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Ruthenium(II)-Catalyzed Hydroarylation of Maleimides Using Carboxylic Acids as a Traceless Directing Group

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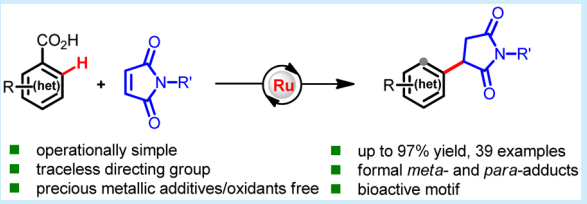
Supporting Information

ABSTRACT: An efficient Ru(II)-catalyzed hydroarylation of maleimides with ready-stock aryl carboxylic acids has been developed based on weak carboxylate-directed *ortho*-C−H alkylation and concomitant decarboxylation processes, fabricating 3-aryl succinimides, a recurrent scaffold in drug molecules, in high yields (up to 97%). The protocol features operational simplicity, avoids the need for precious metal additives/oxidants, and offers broad substrate scope with formal *meta*- and *para*-selectivities. It represents the first example of Ru(II)-catalyzed direct arylation of maleimides with unbiased benzoic acids.



Cyclic imides, particularly succinimides embracing 3-aryl substitution, are pivotal structural motifs frequently encountered in natural products and pharmaceuticals with diverse biological activities (Figure 1).[1] They have potential applications in material science[2] and also serve as useful synthetic intermediates for the construction of important heterocyclic frameworks such as pyrrolidines and γ-lactams.[3] Consequently, synthetic endeavors toward this scaffold are in high demand.

A straightforward route to access 3-aryl succinimides would be the catalytic hydroarylation of maleimides through direct cleavage of unactivated C−H bond of arenes (Scheme 1). In this context, Prabhu et al. reported conjugate addition of aryl ketones and amides to malemides under ruthenium catalysis.[4] However, a stoichiometric amount of copper salt was essential to promote the reaction, limiting its practicability. The Kim group has used precious rhodium catalysts for such transformations under acidic conditions.[5] Recently, Ackermann and Li et al. disclosed cobalt(III) catalysis for C−H alkylation of arenes with maleimides, where substrates were modified through the installation of a strongly coordinating pyrimidine unit as a directing group.[6] Apart from these selective accomplishments, hydroarylation of maleimides through a C−H bond activation strategy that maximizes step and atom economy remains unsatisfied and urges immediate attention.[7]

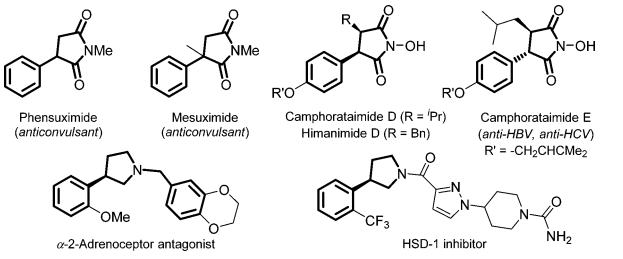
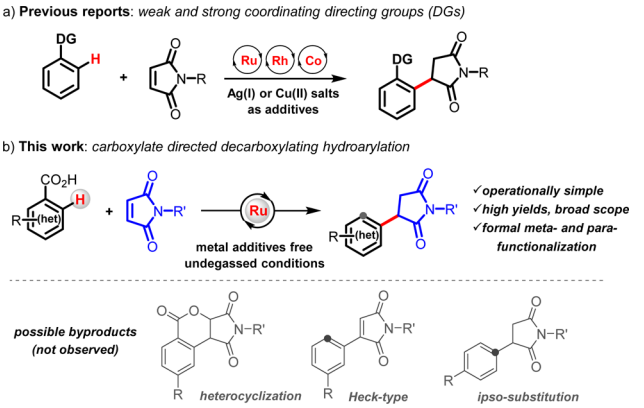


Figure 1. Examples of bioactive molecules featuring succinimide and its derivatives.

Scheme 1. Transition-Metal-Catalyzed Hydroarylation of Maleimides



In recent years, aromatic carboxylic acids have gained considerable momentum in the arena of transition-metal-catalyzed directed C−H bond activation/functionalization processes.[8] They are cheap and widely available in great structural diversity, shelf-stable, and nontoxic, and the acid group is easily modifiable to a variety of functional moieties. Importantly, the carboxyl functionality could also be tracelessly removed by protodecarboxylation and offers formal *meta*- or *para*-functionalization of arenes depending on the existing substitution pattern.[9] However, progress of the traceless directing group strategies using carboxylate substrates has primarily been confined under Pd,[10] Rh,[11] and Ir[12] catalysis pioneered by Miura, Gooßen, Larossa, Yu, and others. Application of Ru catalysis has been realized very recently

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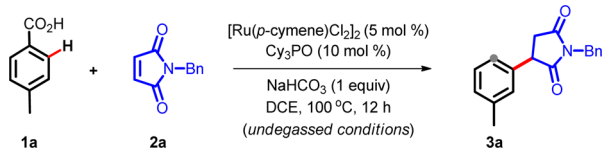
Table 1. Optimization of Hydroarylation Reaction[a]

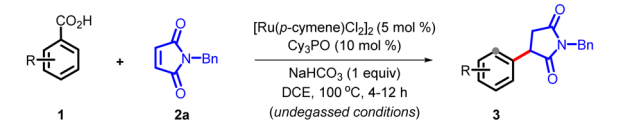


1a 2a 3a

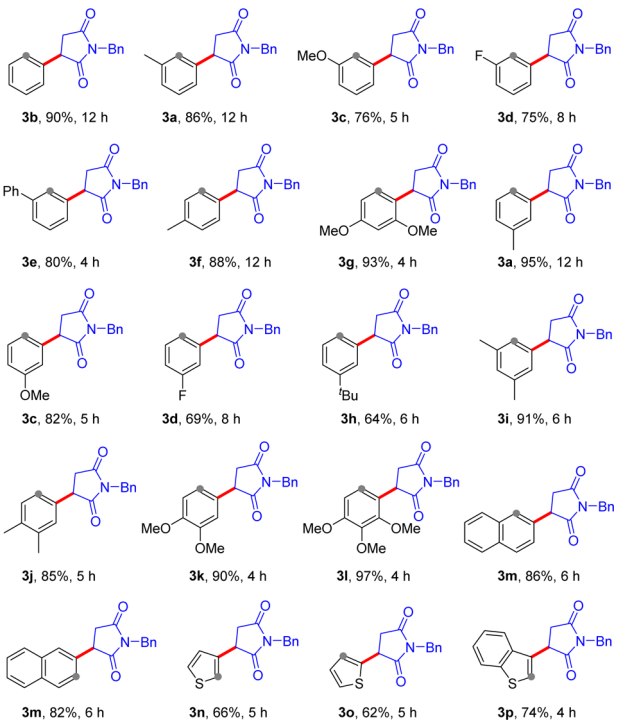
entry	deviation from standard conditions	yield [%][b]
1	without Cy_3PO	73
2	**none**	**95**
3	without Ru(II) catalyst	0
4	without $NaHCO_3$	0
5	with (*p*-cymene)$Ru(PPh_3)Cl_2$ catalyst	-[c]
6	Na_2CO_3 instead of $NaHCO_3$	42
7	K_2CO_3 instead of $NaHCO_3$	49
8	K_3PO_4 instead of $NaHCO_3$	63
9	Li_2CO_3 instead of $NaHCO_3$	trace[c]
10	$KHCO_3$ instead of $NaHCO_3$	46
11	NH_4HCO_3 instead of $NaHCO_3$	trace[c]
12	toluene instead of DCE	trace[c]
13	1,4-dioxane instead of DCE	12
14	chlorobenzene	9
15	DMF instead of DCE	-[c]
16	DME instead of DCE	-[c]
17	MeOH instead of DCE	-[c]
18	at 120 °C	55
19	at 80 °C	64
20	Ph_3P instead of Cy_3PO	52

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), Cy_3PO (10 mol %), base (1 equiv), solvent (2 mL), 12 h. [b]Isolated yields. [c]TLC showed the presence of both starting materials **1a** and **2a**.

Scheme 2. Scope of Hydroarylation of Maleimides with Respect to Benzoic Acids[a]



1 2a 3



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), Cy_3PO (10 mol %), $NaHCO_3$ (1 equiv), DCE (2 mL). Yields of isolated products are given.

when Hartwig and Zhao, Ackermann, and Gooßen independently disclosed hydroarylation of alkyne via a C−H alkenylation−decarboxylation sequence and demonstrated that, in contrast to other transition-metal catalysts, ruthenium catalyst could facilitate the decarboxylation process under mild conditions without the aid of copper or silver metal.[13] Encouraged by these works and our recent interest in the ruthenium catalysis,[14a,b] we posited that reactions of aromatic carboxylic acids with maleimides under Ru(II) catalysis could be an effective transformative alternative for the hydroarylation of maleimides (Scheme 1b).[15] Herein, we report the development of this approach and present the first example of Ru(II)-catalyzed, precious metallic additive free decarboxylative hydroarylation of maleimides en route to synthesis of 3-aryl succinimides under mild conditions. Notably, the reaction is highly regiospecific and overrides competitive formal [4 + 2] heterocyclization, Heck type addition, and ipso-substitution processes (Scheme 1b).

Our investigation commenced by studying the model reaction of *p*-toluic acid **1a** with maleimide **2a** based on carboxylate-directed *ortho* C−H alkylation and a concomitant decarboxylation process (Table 1, a detailed summary is provided in the Supporting Information). The bench-stable [Ru(*p*-cymene)Cl_2]$_2$ was considered as a preferred catalyst. To our delight, when a mixture of **1a** and **2a** was exposed to ruthenium(II) catalyst (5 mol %) in the presence of $NaHCO_3$ base in DCE solvent at 100 °C, the hydroarylation reaction proceeded efficiently, delivering aryl succinimide **3a** in 73% isolated yield with desired *meta*-selectivity (Table 1, entry 1). Previously, we have found an improved reactivity of ruthenium(II) catalyst in the presence of phosphine oxide.[14a,c] Thus, Cy_3PO (10 mol %) was introduced into the reaction conditions, and a remarkable enhancement in yield was observed, rendering the desired product in 95% isolated yield (entry 2). The reaction was unfruitful in the absence of either [Ru(*p*-cymene)Cl_2]$_2$ or $NaHCO_3$, signifying indispensable roles of catalyst and base (entries 3 and 4). The reaction completely shut down when [Ru(*p*-cymene)Cl_2]$_2$ catalyst was replaced with (*p*-cymene)$Ru(PPh_3)Cl_2$ (entry 5). Screening of other bases gave inferior results (entries 6−11). Except DCE, other tested solvents did not affect the hydroarylation process (entries 12−17). The output was also strongly governed by the reaction temperature; the yield reduced significantly upon lowering (80 °C) as well as increasing (120 °C) the reaction temperature (entries 18 and 19). Examination of a phosphine ligand such as Ph_3P had a deleterious effect (entry 20).

Under the optimized reaction conditions, the scope of this hydroarylation process was explored (Scheme 2). The reaction is quite general. Parent benzoic acid and a broad range of aromatic carboxylic acids bearing electron-donating as well as electron-withdrawing groups at *ortho*-, *meta*-, and *para*-positions reacted smoothly with maleimide **2a** to afford 3-aryl succinimides **3a−h** in high yields (Scheme 2, 64−95% yields). Di- and trisubstituted hindered benzoic acids also effectively participated in this reaction delivering desired products **3i−l** in excellent yields. In general, the reaction proceeded faster with

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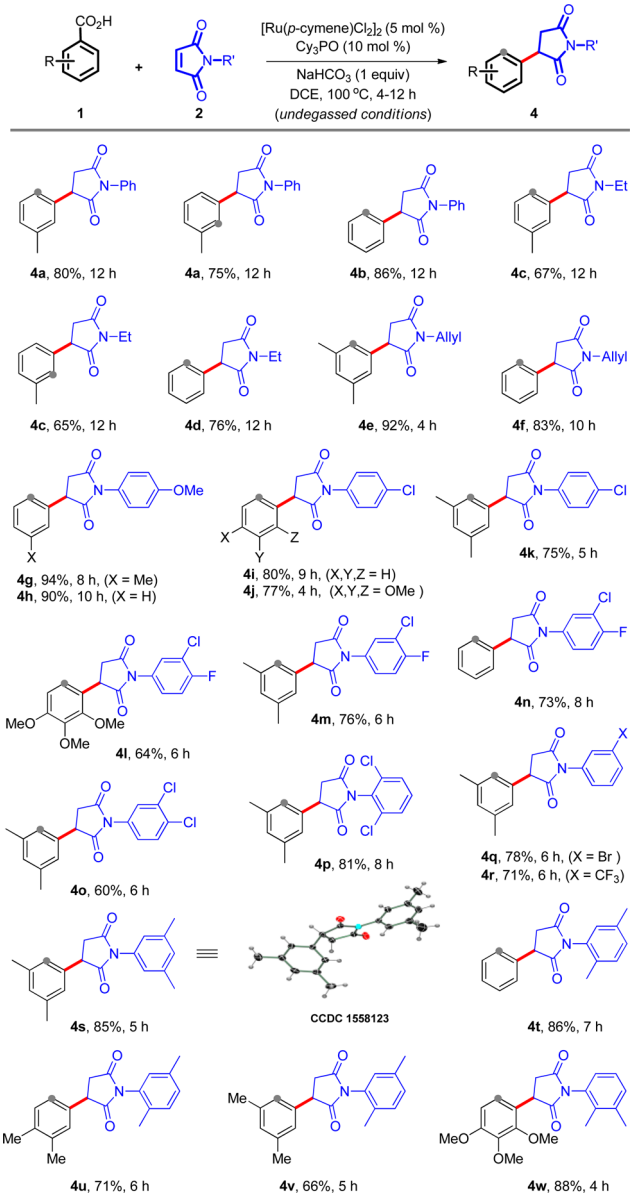
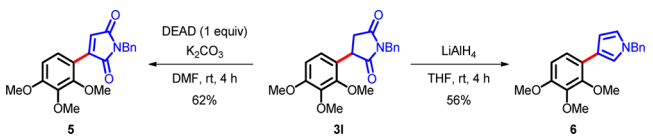
Scheme 3. Scope of the Hydroarylation Process with Respect to Maleimides[a]

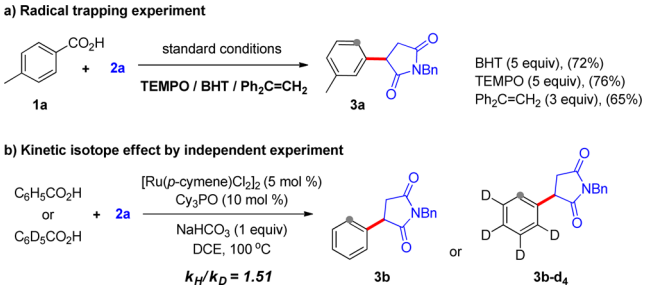


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), [Ru(*p*-cymene)-$Cl_2]_2$ (5 mol %), Cy_3PO (10 mol %), $NaHCO_3$ (1 equiv), DCE (2 mL). Yields of isolated products are given.

Scheme 4. Synthesis of Maleimide and Pyrrole Heterocycle



Scheme 5. Control Experiments



electron-rich aromatic carboxylic acids. The regioselectivity pattern of this process is alluring. The reactions with *ortho*- (**3a**, **3c**−**e**) and *para*-substituted benzoic acids (**3a**,**c**,**d**, and **3h**) provided *meta*-functionalized products. In the case of *meta*-substituted benzoic acids, the hydroarylation occurred at the less hindered site to provide *para*-functionalized products exclusively (**3f**,**g**). Satisfyingly, both 1- and 2-naphthoic acid, respectively, furnished 86% and 82% yields of the succinimide **3m**. Furthermore, heteroaryl carboxylic acids such as thiophenecarboxylic acids (**1n**−**o**) and benzothiophene-2-carboxylic acid (**1p**) were also suitable for this process and offered 3-heteroarylated succinimides **3n**−**p** in good yields.

The scope of this reaction with respect to maleimides was also investigated (Scheme 3). The reactions of maleimides having *N*-phenyl (**4a**,**b**), *N*-alkyl (**4c**,**d**), and sensitive *N*-allyl (**4e**,**f**) functionalities readily furnished desired products in high yields with envisioned *meta*-selectivity. Evaluation of electronic effects on the aryl ring of *N*-aryl maleimides turned out marginal; both electron-donating substituents such as methoxy (**4g**,**h**) and methyl (**4s**−**w**) and electron-withdrawing groups, for instance fluoro (**4l**−**n**) and trifluoromethyl (**4r**), effortlessly led to the desired products. Compound **4s** was crystallized, and the X-ray analysis unambiguously established the observed regioselectivity. The protocol tolerates different halogen substituents (**4i**−**q**), which are useful synthetic handles for further functionalization to complex molecules.

The synthetic utility of this process was further highlighted through the oxidation of succinimide **3l** to produce 3-arylated maleimide **5** in 62% yield (Scheme 4). It is worth noting that 3-aryl maleimides are an emerging scaffold for drug discovery and diagnosis.[16] Synthesis of pyrrole heterocycle **6** was also accomplished by treating **3l** with $LiAlH_4$ in THF at room temperature (Scheme 4).

To gain insight into the reaction mechanism, various controlled experiments were performed (Scheme 5). The presence of radical scavengers such as TEMPO, BHT, and 1,1-diphenylethylene did not significantly affect the hydroarylation process, and thus, the involvement of radical species is very unlikely (Scheme 5a). The kinetic isotope effect studied through independent parallel experiment revealed k_H/k_D = 1.51, indicating that the C−H bond breaking may be involved in the rate-determining step (Scheme 5b). In-depth mechanistic investigations are underway to fully elucidate the reaction pathway.

In summary, we have disclosed direct hydroarylation of maleimides through regioselective *ortho*-alkylation of benzoic acids using carboxylic acid as a traceless directing group. The reaction is catalyzed by readily available Ru(II) catalyst and insensitive to air and moisture, avoids the use of metallic oxidants or cocatalysts, and produced biologically relevant 3-aryl succinimide in high yields under mild conditions. Notably, this simple protocol, while circumventing other putative organometallic processes, offers formal *meta*-functionalized products from *ortho*- and *para*-substituted benzoic acids and *para*-functionalized adducts from *meta*-substituted substrates. We anticipate that this reaction will find application in the synthesis of important pharmaceuticals. Furthermore, the

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effectiveness of this strategy for various C−H bond functionalizations is currently being explored in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01964.

Complete experimental details and characterization data for the prepared compounds (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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