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Rh(I)-Catalyzed C6-Selective Decarbonylative Alkylation of 2-Pyridones with Alkyl Carboxylic Acids and Anhydrides

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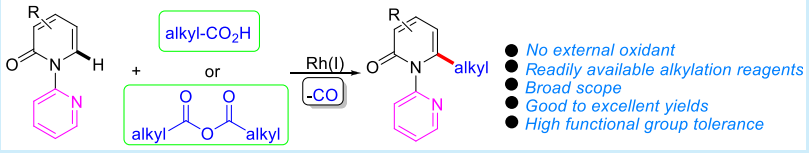


ABSTRACT: A Rh-catalyzed chelation-assisted C6-selective C−H activation/alkylation of 2-pyridones with readily available alkyl carboxylic acids or anhydrides is introduced. The reaction proceeds via substrate decarbonylation. This approach merges C−H functionalization with readily available anhydrides, allowing for the efficient synthesis of various C6-alkylated 2-pyridones with good functional group tolerance.

The 2-pyridone motif is found in numerous bioactive natural products and synthetic compounds (Figure 1)

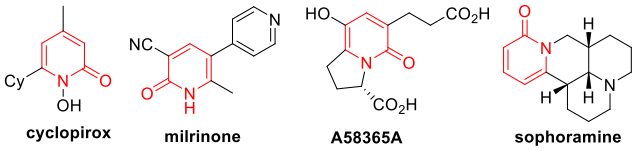
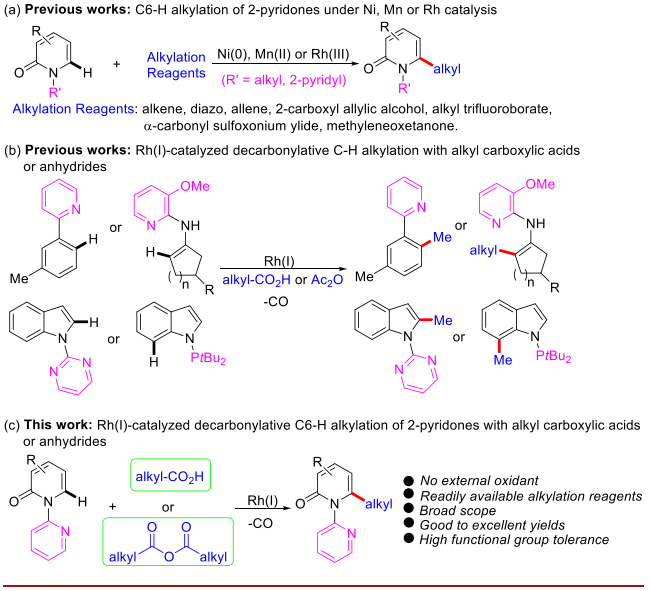


Figure 1. Biologically active 2-pyridones.

and plays an important role in their bioactivity.[1] Accordingly, there is long-standing interest in the development of efficient methods for their synthesis.[2] Among approaches to functionalized 2-pyridones, the elaboration of the parent heterocycle is efficient and frequently adopted. Early studies focused on transition-metal-catalyzed cross-coupling reactions of halogenated 2-pyridones to access functionalized derivatives.[3] More recently, catalytic C−H functionalizations with transition metals at the C3, C4, C5, and C6 positions[4−7] have gained traction.[8] In particular, advances in the transition-metal-catalyzed C6-selective C−H alkylation of 2-pyridones (Scheme 1a) have been reported.[7] Nakao[7a,b] and Cramer[7c,k] reported direct C6-alkylation of 2-pyridones with alkene substrates under Ni/Al cooperative catalysis. Notably, easily attachable and detachable pyridine-based directing groups on the nitrogen of the 2-pyridone facilitated metal-catalyzed C−H alkylation (Ni, Mn, Rh, and Co).[7d−k,m] Using this strategy, researchers conducted the C−H activation/functionalization with diazomalonates,[7d] alkyl trifluoroborates,[7e] 3-bromo-2,2-difluoropropene,[7f] alkenes,[7g,l] methyleneoxetanones,[7h] allenes,[7i] α-carbonyl sulfoxonium ylides,[7j] 2-carboxyl allylic alcohols,[7k] and both enone and aldehyde[7m] coupling partners

Scheme 1. Catalytic Direct C−H Alkylation of 2-Pyridones at the C6 Position



at C6. Despite these advances, there remains room for improvement, in terms of catalytic efficiency, substrate scope,

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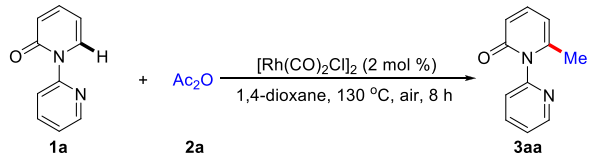
availability of the alkylation reagents, and functional group tolerance.

The availability, stability, diversity, and low cost of alkyl carboxylic acids has resulted in their widespread use.[9] Since the pioneering work of Minisci, the decarboxylative alkylation of heteroarene C−H bonds with alkyl carboxylic acids has been a topic of sustained interest.[10,11] These reactions exhibit substrate-controlled site selectivity. Transition-metal catalysis with directing groups, however, enable greater C−H selectivity and functionalization.[12] The first chelation-assisted alkylation of *N*-pyrimidyl indolines, 2-phenylpyridines, and azobenzenes with alkyl carboxylic acids via decarboxylation was achieved by Jain's group using a Pd(II) catalyst. The catalyst loading, excessive oxidant, and narrow scope of alkyl carboxylic acid coupling partner left room for improvement.[13] Shi and Sun and their co-workers, as well as our team, recently disclosed Rh(I)-catalyzed chelation-assisted decarbonylative C−H alkylation of pyridyl-substituted arenes, cyclic enamines, and indoles with alkyl anhydrides in the absence of added oxidant (Scheme 1b).[14a−c] The alkyl anhydride partners were conveniently generated from carboxylic acids. In one example, Shi and co-workers realized the Rh(I)-catalyzed directed C7-selective decarbonylative methylation of indoles using acetic anhydride as the methyl group source.[14d] This procedure was incompatible with other alkyl anhydrides, possibly due to β-hydride elimination. We recently achieved the Rh(I)-catalyzed regioselective and stereoselective C6-alkenylation of 1-(2-pyridyl)-2-pyridones with alkenyl and conjugated polyenyl carboxylic acids.[7n] We next envisage that 1-(2-pyridyl)-2-pyridones might undergo Rh(I)-catalyzed decarbonylative C6-alkylation with alkyl carboxylic acids or anhydrides. Such a method could offer facile access to 6-alkylated 2-pyridones. Herein, we describe development of a selective C6-alkylation of 1-(2-pyridyl)-2-pyridones that proceeds in high yields with a wide substrate scope and good functional group tolerance (Scheme 1c).

Considering the importance of methylation reactions in medicinal chemistry,[15] the methylation of 1-(2-pyridyl)-2-pyridone (**1a**) with acetic anhydride (**2a**) was selected for the identification of the optimal alkylation conditions (Table 1). By evaluating different parameters, the optimal reaction conditions were $[Rh(CO)_2Cl]_2$ (2 mol %) in 1,4-dioxane at 130 °C for 8 h, leading to product 6-ethyl-2*H*-[1,2′-bipyridin]-2-one (**3aa**) in 92% isolated yield (Table 1, entry 1). Other frequently employed Rh(I) complexes proved to be ineffective (Table 1, entries 2 and 3). Using $[Rh(CO)_2Cl]_2$ and switching solvents from 1,4-dioxane to DCE, toluene, or PhCl resulted in lower yields (14%−33%; see Table 1, entries 4−6). Lowering the reaction temperature to 120 °C or halving the catalyst loading decreased the yield of **3aa** by more than 20% (Table 1, entries 7 and 8). Not surprisingly, control experiments in the absence of $[Rh(CO)_2Cl]_2$ did not provide **3aa** (Table 1, entry 9). Notably, using free 2-pyridone or 2-pyridone substrates bearing other substituents on the nitrogen (Me, Bn, Ph, 2-pyrimidyl, Ac, Piv, or Ts) did not form coupling products, highlighting the importance of the 2-pyridyl directing group under these conditions (see Table S3 in the Supporting Information).

While alkyl carboxylic anhydrides are potentially useful starting materials for alkylation reactions, there are drawbacks to their use. These include (1) they are rarely commercially available, (2) they are hydrolytically unstable, and (3) their preparation and isolation is often tedious and/or employs

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	deviation	yield of 3aa[b] (%)
1	none	92
2	$[Rh(COD)Cl]_2$ instead of $[Rh(CO)_2Cl]_2$	22
3	$[Rh(COD)_2]OTf$ instead of $[Rh(CO)_2Cl]_2$	57
4	DCE as the solvent	14
5	toluene as the solvent	33
6	PhCl as the solvent	21
7	Reaction temperature 120 °C	73
8	$[Rh(CO)_2Cl]_2$ (1 mol %)	54
9	without $[Rh(CO)_2Cl]_2$	0
10[c]	in situ generation of anhydride from PivCl and AcOH	32
11[c]	in situ generation of anhydride from Piv_2O and AcOH	90
12[c]	in situ generation of anhydride from Boc_2O and AcOH	39
13[c,d]	in situ generation of anhydride from Boc_2O, PivOH, and AcOH	91

[a]General reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), $[Rh(CO)_2Cl]_2$ (2 mol %), 1,4-dioxane (2.0 mL), 130 °C, 8 h. [b]Isolated yield. [c]AcOH (0.22 mmol) and activator (0.24 mmol) and were employed. [d]AcOH (0.22 mmol), Boc_2O (0.24 mmol), and PivOH (0.24 mmol) were employed.

corrosive or toxic reagents. To circumvent these shortcomings, researchers have used carboxylic acids in combination with in situ activation.[14,16] For our chemistry, we explored the feasibility of in situ formation of acetic anhydride from acetic acid and several activators. Among activators tested (Table 1, entries 10−12), commercially available Piv_2O proved the best choice (Table 1, entry 11). Interestingly, the combination of Boc_2O, PivOH and AcOH also performed very well, affording **3aa** in 91% yield (Table 1, entry 13). In view of the high price of Piv_2O, the combination of Boc_2O and PivOH was used moving forward.

We next proceeded to explore the methylation of a series of 2-pyridones with **2a**. As illustrated in Scheme 2, a range of 3- and 4-substituted 2-pyridones (**1b−1l**) bearing electron-rich and electron-deficient groups underwent smooth methylation to deliver products **3ba−3la** in 81%−92% yields. The structure of **3ga** was confirmed by single-crystal X-ray diffraction (CCDC 1834644, Scheme 2). Importantly, a variety of functional groups (OBn, F, Cl, Br, CF_3, CN, and CO_2Me) were tolerated. Despite the steric hindrance, the 5-substituted 2-pyridones (**1m−1q**) delivered products **3ma−3qa** in 54%−86% yield. In these reactions, electron-rich 2-pyridones generally exhibited slightly better yields. Furthermore, the disubstituted 2-pyridones **1r−1s**) provided products **3ra−3sa** in 72% and 81% yields. It is noteworthy that the installation of substituents on the pyridyl directing group did not affect the methylation, and products **3ta−3va** were obtained in 85%−89% yields. The versatility of this system was further reflected by the methylation of 3-(pyridin-2-yl)quinazolin-4(3*H*)-one (**1w**), 1-(pyridin-2-yl)quinolin-4(1*H*)-one (**1x**), and 4*H*-[1,2′-bipyridin]-4-one (**1y**) in 71%−82% yields.

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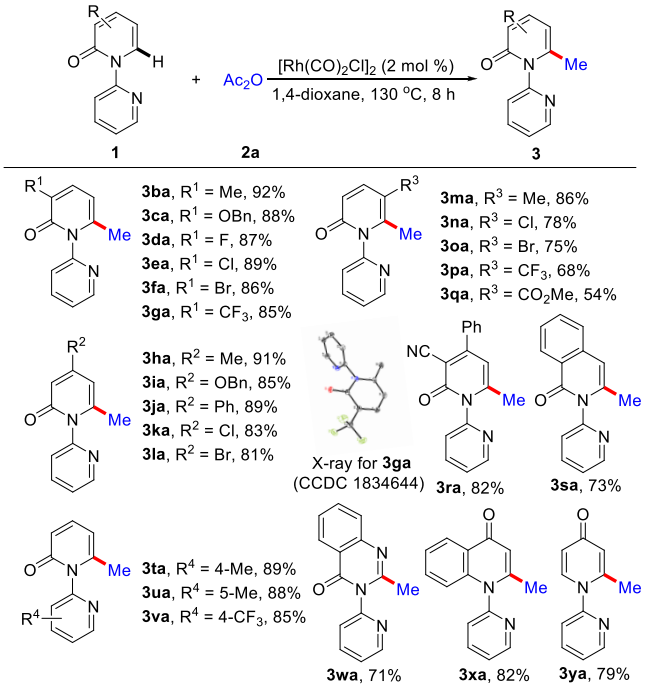
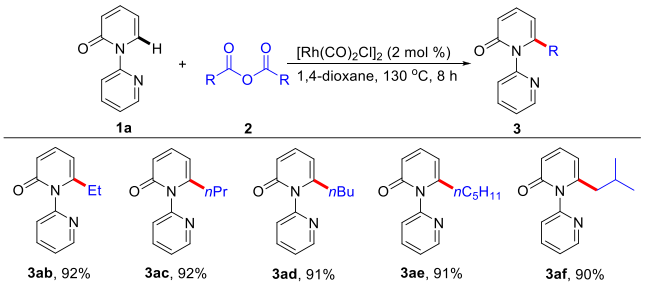
Scheme 2. Direct Methylation of 2-Pyridones with 2a[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), [Rh(CO)$_2$Cl]$_2$ (2.0 mol %), 1,4-dioxane (3.0 mL), 130 °C, 8 h, in air. [b]Isolated yield.

As shown in Scheme 3, several commercially available alkyl carboxylic anhydrides including propionic anhydride (**2b**), butyric anhydride (**2c**), valeric anhydride (**2d**), hexanoic anhydride (**2e**), and isovaleric anhydride (**2f**) reacted effectively with **1a** to afford C6-alkylated products **3ab**−**3af** in 90%−92% yields. The high yields indicate that *β*-hydride elimination does not compete with reductive elimination (see the mechanistic discussion below).

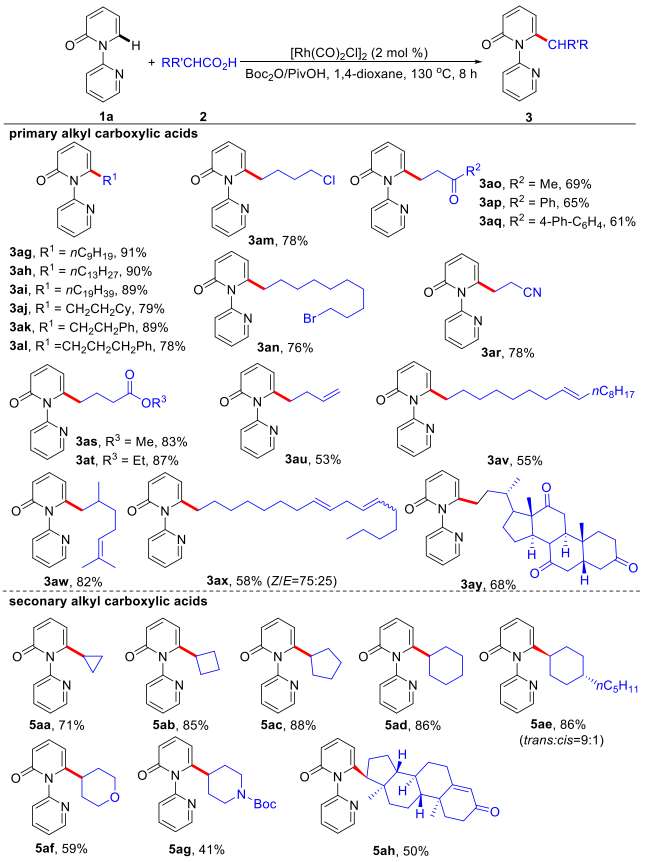
Scheme 3. Direct Alkylation of 1a with Alkyl Carboxylic Anhydrides[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), [Rh(CO)$_2$Cl]$_2$ (2.0 mol %), 1,4-dioxane (3.0 mL), 130 °C, 8 h, in air. [b]Isolated yield.

We next turned our attention to reactions of aliphatic acids with **1a** in the presence of Boc$_2$O and PivOH (Scheme 4). Regardless of the alkyl chain length, aliphatic acids **2g**−**2l** coupled efficiently with **1a** in 78%−91% yields. Sensitive functional groups, such as halogens (**2m** and **2n**), ketones (**2o**−**2q**), nitriles (**2r**), and esters (**2s** and **2t**), were compatible with the reaction conditions, leading to C6-alkylated 2-pyridones **3am**−**3at** in 61%−87% yields. Alkene-containing

Scheme 4. Direct Alkylation of 1a with Alkyl Carboxylic Acids[a,b]



[a]Reaction Conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), [Rh(CO)$_2$Cl]$_2$ (2.0 mol %), Boc$_2$O (0.24 mmol), PivOH (0.24 mmol), and 1,4-dioxane (3.0 mL), 130 °C, 8 h, in air. [b]Isolated yield.

carboxylic acids **2u**−**2x** gave **3au**−**3ax** in 53%−82% yields, leaving the alkene intact. Moreover, subjecting dehydrocholic acid (**2y**) to **1a** delivered product **3ay** in 68% yield, highlighting the applicability of this method to late-stage functionalization of complex molecules.

To demonstrate the utility of our catalytic system, secondary alkyl carboxylic acids were examined (Scheme 4). The cyclic acids (**4a**−**4e**) with 3-membered to 6-membered rings reacted smoothly with **1a**, affording **5aa**−**5ae** (71%−88% yield). For **5ae**, the stereochemistry of the major diastereomer was *trans* by ^{1}H NMR (*trans*:*cis* = 9:1). Tetrahydropyran-4-carboxylic acid (**4f**) and *N*-Boc-piperidine-4-carboxylic acid (**4g**) coupled, albeit in reduced yield (59% and 41%, respectively). The biologically relevant complex molecule, 3-keto-4-etiocholenic acid (**4h**), reacted to furnish **5ah** in 50% yield.

To demonstrate the synthetic utility, gram-scale reactions of **1a** with **2a** and **2k** were performed, affording **3aa** and **3ak** in 88 and 82% yields, respectively (Scheme 5a). Derivatizations of C6-alkylated 2-pyridone products were then explored. It was found that **3aa** underwent hydrogenation to give **6** in 85% yield. Removal of the 2-pyridyl directing group from **3aa** by the "quaternization and alcoholysis"[7a,8e] furnished the free 2-pyridone derivative **7** in 68% yield.

To gain insight into the reaction mechanism, a series of experiments were performed. First, analyzing the head gas of the reaction mixtures with [Rh(CO)$_2$Cl]$_2$ or [Rh(COD)$_2$]OTf (GC-TDC) confirmed CO byproducts, supporting a decarbon-

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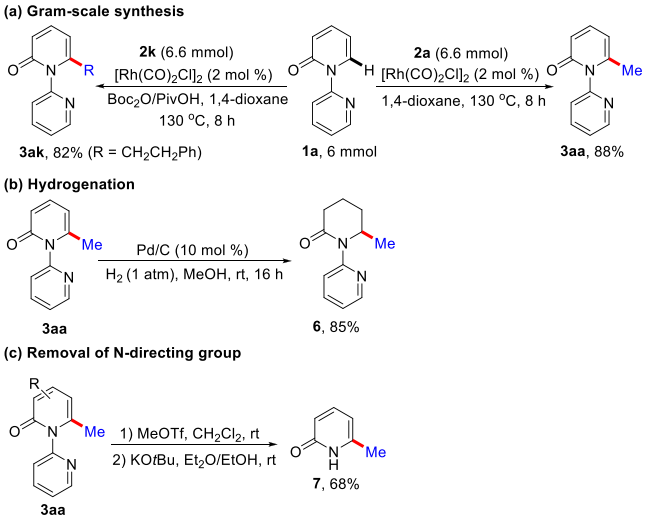
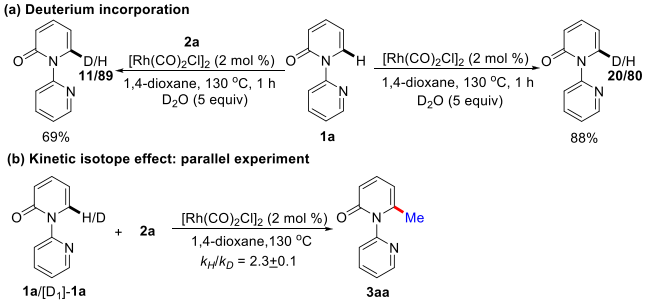
Scheme 5. Synthetic Applications



ylation step (see the Supporting Information for details). H/D scrambling experiments were performed by conducting the reaction in the presence of D_2O both with and without acetic anhydride (**2a**). The observation of deuterium in the recovered starting material of both reactions suggested that the C−H activation is reversible (Scheme 6a). A kinetic isotope effect

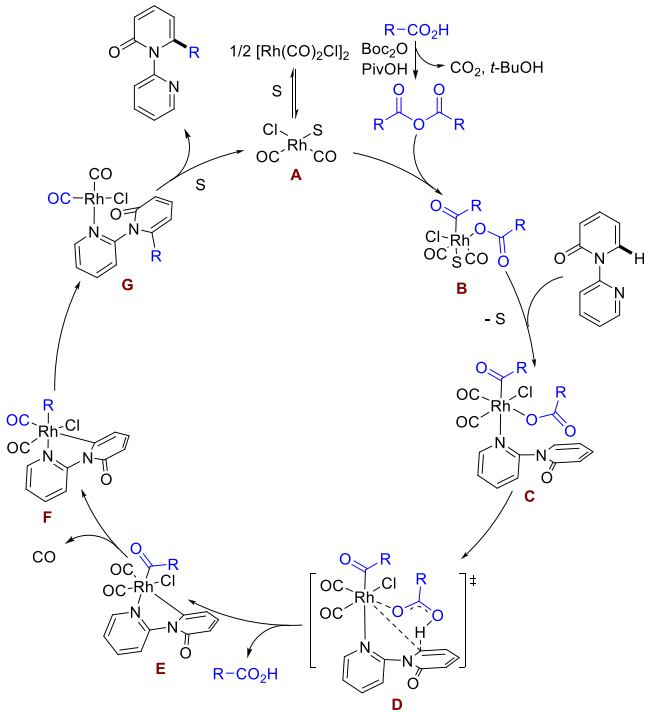
Scheme 6. Mechanistic Studies



(KIE) of 2.3 ± 0.1 was observed from the parallel reactions between **1a** or [D_1]-**1a** with **2a** (Scheme 6b), implying that the Rh-catalyzed C−H bond cleavage was involved in the turnover-limiting step.

On the basis of the aforementioned results and previous reports,[14,17] a plausible mechanism is proposed (Scheme 7). The reaction likely starts with dissociation of $[Rh(CO)_2Cl]_2$ in the presence of coordinating solvent or the pyridine-containing substrate (both denoted as S) with the formation of the monomer **A** [(S)$Rh(CO)_2Cl$]. Meanwhile, the acid reacts with Boc_2O and PivOH to generate the alkyl anhydride (either the symmetrical anhydride or the mixed anhydride with pivalic acid), which undergoes oxidative addition to Rh(I) **A** to give the Rh(III) intermediate **B**. Ligand exchange (for S = solvent) leads to **C** with the bound substrate. Subsequently, a concerted metalation deprotonation (CMD) by the carboxylate ligand via transition state **D** generates acid and the cyclometalated species **E** with the key Rh−C bond. The liberated acid from this step can react with Boc_2O or an anhydride intermediate (such as Piv_2O) to generate an anhydride poised to re-enter the catalytic cycle. Intermediate **E** is envisioned to undergo loss of coordinated CO and then deinsertion of the acyl to afford the Rh-alkyl intermediate **F**. Reductive elimination of **F**

Scheme 7. Plausible Mechanism



regenerates Rh(I) with the pyridine-bound product **G**. Finally, **G** undergoes exchange with the solvent or additional substrate to release the product and close the catalytic cycle. We favor this mechanism over initial oxidative addition of the 2-pyridone substrate to Rh(I) to give a Rh(III) intermediate because subsequent oxidative addition of the anhydride would give Rh(V), which is an unusual oxidation state for rhodium in such systems.

In summary, an efficient protocol for Rh-catalyzed chelation-assisted regioselective C6−H bond alkylation of 2-pyridones with abundant and inexpensive alkyl carboxylic acids or anhydrides is introduced. This protocol provides efficient access to C6-alkylated 2-pyridones, including those that are difficult to prepare with conventional methods. The utility of this reaction was demonstrated in drug synthesis and late-stage functionalization of complex molecules. The operational simplicity, broad scope, high functional-group compatibility, and ease of scalability make this reaction a practical and attractive alternative to the currently known methods for 2-pyridone alkylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01277.

Details of the experimental procedures, compound characterization data for all new compounds, and X-ray data for compound **3ga** (PDF)

FAIR data, including the primary NMR FID files for compounds **3aa**−**8** (ZIP)

Accession Codes

CCDC 1834644 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cam-

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Notes

The authors declare no competing financial interest.

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