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

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Abstract: Ru(II)/carboxylate/PPh_3 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 *ß*-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 $[RuCl_2(p\text{-cymene})]_2$ as a catalyst [68].

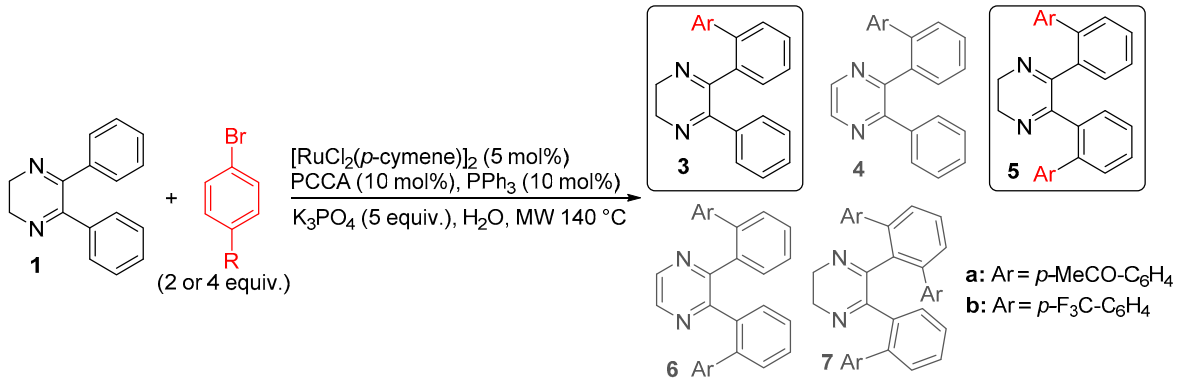
In the present study, we have investigated the functionalization of *ortho*-C–H bonds of diphenylpyrazine derivatives with ruthenium(II) catalysts. Our aim was to show limitations for pyrazine-directed multiple C–H arylations of two specific pyrazine derivatives, 5,6-diphenyl-2,3-dihydropyrazine (**1**) 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 $[RuCl_2(p\text{-cymene})]_2$/1-phenylcyclopentane-1-carboxylic acid (PCCA)/PPh_3 together with a large excess of K_3PO_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 $[RuCl_2(p\text{-cymene})]_2$ precatalyst, PCCA and PPh_3 ligands (10 mol%), and K_3PO_4 base (5 equiv.) in water at 140 °C under MW heating, a 96% conversion of **1** was attained in only 1 h leading to a complex mixture of mono- and diarylated dihydropyrazine products **3a**/**5a** and their aromatic analogs **4a**/**6a** (Scheme 1, entry 1). Upon decreasing the reaction temperature from 140 °C to 120 °C, appreciable monoarylation 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 monoarylated product **3a** was still a major product (Scheme 1, entry 3). The entries 1–4 in the table in Scheme 1 illustrate that diarylation of **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 **1** and ratio of products **3a**/**4a**/**5a**/**6a**/**7a** for achieving a satisfactory monoarylation selectivity (Scheme 1, entry 4). The obtained 86% conversion enabled isolation of monoarylated dihydropyrazine **3a** in 53% yield together with 7% of diarylated product **5a**. The use of 4 equiv. of 4-bromoacetophenone under optimized conditions led to a quantitative conversion of **1** in 1 h, and to the excellent preference of diarylation over monoarylation (Scheme 1, entry 5). Unfortunately, this diarylation reaction was accompanied by the significant extent of triarylation (**7a**, 10% yield), even if the reaction time was reduced to 0.5 h (Scheme 1, entries 5 and 6). Direct *ortho*-arylation of **1** was also accomplished with four equiv. of 1-bromo-4-(trifluoromethyl)benzene to give the diarylated product **5b** in moderate 45% yield together with 13% of triarylated product **7b** (Scheme 1, entry 7).



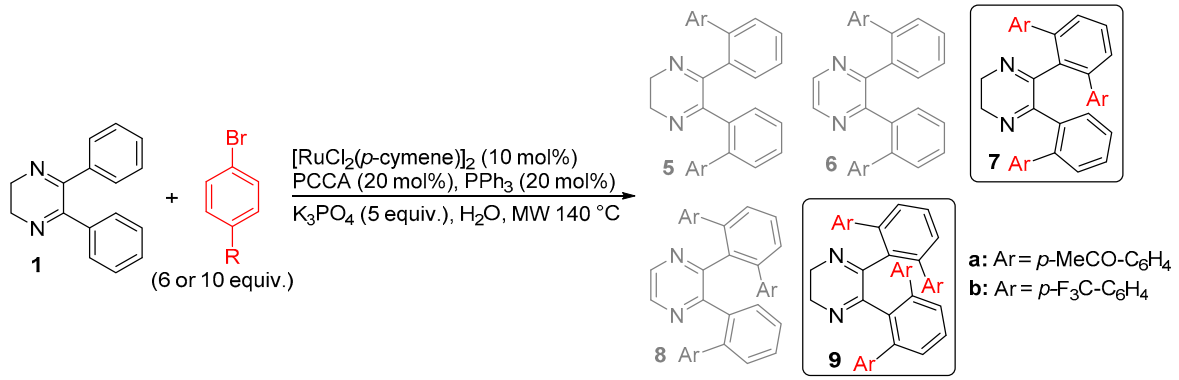
Entry	R (equiv.)	React. time (h)	Conv.[b] (%)	3/4/5/6/7[b](%)[c]
1	MeCO (2)	1	96	31/10/50/2/7
2[d]	MeCO (2)	1	77	86/4/10/0/0
3[d]	MeCO (2)	1.25	93	64/4/28/1/3
4	MeCO (2)	0.5	86	75(53)/3/22(7%)/0/0
5	MeCO (4)	1	100	0/5/73(58%)/6(3%)/16(10%)
6	MeCO (4)	0.5	100	20/4/65/1/10
7	CF_3 (4)	1	100	0/7(5%)/70(45%)/5/18(13%)

[a] Reaction conditions: **1** (0.25 mmol), ArBr (0.5 or 1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), 1-phenylcyclopentane-1-carboxylic acid (0.025 mmol), PPh_3 (0.025 mmol), K_3PO_4 (1.25 mmol), H_2O (1 mL), MW 140 °C, argon. [b] Conversion and ratio determined by NMR analysis without internal standard. [c] Yield of isolated product. [d] 120 °C instead of 140 °C.

Scheme 1. Mono- and diarylation of dihydropyrazine **1**.[a]

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

or 1-bromo-4-(trifluoromethyl)benzene at 140 °C under MW-irradiation for 1 h, and increased quantities of $[RuCl_2(p\text{-cymene})]_2$ (10 mol%), PCCA and PPh_3 (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.



Entry	R (equiv.)	React. time (h)	5/6/7/8/9[c](%)[d]
1	MeCO (6)	1	0/6/78(65%)/2/14(10%)
2	CF_3 (6)	1	22(9%)/14(8%)/60(40%)/4/0
3	MeCO (10)	1	0/6/67/5/22
4	MeCO (10)	2	0/7/55(40%)/8/30(19%)
5[e]	MeCO (10)	4	0/2/23(10%)/14(9%)/58(38%)
6[e]	MeCO (10)	8	0/2/20(10%)/16(10%)/61(40%)

[a] Reaction conditions: **1** (0.25 mmol), ArBr (1.5 or 2.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), PCCA (0.05 mmol), PPh_3 (0.05 mmol), K_3PO_4 (1.25 mmol), H_2O (1 mL), MW 140 °C, argon. [b] Quantitative conversion of **1** confirmed by NMR analysis. [c] Ratio determined by NMR analysis without internal standard. [d] Yield of isolated product. [e] Traces (1–3%) of aromatic product **10a** detected by NMR spectroscopy (**10a** is an aromatized product of **9a**).

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: $[RuCl_2(p\text{-cymene})]_2$ (10 mol%), PCCA and PPh_3 (20 mol%). Upon one-hour-heating of the reaction mixture of **1** and 10 equiv. of 4-bromoacetophenone under MW conditions at 140 °C, the triarylated dihydropyrazine product **7a** still dominated (Scheme 2, entry 3). It is evident from entries 3–5 in Scheme 2 that the relative amount of tetraarylated dihydropyrazine **9a** increased from 22% to 58% as the reaction time was extended from 1 to 4 h, but triarylated product **7a** was present throughout in a significant amount. Even when the reaction mixture was irradiated for 8 h, no further improvement in tetraarylation selectivity was observed. Not only that, it was difficult to achieve satisfactory selectivity; the in situ aromatization of arylated dihydropyrazine products additionally contributed to the complex reaction mixtures. We noticed that the prolonged MW irradiation slowly favored the aromatization of triarylated dihydropyrazine **7a** into the corresponding pyrazine **8a**; by extending the reaction time from 1 to 8 h the relative amount of **8a** increased from 5 to 16%. Thus, the best yield of tetraarylation product **9a** was 40% after chromatographic separation (Scheme 2, entry 6). The results under entries 3–6 in the table in Scheme 2 indicate that tetra-*ortho*-C–H arylation is more difficult to achieve, probably due to its higher energy barrier compared to those of the first to third cyclometallation-

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-aromatization into **8a** to take place to a larger extent. Further optimizations of the reaction conditions by varying base (K_2CO_3, Na_2CO_3) 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 ^{1}H NMR spectrum recorded in $CDCl_3$ 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 as 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 ^{1}H NMR spectrum in CD_3CN 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 –CH_2CH_2– signal (Figure 1d).

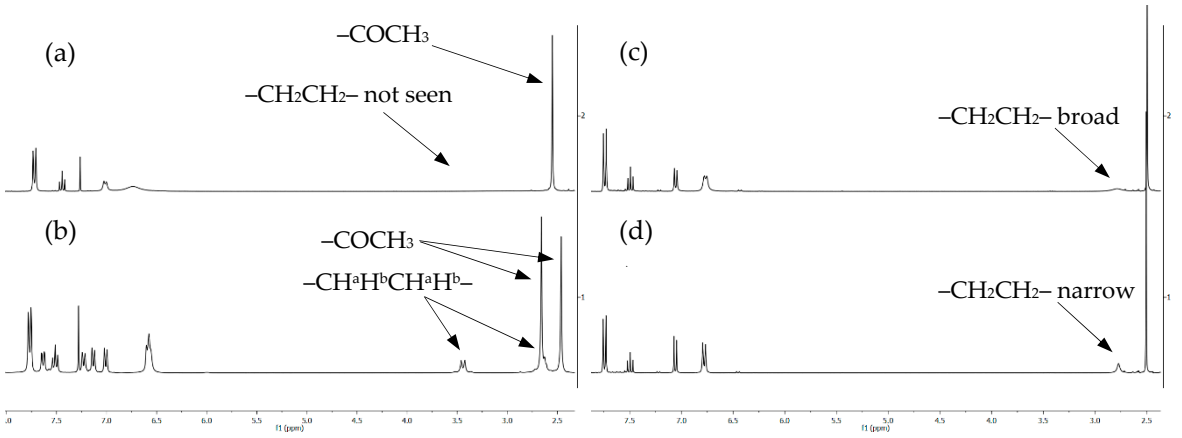


Figure 1. Variable temperature ^{1}H NMR spectra (300 MHz) of **9a**: **a**) in $CDCl_3$ at 302 K, **b**) in $CDCl_3$ at 230 K, **c**) in CD_3CN at 302 K, **d**) in CD_3CN at 320 K.

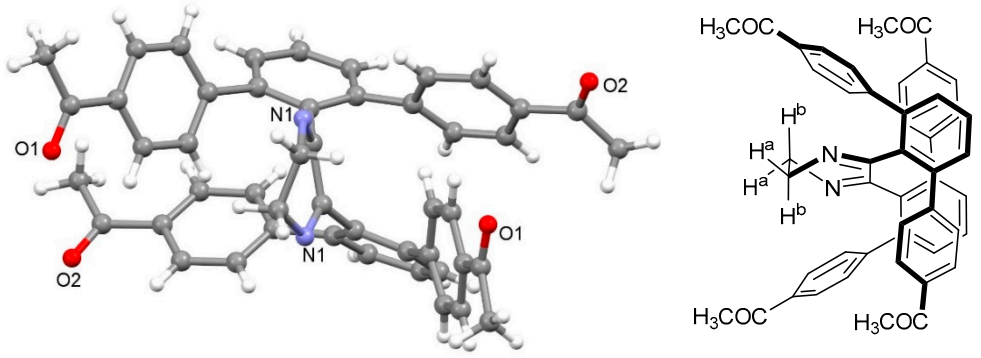
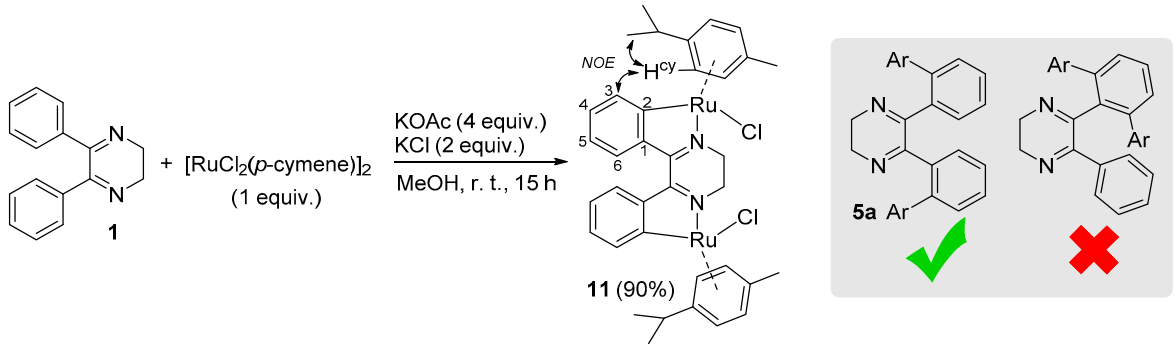


Figure 2. X-ray structure of **9a** and its possible conformation at low temperature.

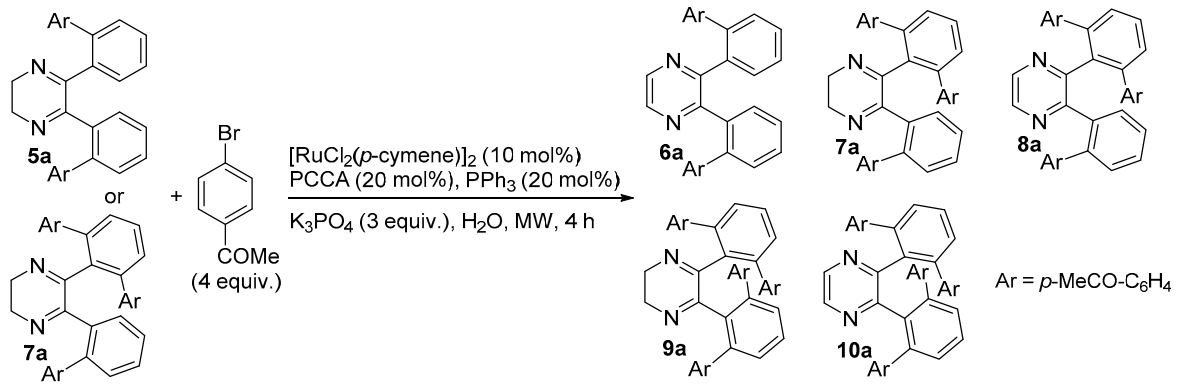
We were also able to isolate metallacycle **11** from the reaction of **1** with 1 equiv. of [Ru(*p*-cymene)Cl_2]$_2$ resulting from double cycloruthenation in MeOH at room temperature in 15 h, by using methodology established by Dixneuf for the synthesis of five-membered ruthenacycles from substrates 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 ^{1}H NMR spectrum ($CDCl_3$) the complex **11** shows only one set of proton resonances suggesting a highly symmetric structure. The cyclometallated phenyl H^6 and H^3 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 ^{1}H–^{1}H NOESY spectrum shows spatial proximity of H^3 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 ^{13}C NMR spectrum, the expected number of carbons corresponding to the symmetrical structure can be seen, and the metallated carbon C^2 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**.

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 [$RuCl_2$(*p*-cymene)]$_2$ (10 mol%), PCCA and PPh_3 (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

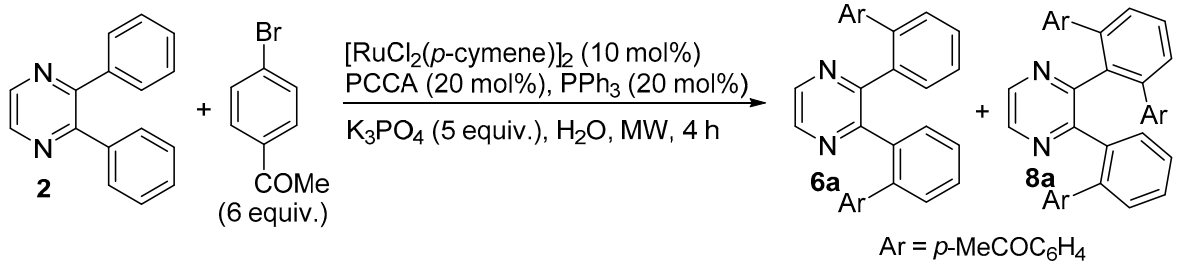
triarylated dihydropyrazine **7a** with 4 equiv. of 4-bromoacetophenone at 140 °C for 4 h delivered a 1:1 mixture of aromatic analog **8a** and tetraarylated dihydropyrazine **9a** but with lower 57% conversion. Raising the temperature to 200 °C allowed full conversion of **7a** into tetraarylated dihydropyrazine 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.



Entry	Starting	React. temperature (°C)	Conv.[b] (%)	6a/7a/8a/9a/10a[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

[a] Reaction conditions: **5a** or **7a** (0.125 mmol), 4-bromoacetophenone (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), PCCA (0.025 mmol), PPh_3 (0.025 mmol), K_3PO_4 (0.375 mmol), H_2O (1 mL), MW, argon. [b] Conversion and ratio of products determined by NMR analysis without internal standard.

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



Entry	React. time (h)	React. temperature (°C)	6a/8a[c](%)[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%)

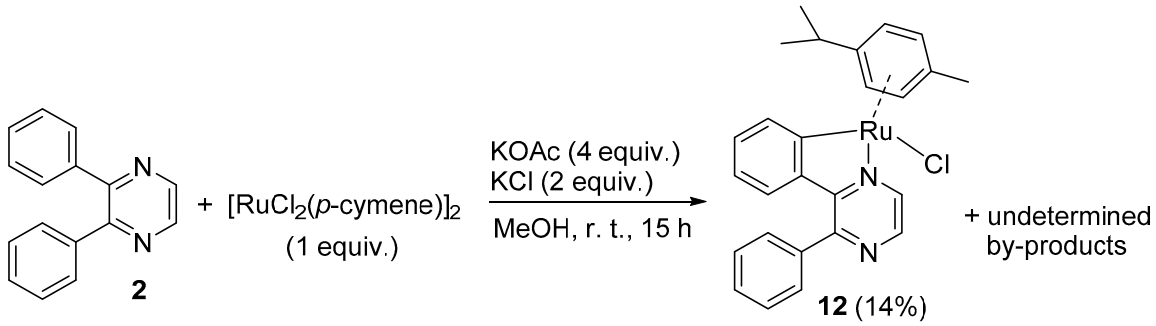
[a] Reaction conditions: **1** (0.25 mmol), 4-bromoacetophenone (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), PCCA (0.05 mmol), PPh_3 (0.05 mmol), K_3PO_4 (1.25 mmol), H_2O (1 mL), MW, argon. [b] Quantitative conversion of **2** confirmed by NMR analysis. [c] Ratio determined by NMR analysis without internal standard. [d] Yield of isolated product.

Scheme 5. Direct arylation of 2,3-diphenylpyrazine (**2**).[a,b.]

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 ([$RuCl_2$(*p*-cymene)]$_2$ (10 mol%), PCCA and PPh_3 (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-bromacetophenone 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.

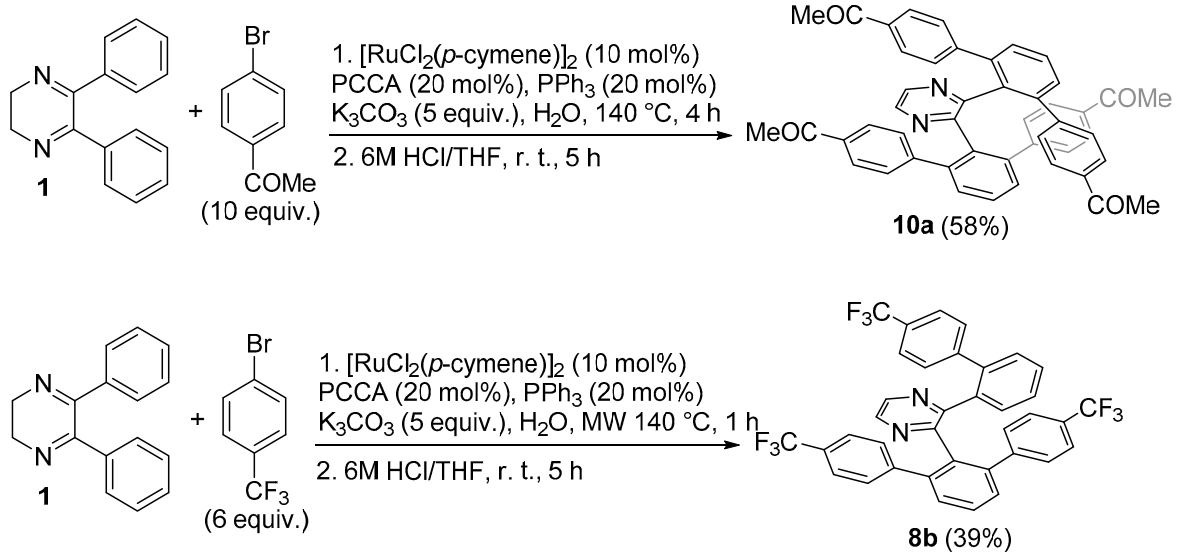
We tried to cyclometallate also pyrazine **2** using the same reaction conditions as for preparation of bis-ruthenacycle **11**. Reaction of **2** with with 1 equiv. of [(*p*-cymene)$RuCl_2$]$_2$ in MeOH in the presence of KCl at room temperature in 15 h gave a complex mixture of products (Scheme 6). 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)$RuCl_2$]$_2$ 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.

Lastly, we attempted to hydrolize the arylated 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 ([$RuCl_2$(*p*-cymene)]$_2$ (10 mol%), PCCA and PPh_3 (20 mol%), H_2O, 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).



Scheme 7. Preparation of highly arylated aromatic pyrazines by the sequential reaction.

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 N^1 in **5b** is by approximately 15° more inclined toward the carbon atom C^6 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.

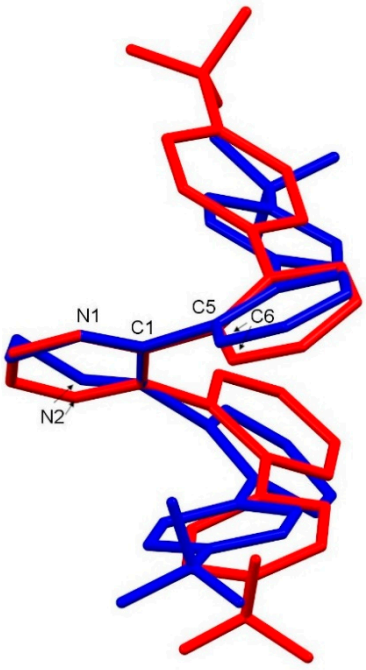


Figure 3. Superposition showing the difference in torsion angle N1–C1–C5–C6 **5b** (blue) and **6b** (red). Disorder on CF_3 groups is omitted for clarity.

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 Al_2O_3 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 PF_{254} containing gypsum (Kieselgel 60 PF_{254}, Merck Group, Darmstadt, Germany) or the mixture of gypsum, fluorescence indicator and Al_2O_3 (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 on 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 ^{1}H and ^{13}C nuclei. Variable temperature (230–320 K) ^{1}H 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), $[RuCl_2(p\text{-cymene})]_2$ (5–10 mol%), 1-phenylcyclopentane-1-carboxylic acid (10–20 mol%), PPh_3 (10–20 mol%), K_3PO_4 (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 H_2O (10 mL). The crude product was extracted with DCM (2 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was further purified by radial chromatography (SiO_2 or Al_2O_3) 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 $NaHCO_3$ (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was further purified by radial chromatography (SiO_2 or Al_2O_3) using mixtures of EtOAc and petroleum ether.

4. Conclusions

In summary, we have demonstrated that Ru(II)/carboxylate/PPh_3 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 ^{1}H and ^{13}C NMR spectra. CCDC 1991671–1991677contain 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.

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