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FULL PAPER

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Synthesis of functionalized pyrimidouracils by ruthenium-catalyzed oxidative insertion of (hetero)aryl methanols into *N*-uracil amidines

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A dehydrogenative coupling of *N*-uracil amidines with (hetero)aryl methanols has been developed, allowing for the facile synthesis of a broad range of structurally diverse pyrimidouracils. By applying $[RuCl_2(p\text{-cymene})]_2/Cs_2CO_3$ as an efficient catalytic system, the easily available, cheap (hetero)aryl methanols were firstly employed for oxidative insertion/C—H amination into the *N*-uracil amidines, providing highly functionalized pyrimido[4,5-*d*]pyrimidine-2,4-diones. Due to the better stability of alcohols than aldehydes, this synthetic protocol is applicable to a broad range of alcoholic substrates and does not required any protection during the whole preparation process. The presented protocol has the potential to prepare valuable products which cannot be accessed presently or extremely arduous to procure by following regular procedure. Hence, this is a remarkably improved protocol compared with the existing methodologies. The overall reaction sequence is an effective oxidation-imination-cyclization tandem process catalyzed by ruthenium catalyst.

KEYWORDS

(hetero)aryl methanols, *N*-uracil amidine, oxidation, pyrimidopyrimidine, ruthenium catalyst, tandem process

1 | INTRODUCTION

Nitrogen-containing heterocycles are very important structural motifs found in numerous natural products and potent pharmaceutical drugs.[1] These molecules also enjoy widespread application in the field of organic synthesis, agrochemicals, pesticides, and pharmaceuticals industries.[2] For these reasons, several efforts have been paid to develop novel and efficient methods for the synthesis of this class of molecules.[3] Over the past decade, the transition metal–catalyzed C—H bond activation/C—H amination has achieved remarkable progress for the construction of nitrogen heterocycles because of its economic, sustainable, and environmentally benign features.[4] Leaving out the necessity for preactivation shortens the total number of required synthetic steps and creates less waste. Transition metal catalyzed such as C—N bond forming reactions is therefore a methodology contributing to the important field of sustainable chemistry.

Pyrimidines are one of the most important nitrogen heterocycles, exhibiting remarkable pharmaceutical activities.[5] Fused pyrimidines scaffolds such as pyrimidouracils and pyrimidopyrimidines are the important classes of annulated pyrimidines found in various drug candidates and natural products showing a broad spectrum of biological activities,[6] such as adenosine potentiating (coronary dilators),[7] anticancer,[8] antiviral,[9] antifungal,[10] antioxidant,[11] antitumor,[12] and hepatoprotective.[13] Compounds with these ring systems are also useful as bronchodilators,[8] vasodilators,[14] antiallergic,[15] and antihypertensive[16] agents. Moreover, similar molecules

have also been act as phosphoribosyl-1-pyrophosphate synthetase inhibitors[17] and dihydrofolate reductase inhibitors.[18] For example, pyrimidopyrimidine-based compound such as dipyridamole is a medicine that performs several functions like phosphodiesterase enzyme inhibition and lowering of pulmonary hypertension.[19] This medicine has also been found to be used in echocardiography and electrocardiogram. Folic acid conjugated pyrimido[4,5-*d*]pyrimidine analogues is currently undergoing clinical trials as an antitumor agent.[20] Although these pyrimido[4,5-*d*]pyrimidines show a broad range of biologically activities, the current synthesis[21–23] of these scaffolds have very limited scope, utilize highly specific reactions, or require harsh reaction conditions. The most frequently used methods to construct pyrimido[4,5-*d*] pyrimidine-2,4-diones (pyrimidouracils) mainly rely on the multicomponent reactions (MCRs) using 6-aminouracils[21] or the cycloaddition reactions involving 6-methylideneaminouracils and electron-deficient substrates.[22] The cycloaddition reactions are limited to electron deficient substrates only, and hence, those not offer liberal scope for the preparation of products. Interestingly, functionalized pyrimidouracils can be synthesized via the direct condensation of aromatic aldehydes and *N*-uracil amidines.[24] However, the use of aldehydes as the coupling partners poses several shortcomings like (a) some active aldehyde groups may undergo an oxidation reaction which can potentially form unwanted by-products, and therefore, for resisting this, inert conditions are required[25]; (b) some reactive aldehydes may undergo a decarbonylation reaction under tough reaction conditions[26]; (c) moreover, high cost or nonavailability of some aldehydes such as heteroaryl ones restricted the synthesis of variable products. In order to alleviate these shortcomings, it is necessary to develop more viable and sustainable chemical procedures for the synthesis of this class of molecules. Recently, a synthetic protocol have been developed by Deb and coworkers for the preparation of 5,6-dihydropyrimidouracils involving three-component reaction between 6-aminouracil, aldehyde and tetrahydroisoquinolines under solid state reaction conditions.[27] We have also shown that pyrimidouracils could be achieved by the direct annulation of *N*-uracil amidines with methylarenes under oxidative reaction conditions.[28] Very recently, Bert and coworkers reported the synthesis of 4-amino-substituted pyrimidouracils by nickel(II)-catalyzed isocyanide insertion into *N*-uracil amidines.[29] Therefore, it is imperative to search for readily available, cheap, and stable substitutes of aldehydes which would usher in fresh avenue for the synthesis of pyrimidouracils.

Of late, in carbon–carbon (C—C) and carbon-nitrogen (C—N) bond formations, the utilization of sustainable alcohols has gained prominence.[30] Alcohols are known to be stable and less toxic. Beside these, they are cheap, readily accessible, and easier to handle than aldehydes. Therefore, it is comfortable to use alcohols as starting material in different chemical transformations. By applying suitable oxidizing reagents, the dehydrogenative oxidation of alcohols leads to in situ formation of aldehydes. Thus, the oxidation of alcohols is to be considered as a key step in the formation of products.[31,32] On the basis of these findings, it can be assumed that alcohols could be applied as *latent* aldehydes for the preparation of aryl substituted pyrimidouracils starting from *N*-uracil amidines (Scheme 1). The use of alcohols has several advantages such as they are inexpensive as compared with aldehydes, thermodynamically more stable, abundance, and sustainable. Therefore, by replacing aldehydes with alcohols would allow us to synthesize functionalized pyrimidouracils of biological interest.

Herein, the endeavor is to develop a new protocol for the synthesis of N1, N3, C5, and C7 tetrasubstituted pyrimidouracils directly from *N*-uracil amidine and (hetero)aryl methanols under ruthenium-catalyzed dehydrogenative oxidation conditions. The starting materials, the *N*-uracil-amidines **1**, can readily be obtained from 6-chlorouracil by the nucleophilic substitution reactions with amidines.[24,33] The overall reaction process is the oxidation-imination-cyclization tandem process catalyzed by ruthenium catalyst. The requisite amidine substrates can be easily prepared from the corresponding nitriles and ammonia by applying Pinner approach.[34] The substituent (R) at C7 position of the products was installed from these amidines. To the best of our knowledge, such synthetic protocol using inexpensive (hetero) aryl methanols was firstly employed for the synthesis of substituted pyrimido[4,5-*d*]pyrimidine-2,4-diones (pyrimidouracils).

2 | RESULTS AND DISCUSSION

With the above described idea in mind, the possibility of direct synthesis of tetrasubstituted pyrimidouracils (**3a**) from *N*-uracil amidine (**1a**) and benzyl alcohol (**2a**) (Table 1) were examined. The reaction was initially conducted at 110°C for 15 h using 1.5 equivalent of K_2CO_3 in dimethylsulfoxide (DMSO). However, even trace amounts of the desired product were not obtained (Table 1, entry 1). The desired product of pyrimido[4,5-*d*] pyrimidine-2,4-dione (**3a**) was obtained in 19% yield when 2 mol% of $RuCl_3$ was introduced into the reaction mixture under the same conditions (Table 1, entry 2). Encouraged by this result, the screening of ruthenium catalysts (Figure 1) using the same reaction conditions was performed (Table 1, entries 2–7). [$RuCl_2$(*p*-

SCHEME 1 Direct oxidative and oxidative imidoylative amination of *N*-uracil-amidines

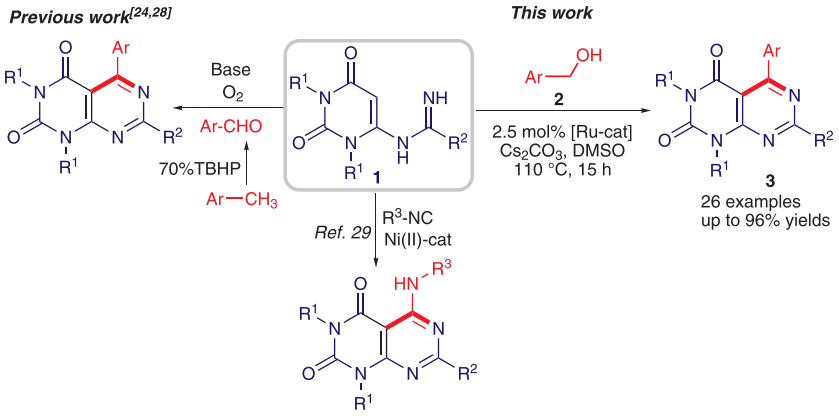
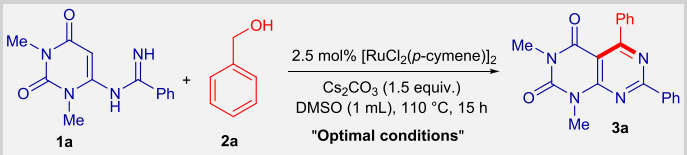


TABLE 1 Optimization of conditions for the oxidative insertion of benzyl alcohol (**2a**) into *N*-uracil benzamidine (**1a**), towards the synthesis of pyrimidouracil (**3a**)



Entry	Catalyst (2 mol%)	Base (1.5 eq.)	Solvent (1 ml)	Yield (%)[a]
1	-	K_2CO_3	DMSO	-
2	Cat 1	K_2CO_3	DMSO	19
3	Cat 2	K_2CO_3	DMSO	27
4	Cat 3	K_2CO_3	DMSO	20
5	Cat 4	K_2CO_3	DMSO	32
6	Cat 5	K_2CO_3	DMSO	43
7	Cat 6	K_2CO_3	DMSO	52
8	Cat 6	K_3PO_4	DMSO	37
9	Cat 6	KOAc	DMSO	31
10	Cat 6	Cs_2CO_3	DMSO	70
11	Cat 6	DBU	DMSO	14
12	Cat 6	Et_3N	DMSO	>10
13	Cat 6	Cs_2CO_3	DMF	61
14	Cat 6	Cs_2CO_3	Toluene	30
15	Cat 6	Cs_2CO_3	THF	37
16	Cat 6	Cs_2CO_3	^{t}BuOH	41
17[b]	Cat 6	Cs_2CO_3	DMSO	69
18[c]	Cat 6	Cs_2CO_3	DMSO	66
19[d]	Cat 6	Cs_2CO_3	DMSO	85
20[e]	Cat 6	Cs_2CO_3	DMSO	84

Note: Reaction conditions: unless otherwise specified, all reactions were performed out without inert gas protection by using **1a** (0.5 mmol, 1 eq.), **2a** (0.75 mmol, 1.5 eq), catalyst (2 mol%), base (0.75 mmol, 1.5 eq), solvent (1 ml), 110°C, 15 h.

Abbreviations: DMF, dimethylformamide; DMSO, dimethylsulfoxide; THF, tetrahydrofuran.

[a]Isolated yield of **3a**.

[b]Reaction time 20 h (entry 17).

[c]Reaction carried out at 120°C (entry 18).

[d]Reaction performed with 2.5 mol% catalyst (entry 19).

[e]Reaction performed with 3 mol% of catalyst (entry 20).

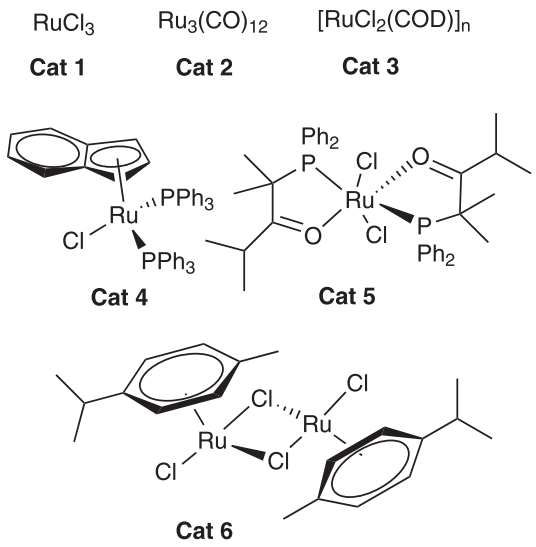


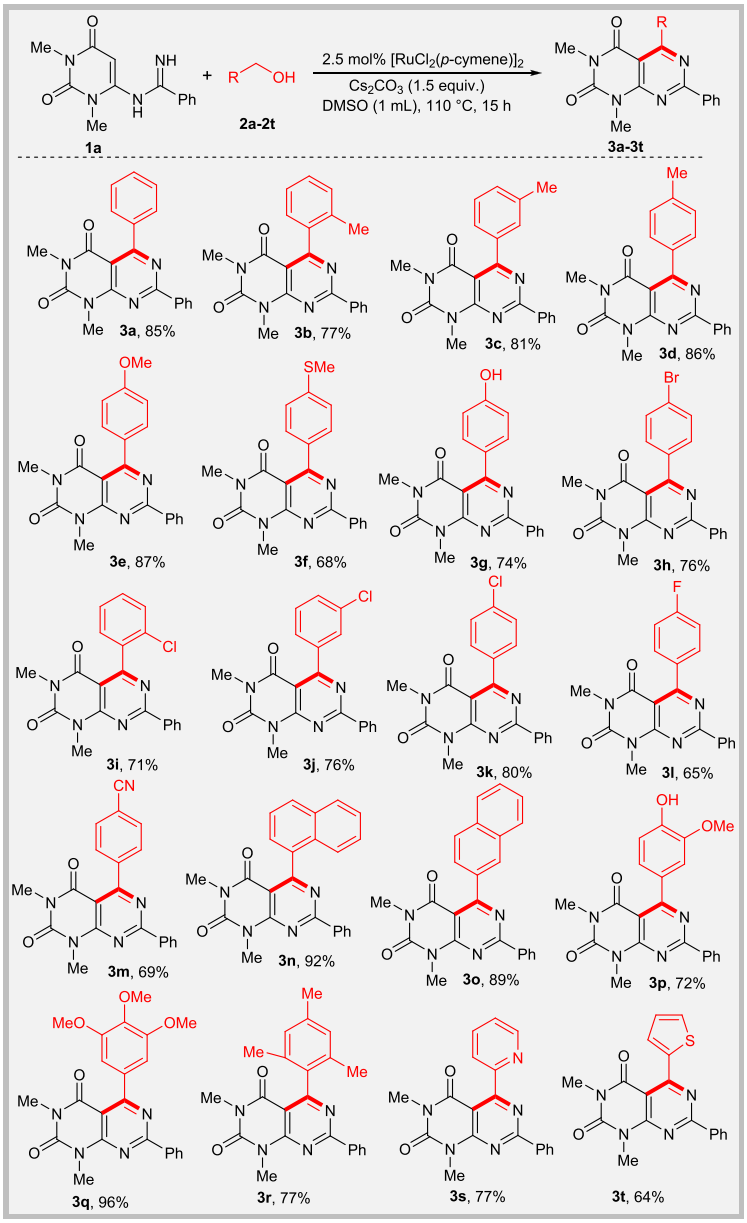
FIGURE 1 Different catalysts used in the optimization reaction

Cymene)]$_2$ (**Cat 6**) was found to be the preferred catalyst, providing the desired product **3a** in 52% yield (Table 1, entry 7). Screening of different bases such as K_3PO_4, KOAc, Cs_2CO_3, Et_3N, and DBU (Table 1, entries 8–12) using [$RuCl_2$(*p*-cymene)]$_2$ as a catalyst in DMSO solvent showed that the organic bases are less effective for the formation of the product (Table 1, entries 11 and 12), whereas Cs_2CO_3 gave a significantly higher yield (Table 1, entry 10). Thus, [$RuCl_2$(*p*-cymene)]$_2$ was selected as preferred catalyst and Cs_2CO_3 as preferred base. Next, screening of other solvents was performed. The results indicated that tested solvents are less effective compared with that of DMSO (Table 1, entries 13–16). When the chosen catalyst, base and solvent were employed, it was observed that the increase of reaction time or reaction temperature did not have any significant effect on this transformation (Table 1, entries 17 and 18). However, when the catalyst loading was increased from 2 to 2.5 mol%, it resulted in an increased yield of the product (85%) (Table 1, entry 19). But further rise in catalyst loading did not have any effect on yield of the product (Table 1, entry 20). Hence, the optimum reaction conditions as far optimized are stated as follows: 2.5 mol % of [$RuCl_2$(*p*-cymene)]$_2$, 1.5 equiv. of Cs_2CO_3, DMSO (1 ml) as solvent, and at 110°C (Table 1, entry 19).

After optimization of the reaction conditions, the scope and limitations of this synthetic protocol were tested. First of all, the reaction of different (hetero)aryl methanols **2** with *N*-uracil benzamidine **1a**, affording pyrimidouracils **3** was investigated. The results of the reactions are summarized in Table 2. The synthetic protocol has been found to work well with a range of (hetero)aryl methanols (**2a—2t**) bearing *ortho*-, *meta*-, and *para*-, or multiple substituents and furnished desired products in good to excellent yields. Under the optimal reaction conditions, aryl methanols bearing electron-donating substituents such as Me, —OMe, —SMe, —OH including halogen (—Cl) produced respective pyrimidouracils **3b–3g** and **3p–3r** in very good yields (68%–96%) whereas aryl methanols bearing strong electron-withdrawing groups such as F and CN produced to some extent lower yield of the products **3l** and **3m**. It has been observed that aryl methanols having *para*- and *meta*-substituents yielded higher products than those with *ortho*-substituents (**2b, 2i, 2r**). This may be due to the steric hindrances in *ortho*-substituted alcohols. Moreover, when the same *N*-uracil amidine (**1a**) is used, the substituents on the aryl ring of aryl methanols possessing different electron properties slightly influence the product yields. In general, electron-rich substrate such as aryl methanols containing methoxy group (—OMe) yielded relatively higher products (**3e**, **3q**), which could be attributed to its better inherent stability compared with other aryl methanols. Apart from this, 1-naphthalenemethanol as well as 2-naphthalenemethanol have been found to smoothly react with *N*-uracil amidine under the optimal reaction conditions providing **3n** and **3o** in 92% and 89% yields, respectively. The oxidation-sensitive functional groups such as a thiomethyl group (**2f**) were found to be compatible with the reaction conditions. The reaction also proceeded smoothly with the use of multiple substituted aryl methanols which delivered the desired products (**3p–3r**) in high yields. Two representative hetero (aryl) methanols such as pyridin-2-ylmethanol (**2s**) and thiophen-2-ylmethanol (**2t**) have been found to smoothly couple with *N*-uracil benzamidine, producing the corresponding pyrimidouracils **3s** and **3t** in 77% and 64% yields, respectively. However, the reaction of aliphatic alcohols such as *n*-propanol and pivalyl alcohol with **1a** failed to yield even trace amounts of the expected products. In the process, not even the starting material **1a** could be isolated. This phenomenon might be attributed to simple aliphatic alcohols being more challenging in respect of dehydrogenation than that of aryl methanols' and the amidine undergoes a decomposition prior to the dehydrogenation of alcohol. Hence, the rate of dehydrogenative oxidation of alcohols is an important factor in the formation of products.

In order to extend the scope of this protocol, the reactions of different *N*-uracil benzimidamides (**1b–1h**) with benzyl alcohol (**2a**) were explored (Table 3). It was observed that a variety of substituents including electron-donating as well as electron-withdrawing groups on the aryl ring of the *N*-uracil benzimidamide were tolerated under the optimum reaction conditions. However, less stable alkyl amidines such as acetamidine having a

TABLE 2 The reactions of *N*-uracil benzamidine (**1a**) with various hetero (aryl) methanols (**2**)[a,b]

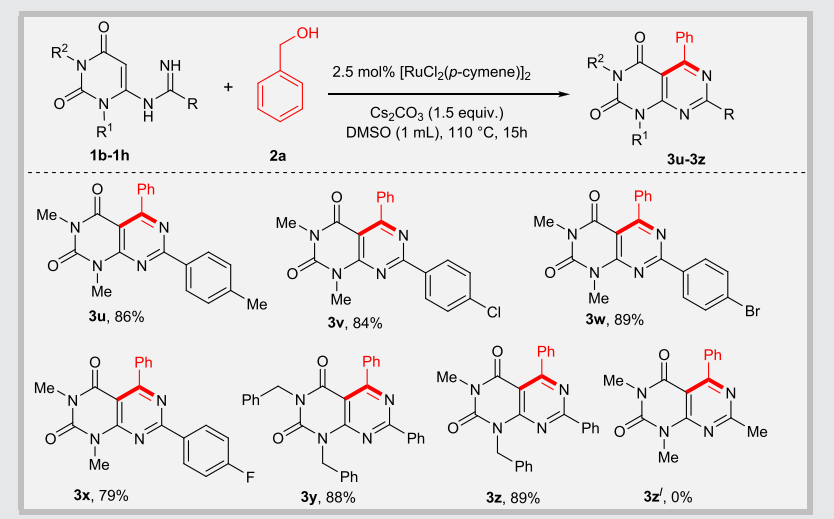


[a]Reaction conditions: Substrate **1a** (0.5 mmol), **2a** (0.75 mmol), Ru-catalyst (2.5 mol%), Cs_2CO_3 (0.75 mmol), DMSO (1 ml), 110°C, 15 h.
[b]Isolated yield.

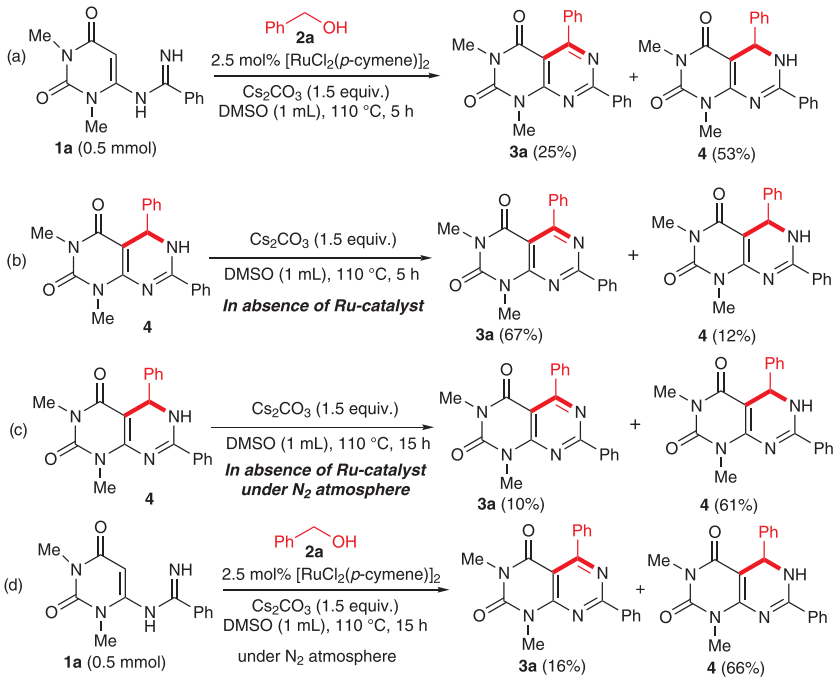
methyl at the R position (**1h**) could not yield the expected product even with benzyl alcohol **2a**. Notably, the *para*-bromo-substituted pyrimidouracils **3h** and **3w** were obtained in very good yields. It was delightful to find this protocol's compatibility for the preparation of fluorine substituted pyrimidouracils (**3l** and **3x**), which have a major influence on the pharmacological properties of a drug.[35] The protocol also goes well with *N*-protected uracils such as *N*-(1,3-dibenzyl uracilyl)benzimidamide (**1f**) and *N*-(1-benzyl-3-methyl uracilyl)benzimidamide (**1g**). When these substrates (**1f** and **1g**) react with benzyl alcohol (**2a**), the corresponding pyrimidouracils **3y** and **3z** are produced in 88% and 89% yields, respectively. Interestingly, deprotection of these products[36] may allow modification on the uracil moiety through *N*-alkylation/*N*-arylation or dehydrochlorination followed by S_NAr reaction. These synthetic modifications are particularly interesting for the drug development purposes in the pharmaceutical industry.[37]

In order to investigate the mechanism for the formation of products (**3**), some control experiments were performed (Scheme 2). It was observed that the compound

TABLE 3 The reactions of various *N*-uracil amidines (**1b–1h**) with benzyl alcohol (**2a**)[a,b]



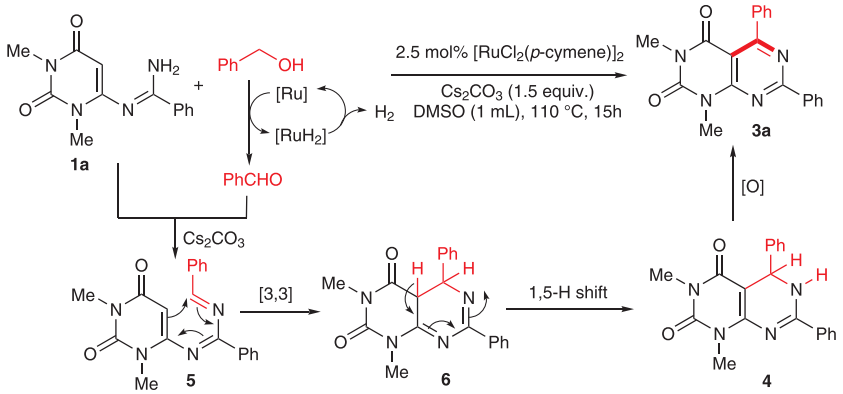
[a]Reaction conditions: Substrate **1a** (0.5 mmol), **2a** (0.75 mmol), Ru-catalyst (2.5 mol%), Cs_2CO_3 (0.75 mmol), DMSO (1 ml), 110°C, 15 h.
[b]Isolated yield.



SCHEME 2 Some control experiments

4 was formed as major product (53%) when the reaction was run for 5 h (Scheme 2a). Interestingly, when substrate **4** was heated at 110°C in absence of ruthenium catalyst, it produced **3a** in good yield along with **4** (12%) (Scheme 2b). From these experiments, it was presumed that the reaction proceeded through the formation of **4** and Ru-catalyst may not be essential for the oxidation of **4** into **3a**. Because the reactions were performed in open air, aerial oxygen might play some important role in the oxidation process. To confirm this, the compound **4** was heated at 110°C for 15 h under N_2 atmosphere in absence of ruthenium catalyst, which resulted only 10% of **3a** (Scheme 2c). Moreover, a control reaction under N_2 atmosphere was performed, which resulted 16% of **3a** and 66% of **4** (Scheme 2d). These reactions confirm that molecular oxygen (O_2) is necessary for the

SCHEME 3 Proposed mechanism for the formation of pyrimido[4,5-*d*]pyrimidin-2,4-diones



dehydrogenative oxidation of **4** into **3a**. However, oxygen balloon is not required for the supply of oxygen. In the whole process, hydrogen and water molecules are produced as by products, confirming the greenness of the protocol.[38]

On the basis of the previous accounts reporting the progress of transition-metal catalyzed oxidation of alcohols[31,32] and boosted by control experiments, a probable reaction mechanism for the generation of **3** is being suggested in Scheme 3. Initially, the ruthenium-catalyzed dehydrogenative oxidation of aryl methanol[31] formed an aldehyde (**A**) which was then reacted with *N*-uracil amidine **1a** to produced intermediate azadiene **5**.[39] The intermediate **5** is then undergoes an intramolecular cycloaddition reaction followed by a [1,5]-hydrogen shift. These resulted in the formation of the intermediate 5,6-dihydropyrimido[4,5-*d*]pyrimidine **4** which on aerial oxidation process yielded the desired product **3a**.

3 | CONCLUSION

To summarize, an efficient and operationally simple protocol has been developed for the synthesis of densely functionalized pyrimidouracils from inexpensive and easily available hetero(aryl) methanols and *N*-uracil amidines by using commercially available $[RuCl_2(p\text{-cymene})]_2$ as a catalyst. Readily available alcohols were employed as effective aldehyde precursors in the oxidation-imination-cyclization transformation. The presented protocol has several advantages such as better inherent stability of alcohols compared with aldehydes, operationally simple, and starting materials are easily accessible. This protocol is a significantly important complement to the existing synthetic methodologies. Considering the importance of pyrimidouracils in pharmacological field,[37] and material chemistry, this synthetic strategy has the potential to be used in applications of not only in drug discovery but also in chemical development projects.

4 | EXPERIMENTAL

4.1 | Instruments and reagents

All the chemicals and reagents were commercially available and purchased from Sigma-Aldrich, Alfa-Aesar, Spectrochem, TCI Chemicals and used as received without further purification. Silica gel, 60-120 and 230-400 mesh were purchased from Spectrochem, India and used for chromatographic separation. Flash column chromatography was performed over silica gel and 230-400 mesh. TLC plates were purchased from Merck and used for thin-layer chromatography (TLC). All solvents were distilled prior to use in extraction and purification purposes. Melting points were measured on silicon oil bath using open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ascend 400 MHz spectrometer (Bruker, Germany) at 400 and 100 MHz, respectively using $CDCl_3$ or DMSO-d_6 solvents. Chemical shifts values are given in parts per million (ppm, δ) with reference to tetramethylsilane (TMS) as internal standard. Proton coupling patterns are described as follows: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; and dt, doublet of triplets. The coupling constants are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were measured on a quadrupole time-of-flight (Q-TOF) mass spectrometer (Make: Waters; Model: Xevo XS) operated in the positive mode by applying an electrospray ionization (ESI) method.

4.2 | General procedure for ruthenium-catalyzed oxidative insertion of hetero(aryl) methanols (2) into *N*-uracil amidines (1) towards the synthesis of pyrimidouracils (3)

N-Uracil amidine (0.5 mmol, 1.0 equiv.), hetero (aryl) methanol (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol, 8 mg) and Cs_2CO_3 (0.75 mmol, 244 mg) were added in an

oven-dried microwave vial (10 ml) equipped with a magnetic stirring bar. To this mixture, 1 ml of DMSO was added by syringe and the tube was sealed without inserting any gas protection. The reaction mixture was stirred in an oil bath at 110°C for 15 h. After completion of reaction, the mixture was cooled to room temperature. The mixture was then stirred with ethyl acetate (10 ml) and brine (10 ml) for 15 min. The aqueous layer was extracted with ethyl acetate (2 × 10 ml). Finally, the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The crude products were purified by either column chromatography on silica gel (60–120 mesh) or flash column chromatography (230–400 mesh) using a mixture of hexane-ethyl acetate as the eluent to afford the title compounds.

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AUTHOR CONTRIBUTIONS

Pradip Debnath: Conceptualization; data curation; formal analysis; funding acquisition; investigation; project administration; supervision. **Gouranga Sahu:** Data curation; formal analysis; methodology. **Utpal De:** Data curation; formal analysis; software.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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