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

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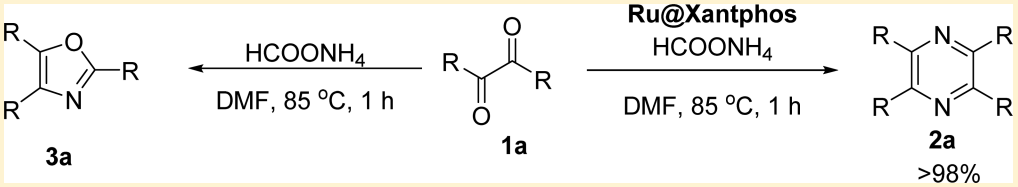
Supporting Information




**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**−**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 a 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, and anti-inflammatory agents and as kinase inhibitors.[1] Pyrazine compounds are of great interest in the cosmetics and food industries as flavoring agents[2] and have also attracted attention in materials science.[3] Typical methods for the preparation of pyrazines involve condensation of vicinal diamines with α-diketones followed by dehydrogenation[4] or autocondensation of α-amino ketones.[5] In addition to these methods, pyrazines have been synthesized using different classes of starting materials such as α-hydroxy ketones,[6] α-halo ketones,[7] α-halo enol acetates,[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-oximino ester 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 favorable physical and chemical properties in comparison to their traditional organometallic complexes.[16] Among these, RuNPs have been some of the most studied nanoparticles in catalytic transformations. Ru particles have been successfully employed in number of catalytic transformations which include 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 the case for 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 tetrasubstituted pyrazines from α-diketones using phosphine-supported RuNPs as catalysts without the need for 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

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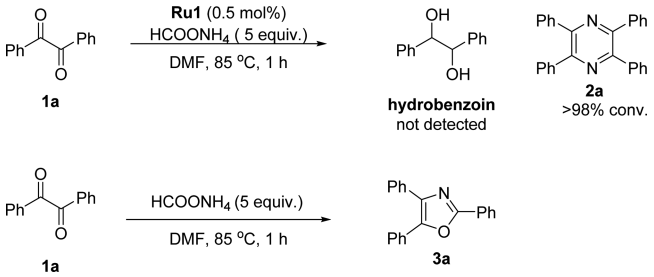
on transfer hydrogenation of benzil (**1a**) to achieve hydrobenzoin with dbdocphos[25] stabilized ruthenium nanoparticles **Ru1** (0.5 mol %). Surprisingly, the reaction outcome was different and led to the formation of tetraphenylpyrazine (**2a**) as a clean product in >98% conversion by GC analysis (the coproducts are water, carbon 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**



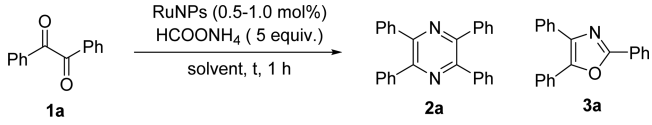

This unusual reactivity of the $\alpha$-diketones with RuNPs allowed us to study and expand the scope of this reaction for the preparation of tetrasubstituted pyrazines.

Several phosphine supported RuNPs were synthesized by the reaction of [Ru(COD)(COT)] in the presence of 0.1 equiv of the appropriate phosphine under 3 bar 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 the synthesis of RuNPs and are labeled **Ru1**−**Ru4**, as shown in Scheme 2.

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

The results obtained after screening of this reaction under different conditions are given in Table 1. At the beginning of the study, to rule out any background reactions for the formation of tetraphenylpyrazine (**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 of triphenyloxazole (**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 a precursor for RuNPs

**Table 1. Screening of Different Reaction Conditions**[a]




| entry | RuNP | solvent | temp (°C) | conversn (%)[b] | 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 | room temp | 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 of the reactions were performed using 1.0 mmol of substrate. N/A = not applicable. [b]Conversion was determined using GC analysis relative to the substrate. [c]0.5 mol % of the catalyst used based on Ru content by elemental analysis. [d]Reaction time 16 h. [e]1.0 mol % of the catalyst used based on Ru content by EDX analysis.

such as the [Ru(COD)(COT)] complex, under the same reaction conditions. However, this reaction proceeded to **2a** slowly in comparison to **Ru1**-catalyzed synthesis (Table 1 entry 4 vs entry 1) and when the reaction was carried out at room temperature (~22 °C) it failed to give the product (Table 1 entry 5). The reaction was also conducted in different solvents such as isopropyl alcohol, ethyl acetate, 1,4-dioxane, and toluene. The reaction in isopropyl alcohol produced a mixture of **2a** and **3a** (Table 1, entry 6), but the remaining solvents failed to produce any product (Table 1, entries 7−10); hence, DMF was adopted as the solvent of choice.

The reactions were also run with different RuNPs such as **Ru2**−**Ru4** under conditions similar to those used for **Ru1**. Among these, Xantphos-supported RuNPs (**Ru4**) showed activity and selectivity similar to those of **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 a 1:1 mixture of Ru(COD)(COT) and Xantphos (both 1.0 mol % of loading) under

**Scheme 2. Synthesis of Ruthenium Nanoparticles with Different Phosphine Ligands**

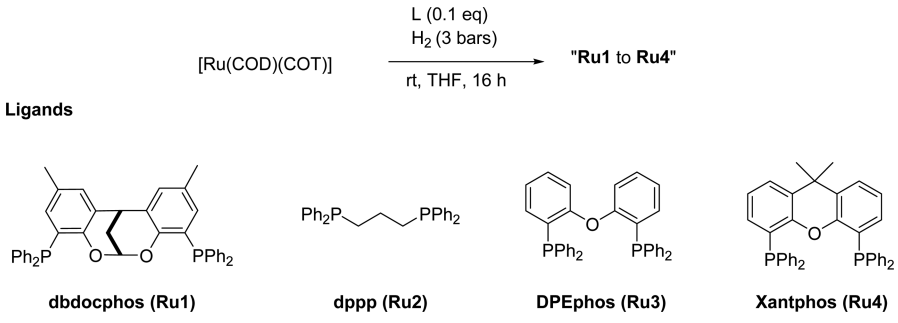





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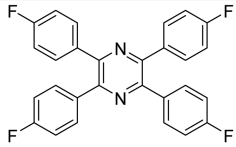
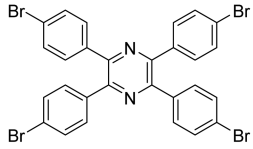
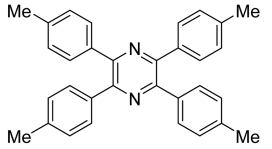
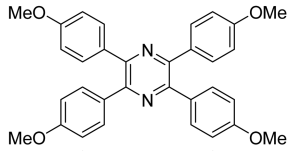
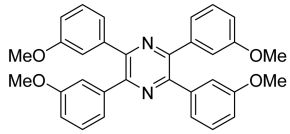
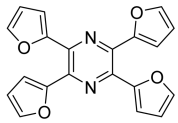
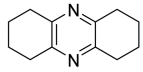
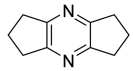
**Table 2. RuNP-Catalyzed Synthesis of Pyrazines from α-Diketones**[a]

| 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 of the reactions were carried out using 1.0 mmol of substrate and 1.0 mol % of Ru catalyst. [b]Conversion determined by crude $^1$H NMR or GC analysis. [c]Isolated yields reported in parentheses. [d]Isolated as a crude product.

reaction conditions similar to those used for **Ru4** catalysis. However, this reaction produced only 16% conversion to pyrazine **2a** (Table 1, entry 13). The second experiment was performed with a freshly prepared molecular complex such as $Ru(Xantphos)_2H_2$, from 1:1 mixture of Ru(COD)(COT) and Xantphos at 150 °C under 3 bar 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 $NH_4OAc$, $NH_4Cl$, and aqueous $NH_3$ solution failed to deliver **2a**, but formation of oxazole **3a** was observed when $NH_4OAc$ was used (30% conversion). On the basis of these studies RuNPs stabilized with dbdocphos **Ru1** and Xantphos **Ru4** were found to be efficient catalysts for this transformation. However, Xantphos is a commercially available and cheaper ligand for the stabilization of RuNPs; hence, we further expanded the substrate scope with Xantphos-stabilized ruthenium nanoparticles **Ru4**, and the results are given 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). First, 4-fluoro-substituted benzil **1b** was screened with nanoparticles **Ru1** and **Ru4** and 5% Ru/C. Ru/C proved to be less reactive (Table 2, entry 1). **Ru1** and **Ru4** gave greater conversion to the product, and in the latter case, the desired pyrazine **2b** was isolated in 86% yield 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** in a yield of 45% (Table 2, entry 4). Substrates containing electron-rich groups on the arene ring such as *p*-methyl- and *p*-methoxide-substituted benzils **1d,e** were found to be less reactive in the reaction. The reaction of **1d** with **Ru4** gave complete conversion to product **2d** after 5 h, 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,



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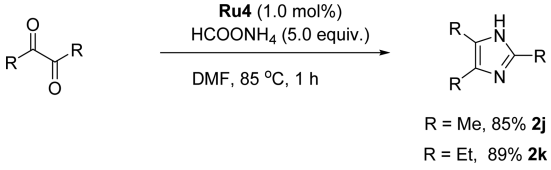
entry 7). A substrate containing a heteroarene substituent such as furil under the same catalytic conditions, after 1 h, produced pyrazine **2g** in 61% yield (Table 2, entry 8). Cyclic substrates such as 1,2-cyclohexanedione **1h** gave complete conversion to the desired product **2i**, and the product was purified over neutral alumina in decent yield (Table 2, entry 9). The reaction with 1,2-cyclopentanedione gave the desired pyrazine in a moderate yield of 51% as a crude product (Table 2, entry 10).

In order to adapt this methodology for the synthesis of alkyl-substituted pyrazines, we screened acyclic $\alpha$-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; instead, the reactions gave trisubstituted imidazoles (Scheme 3). The synthesis of

**Scheme 3. Synthesis of Trisubstituted Imidazoles from Acyclic $\alpha$-Diketones**

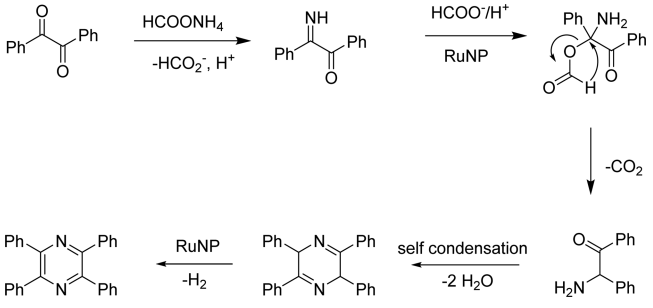



trisubstituted imidazoles from $\alpha$-diketones is a well-known preparation method.[27] However, this reaction requires additional substrate aldehyde along with $\alpha$-diketones and also needed superheating conditions and microwave irradiation or a micro reactor system under pressure.[28] Our reaction conditions with **Ru4** for the first time yield imidazoles from $\alpha$-diketones without requiring aldehydes in the reaction and with mild conditions. We believe that the reaction proceeds in situ, giving rise to the generation of an acyl equivalent from the diketone via retro aldol condensation followed by condensation with diketone and ammonium formate under conditions similar to those reported in the literature.

The proposed mechanism for the formation of pyrazines assumes that the $\alpha$-diketone undergoes reductive amination under transfer hydrogenation conditions to produce the $\alpha$-amino ketone in the 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).

In order to demonstrate the general synthetic utility of this methodology, we chose to synthesize biologically important pyrazines such as **2l,m**. The pyrazine **2l** is an estrogen receptor which has been synthesized in the literature in two steps: first, condensation between *p*-anisil and 1,2-bis(4-methoxyphenyl)-

**Scheme 4. Proposed Mechanism for the Formation of Pyrazines**




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 the marine cytotoxic natural product Dragmacidin B. There are several synthetic routes reported in the literature for the preparation of **2m**, which include condensation of bromo-substituted oxotryptamine in ethanol/xylene at 135 °C for 72 h or Pd-catalyzed Suzuki coupling of 2,5-dibromopyrazine.[31] Our approach to the synthesis of **2m** involved starting with diketone **1m**, which was obtained by treatment of 5-bromoindole with oxalyl chloride followed by reduction with $nBu_3SnH$;[32] **1m** was then subjected to **Ru4**-catalyzed conditions to give pyrazine **2m** in 40% yield (Scheme 5).

## CONCLUSION

In conclusion, during our attempts at transfer hydrogenation with Ru NPs with formate as a hydrogen donor we have discovered a new general synthetic protocol for the synthesis of substituted pyrazines and imidazoles from readily available $\alpha$-diketones. The Ru NPs play a role in hydrogen borrowing during this reaction and as dehydrogenation catalysts. 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 and mild reaction conditions and shows a good substrate scope. The catalyst can be removed by adsorption on silica or alumina. Aryl and alkyl diketones reacted differently with RuNPs and produced pyrazines and imidazoles, respectively. This newly developed protocol offers rapid access to biological important pyrazine scaffolds such as **2l,m**.

## EXPERIMENTAL SECTION

**General Remarks.** All air- and moisture-sensitive reactions were performed under an 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 of the dry solvents were obtained from a 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 chemical shifts of $^1H$ and $^{13}C$ are reported in ppm. Signal multiplicities are quoted as s (singlet), d (doublet), dd (doublet of doublets), m (multiplet), and b (broad).

All of the $\alpha$-diketones were purchased from commercial sources, and substrates **1l,m** were prepared according to literature protocols.[29,31] Ru(COD)(COT) was purchased from NanoMePS and used as received. Xantphos, DPEphos, and dppp were purchased, and dbdocphos was prepared according to a 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 by drop-casting (from THF solution) 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 placed the appropriate phosphine ligand (0.1 equiv) and anhydrous degassed THF (60 mL) under argon. The reaction mixture was cooled to −110 °C with liquid nitrogen and the solution transferred into a Fischer−Porter reactor containing the complex [Ru(COD)(COT)] (60.0 mg, 0.19 mmol, 1.0 equiv) at −110 °C. Then the reactor was pressurized with 3 bar of hydrogen and the mixture stirred at room temperature



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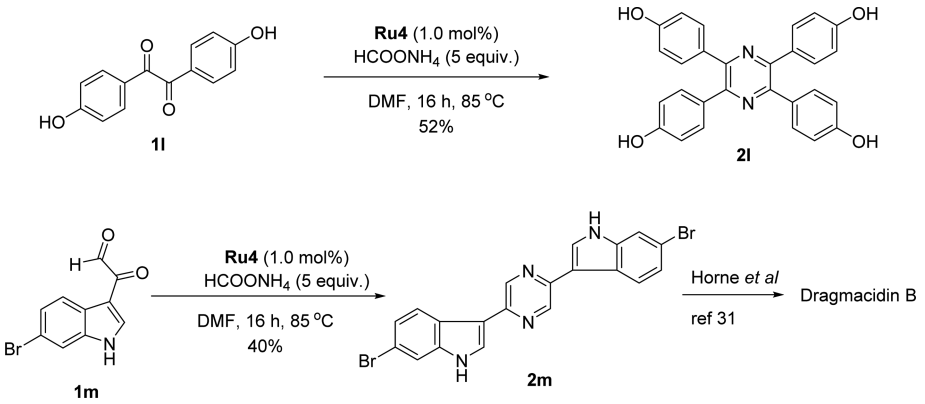
**Scheme 5. Synthetic Application of the Methodology for the Preparation of 2l,m**




for 16 h. The reaction mixture turned into a black solution, and a drop of this solution was deposited on a 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 (2 × 10 mL). The resulting particles were dried in vacuo overnight. The obtained RuNPs were stored in Schlenk tubes 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 were charged benzil (**1a**; 210 mg, 1.0 mmol), anhydrous DMF (3.0 mL), and ammonium formate (315 mg, 5.0 mmol) under an 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 (2 × 10.0 mL) and brine (2 × 10 mL) and 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, $CDCl_3$): $\delta$ 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). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ 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 were charged an $\alpha$-diketone (**1a−m**; 1.0 mmol), anhydrous DMF (3.0 mL), and ammonium formate (5.0 mmol) under an argon atmosphere. The reaction mixture was degassed by three vacuum/argon cycles, and then ruthenium nanoparticles (**Ru4**; 1.0 mol %) were added. The resulting mixture was stirred at 85 °C for the appropriate time (1−12 h). The reaction mixture was poured into water (5 mL) and extracted with EtOAc (2 × 10.0 mL). The combined organic layers were washed with water (2 × 10.0 mL) and brine (2 × 10 mL) and 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−h** and imidazoles.

*2,3,5,6-Tetraphenylpyrazine (**2a**).*[34] This compound was synthesized according to the 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 °C for 1 h. The title compound was obtained after flash column chromatography ($SiO_2$, hexane/EtOAc 95/5) as a white solid (177 mg, 92%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.32−7.39 (m, 12 H), 7.66−7.69 (m, 8 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ 128.4, 128.7, 130.0, 138.6, 148.6.

*2,3,5,6-Tetrakis(4-fluorophenyl)pyrazine (**2b**).*[12] This compound was synthesized according to the 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 °C for 1 h. The title compound was obtained after flash column chromatography ($SiO_2$, hexane/EtOAc 95/5) as a pale yellow solid (197 mg, 86%). Mp: 232−235 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.99−7.10 (m, 8 H), 7.53−7.64 (m, 8 H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): $\delta$ 115.6, 115.7, 131.7, 131.8, 134.2, 134.3, 147.5, 162.4, 164.3. HRMS (ESI): $C_{28}H_{16}F_4N_2$ $[M]^+$ calculated 456.1250, found 456.1230.

*2,3,5,6-Tetrakis(4-bromophenyl)pyrazine (**2c**).*[35] This compound was synthesized according to the 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 °C for 1 h. The title compound was isolated after flash column chromatography ($SiO_2$; hexane/EtOAc 95/5) as a white solid (158 mg, 45.2% yield). $^1$H NMR (500 MHz, $C_6D_6$): $\delta$ 7.18−7.20 (m, 8 H), 7.28−7.30 (m, 8 H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): $\delta$ 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-tolylpyrazine (**2d**).*[33] This compound was synthesized according to the 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 5 h. 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 21.3, 128.9, 129.7, 135.9, 138.4, 147.8. HRMS (MALDI): calculated for $C_{32}H_{28}N_2{}^+$, $[M]^+$ 440.2247, found 440.2252.

*2,3,5,6-Tetrakis(4-methoxyphenyl)pyrazine*[1] *(**2e**).*[29] This compound was synthesized according to the 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 ($CDCl_3$): $\delta$ 3.83 (s, 12 H), 6.85 (d, $J$ = 8.9 Hz, 8 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, $CDCl_3$): $\delta$ 55.2, 113.7, 131.0, 131.2, 146.8, 159.8.

*2,3,5,6-Tetrakis(3-methoxyphenyl)pyrazine (**2f**).*[33] This compound was synthesized according to the 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 55.4, 115.0, 115.1, 122.6, 129.4, 139.9, 148.4, 159.6.

*2,3,5,6-Tetra-2-furylpyrazine (**2g**).*[6a] This compound was synthesized according to the general procedure; 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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°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, $CDCl_3$): $\delta$ 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{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ 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] This compound was synthesized according to the general procedure; 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 °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, $CDCl_3$): $\delta$ 1.88−1.91 (m, 8 H), 2.85−2.90 (m, 8 H). $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ 23.0, 31.8, 149.5.

*1,2,3,5,6,7-Hexahydrodicyclopentapyrazine (2i).*[36] This compound was synthesized according to the 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 °C for 2 h. The title compound was isolated as the crude product (41.0 mg, 51% yield). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 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-1H-imidazole (2j).*[26] This compound was synthesized according to the 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 °C for 1 h. The title compound was isolated by flash chromatography as a gray solid (62 mg, 85%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.10 (s, 6 H), 2.30 (s, 3 H). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$): $\delta$ 10.6, 13.8, 125.8, 141.9.

*2,4,5-Triethyl-1H-imidazole (2k).*[37] This compound was synthesized according to the 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 °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, $CDCl_3$): $\delta$ 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] This compound was synthesized according to the 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 %) in anhydrous DMF (3.0 mL) were stirred at 85 °C for 16 h. The title compound was isolated by flash chromatography ($SiO_2$, 0−30% EtOAC in hexane) as a gray solid (57 mg, 51% yield). $^1$H NMR (300 MHz, acetone): $\delta$ 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).*[30] This compound was synthesized according to the 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 silica gel using 10% EtOAc in hexane as a yellow solid (93 mg, 40% yield). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 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).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03032.

NMR spectra of all compounds in the Experimental Section and TEM images, UV, TGA, and HRMS spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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