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Ru(II)-catalyzed oxidative (4+3) C–H/C–H annulation of 2-aryl-4H-pyrido[1,2-a]pyrimidin-4-ones with allyl alcohol†

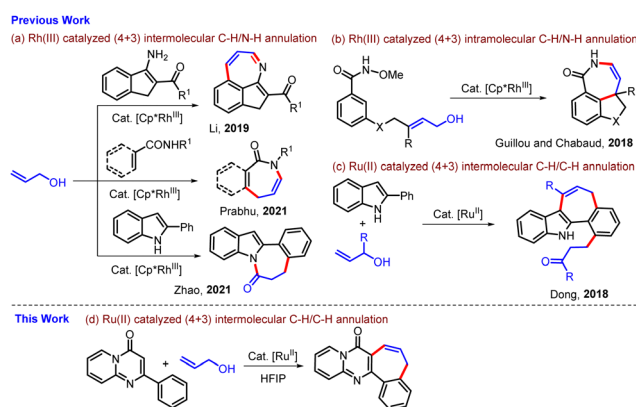
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A ruthenium(II)-catalyzed direct oxidative (4+3) C–H/C–H annulation of 2-aryl-4H-pyrido[1,2-a]pyrimidin-4-ones with allyl alcohol has been described. The developed method yielded the corresponding annulated products in moderate to good yields. In addition, based on the control experimental results, a possible reaction mechanism has been proposed for the (4+3) C–H/C–H annulation reaction.

Over the past few decades, transition metal-catalyzed C–H bond functionalization of inert C–H bonds has become an attractive and reliable alternative strategy to conventional cross-coupling methods in organic synthesis.¹ This approach is step- and atom-economic, avoids pre-functionalization of C–H bonds, and reduces the generation of salt wastes. In particular, a great deal of effort has been devoted to the direct functionalization of C(sp²)–H bonds with various transition metal catalysts by utilizing different coupling partners.² Among a large number of coupling partners such as alkynes, maleimides, alkenes, α -diazoketones, sulfonyl ylides, and strained rings, the use of allyl alcohols as coupling partners has attracted significant attention due to their relatively easy availability, unique reactivity, and stability.³ Several groups have reported transition metal-catalyzed (4+1),⁴ (4+2),⁵ (3+2),⁶ and (3+3)⁷-annulation reactions involving sequential C–H activation/intramolecular cyclization using allyl alcohol as a coupling partner for the synthesis of five- and six-membered rings. Synthesis of seven-membered ring motifs employing allyl alcohol as a coupling partner is limited and challenging. In this direction, a few groups

have described Rh(III)-catalyzed (4+3) intermolecular C–H/N–H annulation to construct an azepine ring using allyl alcohol as a coupling partner (Scheme 1a).⁸

Li's group, in their work on Rh(III)-catalyzed reaction of arylimides with allyl alcohols, observed that 3-aminoindenes, which were obtained as isolable intermediates on subsequent reaction with monosubstituted allyl alcohol, afforded densely fused azepines in moderate to good yields (Scheme 1a).^{8a} The reaction involves multiple oxidative C–H Heck reactions using allylic alcohols. The Prabhu group^{8b} synthesized benzazepinones and azepinones by the Rh(III)-catalyzed oxidative (4+3) C–H/N–H annulation of benzamides and cinnamamides with allyl alcohol while the Zhao group^{8c} prepared indolo[2,1-a]benzazepinones by Rh(III)-catalyzed (4+3) oxidative C–H/N–H annulation of 2-arylindoles with allyl alcohols (Scheme 1a). Guillou and Chabaud reported an Rh(III)-catalyzed intramolecular (4+3) oxidative C–H/N–H annulation of benzamide tethered allylic alcohols to prepare a variety of tricyclic benzazepinones (Scheme 1b).^{8d} Most of the reactions leading to seven-membered rings involving allyl alcohol are C–H/N–H annulation, and C–H/C–H annulation using allyl alcohol as a coupling partner is a rare and challenging task. In 2018,



Scheme 1 Transition metal-catalyzed (4+3) annulation using allyl alcohol leading to seven-membered rings.

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† Electronic supplementary information (ESI) available: Optimization table, experimental procedures, spectral data and copies of ¹H and ¹³C{¹H} NMR spectra of products 3aa–6aa and 7, and single crystal X-ray data for 3da. CCDC 2381520. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5cc00318k>

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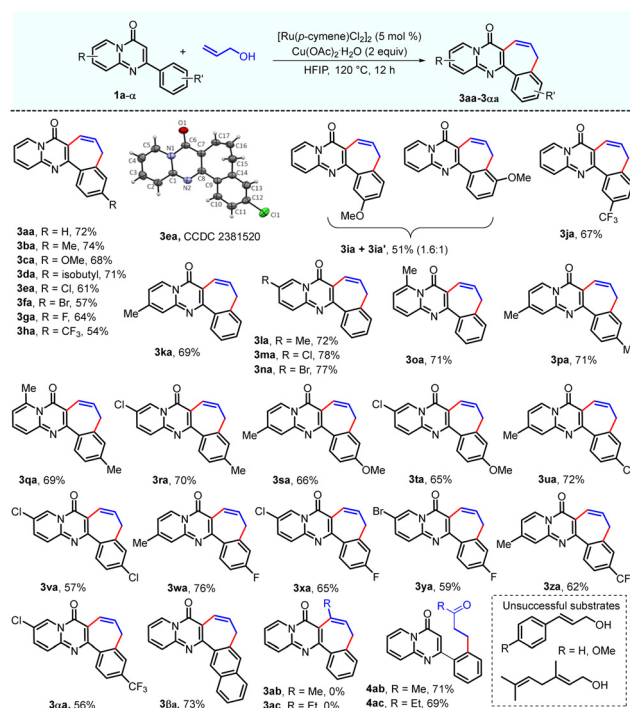
Dong and co-workers, in their work on Ru(II)-catalyzed coupling of allyl alcohols with indoles, showed a few examples of (4+3) C-H/C-H annulation reactions of allylic alcohols with 2-arylindoles leading to *ortho*-alkylated 5,12-dihydrobenzo[6,7]cyclohepta[1,2-*b*]indoles in moderate yields (Scheme 1c).^{8e} Learning from these examples and our continuing interest in transition metal-catalyzed functionalization of heterocycles,^{5b,9} herein, we report Ru(II)-catalyzed oxidative (4+3) C-H/C-H annulation of 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with allyl alcohol to synthesize benzo[6,7]cyclohepta[1,2-*d*]pyrido[1,2-*a*]pyrimidin-8(5*H*)-ones (Scheme 1d).

We started our investigation using 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1a**) and allyl alcohol (**2a**) as the starting materials. To our delight, a (4+3) C-H/C-H annulated product, benzo[6,7]cyclohepta[1,2-*d*]pyrido[1,2-*a*]pyrimidin-8(5*H*)-one (**3aa**), was obtained in 72% yield when **1a** was treated with **2a** in the presence of [Ru(*p*-cymene)Cl₂]₂ (5 mol%) as a catalyst and Cu(OAc)₂·H₂O (2 equiv.) as an oxidant in HFIP at 120 °C for 12 h (Table 1, entry 1). The replacement of HFIP by alternative solvents, such as TFE, DCE, DMF, 1,4-dioxane, and toluene (Table 1, entries 2–4; Table S1, ESI[†], entries 8 and 9), did not furnish the desired product except for TFE, which afforded **3aa** in 44% yield together with the *ortho*-C-H alkylated product (**4aa**) in 20% yield. In the case of DCE and 1,4-dioxane as the solvent, the (4+2) annulated product, 7-oxo-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazoline-6-carbaldehyde, (**5aa**) was obtained as the major product together with *ortho*-C-H alkylated product **4aa**. Results from solvent screening highlight the unique role of fluorinated alcohols (HFIP and TFE) for this annulative transformation. Lowering of the reaction temperature led to a decrease in the yield of **3aa** and an increase in the yield of **4aa** (Table 1, entries 5–7). We then scrutinized various other conditions to optimize the reaction conditions for this annulative reaction (see Table S1, ESI[†]). The best yield for **3aa** was obtained in HFIP using [Ru(*p*-cymene)Cl₂]₂ as a catalyst and Cu(OAc)₂·H₂O (2 equiv.) as an oxidant (Table 1, entry 1).

With the optimized reaction conditions in hand, the reactivity of different 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was investigated (Table 2). A series of 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-

4-ones (**1a–h**) featuring both electron-donating and electron-withdrawing groups on the *para*-position of the C2-phenyl ring were converted to the corresponding products (**3aa–ha**) in moderate to good (54–74%) yields. 2-(3-Methoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1i**) underwent the reaction to afford two regioisomeric products (**3ia** and **3ia'**) in a 1.6:1 ratio. This may be due to the coordination of the –OMe group with Ru metal in the catalytic cycle. However, 2-(3-(trifluoromethyl)-phenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1j**) produced only one regioisomer of the annulated product (**3ja**) by oxidative coupling at the less sterically hindered site, *i.e.* the *para*-position of the CF₃ group. It was observed that substrates with electron-donating groups at the *para*-position of the C2-phenyl ring produced higher yields of the corresponding annulated product as compared with those having electron-withdrawing groups at the *para*-position of the C2-phenyl ring. On the contrary, substrates with electron-donating groups at the *meta*-position of the C2-phenyl ring produced lower yields of the corresponding annulated products as compared with those having electron-withdrawing groups. This was also established by two independent one-pot competitive reactions of **1c/1h** with **2a** and **1i/1j** with **2a**, which produced the corresponding products **3ca/3ha** in 10:1 and (**3ia** + **3ia'**)/**3ja** in 1:13 ratios, respectively. Gratifyingly, the oxidative annulation of various 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**1k–o**) with substituents at different positions of the pyrido ring afforded the corresponding annulated products (**3ka–oa**) in good (69–78%) yields.

Table 2 Substrate scope for 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and allyl alcohols^{ab}



^a Reaction conditions: **1** (0.22 mmol), **2** (0.45 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol%), Cu(OAc)₂·H₂O (2 equiv.), HFIP (1.0 mL) in a sealed tube at 120 °C for 12 h. ^b Isolated yields.

Table 1 Optimization of the reaction conditions for **3aa**^a

Entry	Deviation from standard conditions	Yield ^b (%)		
		3aa	4aa	5aa
1	None	72	—	—
2	TFE was used as solvent	44	20	—
3	DCE was used as solvent	—	14	32
4	1,4-Dioxane was used as solvent	—	10	16
5	Reaction at 100 °C	58	12	—
6	Reaction at 80 °C	28	40	—
7	Reaction at 60 °C for 24 h	—	48 ^c	—

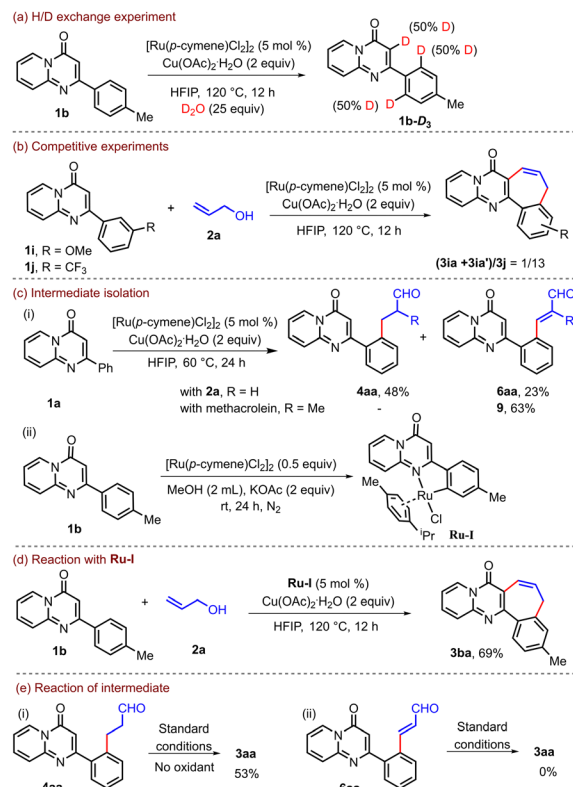
^a Reaction conditions: **1a** (0.22 mmol), **2a** (0.45 mmol, 2.0 equiv.), catalyst (5 mol%), oxidant (2 equiv.), solvent (1.0 mL) in a sealed tube at 120 °C for 12 h. ^b Isolated yield. ^c 3-(2-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)phenyl)acrylaldehyde (**6aa**) was also obtained in 23% yield.



The reaction of 2-aryl-4H-pyrido[1,2-a]pyrimidin-4-ones (**1p-α**) having substituents both on the C2-phenyl ring and pyrido ring with allyl alcohol (**2a**) also delivered the desired annulated products (**3pa-αa**) in moderate to good (56–76%) yields. Finally, the reaction of 2-(naphthalen-2-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**1β**) could also participate in this oxidative annulation to produce the corresponding annulated product **3βa** in a 73% yield. Reaction of **1a** with secondary allyl alcohols, but-3-en-2-ol (**b2**) and pent-1-en-3-ol (**c2**), produced the corresponding *ortho*-alkylated derivatives **4ab** and **4ac** in 71% and 69% yields, respectively, but failed to afford the desired annulated products **3ab** and **3ac** under these conditions. The γ -substituted allylic alcohols did not react under standard conditions. Notably, the protocol exhibited excellent compatibility for the halogen (F, Cl, and Br) groups that can be further engaged in additional late-stage functionalization of the products. The structure of all the synthesized products was confirmed by NMR (^1H and $^{13}\text{C}\{^1\text{H}\}$) and HRMS data. The structure of **3ea** was also unambiguously confirmed by a single crystal X-ray diffraction study (CCDC 2381520[†]).

To highlight the utility of the developed protocol, we successfully scaled the reaction of **1a** to 6 mmol. The reaction of **1a** (1.33 g, 6 mmol) with **2a** (0.70 g, 12 mmol) in the presence of $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ (5 mol%) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2 equiv.) in HFIP (8 mL) at 120 °C after 12 h produced **3aa** in 71% (1.11 g) yield (Scheme 2). The potential of **3aa** as a valuable scaffold for further synthetic transformations was then considered. The reaction of **3aa** with Lawesson's reagent^{8c} and NBS/MeOH^{8b} produced corresponding thio derivative **7** and bromomethoxylated product **8** in 71% and 78% yields, respectively (Scheme 2).

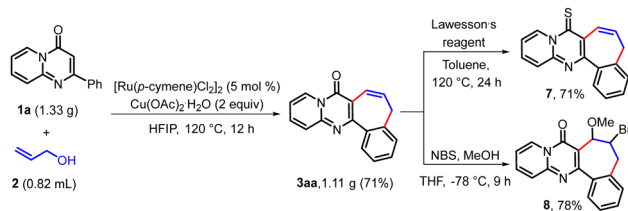
To learn more about the reaction mechanism, a few control experiments were performed (Scheme 3). A 50% hydrogen/deuterium exchange at both *ortho*-positions of the C2-phenyl ring and at the C3-position of the pyrido[1,2-a]pyrimidin-4-one nucleus was observed when the reaction of 2-(*p*-tolyl)-4H-pyrido[1,2-a]pyrimidin-4-one (**1b**) was conducted in HFIP/ D_2O under standard conditions in the absence of allyl alcohol (Scheme 3a). This result indicated that the *ortho* C–H bond is involved in the ruthenacycle formation during C–H activation, and this C–H bond activation is of a reversible nature. Intermolecular competition reaction of substrates with electron-donating and electron-withdrawing groups at the *meta*-position of the C2-phenyl ring **1i** and **1j** with **2a** produced the corresponding annulated products (**3ia** + **3ia'**) and **3ja** in 1:13 ratio in favor of C2-phenyl ring with an electron-withdrawing group at the *meta*-position (Scheme 3b). This result supports that the reaction proceeds *via* a concerted metalation-deprotonation (CMD)¹⁰ pathway rather than a Friedel–Craft-type



Scheme 3 Control experiments.

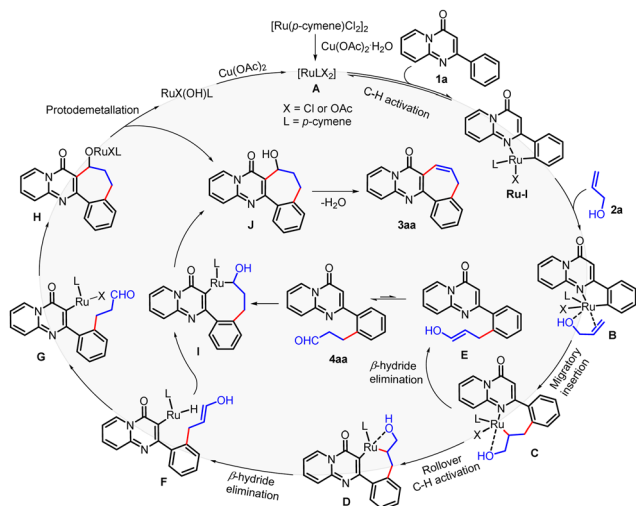
electrophilic aromatic substitution pathway. The reaction of **1a** with **2a** in the presence of $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ (5 mol%) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2 equiv.) in HFIP at 60 °C for 24 h produced an *ortho*-alkylated product (**4aa**) and *ortho*-alkenylated product (**6aa**) in 48% and 23% yields, respectively (Scheme 3c(i)). Furthermore, the reaction of **1a** with methacrolein produced only alkenylated product **9** in 63% yield (Scheme 3c(ii)). The stoichiometric reaction of **1b** with $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ in methanol at room temperature produced a five-membered ruthenacycle intermediate **Ru-I** (Scheme 3c(ii)). Subsequently, the reaction of **1b** and **2a** under the optimal conditions using **Ru-I** (5 mol%) as a catalyst instead of $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ afforded **3ba** in 69% yield (Scheme 3d), indicating that the developed annulation reaction proceeds through cyclometalated complex **Ru-I**. Finally, the reaction of intermediate **4aa** under standard reaction conditions without an oxidant gave the desired product **3aa** in 53% yield, whereas intermediate **6aa** failed to produce **3aa** (Scheme 3e).

Although the mechanism of the (4+3) C–H/C–H annulative reaction still remains to be established, on the basis of preliminary results from control experiments and previous literature reports¹¹ we proposed a plausible mechanistic sequence for the formation of product **3** (Scheme 4). After the generation of active ruthenium complex intermediate **A**, it reacts with **1a** to form five-membered ruthenacycle intermediate **Ru-I** *via* reversible C–H bond activation through a concerted metalation-deprotonation (CMD) mechanism.¹⁰ Coordination of **2a** with **Ru-I** produces complex **B** which on subsequent 1,2-migratory insertion into the Ru–C bond of **Ru-I** produces a seven-membered ruthenacycle **C**.



Scheme 2 Gram-scale synthesis and chemical transformations of **3aa**.





Scheme 4 Proposed reaction mechanism.

Next, intermediate **C** undergoes 'rollover C-H activation',¹² to produce a seven-membered ruthenacycle intermediate **D**, which on β -hydride elimination produces intermediate **F**. Intermediate **F** tautomerizes to **G** (detected in LC-HRMS m/z 513.1121 $[M]^+$) which then either produces intermediate **H** or ruthenacycle **I**. Protodemetalation of **H** or reductive elimination of **I** generates intermediate **J** (detected in LC-HRMS m/z 279.1125 $[M + H]^+$), which on dehydration produces the desired product **3aa**. The catalytic cycle involving the formation of intermediate **4aa** from seven-membered ruthenacycle **C** by reductive elimination followed by tautomerization cannot be ruled out. Ruthenium and HFIP-assisted cyclodehydration of intermediate **4aa** can produce the desired (4+3) annulated product **3aa**.

In summary, we have developed a Ru(II)-catalyzed (4+3) oxidative C-H/C-H annulation of 2-aryl-4H-pyrido[1,2-*a*]pyrimidin-4-ones with allyl alcohols leading to the formation of benzo[6,7]cyclohepta[1,2-*d*]pyrido[1,2-*a*]pyrimidin-8(5H)-one derivatives in moderate to good yields. The reaction features good substrate scope with respect to pyrido[1,2-*a*]pyrimidin-4-one with excellent functional group tolerance. The efficacy of the method was demonstrated by gram-scale synthesis of **3aa**. In addition, based on a preliminary mechanistic study, a plausible mechanism of (4+3) C-H/C-H annulation reaction is proposed.

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crystallographic data. A. K. designed and developed this project, and wrote the manuscript with the help of all of the authors.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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