**Rhodium(i)-catalyzed C6-selective C–H alkenylation and polyenylation of 2-pyridones with alkenyl and conjugated polyenyl carboxylic acids†**

Haoqiang Zhao,ac Xin Xu,a Zhenli Luo,a Lei Cao,a Bohan Li,a Huanrong Li,a Lijin Xu,b Leixb Xinghua Fan,b and Patrick J. Walshc

A versatile Rh(i)-catalyzed C6-selective decarbonylative C–H alkenylation of 2-pyridones with readily available, and inexpensive alkenyl carboxylic acids has been developed. This directed dehydrogenative cross-coupling reaction affords 6-alkenylated 2-pyridones that would otherwise be difficult to access using conventional C–H functionalization protocols. The reaction occurs with high efficiency and is tolerant of a broad range of functional groups. A wide scope of alkenyl carboxylic acids, including challenging conjugated polyprene carboxylic acids, are amenable to this transformation and no addition of external oxidant is required. Mechanistic studies revealed that (1) Boc2O acts as the activator for the in situ transformation of the carboxylic acids into anhydrides before oxidative addition by the Rh catalyst, (2) a decarbonylation step is involved in the catalytic cycle, and (3) the C–H bond cleavage is likely the turnover-limiting step.

**Introduction**

The 2-pyridone motif is found in numerous naturally occurring molecules and synthetic organic compounds that possess a broad spectrum of bioactivities. For example, A58365A, isolated from the fermentation broth of a soil bacterium, serves as an angiotensin-converting enzyme inhibitor;\(^\text{6}\) fredericamycin A, isolated from Streptomyces griseus, is a potent antitumor antibiotic;\(^\text{7}\) ciclopirox is a widely used synthetic antifungal agent;\(^\text{8}\) and milrinone is a phosphodiesterase 3 inhibitor used to treat heart failure (Fig. 1).\(^\text{9}\) 2-Pyridones are also valued as building blocks, because they can be converted to pyridines, piperidines, quinolizidines and indolizidines.\(^\text{10}\) As a result of their widespread utility, the construction of 2-pyridones has been a vibrant research area in the synthetic community, and numerous methods for their synthesis are available.\(^\text{11,12}\)

Several approaches for the functionalization of 2-pyridones have employed transition metals. Early studies focused on transition-metal catalyzed cross-coupling of functionalized 2-pyridones.\(^\text{13}\) More recent efforts to elaborate the 2-pyridone motif have been devoted to their direct catalytic C–H functionalization.\(^\text{14}\) In this context, rapid progress in site-selective C–H functionalization at C3, C5 and C6 positions of 2-pyridones has been advanced.\(^\text{15,16}\) Notably, Miura and co-workers found that the use of easily attachable and detachable 2-pyridyl directing groups at the nitrogen of the 2-pyridones could effectively facilitate the copper-mediated C6-selective dehydrogenative heteroarylation with 1,3-azoles.\(^\text{17}\)

Following this seminal work, transition-metal catalyzed directed alkylation,\(^\text{18}\) arylation,\(^\text{19}\) alkylation,\(^\text{20}\) borylation,\(^\text{21}\) thiolation,\(^\text{22}\) annulation,\(^\text{23}\) alkylation,\(^\text{24}\) and amidation\(^\text{25}\) of 1-(2-pyridyl)-2-pyridones at the C6 positions have been successfully accomplished. In general, installation of vinyl groups has proven considerably more challenging than aryl or alkyl substituents, and this holds true for the vinylation of 2-pyridones at the C6 position. Naka and co-workers reported an impressive C6-alkenylation of 2-pyridones via C–H hydroarylation of N-alkylated 2-pyridones with alkenes at the C6 position under Ni/Al cooperative catalysis, albeit with limited substrate scope and low functional group efficiency and is

*Department of Chemistry, Renmin University of China, Beijing 100872, China. E-mail: 20050062@ruc.edu.cn

†Beijing National Laboratory for Molecular Sciences and Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, China. E-mail: fanqh@iccas.ac.cn

‡Roy and Diana Vagelos Laboratories, Penn/merck Laboratory for High-Throughput Experimentation, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, USA. E-mail: pwalsh@sas.upenn.edu

† Electronic supplementary information (ESI) available. CCDC 1874166. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc03672e

**Fig. 1** Biologically active 2(1H)-pyridone molecules.
tolerance (Scheme 1a). Very recently, the group of Hirano and Miura reported Rh(III)-catalyzed (10 mol%) C6-selective alkenylation of 1-(2-pyridyl)-2-pyridones with acrylates and styrenes (Scheme 1b).\textsuperscript{a,b}

Recently, the use of readily available and inexpensive \(\alpha,\beta\)-unsaturated carboxylic acids in transition metal catalyzed decarboxylative and decarboxylative alkenylation reactions has gained attention.\textsuperscript{c–e} We envisioned that 6-alkenylated 2-pyridones might be accessible from 1-(2-pyridyl)-2-pyridones and \(\alpha,\beta\)-unsaturated acids under transition metal catalysis. In connection with our ongoing interests in direct alkenylation of C–H bonds,\textsuperscript{f} herein we report a Rh(I)-catalyzed C6-selective C–H alkenylation of 2-pyridones using alkyl carboxylic acids as the vinyl source (Scheme 1c). This protocol features a simple and easy-to-handle catalytic system, high efficiency, very broad substrate scope and high functional group tolerance.

Results and discussion

Recent studies have revealed that catalytic systems based on Rh(III), Ru(II) and Pd(II) complexes perform well in directed alkenylation of relatively inert (hetero)arene and alkene C–H bonds.\textsuperscript{g–i} Inspired by these reports, we first attempted the alkenylation of the model substrate 1-(2-pyridyl)-2-pyridone (1a) with styrene using Rh(III), Ru(II) and Pd(II) complexes (ESI, Table S1†). Unfortunately, various catalytic systems, including those that have been shown to efficiently catalyze direct alkenylation of structurally similar 2-phenylpyrimidines, 1-[pyrimidin-2-yl]-1H-indoles and 2-(1H-pyrrol-1-yl)pyrimidines,\textsuperscript{i,j} did not furnish the desired products (Scheme 2a). Liu and co-workers recently described Rh(III)-catalyzed site-selective C–H alkylation and arylation of 1-(2-pyridyl)-2-pyridones at the C6 position with potassium trifluoroacetates.\textsuperscript{k} Expanding the substrate scope of this reaction to include potassium vinyl trifluoroacetates, however, was unsuccessful in our hands using a similar Rh(III) catalyst (Scheme 2b and ESI, Table S2†). Likewise, Ru(II)-catalyzed alkenylation of 1a with styrylboronic acids did not afford the desired alkenylation product (Scheme 2c and ESI, Table S2†).

We then turned our attention to the coupling reaction of vinyl carboxylic acids with 2-pyridones. We were pleased to discover that the reaction of 1a and trans-cinnamic acid (2a) in the presence of [Rh(CO)\(_2\)Cl]\(_2\) (1.0 mol%) and Boc\(_2\)O (1.5 equiv.) at 130 °C in 1,4-dioxane, provided the desired product 3aa in 93% yield (Scheme 2d).

### Table 1: Optimization of the reaction conditions\textsuperscript{a}

| Entry | Catalyst | Activator | Solvent | Yield (%)\textsuperscript{d} |
|-------|----------|-----------|---------|-------------------------------|
| 1     | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | 1,4-Dioxane | 93 |
| 2     | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | Toluene | 15 |
| 3     | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | PhCl | 11 |
| 4     | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | p-Xylene | 15 |
| 5     | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | THF | NR |
| 6     | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | CH\(_2\)CN | NR |
| 7     | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | DCE | 10 |
| 8     | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | DMF | NR |
| 9     | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | DME | NR |
| 10    | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | 1,4-Dioxane | <5 |
| 11    | [Rh(COD)\(_2\)]Cl\(_2\) | Boc\(_2\)O | 1,4-Dioxane | NR |
| 12    | [Rh(COD)\(_2\)BF\(_4\)] | Boc\(_2\)O | 1,4-Dioxane | NR |
| 13    | [Cp*RhCl\(_2\)]Cl\(_2\) | Boc\(_2\)O | 1,4-Dioxane | NR |
| 14    | [Ru(p-cymene)\(_2\)]Cl\(_2\) | Boc\(_2\)O | 1,4-Dioxane | NR |
| 15    | [Cp*RhCl\(_2\)]Cl\(_2\) | Boc\(_2\)O | 1,4-Dioxane | NR |
| 16    | Pd(OAc)\(_2\) | Boc\(_2\)O | 1,4-Dioxane | NR |
| 17    | [Rh(CO)\(_2\)Cl]\(_2\) | (MeOCO)\(_2\)O | 1,4-Dioxane | 22 |
| 18    | [Rh(CO)\(_2\)Cl]\(_2\) | Tf\(_2\)O | 1,4-Dioxane | NR |
| 19    | [Rh(CO)\(_2\)Cl]\(_2\) | (CF\(_3\)CO)\(_2\)O | 1,4-Dioxane | NR |
| 20    | [Rh(CO)\(_2\)Cl]\(_2\) | PivCl | 1,4-Dioxane | 39 |
| 21    | [Rh(CO)\(_2\)Cl]\(_2\) | Piv\(_2\)O | 1,4-Dioxane | 92 |
| 22\* | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | 1,4-Dioxane | 55 |
| 23\* | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | 1,4-Dioxane | 43 |
| 24    | None | Boc\(_2\)O | 1,4-Dioxane | NR |
| 25    | [Rh(CO)\(_2\)Cl]\(_2\) | None | 1,4-Dioxane | NR |
| 26\* | [Rh(CO)\(_2\)Cl]\(_2\) | Boc\(_2\)O | 1,4-Dioxane | 31 |

\textsuperscript{a} Reaction conditions: 1a (0.2 mmol), 2a (0.22 mmol), catalyst (1.0 mol%), activator (1.5 equiv.), solvent (2.0 mL), 130 °C, 6 h, in air. \textsuperscript{b} Isolated yield. \textsuperscript{c} Reaction temperature 120 °C. \textsuperscript{d} [Rh(CO)\(_2\)Cl]\(_2\) (0.5 mol%) was used. \textsuperscript{e} 1-(Pyrimidin-2-yl)pyridin-2(1H)-one was employed.

### Scheme 1: Catalytic direct C–H alkenylation of 2-pyridones at the C6 position: (a) alkenylation with alkynes, (b) alkenylation with acrylates and styrenes, and (c) decarboxylative alkenylation.
92% yield after 6 h (Table 1, entry 1). A solvent screen revealed that 1,4-dioxane outperformed other frequently employed solvents, such as toluene, PhCl, p-xylene, THF, CH₂CN, DCE, DMF and DME (Table 1, entries 2–9). Changing the rhodium source to [Rh(COD)Cl]₂, [RhCl(PPh₃)₃], [Rh(COD)₂BF₄] or [Cp*RhCl₂] did not lead to any improvement in the yield of 3aa (Table 1, entries 10–13). Other transition metal complexes such as [Ru(p-cymene)Cl]₂, [Cp*IrCl₂] and Pd(OAc)₂ were also ineffective in this transformation (Table 1, entries 14–16).

We next screened different electrophiles to activate the unsaturated acid. Poor conversion was obtained with (MeOCO)₂O (22%), Tf₂O (NR), (CF₃CO)₂O (NR), or PivCl (39%) as the acid activators (Table 1, entries 17–20). In contrast, Piv₂O was effective and gave 3aa in 92% yield (Table 1, entry 21). Considering the price and compatibility, however, more economical and milder Boc₂O was preferred.

Further optimization involving decreasing the reaction temperature or the catalyst loading led to dramatically lowered yields (Table 1, entries 22 and 23). Notably, the reaction did not proceed in the absence of either a rhodium catalyst or acid activator (Table 1, entries 24 and 25). Finally, the effect of the N-directing group in this reaction was examined. No reaction occurred when free 2-pyridone or 2-pyridone substrates bearing other substituents on the nitrogen, such as Me, Bn, Ph, or 3-pyridyl. The 2-pyrimidyl resulted in only 31% yield (Table 1, entry 24). Other substituents on the nitrogen, such as Me, Bn, Ph, or 3-pyridyl, also participated in the alkenylation with 2a to exclusively furnish the desired C₆-alkenylation (CCDC 1874166). Similarly, the dialkenylated product was observed in the case of 1w.

Subsequently, we explored the reactivity of various cinnamic acids with 1a. As shown in Table 3, a wide range of cinnamic acids (2b–2p) with mono-substituted aromatic rings efficiently participated in the alkenylation with 1a to exclusively furnish the desired C₆-alkenylation (CCDC 1874166). Similarly, the dialkenylated product was confirmed by single-crystal X-ray diffraction (CCDC 1874166). Similarly, the dialkenylated product was observed in the case of 1w.

**Table 2** Catalytic alkenylation of various 2-pyridones with 2a.<sup>a,b</sup>

| 2a | 3a |
|----|----|
| ![Reagent](image1.png) | ![Product](image2.png) |
| 2b | 3b |
| ![Reagent](image3.png) | ![Product](image4.png) |
| 2c | 3c |
| ![Reagent](image5.png) | ![Product](image6.png) |
| 2d | 3d |
| ![Reagent](image7.png) | ![Product](image8.png) |
| 2e | 3e |
| ![Reagent](image9.png) | ![Product](image10.png) |
| 2f | 3f |
| ![Reagent](image11.png) | ![Product](image12.png) |
| 2g | 3g |
| ![Reagent](image13.png) | ![Product](image14.png) |
| 2h | 3h |
| ![Reagent](image15.png) | ![Product](image16.png) |
| 2i | 3i |
| ![Reagent](image17.png) | ![Product](image18.png) |
| 2j | 3j |
| ![Reagent](image19.png) | ![Product](image20.png) |
| 2k | 3k |
| ![Reagent](image21.png) | ![Product](image22.png) |
| 2l | 3l |
| ![Reagent](image23.png) | ![Product](image24.png) |
| 2m | 3m |
| ![Reagent](image25.png) | ![Product](image26.png) |
| 2n | 3n |
| ![Reagent](image27.png) | ![Product](image28.png) |
| 2o | 3o |
| ![Reagent](image29.png) | ![Product](image30.png) |
| 2p | 3p |
| ![Reagent](image31.png) | ![Product](image32.png) |

<sup>a</sup> Reaction conditions: 1a (0.2 mmol), 2a (0.22 mmol), [Rh(CO)₂Cl]₂ (1.0 mol%), Boc₂O (1.5 equiv.), 1,4-dioxane (2.0 mL), 130 °C, 6 h, in air.  
<sup>b</sup> Isolated yield.  
<sup>c</sup> 2a (0.44 mmol) was employed.

**Table 3** Direct olefination of 1a with cinnamic acids.<sup>a</sup>

| 2a | 3a |
|----|----|
| ![Reagent](image33.png) | ![Product](image34.png) |
| 2b | 3b |
| ![Reagent](image35.png) | ![Product](image36.png) |
| 2c | 3c |
| ![Reagent](image37.png) | ![Product](image38.png) |
| 2d | 3d |
| ![Reagent](image39.png) | ![Product](image40.png) |
| 2e | 3e |
| ![Reagent](image41.png) | ![Product](image42.png) |
| 2f | 3f |
| ![Reagent](image43.png) | ![Product](image44.png) |
| 2g | 3g |
| ![Reagent](image45.png) | ![Product](image46.png) |
| 2h | 3h |
| ![Reagent](image47.png) | ![Product](image48.png) |
| 2i | 3i |
| ![Reagent](image49.png) | ![Product](image50.png) |
| 2j | 3j |
| ![Reagent](image51.png) | ![Product](image52.png) |
| 2k | 3k |
| ![Reagent](image53.png) | ![Product](image54.png) |
| 2l | 3l |
| ![Reagent](image55.png) | ![Product](image56.png) |
| 2m | 3m |
| ![Reagent](image57.png) | ![Product](image58.png) |
| 2n | 3n |
| ![Reagent](image59.png) | ![Product](image60.png) |
| 2o | 3o |
| ![Reagent](image61.png) | ![Product](image62.png) |
| 2p | 3p |
| ![Reagent](image63.png) | ![Product](image64.png) |

<sup>a</sup> Reaction conditions: 1a (0.2 mmol), 2a (0.22 mmol), [Rh(CO)₂Cl]₂ (1.0 mol%), Boc₂O (1.5 equiv.), 1,4-dioxane (2.0 mL), 130 °C, 6 h, in air.  
<sup>b</sup> Isolated yield.
the more complex cinnamic acids (2q–2v), with polysubstituted aromatic rings, displayed good reactivity, affording the target products (3aq–3av) in 70–90% yields. Notably, a vinyl group bearing a pentafluoro phenyl provided the product (3au) in 70% yield. Heteroaryl groups are vital substructures in medicinal chemistry.\(^{23}\) We, therefore, examined the compatibility of heteroaryl cinnamic acids with 1a. Heteroaryl cinnamic acids bearing 3-pyridyl, 2-furanyl, and 2-thiofuranyl (2w–2y) reacted smoothly with 1a to give the desired products (3aw–3ay) in 82–90% yields. Importantly, the estrone-derived cinnamic acid 2z proved to be equally effective in this transformation, indicating the robustness of the current catalytic system.

To further demonstrate the potential of our catalytic system, the reaction was extended to other substituted alkenyl carboxylic acids, and the results are summarized in Table 4. It was found that treatment of various β-alkylated acrylic acids (4a–4d) with 1a resulted in exclusive formation of C6-alkenylated 2-pyridone products (5aa–5ad) in 85–92% yields, irrespective of the nature of the β-alkyl groups. In the case of acid 4e containing a sensitive Cl group, the reaction furnished the desired product 5ae in 87% yield without dechlorination. Notably, the simple acrylic acid (4f) was also reactive, giving rise to the C6-vinylated 2-pyridone product 5af in 73% yield. Likewise, the α-substituted acrylic acids 4g and 4h were competent substrates, delivering 5ag and 5ah both in 80% yield. Furthermore, trisubstituted acrylic acids (4i–4n), including the naturally occurring geranic acid (4k), shikimic acid (4m) and perillic acid (4n), were good substrates, producing 5ai–5an in 63–91% yields. Potentially reactive groups, like OH and C=C, were not detrimental to the overall yields. Remarkably, a variety of conjugated polynene carboxylic acids were also efficient coupling partners in this transformation. More substituted and less sensitive conjugated dienyl carboxylic acids (4o–4s) formed the desired products (5ao–5as) in 65–86% yields. The formation of a mixture of Z/E isomers in the case of 5ar was due to the low stereoechemical purity of the starting trienoic acid 4r (4Z/4E ratio 1:1). Surprisingly, both the bioactive retinoic acid (4t) and its derivative 4u containing a conjugated hexaene unit, formed the corresponding products (5at and 5au) in 72% and 65% yields, respectively. Application of 5-phenylpent-2-en-4-ynoic acid (4v) led to the formation of 5av in 67% yield, with the alkyne having no obvious adverse effect on the reaction outcome.

In order to explore the synthetic practicality of this transformation, a gram scale reaction of 1a and 2a was performed to deliver 3aa in 88% yield (Scheme 3a). Further transformations of the products were then explored. As depicted in Scheme 3b, hydrogenation of 3aa at room temperature favored the reduction of the alkene moiety to generate the C6-alkylated 2-pyridone product 6 in 84% yield. Increasing the reaction temperature to 50 °C, however, enabled formation of piperidino-2-one product 7 (92% yield). The pyridine directing group could be conveniently removed by treatment with MeOTf and KOBu to give the C6-alkylated 2-pyridone products in 68–73% yield (Scheme 3c).\(^7\)

We next desired to probe the basic steps of the reaction mechanism. Activation of the carboxylic acid was envisioned to proceed via an anhydride derivative.\(^{16}\) To test this hypothesis, a control experiment with cinnamic anhydride 11 and 1a demonstrated that the coupling worked equally (91% yield) as well as acid 2a with Boc₂O (93% yield). Treatment of acid 2a with an equimolar amount of Boc₂O in 1,4-dioxane at 130 °C for 6 h led to the predominant formation of cinnamic anhydride 11 in 85% yield. This observation supports the involvement of in situ generation of the anhydride in the vinylation reaction.\(^{16}\) The

### Table 4 Direct olefination of 1a with substituted alkenyl carboxylic acids\(^{1,2}\)

| Substituted acrylic acids | Reaction yield |
|--------------------------|----------------|
| 5aa, R² = H, 91%         |                |
| 5ah, R² = Et, 60%        |                |
| 5ai, R² = Me, 75%        |                |
| 5aj, R² = Ph, 81%        |                |
| 5ak, R² = Ph, 81%        |                |
| 5al, R² = H, 91%         |                |
| 5an, R² = H, 91%         |                |
| 5ao, R² = Me, 75%        |                |
| 5ap, R² = Ph, 81%        |                |
| 5aq, R² = Ph, 81%        |                |
| 5ar, R² = H, 91%         |                |
| 5as, R² = Me, 75%        |                |
| 5at, R² = H, 91%         |                |
| 5au, R² = Ph, 81%        |                |
| 5av, R² = Ph, 81%        |                |
| 5aw, R² = H, 91%         |                |
| 5ax, R² = Ph, 81%        |                |
| 5ay, R² = Ph, 81%        |                |
| 5az, R² = Ph, 81%        |                |

\(^{a}\) Reaction conditions: 1a (0.2 mmol), 2a (0.22 mmol), [Rh(CO)₂Cl]₂ (1.0 mol%), Boc₂O (1.5 equiv.), 1,4-dioxane (2.0 mL), 130 °C, 6 h, in air. \(^{b}\) Isolated yield. \(^{c}\) Ratio of isomers (E/Z).

### Scheme 3 Synthetic applications: (a) gram-scale synthesis, (b) hydrogenation, and (c) deprotection.
generation of CO gas during the reaction was confirmed by analyzing the head gas of the reaction mixture with GC-TDC (ESI, Fig. S1†). Moreover, employing [Rh(COD)Cl]2 as the catalyst also generated CO gas albeit with a longer reaction time (18 h) and lower yield of 3aa (50%) (ESI, Fig. S2†). These results rule out the possibility that CO gas might be derived from [Rh(CO)2Cl]2, thus indicating the presence of a decarbonylation step in the catalytic cycle. As shown in Scheme 4b, treatment of 1a with D2O (5 equiv.) under the standard conditions for 1 h, in the absence or presence of 2a resulted in approximately 38% and 27% deuteration at the C6-position, respectively, suggesting the reversibility of the C–H activation step under these conditions.

To gain insight into the turnover-limiting step, we conducted initial rate studies and a parallel kinetic isotope effect (KIE) on 1a. The kinetic analyses highlighted a first-order \( n = 1.30 \pm 0.09 \) dependence on the concentration of 1a for the reaction (Scheme 4c and ESI†). In separate reaction vessels, 1a and [D1]-1a were subjected to identical reaction conditions (ESI†); it was observed that 1a was alkenylated to 3aa at a greater rate than the corresponding deuterium-labelled substrate. The KIE value determined from the average of five runs via the method of initial rates was 1.9 ± 0.1. This result implies that the C–H bond cleavage is likely involved in the turnover-limiting step.

Based on the aforementioned results and literature precedence,17 a plausible mechanism highlighting the key steps is presented in Scheme 5. First, solvent (S) or the substrate pyridine breaks up the dimer [Rh(CO)2Cl]2 to give the monomer and enter the catalytic cycle. Meanwhile, the acid reacts with Boc2O to generate the anhydride, which undergo oxidative addition to a Rh(I) species A and leads to the formation of the Rh(III) intermediate B. If the substrate is solvent, ligand exchange for the substrate follows, giving intermediate C. Rather than a second oxidative addition, we prefer a concerted metalation deprotonation (CMD) by the carboxylate ligand via transition state D to generate the acid and the cyclometallated species with the key Rh–C bond. The liberated acid can react with the Boc2O to re-enter the cycle as the anhydride. E is envisioned to undergo loss of coordinated CO and then deinsertion of CO to afford the Rh–vinyl intermediate. Reductive elimination regenerates Rh(i) with the bound product G, which undergoes exchange with the solvent to liberate the product and close the catalytic cycle to form A. At this point, the exact ordering of the steps remains to be determined.
Conclusions

We have developed the first Rh(i)-catalyzed decarboxylative alkenylation at C6 of 2-pyridones using readily available and inexpensive alkenyl carboxylic acids. This C6 alkenylation of 2-pyridones is applicable to the coupling of a wide range of substituted acyclic acids and conjugated polye carbonylic acids. The reaction proceeds under oxidant-free conditions, enabling facile access to C6-alkenylated 2-pyridones in high yields with a broad functional group tolerance. Mechanistic studies support the following steps: initial activation of the carboxylic acid, coordination of the substrate followed by H bond cleavage and activation of the activated acid, coordination of the substrate followed by CMD to cleave the C–H bond. Dissociation of CO is followed by decarboxylation of the acyl group to generate the Rh-bound vinyl, and finally reductive elimination and liberation of product closes the cycle. A turnover limiting C–H bond cleavage is likely based on the observed KIE. Further investigation of the mechanism of this reaction and synthetic applications are underway in our laboratories.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

H. Z. thanks the Program for China Scholarship Council (201806360122), National Natural Science Foundation of China (21372258) and the Beijing National Laboratory for Molecular Sciences (BNLMS201845) for financial support. P. J. W. thanks the US National Science Foundation (CHE-1902509).

Notes and references

1 (a) I. M. Lagoja, *Chem. Biodiversity*, 2005, 2, 1; (b) H. Jessen and J. K. Gademann, *Nat. Prod. Rep.*, 2010, 27, 1168; (c) S. Heeb, M. P. Fletcher, S. R. Chhabra, S. P. Diggle, P. Williams and M. Camara, *FEMS Microbiol. Rev.*, 2011, 35, 247; (d) F. Christ, A. Voet, A. Marchand, S. Nicolet, B. A. Desimmin, D. Marchand, D. Bardiot, N. J. V. der Veken, B. V. Remoortel, S. V. Strelkov, M. D. Maeyer, P. Chaltin and Z. Debayer, *Nat. Chem. Biol.*, 2010, 6, 442; (e) P. Schroder, T. Forster, S. Kleine, C. Becker, A. Richters, S. Ziegler, S. Rauh, K. Kumar and H. Waldmann, *Angew. Chem.*, *Int. Ed.*, 2015, 54, 12398; (f) P. L. Wong and K. D. Moeller, *J. Am. Chem. Soc.*, 1993, 115, 11434; (g) T. R. Kelly, S. H. Bell, N. Ohashi and R. J. Armstrong-Chong, *J. Am. Chem. Soc.*, 1988, 110, 6471; (h) D. Monti, L. Saccomani, P. Chetoni, S. Burgalassi, S. Tampucci and F. Maillard, *Br. J. Dermatol.*, 2011, 165, 99; (i) K. T. Santhosh, O. Elkhateeb, N. Nollette, O. Oubih, A. J. Halayko and S. Dakshinamurti, *Br. J. Pharmacol.*, 2011, 163, 1223; (j) W. Lwowski and A. R. Katritzky, in *Comprehensive heterocyclic chemistry: the structure, reactions, synthesis and uses of heterocyclic compounds*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 8.

2 (a) M. Torres, S. Gil and M. Parra, *Curr. Org. Chem.*, 2005, 9, 1757; (b) K. Hirano and M. Miura, *Chem. Sci.*, 2018, 9, 22–32; (c) A. M. Prendergast and G. P. McGlacken, *Eur. J. Org. Chem.*, 2018, 2018, 6068–6082; (d) A. Brossi, Mammalian alkaloids II, in *The alkaloids: chemistry and pharmacology*, Elsevier, New York, NY, 1993; vol. 43, pp. 119–183; (e) In *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pellietier, Wiley, New York, 1983, pp. 1–31.

3 For selected examples, see: (a) I. Hachiya, K. Oghara and M. Shimizu, *Org. Lett.*, 2002, 4, 2755; (b) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2005, 127, 605; (c) H. Imase, K. Noguchi, M. Hirano and K. Tanaka, *Org. Lett.*, 2008, 10, 3563; (d) T. K. Hyster and T. Rovis, *Chem. Sci.*, 2011, 2, 1606; (e) Y. Su, M. Zhao, K. Han, G. Song and X. Li, *Org. Lett.*, 2010, 12, 5462; (f) L. Ackermann, A. V. Lyygin and N. Hofmann, *Org. Lett.*, 2011, 13, 3278; (g) M. Fujii, T. Nishimura, T. Koshiha, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2013, 15, 232; (h) M. S. Akhtar, J. J. Shim, S. H. Kim and Y. R. Lee, *New J. Chem.*, 2017, 41, 13027; (i) G. Hu, J. Xu and P. Li, *Org. Biomol. Chem.*, 2016, 14, 4151–4158; (j) D. Bai, X. Wang, G. Zheng and X. Li, *Angew. Chem., Int. Ed.*, 2018, 57, 6633–6637; (k) A. D. Elbein and R. J. Molyneux, in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pellietier, Wiley, New York, 1981, vol. 5, pp. 1–54.

4 (a) L. A. Hasvold, W. Wang, S. L. Gwaltney, T. W. Rockway, L. T. G. Nelson, R. A. Mantei, S. A. Fakhoury, G. M. Sullivan, Q. Li, N.-H. Lin, L. Wang, H. Zhang, J. Cohen, W.-Z. Gu, K. Marsh, J. Bauch, S. Rosenberg and H. L. Sham, *Bioorg. Med. Chem. Lett.*, 2003, 13, 4001; (b) D. Conreaux, E. Bossharsh, N. Monteiro, P. Desbordes, J.-P. Vors and G. Balme, *Org. Lett.*, 2007, 9, 271; (c) M. D. Hill and M. Movassagh, *Chem.–Eur. J.*, 2008, 14, 6836; (d) C. Bengtsson and F. Almqvist, *J. Org. Chem.*, 2010, 75, 972; (e) D. Conreaux, S. Belot, P. Desbordes, N. Monteiro and G. Balme, *J. Org. Chem.*, 2008, 73, 8619; (f) C. Bengtsson and F. Almqvist, *J. Org. Chem.*, 2010, 75, 972; (g) S.-S. P. Chou, Y.-C. Chung, P.-A. Chen, S.-L. Chiang and C.-J. Wu, *J. Org. Chem.*, 2011, 76, 692; (h) C. J. McElhinney Jr, F. I. Carroll and A. H. Lewin, *Synthesis*, 2012, 44, 57; (i) D. S. Ziegler, R. Greiner, H. Lume, L. Kqiku, K. Karaghiosoff and P. Knochel, *Org. Lett.*, 2017, 19, 5760.

5 For C3-selective C–H functionalization, see: (a) A. Nakatani, K. Hirano, T. Satoh and M. Miura, *Chem.–Eur. J.*, 2013, 19, 7691; (b) A. Nakatani, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2014, 79, 1377; (c) E. E. Anagnostaki, A. D. Fedotidou, V. Demertzidou and A. L. Zografos, *Chem. Commun.*, 2014, 50, 6879; (d) A. Modak, S. Rana and D. Maiti, *J. Org. Chem.*, 2015, 80, 296; (e) H. U. Lah, F. Rasool and S. K. Youssuf, *RSC Adv.*, 2015, 5, 78958–78961; (f) A. Najib, S. Tabuchi, K. Hirano and M. Miura, *Heterocycles*, 2016, 92, 1187; (g) P. Chauhan, M. Ravi, S. Singh, P. Prajapati and P. P. Yadav, *RSC Adv.*, 2016, 6,
For C6-selective C–H functionalization, see: (a) T. Itahara and F. Ouseto, *Synthesis*, 1984, 488–489; (b) Y. Y. Chen, F. Wang, A. Q. Jia and X. W. Li, *Chem. Sci.*, 2012, 3, 3231; (c) U. Dutta, A. Deb, D. W. Lupton and D. Maiti, *Chem. Commun.*, 2015, 51, 17744; (d) Y. Li, F. Xie and X. Li, *J. Org. Chem.*, 2016, 81, 715; (e) S. Maity, D. Das, S. Sarkar and R. Samanta, *Org. Lett.*, 2018, 20, 5167–5171.

For C6-selective C–H alkylation with alkynyl carboxylates, see: (a) H. Yang, P. Sun, Y. Zhu, H. Yan, L. Lu, X. Qu, T. Li and J. Mao, *Chem. Commun.*, 2012, 48, 7847–7849; (b) Z. Cui, X. Shang, X. F. Shao and Z. Q. Liu, *Chem. Sci.*, 2012, 3, 2853–2858; (c) Y. Yang, J. Yao and Y. Zhang, *Org. Lett.*, 2013, 15, 3206–3209; (d) J. M. Neely and T. Rovis, *J. Am. Chem. Soc.*, 2014, 136, 2735–2738; (e) K. Rousee, C. Schneider, S. Couve-Bonnaire, X. Panneconeck, V. Levacher and C. Hoarau, *Chem.–Eur. J.*, 2014, 20, 15000–15004; (f) X. Wang, S. Y. Li, M. Pan, H. S. Wang, Z. F. Chen and K. B. Huang, *J. Org. Chem.*, 2015, 80, 2407–2412; (g) N. Zhang, D. Yang, W. Wei, L. Yuan, F. Nie, L. Tian and H. Wang, *J. Org. Chem.*, 2015, 80, 3258–3263; (h) S. Agasti, U. Sharma, T. Naveen and D. Maiti, *Chem. Commun.*, 2015, 51, 5375–5378; (i) B. Gao, Y. Xie, L. Yang and H. Huang, *Org. Biomol. Chem.*, 2016, 14, 2399–2402; (j) S. Agasti, A. Dey and D. Maiti, *Chem. Commun.*, 2016, 52, 12191–12194; (k) C. Wang, Y. Lei, M. Guo, Q. Shang, H. Liu, Z. Xu and R. Wang, *Org. Lett.*, 2017, 19, 6412–6415; (l) J. B. E. Y. Rouchet, M. Hachem, C. Schneider and C. Hoarau, *ACS Catal.*, 2017, 7, 5363–5369; (m) S. W. Youn, T. Y. Ko and Y. H. Jang, *Angew. Chem., Int. Ed.*, 2017, 56, 6636–6640; (n) K. Xu, Z. Tan, H. Zhang, J. Liu, S. Zhang and Z. Wang, *Chem. Commun.*, 2017, 53, 10719–10722; (o) Z. Luo, X. Han, Y. Fang, P. Liu, C. Feng, Z. Li and X. Xu, *Organ. Chem. Front.*, 2018, 5, 3299–3305; (p) J. F. Zhao, X. H. Duan, Y. R. Gu, P. Gao and L. N. Guo, *Org. Lett.*, 2018, 20, 4614–4617.

For catalytic decarboxylative C–H alkylation with alkynyl carboxylic acids, see: (a) Z. Q. Lei, J. H. Ye, J. Sun and Z. J. Shi, *Org. Chem. Front.*, 2014, 1, 634–638; (b) L. Zhang, R. Qiu, X. Xue, Y. Pan, C. Xu, D. Wang, X. Wang, L. Xu and H. Li, *Chem. Commun.*, 2014, 50, 12385–12388; (c) S. Kwon, D. Kang and S. Hong, *Eur. J. Org. Chem.*, 2015, 2015, 3671–3678; (d) R. Qiu, L. Zhang, C. Xu, X. Pan, H. Pang, L. Xu and H. Li, *Adv. Synth. Catal.*, 2015, 357, 1229–1236; (e) C. Xu, L. Zhang, J. Xu, Y. Pan, F. Li, H. Li and L. Xu, *ChemistrySelect*, 2016, 4, 653–658; (f) J. X. Cui, C. Chen, H. Zhao, C. Xu, Y. Pan, X. Xu, H. Li, L. Xu and B. Fan, *Org. Chem. Front.*, 2018, 5, 734–740; (g) X. Qiu, P. Wang, D. Wang, M. Wang, Y. Yuan and Z. Shi, *Angew. Chem., Int. Ed.*, 2019, 58, 3100–3120.

For reviews, see: (a) L. J. Goossen, N. Rodriguez and K. Goossen, *Angew. Chem., Int. Ed.*, 2008, 47, 3100–3120; (b) N. Rodriguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, 40, 5030–5048; (c) W. I. Dzik, P. P. Lange and L. J. Goossen, *Chem. Sci.*, 2012, 3, 2671–2678; (d) K. Park and S. Lee, *RSC Adv.*, 2013, 3, 14163–14165; (e) A. J. Borah and G. Yan, *Org. Biomol. Chem.*, 2015, 13, 8094–8115; (f) Y. Wei, P. Hu, M. Zhang and W. Su, *Chem. Rev.*, 2017, 117, 8864–8907; (g) G. J. P. Perry and I. Larrosa, *Eur. J. Org. Chem.*, 2017, 2017, 3517–3527; (h) J. Schwarz and B. Konig, *Green Chem.*, 2018, 20, 323–361; (i) J. Buchspies and M. Szostak, *Catalysts*, 2019, 9, 53; (j) C. Liu, C. L. Ji, X. Hong and M. Szostak, *Angew. Chem.*, 2018, 130, 16963–16968.
B. S. Kim, M. Li and P. J. Walsh, *Org. Lett.*, 2016, 18, 2371–2374; (e) M. Li, O. Gutierrez, S. Berritt, A. Pascual-Escudero, A. Yeşilcimen, X. Yang, J. Adrio, G. Huang, E. Nakamaru-Ogiso, M. C. Kozlowski and P. J. Walsh, *Nat. Chem.*, 2017, 9, 997; (f) S. Duan, M. Li, X. Ma, W. Chen, L. Li, H. Zhang, X. Yang and P. J. Walsh, *Adv. Synth. Catal.*, 2018, 360, 4837–4842; (g) C. Wu, S. Berritt, X. Liang and P. J. Walsh, *Org. Lett.*, 2019, 21, 960–964.

13 For reviews of transition-metal-catalyzed direct alkenylation of C–H bonds with alkenes, see: (a) L. Brás and J. Muzart, *Chem. Rev.*, 2011, 111, 1170–1214; (b) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, 4, 886–896; (c) Y. Wu, J. Wang, F. Mao and F. K. Kwong, *Chem.–Asian J.*, 2014, 9, 26–47; (d) L. Zhou and W. Lu, *Chem.–Eur. J.*, 2014, 20, 634–642; (e) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi and A. Lei, *Chem. Rev.*, 2015, 115, 12138–12204; (f) S. Bag and D. Maiti, *Synthesis*, 2016, 48, 804–815; (g) W. Ma, P. Gandeepan, J. Li and L. Ackermann, *Org. Chem. Front.*, 2017, 4, 1435–1467; (h) R. Manikandan and M. Jegamohan, *Chem. Commun.*, 2017, 53, 8931–8947.

14 (a) Y. Takahama, Y. Shibata and K. Tanaka, *Chem.–Eur. J.*, 2015, 21, 9053–9056; (b) X. F. Yang, X. H. Hu, C. Feng and T. P. Loh, *Chem. Commun.*, 2015, 51, 2532–2535; (c) Y. Lu, H. W. Wang, J. E. Spangler, K. Chen, P. P. Cui, Y. Zhao, W. Y. Sun and J. Q. Yu, *Chem. Sci.*, 2015, 6, 1923–1927; (d) K. Muralirajan, R. Haridharan, S. Prakash and C. H. Cheng, *Adv. Synth. Catal.*, 2015, 357, 761–766; (e) Z. Song, R. Samanta and A. P. Antonchick, *Org. Lett.*, 2013, 15, 5662–5665; (f) B. Liu, Y. Fan, Y. Gao, C. Sun, C. Xu and J. Zhu, *J. Am. Chem. Soc.*, 2012, 134, 468–473; (g) C. Feng and T. P. Loh, *Chem. Commun.*, 2011, 47, 10458–10460; (h) C. Wang, H. Chen, Z. Wang, J. Chen and Y. Huang, *Angew. Chem., Int. Ed.*, 2012, 51, 7242–7245; (i) X. Wei, F. Wang, G. Song, Z. Du and X. Li, *Org. Biomol. Chem.*, 2012, 10, 5521–5524; (j) D. Zhao, S. Vázquez-Céspedes and F. Glorius, *Angew. Chem., Int. Ed.*, 2015, 54, 1657–1661; (k) S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, 133, 2350–2353; (l) B. Gong, J. Shi, X. Wang, Y. Yan, Q. Li, Y. Meng, H. E. Xu and W. Yi, *Adv. Synth. Catal.*, 2014, 356, 137–143; (m) F. W. Patureau, T. Besset and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, 50, 1064–1067; (n) H. Wang, B. Beiring, D. G. Yu, K. D. Collins and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, 52, 12430–12434; (o) B. Li, J. Ma, W. Xie, H. Song, S. Xu and B. Wang, *Chem.–Eur. J.*, 2013, 19, 11863–11868; (p) P. Lu, C. Feng and T. P. Loh, *Org. Lett.*, 2015, 17, 3210–3213; (q) J. Wen, A. Wu, M. Wang and J. Zhu, *J. Org. Chem.*, 2015, 80, 10457–10463; (r) S. Rej and N. Chatani, *ACS Catal.*, 2018, 8, 6699–6706; (s) M. D. Boele, G. P. van Strijdonck, A. H. De Vries, P. C. Kamer, J. G. de Vries and P. W. van Leeuwen, *J. Am. Chem. Soc.*, 2002, 124, 1586–1587; (t) G. Cai, Y. Fu, Y. Li, X. Wan and Z. Shi, *J. Am. Chem. Soc.*, 2007, 129, 7666–7673; (u) A. García-Rubia, R. G. Arrayáis and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2009, 48, 6511–6515; (v) L. Ackermann, L. Wang, R. Wolfram and A. V. Lygin, *Org. Lett.*, 2012, 14, 728–731; (w) B. Li, J. Ma, N. Wang, H. Feng, S. Xu and B. Wang, *Org. Lett.*, 2012, 14, 736–739; (x) R. Manikandan, P. Madasamy and M. Jegamohan, *ACS Catal.*, 2015, 6, 230–234.

15 (a) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, 57, 10275–10274; (b) R. D. Taylor, M. MacCoss and A. D. Lawson, *J. Med. Chem.*, 2014, 57, 5845–5859.

16 (a) L. J. Goossen, J. Paetzold and L. Winkel, *Synlett*, 2002, 2002, 1721–1723; (b) L. J. Goossen and A. Döhring, *Synlett*, 2004, 2004, 263–266; (c) C. Zhao, X. Jia, X. Wang and H. Gong, *J. Am. Chem. Soc.*, 2014, 136, 17645–17651.

17 (a) R. Kakino, H. Narahashi, I. Shimizu and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2002, 75, 1333–1345; (b) L. J. Goossen and K. Ghosh, *Eur. J. Org. Chem.*, 2002, 2002, 3254–3267; (c) Y. T. Hong, A. Barchuk and M. J. Krische, *Angew. Chem., Int. Ed.*, 2006, 45, 6885–6888; (d) X. D. Zhao and Z. Yu, *J. Am. Chem. Soc.*, 2008, 130, 8136–8137; (e) W. Jin, Z. Yu, W. He, W. Ye and W. J. Xiao, *Org. Lett.*, 2009, 11, 1317–1320; (f) X. Qi, Y. Li, R. Bai and Y. Lan, *Acc. Chem. Res.*, 2017, 50, 2799–2808.