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Nickel-Catalyzed Oxidative Decarboxylative Annulation for the Synthesis of Heterocycle-Containing Phenanthridinones

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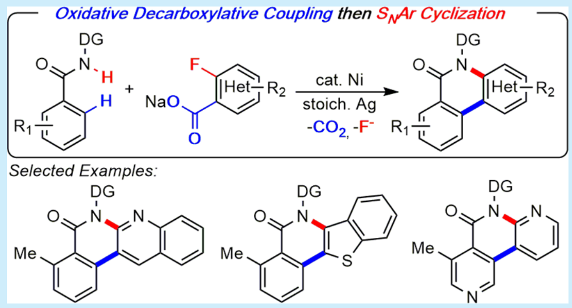
Supporting Information

ABSTRACT: A nickel-catalyzed oxidative decarboxylative annulation reaction of simple benzamides and (hetero)aromatic carboxylates has been developed. This reaction provides access to a large array of phenanthridinones and their heterocyclic analogues, highlighting the utility and versatility of oxidative decarboxylative coupling strategies for C−C bond formation.

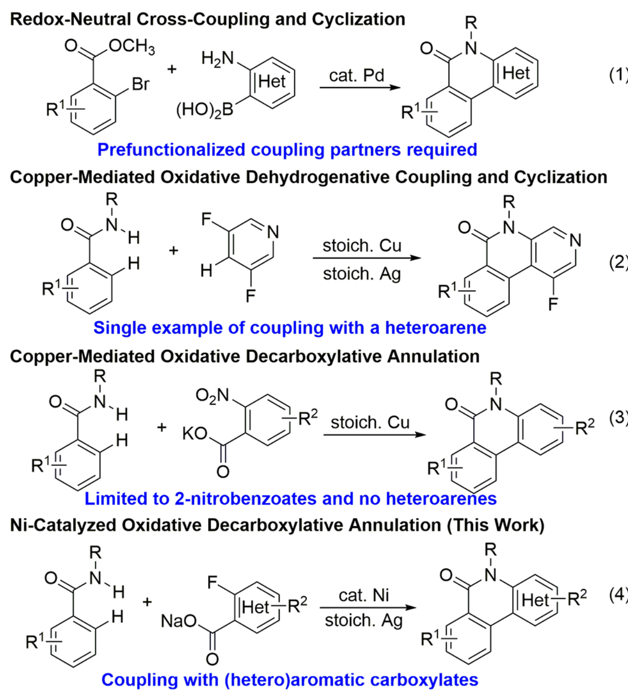


Phenanthridinones are key structures found in a variety of natural products and biologically active compounds[1] including antiviral and anticancer therapeutics,[2] aurora kinase,[3] and polymerase (PARP) inhibitors[4] as well as serve as important building blocks toward complex polycyclic targets.[5] The corresponding heterocycle-containing phenanthridinones, however, are less explored due, in part, to a shortage of efficient synthetic routes to these compounds. Because of the prevalence of heterocycles with important biological properties,[6] the ability to access such heterocycle-containing phenanthridinones could provide new libraries of compounds with novel properties and activities.

Typically, construction of these scaffolds[7,8] relies on traditional cross-coupling reactions,[3] such as Suzuki−Miyaura coupling (Scheme 1, eq 1) or Buchwald−Hartwig amination reactions.[9] These methods, however, require prefunctionalized aryl halide and arylboronic ester or acid coupling partners. Alternatively, oxidative C−H arylation routes enable the utilization of simple arenes as coupling partners,[10] yet we are aware of only a single report in which efficient incorporation of heteroarenes into phenanthridinone structures is achieved (Scheme 1, eq 2).[10f] Baidya and co-workers have reported the copper-mediated dehydrogenative annulation of amides with fluorinated arenes in which 3,5-difluoropyridine is also a competent coupling partner (Scheme 1, eq 2).

More recently, transition-metal catalyzed oxidative decarboxylative coupling (ODC) reactions[11] have been applied to the synthesis of phenanthridinones. Wang and co-workers reported the synthesis of phenanthridinones utilizing a Pd-catalyzed ODC strategy to effect the coupling of aryl acyl peroxides in fair yields.[12] Similarly, Miura[13] and co-workers reported an analogous copper-mediated ODC reaction for the synthesis of phenanthridinones from *ortho*-nitrobenzoates (Scheme 1, eq 3). Unfortunately, both catalyst systems are limited to select benzoic acids, and heteroaryl carboxylates are

Scheme 1. Selected Examples of Synthetic Routes to Phenanthridinones



ineffective coupling partners under these reported conditions. We have recently developed a new nickel catalyst system for the efficient ODC reactions of a large scope of heteroaryl carboxylates.[14] In this work, we highlight the utility of a related nickel-catalyzed oxidative decarboxylative annulation strategy

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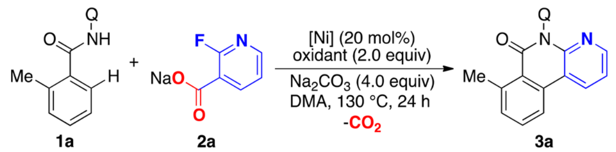
Org. Lett. XXXX, XXX, XXX−XXX

for the synthesis of heterocycle-containing phenanthridinones (Scheme 1, eq 4).

During the course of our previous studies, we observed the formation of the oxidative decarboxylative annulation product **3** in low yields when *ortho*-fluoro substituted (hetero)aromatic carboxylates **2** were employed as coupling partners. Following this initial discovery, we focused our attention on optimizing the conditions for the coupling of quinolinylbenzamide **1a**[15] with the 2-fluoronicotinic carboxylate **2a** (Table 1). $Ni(OAc)_2\cdot$

Table 1. Optimization of Reaction Conditions[a]



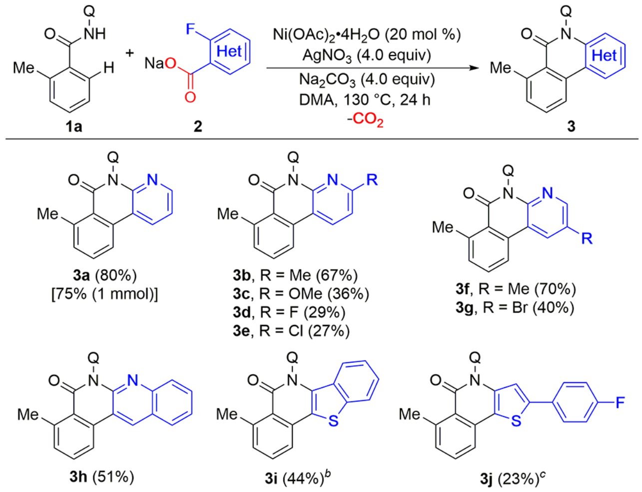
entry	[Ni]	oxidant[b]	yield **3a** (%)[c]
1	$Ni(acac)_2$	Ag_2CO_3	4
2	$Ni(OTf)_2$	Ag_2CO_3	3
3	$NiCl_2$	Ag_2CO_3	5
4	$Ni(OAc)_2\cdot 4H_2O$	Ag_2CO_3	25
5	$Ni(OAc)_2\cdot 4H_2O$	AgOPiv	63
6	$Ni(OAc)_2\cdot 4H_2O$	AgOAc	51
7	$Ni(OAc)_2\cdot 4H_2O$	Ag_3PO_4	35
8	$Ni(OAc)_2\cdot 4H_2O$	$AgNO_3$	72
9[d]	**$Ni(OAc)_2\cdot 4H_2O$**	**$AgNO_3$**	**81 (80)**[e]
10[d]	—	$AgNO_3$	0
11[d]	$Ni(OAc)_2\cdot 4H_2O$	—	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol) in DMA (2 mL). Q = 8-quinolyl. [b]4.0 equiv of Ag were used in all reactions (0.4 mmol of Ag_2CO_3, 0.8 mmol of AgOPiv, AgOAc, and $AgNO_3$, and 0.26 mmol of Ag_3PO_4). [c]^1H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. [d]**2a** (0.4 mmol). [e]Isolated yield.

$4H_2O$ was identified to be the most efficient precatalyst generating **3a** in 25% yield (Table 1, entry 4), while all other Ni salts tested provided only low yields of the product (<10%, Table S1). Replacing Ag_2CO_3 with $AgNO_3$ was found to dramatically increase the yield of **3a** to 72% (Table 1, entry 8). Finally, increasing the loading of **2a** to 2 equiv led to an increase in yield of **3a** to 81% (Table 1, entry 9). No coupled product **3a** was observed when either nickel or silver was omitted from the reaction (entries 10 and 11, respectively). Therefore, the optimized reaction conditions employ 20 mol % $Ni(OAc)_2\cdot 4H_2O$, $AgNO_3$ (4.0 equiv), and Na_2CO_3 (4.0 equiv) in DMA at 130 °C for 24 h.

With the optimized reaction conditions in hand, we turned our attention to the heteroaromatic carboxylate coupling partners (Scheme 2). We focused our attention on halide-substituted 2-fluoronicotinic carboxylates because they are the most accessible from existing synthetic routes.[16] The reaction is compatible with both electron-withdrawing (**2d**, **2e**, **2g**) and electron-donating (**2b**, **2c**, **2f**) substituents on the nicotinic carboxylate. Substitution in the 6-position (**2b**−**2e**) resulted in lower yields than that obtained with the parent (**2a**) nicotinate, while substitution in the 5-position was better-tolerated (**2f** and **2g**). This reaction system also tolerates bromo- and chloro-substitution allowing for further functionalization of the cyclized products **3e** and **3g**. Quinoline and thiophene scaffolds are found in pharmacologically active compounds[17] and material sciences,[18] and the corresponding carboxylates **2h**−**2j** also proved to be competent coupling partners under

Scheme 2. Scope of Heteroaromatic Carboxylate Coupling Partners in the Ni-Catalyzed Oxidative Decarboxylative Annulation Reaction[a]

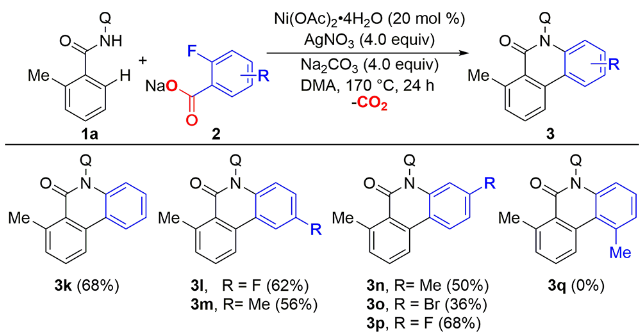


[a]Isolated yields. Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol) in DMA (2 mL). Q = 8-quinolyl. [b]130 °C for 8 h then 170 °C for 16 h. [c]170 °C.

these catalytic conditions. Finally, this protocol could also be conducted on a 1 mmol scale without a significant reduction in yield (75% of **3a**).

We then examined the scope of the substituted benzoate coupling partners (Scheme 3). The decarboxylative annulation

Scheme 3. Scope of Benzoate Coupling Partners in the Ni-Catalyzed Oxidative Decarboxylative Annulation Reaction[a]



[a]Isolated yields. Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol) in DMA (2 mL). Q = 8-quinolyl.

of *ortho*-fluorobenzoates proceeded smoothly at 170 °C when a variety of electron-donating (**2m**, **2n**) and electron-withdrawing substituents (**2l**, **2o**, **2p**) were included. Unfortunately, the di-*ortho*-substituted benzoate **2q** was an ineffective coupling partner under these reaction conditions (Chart S1).

Finally, we explored the scope of substituted benzamide coupling partners (Scheme 4). Although other directing groups have proven valuable in related catalytic coupling reactions,[19] this decarboxylative annulation reaction appears to be limited to the 8-aminoquinoline directing group (Chart S1), which can be removed under oxidizing conditions.[20] Substrates with electron-donating groups *para* to the benzamide functionality (**1r**, **1s**) afforded higher yields (75% and 71%, respectively) than those bearing electron-withdrawing groups (**1t**, 63%).

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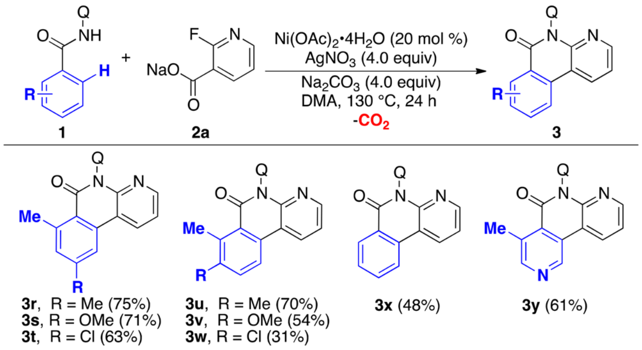
Scheme 4. Scope of Benzamide Coupling Partners in the Ni-Catalyzed Oxidative Decarboxylative Annulation Reaction[a]

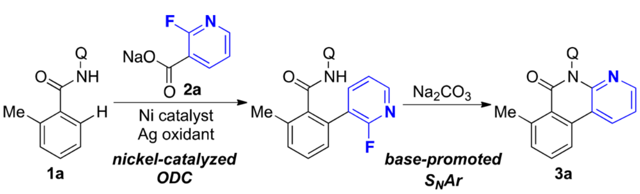


[a]Isolated yields. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol) in DMA (2 mL). Q = 8-quinolyl.

Similarly, substrates with electron-donating groups in the *meta*-position (**1u**, **1v**) provided higher yields (70% and 54% respectively) than those with electron-withdrawing functionalities (**1w**, 31% yield). It should be mentioned that the absence of *ortho*-substitution resulted in a lower yield (**1x**, 48%). This new catalyst system also tolerates heterocyclic benzamide **1y** providing the opportunity to access additional classes of substituted phenanthridinones with this methodology.

We hypothesized that this new decarboxylative annulation reaction likely proceeds via an initial oxidative decarboxylative heteroarylation step,[14] followed by an S_NAr-type ring closing reaction[10f,13,21] (Scheme 5). To explore the possibility of such

Scheme 5. Proposed Pathway for the Ni-Catalyzed Oxidative Decarboxylative Annulation Reaction[a]

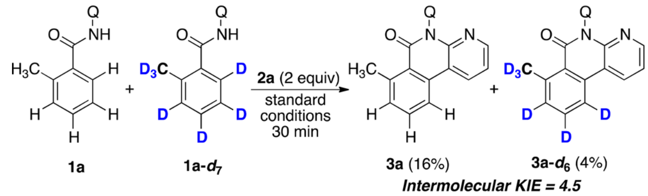


[a]Q = 8-quinolyl.

a pathway, we conducted a series of control experiments. First, we performed the standard reaction in the presence of common radical trapping reagents. The reaction of **1a** and **2a** in the presence of 1.0 equiv of TEMPO or 9,10-dihydroanthracence resulted in only a slight decrease in the yields (74% and 78% respectively, Table S7). These data are consistent with the absence of trappable radical intermediates.[22]

Next, to gain insight into the C−H activation step, we carried out a pair of deuterium-exchange and kinetic isotope effect (KIE) experiments (Scheme 6). First, we measured the KIE from an intermolecular competition experiment. The reaction of an equimolar mixture of **1a** and **1a-*d*$_7$** was treated under the standard reaction conditions. After 30 min, the product was obtained as a mixture of **3a** and **3a-*d*$_6$** in 16% and 4% yields, respectively, giving a KIE of 4.5. We then carried out a hydrogen−deuterium exchange experiment of the deuterated benzamide **1a-*d*$_7$**. When the standard reaction is conducted with **1a-*d*$_7$** for 30 min, less than 1% H incorporation is observed. These combined data suggest that the cleavage of

Scheme 6. Kinetic Isotope Effect in the Ni-Catalyzed Oxidative Decarboxylative Annulation Reaction[a]

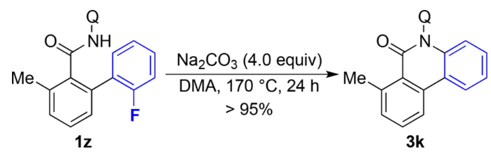


[a]Q = 8-quinolyl.

the C−H bond is an irreversible process, similar to that observed in our prior studies of the Ni-catalyzed ODC reaction.[14]

Finally, we explored the C−N bond-forming step. Treatment of independently synthesized fluorinated biaryl benzamide **1z** with 4.0 equiv of sodium carbonate in the absence of both silver and nickel resulted in the formation of the cyclized product **3k** in nearly quantitative yield (>95%, Scheme 7).

Scheme 7. Base-Promoted S_NAr-Type Cyclization[a]



[a]Q = 8-quinolyl.

Taken together, these data are consistent with a pathway involving initial Ni-catalyzed oxidative decarboxylative arylation followed by a based-promoted ring closing reaction as proposed in Scheme 5.

In conclusion, we have developed the first nickel-catalyzed oxidative decarboxylative annulation reaction for the synthesis of heterocycle-containing phenanthridinones. This new method is effective not only for the coupling of heteroaromatic carboxylates but also for that of *ortho*-fluorobenzoates. As a result, this reaction allows access to a series of new heterocycle-containing phenanthridinones of potential biological importance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03144.

Experimental procedures and characterization data for starting materials and products (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX

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