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Iron Catalyzed Synthesis of Pyrimidines Under Air

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Abstract. Herein we report an iron-catalyzed multicomponent dehydrogenative functionalization of alcohols to pyrimidines under atmospheric conditions. Using a well-defined Fe(II)-complex featuring redox noninnocent 2-phenylazo-(1,10-phenanthroline) ligand, as a catalyst, a wide array of 2,4,6-trisubstituted pyrimidines were prepared via dehydrogenative coupling of primary, and secondary alcohols with amidines under air at 100°C. A few control experiments were carried out to understand and unveil the plausible reaction mechanism.

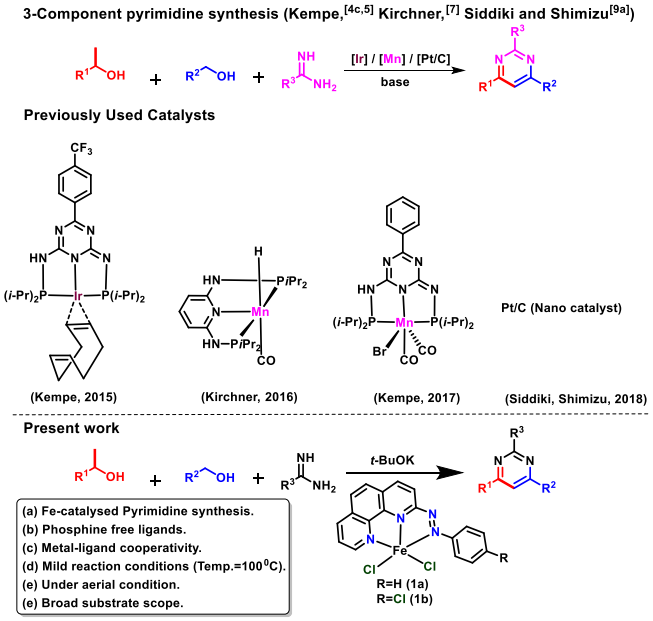
Keywords: redox-active ligands; iron catalysis; metal-ligand cooperativity; multicomponent dehydrogenative coupling; pyrimidines

Introduction

Alcohols have been an environmentally benign and sustainable starting material for synthesis chemistry.[1] Lignocellulose biomass, which is prevalent in nature, can easily serve as the raw material for alcohol production. This, in turn, reduces the dependence on the decreasing fossil fuel resources. Functionalization of alcohol to different important products thus continues to be an active area of research.[1-10]

Over the last decade, several research groups have been working on the functionalization of alcohols to various complex organic molecules, including organo-heterocycles. The groups of Milstein,[2,3] Kempe,[4,5] Kirchner,[6,7] Sun,[8] and a few others[9,10] have made a significant contribution on the synthesis of various N-heterocycles like quinoline, quinazoline, pyrrole, pyrimidine, pyridine, etc. using alcohol as the primary feedstock. Most of these reactions reported till now are mostly based on expensive and scarce late transition metal catalysts such as ruthenium,[2,9f] iridium,[5,9c-e] palladium,[9a] rhenium,[6] etc. However, reports with inexpensive and earth-abundant base metal catalysts are limited.[3,5,7,10] Therefore, to make the sustainable dehydrogenative alcohol functionalization reactions more environmentally benign and economically affordable, the expensive and scarce noble metals need to be substituted by comparatively less costly and environmentally benign base metals such as manganese,[3a-b,5,7,10a-c] iron,[10d] cobalt,[3c-d,10e-f] nickel,[10g-i] etc.

Pyrimidine(s), among the various N-heterocycles, possess a strong identity because of its presence in living systems as well as due to its wide application in medicinal chemistry.[11] Besides, they also function as photoactive materials in light-emitting devices.[12] Traditionally pyrimidines are prepared via transition metal-catalyzed condensation/cyclization reactions, which require expensive noble metals as catalysts, stoichiometric, or excess amounts of strong oxidants and the reactions are carried out at high temperature.[13] Therefore, sustainable and economically affordable mild synthesis of pyrimidines from inexpensive and readily available starting materials is desirable.



Scheme 1. Synthesis of pyrimidines via three-component dehydrogenative coupling using alcohols as key feedstock.

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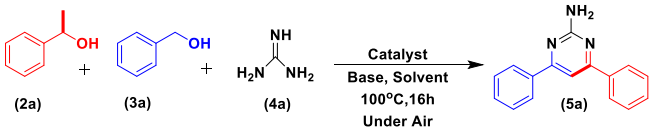
In 2015, Kempe and co-workers reported an iridium-catalyzed sustainable synthesis of pyrimidines via a multicomponent dehydrogenative coupling reaction of alcohols with amidines.[4c] Later on, Kempe[5] and Kirchner[7] independently improvised this strategy using abundantly available manganese-based catalysts. However, the tedious multistep synthesis of air-sensitive phosphine ligands and the requirement of high temperature (≥130°C) may limit its large scale industrial application. Very recently, Siddiki and Shimizu reported a heterogeneous catalytic approach for the synthesis of pyrimidines using platinum nanoparticles as a catalyst.[9a] Therefore, it would be worth to achieve these reactions using abundantly available 3d-base metal catalysts under relatively less demanding conditions.

Recently, we reported catalytic dehydrogenation of alcohols at 75°C under aerial conditions using well defined iron(II)-complexes, [FeL$^{a/b}$Cl$_2$] (**1a**, **1b**) featuring redox-active 2-arylazo-(1,10-phenanthroline) ligands, **L$^{a/b}$** (**L^{a}** = 2-(phenyldiazenyl)-1,10-phenanthroline; **L^{b}** = 2-((4-chlorophenyl)diazenyl)-1,10-phenanthroline) as catalysts (Scheme 1).[14] Mechanistic investigations revealed that iron and the 2-arylazo-(1,10-phenanthroline) moiety participate synergistically during dehydrogenation of alcohols. In the presence of reducing agents or excess *t*-BuOK, the iron(II)-catalyst, **1b** undergoes one-electron ligand-centered reduction to form azo-anion radical species [**1a**]$^-$ which then acts as the active catalyst. The iron-stabilized azo-anion radical abstracts hydrogen atom of the alcohol via a one-electron hydrogen atom transfer (HAT) process to form a ketyl radical intermediate, which on subsequent rapid one-electron oxidation produce the desired carbonyls.[14a] Active participation of azo-anion radical ligand allows avoiding the energetically demanding iron-centered two-electron Fe(II)/Fe(IV) redox events, which in turn made it possible to achieve the dehydrogenation reaction at 75°C. To further expand the scope of the iron-catalyzed dehydrogenation of alcohols, we decided to explore the multicomponent dehydrogenative coupling of primary and secondary alcohols with amidines to construct pyrimidines.[4c,5,7,9a] The catalyst **1b** showed promising activity and yielded a variety of 2,4,6-trisubstituted pyrimidines in moderate to good isolated yields at 100°C under air.

Table 1. Optimization of the reaction conditions for 2,4,6-trisubstituted pyrimidine synthesis.[a-g]



Entry	Catalyst (mol%)	Solvent	Base	Yield (%)
1[b]	**1b** (3.0 mol%)	toluene	*t*-BuOK	52
2	**1b** (3.0 mol%)	xylene	*t*-BuOK	58
3	**1b** (3.0 mol%)	1,4-dioxane	*t*-BuOK	35
4	**1b** (3.0 mol%)	acetonitrile	*t*-BuOK	NR
5	**1b** (3.0 mol%)	*tert*-amyl alcohol	*t*-BuOK	trace
6	**1b** (3.0 mol%)	THF	*t*-BuOK	NR
7	**1b** (3.0 mol%)	DMF	*t*-BuOK	NR
8	**1b** (3.0 mol%)	toluene	*t*-BuONa	71
9	**1b** (3.0 mol%)	toluene	NaOH	63
10	**1b** (3.0 mol%)	toluene	KOH	59
11	**1b** (3.0 mol%)	toluene	K_3PO_4	trace
12	**1b** (3.0 mol%)	toluene	Na_2CO_3	NR
13	**1b** (3.0 mol%)	toluene	DBU	NR
14[c]	**1b** (3.0 mol%)	toluene	*t*-BuOK	82
15	**1b** (3.0 mol%)	toluene	*t*-BuOK	82
16[d]	**1b** (3.0 mol%)	toluene	*t*-BuOK	60
17[e]	**1b** (3.0 mol%)	toluene	*t*-BuOK	80
18[f]	**1b** (3.0 mol%)	toluene	*t*-BuOK	72
19	**1b** (2.0 mol%)	toluene	*t*-BuOK	63
20	**1a** (3.0 mol%)	toluene	*t*-BuOK	68
21	$FeCl_2.6H_2O$ (10.0 mol%)	toluene	*t*-BuOK	trace
22	**L^{1b}**+ $FeCl_2.6H_2O$	toluene	*t*-BuOK	57
23	**1b** (3.0 mol%)	toluene	-	NR
24	-	toluene	*t*-BuOK	trace
25	**L^{1a}** (5.0 mol%)	toluene	*t*-BuOK	39
26	**L^{1b}** (5.0 mol%)	toluene	*t*-BuOK	41

[a] Reaction conditions: Stoichiometry: 1-phenyl ethanol (**2a**) (2.0 mmol), benzyl alcohol (**3a**) (2.0 mmol), guanidine (**4a**) (1.0 mmol); Temperature: 100°C; Base: 0.5 equiv.; Time 16h. [b] Temperature: 75°C; Base: *t*-BuOK (10.0 mol%). [c] Temperature: 120ºC. [d] Temperature: 90ºC [e] Time: 24h. [f] Time: 12h. [g] Isolated yields after column chromatography

Result and Discussion

Two penta-coordinated iron(II)-complexes [FeL^{a}Cl$_2$] (**1a**) and [FeL^{b}Cl$_2$] (**1b**), differing in respect of substitution on the aryl ring of the 2-arylazo-(1,10-phenanthroline) ligand was used as catalyst for the present multicomponent dehydrogenative coupling reaction (Scheme 1).[14] In our previous work, we observed that both the complexes **1a** and **1b** showed the best activity towards dehydrogenation of alcohols when the reaction was performed in toluene at 75°C for 5 h with 3.0 mol% catalyst loading in the presence of 10.0 mol% of *t*-BuOK.[14a] Among the two complexes, **1a** and **1b**, since the catalyst **1b** exhibited better activity during alcohol dehydrogenation reactions, we began our present work using **1b** as the catalyst.

Initially, using benzyl alcohol (**3a**), 1-phenyl ethanol (**2a**), and guanidine (**4a**) as model substrates, we explored the possibility of pyrimidine synthesis under the pre-optimized conditions (Table 1, entry 1).[14a] At 75°C in toluene, in presence of 10.0 mol% *t*-BuOK and 3.0 mol% of catalyst **1b**, 52% of 4,6-diphenylpyrimidin-2-amine (**5a**) was isolated under air (Table 1, entry 1). To further improve the yield of **5a**,

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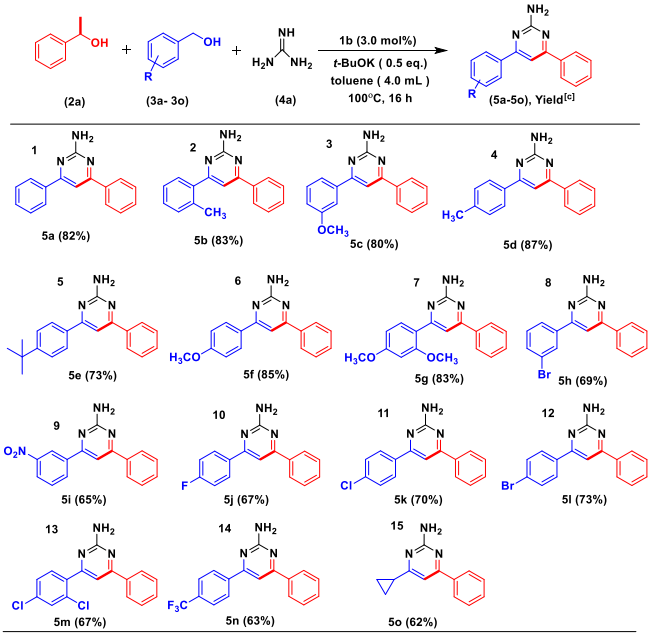
the reaction was performed in different organic solvents such as xylene, 1,4-dioxane, acetonitrile, *tert*-amyl alcohol, THF, DMF (Table 1, entries 2-7). The reaction proceeds well in non-polar solvents like toluene, xylene; however, traces or no product was isolated from polar solvents like THF, 1,4-dioxane, acetonitrile, *tert*-amyl alcohol, DMF. Other than *t*-BuOK, the reaction conditions were also screened for bases like *t*-BuONa, NaOH, KOH, K_3PO_4, Na_2CO_3, DBU (Table 1, entries 8-13). As observed previously during the dehydrogenation of alcohols,[14a] the *t*-BuOK was found to be most effective. The pyrimidine **5a** was isolated at the highest yield of 82% when the coupling of **2a**, **3a**, and **4a** was carried out at 100°C for 16 h in the presence of 0.5 equiv. of *t*-BuOK and 3.0 mol% of **1b**. Increasing the temperature, time, catalyst, or base loading beyond optimized conditions did not produce any notable improvement of yield of **5a** (Table 1, entries 16-19). However, lowering these parameters leads to a significant lowering in yields of **5a**.

Table 2. Synthesis of 2,4,6-trisubstituted pyrimidines from various primary alcohols, 1-phenyl ethanol, and guanidine.[a-d]

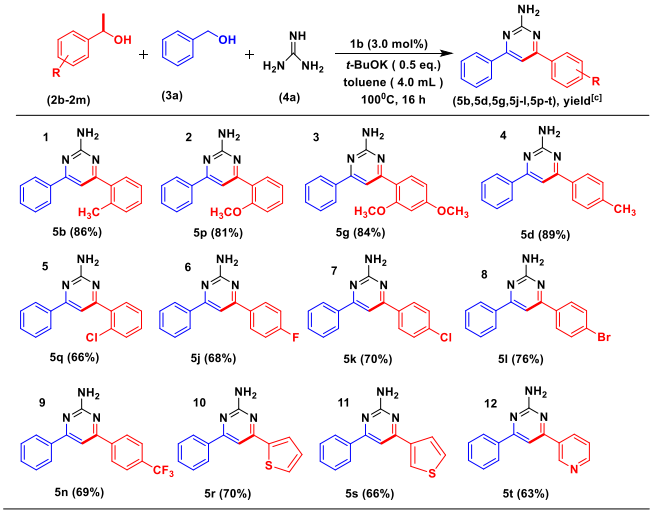


[a] Stoichiometry: 1-phenyl ethanol (**2a**) (2.0 mmol), primary alcohol (**3a**-**3o**) (2.0 mmol), guanidine (**4a**) (1.0 mmol). [b] toluene (4.0 mL). [c] Isolated yields after column chromatography. [d] Under air.

Control experiments using iron-salts like $FeCl_2.6H_2O$, $Fe(ClO_4)_2.6H_2O$, $FeCl_3$ as catalysts afforded **5a** only in trace amounts under the optimized conditions (Table 1, entries 21, 22). The reaction did not proceed in the absence of *t*-BuOK and in the presence of only *t*-BuOK or *t*-BuOK and ligand **($L^{1a,1b}$)** the desired pyrimidine **5a** was obtained in trace, 39, and 41% yields respectively (Table 1, entries 23-26).

Having optimized conditions at hand, we screened a wide variety of substrates under the optimal conditions using **1b** as the catalyst to investigate the scope of the present iron-catalyzed multicomponent synthesis of pyrimidines under air. Initial efforts were given to explore the substrate scope for alcohols (Tables 2, 3). The reaction proceeds well with a variety of electron-donating, -withdrawing, and heteroaryl functionalities present both on primary (Table 2) and secondary (Table 3) alcohols. Pyrimidines were obtained in higher yields in the presence of electron-donating methyl, or methoxy groups at *ortho*-, *meta*- or *para*-positions (Table 2, entries 2-7; Table 3, entries 1-4). Pyrimidines were obtained in slightly higher yields starting from secondary alcohols containing the electron-donating groups than the benzyl alcohols bearing the same functionalities. For example, 4-phenyl-6-(o-tolyl)pyrimidine-2-amine (**5b**) was obtained in 83% yield from the reaction of **2a** and 2-methylbenzyl alcohol (**3b**) with **4a** (Table 2, entry 2) while the same pyrimidine, **5b** was obtained in slightly higher yield, 86% from the reaction of **3a** and 1-(o-tolyl)ethan-1-ol (**2b**) with **4a** (Table 3, entry 1). The reaction was also well tolerant towards strong electron-withdrawing $-NO_2$, $-CF_3$ groups producing the respective pyrimidines **5i** in 65%, **5n** in 63% (Table 2, entries 9, 14) and **5n** in 69% (Table 3, entry 9) yields, respectively. With heteroaryl substitution, the yield varied in the range of 63 to 70% (Table 3, entries 10-12). Reaction also proceeds with aliphatic alcohols. Cyclopropanemethanol yielded the desired pyrimidine **5o** in 62% yield (Table 2, entry 15).

Table 3. Synthesis of 2,4,6-trisubstituted pyrimidines from various secondary alcohols, benzyl alcohol, and guanidine.[a-d]



[a] Stoichiometry: secondary alcohol (**2b-2m**) (2.0 mmol), benzyl alcohol (**3a**) (2.0 mmol), guanidine (**4a**) (1.0 mmol). [b] toluene (4.0 mL). [c] Isolated yields after column chromatography. [d] Under air.

Substrate scope was also explored varying substitution on both primary and secondary alcohols (Table 4). In the presence of electron-donating groups in both primary and secondary alcohols, the respective pyrimidines were obtained in good yields (Table 4, entries 1-3). In the presence of methyl or methoxy groups on both primary and secondary alcohols, the

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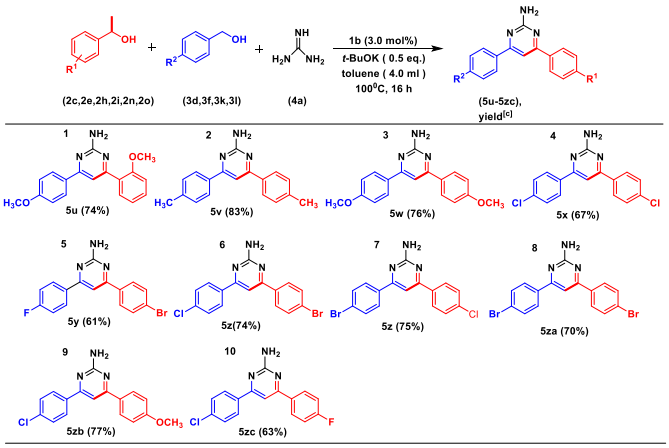
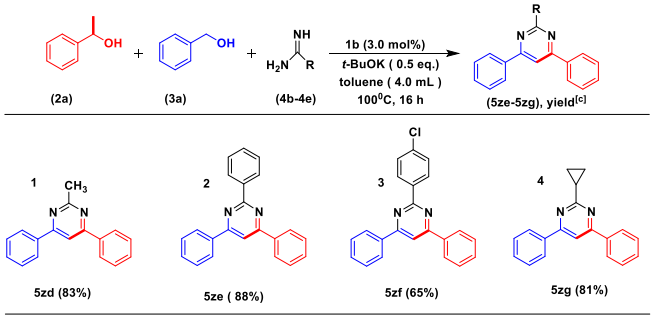
desired pyrimidines **5u**, **5v**, **5w** were obtained in 74-83% yields, respectively. The presence of electron-withdrawing halogens on both alcohols were also well tolerated under our optimal conditions. The respective pyrimidines **5x**, **5y**, **5z**, **5za**, **5zb**, **5zc** were obtained in 61-75% yields, respectively (Table 4, entries 4-8,10). Pyrimidines were also isolated in good yields with primary alcohols containing electron-donating and secondary alcohols bearing an electron-withdrawing group or vice versa (Table 4, entry 9).

Table 4. Synthesis of 2,4,6-trisubstituted pyrimidines from various primary alcohols, secondary alcohols, and guanidine.[a-d]



[a] Stoichiometry: secondary alcohol (**2c,2e,2h,2i,2n,2o**) (2.0 mmol), benzyl alcohol (**3d,3f,3k,3l**) (2.0 mmol), guanidine (**4a**) (1.0 mmol). [b] toluene (4.0 mL). [c] Isolated yields after column chromatography. [d] Under air.

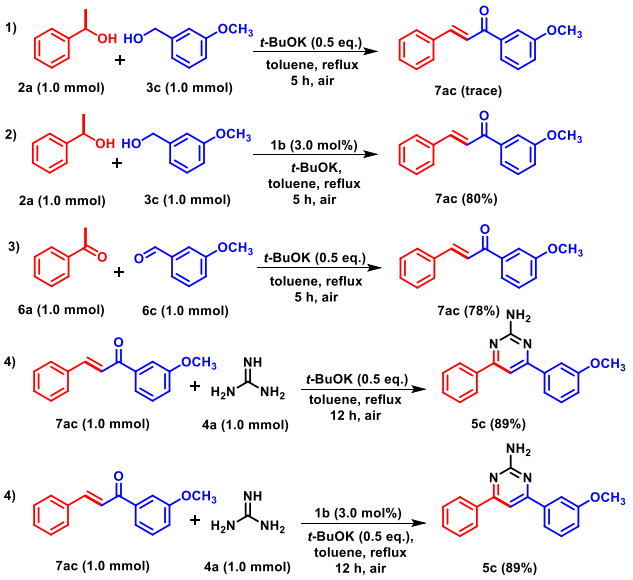
Table 5. Synthesis of 2,4,6-trisubstituted pyrimidines from various amidines, 1-phenyl ethanol, and benzyl alcohol.[a-d]



[a] Stoichiometry: secondary alcohol (**2a**) (2.0 mmol), benzyl alcohol (**3a**) (2.0 mmol), guanidine (**4b-e**) (1.0 mmol). [b] toluene (4.0 mL). [c] Isolated yields after column chromatography. [d] Under air.

To further expand the substrate scope and check the versatility, reactions were carried out with various substituted amidines (Table 5). Reaction of **2a** and **3a** with benzamidine (**4c**) afforded the desired pyrimidine, **5ze** in 88% yield (Table 5, entry 2). With 4-chlorobenzimidamide (**4d**), the corresponding pyrimidine, **5zf** was isolated in 65% yield (Table 5, entry 3). Amidines containing methyl or cyclopropyl groups were also found to be compatible. The corresponding pyrimidines **5zd** and **5zg** were obtained in 83 and 81% yields from the reaction of **2a**, and **3a**, with acetamidine (**4b**) and cyclopropylcarboxamidine (**4e**), respectively (Table 5, entries 1 and 4).

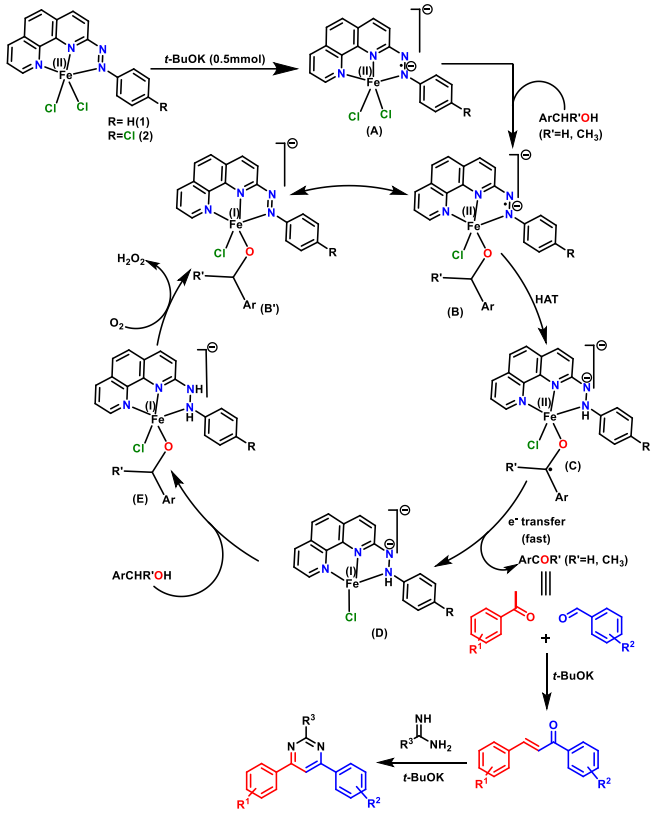
Finally, we performed a few control experiments to explore the plausible steps involved behind the formation of 2,4,6-trisubstituted pyrimidines via selective C−C and C−N bond formation reaction catalyzed by **1b** (Scheme 2).[9a] We have chosen 1-phenyl ethanol (**2a**), 3-methoxybenzyl alcohol (**3c**), and guanidine (**4a**) as the model substrates. In the presence of *t*-BuOK, coupling of **2a** and **3c** yielded trace amount of the intermolecular condensation product, 1-(3-methoxyphenyl)-3-phenylprop-2-en-1-one (**7ac**), after refluxing in toluene at 100˚C for 5h under atmospheric conditions in the absence of **1b**. On the other hand, under optimized catalytic conditions, in the presence of both **1b** and *t*-BuOK, **2a** and **3c** undergoes condensation to produce the α,β-unsaturated ketone **7ac** in 80% yield. The compound **7ac** was also obtained in 78% yield under identical reaction conditions starting from the pre-formed acetophenone **(6a)** and 3-methoxy benzaldehyde **(6c)**. However, in the absence of *t*-BuOK, the coupling of **6a** and **6c** did not produce any **7ac**. These experimental results indicate the involvement of the iron-catalyst **1b** during the dehydrogenation of alcohols as well as the necessity of the *t*-BuOK during the selective C−C bond formation between two in-situ formed carbonyls.



Scheme 2. Control experiments for mechanistic investigations.

The reaction of guanidine (**4a**) with the preformed intermediate **7ac** under the optimized conditions in the presence of catalyst **1b**, afforded 4-(3-methoxyphenyl)-6-phenylpyrimidine-2-amine **(5c)** in 89% yield. Interestingly, the coupling of **4a** and **7ac** yielded **5c** in almost identical yield under the optimal conditions, even in the absence of the catalyst **1b**. On

the other hand, the intermediates obtained from the coupling of **4a** with **6a** or **6c** did not produce **5c** when reacted with the second molecule of the carbonyl compound.



Scheme 3. Plausible mechanism.

A plausible mechanism is depicted in Scheme 2. The reaction begins with the **1b**-catalyzed dehydrogenation of primary and secondary alcohols. In our previous work, we observed that in the presence of *t*-BuOK, the catalyst **1b** undergoes one-electron reduction to form the mono-anionic species [**1b**]$^-$ containing an azo-anion radical ligand.[14] The complex [**1b**]$^-$ then acts as the active catalyst.[14] The iron-stabilized azo-anion radical abstracts hydrogen atom of the alcohol via a one-electron hydrogen atom transfer (HAT) process to form a ketyl radical intermediate, which on subsequent rapid one-electron oxidation produce the respective carbonyls.[14a] The carbonyls formed in-situ undergo base promoted condensation to form the α,β-unsaturated ketone, which upon subsequent base mediated condensation with amidine followed by intramolecular cyclization produce the desired pyrimidines.

Conclusion

In conclusion, herein, we report a sustainable one-pot iron-catalyzed synthesis of various 2,4,6-trisubstituted pyrimidines under aerial conditions at 100˚C via multicomponent dehydrogenative coupling of primary and secondary alcohols with amidines. A large number of polysubstituted pyrimidines were prepared in moderate to good yields under air using alcohol as the primary feedstock. Mechanistic investigation reveals that both the arylazo ligand and iron participate cooperatively during the dehydrogenation of alcohols.[14a] In the presence of excess *t*-BuOK, the iron(II)-catalyst, **1b** undergoes one-electron ligand-centered reduction to form the active azo-anion radical catalyst [**1a**]$^-$.[14a] The iron-stabilized azo-anion radical abstracts hydrogen atom of the alcohol via a one-electron hydrogen atom transfer (HAT) process to form a ketyl radical intermediate, which on subsequent rapid one-electron oxidation produce the desired carbonyls. Synergistic participation of iron and the arylazo ligand allowed to avoid the energetically demanding iron centered two-electron redox events and made it possible to achieve this multicomponent reaction at 100°C in the presence of air. Successful development of such metal-ligand cooperative approaches would possibly enable us to achieve the dehydrogenative functionalization reactions under mild conditions using 3d-base metal catalysts.

Experimental Section

General Information. THF, xylene, 1,4-dioxane, toluene, and other solvents used in this work were distilled and dried following the standard procedures. All other chemicals were used as received from the commercial suppliers without further purification. Analytical TLC and column chromatography were performed by using Merck 60 F254 silica gel plate (0.25 mm thickness) and Merck 60 silica gel (60−120 mesh). ^{1}H and ^{13}C spectra were recorded on a Bruker Avance 400/500 MHz and JEOL 400 MHz spectrometers, and $SiMe_4$ was used as the internal standard.

Catalyst Synthesis. Catalyst **1a** and **1b** were synthesized following the literature procedure.[14]

General Procedure for the Synthesis of Pyrimidine Derivatives. In a 50 mL oven-dried round bottom flask, 2.0 mmol of respective secondary and primary alcohols dissolved in 4.0 mL toluene was taken. To it, the iron catalyst **1b** (3.0 mol%) and *t*-BuOK (0.5 equiv.) were added under atmospheric conditions. The whole reaction mixture was then placed in an oil bath preheated at 100°C. The reaction was continued for 16h. Once the reaction was complete, the residue was concentrated under reduced pressure and purified by silica gel column chromatography using 7:3 (petroleum ether: diethyl ether) as eluent.

Acknowledgments

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