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Phosphine Supported Ruthenium Nanoparticles Catalyzed Synthesis of Substituted Pyrazines and Imidazoles from α-Diketones

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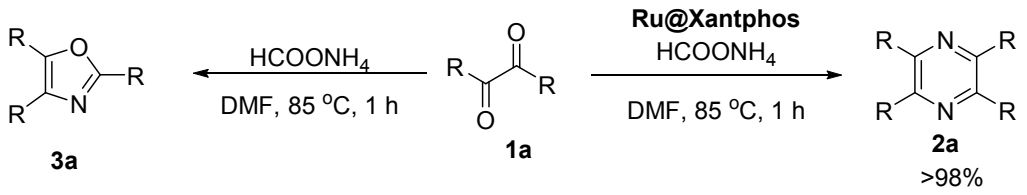


Abstract: A new methodology has been developed for the synthesis of highly substituted nitrogen heterocycles such as pyrazines and imidazoles starting from α-diketones using phosphine supported ruthenium nanoparticles (RuNPs) as catalysts. Ruthenium nanoparticles **(Ru1 Ru2, Ru3 and Ru4)** supported with different phosphines such as dbdocphos, dppp, DPEphos and Xantphos are screened of which **Ru1** and **Ru4** are found to be the most active. Interestingly, aryl substituted and alkyl substituted α-diketones produced different products namely pyrazine and imidazoles respectively. This reaction methodology has been applied to the synthesis of key intermediate (**2m**) of the marine cytotoxic natural product Dragmacidin B and an estrogen receptor (**2l**). This work represents the first examples of pyrazines prepared by RuNPs.

Introduction

Pyrazines represent an important class of nitrogen heterocycles that have important applications in the field of medicine as antibacterial, antiviral, antituberculotic, anti-inflammatory agents and kinase inhibitors.[1] Pyrazine compounds are of great interest in cosmetic and food industries as flavoring

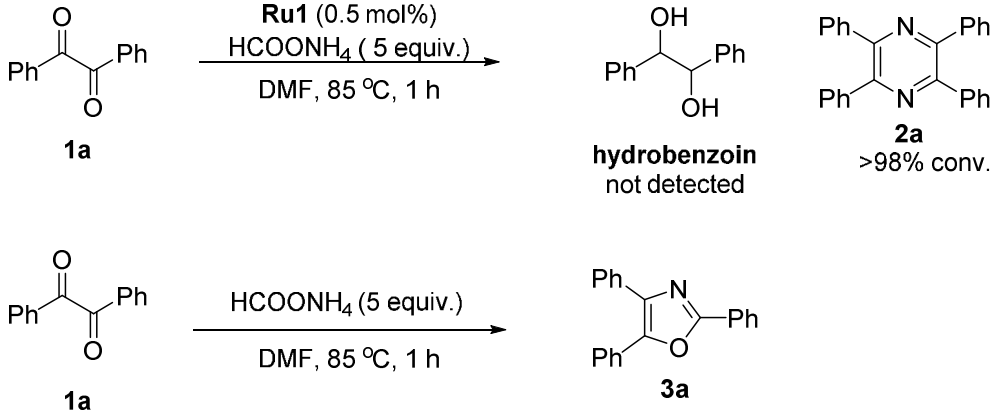
agents[2] and have also attracted attention in material science.[3] Typical methods for the preparation of pyrazines involve condensation of vicinal diamines with α-diketones followed by dehydrogenation,[4] or auto-condensation of α-amino ketones.[5] In addition to these methods, pyrazines have been synthesized using different class of starting materials such as α-hydroxy ketones[6] α-halo ketones,[7] α-halo enolacetates,[8] nitro epoxides,[9] 2*H*-azirines[10] and β-keto-γ-amino esters.[11] Other strategies include Suzuki–Miyaura reactions of tetrachloropyrazine,[12] biocatalytic reduction of β-keto-α-oximinoester with Baker's yeast,[13] two step synthesis via epoxide opening with β-amino alcohol followed by Swern oxidation,[14] and ruthenium pincer complex catalyzed dehydrogenative condensation of β-amino alcohols.[15] However, most of these approaches require more than one class of substrates for the preparation of pyrazines and in some cases additional steps are needed for synthesizing the starting materials. Therefore, the development of new methodologies for the synthesis of pyrazines from simple, readily available inexpensive starting materials is highly desirable.

In recent years, transition metal nanoparticles have attracted great interest in the field of catalysis due to their physical and chemical properties over their traditional organometallic complexes.[16] Amongst these, RuNPs have been considered as one of the most studied nanoparticles in catalytic transformations. Ru particles have been successfully employed in number of catalytic transformations which includes arene hydrogenations,[17] hydrogenation of carbonyl compounds[18] oxidation of alcohols,[19] hydrogen generation from ammonia-borane complexes,[20] CO_2 hydrogenations,[21] and the Fischer-Tropsch process.[22] Unlike organoruthenium complexes the direct application of RuNPs for developing new organic synthetic methodologies is still a challenge and remains less established.[23] Recently, our group reported the synthesis of ruthenium nanoparticles having various stabilizing ligands such as bidentate phosphines containing wide bite angles, secondary phosphine oxides and N-heterocyclic carbenes along with catalytic applications of these nanoparticles in the hydrogenation of aromatics.[24] In this paper, we report a direct synthesis of tetra substituted pyrazines from α-diketones using phosphine supported RuNPs as catalysts without need of vicinal diamines.

Results and Discussion

As part of our ongoing research with catalytic applications of ligand modified RuNPs, our investigations focused on transfer hydrogenation of α-diketones. Initially the reaction was studied on transfer hydrogenation of benzil (**1a**) to achieve hydrobenzoin with dbdocphos[25] stabilized ruthenium nanoparticles **Ru1** (0.5 mol%). Surprisingly the reaction outcome was different and led to the formation of tetraphenyl pyrazine **2a** as a clean product in >98% conversion by GC analysis (coproducts are water, cabon dioxide and dihydrogen). When the reaction was conducted under similar conditions without using **Ru1**, it produced triphenyloxazole (**3a**) in 30% conversion (**Scheme 1**).

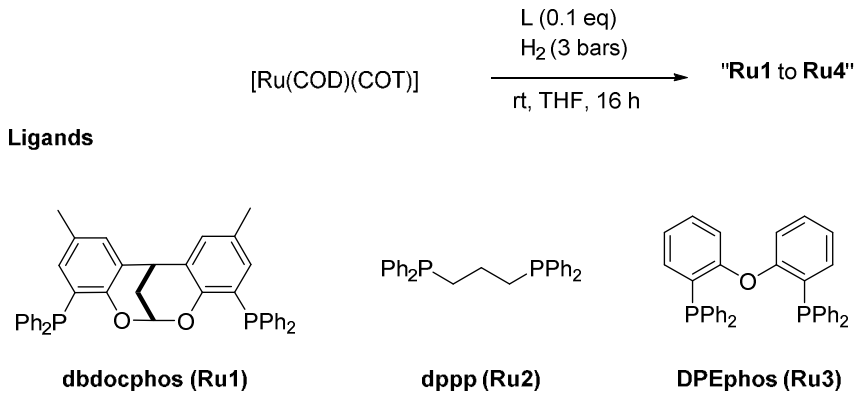
Scheme 1. Attempted catalytic transfer hydrogenation of benzil with ruthenium nanoparticles Ru1



This unusual reactivity of the α-diketones with RuNPs allowed us to study and expand the scope of this reaction for the preparation of tetra substituted pyrazines.

Several phosphine supported RuNPs were synthesized by reaction of [Ru(COD)(COT)] in the presence of 0.1 equiv. of the appropriate phosphine under 3 bars of hydrogen pressure for 16 h according to the procedures reported earlier.[16a,b] Bidentate phosphines such as dbdocphos, dppp, DPEphos and Xantphos were used for synthesis of RuNPs and labelled as **Ru1** to **Ru4** as shown in Scheme 2.

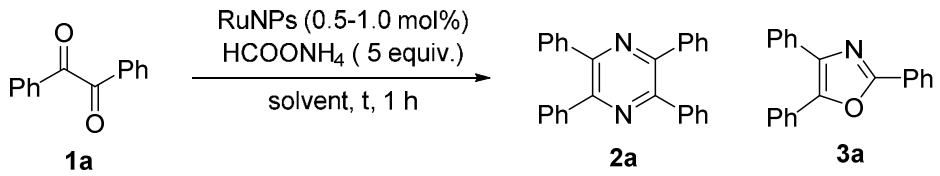
Scheme 2. Synthesis of ruthenium nanoparticles with different phosphine ligands



All the RuNPs stabilized with these phosphine ligands were characterized by transmission electron microscopy (TEM) and the size of the nanoparticles were found to be < 2-3 nm with a broad distribution of size (see supporting information).

The results obtained after screening of this reaction at different conditions are tabulated in **Table 1**. At the beginning of the study, to rule-out any background reactions for the formation of tetraphenyl pyrazine **2a**, experiments were planned without using RuNPs and reactions were run for longer reaction times (16 h) and at higher temperatures. Interestingly, both reactions led to the formation triphenyl oxazole **3a** rather than pyrazine **2a** (Table 1 entries 2 and 3). These reactions clearly evidence that the Ru particles catalyze the reaction and form pyrazine as the clean product. The reactions were also conducted with the precursor for RuNPs such as [Ru(COD)(COT)] complex, under the same reaction conditions. However, this reaction proceeded to **2a** slowly compared to **Ru1** catalyzed synthesis (Table 1 entry 4 *vs* 1) and when the reaction was carried out at room temperature (~ 22 ^{o}C) it failed to give the product (Table 1 entry 5). The reaction was also conducted in different solvents such as isopropanol, ethyl acetate, 1,4-dioxane and toluene. The reaction in isopropanol produced a mixture of **2a/3a** (Table 1 entry 6), but the remaining solvents failed to produce any product (Table entries 7-10) hence DMF was adopted as solvent of choice.

Table 1. Screening of different reaction conditions. [a]



1a **2a** **3a**

entry	RuNPs	solvent	temp	conv. (%)[b]	ratio **2a:3a**
1[c]	**Ru1**	DMF	85	>98	100:0
2[d]	--	DMF	85	>98	0:100
3	--	DMF	156	>98	15:85
4	Ru(COD)(COT)	DMF	85	17	100:0
5[c]	**Ru1**	DMF	rt	0	N/A
6[c]	**Ru1**	IPA	80	45	71:29
7[c]	**Ru1**	EtOAc	76	0	N/A
8[c]	**Ru1**	dioxane	85	0	N/A
9[c]	**Ru1**	Toluene	85	0	N/A
10[e]	**Ru2**	DMF	85	15	81:19
11[e]	**Ru3**	DMF	85	18	100:0
12[e]	**Ru4**	DMF	85	>98	100:0
13	Ru(COD)(COT)+ Xantphos (1:1)	DMF	85	16	100:0
14	$Ru(Xantphos)_2H_2$	DMF	85	7	100:0
15	Ru/C	DMF	85	69	100:0

[a] all the reactions were performed using 1.0 mmol of substrate; [b] conversion is determined using GC analysis relative to the substrate; [c]0.5 mol% of the catalyst used based on Ru content by elemental analysis elemental analysis; [d] reaction time 16 h.; [e] 1.0 mol% of the catalyst used based on Ru content by EDX analysis; N/A = not applicable.

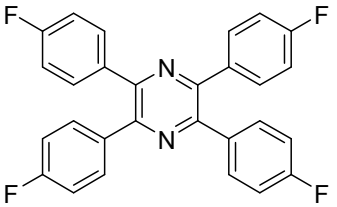
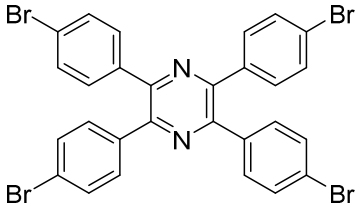
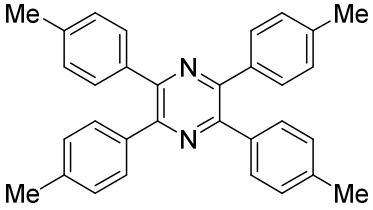
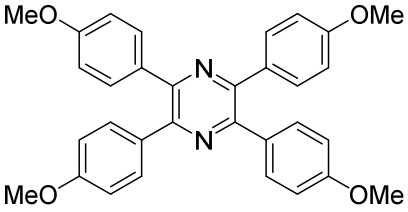
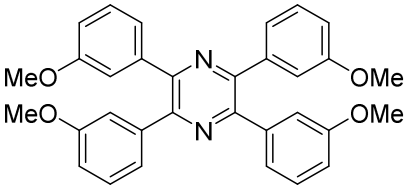
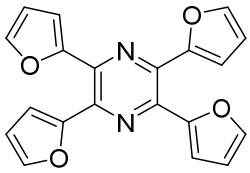
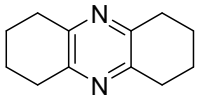
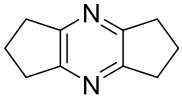
The reactions were also run with different RuNPs such as **Ru2**, **Ru3** and **Ru4** under similar conditions as those used for **Ru1**. Amongst these Xantphos supported RuNPs (**Ru4**) showed activity and selectivity similar to (**Ru1**) (Table 1, entries 11-13). In order to find if any traces of molecular complex Ru(Xantphos) present in the RuNPs were acting as the catalyst, we conducted the reaction using 1:1 mixture of Ru(COD)(COT) and Xantphos (both 1.0 mol% of loading) under similar reaction conditions used for **Ru4** catalysis. However, this reaction produced only 16% conversion to pyrazine **2a** (Table 1, entry 13). The second experiment was performed with freshly prepared molecular complex such as $Ru(Xantphos)_2H_2$, from 1:1 mixture of Ru(COD)(COT) and Xantphos at 150 ^oC under 3 bars of hydrogen.[26] This reaction also failed to produce the desired product in good conversion (Table 1, entry 14). The reaction was also carried out with commercially available 5%

ruthenium on carbon (Ru/C) under the same reaction conditions which produced 69% conversion to pyrazine **2a**. Thus, Ru metal surfaces show activity for this reaction, but phosphine modified RuNPs show a much higher reactivity as was found before for arene hydrogenation.[24a]

The reactions conducted with different nitrogen sources such as NH_4OAc, NH_4Cl, aqueous NH_3 solution failed to deliver the **2a**, but formation of oxazole **3a** was observed when NH_4OAc was used (30% conversion). Based on these studies RuNPs stabilized with dbdocphos **Ru1** and Xantphos **Ru4** were found to be the efficient catalysts for this transformation. However, Xantphos is commercially available and cheaper ligands for the stabilization of RuNPs hence we further expanded the substrate scope with Xantphos stabilized ruthenium nanoparticles **Ru4** and the results are tabulated in **Table 2**.

Having established the screening conditions with **Ru4** (Table 1 entry 13), we next sought to screen the major substrate scope with **Ru4** as the catalyst (Table 2). Firstly, 4-fluoro substituted benzil **1b** was screened with nanoparticles **Ru1, Ru4** and 5% Ru/C. Ru/C proved to be less reactive (Table 2, entry1). **Ru1** and **Ru4** gave greater conversion to the product and in the latter case, the desired pyrazine **2b** was isolated in 86% after flash chromatography (Table 2 entries 2 and 3). The reaction of bromo substituted benzil **1c** with **Ru4** nanoparticles gave complete conversion to pyrazine **2c** with an yield of 45% (Table 2, entry 4). The substrates containing electron rich groups on the arenes ring such as *p*-methyl **1d** and *p*-methoxide substituted benzils **1e** were found to be less reactive in the reaction. The reaction of **1d** with **Ru4** gave complete conversion to product **2d** after 5h and the desired product was isolated in 91% yield (Table 2, entry 5). Similarly, *p*-anisil **1e** required longer reaction times (12 h) and the desired pyrazine was isolated in 78% yield (Table 2, entry 6). The reaction conducted with *m*-anisil **1f** was found to be faster than that of *p*-anisil and the reaction was complete in 1 h and the corresponding pyrazine **2f** was isolated in 72% yield (Table 2 entry 7). The substrate containing heteroarene substituent such as furil, under the same catalytic conditions, after 1h, produced pyrazine **2g** in 61% yield (Table 2, entry 8). The cyclic substrates such as 1,2-cyclohexanedione **1h** gave complete conversion to the desired products **2i** and the product was purified over neutral alumina in decent yield (Table 2, entry 9). The reaction with 1,2-cyclopentadione gave the desired pyrazine in moderate yield of 51% as crude product (Table 2, entry 10).

Table 2. RuNPs catalyzed synthesis of pyrazines from α-diketones.[a]

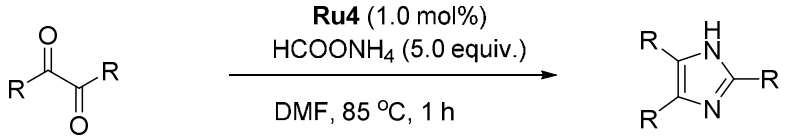
entry	RuNPs	product		time (h)	yield (%)[b,c]
1	**5% Ru/C**		**2b**	1	12
2	**Ru1**			2	79
3	**Ru4**			1	>98 (86)
4	**Ru4**		**2c**	1	>98 (45)
5	**Ru4**		**2d**	5	>98 (84)
6	**Ru4**		**2e**	12	>98 (76)
7	**Ru4**		**2f**	1	>98 (72)
8	**Ru4**		**2g**	1	>98 (61)
9	**Ru4**		**2h**	1	>98 (78)
10	**Ru4**		**2i**	2	>98 (51)[d]

[a] all the reactions were carried out using 1.0 mmol of substrate and 1.0 mol% Ru catalyst; [b] conversión determined either crude 1HNMR/GC analysis; [c] yields reported in parenthesis; [d] isolated as a crude product

In order to adapt this methodology for the synthesis of alkyl-substituted pyrazines, we screened acyclic α-diketones such as biacetyl and 3,4-hexanedione under the same reaction conditions as those

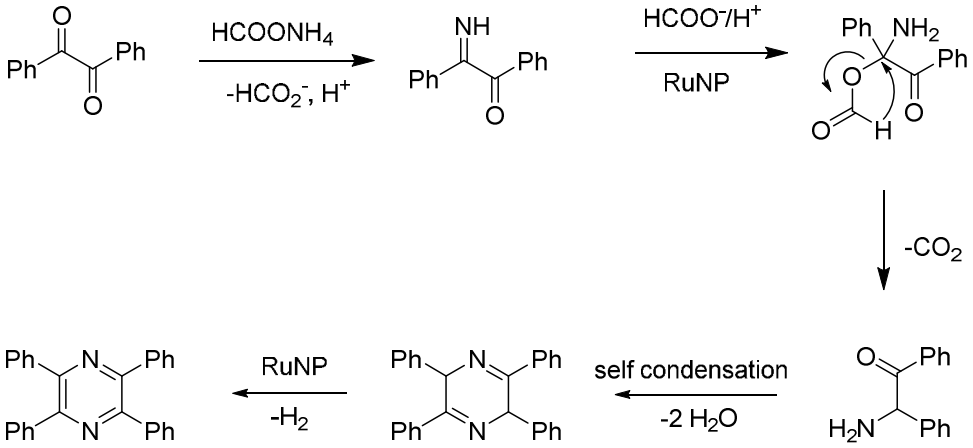
for **Ru4**. Surprisingly, these reactions failed to produce the expected alkyl pyrazines, but instead the reactions gave trisubstituted imidazoles (Scheme 3). Synthesis of trisubstituted imidazoles from α-diketones is a well-known preparation method.[27] However, this reaction requires additional substrate aldehyde along with α-diketones, also needed super heating conditions and microwave irradiation or micro reactor system under pressure.[28] Our reaction conditions with **Ru4** for the first time yields imidazoles from α-diketones without requiring aldehydes in the reaction with mild conditions. We believe that the reaction proceeds *in situ* giving rise to the generation of acyl equivalent from the diketone *via* retro aldol condensation followed by condensation with diketone and ammonium formate under similar conditions as reported in the literature.

Scheme 3. Synthesis of trisubstituted imidazoles from acyclic α-diketones



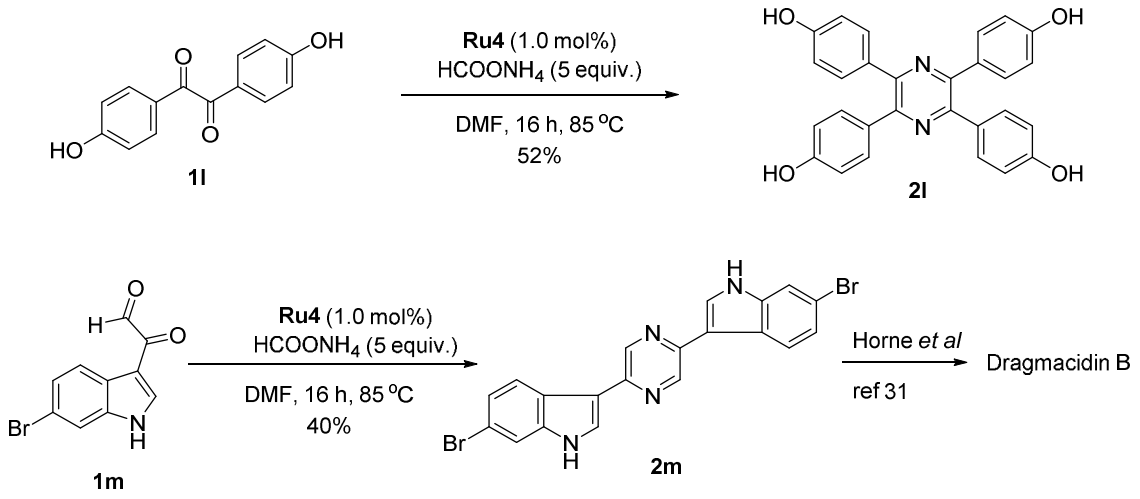
The proposed mechanism for the formation of pyrazines assumes that α-diketone undergo reductive amination under transfer hydrogenation conditions to produce α-amino ketone in presence of RuNPs followed by self-condensation to give the intermediate 2,3,5,6-tetraphenyl-2,5-dihydropyrazine which then aromatizes to give the pyrazines (Scheme 4).

Scheme 4. Proposed mechanism for the formation of pyrazines



In order to demonstrate the general synthetic utility of this methodology, we chose to synthesize biologically important pyrazines such as **2l** and **2m**. The pyrazine **2l** is an estrogen receptor which has been synthesized in the literature in 2 steps, first, condensation between *p*-anisil and 1,2-bis(4-methoxyphenyl)ethylenediamine to give the pyrazine which was demethylated with BF_3.DMS to give the pyrazine **2l**.[29] We were able to synthesize this pyrazine **2l** from diketone **1l**[30] under our optimized reaction conditions with **Ru4** (1.0 mol%) in 52% isolated yield. Pyrazine **2m** is a key intermediate for a marine cytotoxic natural product Dragmacidin B. There are several synthetic routes reported in literature for the preparation of **2m** which include condensation of bromo substituted oxotryptamine in ethanol/xylene at 135 ^{o}C for 72 h or Pd-catalyzed Suzuki coupling of 2,5-dibromopyrazine.[31] Our approach for the synthesis of **2m** involves starting with diketone **1m** which is obtained by treating with 5-bromo-indole with oxalyl chloride followed by reduction with nBu_3SnH,[32] which then was subjected under **Ru4** catalyzed conditions to give pyrazine **2m** in 40% yield (Scheme 5).

Scheme 5. Synthetic application of the methodology for the preparation of 2l and 2m.



Conclusion

In conclusion, during our attempts of transfer hydrogenation with Ru NPs and formate as a hydrogen donor we have discovered a new general synthetic protocol for the synthesis of substituted pyrazines and imidazoles from readily available α-diketones. The Ru NPs play a role in hydrogen borrowing during this reaction and as dehydrogenation catalyst. Phosphine ligands influence the catalyst properties, and as Xantphos performed well, the scope was studied with this commercially available

ligand. This ruthenium based catalytic system requires only low catalyst loadings, mild reaction conditions and shows a good substrate scope. The catalyst can be removed by adsorption on silica or alumina. Aryl and alkyl diketones reacts differently with RuNPs and produced pyrazines and imidazoles respectively. This newly developed protocol offers rapid access to biological important pyrazine scaffolds such as 2l and 2m.

Experimental section

1. General remarks

All air and moisture sensitive reactions were performed under argon atmosphere using oven-dried glassware by standard Schlenk-line techniques. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. All the dry solvents were obtained from solvent purification system (SPS). Thin-layer chromatography was performed on aluminum sheets (silica gel 60); detection was by UV and by coloration with vanillin. Flash column chromatography was performed using silica gel 60 (230−400 mesh).

NMR spectra were recorded on 500, 400 and 300 MHz spectrometers at room temperature. All NMR spectra are referenced relative to the solvent residual peak. All the Chemical shifts of ^{1}H, ^{13}C and are reported in ppm. Signals are quoted as s (singlet), d (doublet), dd (double doublet), m (multiplet), b (broad).

All the α-diketones were purchased from commercial sources and the substrates **1l** and **1m** were prepared according to literature protocols.[29,31] Ru(COD)(COT) was purchased from NanoMePS (and used as received. Xantphos, DPEphos, dppp were purchased and dbdocphos was prepared according to literature procedure.

TEM analyses were performed on a Zeiss 10 CA electron microscope at 100 kV with a resolution of 3 Å. Samples were prepared drop casting (from various THF) onto a holey Formvar/carbon-coated copper grid.

General procedure for synthesis of Ruthenium nanoparticles[24]

In an oven dried 100 mL Schlenk tube was added appropriate phosphine ligand (0.1 equiv.) and anhydrous degassed THF (60 mL) under argon. The reaction mixture was cooled to -110 ^{o}C with

liquid nitrogen and transferred the solution into a Fischer-porter reactor containing [Ru(COD)(COT)] complex (60.0 mg 0.19 mmol, 1.0 equiv.) at -110 ^{o}C. Then the reactor was pressurized with 3 bars of hydrogen and stirred at room temperature for 16 h. Reaction mixture turned to black solution and a drop of solution was deposited on copper grid for TEM analysis. Degassed pentane was added to the solution to precipitate the nanoparticles and the solvent was removed *in vacuo*, the resulting solid nanoparticles were washed with degassed pentane (2x 10 mL). The resulting particles were dried in vacuo overnight. The obtained RuNPs were stored in Schlenk tube under argon for the catalytic reactions.

Ru1 Elemental analysis: Ru 32.02, P 5.71, C 27.13, H 4.45

Ru2 EDX analysis: Ru 43.95, P 2.18, C 17.59, O 33.03, Si 3.24

Ru3 EDX analysis: Ru 48.29, P 1.28, C 15.77, O 30.11, Si 4.55

Ru4 EDX analysis: Ru 47.45, P 2.42, C 20.61, O 28.53, Si = 0.99

2,4,5-Triphenyloxazole (3a)[33]

In an oven-dried Schlenk tube benzil (**1a**) (210 mg, 1.0 mmol), anhydrous DMF (3.0 mL) and ammonium formate (315 mg, 5.0 mmol) were charged under argon atmosphere. The resulting reaction mixture was stirred at 85 °C for 16 h. The reaction mixture was poured into water and extracted with EtOAc (2×10.0 mL). The combined organic layers were washed with water (2x10.0 mL), brine (2x10 mL) dried over Na_2SO_4. The volatiles were removed under reduced pressure to afford the crude product, which was purified by flash column chromatography (SiO_2; 0-10% EtOAc in hexane) to afford the title compound **3a** as a white solid (174 mg, 87%).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.45 (m, 6 H), 7.46-7.52 (m, 3 H), 7.60-7.72 (m, 2 H), 7.75-7.77 (m, 2 H), 8.17-8.20 (m, 2 H); $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$): δ 126.8, 126.9, 127.8, 128.5, 128.6, 128.9, 129.0, 129.1, 129.4, 130.7, 133.0, 137.2, 145.9, 160.5.

General Procedure for the Preparation of Pyrazines and imidazoles using Ru4.

In an oven-dried Schlenk tube, a α-diketone (**1a-1m**) (1.0 mmol), anhydrous DMF (3.0 mL) and ammonium formate (5.0 mmol) were charged under argon atmosphere. The reaction mixture was degassed by three vacuum/argon cycles, followed by ruthenium nanoparticles (**Ru4,** 1.0 mol%) were added. The resulting mixture was stirred at 85 °C for the appropriate time (1 h to 12 h). Reaction

mixture was poured into water (5 mL) and extracted with EtOAc (2x10.0 mL). The combined organic layers were washed with water (2x10.0 mL), brine (2x10 mL), dried over Na_2SO_4. The solvent was removed in vacuo to afford the crude product, which was purified by flash column chromatography (SiO_2 or neutral alumina; hexane/EtOAc) to afford the pyrazines (**2a-2h**) and imidazoles.

2,3,5,6-Tetraphenylpyrazine (2a)[34]

Synthesized according to General procedure, substrate **1a** (210.0 mg, 1.0 mmol), ammonium formate (315.0 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%) in anhydrous DMF (3.0 mL) were stirred at 85 ^oC for 1h. The title compound was obtained after flash column chromatography (SiO_2, hexane/EtOAc 95:5) as a white solid (177 mg, 92%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 - 7.39 (m, 12 H), 7.66 - 7.69 (m, 8 H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 128.4, 128.7, 130.0, 138.6, 148.6.

2,3,5,6-Tetrakis(4-fluorophenyl)pyrazine (2b)[12]

Synthesized according to General procedure, substrate **1b** (246.0 mg, 1.0 mmol), ammonium formate (315.0 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%)) in anhydrous DMF (3.0 mL) were stirred at 85 ^oC for 1h. The title compound obtained after flash column chromatography (SiO_2, hexane/EtOAc 95:5) as a pale yellow solid (197 mg, 86%). MP: 232-235 ^oC; IR (DCM): ^1H NMR (500 MHz, $CDCl_3$): δ 6.99-7.10 (m, 8 H), 7.53-7.64 (m, 8 H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 115.6, 115.7, 131.7, 131.8, 134.2, 134.3, 147.5, 162.4, 164.3; HRMS (ESI): $C_{28}H16F_4N_2$ [M]+ calculated: 456.1250, found: 456.1230.

2,3,5,6-Tetrakis(4-bromophenyl)pyrazine (2c)[35]

Synthesized according to General procedure, substrate **1c** (365.0 mg, 1.0 mmol), ammonium formate (315.0 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%)) in anhydrous DMF (3.0 mL) were stirred at 85 ^oC for 1h. The title compound was isolated after flash column chromatography (SiO_2; hexane/EtOAc 95:5) as a white solid (158 mg, 45.2% yield**);** ^1H NMR (500 MHz, C_6D_6): δ 7.18-7.20 (m, 8 H), 7.28-7.30 (m, 8 H); $^{13}C\{^1H\}$NMR (126 MHz, $CDCl_3$): δ 123.8, 131.5, 131.9, 136.8, 147.5; HRMS (MALDI): calculated for $(C_{28}H_{17}{}^{79}Br_3{}^{81}BrN_2)$+, [M+H]+: 698.8099, found: 698.8120.

2,3,5,6-Tetra-(*p*-tolyl)pyrazine (2d)[33]

Synthesized according to General procedure, substrate **1d** (238.0 mg, 1.0 mmol), ammonium formate (315 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%)) in anhydrous DMF (3.0 mL) were

stirred at 85 °C for 5h. The title compound was isolated after flash column chromatography (SiO_2; hexane/EtOAc 95:5) as a white solid (186.0 mg, 84% yield**)**. H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 12 H), 7.17 – 7.04 (m, 8 H), 7.54 (d, *J* = 8.1 Hz, 1H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 21.3, 128.9, 129.7, 135.9, 138.4 147.8; HRMS (MALDI) calculated for $C_{32}H2_8N_2^+$., [M]+: 440.2247, found: 440.2252.

2,3,5,6-Tetrakis(4-methoxyphenyl)pyrazine[1] (2e)[29]

Synthesized according to General procedure, substrate **1e** (270.0 mg, 1.0 mmol), ammonium formate (315 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%)) in anhydrous DMF (3.0 mL) were stirred at 85 °C for 12 h. The title compound was isolated after flash column chromatography (SiO_2; hexane/EtOAc 90:10) as a white solid (192.0 mg, 76% yield**)**. ^{1}H NMR ($CDCl_3$ δ 3.71 (s, 6 H), 6.89 (dd, *J* = 2.7, 1.4 Hz, 1 H), 6.90 (dd, *J* = 2.6, 1.4 Hz, 1 H), 7.16-7.25 (m, 6 H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 55.4, 115.0, 115.1, 122.6, 129.4, 139.9, 148.4, 159.6.

2,3,5,6-Tetrakis(3-methoxyphenyl)pyrazine (2f)[33]

Synthesized according to General procedure, substrate **1f** (270.0 mg, 1.0 mmol), ammonium formate (315 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%)) in anhydrous DMF (3.0 mL) were stirred at 85 °C for 5 h. The target compound was isolated after flash column chromatography (SiO_2; hexane/EtOAc 95:5) as a white solid (182.0 mg, 72% yield**)**; ^{1}H NMR (500 MHz, $CDCl_3$):δ 3.71 (s, 12 H), 6.89 (dd, *J* = 2.7, 1.4 Hz, 4 H), 6.90 (dd, *J* = 2.6, 1.4 Hz, 4 H), 7.16-7.25 (m, 8 H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 55.4, 115.0, 115.1, 122.6, 129.4, 139.9, 148.4, 159.6.

2,3,5,6-Tetrakis(2-furyl)pyrazine (2g)[6a]

Synthesized according to General procedure I, substrate **1g** (190.0 mg, 1.0 mmol), ammonium formate (315 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%) in anhydrous DMF (3.0 mL) were stirred at 85 °C for 1 h. The title compound was isolated after flash column chromatography (SiO_2; 0-20% EtOAc in hexane) as a white solid (105.0 mg, 61% yield**)**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.54 (dd, *J* = 3.6, 1.8 Hz, 4 H), 6.80 (dd, *J* = 3.4, 0.8 Hz, 4 H), 7.56 (dd, *J* = 1.8, 0.8 Hz, 4 H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 112.0, 112.9, 138.0, 144.1, 150.7; HRMS (ESI) calculated for $C_{20}H_{12}N_2O_4$, $[M+Na]^+$: 367.0687, found: 367.0685.

1,2,3,4,6,7,8,9-Octahydrophenazine (2h)[14]

Synthesized according to General procedure I, substrate **1h** (112.0 mg, 1.0 mmol), ammonium formate (315 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%)) in anhydrous DMF (3.0 mL) were stirred at 85 ^{o}C for 2 h. The title compound was isolated by flash column chromatography (neutral Al_2O_3; 1-5% EtOAc in hexane) as a white solid (73.0 mg, 78% yield**)**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.88-1.91 (m, 8 H), 2.85-2.90 (m, 8 H); $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$): δ 23.0, 31.8, 149.5.

1,2,3,5,6,7-Hexahydro-dicyclopentapyrazine (2i)[36]

Synthesized according to General procedure, substrate **1i** (98.0 mg, 1.0 mmol), ammonium formate (315 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%)) in anhydrous DMF (3.0 mL) were stirred at 85 ^{o}C for 2 h. The title compound was isolated as the crude product. (41.0 mg, 51% yield**)**.^{1}H NMR (500 MHz, $CDCl_3$): δ 2.04 (dt, *J* = 14.1, 6.7 Hz, 4 H), 2.48 (t, *J* = 7.1 Hz, 3 H), 2.62 (t, *J* = 6.7 Hz, 5 H).

2,4,5-Trimethyl-1*H*-imidazole (2j)[26a]

Synthesized according to General procedure, substrate **1j** (86.0 mg, 1.0 mmol), ammonium formate (315 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%) in anhydrous DMF (3.0 mL) were stirred at 85 ^{o}C for 1 h. The title compound was isolated by flash chromatography as a grey solid (62 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.10 (s, 6 H), 2.30 (s, 3 H); $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$): δ 10.6, 13.8, 125.8, 141.9.

2,4,5-Triethyl-1*H*-imidazole (2k)[37]

Synthesized according to General procedure, substrate **1l** (114.0 mg, 1.0 mmol), ammonium formate (315 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%)) in anhydrous DMF (3.0 mL) were stirred at 85 ^{o}C for 16 h. The title compound was isolated after flash chromatography as a viscous oil (90 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.6 Hz, 6 H), 1.24 (t, *J* = 7.6 Hz, 3 H), 2.50 (q, *J* = 7.7 Hz, 4 H), 2.67 (q, *J* = 7.7 Hz, 2 H), 5.5-6.0 (bs, 1H).

4,4',4'',4'''-(pyrazine-2,3,5,6-tetrayl) Tetraphenol (2l)[12]

Synthesized according to General procedure, substrate **1l** (121 mg, 0.5 mmol), ammonium formate (175 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 1.1 mg, 1.0 mol%) 1.0 mg) in anhydrous DMF (3.0 mL)

were stirred at 85 °C for 16 h. The title compound isolated by flash chromatography (SiO_2, 0-30% EtOAC in hexane) as a grey solid (57 mg, 51% yield). ^{1}H NMR (300 MHz, Acetone): δ 6.82 (dd, 8H), 7.52 (dd, 8H), 8.60 (s, 4H).

6-Bromo-3-(5-(6-bromo-3a,7a-dihydro-1H-indol-3-yl)pyrazin-2-yl)-1H-indole (2m)[30a]

Synthesized according to General procedure, substrate **1m** (252.0 mg, 1.0 mmol), ammonium formate (315 mg, 5.0 mmol) and **Ru4** (47.5 wt% Ru, 2.2 mg, 1.0 mol%) in anhydrous DMF (3.0 mL) were stirred at 85 °C for 16 h. The product was isolated after flash chromatography on silicagel using 10% EtOAc in hexane as yellow solid (93 mg, 40% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.33 (dt, J = 8.6, 2.0 Hz, 1H), 7.71 (q, J = 1.7 Hz, 1H), 8.32 (t, J = 2.5 Hz, 1H), 8.41 (dd, J = 8.6, 2.7 Hz, 1H), 8.88 (d, J = 2.3 Hz, 1H), 11.85 (s, 1H).

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Supporting Information

NMR spectra of all compounds in the Experimental Section and TEM images, UV, TGA and HRMS spectra are available in the supporting information document. This material is available free of charge via the Internet at http:// pubs.acs.org.

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