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Rhodium-Catalyzed C4-Selective C−H Alkenylation of 2-Pyridones by Traceless Directing Group Strategy

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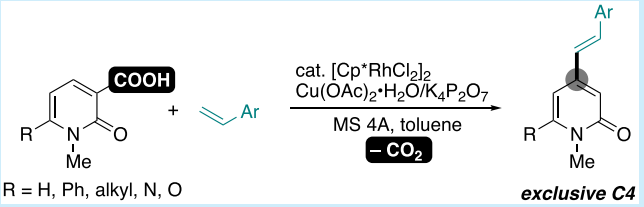
ABSTRACT: A rhodium-catalyzed C4-selective C−H alkenylation of 3-carboxy-2-pyridones with styrenes has been developed. The carboxylic group at the C3 position works as the traceless directing group, and the corresponding C4-alkenylated 2-pyridones are obtained exclusively with concomitant decarboxylation. Unlike the reported procedures, the exclusive C4 selectivity is uniformly observed even in the presence of potentially more reactive C−H bonds at the C5 and C6 positions. By using this strategy, the multiply substituted 2-pyridone can be prepared via sequential C−H functionalization reactions.



A 2-pyridone that has the unique unsaturated system in the *N*-containing six-membered ring is one of the most widely occurring heterocyclic cores in natural products, biologically active molecules, and pharmaceutical agents.[1] Such ubiquity has promoted the development of protocols for the preparation of 2-pyridones, particularly, the multiply substituted ones in synthetic communities. Strategically, the substituted 2-pyridone can be obtained either by functionalization of the pyridone ring[2] or by constructing the ring from suitable acyclic precursors.[1a] The former can provide a more convergent and modular approach to the target structure, but the reported methodologies largely relied on the stoichiometric halogenation and metalation.

In the past two decades, the metal-mediated C−H activation has been utilized for a wide range of transformations of C−H bonds to C−C or C−heteroatom bonds with better atom efficiency compared to the traditional cross-coupling methodologies.[3] In this context, synthetic chemists have been greatly prompted to adopt the 2-pyridone in the C−H activation.[4] However, there are four possibly reactive C−H bonds on the 2-pyridone ring, and the control of site selectivity is thus the most important and challenging issue. While the C3-, C5-, and C6-selective C−H functionalizations have greatly progressed to date, the selective access to the C−H bond at the C4 position still remains largely elusive (Figure 1). To the best of our knowledge, only a few successful examples include the in situ protection/lithiation strategy using CO_2 and BuLi/*t*-BuLi (Scheme 1a),[5] Ni/Al-cooperative alkylation with alkenes (Scheme 1b),[6] and sterically controlled Ir-catalyzed borylation with pinB−Bpin (Scheme 1c).[7] The former is the stoichiometric reaction and suffers from the harsh conditions associated with the strongly basic organolithium reagents. The latter two cases are more attractive catalytic reactions, but the high C4-selectivity is obtained only when the competitively reactive C−H at the C6 position is blocked by substituents.

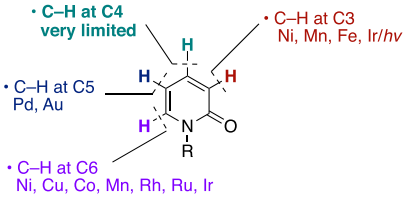


Figure 1. Reactivity profile of C−H bonds on 2-pyridone in metal-mediated C−H activation.

Thus, there still remains a large demand for the C4 site selectivity that is independent of the substituent. Herein, we report a Cp*Rh(III)-catalyzed, carboxylic acid directed highly C4-selective C−H alkenylation of 2-pyridones with styrenes (Scheme 1d): the key to success is the introduction of the carboxylic acid group at the C3 position, which works as the traceless directing group,[8] and the corresponding C4-alkenylated 2-pyridones are obtained with the concomitant decarboxylation. The introduction of the carboxyl group at the C3 position sometimes requires some synthetic steps (see the Supporting Information for details), but unlike the aforementioned precedents, the exclusive C4 selectivity is uniformly observed even in the presence of the potentially more reactive C−H bond at the C6 position. Additionally, the installation of the vinyl group is possible, which is difficult to achieve by other C4-selective C−H functionalization protocols and thus complementary and useful from the synthetic point of view.

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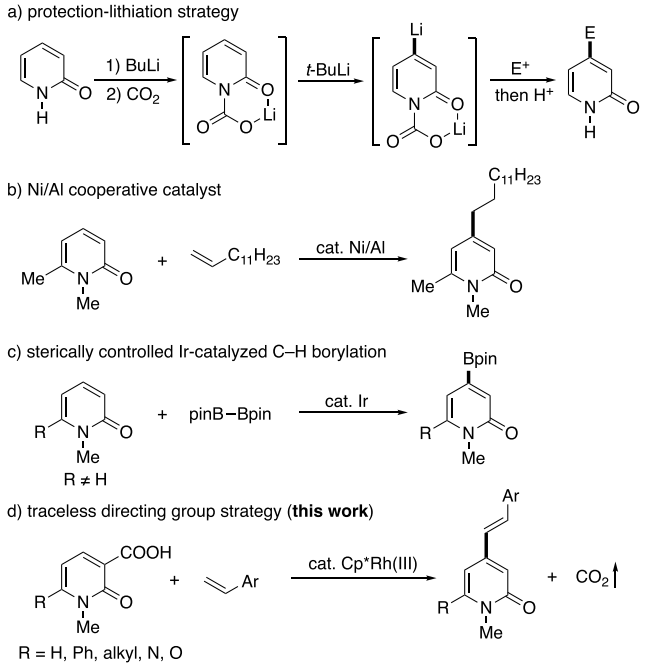
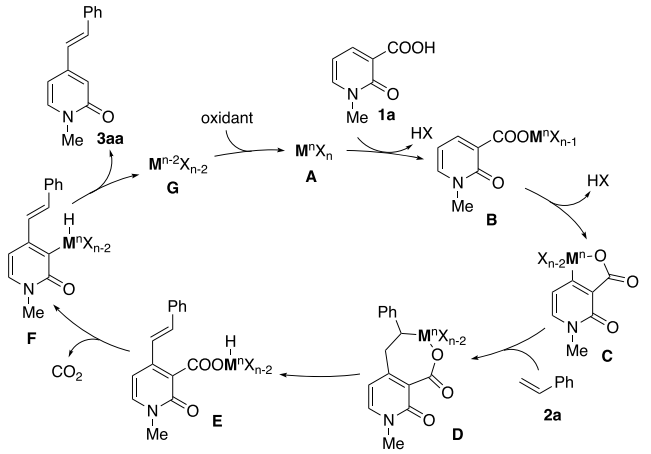
Scheme 1. C4-Selective C−H Functionalizations on 2-Pyridones



The blue print for the catalytic C4-selective C−H functionalization of 2-pyridones is based on the recent progress of carboxylic acid directed formal *meta*-selective C−H functionalization of benzenes, which was developed by our group,[9] Larrosa,[10] and others.[11] Our working hypothesis is shown in Scheme 2. The initial ligand exchange between the

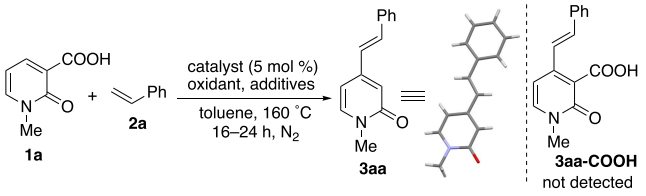
Scheme 2. Working Hypothesis of Carboxylic Acid-Directed C4-Selective C−H Alkenylation of 2-Pyridone 1a with Styrene 2a with Concomitant Decarboxylation



catalyst **A** and 3-carboxy-2-pyridone **1a** is followed by the directed C−H cleavage to form the corresponding metallacycle **C**. Subsequent insertion of styrene **2a** into the pyridone C(4)−**M** bond and *β*-H elimination afford the intermediate **E**. The C4-alkenylated product **3aa** then follows from decarboxylation and reductive elimination. The catalytic cycle is closed by the reoxidation of reduced **G** with the external oxidant.

On the basis of the above assumption, we started the optimization studies with **1a** (0.20 mmol) and **2a** (0.40 mmol; Table 1). After the initial screening of catalyst, oxidant,

Table 1. Optimization Studies for Decarboxylative C4-Selective C−H Alkenylation of 1a with 2a[a]



entry	catalyst	oxidant	additives	yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	K_2HPO_4	43
2	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2·H_2O$	K_2HPO_4	0
3	$Cp^*Co(CO)I_2$	$Cu(OAc)_2·H_2O$	K_2HPO_4	0
4	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2·H_2O$	K_2HPO_4	0
5	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$	K_2HPO_4	0
6	$[Cp^*RhCl_2]_2$	AgOAc	K_2HPO_4	11
7	$[Cp^*RhCl_2]_2$	Ag_2CO_3	K_2HPO_4	17
8[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	K_2HPO_4 MS 4A	60
9[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	Na_2CO_3 MS 4A	26
10[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	K_2CO_3 MS 4A	11
11[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	Cs_2CO_3 MS 4A	0
12[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	$NaHCO_3$ MS 4A	23
13[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	$KHCO_3$ MS 4A	25
14[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	$K_4P_2O_7$ MS 4A	82 (78)

[a]Conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), catalyst (0.010 mmol on metal), oxidant (0.20 mmol), additives (0.40 mmol), toluene (1.0 mL), 160 °C, 16−24 h, N_2. [b]Estimated by ^1H NMR with CH_2Br_2 as the internal standard. Isolated yield in parentheses. [c]With 0.60 mmol of **2a** and 100 mg of MS 4A.

additive, and solvent, we were pleased to find that the reaction proceeded in the presence of $[Cp^*RhCl_2]_2$ catalyst, $Cu(OAc)_2·H_2O$ oxidant, and K_2HPO_4 base in heated toluene (160 °C) to deliver the targeted **3aa** in 43% ^1H NMR yield (entry 1). Notably, the C−C bond formation occurred exclusively at the C4 position, and the COOH-remaining byproduct **3aa-COOH** was not detected at all. Additionally, the structure of **3aa** was unambiguously confirmed by X-ray analysis (CCDC 2032339). No alkenylated product **3aa** was observed with other catalysts including $[Cp^*IrCl_2]_2$, $Cp^*Co(CO)I_2$, $[RuCl_2(p\text{-cymene})]_2$, and $Pd(OAc)_2$ (entries 2−5), some of which are known to promote the related decarboxylative C−H functionalization of benzene derivatives.[8−11] The $Cu(OAc)_2·H_2O$ was found to be better than the Ag-based oxidants (entries 6 and 7). The ^1H NMR yield further increased to 60% by using 3.0 equiv of **2a** and addition of MS 4A (entry 8). Final investigation of base (entries 9−14) revealed that $K_4P_2O_7$ showed the best performance,[12] and **3aa** was finally isolated in 78% yield (82% ^1H MR yield; entry 14). Some additional observations are to be noted: the carboxylic acid group was indispensable for the alkenylation, and no conversion of the corresponding ester and simple 2-pyridone substrate was observed. Other ethereal, halogenated, and polar solvents were also tested, but toluene proved to be best.[13]

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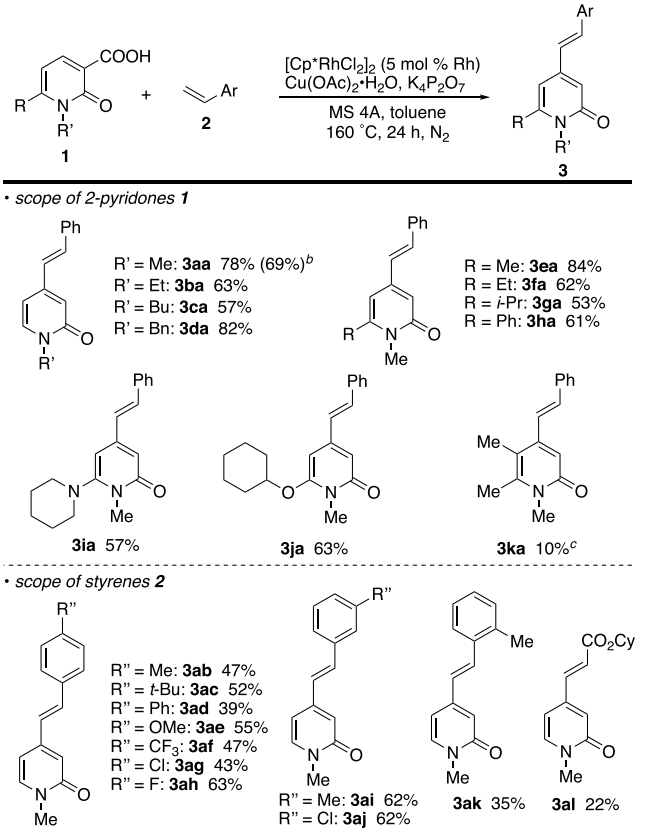
With the optimal conditions in hand (Table 1, entry 14), we examined the scope and limitation of this strategy (Scheme 3).

Scheme 3. Rhodium-Catalyzed C4-Selective C−H Alkenylation of 3-Carboxy-2-pyridones 1 with Styrenes 2 by Traceless Directing Group Strategy[a]



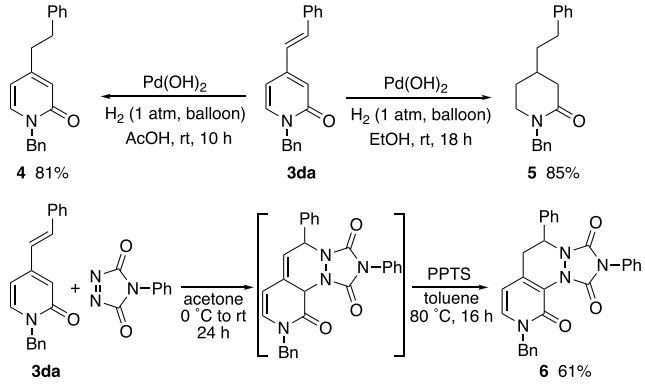
[a]Reaction conditions: **1** (0.20 mmol), **2** (0.60 mmol), $[Cp^*RhCl_2]_2$ (0.0050 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.20 mmol), $K_4P_2O_7$ (0.40 mmol), MS 4A (100 mg), toluene (1.0 mL), 160 °C, 24 h, N_2. Isolated yields are shown. [b]On a 1.0 mmol scale. [c]NMR yield.

The larger alkyl groups on the pyridone nitrogen were compatible to form the corresponding C4-alkenylated 2-pyridones **3ba**−**da** in good yields. The substituents at the C6 position were also accommodated (**3ea**−**ha**). Particularly notable is the successful reaction of 2-pyridones that bear the amino (**3ia**) and alkoxyl (**3ja**) functionalities. On the other hand, the C5-substituted pyridone was the reluctant substrate probably due to the steric factors (**3ka**). The reaction was scalable, and **3aa** was obtained in 69% yield on a 1.0 mmol scale.

Several *para*-substituted styrenes were smoothly coupled with **1a**: electron-donating and -withdrawing as well as halogenated substituents all were tolerated under the reaction conditions (**3ab**−**3ah**).[14] The *meta*-substituted substrates were also viable substrates (**3ai** and **3aj**), but the sterically demanding *ortho*-substitution was somewhat detrimental to the reaction (**3ak**). Unfortunately, the acrylate showed lower reactivity than the styrene derivatives (**3al**), but the reactivity trend was highly dependent on the position of carboxy group (vide infra).

The obtained product **3da** underwent some derivatizations (Scheme 4). The vinylene selective reduction was possible under the hydrogenation conditions using $Pd(OH)_2/H_2$ in

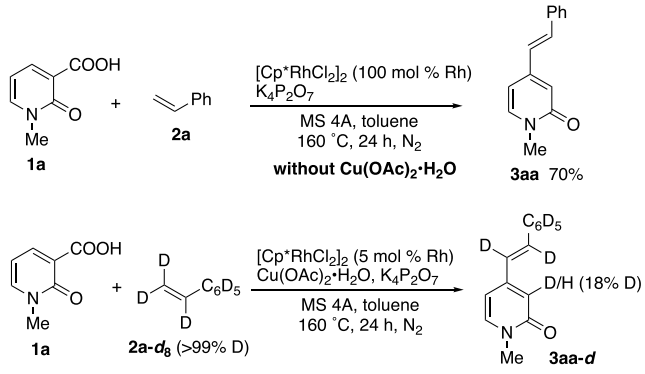
Scheme 4. Derivatizations of 3da



AcOH solvent to furnish the C4-alkylated 2-pyridone **4** in 81% yield. On the other hand, the saturated piperidin-2-one structure **5** was selectively obtained under the hydrogenation in EtOH. Additionally, the 2-pyridone has an electron-rich vinylogous enamide character, and **3da** thus underwent the Diels−Alder reaction with the triazoledione. After additional treatment with PPTS,[15] the corresponding tricyclic system **6** was isolated in 61% overall yield.

We next implemented some control experiments to gain mechanistic insight (Scheme 5). First, to check the role of

Scheme 5. Control Experiments



$Cu(OAc)_2$, the stoichiometric reaction to Rh was performed in the absence of $Cu(OAc)_2$: the targeted **3aa** was formed in 70% yield without any difficulties. Thus, $Cu(OAc)_2$ can work as just an oxidant in the catalyst regeneration step (**G** to **A** in Scheme 2). Additionally, the reaction with styrene-d_8 (**2a**-d_8) successfully incorporated a partial but significant amount of deuterium selectively at the C3 position.[16] These outcomes suggest that as shown in Scheme 2 the decarboxylative C−C bond forming process is operated by the Rh alone rather than the stepwise C−C bond formation and Cu-promoted protodecarboxylation, which is consistent with no observation of COOH-remaining **3aa-COOH** (Table 1) and the lower yield of **3aa** in the presence of Ag-based oxidants (entries 6 and 7 in Table 1) that more strongly accelerate the nonproductive simple protodecarboxylation.[17] A similar reaction mechanism was proposed in the related Ru-catalyzed decarboxylative C−H alkenylation with alkynes.[11a−c]

We also investigated the applicability and site selectivity of this strategy in the reaction of regioisomeric carboxy-2-pyridones (Scheme 6). As a general trend, K_2HPO_4 instead of $K_4P_2O_7$ showed better performance in these cases. The 4-

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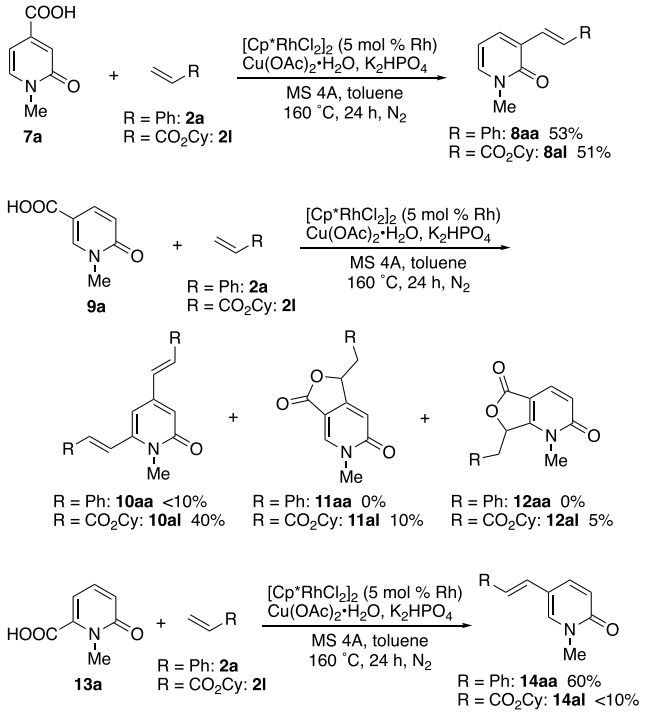
Scheme 6. Attempts To Apply Regioisomeric Carboxy-2-pyridones

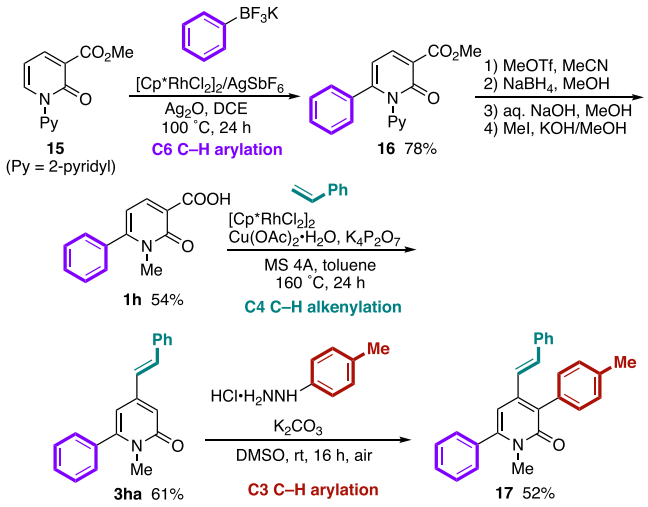


carboxy-2-pyridone **7a** afforded the C3-alkenylated product **8aa** exclusively, the site selectivity of which can be controlled by the additional coordination of the pyridone carbonyl.[18] Additionally notable is the successful coupling of acrylate in this case (**8al**). The 5-carboxy-2-pyridone **9a** specifically reacted only with the acrylate **2l** to form the C4- and C6-doubly alkenylated **10al** as the major product. A mixture of the corresponding five-membered lactones[19] **11al** and **12al** was also isolated, thus suggesting the competitive reaction order at the C3 and C6 positions. In the reaction of the 6-carboxy-2-pyridone **13a**, as in the case of the 3-carboxy-2-pyridone **1a**, only the styrene **2a** was reactive, and the expected C5-alkenylated product **14aa** was obtained in 60% yield.

Finally, we attempted to synthesize the multiply substituted 2-pyridone by the sequential site-selective C−H functionalization reactions (Scheme 7). The starting platform is the *N*-(2-pyridyl)-3-methoxycarbonyl-2-pyridone (**15**), and the rhodium-catalyzed, pyridine-directed C6-selective C−H arylation with the aryltrifluoroborate[20] was first conducted to afford **16** in 78% yield. The subsequent ester hydrolysis and *N*-substituent switch from Py to Me formed **1h** in 54% (4 steps). The styryl group was introduced at the C4 position by the present traceless directing group strategy (**3ha**). The C−H at the C3 position was then selectively arylated with the hydrazine derivative under radical conditions[21] to form the trisubstituted 2-pyridone **17** with two different aryl groups and one alkenyl group at the C3, C6, and C4 positions. As demonstrated in Scheme 7, the combination of the presently developed protocol and literature procedures can provide a modular C−H functionalization approach to the multiply substituted 2-pyridones, which will find wide applications in the development of more complex, pyridone-based bioactive molecules.[1]

In conclusion, we have developed a rhodium-catalyzed decarboxylative C4-selective C−H alkenylation of 3-carboxy-2-

Scheme 7. Synthesis of Multiply Substituted 2-Pyridone 17 by Sequential Site-Selective C−H Functionalization Reactions



pyridones with styrenes. Taking advantage of the carboxy group as the traceless directing group, we can access the otherwise challenging C−H bond at the C4 position, irrespective of the substituents at the competitively reactive C6 position. Additionally, by using the newly developed strategy, the multiply substituted 2-pyridone can be prepared via sequential C−H functionalization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00050.

^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra, ORTEP drawing, detailed optimization studies, detailed D-labeling experiments, and protodecarboxylation test (PDF)

Accession Codes

CCDC 2032339 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 Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(14) We have no explanation for the reason why the yields of **3ab**, **3ad**, and **3af** were lower at this stage. We repeated these reactions two times, but almost the same yields were observed.

(15) The initially formed Diels−Alder adduct was somewhat unstable and gradually underwent the olefin isomerization into **6**, which was accelerated by addition of acid such as PPTS.

(16) We confirmed that the deuterium content at the C3 position did not increase in the reaction even with anhydrous $Cu(OAc)_2$ and toluene-d_8. Additionally, the isolated **3aa** underwent just a partial H/D exchange (9%) at the C3 position with AcOH-d_4 under otherwise identical conditions (see the Supporting Information for details). Thus, we believe that the lower deuterium content is mainly attributed to the H/D exchange on Rh−H species (**E** and/or **F** in Scheme 2) with the carboxylic acid H of the starting pyridone.

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