Conformationally Driven Ru(II)-Catalyzed Multiple ortho-C–H Bond Activation in Diphenylpyrazine Derivatives in Water: Where is the Limit?

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Received: 24 March 2020; Accepted: 7 April 2020; Published: 12 April 2020

Abstract: Ru(II)/carboxylate/PPh₃ catalyst system enabled the preparation of highly conjugated pyrazine derivatives in water under microwave irradiation. Both nitrogen atoms efficiently dictated cleavage of the ortho-C–H bonds in both benzene rings of 2,3-diphenylpyrazine substrates through chelation assistance. In conformationally more flexible diphenyldihydropyrazine 1, the arylation of four ortho-C–H bonds was possible, while in the aromatic analog 2, the triarylation was the limit.

Keywords: ruthenium catalysts; heterocycles; green chemistry; microwave; direct arylation

1. Introduction

Catalytic C–H bond activation and subsequent formation of new C–C bonds, or C–heteroatom bonds, have remarkably contributed to the development of chemical transformations which enable the construction of complex molecular architectures from readily available precursors by shortening synthetic pathways and reducing waste production [1–7]. Heteroarylation via C–H bond activation has been largely applied to material science, for example, the synthesis of conjugated dyes [8] and polymers [9]. Although Pd [10–14] and Rh [15–18] catalysts are very efficient in enabling the selective functionalization of C–H bonds, the use of easy-to-prepare, air-stable, often stable in water and functional groups tolerant Ru(II) complexes have attracted much interest in the development of efficient catalytic systems for these processes [19–26]. Despite the ubiquity of C–H bonds in organic molecules, the regioselectivity of C–H bond functionalization can elegantly be controlled by chelation assistance of directing groups [27–32]. A great number of them are based on nitrogen as the metal-coordinating atom, the pyridine ring being prevalent, although other azaheterocycles, such as pyrazole, oxazoline, and quinoline have also been successfully employed in transition-metal-catalyzed ortho-C–H bond functionalization [33]. Požgan and co-workers have demonstrated that the quinazolinyl [34,35] and pyrimidinyl [36] groups efficiently allow regioselective ortho-arylations in the presence of Ru(II)-carboxylate catalyst, even in water as the solvent in some cases [37,38]. The success of Ru(II) catalysts is most likely ascribed to the easy formation of ruthenacyclic intermediate stable in water via C–H bond deprotonation with the assistance of directing groups [35,37,39–43].

The pyrazine scaffold is one of the privileged azaheterocyclic structural motifs in many natural products [44] and synthetic compounds [45] with biological activities, as well as in functional materials [46]. 2,3-Dihydropyrazines, which are direct precursors of pyrazines, are known to have an important role as flavorants [47] and are assumed to actively participate in DNA strand cleavage [48–50] and cyclooxygenase inhibition [51]. In addition, the pyrazine derivatives can efficiently act as
ligands in the construction of metallosupramolecular architectures because of their two N-coordinating sites [52–57], as well as building blocks in the design of photoluminescence devices [46]. For these reasons, many synthetic methods for the construction of pyrazine derivatives have been developed [58–63], yet there is still great demand for the generation of novel pyrazine libraries. As a part of our ongoing interest in metal-catalyzed functionalization of (hetero)arenes via C–H bond activation [34–38], we reasoned that a pyrazine nucleus could direct cleavage and further functionalization of ortho-C–H bonds of the benzene ring in phenyl-substituted pyrazines. Moreover, by using 2,3-diphenylpyrazines as substrates, both nitrogen atoms could cooperate with the catalytic metal center to hypothetically promote four ortho-C–H bond activations, thus enabling the construction of highly functionalized, especially arylated or π-conjugated pyrazine derivatives. However, the examples of the pyrazine-directed catalytic C–H bond functionalization are very scarce. The most significant contribution has recently been achieved by Gramage-Doria and co-workers who demonstrated that 2-alkenylpyrazines underwent smooth β-arylation in the presence of Ru(II)-KOAc catalyst system in NMP as solvent by the favorable formation of a five-membered metallacyclic intermediate [64]. Pd(OAc)$_2$ was used as a catalyst for regioselective C–H bond ortho-monofluorination of the benzene ring in 2-phenylpyrazines [65] and was also a catalyst of choice for ortho-monoacetoxylation of benzylpyrazine with PhI(OAc)$_2$ via otherwise less stable six-membered palladacycle intermediate [66]. A bidentate pyrazine-2-carboxamide group efficiently directed Pd(II)-catalyzed acetoxylation of remote ε-C(sp$^2$)-H bonds in 3-phenylthiophene substrates [67]. To the best of our knowledge, there is no example of direct arylation of ortho-C–H bonds of 2,3-diphenylpyrazines under Ru(II)-catalyzed conditions, whereas Doucet and co-workers have shown that fused analogs, 2,3-diphenylquinoxalines underwent Pd-catalyzed ortho-C–H bond functionalization leading to monoarylated products, while the arylation reaction did not occur in the presence of [RuCl$_2$(p-cymene)] as a catalyst [68].

In the present study, we have investigated the functionalization of ortho-C–H bonds of diphenylpyrazine derivatives with ruthenium(II) catalysts. Our aim was to show limitations for pyrazine-directed multiple C–H arylations of two specific pyrazine derivatives, 5,6-diphenyl-2,3-dihydropyrazine (1) and 2,3-diphenylpyrazine (2). It is disclosed that (i) both nitrogen atoms in diphenylpyrazines 1 and 2 are capable of bringing the reactive ruthenium(II) center into close proximity of ortho-C–H bonds of both benzene rings via chelation-assistance thus promoting their cleavage followed by arylation at these positions, (ii) conformationally more flexible 2,3-dihydropyrazine 1 undergoes up to four ortho-arylations via the easier formation of a ruthenacyclic intermediate than its aromatic analog 2, and (iii) C–H bond activation is accompanied by in situ aromatization of a dihydropyrazine ring.

2. Results and Discussion

We initiated our study by the reaction of 5,6-diphenyl-2,3-dihydropyrazine (1) with 4-bromoacetophenone as sterically non-demanding arylating agent, using the methodology for microwave-promoted Ru(II)-catalyzed arylation of 2-phenylpyrimidines in water developed within our group [37]. Due to the presence of the four ortho-C–H bonds in diphenylpyrazine 1, up to four arylations were expected. Even though we intended to directly apply the previously established catalytic conditions [37] for the present arylation of dihydropyrazine substrate 1, the effect of base, solvent, ligands, and temperature was briefly investigated under conventional heating (see SI). The system comprising [RuCl$_2$(p-cymene)]/1-phenylcyclopentane-1-carboxylic acid (PCCA)/PPh$_3$ together with a large excess of K$_3$PO$_4$ base has once again proven to be a catalyst system of choice, since quantitative conversions of 1 with four-equivalents of 4-bromoacetophenone into arylated pyrazine products in satisfactory diarylation selectivities were attained in water at 140 °C after 24 h. In order to shorten reaction times and to suppress aromatization of starting dihydropyrazine 1 and its arylated products, the reactions were performed in water under microwave (MW) heating conditions.

Initially, the best reaction preferentially enabling diarylation of dihydropyrazine 1 was searched by employing two or four equiv. of 4-bromoacetophenone. When 1 was reacted with 2 equiv. of 4-
bromoacetophenone in the presence of 5 mol% of [RuCl\(_2\)(p-cymene)]\(_2\); precatalyst, PCCA and PPh\(_3\) ligands (10 mol%), and K\(_3\)PO\(_4\) base (5 equiv.) in water at 140 °C under MW heating, a 96% conversion of \(\text{1}\) was attained in only 1 h leading to a complex mixture of mono- and diarylated dihydropyrazine products \(\text{3a}/\text{5a}\) and their aromatic analogs \(\text{4a}/\text{6a}\) (Scheme 1, entry 1). Upon decreasing the reaction temperature from 140 °C to 120 °C, appreciable monoaarylation selectivity was observed, but the conversion significantly dropped (Scheme 1, entry 2). The conversion again increased as the irradiation time was prolonged to 1.25 h while maintaining the reaction temperature at 120 °C, but the monoaarylated product \(\text{3a}\) was still a major product (Scheme 1, entry 3). The entries 1–4 in the table in Scheme 1 illustrate that diarylation of \(\text{1}\) with 2 equiv. of 4-bromoacetophenone is somehow troublesome, and that the use of standard reaction conditions within only 0.5 h provided the best compromise between conversion of \(\text{1}\) and ratio of products \(\text{3a}/\text{4a}/\text{5a}/\text{6a}/\text{7a}\) for achieving a satisfactory monoaarylation selectivity (Scheme 1, entry 4). The obtained 86% conversion enabled isolation of monoaarylated dihydropyrazine \(\text{3a}\) in 53% yield together with 7% of diarylated product \(\text{5a}\). The use of 4 equiv. of 4-bromoacetophenone under optimized conditions led to a quantitative conversion of \(\text{1}\) in 1 h, and to the excellent preference of diarylation over monoaarylation (Scheme 1, entry 5). Unfortunately, this diarylation reaction was accompanied by the significant extent of triarylation \(\text{7a}, 10\%\) yield, even if the reaction time was reduced to 0.5 h (Scheme 1, entries 5 and 6). Direct orthoaarylation of \(\text{1}\) was also accomplished with four equiv. of 1-bromo-4-(trifluoromethyl)benzene to give the diarylated product \(\text{5b}\) in moderate 45% yield together with 13% of triarylated product \(\text{7b}\) (Scheme 1, entry 7).

![Scheme 1](image)

**Scheme 1.** Mono- and diarylation of dihydropyrazine \(\text{1}\).* 

The above-mentioned formation of by-products \(\text{7}\) suggests that despite the increased steric hindrance in the diarylated product \(\text{5}\) originating from large biphenyl groups formed after two ortho-moaarylations, the cleavage of the second ortho-C–H bond on the same benzene ring is feasible. Isolation of compounds \(\text{7a,b}\) in noticeable amounts by employing 4 equiv. of 4-bromoacetophenone prompted us to find the reaction conditions preferentially leading to triarylated dihydropyrazine products \(\text{7}\). Pleasingly, when dihydropyrazine \(\text{1}\) was reacted with 6 equiv. of 4-bromoacetophenone

| Entry | R (equiv.) | React. time (h) | Conv. (%) | 3/4/5/6/7 (%) |
|-------|-----------|----------------|-----------|--------------|
| 1     | MeCO (2)  | 1              | 96        | 31/10/50/2/7 |
| 2a    | MeCO (2)  | 1              | 77        | 86/4/10/0/0  |
| 3a    | MeCO (2)  | 1.25           | 93        | 64/4/28/1/3  |
| 4     | MeCO (2)  | 0.5            | 86        | 75(53)/3/22(7%)/0/0 |
| 5     | MeCO (4)  | 1              | 100       | 0/5/73(58%)/6(3%)/16(10%) |
| 6     | MeCO (4)  | 0.5            | 100       | 20/4/65/1/10 |
| 7     | CF\(_3\)  | 1              | 100       | 0/7/18(13%) |

* Reaction conditions: \(\text{1} (0.25\ mmol), \text{ArBr (0.5 or 1 mmol), [RuCl}\(_2\)(p-cymene)]\(_2\) (0.0125 mmol), 1-phenylcyclopentane-1-carboxylic acid (0.025 mmol), PPh\(_3\) (0.025 mmol), K\(_3\)PO\(_4\) (1.25 mmol), H\(_2\)O (1 mL), MW 140 °C, argon. * Conversion and ratio determined by NMR analysis without internal standard. * Yield of isolated product. * 120 °C instead of 140 °C.
or 1-bromo-4-(trifluoromethyl)benzene at 140 °C under MW-irradiation for 1 h, and increased quantities of [RuCl₂(p-cymene)]₂ (10 mol%), PCCA and PPh₃ (20 mol%) were used, the triarylated dihydropyrazine products 7a and 7b dominated in the crude reaction mixture. By employing 4-bromoacetophenone as a coupling partner, the product 7a was isolated in good 65% yield, even if it was accompanied by a significant quantity of a side product, tetraarylated dihydropyrazine 9a (10% yield) (Scheme 2, entry 1). 1-Bromo-4-(trifluoromethyl)benzene was somehow less reactive, as the diarylation product 5b was still present in the crude reaction mixture, and consequently, the product 7b was isolated in the lower 40% yield (Scheme 2, entry 2). However, we were not able to detect analogous tetraarylation products in the reaction of 1 and 1-bromo-4-(trifluoromethyl)benzene under these conditions.

![Scheme 2](image)

**Scheme 2.** Tri- and tetraarylation of dihydropyrazine 1.a,b.

In order to improve the tetra-ortho-C–H arylation selectivity of dihydropyrazine substrate 1, a large excess of arylating reagent was employed under standard conditions: [RuCl₂(p-cymene)]; (0.025 mmol), PCCA (0.05 mmol), PPh₃ (0.05 mmol), K₃PO₄ (1.25 mmol), H₂O (1 mL), MW 140 °C, argon. a Yield of isolated product. b Traces (1–3%) of aromatic product 10a detected by NMR spectroscopy (10a is an aromatized product of 9a).

| Entry | R (equiv.) | React. time (h) | 5/6/7/8/9 (%) | 5/6/7/8/9 (%) |
|-------|------------|-----------------|---------------|---------------|
| 1     | MeCO (6)   | 1               | 0/6/78(65%)/2/14(10%) |               |
| 2     | CF₃ (6)    | 1               | 22(9%)/14(8%)/60(40%)/4/0 |               |
| 3     | MeCO (10)  | 1               | 0/67/5/22     |               |
| 4     | MeCO (10)  | 2               | 0/755(40%)/8/30(19%) |               |
| 5     | MeCO (10)  | 4               | 0/2/23(10%)/14(9%)/58(38%) |               |
| 6     | MeCO (10)  | 8               | 0/2/20(10%)/16(10%)/61(40%) |               |

* Reaction conditions: 1 (0.25 mmol), ArBr (1.5 or 2.5 mmol), [RuCl₂(p-cymene)]; (0.025 mmol), PCCA (0.05 mmol), PPh₃ (0.05 mmol), K₃PO₄ (1.25 mmol), H₂O (1 mL), MW 140 °C, argon. b Quantitative conversion of 1 confirmed by NMR analysis. c Ratio determined by NMR analysis without internal standard.
deprotonation processes. This might be primarily associated with highly increased steric hindrance as the reaction proceeds to the cleavage of the last remaining ortho-C–H bond with subsequent arylation in 7a. Consequently, 7a is not so efficiently converted into 9a, thus allowing self-arylation into 8a to take place to a larger extent. Further optimizations of the reaction conditions by varying base (K2CO3, Na2CO3) and other carboxylate ligands (KOPiv, KOAc) did not lead to the improvement of either tri- or tetraarylation selectivity. It should be mentioned that in all arylation reactions of dihydropyrazine 1 also traces (around 2%) of aromatic pyrazine 2 were detected by NMR spectroscopy.

We have noticed that compound 9a exhibited an interesting NMR feature in solution (Figure 1). The signals for methylene protons were not found in the 1H NMR spectrum recorded in CDCl3 at room temperature (302 K) (Figure 1a). When NMR measurement was performed at 230 K, two multiplets at 2.70, and 3.53 ppm, each integrating for two protons appeared (Figure 1b). These NMR observations could be attributed to conformational fluxionality of a dihydropyrazine ring, which is at 230 K slowed down to such an extent that quasi axial and quasi equatorial protons can be distinguished. In addition, while all four methyl groups are magnetically equivalent at room temperature, two singlets are observed at low temperatures, implying that limited rotations of terphenyl groups together with a slow rate of a ring interconversion force two-by-two p-acetylphenyl moieties into distinct environments (Figure 1a vs. Figure 1b). The exhibited low-temperature NMR characteristics of 9a are in line with its solid-state structure as it was revealed by single-crystal X-ray analysis (Figure 2). The observed molecular dynamics is also solvent-dependent, since in the 1H NMR spectrum in CD3CN at 302 K the resonance for all four methylene protons is detected as one particularly broad signal (Figure 1c), and is speeded up at 320 K as indicated by narrowing of the –CH2CH2– signal (Figure 1d).

![Figure 1](image1.png)

**Figure 1.** Variable temperature 1H NMR spectra (300 MHz) of 9a: a) in CDCl3 at 302 K, b) in CDCl3 at 230 K, c) in CD3CN at 302 K, d) in CD3CN at 320 K.

![Figure 2](image2.png)

**Figure 2.** X-ray structure of 9a and its possible conformation at low temperature.
We were also able to isolate metallacycle 11 from the reaction of 1 with 1 equiv. of [Ru(p-cymene)Cl₂]; resulting from double cycloruthenation in MeOH at room temperature in 15 h, by using methodology established by Dixneuf for the synthesis of five-membered ruthenacycles from substrates with various N-containing functionalities [40,41]. The successful generation of bis-ruthenacycle 11 (90% yield) might suggest that ortho-C–H activations on the two phenyl groups could occur simultaneously. This is somehow reflected by the smooth formation of diarylated product 5a, while the product with two arylated ortho-positions on the same benzene ring was not detected (Scheme 3). Although we were not able to prepare suitable monocrystals of 11 for X-ray analysis, its solution structure was revealed by HRMS, and by one- and two-dimensional NMR techniques (see SI). The HRMS mass spectrum of the compound 11 shows the molecular peak [M + H]+, m/z = 775.0744 (calculated: 775.0734) and in ¹H NMR spectrum (CDCl₃) the complex 11 shows only one set of proton resonances suggesting a highly symmetric structure. The cyclometallated phenyl H₆ and H₃ protons are displayed as two non-equivalent doublets at δ = 7.58 ppm and δ = 8.24 ppm, respectively. The isopropyl group of the p-cymene is observed as two non-equivalent doublets at δ = 0.89 and 1.07 ppm, and its four aromatic protons exhibit four different resonances between 4.98 and 5.66 ppm as expected for a p-cymene ligand in a chiral-at-metal Ru(II) complex center. Methylene protons of the dihydropyrazine ring are observed as two multiplets at 4.23 and 4.63 ppm indicative of hampered conformational flexibility generating quasi equatorial and axial proton positions. The ¹H–¹H NOESY spectrum shows spatial proximity of H₃ proton of the cyclometallated group and aromatic p-cymene proton, which has a through-space interaction also with one methyl group of the isopropyl group. In the ¹³C NMR spectrum, the expected number of carbons corresponding to the symmetrical structure can be seen, and the metallated carbon C₂ is observed at 194.0 ppm. The C=N carbon is observed at 167.9 ppm, while the methylene carbons resonate at 58.7 ppm. Cyclometallation of 1 with palladium has been previously carried out by reaction with lithium tetrachloropalladate to prepare similar bis-cyclopalladated products [69].

![Scheme 3. Synthesis of cyclometallated complex 11.](image)

We designed additional experiments to demonstrate the reactivity of isolated arylated dihydropyrazine products 5a and 7a in further C–H bond functionalization under MW heating in water (Scheme 4). When diarylated dihydropyrazine 5a was subjected to reaction with 4 equiv. of 4-bromoacetophenone at 140 °C for 4 h in the presence of [RuCl₂(p-cymene)]; (10 mol%). PCCA and PPh₃ (20 mol%), tri- and tetraarylated products were formed, but no selectivity issues were observed (Scheme 4, entry 1). Moreover, this arylation reaction was accompanied by the appreciable extent of aromatization of the starting dihydropyrazine 5a into 6a. On the contrary, the reaction of 1 with an excess of 4-bromoacetophenone under otherwise identical conditions, but in only 1 h, exhibited a 58% tetraarylation selectivity to furnish 9a while only traces of aromatic diarylated product 6a were formed (Scheme 2, entry 4). An obvious difference in these two reaction outcomes suggests that the arylation of the second ortho-C–H bond on the same benzene ring of 5a occurs easily whilst the ruthenium catalytic center is still coordinated to the nitrogen atom after executing first ortho-arylation, thus also preventing substantial aromatization of a dihydropyrazine ring. However, when the reaction temperature was raised to 200 °C, aromatic tri- and tetraarylated products, 8a and 10a were obtained in an approximate ratio of 3:2 (Scheme 4, entry 2). Similarly, the reaction of the
triarylated dihydropyrazine 7a with 4 equiv. of 4-bromoacetophenone at 140 °C for 4 h delivered a 1:1 mixture of aromatic analog 8a and tetraarylated dihydropyrazine 9a but with lower 57% conversion. Raising the temperature to 200 °C allowed full conversion of 7a into tetraarylated dihydropyrazine and aromatic products, 9a and 10a, respectively, with the concomitant decrease in aromatization of 7a into 8a. These experiments indicate that both, further arylation and aromatization are favored at elevated temperatures. But arylation should be faster than aromatization, because triarylated pyrazine 8a cannot undergo further arylation under applied conditions, vide infra, Scheme 5.

\[
\text{Entry} \quad \text{Starting} \quad \text{React. temperature (°C)} \quad \text{Conv. (%)} \quad 6a/7a/8a/9a/10a^{\text{b}}
\]

| Entry | Starting | React. temperature (°C) | Conv. (%) | 6a/7a/8a/9a/10a^{\text{b}} |
|-------|----------|-------------------------|-----------|----------------------------|
| 1     | 5a       | 140                     | 100       | 30/30/23/17/0              |
| 2     | 5a       | 200                     | 100       | 9/0/54/0/37                |
| 3     | 7a       | 140                     | 57        | 0/0/46/52/2                |
| 4     | 7a       | 200                     | 100       | 0/0/9/25/66                |

\text{a} Reaction conditions: 5a or 7a (0.125 mmol), 4-bromoacetophenone (0.5 mmol), \([\text{RuCl}_2(\text{p-cymene})]_2\) (0.0125 mmol), PCCA (0.025 mmol), PPh\(_3\) (0.025 mmol), K\(_3\)PO\(_4\) (0.375 mmol), H\(_2\)O (1 mL), MW, argon. \text{b} Conversion and ratio of products determined by NMR analysis without internal standard.

**Scheme 4.** Further arylation of ortho-arylated dihydropyrazines 5a and 7a.

\[
\text{Entry} \quad \text{React. time (h)} \quad \text{React. temperature (°C)} \quad 6a/8a^{\text{c}}(\%)^{\text{d}}
\]

| Entry | React. time (h) | React. temperature (°C) | 6a/8a^{\text{c}}(\%)^{\text{d}} |
|-------|-----------------|-------------------------|-------------------------------|
| 1     | 1               | 140                     | 80/20                         |
| 2     | 1               | 200                     | 50(20%/)/50(27%)              |
| 3     | 4               | 140                     | 50(50%)                       |
| 4     | 4               | 200                     | 35(11%)/60(19%)               |

\text{a} Reaction conditions: 1 (0.25 mmol), 4-bromoacetophenone (1.5 mmol), \([\text{RuCl}_2(\text{p-cymene})]_2\) (0.025 mmol), PCCA (0.05 mmol), PPh\(_3\) (0.05 mmol), K\(_3\)PO\(_4\) (1.25 mmol), H\(_2\)O (1 mL), MW, argon. \text{b} Quantitative conversion of 2 confirmed by NMR analysis. \text{c} Ratio determined by NMR analysis without internal standard. \text{d} Yield of isolated product.

**Scheme 5.** Direct arylation of 2,3-diphenylpyrazine (2).

We speculated that conformationally more flexible dihydropyrazines more easily adopt quasi planar topology between nitrogen atoms and aryl groups for subsequent ruthenacycle formation than
the corresponding aromatic pyrazines, even if the phenyl groups are already ortho-functionalized. In this context, the extent of catalytic multiple ortho-arylations of aromatic pyrazine 2 was next investigated (Scheme 5). Reaction of 2 with 6 equiv. of 4-bromoacetophenone under established conditions ([RuCl2(p-cymene)]2 (10 mol%), PCCA and PPh3 (20 mol%), MW 140 °C, 1 h) led to the preferential formation of diarylated product 6a (Scheme 5, entry 1). In order to achieve appreciable triarylation, the reaction time had to be extended and the reaction temperature raised from 140 to 200 °C (Scheme 5, entries 2–4). Even upon heating the reaction mixture at highly elevated temperature for 4 h, only traces of tetraarylated product 10a were detected in the crude reaction mixture. For comparison, a four-hour-reaction of dihydropyrazine 1 with 4-bromoacetophenone at only 140 °C smoothly delivered tetraarylated dihydropyrazine 9a in 38% yield. A significant difference in reactivity between 1 and 2 can be intrinsically attributed to higher conformational flexibility of a dihydropyrazine ring thus enabling arylation of all four ortho-C–H bonds. On the other hand, the steric interactions of the ortho-arylated phenyl groups in 2 highly increase after three C–H arylations thus preventing coplanarity of the biphenyl group with the rigid aromatic pyrazine ring. Hence, a ruthenacyclic intermediate cannot be effectively formed, and consequently the fourth C–H bond functionalization in 2 is practically shut down.

We tried to cyclometallate also pyrazine 2 using the same reaction conditions as for preparation of bis-ruthenacycle 11. Reaction of 2 with with 1 equiv. of [(p-cymene)RuCl2]2 in MeOH in the presence of KCl at room temperature in 15 h gave a complex mixture of products (Scheme 6). However, we were able to isolate a small quantity (14% yield) of mono-ruthenacycle 12 only. The double cyclometallation of 1 but not 2 on reaction with [(p-cymene)RuCl2]2 is probably attributable to the greater flexibility of the dihydropyrazine ring than that which is possible in the planar aromatic pyrazine ring in 2.

![Scheme 6: Cyclometallation of pyrazine 2.](image)

Lastly, we attempted to hydrolyze the aryalted dihydropyrazine products, which can be regarded as cyclic bisimines, to restore a dicarbonyl compound. This would represent a surrogate to obtain highly conjugated 1,2-diketones since a carbonyl group is known to act as weak directing group but can be easily transformed into better coordinating imine [70–72]. Namely, direct arylation of benzil with 4-bromoacetophenone under optimized conditions ([RuCl2(p-cymene)]2 (10 mol%), PCCA and PPh3 (20 mol%), H2O, 140 °C, MW 1 h) failed. Surprisingly, by treating a pure tetraarylated dihydropyrazine 9a with 6 M HCl a quantitative transformation into the corresponding aromatic product 10a occurred. On the other hand, the starting dihydropyrazine 1 was smoothly hydrolysed to give benzil under otherwise identical conditions. Obviously, two terphenyl groups in 9a prevent the water molecule to approach an imine carbon for subsequent nucleophilic attack. Hence, the hydrolysis cannot occur and thermodynamically favourable aromatization takes place, which is, however, strongly facilitated by a Brønsted acid. It is noteworthy, that heating of 9a in water at 60 °C for 4 h but in the absence of an acid did not lead either to aromatized product 10a or to hydrolysis products. Thus highly sterically congested tetraarylated pyrazine 10a was accessed by arylation of 1 with 4-bromoacetophenone followed by treatment of the crude reaction mixture with 6 M HCl (Scheme 7). The desired product 10a was isolated in good 58% yield after chromatographic separation. Similarly, the triarylated pyrazine product 8b bearing trifluoromethyl groups was prepared using
this two-step reaction in 39% yield (Scheme 7). It should be also mentioned, that 9a spontaneously aromatized in solid (10% conversion in 14 days) and in dichloromethane solution (50% conversion in 14 days).

To get more insight into conformational properties and to confirm the structures of dihydropyrazines and their aromatic analogs, single-crystal X-ray analyses of compounds 3a, 5b, 6b, 7b, 8b, 9a, and 10a were performed (see SI). A detailed inspection of dihedral angles in diarylated dihydropyrazine 5b and its aromatic analog 6b revealed that the nitrogen atom N1 in 5b is by approximately 15° more inclined toward the carbon atom C6 of the second free ortho-C–H bond than in 6b (Figure 3). This could imply that a five-membered ruthenacycle intermediate can be more easily formed with 5b than with 6b. Consequently, the subsequent arylation occurs easier with dihydropyrazines than with aromatic analogs as illustrated by the aforementioned experiments.

Figure 3. Superposition showing the difference in torsion angle N1–C1–C5–C6 5b (blue) and 6b (red). Disorder on CF3 groups is omitted for clarity.
3. Materials and Methods

3.1. Materials

All reagents were purchased from commercial suppliers and were used without further purification. Starting 1 [73] and 2 [69] were prepared according to literature procedures. The reactions with microwave heating were performed with a CEM Discovery Microwave (CEM Corporation, Matthews, NC, USA). Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The reactions were monitored by analytical thin-layer chromatography using silica gel plates (Kieselgel F254, Fluka, Honeywell, Charlotte, NC, USA) or Al2O3 plates (Aluminiumoxid 60 F 254 neutral, Typ E, Fluka, Honeywell, Charlotte, NC, USA). Radial chromatography purification was performed with a Harrison Research chromatotron, model 7924 T. Commercially available silica gel 60 PF254 containing gypsum (Kieselgel 60 PF254, Merck Group, Darmstadt, Germany) or the mixture of gypsum, fluorescence indicator and Al2O3 (Aluminiumoxid 60 G neutral, Typ E, Merck Group, Darmstadt, Germany) was used to prepare chromatotron plates. Compounds were visualized by 254 nm UV lamp. Melting points (mp [°C]) were determined on a Kofler micro hot stage instrument and are uncorrected. The NMR spectra were recorded either on a Bruker DPX 300 (Bruker, Billerica, MA, USA) or an Avance III 500 MHz (Bruker, Billerica, MA, USA) spectrometer operating at 300 MHz or 500 MHz and 75.5 MHz or 126 MHz for 1H and 13C nuclei. Variable temperature (230–320 K) 1H NMR spectra were measured with a Bruker DPX 300 MHz. The infrared (IR) spectra were obtained with a Bruker ALPHA FT-IR (Bruker, Billerica, MA, USA) spectrophotometer and are reported in reciprocal centimeters (cm⁻¹). The high-resolution mass spectra (HRMS) were recorded with an Agilent 6224 Accurate Mass TOF LC/MS (Agilent Tehnologies, Santa Clara, CA, USA) instrument. X-ray structures were recorded on a SuperNova Dual diffractometer (Agilent Technologies Ltd., Yarnton, UK).

3.2. General Method for Catalytic Direct Arylation of Diphenylpyrazine Derivatives

A thick wall vessel was loaded with 5,6-diphenyl-2,3-dihydropyrazine (1) or 2,3-pyrazine (2) (58.6 mg, 0.25 mmol), [RuCl2(p-cymene)]2 (5–10 mol%), 1-phenylcyclopentane-1-carboxylic acid (10–20 mol%), PPh3 (10–20 mol%), K3PO4 (5 equiv.), corresponding aryl halide (2–10 equiv.). The mixture was suspended in 1 mL of deionized water and bubbled with argon for 5 min. The reactions were carried out under microwave irradiation at temperature and for the indicated period of time. The reaction mixture was then cooled to room temperature and diluted with H2O (10 mL). The crude product was extracted with DCM (2 × 10 mL). The combined organic phases were dried over anhydrous Na2SO4, filtered and evaporated under reduced pressure. The crude product was further purified by radial chromatography (SiO2 or Al2O3) using different mixtures of EtOAc and petroleum ether.

3.3. General Method for Preparation of Arylated Aromatic Pyrazine Products

The extracted crude product from the arylation reaction of 1 as described in 3.2 was dissolved in THF (3 mL), and 6 M aqueous HCl (3 mL) was added and stirred at room temperature for 5 h. After completion of the reaction, the mixture was diluted with DCM (10 mL) and extracted with saturated aqueous NaHCO3 (3 × 10 mL). The organic phase was dried over anhydrous Na2SO4, filtered and evaporated under reduced pressure. The crude product was further purified by radial chromatography (SiO2 or Al2O3) using different mixtures of EtOAc and petroleum ether.

4. Conclusions

In summary, we have demonstrated that Ru(II)/carboxylate/PPh3 catalyst system enables direct arylation of 2,3-diphenylpyrazine derivatives 1 and 2 in water as solvent under microwave irradiation, where both nitrogen atoms cooperate with a catalytic metal center to allow selective deprotonation of ortho-C–H bonds in both benzene rings. Our results on multiple arylations of pyrazines 1 and 2 are in sharp contrast with Pd-catalyzed monoarylation of fused analogs, 2,3-diphenylquinoxalines [66], thus showing unique performance of Ru(II) catalysts. With more flexible
dihydropyrazine substrate 1, it was possible to achieve up to four ortho-C–H arylations, while planar pyrazine ring in 2 allowed for up to three arylations. The success of multiple arylations of diphenylpyrazine derivatives is most probably due to Ru(II)/microwave/water cooperation. This green methodology provides a series of π-extended pyrazine derivatives through a five-membered ruthenacyclic intermediate. Although selectivities still need to be improved by utilizing more powerful catalyst systems, these observations confirm, at least partially, our hypothesis about conformationally driven ortho-C–H bond arylation, which is easier to occur in dihydropyrazine 1 than in its aromatic analog 2.

**Supplementary Materials:** The following are available online at www.mdpi.com/2073-4344/10/4/421/s1: Experimental procedures, tables of crystallographic details, the analytical and spectroscopic data, and the 1H and 13C NMR spectra. CCDC 1991671–1991677 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallography Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

**Author Contributions:** Conceptualization, F.P.; Methodology, S.H., M.D. and F.P.; Validation, S.H., M.D., U.G., J.S. and B.Š.; Investigation, S.H., M.D., F.P. and F.P.; Writing—Original Draft Preparation, F.P.; Writing—Review & Editing, U.G., F.P., J.S., B.Š. and F.P.; Supervision, F.P.; Project Administration, F.P.* All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by Slovenian Research Agency (grants P1-0179 and P1-0175).

**Acknowledgments:** Financial support from the Slovenian Research Agency through grants P1-0179 and P1-0175 is gratefully acknowledged. We thank EN-FIST Centre of Excellence, Dunajska 156, 1000 Ljubljana, Slovenia, for using Bruker Alpha FTIR spectrophotometer and Supernova diffractometer. We thank Prof. Pierre H. Dixneuf (Institut des Sciences Chimiques, Université de Rennes) for discussions and evaluation of this manuscript.

**Conflicts of Interest:** The authors declare no conflict of interest.

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