catalysts. Although pioneering studies have demonstrated that the installation of removable directing groups endowed parent substrates with new reactivity and selectivity, most of these methods required additional steps to remove the undesired directing groups from the products. It is highly desirable to exploit traceless directing group methods with which C–H functionalization and removal of the directing group can be achieved in a one-pot fashion.

Serving as versatile arylating reagents through metal-mediated decarboxylation to generate aryl–metal intermediates,[4] aryl carboxylic acids can undergo cross-coupling reactions with aryl halides,[5] olefins,[6] (hetero)arenes,[7] and even other aryl carboxylic acids;[8] in these processes, the reaction takes place at the original aryl position of the carboxylic acid group. The reaction that occurs by a tandem carboxyl-directed C–H functionalization[9]/protodecarboxylation[10] sequence, however, would lead to the *ortho*-selective formation of the decarboxylated cross-coupling products and thus be complementary to the previously established *ipso*-selective decarboxylative cross-coupling reactions. Such reactions were pioneered by the groups of Satoh, Miura, Larrosa, and Gooßen.[11] An interesting example reported by Larrosa and co-workers[11d] entails the use of an in situ installed carboxylic acid as a traceless directing group for the facile synthesis of *meta*-arylated phenols, a class of compounds that are generally synthesized from the parent phenols through lengthy synthetic sequences. This example clearly illustrates that strategies using carboxylic acids as traceless directing groups have great potential to streamline the syntheses of diversely substituted arenes. However, to date, examples of the use of carboxylic acids as traceless directing groups for decarboxylative cross-couplings have been scarce.[11] Herein, we report the first example of the application of a carboxylic acid in a traceless directing group strategy for a C–H/C–H cross-coupling reaction. With $[(Cp^*RhCl_2)_2]/Ag_2CO_3$ as the catalyst system, we have achieved the decarboxylative *ortho*-arylation of aryl carboxylic acids with thiophenes (Scheme 1 b). This method is compatible with diverse substitution patterns on the aryl ring of the benzoic acid and a broad range of functional groups. Its practical applicability was illustrated by the gram-scale synthesis of a biologically active compound that is hard to access through conventional synthetic routes.

The decarboxylative *ortho* arylation of aryl carboxylic acids was designed based on the proposed mechanism



Scheme 1. Two kinds of decarboxylative arylation reactions of aryl carboxylic acids with heterocycles. Cp* = pentamethyl cyclopentadienyl, Cy = cyclohexyl.

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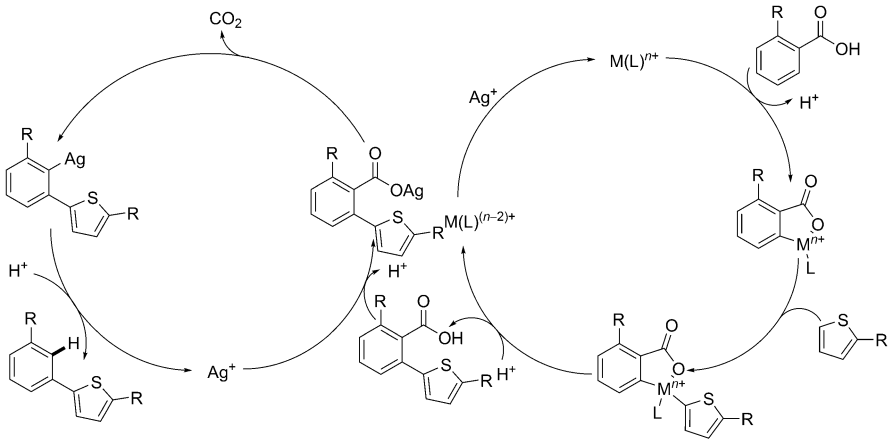
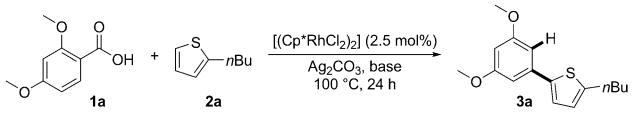


Scheme 2. Working hypothesis for the *ortho*-selective decarboxylative C–H arylation of aryl carboxylic acids with thiophenes.

(Scheme 2), which consists of two catalytic cycles: 1) metal-catalyzed carboxylic acid directed *ortho* arylation, and 2) silver-catalyzed protodecarboxylation. To achieve such a decarboxylative *ortho* arylation, the reaction conditions must ensure that the carboxylic acid directed *ortho* arylation occurs prior to the Ag-catalyzed decarboxylation. Computational studies revealed that *ortho*-disubstituted aryl carboxylic acids were more reactive towards the Ag-promoted decarboxylation than *ortho*-monosubstituted ones.[12] As a result, the introduction of an aryl group at the *ortho* position of aryl carboxylic acids would lead to an increase in reactivity towards decarboxylation compared with the original aryl carboxylic acids, suggesting that the decarboxylative *ortho* arylation of aryl carboxylic acids is viable. In spite of this, the competition between *ipso*-selective and *ortho*-selective decarboxylative arylation reactions should remain as the *ortho*-monosubstituted aryl carboxylic acids are capable of participating in protodecarboxylation.[10] Furthermore, several other unwanted side reactions, such as thiophene homocoupling and the protodecarboxylation of the unreacted aryl carboxylic acids, potentially impede the realization of the decarboxylative *ortho* arylation of aryl carboxylic acids.

The reaction of 2,4-dimethoxybenzoic acid (**1a**) with 2-*n*-butylthiophene (**2a**) was chosen as a model system for the optimization of the reaction conditions. Taking into account the previous studies on Pd^{II}/Ag^{I} systems,[6–9,11c,d] we assumed that a Pd catalyst in combination with silver salts may work for the *ortho*-selective decarboxylative arylation of aryl carboxylic acids. However, such catalyst systems failed to deliver the target product; instead, they gave rise to the dimerization of 2-*n*-butylthiophene (see the Supporting Information, Table S1). Therefore, we turned our attention towards rhodium catalysts, considering that Rh^{III} catalysts have been shown to be effective in many C–H bond functionalization reactions.[1d,e,13] Initially, we found that the reaction did not afford any product in various solvents in the absence of additional base using $[(Cp^*RhCl_2)_2]$ as the catalyst and Ag_2CO_3 as the oxidant (Table 1, entries 1–4). Once K_2HPO_4 had been introduced as an additional base, we were pleased to find that the reaction conducted in DMF afforded the desired product in 63% yield (entry 5). As we observed that the reaction of potassium 2,4-dimethoxybenzoate with 2-*n*-butylthiophene gave only 14% yield in the absence of K_2HPO_4 under otherwise identical conditions, we speculate that K_2HPO_4 may act as a base to accept protons generated during the C–H/C–H cross-coupling process. The yield increased to 70% when 1.5 equivalents of 2-*n*-butylthiophene were used (entry 6). Despite the fact that $AgSbF_6$ helps to release a more active cationic rhodium catalyst for C–H bond activation,[13k,l] $AgSbF_6$ did not display any beneficial effects on this reaction (entry 7). Gratifyingly, TEMPO was observed to exert a positive effect on the reaction outcome presumably as it accelerates the oxidation of Rh^{I} to Rh^{III} as an electron transfer intermediate (entries 8 and 9).[14] Interestingly, increasing the catalyst loading decreased the yield whereas lowering the catalyst loading to 2 mol% gave the best yield (entries 10–12). In fact, GC-MS analysis revealed that 5 mol% of $[(Cp^*RhCl_2)_2]$ led to homocoupling of 2-*n*-butylthiophene, which decreased the efficiency of the target

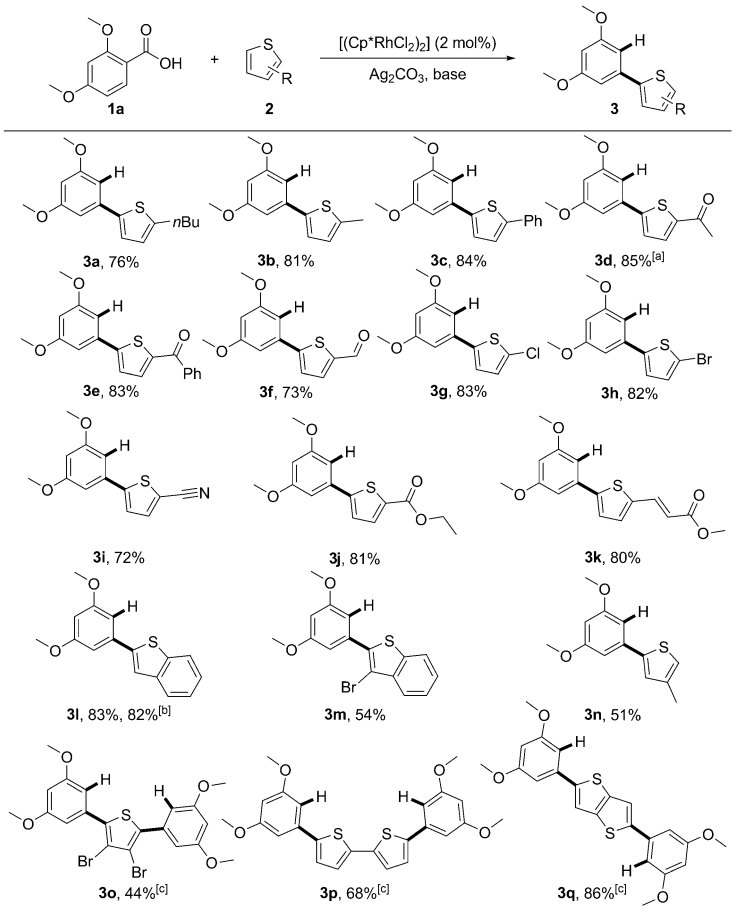
Table 1: Optimization of the reaction conditions.[a]



1a 2a 3a

Entry	**1a**/**2a**	Base	Solvent	Yield [%][b]
1	1:1.2	–	dioxane	0
2	1:1.2	–	DMF	0
3	1:1.2	–	DMSO	0
4	1:1.2	–	DCE	0
5	1:1.2	K_2HPO_4	DMF	63
6	1:1.5	K_2HPO_4	DMF	70
7[c]	1:1.5	K_2HPO_4	DMF	67
8[d]	1:1.5	K_2HPO_4	DMF	76
9[e]	1:1.5	K_2HPO_4	DMF	76
10[d,f]	1:1.5	K_2HPO_4	DMF	65
11[d,g]	**1:1.5**	**K_2HPO_4**	**DMF**	**82 (76)**
12[d,h]	1:1.5	K_2HPO_4	DMF	56
13[d,g]	1:1.5	Na_2CO_3	DMF	64
14[d,g]	1:1.5	NaOAc	DMF	56
15[d,g]	1:1.5	CsOPiv	DMF	29

[a] Reaction conditions: $[(Cp^*RhCl_2)_2]$ (2.5 mol%), Ag_2CO_3 (2 equiv), base (1.5 equiv), solvent (2 mL), 100°C, 24 h. [b] Yield determined by GC analysis using dodecane as an internal standard; yields of isolated products given in parentheses. [c] With $AgSbF_6$ (10 mol%). [d] With TEMPO (20 mol%). [e] With TEMPO (50 mol%). [f] $[(Cp^*RhCl_2)_2]$ (5 mol%). [g] $[(Cp^*RhCl_2)_2]$ (2 mol%). [h] $[(Cp^*RhCl_2)_2]$ (1 mol%). Piv = pivaloyl, TEMPO = 2,2,6,6-tetramethyl-l-piperidinoxyl.



Scheme 3. Variation of the thiophene. Reaction conditions: **1a** (0.2 mmol), **2** (1.5 equiv), $[(Cp^*RhCl_2)_2]$ (2 mol%), TEMPO (20 mol%), Ag_2CO_3 (2 equiv), K_2HPO_4 (1.5 equiv), DMF (2 mL), 100°C, 24 h. Yields of isolated products are given. [a] **1a** (1.5 equiv), **2** (0.2 mmol), $[(Cp^*RhCl)_2]$ (2.5 mol%), Ag_2CO_3 (2 equiv), Na_2CO_3 (1.5 equiv). [b] 5 mmol scale, yield of isolated product: 1.11 g. [c] **1a** (3 equiv), **2** (0.2 mmol), $[(Cp^*RhCl_2)_2]$ (5 mol%), Ag_2CO_3 (4 equiv), K_2HPO_4 (3 equiv).

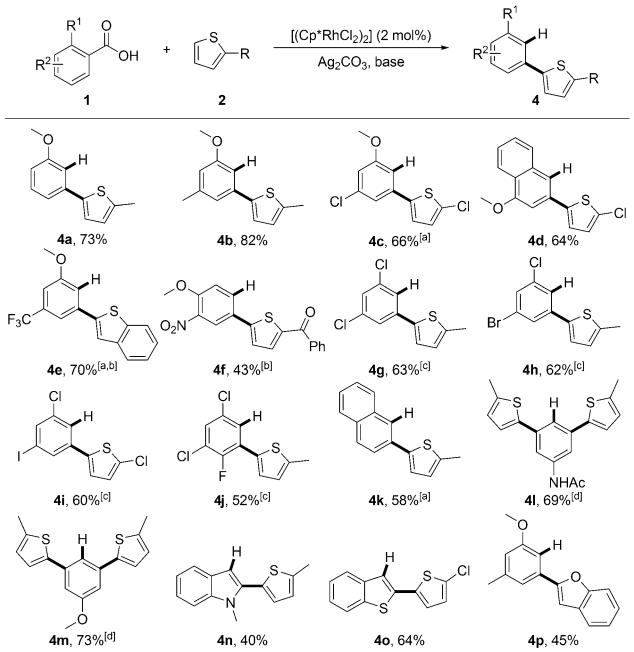
reaction. Other bases and silver salts were inferior to K_2HPO_4 and Ag_2CO_3, respectively (entries 13–15; see also Table S2).

With the optimized reaction conditions in hand, we evaluated the substrate scope of the reaction with respect to the thiophene component. As depicted in Scheme 3, methyl- and phenyl-substituted thiophenes gave satisfying yields of 81% and 84%, respectively (**3b** and **3c**). Thiophenes bearing keto, formyl, ester, alkenyl, chloro, or bromo substituents could be smoothly transformed into the corresponding products in good to excellent yields (**3d–e, 3j–k**). Surprisingly, this reaction was also compatible with a nitrile group in spite of its coordinating abilities as **3i** was formed in 72% yield. Benzothiophenes were suitable substrate as well (**3l** and **3m**). Diarylation occurred swimmingly with moderate to excellent yields (**3o–3q**) when two possible reaction positions are available on the thiophene. These reactions formed extended π-conjugated systems bearing thiophene subunits (**3o–3q**), an important family of optical materials in material science,[15] and thus provide a complement to our previously reported method.[7f]

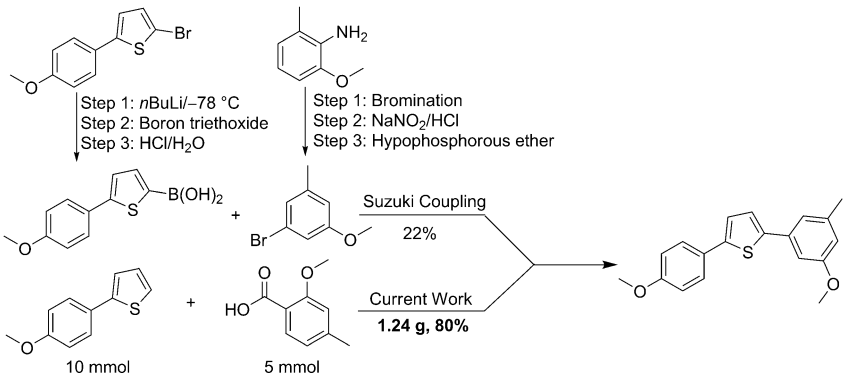
Subsequently, we investigated the substrate scope with regard to the benzoic acids (Scheme 4). Unlike for the thiophene component, the reaction conditions had to be varied depending on whether electron-rich or electron-deficient carboxylic acids were used, presumably because of differences in acidity and reactivity. Hence, the base was crucial to accomplish the reactions. Under the optimized conditions, **4a** was formed in only 15% yield. Gratifyingly, when the reaction mixture was additionally heated to 140°C for six hours in NMP, the yield increased to 73%. This result further confirmed our previous hypothesis and indicated that the temperature was an important factor influencing the overall yield. With this hypothesis in mind, satisfying yields were obtained when methyl, chloro, trifluoromethyl, or nitro substituents were present in the carboxylic acid scaffold (**4b–f**). K_2HPO_4 was an ineffective base for 2,4-dichlorobenzoic acid. Luckily, the corresponding products were formed when Li_2CO_3 was used as an additional base (**4g–j**). This approach is especially attractive for the synthesis of **4h**, **4i**, and **4j** because very few methods to access this important class of compounds were previously available. The absence of *ortho* substituents resulted in the formation of the diarylated products in good yields (**4l** and **4m**). Heterocyclic carboxylic acids were also suitable substrates (**4n** and **4o**). Furthermore, benzofuran, a different heterocycle, also served as an arylating reagent and participated in this transformation (**4p**).

The presence of the 2-arylthiophene structural motif in natural products[16a–c] and biologically active molecules[16d–h] inspired us to explore the feasibility of its preparation by utilizing the established method. To our delight, this decarboxylative cross-coupling method was applicable to the one-step and gram-scale synthesis of an intermediate for a 17β-hydroxysteroid dehydrogenase type 1 inhibitor from inexpensive and commercially available materials,[17a] which furnished the isolated product in up to 80% yield (Scheme 5). Previously, this compound was synthesized in low overall yields by way of a Suzuki reaction of two coupling partners, that is, 5-(4-methoxyphenyl)thiophen-2-ylboronic acid and 1-bromo-3-methoxy-5-methylbenzene, which both require lengthy synthetic sequences for their preparation (Scheme 5).[17b,c] Aside from step economy, our approach effectively avoided the use of unwelcome bromine and strong bases or acids and therefore provides rapid and convenient access to such biologically active 3,5-substituted 2-arylthiophenes.

In conclusion, we have developed a versatile catalyst system for the decarboxylative *ortho* C–H arylation of aryl carboxylic acids with thiophenes by a tandem Rh^{III}-catalyzed C–H arylation/Ag-catalyzed decarboxylative protonation sequence. The success in the use of a carboxylic acid moiety as a traceless directing group is, to large extent, ascribed to the fact that the *ortho*-disubstituted products of the C–H/C–H cross-coupling process undergo protodecarboxylation more easily than the *ortho*-monosubstituted precursor carboxylic



Scheme 4. Variation of the (hetero)aryl carboxylic acid. Reaction conditions: **1** (0.2 mmol), **2** (2 equiv), $[(Cp^*RhCl_2)_2]$ (2 mol%), TEMPO (20 mol%), Ag_2CO_3 (3 equiv), K_2HPO_4 (1.5 equiv), NMP (2 mL), 100°C, 24 h, then stirring for a further 6 hours at 140°C. Yields of isolated products are given. [a] Stirring for a further 6 hours at 160°C. [b] $[(Cp^*RhCl_2)_2]$ (2 mol%), Li_2CO_3 (1.5 equiv), DMF. [c] $[(Cp^*RhCl_2)_2]$ (4 mol%), Li_2CO_3 (1.0 equiv), DMF. [d] **2** (4 equiv), $[(Cp^*RhCl_2)_2]$ (2 mol%), Ag_2CO_3 (6 equiv), DMF.



Scheme 5. Gram-scale synthesis of an intermediate for a 17β-hydroxysteroid dehydrogenase type 1 inhibitor.

acids. This method is quite general and compatible with a broad range of functional groups and substitution patterns on the arene rings, offering a complement to the existing methods for biaryl synthesis.

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