Ruthenium(II)-Catalyzed C–H (Hetero)Arylation of Alkenylic 1, n -Diazines (n = 2, 3, and 4): Scope, Mechanism, and Application in Tandem Hydrogenations

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Rafael Gramage-Doria,[†]* Sylvain Achelle,[†] Christian Bruneau,[†] Françoise Robin-le Guen,[†] Vincent Dorcet,[†] and Thierry Roisnel[†]

[†]Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes) - UMR 6226, F-35000 Rennes, France.

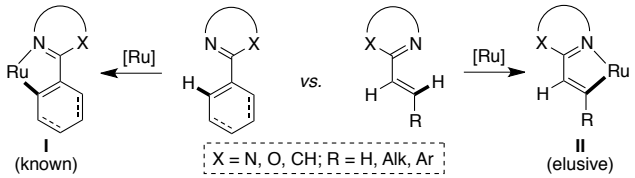
Supporting Information

ABSTRACT: A general ruthenium(II)-catalyzed methodology enabling the (hetero)arylation of alkenylic C-H bonds utilizing a series of synthetically appealing diazines as directing groups is presented. Despite the presence of additional nitrogen lone pairs remote from the C-H bond activation site, which could eventually poison the catalyst, the reaction times are short (3 hours), thus being suitable for selective double C-H bond arylation. Mixtures of *E*:*Z* isomeric products were observed in some cases, which were further hydrogenated in a tandem manner in the presence of the remaining ruthenium catalyst from the first step; representing an alternative approach to more difficult C(sp^3)-H bond functionalization. According to mechanistic studies, the unexpected *E*:*Z* product formation seems to occur by thermal C=C bond isomerization after the reductive elimination step. **KEYWORDS:** *diazines, C-H activation, cross-coupling, ruthenium, hydrogenation*

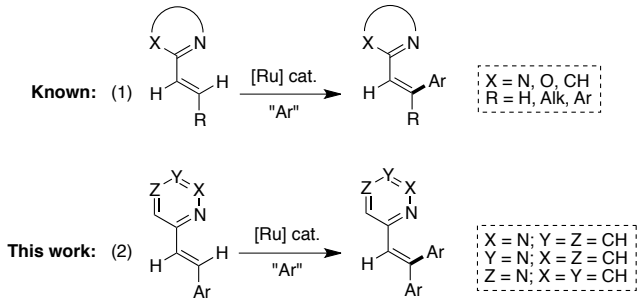
■ INTRODUCTION

Transition metal-catalyzed C-H bond functionalization has emerged in the last decades as a sustainable and efficient approach to convert a myriad of low-functionalized starting materials into high added value chemicals.[1] Consequently, the formation of new carbon-carbon bonds from C-H bonds is a powerful approach since it reduces the number of synthetic steps and costs devoted to the functionalization of the starting materials, and it reduces the amount of chemical waste as compared to classical cross-coupling reactions such as Suzuki, Heck, Kumada, Stille, Negishi, and others.[2] In particular, palladium,[3] rhodium[4] and iridium[5] are the metals of choice to perform such types of C-H bond functionalization due to their high intrinsic catalytic reactivity. However, expanding the catalytic performance to readily available and more abundant transition metals such as ruthenium[6] or cobalt[7] is highly attractive. For instance, the ruthenium(II)-catalyzed (hetero)arylation of C(sp^2)-H bonds belonging to 1,2-disubstituted alkene groups (Scheme 1, right) have been much less explored as compared to C(sp^2)-H bonds belonging to aromatic (or trisubstituted) alkene groups (Scheme 1, left).[6] Since the bond dissociation energies of such C(sp^2)-H bonds are rather similar (ΔG^o = 112.9 kcal/mol for phenyl *vs* ΔG^o = 110.7 kcal/mol for vinyl),[8] the lower number of studies associated to alkenylic C-H bonds compared to aromatic ones in ruthenium(II) catalysis might be attributed to the difficulty to accommodate the key metallacycle intermediate **II** *vs* **I** (Scheme 1).[9] Presumably, a higher degree of flexibility needs to be overcome for the formation of **II** as compared to the formation of the more rigid **I** (Scheme 1). To circumvent this issue, very strong directing groups (i.e. pyridine, oxazoline, imidazole) are traditionally installed at close proximity of the alkene C-H bond expected to be cross-coupled (Scheme 2, eq 1).[10] Herein we report on ruthenium(II) catalysis enabling the mono- and bis-(hetero)arylation of alkenylic C(sp^2)-H bonds in the presence of directing groups bearing also remote nitrogen lone pairs such as 4-pyrimidine, 2-pyrazine and 3-pyridazine (Scheme 2, eq 2). It is disclosed that (i) the presence of additional nitrogen lone pairs in the directing group remote from the C-H bond activation site does not poison the activity of the ruthenium catalyst in the (hetero)arylation of alkenylic C-H bonds and (ii) the ruthenium-catalyzed C-H bond cross-coupling reactions are compatible with subsequent C=C double bond hydrogenation leaving the heteroaromatic ring unreacted.

Scheme 1. Differences Associated to Key Ruthenacycle Intermediates in C(sp^2)-H Bond Activation



Scheme 2. Ruthenium(II)-Catalyzed C(sp^2)-H Arylation of 1,2-Disubstituted Alkenes



These types of diazines are relevant motifs in fields as diverse as biology[11] and materials science.[12] For example, trisubstituted alkene-containing diazine **III** displays antiuterotropic and antiestrogenic properties,[13a] **IV** displays trichomonacidal and antiinflammatory properties,[13b] and **V** (with the alkene double bond hydrogenated or not) is an inhibitor of the phosphodiesterase 4 (Figure 1).[13c,d] Their preparation, however, relies on long and tedious multi-step synthesis generating large amounts of chemical waste.[13] For this reason, providing new and more efficient synthetic shortcuts is highly desired.[14] Furthermore, diazine-containing molecules can be hydrogenated to relevant cyclic amines.[15]

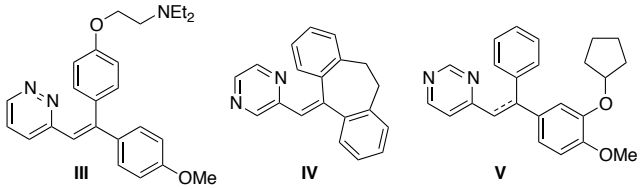
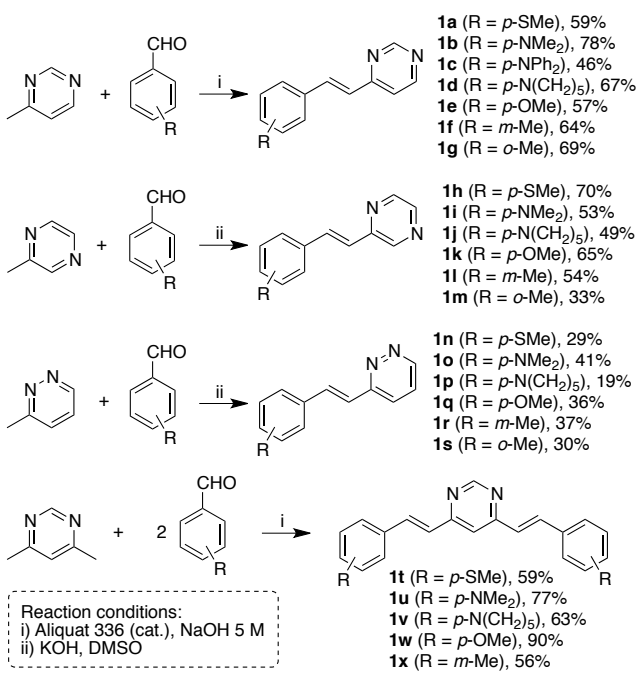


Figure 1. Selected examples of pharmaceutically-relevant alkene- and alkane-containing diazines.

■ RESULTS AND DISCUSSION

Synthesis of the Starting Materials. The 1,2-*trans*-disubstituted alkene moieties bearing 4-pyrimidine (**1a**-**1g**), 2-pyrazine (**1h**-**1m**) and 3-pyridazine (**1n**-**1s**) as directing groups were prepared by base-mediated condensation of the functionalized benzaldehydes with the corresponding methyldiazines, respectively (Scheme 3). A similar procedure applied to 4,6-dimethylpyrimidine and using 2 equivalents of the functionalized benzaldehydes enabled the synthesis of the corresponding 4,6-bis((*E*)-styryl)pyrimidines **1t**-**1x**. Some of these compounds have been reported elsewhere[16] and the new compounds have been fully characterized (see SI).

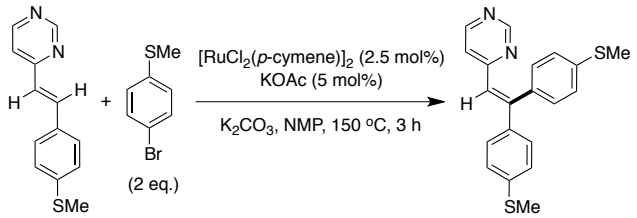
Scheme 3. Synthesis of 1



Searching for the Optimal Reaction Conditions. The best reaction conditions enabling the arylation of **1a** leading to product **2a** in the presence of two equivalents of 4-bromothioanisole were searched (Table 1). Full conversion of **1a** was observed according to TLC and GC-MS analysis after 3 hours by using 2.5 mol% of $[RuCl_2(p\text{-cymene})]_2$ as precatalyst, KOAc (5 mol%) and K_2CO_3 (3 equiv) in *N*-methyl-2-pyrrolidone (NMP) under argon atmosphere at 150 °C. It is noteworthy that similar reaction conditions were suitable for the arylation of arylpyridine and benzoylpyridines.[17] The ^{1}H NMR spectrum of the crude reaction mixture indicated the exclusive formation of a single product (**2a**) that was recovered by column chromatography with an isolated yield of 94% (Table 1, entry 1). The ^{1}H NMR spectrum of product **2a** indicated the disappearance of the doublet centered at δ = 7.83 ppm corresponding to the olefinic C-H bond expected to react, and the appearance of the non-reacted alkenylic C-H bond as a singlet at δ = 6.99 ppm. The molecular structure of **2a** was further determined by a single-crystal X-ray diffraction study (see SI).[18] Further experiments indicated the need of all reagents for the success of the reaction (Table 1, entries 2-4). The use of stoichiometric amounts of KOAc provided similar results (Table 1, entry 5) as the standard reaction conditions, indicating that catalytic amounts of KOAc were enough to reach such a high reactivity; likely due to the in situ formation of catalytically active $[Ru(OAc)_2(p\text{-cymene})]$ species as it was evidenced when employing $[Ru(OAc)_2(p\text{-cymene})]$ as pre-catalyst (Table 1, entry 6).[19] Other potassium carboxylate salts such as pivalate and mesylate were found as efficient as acetate (Table 1, entries 7-8). PPh_3 as additive did not change the outcome of the reaction, however a yield of only 46% of **2a** was obtained because the chromatographic separation became troublesome (Table 1,

entry 9). The presence of air and the decrease of the reaction temperature were detrimental to the reaction (Table 1, entries 10-12).

Table 1. Optimization of the Reaction Conditions[a]



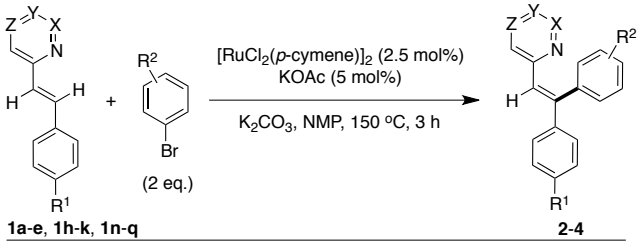
1a **2a** (X-ray)

Entry	Deviation from standard conditions	**2a** (%)[b]
1	none	>99 (94)[c]
2	without $[RuCl_2(p\text{-cymene})]_2$	0
3	without KOAc	35
4	without K_2CO_3	0
5	100 mol% KOAc	>99
6	with $[Ru(OAc)_2(p\text{-cymene})]$[d]	>99
7	KOPiv instead of KOAc	>99
8	$MesCO_2K$ instead of KOAc	>99
9	with 10 mol% PPh_3	>99 (46)[c]
10	Air instead of Argon	0
11	100 °C instead of 150 °C	traces
12	120 °C instead of 150 °C	traces

[a]**1a** (0.25 mmol), 4-bromothioanisole (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), KOAc (5 mol%), K_2CO_3 (0.75 mmol), NMP (1 mL, 0.25 M) at 150 °C for 3 h under Argon atmosphere. [b]Yield estimated by GC-MS and ^1H NMR spectroscopy. [c]Isolated yields. [d]5 mol% of $[Ru(OAc)_2(p\text{-cymene})]$ was used instead of 2.5 mol% of $[RuCl_2(p\text{-cymene})]_2$ and 5 mol% of KOAc.

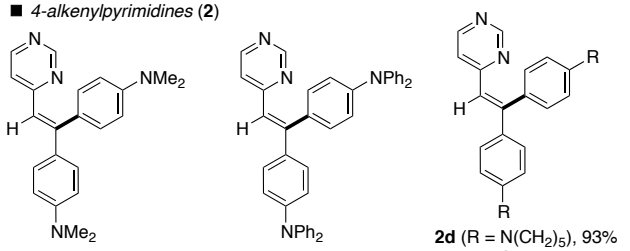
Substrate Scope. The methodology was applied to other 4-alkenylpyrimidines leading to the corresponding arylated products **2** in high yields (Table 2). The bis-aryl symmetrical compounds containing *para*-substituted linear aliphatic amines such as NMe_2 (**2b**), aromatic amines such as NPh_2 (**2c**) and cyclic aliphatic amines such as $N(CH_2)_5$ (**2d**) were obtained in 96%, 89% and 93% yield, respectively. The methodology was found to be compatible with *para*-OMe groups providing compound **2e** in 96% isolated yield. 2-Alkenylpyrazines **3** were also obtained under the standard reaction conditions (Table 2). The bis-aryl symmetrical *para*-substituted compounds **3a**-**3d** were obtained in 97% (SMe), 94% (NMe_2), 85% ($N(CH_2)_5$) and 93% (OMe) isolated yields, respectively. When bromobenzene was used as coupling partner, **3e** was obtained in 94% yield as a single isomer. Other non-symmetrical di-aryl products were also formed but unexpectedly as mixtures of *E*:*Z* isomers at some extents (Table 2). As such, *para*-substituted *tert*-butyl derivative **3f** was obtained in 97% yield with a 86:14 isomeric ratio (non-isomerized:isomerized product ratio). Biphenyl **3g** and styrene **3h** derivatives were obtained in 96% and 95% yield, respectively, both with a 96:4 isomeric ratio. Esters and ketones were tolerated under the studied reaction conditions as exemplified in the synthesis of **3i** and **3j** in 95% and 96% yield, respectively. In these cases the isomeric ratio was *ca.* 75:25. The *para*-CN-containing product **3k** was obtained in 91% yield and 85:15 isomeric

Table 2. Scope of the Alkenylic C-H Bond Arylation[a,b]



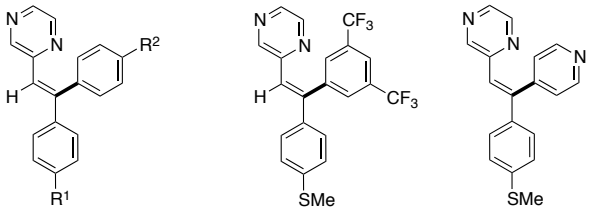
1a-e, **1h-k**, **1n-q** **2-4**

■ *4-alkenylpyrimidines* (**2**)

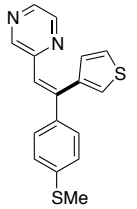


2b, 96% **2c**, 89% **2d** (R = $N(CH_2)_5$), 93% **2e** (R = OMe), 95%

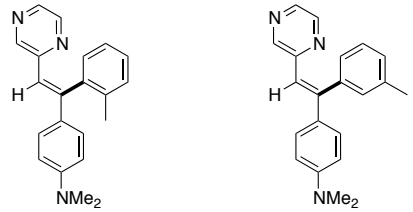
■ *2-alkenylpyrazines* (**3**)



3a (R^1 = R^2 = SMe), 97% **3m**, 77% (75:25) **3n**, 68% (88:12)
3b (R^1 = R^2 = NMe_2), 94% (X-ray)
3c (R^1 = R^2 = $N(CH_2)_5$), 85%
3d (R^1 = R^2 = OMe), 93%
3e (R^1 = NMe_2, R^2 = H), 94% (X-ray)
3f (R^1 = NMe_2, R^2 = *t*Bu), 97% (86:14)
3g (R^1 = SMe, R^2 = Ph), 96% (96:4)
3h (R^1 = SMe, R^2 = $CH{=}CH_2$), 95% (96:4)
3i (R^1 = NMe_2, R^2 = CO_2Me), 95% (76:24)
3j (R^1 = NMe_2, R^2 = C(O)Me), 96% (75:25)
3k (R^1 = NMe_2, R^2 = CN), 91% (85:15)
3l (R^1 = NMe_2, R^2 = F), 85% (85:15)

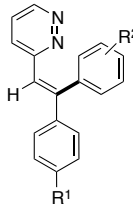


3o, 58% (95:5)



3p, 92% (93:7) **3q**, 95% (93:7)

■ *3-alkenylpyridazines* (**4**)



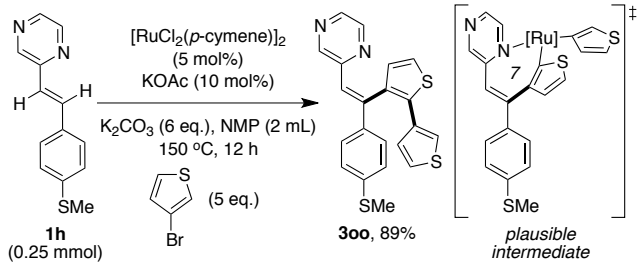
4a (R^1 = SMe, R^2 = *p*-SMe), 94%
4b (R^1 = NMe_2, R^2 = *p*-NMe_2), 91% (X-ray)
4c (R^1 =$N(CH_2)_5$, R^2 = *p*-$N(CH_2)_5$), 88%
4d (R^1 = OMe, R^2 = *p*-OMe), 95%
4e (R^1 = NMe_2, R^2 = H), 94% (93:7) (X-ray)
4f (R^1 = SMe, R^2 = *m*-Me), 86% (57:43)
4g (R^1 = SMe, R^2 = *p*-Me), 93% (68:32)
4h (R^1 = $N(CH_2)_5$, R^2 = *p*-OMe), 71% (58:42)
4i (R^1 = NMe_2, R^2 = 6-methoxynaphthalen-2-yl), 84% (56:44)

[a]As Table 1, entry 1. [b]Isolated yields. Isomeric ratio (non-isomerized:isomerized product ratio) determined by ^1H NMR spectroscopy analysis are displayed in brackets.

ratio. The same ratio was observed with *para*-F-containing **3l** (85% yield). Substituents with different Hammet sigma constants (i.e. σ_p = +0.66 for CN and σ_p = +0.06 for F) provided the same isomeric ratio (85:15), thus making difficult to correlate the isomeric ratio with the electronic properties of the different substituents. Trifluoromethyl derivative **3m** was prepared in 77% yield and an isomeric ratio of 75:25. Heteroaromatic coupling partners were also successfully cross-coupled *via* the ruthenium(II)-catalyzed alkenylic C-H bond functionalization (Table 2). For instance, 4-pyridine substituted and 3-thiophene substituted pyrazines **3n** and **3o** were isolated in 68% and 58% yield, respectively, with an isomeric ratio of 88:12 and 95:5, respectively. *Ortho*- and *meta*-methyl substituted derivatives **3p** and **3q** were obtained in 92% and 95% yield, respectively, with a 93:7 isomeric ratio.

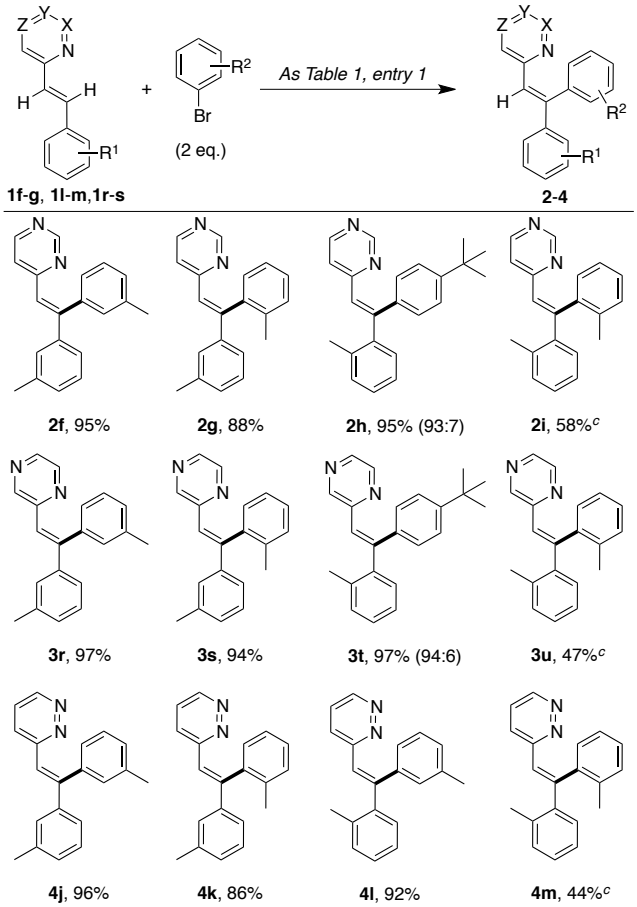
During the synthesis of **3o** small amounts of the bis-thiophene derivative **3oo** were identified by GC-MS analysis. Furthermore, performing the ruthenium(II)-catalyzed reaction with **1h** as substrate in the presence of 5 equivalents of 3-bromothiophene, 6 equivalents of K_2CO_3, 10 mol% of KOAc and 5 mol% of $[RuCl_2(p\text{-cymene})]_2$ as precatalyst during 12 h afforded this bis-thiophene **3oo** in 89% isolated yield (Scheme 4).[20] The arylation at the C2 position of the firstly introduced thiophene moiety was inferred by multidimensional NMR spectroscopy analysis (see SI). It was also found that **3o** did not afford **3oo** without the presence of the ruthenium catalyst. Further work will have to be performed to verify whether the reaction proceeded *via* an unprecedented seven-membered ruthenacycle intermediate (Scheme 4) or if other mechanisms (electrophilic aromatic substitution, concerted metallation deprotonation or Heck-type) were also operating at some extent.[19,21]

Scheme 4. In situ Alkenylic C-H Bond Functionalization and C2 Hetero(Arylation) on Thiophene



Pyridazines (**4**) featuring the other diazine directing group of the series, were found to behave in a similar manner (Table 2) as pyrimidines (**2**) and pyrazines (**3**). For instance, the symmetrical products containing *p*-SMe (**4a**), *p*-NMe_2 (**4b**), *p*-$N(CH_2)_5$ (**4c**) and *p*-OMe (**4d**) were obtained in 88-95% isolated yields. The ruthenium(II)-catalyzed alkenylic C-H bond arylation was also compatible (*ca.* 90% yield) with phenyl derivatives (**4e**) and *meta*- and *para*-tolyl derivatives **4f** and **4g**, although with variable isomeric ratios. **4h** was obtained in 71% yield and an isomeric ratio of 58:42. Methoxynaphthalene-containing derivative **4i** was obtained in 84% yield (56:44 isomeric ratio). Additionally, the molecular structures of pyrazine derivatives **3b** and **3e**; and pyridazines **4b** and **4e** were determined by single crystal X-ray diffraction studies (see SI).[18] Unfortunately, the starting materials were fully recovered when using 4-bromonitrobenzene, 4-bromobenzaldehyde and bromoferrocene as coupling partners.[17b] The catalytic system was found also unsuitable for methylation and benzylation with methyl iodide and benzylbromide as coupling partners, respectively. To further evaluate the potential of the ruthenium(II)-catalyzed arylation, the catalyst loading was decreased for the formation of product **2e**. With 5 times less ruthenium complex (0.5 mol% of $[RuCl_2(p\text{-cymene})]_2$) full conversion was retained (TON = 100 per Ru-center) and with 0.01 mol% of $[RuCl_2(p\text{-cymene})]_2$ (which corresponds to a substrate:catalyst ratio of 5000:1) a TON of 500 was observed but with a low 10% conversion.

Table 3. Scope with Bulky Coupling Partners[a,b]



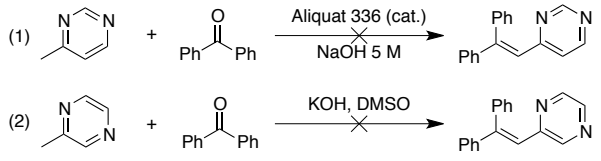
[a]As Table 1, entry 1. [b]Isolated yields. [c]After 18 h. Isomeric ratio (non-isomerized:isomerized product ratio) determined by ^{1}H NMR spectroscopy analysis are displayed in brackets.

The ruthenium(II)-catalyzed C-H bond arylation was applied for more challenging both bulky substrates and bulky aryl bromides (Table 3). The three types of diazines bearing methyl substituents at *meta* position reacted in an efficient manner (3 h) in the presence of the in situ generat-

ed ruthenium catalyst with 3-bromotoluene and 2-bromotoluene, respectively, leading to **2f**, **2g**, **3r**, **3s**, **4j** and **4k** in 95%, 88%, 97%, 94%, 96% and 86% yield as single isomers, respectively. Bulky diazines containing a methyl substituent at *ortho* position reacted under standard reaction conditions with less bulky 1-bromo-4-*tert*-butylbenzene leading to **2h** and **3t** in 95% and 97% yield, respectively, containing <8% of the isomerized product. A pyridazine derivative containing a methyl substituent in *ortho* position of the phenyl ring led to **4l** after reaction with 3-bromotoluene in 92% isolated yield as a single isomer. On the other hand, the three types of diazines bearing methyl substituents at *ortho* position reacted with bulky 2-bromotoluene leading to **2i**, **3u**, and **4m** in moderate yields of 58%, 47% and 44%, respectively, after long reaction times of 18 hours. Although **1** was fully converted under these reaction conditions, other unidentified byproducts were formed at the end of the reactions during the synthesis of **2i**, **3u** and **4m**, highlighting that the catalysis is sensitive to the simultaneous bulkiness of both coupling partners. In all these examples of bulky coupling partners, nearly no isomerization was observed in the resulting products.

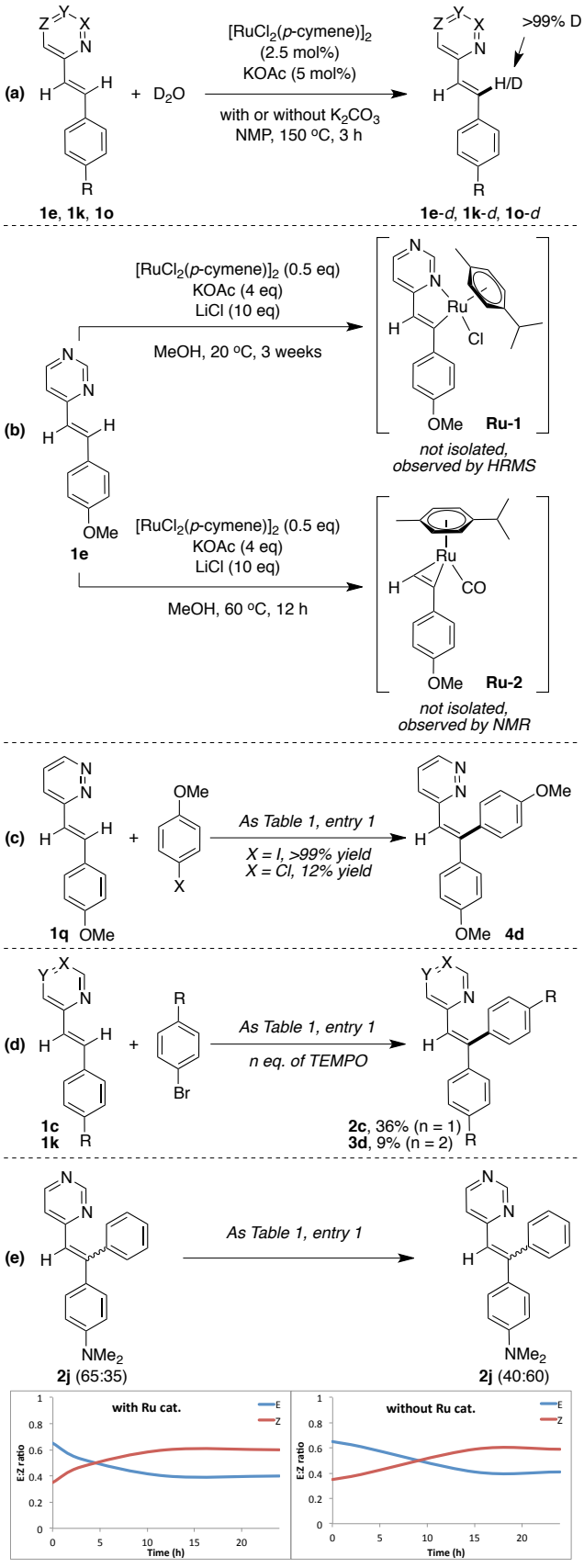
It is relevant to mention that 4-methylpyrimidine (Scheme 5, eq 1) and 2-methylpyrazine (Scheme 5, eq 2), respectively, did not react with benzophenone applying the classical reactions conditions reported in Scheme 3. Consequently, the presented ruthenium(II)-catalyzed methodology represents an efficient entry to access trisubstituted alkenes containing this type of diazines as heteroyclic motifs. The step- and atom-economy in this method is obvious as compared to classical reactions that also lead to trisubstituted alkene motifs at the expenses of large amounts of chemical waste such as lithium salts (Peterson olefination),[22] titanium and zinc salts (McMurry reaction)[23] or phosphonium salts (Wittig reaction).[24]

Scheme 5. Attempts to Synthesize Molecules Similar to 2 and 3 *via* Classical Procedures



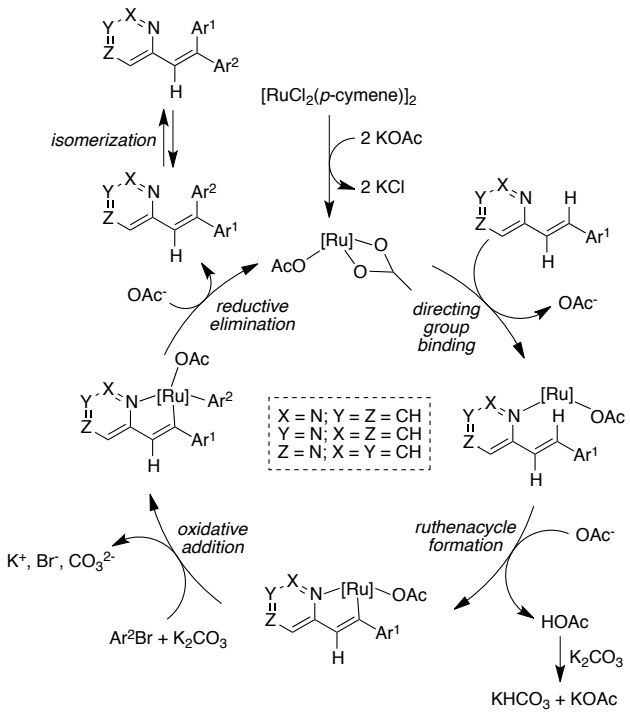
Mechanistic studies. To gain a better understanding of the reaction mechanism operating under the studied reaction conditions, deuteration experiments were performed using argon-bubbled NMP:D_2O (*v*/*v* 9:1) as a solvent mixture with compounds bearing the three different diazine directing groups (Figure 2a). In all cases, >99% deuteration occurred in the alkenylic C-H bond that is functionalized in the catalytic experiments (Figure 2a). The deuteration was fast (3 h) regardless of the presence of base (K_2CO_3). This observation is in line with a reversible 5-membered ruthenacycle formation that cleaves the C-H bond.[25] The isolation of the postulated ruthenacycle **Ru-1** was also attempted starting from substrate **1e** (Figure 2b). Applying standard reaction conditions for the synthesis of ruthenacycles with aromatic C(sp^2)-H bonds (KOAc, LiCl, MeOH, 20 ^oC, 24-72 h)[9] failed leading to mixture of species containing free substrate, substrate-coordinated ruthenium species and ruthenacycle species (see SI). However, when leaving the reaction mixture for a very long time (three weeks), and besides formation of variable amounts of insoluble species, a ruthenium complex **Ru-1** was formed. The molecular structure of **Ru-1**, which could not be isolated due to its lack of stability, was inferred from HRMS analysis whose spectrum displayed strong peaks having exactly the isotopic profile expected for **Ru-1** (see SI). Attempts to perform the synthesis of **Ru-1** by increasing the temperature to 60 ^oC for 12 h led to decomposition of the starting material and recovery of the unexpected ruthenium complex **Ru-2** (Figure 2b). The molecular structure of **Ru-2** was fully characterized by multidimensional NMR analysis, including DOSY and molecular modeling (see SI).[26] So far, we cannot conclude whether carbon monoxide in **Ru-2** originated from dehydrogenation of methanol or from decomposition of acetate anions. We also detected formation of free *p*-cymene when performing attempts to identify ruthenacycle intermediates based on **1** at higher temperatures (see SI). In addition, the catalysis was also evaluated in the formation of **4d** starting from diazine **1q** and other aryl halides (Figure 2c). The catalytic reaction was found equally efficient with 4-iodoanisole, whereas 4-chloroanisole provided the expected product in a low yield of 12% (Figure 2c). Such findings might indicate that the rate-limiting step could be the oxidative addition of the aryl halide on ruthenium(II) species going to ruthenium (IV) species. Performing the catalytic reaction in the presence of a radical scavenger, namely 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), provided the expected products in low yields depending on the equivalents of TEMPO used (Figure 2d), which makes difficult to completely rule out a SET-type (SET = single electron transfer) aryl-bromide cleavage process before the reductive elimination step.[10d,27] We also noted that the outcome of the catalytic reaction was unaffected by the presence of mercury,[28] thus suggesting that the catalytic system operated under a homogeneous regime (see SI). The fact that mixtures of isomerized products were obtained was also investigated. We noticed that substrates **1** did not undergo isomerization under the reaction conditions and that the *trans*-configuration was retained at 150 ^oC over at least 24 h. The isomerization compound **2j** was followed on time with and without the presence of the ruthenium catalyst under the standard reaction conditions (Figure 2e). The isomerization took place regardless of the presence of the ruthenium catalyst, although in the presence of the ruthenium catalyst the thermodynamic equilibrium was reached faster (*ca.* 12 h) than in the absence of the ruthenium catalyst (*ca.* 15 h). Using toluene as solvent and potassium mesylate as additive provided similar results highlighting that the nature of the solvent or the potassium salt had little impact on the isomerization process. Consequently, the product isomerization is likely to be caused by thermal flip of the sterically-encumbered C=C double bond within the final product.[29]

Figure 2. Mechanistic Investigations



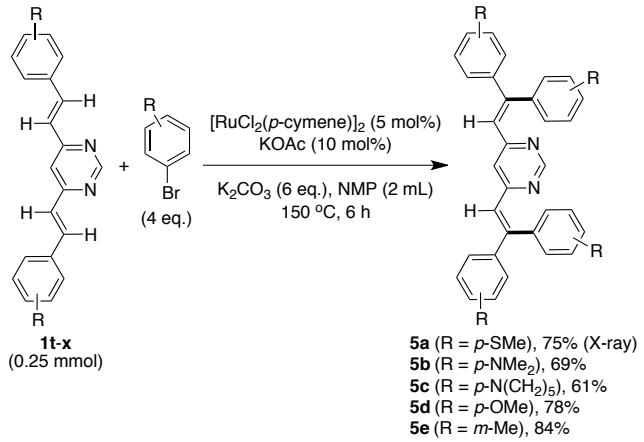
Considering the above-stated findings and previous reports[10,19,25,27] a mechanism is proposed in Scheme 6, which involves first, formation of ruthenium-carboxylate species as the active catalyst that binds to the substrate *via* *N*-coordination. Carboxylate and carbonate anions might facilitate deprotonation and reversible ruthenacycle formation. Oxidative addition on the aryl halide, probably *via* SET, followed by reductive elimination leads to the product that isomerized until reaching the thermodynamic equilibria.

Scheme 6. Postulated Mechanism



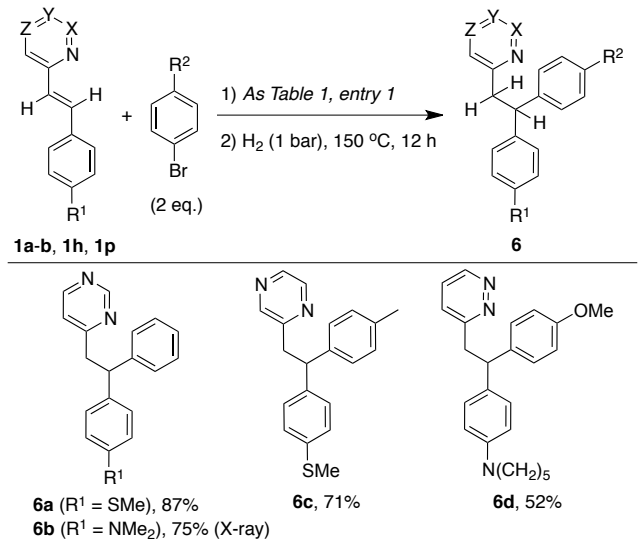
Extension and Application of the Methodology. The efficiency of the catalytic system was further evaluated for pyrimidines appended with two alkene groups, namely 4,6-dialkenylpyrimidines **1t-x** (Scheme 7). In this case, the ruthenium catalyst loading and the reaction time were doubled as compared to the standard reaction conditions; and the concentration was reduced by an order of two to ensure a proper solubility of the reagents into the reaction mixture. Under these reaction conditions, bis-arylation proceeded selectively leading to **5a-5e** in good yields (61 to 84% isolated yields). The reaction was found to be compatible with thioethers (**5a**), linear aliphatic amines (**5b**), cyclic aliphatic amines (**5c**), ethers (**5d**) and alkyl groups, including substituents at *meta* position (**5e**). The molecular structure of **5a** was also confirmed by X-ray crystallographic analysis (see SI).[18] Unfortunately, when using aryl bromides that would lead to non-symmetrical products, mixtures of all possible isomers were obtained.

Scheme 7. Ruthenium(II)-Catalyzed Double Arylation of Alkenylic C(sp^2)-H Bonds



Nevertheless, advantage was taken from the unexpected mixture of isomeric products in order to obtain a sole final product by performing a tandem selective alkene hydrogenation with molecular hydrogen in the presence of the remaining ruthenium species as catalyst (Table 4).[17b] In this way, 4-alkylpyrimidines **6a** and **6b** were synthesized in 87% and 75% yields, respectively. The racemic mixture of the hydrogenated products was further confirmed by an X-ray diffraction study on **6b** that showed the presence of both enantiomers (see SI).[18] 2-Alkylpyrazine **6c** and 3-alkylpyridazine **6d** were obtained in 71% and 52% yields, respectively. The three diazine directing groups were found to be compatible with the reaction conditions employed in the hydrogenation step and different functional groups (Ph, Me, SMe, NMe_2, OMe, $N(CH_2)_5$) were tolerated. Replacing NMP by toluene as solvent did not change the outcome of the C-H bond functionalization step, however it poisoned the hydrogenation step, indicating that polar solvents are more suitable for this type of tandem reactions.[17b]

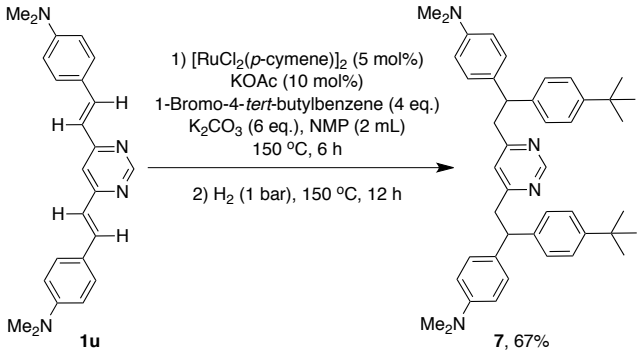
Table 4. Tandem C-H Bond Arylation/Hydrogenation[a,b]



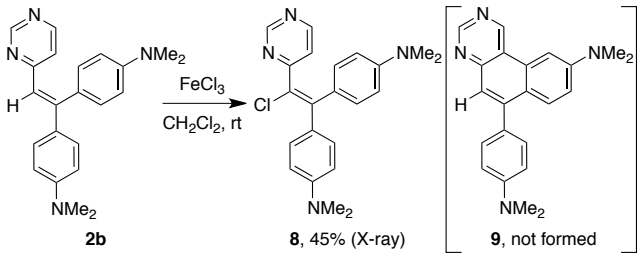
[a]First step as Table 1, entry 1 and second step by introducing a balloon filled with molecular hydrogen. [b]Isolated yields.

We further extended such approach for the tandem double C-H bond arylation and double hydrogenation as exemplified in the synthesis of **7** in 67% yield (Scheme 8). Such approach overcomes the issue of obtaining mixture of *E*:*Z* isomers during the C-H bond functionalization and it actually constitutes an alternative pathway to directly performing a more difficult ruthenium-catalyzed C(sp^3)-H functionalization.[30] Additionally, attempting an intramolecular oxidative C-C coupling reaction from **2b** in the presence of $FeCl_3$ (3.5 equiv) further evidenced the unique reactivity of such compounds (Scheme 9).[31] The expected product **9** was not formed and the product resulting from a Friedel-Crafts transformation was observed (**8**). The molecular structure of **8** was further confirmed by X-ray crystallographic analysis (see SI).[18] This observation indicates that the products resulting from the catalytic experiments have different reactivity when compared to all-carbon polyaromatic compounds.[32] The chloro-containing compound **8** might be used for the further design of new aromatic or conjugated species containing unique diazine moieties.

Scheme 8. Tandem Double Alkenylic C-H Bond Arylation and Hydrogenation



Scheme 9. Friedel-Crafts Reaction under Oxidative C-C Coupling Reaction Conditions



■ CONCLUSION

In summary, we have developed a ruthenium(II)-catalyzed methodology enabling the (hetero)arylation of 1,2-disubstituted alkenylic C(sp^2)-H bonds with synthetically useful diazine directing groups such as pyrimidines, pyrazines and pyridazines. Despite the presence of additional nitrogen lone pairs remote from the C-H bond activation site, the catalytic reactions were fast and efficient affording the desired products in high yields. The presented ruthenium-catalyzed protocol represents a new pathway to access trisubstituted heteroaromatic-containing alkenes, otherwise impossible (or very difficult) to obtain by traditional synthetic routes. Mechanistic investigations of the ruthenium catalysis indicated that the key ruthenacycle intermediate of

type **II** (Scheme 1 and Figure 2b) is kinetically difficult to trap, which in turn was probably responsible for the high reactivity thereby observed. Such observation strongly contrasts with the ease of the formation of ruthenacycles of type **I** (Scheme 1) based on trisubstituted olefinic C-H bonds.[9] The mixture of isomeric products observed in some catalytic experiments is a consequence of the high temperature used. The ruthenium(II)-based catalytic system was found to be applicable for double arylation and for the tandem C-H bond arylations/hydrogenations using the same ruthenium complex for both transformations. This route constitutes a masked approach for the functionalization of C(sp^3)-H bonds and it highlights the suitability of ruthenium species as catalysts for tandem reactions including C-H bond functionalizations.[10b,17b] The resulting products obtained in the catalytic experiments were found to behave differently from what would be expected in intramolecular oxidative C-C coupling reactions providing the Friedel-Crafts-like product.

■ EXPERIMENTAL SECTION

General Methods. All reagents were obtained from commercial sources and used as supplied. All reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Catalytic experiments were performed in Schlenk-type flasks under argon atmosphere unless otherwise noted. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin-layer chromatography (TLC) was carried out on 0.25 mm Merck silica gel (60-F254). Flash column chromatography was performed using silica gel Silica 60 M, 0.04-0.063 mm. *N*-methyl-2-pyrrolidone (NMP) was distilled under reduced pressure and stored under molecular sieves and argon atmosphere. Technical grade petroleum ether (40-60) and ethyl acetate containing 1% of triethylamine were used for column chromatography. $CDCl_3$ was stored under nitrogen over molecular sieves. NMR spectra were recorded on an AVANCE III 400 spectrometer and a Bruker AC-300 spectrometer. ^{1}H NMR spectra were referenced to residual protiated solvent (δ = 7.26 ppm for $CDCl_3$ and δ = 2.05 ppm for acetone-d_6) and ^{13}C chemical shifts are reported relative to deuterated solvents (δ = 77.0 ppm for $CDCl_3$ and δ = 29.8 ppm for acetone-d_6) [Note: acetone-d_6 contains traces of water at *ca.* 3 ppm]. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br. for broad. HRMS were recorded on a Waters Q-Tof 2 mass spectrometer at the corresponding facilities of the CRMPO, Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1.

Synthesis and characterization of substrates (1). *(i): General Procedure for the Synthesis of 4-((E)-styryl)pyrimidines (**1a-1g**).* A stirred mixture of the corresponding 4-methylpyrimidine derivative (1 mmol) and the corresponding aldehyde (1 mmol) in aqueous sodium hydroxide (5 M, 15 mL) containing Aliquat 336 (0.1 mmol) was heated under reflux for 2 h. The mixture was allowed to cool down and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was dried with $MgSO_4$ and the solvents evaporated. The crude product was purified by silica gel column chromatography with mixtures of petroleum ether and ethyl acetate as the eluent. Substrates **1a-1d**[16a] and **1e**[16b,16c] have been reported and characterized elsewhere.

*(E)-4-(3-Methylstyryl)pyrimidine (**1f**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 70:30, *v*/*v*) as a pale yellow oil that crystallize slowly (126 mg, 64% yield). Mp 61-62°C. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 8.62 (d, 1 H, J = 5.4 Hz), 7.83 (d, 1 H, J = 15.9 Hz), 7.38-7.36 (m, 2 H), 7.28-7.23 (m, 2 H), 7.16-7.13 (m, 1 H), 7.00 (d, 1 H, J = 15.9 Hz), 2.35 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (JMOD, 75 MHz, $CDCl_3$): δ = 162.3, 158.8, 157.3, 138.5, 137.6, 135.5, 130.4, 128.8, 128.3, 125.3, 124.9, 118.6, 21.4 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{13}H_{13}N_2$: 197.10732; found 197.1073 (0 ppm).

*(E)-4-(2-Methylstyryl)pyrimidine (**1g**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 70:30, *v*/*v*) as a colourless oil (136 mg, 69% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.18 (s, 1 H), 8.67 (d, 1 H, J = 5.4 Hz), 8.19 (d, 1 H, J = 15.9 Hz), 7.67-7.64 (m, 1 H), 7.30-7.23 (m, 4 H), 6.97 (d, 1 H, J = 15.9 Hz), 2.50 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (JMOD, 75 MHz, $CDCl_3$): δ = 162.3, 158.9, 157.3, 137.2, 135.2, 134.6, 130.8, 129.3, 126.7, 126.3, 126.0, 118.8, 19.9 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{13}H_{13}N_2$: 197.10732; found 197.1072 (1 ppm).

*(ii): General Procedure for the Synthesis of 2-((E)-styryl)pyrazines (**1h-1m**).* 2-methylpyrazine (5 mmol) and the corresponding aldehyde (5 mmol) were dissolved in DMSO (3 mL). Powdered KOH (1.1 g, 20.0 mmol) was added and the reaction mixture was stirred at room temperature for 8 h. The mixture was then poured into 75 mL of water. The aqueous layer was extracted with ethyl acetate (5 × 15 mL) and the combined organic extract was dried with $MgSO_4$ and the solvents evaporated (In some cases, the crude product can be directly obtained by filtration). The crude product was purified by silica gel column chromatography with mixtures of petroleum ether and ethyl acetate as the eluent, or by crystallization from the indicated solvent. Substrates **1i**[16a,16d] and **1k**[16c,16d] have been reported and characterized elsewhere.

*(E)-2-(4-(Methylthio)styryl)pyrazine (**1h**).* Purified by crystallization from a mixture of CH_2Cl_2/*n*-heptane as a beige solid (649 mg, 70% yield). Mp 134-135°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (br. s, 1 H), 8.52 (br. s, 1 H), 8.38 (d, 1 H, J = 2.4 Hz), 7.69 (d, 1 H, J = 15.9 Hz), 7.51 (d, 2 H, J = 8.7 Hz), 7.25 (d, 2 H, J = 8.7 Hz), 7.10 (d, 1 H, J = 15.9 Hz), 2.51 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (JMOD, 75 MHz, $CDCl_3$): δ = 151.4, 144.3, 143.7, 142.6, 140.0, 134.6, 132.8, 127.7, 126.4, 123.2, 15.5 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{13}H_{13}N_2S$: 229.0794; found 229.0792 (1 ppm).

*(E)-2-(4-(Piperidin-1-yl)styryl)pyrazine (**1j**).* Purified by crystallization from a mixture of CH_2Cl_2/*n*-heptane as a yellow solid (649 mg, 49% yield). Mp 146-147. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (br.s, 1 H), 8.48 (br. s, 1 H), 8.31 (d, 1 H, J = 2.4 Hz), 7.65 (d, 1 H, J = 15.9 Hz), 7.48

(d, 2 H, J = 8.7 Hz), 6.96 (d, 1 H, J = 15.9 Hz), 6.90 (d, 2 H, J = 8.7 Hz), 3.25 (t, 4 H, J = 4.8 Hz), 1.69-1.60 (m, 6 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 152.3, 152.1, 144.2, 143.4, 141.8, 135.2, 128.6, 126.2, 120.3, 115.5, 49.6, 25.6, 24.3 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{17}H_{20}N_3$: 266.1652; found 266.1658 (2 ppm).

*(E)-2-(3-(Methyl)styryl)pyrazine (**1l**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 50:50, *v*/*v*) as a pale yellow oil (525 mg, 54% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (br. s, 1 H), 8.53 (br. s, 1 H), 8.40 (br. s, 1 H), 7.72 (d, 1 H, J = 15.9 Hz), 7.42-7.39 (m, 2 H), 7.32-7.29 (m, 1 H), 7.18-7.12 (m, 2 H), 2.40 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 151.5, 144.3, 143.7, 142.6, 138.4, 136.0, 135.3, 129.8, 128.7, 128.0, 124.6, 123.9, 21.4 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{13}H_{13}N_2$: 197.1073; found 197.1075 (1 ppm).

*(E)-2-(2-(Methyl)styryl)pyrazine (**1m**)*. Purified by crystallization from a mixture of CH_2Cl_2/*n*-heptane as a beige solid (323 mg, 33% yield). Mp 65-66°C. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.65 (br. s, 1 H), 8.57 (br. s, 1 H), 8.43 (br. s, 1 H), 8.05 (d, 1 H, J = 15.9 Hz), 7.70-7.67 (m, 1 H), 7.28-7.25 (m, 3 H), 7.08 (d, 1 H, J = 15.9 Hz), 2.51 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 151.5, 144.3, 143.8, 142.7, 136.9, 135.1, 133.0, 130.7, 128.8, 126.3, 125.8, 125.2, 19.9 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{13}H_{13}N_2$: 197.1073; found 197.1075 (1 ppm).

*(iii): General Procedure for the Synthesis of 3-(E)-styrylpyridazines (**1n-1s**)*. 3-methylpyridazine (5 mmol) and the corresponding aldehyde (5 mmol) were dissolved in DMSO (3 mL). Powdered KOH (1.1 g, 20.0 mmol) was added and the reaction mixture was stirred at room temperature for 8 h. The mixture was then poured into 75 mL of water. The aqueous layer was extracted with ethyl acetate (5 × 15 mL) and the combined organic extract was dried with $MgSO_4$ and the solvents evaporated (In some cases, the crude product can be directly obtained by filtration). The crude product was purified by silica gel column chromatography with mixtures of petroleum ether and ethyl acetate as the eluent, or by crystallization from the indicated solvent. Substrates **1o**[16a,16e] and **1q**[16c,16e] have been reported and characterized elsewhere.

*(E)-3-(4-(Methylthio)styryl)pyridazine (**1n**)*. Purified by silica gel column chromatography (AcOEt) as a beige solid (272 mg, 29% yield). Mp 144-145°C. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.04 (dd, 1 H, J = 4.8 Hz, J = 1.5 Hz), 7.67-7.59 (m, 2 H), 7.52 (d, 2 H, J = 8.7 Hz), 7.43 (dd, 1 H, J = 8.4 Hz, J = 4.8 Hz), 7.30 (d, 1 H, J = 15.9 Hz), 7.32-7.26 (d, 2 H, J = 8.7 Hz), 2.52 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 158.3, 149.5, 140.1, 134.5, 132.6, 127.7, 126.4, 126.3, 124.3, 123.9, 15.4 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{13}H_{13}N_2S$: 229.0794; found 229.0796 (1 ppm).

*(E)-3-(4-(Piperidin-1-yl)styryl)pyridazine (**1p**)*. Purified by silica gel column chromatography (AcOEt) as a yellow solid (246 mg, 19% yield). Mp 180-181°C. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.96 (dd, 1 H, J = 4.8 Hz, J = 1.5 Hz), 7.60-7.54 (m, 2 H), 7.47 (d, 2 H, J = 8.7 Hz), 7.35 (dd, 1 H, J = 8.4 Hz, J = 4.8 Hz), 7.12 (d, 1 H, J = 15.9 Hz), 6.89 (d, 2 H, J = 8.7 Hz), 3.24 (t, 4 H, J = 4.8 Hz), 1.68-1.59 (m, 6 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 158.9, 152.3, 149.1, 135.2, 128.6, 126.3, 126.0, 123.4, 121.3, 115.4, 49.5, 25.6, 24.3 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{17}H_{20}N_3$: 266.1652; found 266.1650 (1 ppm).

*(E)-2-(3-(Methyl)styryl)pyridazine (**1r**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 50:50, *v*/*v*) as a pale yellow oil (360 mg, 37% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.04 (dd, 1 H, J = 4.8 Hz, J = 1.8 Hz), 7.67-7.59 (m, 2 H), 7.44-7.35 (m, 3 H), 7.30-7.25 (m, 2 H), 7.16-7.13 (m, 1 H), 2.38 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 158.3, 149.6, 138.4, 135.9, 135.3, 129.9, 128.8, 128.0, 126.4, 124.9, 124.5, 123.9, 21.4 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{13}H_{13}N_2$: 197.1073; found 197.1073 (0 ppm).

(*E)-2-(2-(Methyl)styryl)pyridazine (**1s**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 50:50, *v*/*v*) as a pale yellow oil (295 mg, 30% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.04 (dd, 1 H, J = 4.8 Hz, J = 1.8 Hz), 8.00 (d, 1 H, J = 15.9 Hz), 7.70-7.67 (m, 1 H), 7.61 (dd, 1 H, J = 8.7 Hz, J = 1.8 Hz), 7.44 (dd, 1 H, J = 8.4 Hz, J = 4.8 Hz), 7.27-7.21 (m, 4 H), 2.48 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 158.4, 149.6, 136.8, 135.0, 133.0, 130.7, 128.9, 126.5, 126.4, 126.2, 125.9, 124.2, 19.9 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{13}H_{13}N_2$: 197.1073; found 197.1075 (1 ppm).

*(iv): General procedure for the synthesis 4,6-bis((E)-styryl)pyrimidines (**1t-1x**)*. A stirred mixture of 4,6-dimethylpyrimidine (1 mmol) and the corresponding aldehyde (2 mmol) in aqueous sodium hydroxide (5 M, 15 mL) containing Aliquat 336 (0.1 mmol) was heated under reflux for 2 h. The mixture was allowed to cool, and the precipitate was filtered off, washed with water, and purified by crystallization from a mixture of CH_2Cl_2/*n*-heptane. Substrates **1u**[16f] and **1w**[16b,16g] have been reported and characterized elsewhere.

*4,6-bis((E)-4-(Methylthio)styryl)pyrimidine (**1t**)*. Obtained as a pale yellow solid (223 mg, 59% yield). Mp 138-139°C. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.06 (s, 1 H), 7.84 (d, 2 H, J = 15.9 Hz), 7.52 (d, 4 H, J = 8.4 Hz), 7.26 (s, 1 H), 7.24 (d, 4 H, J = 8.4 Hz), 7.01 (d, 2 H, J = 15.9 Hz), 2.51 (s, 6 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 162.8, 158.7, 140.7, 136.4, 132.4, 128.0, 126.3, 124.9, 116.2, 15.4 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{22}H_{21}N_2S_2$: 377.1141; found 377.1146 (1 ppm).

*4,6-bis((E)-4-Piperidin-1-ylstyryl)pyrimidine (**1v**)*. Obtained as a yellow solid (283 mg, 63% yield). Mp 181-182°C. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.00 (s, 1 H), 7.80 (d, 2 H, J = 15.9 Hz), 7.50 (d, 4 H, J = 8.7 Hz), 7.19 (s,1 H), 6.91 (d, 4 H, J = 8.7 Hz), 6.88 (d, 2 H, J = 15.9 Hz), 3.27 (t, 8 H, J = 4.8 Hz), 1.70-1.61 (m, 12 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 163.0, 158.6, 152.5, 136.8, 129.0, 125.8, 122.1, 115.3, 49.5, 25.6, 24.3 ppm.

HRMS m/z $[M+H]^+$ Calculated for $C_{30}H_{35}N_4$: 451.2856; found 451.2863 (2 ppm).

*4,6-bis((E)-3-Methylstyryl)pyrimidine (**1x**).* Obtained as a cream solid (174 mg, 56% yield). Mp 139-140°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.10 (s, 1 H), 7.87 (d, 2 H, J = 15.9 Hz), 7.43-7.40 (m, 4 H), 7.32-7.26 (m,3 H), 7.19-7.16 (m, 2 H), 7.06 (d, 2 H, J = 15.9 Hz), 2.40 (s, 6 H) ppm. $^{13}C\{^1H\}$ NMR (JMOD, 75 MHz, $CDCl_3$): δ = 162.8, 158.7, 138.5, 137.2, 135.7, 130.2, 128.8, 128.3, 125.7, 124.9, 116.3, 21.4 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{22}H_{21}N_2$: 313.1699; found 313.1695 (1 ppm).

General Procedure for the Ruthenium-Catalyzed mono-Arylation and Characterization of Products (2-4). The corresponding substrate **1** (0.25 mmol, 1 eq.), the corresponding arylbromide (0.5 mmol, 2 eq.), K_2CO_3 (0.75 mmol, 0.104 g, 3 eq.), KOAc (0.0125 mmol, 0.0012 g, 0.05 eq.), $[RuCl_2(p\text{-cymene})]_2$ (0.00625 mmol, 0.0038 g, 0.025 eq.) and NMP (1 mL) were introduced in a dry Schlenk tube under Argon atmosphere. The reaction mixture was stirred at 150 °C during 3 h. Then, the reaction mixture was cooled down to room temperature and poured into 30 mL of water. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extract was dried with $MgSO_4$. After solvents evaporation, the desired product was purified by silica gel column chromatography with mixtures of petroleum ether and ethyl acetate containing 1% of triethylamine as the eluent.

*4-(2,2-bis(4-(Methylthio)phenyl)vinyl)pyrimidine (**2a**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 80:20 to 60:40, *v*/*v*) as a colourless solid (82 mg, 94%). Mp 155-157°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 9.00 (d, 1 H, J = 1.0 Hz), 8.40 (d, 1 H, J = 5.4 Hz), 7.32-7.34 (m, 4 H), 7.28 (d, 2 H, J = 8.7 Hz), 7.14 (d, 2 H, J = 8.3 Hz), 6.99 (s, 1 H), 6.73 (dd, 1 H, J = 5.4 Hz, 1.2, Hz), 2.54 (s, 3 H), 2.52 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ =164.0, 159.6, 157.0, 150.1, 141.2, 140.5, 139.1, 136.2, 131.1, 129.2, 127.0, 126.5, 126.4, 120.9, 15.0, 15.0 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{20}H_{19}N_2S_2$: 351.09842; found 351.0979 (2 ppm), $[M+Na]^+$ calculated for $C_{20}H_{18}N_2S_2Na$: 373.08036; found 370.0801 (1 ppm). Crystals suitable for single crystal X-ray diffraction studies were grown by slow diffusion of *n*-hexane into a concentrated solution of **2a** in ethyl acetate at room temperature.

*4,4'-(2-(Pyrimidin-4-yl)ethene-1,1-diyl)bis(N,N-dimethylaniline) (**2b**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 80:20 to 70:30, *v*/*v*) as a yellow solid (83 mg, 96%). Mp 160-162°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.94 (d, 1 H, J = 1.2 Hz), 8.25 (d, 1 H, J = 5.5 Hz), 7.26 (d, 2 H, J = 8.8 Hz), 7.01 (d, 2 H, J = 8.8 Hz), 6.78 (d, 2 H, J = 8.8 Hz), 6.76 (s, 1 H), 6.73 (d, 2 H, J = 8.8 Hz), 6.59 (dd, 1 H, J = 5.5 Hz, 1.2 Hz), 3.00 (s, 6 H), 3.01 (s, 6 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 165.3, 159.6, 156.0, 152.5, 152.1, 151.6, 131.6, 130.7, 130.1, 127.5, 122.2, 120.1, 113.0, 112.5, 40.3, 40.4 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{22}H_{25}N_4$: 345.20737; found 345.2074 (0 ppm), $[M+Na]^+$ Calculated for $C_{22}H_{24}N_4Na$: 367.18932; found 367.1891 (1 ppm).

*4,4'-(2-(Pyrimidin-4-yl)ethene-1,1-diyl)bis(N,N-diphenylaniline) (**2c**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as an orange solid (132 mg, 89%). Mp 167-169°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.99 (s, 1 H), 8.43 (d, 1 H, J = 5.4 Hz), 7.30-7.37 (m, 10 H), 7.04-7.15 (m, 16 H), 6.98 (d, 2 H, J = 8.7 Hz), 6.95 (s , 1 H), 6.75 (d, 1 H, 4.8 Hz) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 164.4, 159.6, 156.6, 150.6, 149.6, 149.0, 148.4, 148.1, 135.6, 133.6, 131.6, 130.4, 130.3, 129.7, 125.9, 125.5, 125.2, 124.6, 124.3, 124.0, 122.6, 120.8 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{42}H_{33}N_4$: 593.26997; found 593.2703 (1 ppm).

*4-(2,2-bis(4-(Piperidin-1-yl)phenyl)vinyl)pyrimidine (**2d**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v*/*v*) as a yellow solid (99 mg, 93%). Mp 176-177°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.96 (d, 1 H, J = 0.7 Hz), 8.27 (d, 1 H, J = 5.4 Hz), 7.26 (d, 2 H, J = 8.9 Hz), 7.02 (d, 2 H, J = 8.9 Hz), 6.98 (d, 2 H, J = 8.9 Hz), 6.92 (d, 2 H, J = 8.9 Hz), 6.80 (s, 1 H), 6.60 (dd, 1 H, J = 5.4 Hz, 1.1 Hz), 3.25-3.27 (m, 8 H), 1.61-1.71 (m, 12 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 165.0, 159.6, 156.2, 153.2, 153.0, 151.9, 132.4, 131.4, 129.9, 129.6, 123.1, 120.3, 116.4, 115.6, 50.3, 50.0, 26.4, 26.3, 25.1, 25.0 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{28}H_{33}N_4$: 425.26997; found 425.2703 (1 ppm).

*4-(2,2-bis(4-Methoxyphenyl)vinyl)pyrimidine (**2e**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a cream solid (76 mg, 95%). Mp 152-153°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.99 (d, 1 H, J = 1.1 Hz), 8.34 (d, 1 H, J = 5.4 Hz), 7.34 (d, 2 H, J = 8.9 Hz), 7.11 (d, 2 H, J = 8.8 Hz), 7.00 (d, 2 H, J = 8.8 Hz), 6.95 (d, 2 H, J = 8.9 Hz), 6.89 (s, 1 H), 6.62 (dd, 1 H, J = 5.4 Hz, 1.1 Hz), 3.86 (s, 3 H), 3.83 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 164.5, 161.4, 160.9, 159.6, 156.6, 150.7, 135.3, 132.1, 131.9, 130.2, 125.1, 120.6, 115.2, 114.7, 55.7, 55.6 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{20}H_{19}N_2O_2$: 319.1441; found 319.1442 (0 ppm), $[M+Na]^+$ calculated for $C_{20}H_{18}N_2O_2Na$: 341.12605; found 341.1258 (1 ppm).

*4-(2,2-di-m-Tolylvinyl)pyrimidine (**2f**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v*/*v*) as a colourless solid (68 mg, 95%). Mp 130-132°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 9.02 (d, 1 H, J = 0.6 Hz), 8.34 (d, 1 H, J = 5.4 Hz), 7.32 (t, 1 H, J = 7.5 Hz), 7.28-7.24 (m, 3 H), 7.20 (d, 1 H, J = 7.6 Hz), 7.22 (d, 1 H, J = 7.6 Hz), 7.03-6.98 (m, 3 H), 6.59 (dd, 1 H, J = 5.4 Hz, J = 1.1 Hz), 2.32 (s, 3 H), 2.31 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 163.9, 159.6, 156.8, 151.4, 142.7, 140.0, 139.5, 138.8, 130.8, 130.4, 129.9, 129.7, 129.2, 129.1, 127.4, 127.1, 125.9, 120.7, 21.4, 21.3 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{20}H_{18}N_2Na$: 309.13622; found 309.1362 (0 ppm).

*(Z)-4-(2-(m-Tolyl)-2-(o-tolyl)vinyl)pyrimidine (**2g**).* Purified by silica gel column chromatography (petroleum

ether/AcOEt, 90:10, *v*/*v*) as a colourless solid (63 mg, 88%). Mp 128-130°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 9.02 (br s, 1 H), 8.35 (d, 1 H, J = 5.3 Hz), 7.38-7.36 (m, 2 H), 7.31-7.29 (m, 2 H), 7.26 (d, 1 H, J = 7.6 Hz), 7.21-7.15 (m, 3 H), 7.10 (d, 1 H, J = 7.6 Hz), 2.33 (s, 3 H), 2.04 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 163.5, 159.6, 157.2, 150.5, 141.4, 139.4, 139.0, 136.7, 131.6, 130.5, 130.0, 129.4, 129.3, 128.2, 127.4 (x 2), 125.1, 119.8, 21.4, 19.6 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{20}H_{18}N_2Na$: 309.13622; found 309.1366 (1 ppm).

(E)-4-(2-(4-(tert-Butyl)phenyl)-2-(o-tolyl)vinyl)pyrimidine ***(2h)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 95:5, *v*/*v*) as a cream solid (78 mg, 95%). Mp 141-143°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 9.01 (d, 1 H, J = 1.1 Hz), 8.33 (d, 1 H, J = 5.4 Hz), 7.44 (d, 2 H, J = 8.5 Hz), 7.41-7.35 (m, 2 H), 7.35 (d, 2 H, J = 8.5 Hz), 7.30 (ddd, 1 H, J =7.1 Hz, J =7.1 Hz, J =1.9 Hz), 7.20 (s, 1 H), 7.10 (d, 1 H, J = 7.4 Hz), 6.45 (dd, 1 H, J = 5.4 Hz, J = 1.1 Hz), 2.04 (s, 3 H), 1.32 (s, 9 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 163.5, 159.6, 157.1, 152.9, 150.1, 139.5, 138.3, 136.6, 131.6, 129.9, 129.2, 127.5, 127.5, 126.7, 126.4, 119.6, 35.2, 31.4, 19.6 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{23}H_{24}N_2Na$: 351.18317; found 351.1830 (0 ppm), [M+H]$^+$ Calculated for $C_{23}H_{25}N_2$: 329.20122; found 329.2009 (1 ppm).

4-(2,2-di-o-Tolylvinyl)pyrimidine ***(2i)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v*/*v*) as a colourless solid (42 mg, 58%). Mp 129-131°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 9.03 (s, 1 H), 8.39 (d, 1 H, J = 5.1 Hz), 7.32-7.09 (8 H), 6.74 (s, 1 H), 6.63 (dd, 1 H, J = 5.1 Hz, J = 1.2 Hz), 2.37 (s, 3 H), 2.06 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 163.8, 159.6, 157.1, 150.4, 142.5, 140.3, 136.6, 136.5, 132.0, 131.7, 131.5, 130.7, 130.4, 129.2, 128.9, 127.1, 126.6, 120.4, 21.0, 20.0 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{20}H_{18}N_2Na$: 309.13622; found 309.1364 (1 ppm).

2-(2,2-bis(4-(Methylthio)phenyl)vinyl)pyrazine ***(3a)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a cream solid (85 mg, 97%). Mp 132-133°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.48 (br s, 1 H), 8.26 (d, 1 H, J = 2.2 Hz), 8.01 (s, 1 H), 7.35 (d, 2 H, J = 8.6 Hz), 7.31 (d, 2 H, J = 8.3 Hz), 7.28 (d, 2 H, J = 8.6 Hz), 7.14 (d, 2 H, J = 8.3 Hz), 7.07 (s, 1 H), 2.53 (s, 3 H), 2.52 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 153.5, 147.5, 145.8, 144.9, 142.2, 140.7, 140.2, 139.3, 136.6, 131.3, 129.1, 127.0, 126.6, 125.5, 15.1, 15.0 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{20}H_{18}N_2NaS_2$: 373.08036; found 373.0804 (0 ppm).

4,4'-(2-(Pyrazin-2-yl)ethene-1,1-diyl)bis(N,N-dimethylaniline) ***(3b)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 80:20, *v*/*v*) as an orange solid (81 mg, 94%). Mp 135-136°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.43 (dd, 1 H, J = 2.2 Hz, J = 1.8 Hz), 8.13 (d, 1 H, J = 2.5 Hz), 7.91 (d, 1 H, J = 1.1 Hz), 7.26 (d, 2 H, J = 8.9 Hz), 7.01 (d, 2 H, J = 8.7 Hz), 6.81 (s, 1 H), 6.76 (d, 2 H, J = 8.7 Hz), 6.73 (d, 2 H, J = 8.9 Hz), 2.99 (s, 6 H), 2.99 (s, 6 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 154.9, 151.8, 151.4, 149.3, 145.7, 144.6, 140.8, 131.7, 131.0, 129.8, 127.9, 121.5, 113.1, 112.6, 40.3 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{22}H_{24}N_4Na$: 367.18932; found 367.1893 (0 ppm), [M+H]$^+$ calculated for $C_{22}H_{25}N_4$: 345.20737; found 345.2073 (0 ppm). Crystals suitable for single crystal X-ray diffraction studies were grown by slow diffusion of *n*-hexane into a concentrated solution of **3b** in ethyl acetate at room temperature.

2-(2,2-bis(4-(Piperidin-1-yl)phenyl)vinyl)pyrazine ***(3c)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as an orange solid (90 mg, 85%). Mp 159-160°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.37 (s, 1 H), 8.08 (s, 1 H), 7.91 (s, 1 H), 7.21 (d, 2 H, J = 8.7 Hz), 6.98 (d, 2 H, J = 8.7 Hz), 6.85-6.80 (m, 5 H), 3.17 (m, 8 H), 1.64 (m, 8 H), 1.56 (m, 4 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 154.6, 153.0, 152.7, 148.8, 145.7, 144.7, 141.1, 132.8, 131.6, 130.0, 129.7, 122.5, 116.5, 115.8, 50.2, 50.1, 26.4, 26.3, 25.1 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{28}H_{32}N_4Na$: 447.25192; found 447.2518 (0 ppm), [M+H]$^+$ calculated for $C_{28}H_{33}N_4$: 425.26997; found 425.2698 (0 ppm).

2-(2,2-bis(4-Methoxyphenyl)vinyl)pyrazine ***(3d)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a yellow solid (74 mg, 93%). Mp 129-130°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.46 (dd, 1 H, J = 2.3 Hz, J = 1.7 Hz), 8.21 (d, 1 H, J = 2.5 Hz), 7.92 (d, 1 H, J = 1.1 Hz), 7.34 (d, 2 H, J = 8.9 Hz), 7.11 (d, 2 H, J = 8.8 Hz), 6.97 (d, 2 H, J = 8.8 Hz), 6.96 (s, 1 H), 6.94 (d, 2 H, J = 8.9 Hz), 3.84 (s, 3 H), 3.83 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 161.1, 160.7, 154.0, 147.9, 145.7, 144.8, 141.7, 135.5, 132.5, 132.0, 130.0, 124.2, 115.1, 114.6, 55.6, 55.5 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{20}H_{18}N_2O_2Na$: 341.12605; found 341.1261 (0 ppm), [M+H]$^+$ Calculated for $C_{20}H_{19}N_2O_2$: 319.14410; found 319.1440 (0 ppm).

(E)-N,N-Dimethyl-4-(1-phenyl-2-(pyrazin-2-yl)vinyl)aniline ***(3e)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a yellow solid (71 mg, 94%). Mp 147-148°C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.42 (t, 1 H, J = 1.8 Hz), 8.13 (d, 1 H, J = 1.8 Hz), 7.83 (s, 1 H), 7.38-7.36 (m, 3 H), 7.27 (d, 2 H, J = 8.9 Hz), 7.24-7.21 (m, 2 H), 7.02 (s, 1 H), 6.66 (d, 2 H, J = 8.9 Hz), 2.99 (s, 6 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.3, 150.6, 148.2, 145.0, 143.6, 140.2, 139.8, 129.9, 129.3, 128.9, 128.8, 128.1, 121.5, 111.7.7, 40.2 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{20}H_{19}N_3Na$: 324.14712; found 324.1469 (1 ppm). Crystals suitable for single crystal X-ray diffraction studies were grown by slow diffusion of *n*-hexane into a concentrated solution of **3e** in ethyl acetate at room temperature.

(E)-4-(1-(4-(tert-Butyl)phenyl)-2-(pyrazin-2-yl)vinyl)-N,N-dimethylaniline ***(3f)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v*/*v*) as a yellow solid (87 mg, 97%). Mp 126-127°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.43 (dd, 1 H, J = 2.4 Hz, J = 1.7 Hz), 8.15 (d, 1 H, J = 2.4 Hz), 7.78 (d, 1 H, J = 1.2 Hz), 7.47 (d, 2 H, J = 8.3 Hz), 7.24 (d, 2 H, J = 9.0 Hz), 7.14 (d, 2 H, J = 8.3

Hz), 6.96 (s, 1 H), 6.71 (d, 2 H, J = 9.0 Hz), 2.98 (s, 6 H), 1.36 (s, 9 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 154.1, 151.8, 151.7, 148.6, 145.4, 144.7, 141.3, 138.0, 130.4, 130.2, 129.5, 126.6, 122.3, 112.6, 40.3, 35.2, 31.6 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{24}H_{27}N_3Na$: 380.20972; found 380.2097 (0 ppm), $[M+H]^+$ calculated for $C_{24}H_{28}N_3$: 358.22777; found 358.2274 (1 ppm).

*(E)-2-(2-([1,1'-Biphenyl]-4-yl)-2-(4-(methylthio)phenyl)vinyl)pyrazine (**3g**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a colourless solid (91 mg, 96%). Mp 119-120°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.48 (dd, 1 H, J = 2.4 Hz, J = 1.7 Hz), 8.25 (d, 1 H, J = 2.4 Hz), 8.04 (d, 1 H, J = 1.2 Hz), 7.75-7.72 (m, 4 H), 7.48 (dd, 2 H, J = 8.0 Hz, J = 7.3 Hz), 7.40-7.36 (m, 3 H), 7.31-7.28 (m, 4 H), 7.13 (s, 1 H), 2.52 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 153.4, 147.5, 145.8, 144.9, 142.3, 141.6, 141.0, 140.7, 139.4, 139.3, 131.4, 129.8, 129.0, 128.5, 128.1, 127.6, 126.6, 125.7, 15.1 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{25}H_{20}N_2SNa$: 403.12394; found 403.1241 (0 ppm).

*(E)-2-(2-(4-(Methylthio)phenyl)-2-(4-vinylphenyl)vinyl)pyrazine (**3h**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a colourless solid (78 mg, 95%). Mp 124-125°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.47 (dd, 1 H, J = 2.3 Hz, J = 1.7 Hz), 8.24 (d, 1 H, J = 2.5 Hz), 7.98 (d, 1 H, J = 1.3 Hz), 7.52 (d, 2 H, J = 8.2 Hz), 7.34 (d, 2 H, J = 8.6 Hz), 7.27 (d, 2 H, J = 8.6 Hz), 7.17 (d, 2 H, J = 8.2 Hz), 7.10 (s, 1 H), 6.81 (dd, 1 H, J = 17.6 Hz, J = 11.0 Hz), 5.88 (dd, 1 H, J = 17.6 Hz, J = 0.5 Hz), 5.30 (dd, 1 H, J = 11.0 Hz, J = 0.5 Hz), 2.51 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 153.3, 147.6, 145.8, 144.8, 142.2, 140.7, 139.8, 139.1, 138.4, 137.2, 131.0, 129.0, 127.6, 126.6, 125.5, 114.9, 15.1 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{21}H_{18}N_2SNa$: 353.10829; found 353.1084 (0 ppm).

*(E)-Methyl-4-(1-(4-(dimethylamino)phenyl)-2-(pyrazin-2-yl)vinyl)benzoate (**3i**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a yellow solid (85 mg, 95%). Mp 130-132°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.38 (dd, 1 H, J = 2.7 Hz, J = 1.2 Hz), 8.19 (d, 1 H, J = 2.4 Hz), 8.04 (d, 2 H, J = 8.3 Hz), 7.92 (d, 1 H, J = 1.2 Hz), 7.33 (d, 2 H, J = 8.3 Hz), 7.22 (d, 2 H, J = 9.0 Hz), 7.05 (s, 1 H), 6.72 (d, 2 H, J = 9.0 Hz), 3.91 (s, 3 H), 2.98 (s, 6 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 166.9, 153.5, 151.8, 147.8, 146.3, 145.6, 144.7, 141.8, 131.1, 130.5, 130.1, 129.4, 129.0, 122.3, 112.7, 52.4, 40.2 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{22}H_{21}N_3O_2Na$: 382.15260; found 382.1527 (0 ppm).

*(E)-1-(4-(1-(4-(Dimethylamino)phenyl)-2-(pyrazin-2-yl)vinyl)phenyl)ethanone (**3j**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a yellow solid (82 mg, 96%). Mp 117-118°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.39 (dd, 1 H, J = 2.4 Hz, J = 1.6 Hz), 8.19 (d, 1 H, J = 2.6 Hz), 8.02 (d, 2 H, J = 8.3 Hz), 7.92 (d, 1 H, J = 1.3 Hz), 7.33 (d, 2 H, J = 8.3 Hz), 7.22 (d, 2 H, J = 9.0 Hz), 7.05 (s, 1 H), 6.72 (d, 2 H, J = 9.0 Hz), 2.98 (s, 6 H), 2.62 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 197.5, 153.5, 151.8, 147.8, 146.1, 145.6, 144.7, 141.8, 137.4, 131.1, 129.4, 129.1, 129.0, 122.4, 112.6, 40.2, 26.7 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{22}H_{21}N_3ONa$: 366.15768; found 366.1577 (0 ppm).

*(E)-4-(1-(4-(Dimethylamino)phenyl)-2-(pyrazin-2-yl)vinyl) benzonitrile (**3k**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 70:30, *v*/*v*) as an orange solid (74 mg, 91%). Mp 122-123°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.34 (dd, 1 H, J = 2.2 Hz J = 1.7 Hz), 8.22 (d, 1 H, J = 2.4 Hz), 8.06 (d, 1 H, J = 1.3 Hz), 7.80 (d, 2 H, J = 8.3 Hz), 7.39 (d, 2 H, J = 8.3 Hz), 7.21 (d, 2 H, J = 8.9 Hz), 7.08 (s, 1 H), 6.73 (d, 2 H, J = 8.9 Hz), 2.99 (s, 6 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 153.1, 151.9, 147.2, 146.5, 145.9, 144.6, 142.1, 133.2, 131.9, 129.5, 129.1, 122.2, 119.3, 112.7, 112.1, 40.2 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{21}H_{18}N_4Na$: 349.14237; found 349.1421 (1 ppm).

*(Z)-4-(1-(4-Fluorophenyl)-2-(pyrazin-2-yl)vinyl)-N,N-dimethylaniline (**3l**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v*/*v*) as a yellow solid (68 mg, 85%). Mp 119-120°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.41 (dd, 1 H, J = 1.7 Hz, J = 2.1 Hz), 8.18 (d, 1 H, J = 2.5 Hz), 7.89 (d, 1 H, J = 1.1 Hz), 7.25-7.15 (m, 4 H), 7.23 (d, 2 H, J = 9.0 Hz), 6.99 (s, 1 H), 6.72 (d, 2 H, J = 9.0 Hz), 2.98 (s, 6 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 163.3 (d, $J_{C,F}$ = 245.7 Hz), 153.8, 151.8, 147.6, 145.6, 144.7, 141.6, 137.2 (d, $J_{C,F}$ = 3.4 Hz), 132.8 (d, $J_{C,F}$ = 8.1 Hz), 129.9, 129.4, 122.3, 116.4 (d, $J_{C,F}$ = 21.6 Hz), 112.6, 40.3 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, acetone-d_6): δ = -115.2 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{20}H_{18}N_3FNa$: 342.13770; found 342.1381 (1 ppm).

*(Z)-4-(1-(3,5-bis(Trifluoromethyl)phenyl)-2-(pyrazin-2-yl) vinyl)-N,N-dimethylaniline (**3m**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v*/*v*) as a yellow solid (84 mg, 77%). Mp 105-107°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.33 (d, 1 H, J = 1.0 Hz), 8.25 (d, 1 H, J = 2.4 Hz), 8.22 (dd, 1 H, J = 2.3 Hz, J = 1.5 Hz), 8.04 (s, 1 H), 7.80 (s, 2 H), 7.24 (d, 2 H, J = 8.9 Hz), 7.19 (s, 1 H), 6.75 (d, 2 H, J = 8.9 Hz), 3.00 (s, 6 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 152.5, 152.0, 146.5, 144.3, 142.7, 131.9 (q, $J_{C,F}$ = 33.2 Hz), 131.6, 131.8, 129.6, 129.2 (q, $J_{C,F}$ = 3.7 Hz), 124.5 (q, $J_{C,F}$ = 272.9 Hz), 122.3, 121.9 (h, $J_{C,F}$ = 3.7 Hz), 113.1, 112.7, 40.2 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, acetone-d_6): δ = -62.1 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{22}H_{17}N_3F_6Na$: 460.12189; found 460.1220 (0 ppm), $[M+H]^+$ calculated for $C_{22}H_{18}N_3F_6$: 438.13994; found 438.1388 (3 ppm).

*(Z)-2-(2-(4-(Methylthio)phenyl)-2-(pyridin-4-yl)vinyl)pyrazine (**3n**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 60:40 to 50:50, *v*/*v*) as a cream solid (52 mg, 68%). Mp 109-110°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.61 (d, 2 H, J = 5.6 Hz), 8.40 (dd, 1 H, J = 2.6 Hz, J = 1.4 Hz), 8.31 (d, 1 H, J = 2.6 Hz), 8.21 (d, 1 H, J = 1.2 Hz), 7.33 (d, 2 H, J = 8.7 Hz), 7.29 (d, 2 H, J = 8.7 Hz), 7.23 (s, 1 H), 7.19 (d, 2 H, J = 5.9 Hz), 2.52 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 152.4,

151.0, 148.5, 146.1, 145.5, 144.8, 143.0, 141.1, 128.8, 126.7, 125.7, 125.6, 125.4, 15.0 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{18}H_{15}N_3SNa$: 328.08789; found 328.0878 (0 ppm).

(Z)-2-(2-(4-(Methylthio)phenyl)-2-(thiophen-3-yl)vinyl)pyrazine ***(3o)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v/v*) as a colourless solid (45 mg, 58%). Mp 97-98°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.50 (dd, 1 H, J = 2.4 Hz, J = 1.6 Hz), 8.27 (d, 1 H, J = 2.4 Hz), 8.00 (d, 1 H, J = 1.4 Hz), 7.60 (dd, 1 H, J = 4.9 Hz, J = 2.9 Hz), 7.37 (d, 2 H, J = 8.6 Hz), 7.30-7.29 (m, 1 H), 7.28 (d, 2 H, J = 8.6 Hz), 7.07 (s, 1 H), 6.94 (dd, 1 H, J = 4.9 Hz, J = 1.2 Hz), 2.52 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 153.4, 145.5, 144.8, 142.5, 142.3, 140.7, 140.2, 138.9, 129.7, 128.7, 127.7, 126.6, 126.2, 126.1, 15.1 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{17}H_{14}N_2S_2Na$: 333.04906; found 333.0491 (0 ppm).

(Z)-N,N-Dimethyl-4-(2-(pyrazin-2-yl)-1-(o-tolyl)vinyl)aniline ***(3p)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v/v*) as a yellow solid (73 mg, 92%). Mp 124-125°C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 8.13 (d, 1 H, J = 1.8 Hz), 7.68 (s, 1 H), 7.33-7.21 (m, 5 H), 7.16 (s, 1 H), 7.11 (d, 1 H, J = 7.4 Hz), 6.65 (d, 1 H, J = 8.8 Hz), 2.97 (s, 6 H), 2.07 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 152.9, 150.5, 147.0, 144.0, 143.6, 140.3, 139.0, 136.2, 130.8, 129.4, 128.2, 128.0, 127.9, 126.6, 121.5, 111.9, 40.2, 19.4 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{21}H_{21}N_3Na$: 338.16277; found 338.1624 (1 ppm), $[M+H]^+$ calculated for $C_{21}H_{22}N_3$: 316.18082; found 316.11803 (2 ppm).

(Z)-N,N-Dimethyl-4-(2-(pyrazin-2-yl)-1-(m-tolyl)vinyl)aniline ***(3q)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v/v*) as a yellow solid (75 mg, 95%). Mp 122-123°C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.42 (t, 1 H, J = 1.8 Hz), 8.13 (d, 1 H, J = 2.5 Hz), 7.83 (s, 1 H), 7.28 (d, 2 H, J = 8.9 Hz), 7.25 (d, 1 H, J = 7.7 Hz), 7.18 (d, 1 H, J = 7.6 Hz), 7.07 (s, 1 H), 7.02 (t, 1 H, J = 8.0 Hz), 7.00 (s, 1 H), 6.66 (d, 2 H, J = 8.9 Hz), 2.98 (s, 6 H) 2.31 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.4, 150.6, 148.4, 145.0, 143.6, 140.0, 139.7, 138.6, 130.3, 129.3, 128.9, 128.8, 128.8, 126.6, 121.3, 111.7, 40.2, 21.4 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{21}H_{21}N_3Na$: 338.16277; found 338.1624 (1 ppm), $[M+H]^+$ calculated for $C_{21}H_{22}N_3$: 316.18082; found 316.1801 (2 ppm).

2-(2,2-di-m-Tolylvinyl)pyrazine ***(3r)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v/v*) as a colourless solid (69 mg, 97%). Mp 106-107°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.49 (br s, 1 H), 8.25 (br s, 1 H), 7.90 (br s, 1 H), 7.30 (t, 1 H, J = 7.5 Hz), 7.27-7.23 (m, 3 H), 7.18 (d, 1 H, J = 7.9 Hz), 7.16 (d, 1 H, J = 7.9 Hz), 7.07 (s, 1 H), 7.03 (br s, 1 H), 6.99 (d, 1 H, J = 7.4 Hz), 2.32 (s, 3 H), 2.30 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 153.4, 148.7, 145.6, 144.8, 142.9, 142.2, 140.5, 139.5, 138.7, 131.0, 130.0, 129.7 (x 2), 129.1, 129.0, 127.6, 126.2, 125.8, 21.4, 21.3 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{20}H_{19}N_2$: 287.15427; found 287.1540 (1 ppm), $[M+Na]^+$ calculated for $C_{20}H_{18}N_2Na$: 309.13622; found 309.1364 (1 ppm).

(Z)-2-(2-(m-Tolyl)-2-(o-tolyl)vinyl)pyrazine ***(3s)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v/v*) as a colourless solid (67 mg, 94%). Mp 104-105°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.48 (dd, 1 H, J = 2.4 Hz, J = 1.5 Hz), 8.25 (d, 1 H, J = 2.4 Hz), 7.79 (d, 1 H, J = 0.8 Hz), 7.36-7.34 (m, 2 H), 7.29-7.24 (m, 4 H), 7.19-7.15 (m, 2 H), 7.11 (d, 1 H, J = 7.4 Hz), 2.32 (s, 3 H), 2.05 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 153.0, 147.6, 144.9 (x 2), 142.5, 141.7, 139.8, 138.9, 137.0, 131.6, 130.4, 130.1, 129.3, 129.2, 128.1, 127.4, 126.6, 124.9, 21.4, 19.7 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{20}H_{19}N_2$: 287.15427; found 287.1538 (2 ppm), $[M+Na]^+$ calculated for $C_{20}H_{18}N_2Na$: 309.13622; found 309.1361 (0 ppm).

(E)-2-(2-(4-(tert-Butyl)phenyl)-2-(o-tolyl)vinyl)pyrazine ***(3t)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v/v*) as a colourless solid (80 mg, 97%). Mp 117-118°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.52 (dd, 1 H, J = 2.4 Hz, J = 1.5 Hz), 8.31 (d, 1 H, J = 2.4 Hz), 8.16 (d, 1 H, J = 1.2 Hz), 7.35 (d, 2 H, J = 8.4 Hz), 7.33-7.30 (m, 1 H), 7.27-7.21 (m, 3 H), 7.08 (d, 2 H, J = 8.4 Hz), 6.63 (s, 1 H), 2.14 (s, 3 H), 1.30 (s, 9 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 153.6, 151.9, 149.0, 145.9, 144.9, 144.0, 142.5, 137.5, 136.6, 131.4, 130.5, 130.0, 128.8, 128.0, 126.6, 126.2, 35.1, 31.5, 20.5 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{23}H_{25}N_2$: 329.20122; found 329.2018 (2 ppm), $[M+Na]^+$ calculated for $C_{23}H_{24}N_2Na$: 351.18317; found 351.1834 (1 ppm).

2-(2,2-di-o-Tolylvinyl)pyrazine ***(3u)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v/v*) as a colourless solid (34 mg, 47%). Mp 105-106°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.50 (dd, 1 H, J = 2.3 Hz, J = 1.6 Hz), 8.28 (d, 1 H, J = 2.4 Hz), 7.91 (d, 1 H, J = 1.3 Hz), 7.29-7.16 (m, 7 H), 7.10 (d, 1 H, J = 7.3 Hz), 6.81 (s, 1 H), 2.36 (s, 3 H), 2.05 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 153.2, 147.8, 145.3, 145.0, 142.8, 140.6, 136.7, 136.5, 132.0, 131.7, 131.0, 130.5, 130.4, 129.0, 128.7, 127.1, 126.6, 21.0, 20.0 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{20}H_{18}N_2Na$: 309.13622; found 309.1363 (0 ppm), $[M+H]^+$ calculated for $C_{20}H_{18}N_2$: 287.15427; found 287.1539 (1 ppm).

3-(2,2-bis(4-(Methylthio)phenyl)vinyl)pyridazine ***(4a)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 50:50 to 40:60, *v/v*) as a cream solid (82 mg, 94%). Mp 156-157°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.91 (dd, 1 H, J = 4.9 Hz, J = 1.5 Hz), 7.36-7.24 (m, 8 H), 7.12 (d, 2 H, J = 8.3 Hz), 6.89 (dd, 1 H, J = 8.7 Hz, J = 1.5 Hz), 2.53 (s, 3 H), 2.52 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 160.2, 149.8, 147.8, 140.7, 139.4, 136.2, 131.3, 129.0, 127.1, 126.8, 126.6, 126.0, 125.7, 15.1, 15.0 ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{20}H_{18}N_2NaS_2$: 373.08036; found 373.0802 (0 ppm).

*4,4'-(2-(pyridazin-3-yl)ethene-1,1-diyl)bis(N,N-dimethylaniline) (**4b**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 50:50 to 30:70, *v*/*v*) as a yellow solid (78 mg, 91%). Mp 189-190°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.91 (dd, 1 H, J = 4.8 Hz, J = 1.5 Hz), 7.36 (d, 2 H, J = 8.9 Hz), 7.25 (dd, 1 H, J = 8.7 Hz, J = 4.8 Hz), 7.21 (s, 1 H), 7.08 (d, 2 H, J = 8.8 Hz), 6.90 (dd, 1 H, J = 8.8 Hz, J =1.5 Hz), 6.84 (d, 2 H, J = 8.3 Hz), 6.82 (d, 2 H, J = 8.7 Hz), 3.08 (s, 6 H), 3.08 (s, 6 H) ppm.^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 161.4, 151.8, 151.4, 149.8, 149.0, 131.7, 131.1, 129.8, 127.5, 126.3, 125.4, 121.3, 113.1, 112.6, 40.3 ppm. HRMS *m/z* [M+Na]$^{+}$ Calculated for $C_{22}H_{24}N_4Na$: 367.18932; found 367.1894 (0 ppm), [M+H]$^{+}$ calculated for $C_{22}H_{25}N_4$: 345.20737; found 345.2072 (0 ppm). Crystals suitable for single crystal X-ray diffraction studies were grown by slow diffusion of *n*-hexane into a concentrated solution of **4b** in ethyl acetate at room temperature.

*3-(2,2-bis(4-(Piperidin-1-yl)phenyl)vinyl)pyridazine (**4c**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 50:50, *v*/*v*) as a yellow solid (79 mg, 88%). Mp 176-178°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.83 (dd, 1 H, J = 4.6 Hz, J = 1.5 Hz), 7.27 (d, 2 H, J = 8.9 Hz), 7.17 (s, 1 H), 7.16 (dd, 1 H, J = 8.5 Hz, J = 4.8 Hz), 7.01-6.90 (m, 6 H), 6.80 (dd, 1 H, J = 8.6 Hz, J =1.4 Hz), 3.26-3.21 (m, 8 H), 1.68-1.60 (m, 12 H) ppm.^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 161.2, 153.0, 152.8, 149.3, 149.2, 149.1, 132.9, 131.6, 129.6, 126.4, 125.6, 122.3, 116.5, 115.8, 50.3, 50.2, 26.4, 26.3, 25.1, 25.0 ppm. HRMS *m/z* [M+Na]$^{+}$ Calculated for $C_{28}H_{32}N_4Na$: 447.25192; found 447.2521 (0 ppm), [M+H]$^{+}$ calculated for $C_{28}H_{33}N_4$: 425.26997; found 425.2701 (0 ppm).

*3-(2,2-bis(4-Methoxyphenyl)vinyl)pyridazine (**4d**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 50:50 to 40:60, *v*/*v*) as a cream solid (76 mg, 95%). Mp 147-148°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.88 (dd, 1 H, J = 4.7 Hz, J = 1.2 Hz), 7.35 (d, 2 H, J = 8.8 Hz), 7.24 (s, 1 H), 7.22 (dd, 1 H, J = 8.9 Hz, J = 5.0 Hz), 7.10 (d, 2 H, J = 8.7 Hz), 6.97 (d, 2 H, J = 8.7 Hz), 6.95 (d, 2 H, J = 9.0 Hz), 6.80 (dd, 1 H, J = 8.7 Hz, J =1.4 Hz), 3.84 (s, 3 H), 3.83 (s, 3 H) ppm.^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 161.1, 160.7, 160.6, 149.5, 148.4, 135.5, 132.1, 132.0, 129.9, 126.5, 125.8, 124.2, 115.2, 114.6, 55.6, 55.5 ppm. HRMS *m/z* [M+H]$^{+}$ Calculated for $C_{20}H_{19}N_2O_2$: 319.14410; found 319.1442 (0 ppm), [M+K]$^{+}$ calculated for $C_{20}H_{18}N_2O_2K$: 357.09999; found 357.1000 (0 ppm).

*(E)-N,N-Dimethyl-4-(1-phenyl-2-(pyridazin-3-yl)vinyl)aniline (**4e**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 70:30 to 80:20, *v*/*v*) as a yellow solid (71 mg, 94%). Mp 125-126°C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.81 (d, 1 H, J = 4.0 Hz), 7.38-7.37 (m, 4 H), 7.28 (d, 2 H, J = 8.9 Hz), 7.23-7.20 (m, 2 H), 6.95 (dd, 1 H, J = 8.7 Hz, J = 4.8 Hz), 6.66 (d, 2 H, J = 8.9 Hz), 6.58 (dd, 1 H, J = 8.8 Hz, J = 1.1 Hz), 2.98 (s, 6 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 160.2, 150.6, 148.6, 148.2, 139.6, 129.9, 129.1, 128.9, 128.8, 128.1, 125.8, 124.8, 121.3, 111.7, 40.2 ppm. HRMS *m/z* [M+Na]$^{+}$ Calculated for $C_{20}H_{19}N_3Na$: 324.14712; found 324.1473 (1 ppm). Crystals suitable for single crystal X-ray diffraction studies were grown by slow diffusion of *n*-hexane into a concentrated solution of **4e** in ethyl acetate at room temperature.

*(Z)-3-(2-(4-(Methylthio)phenyl)-2-(m-tolyl)vinyl)pyridazine (**4f**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 60:40, *v*/*v*) as a cream solid (68 mg, 86%). Mp 118-119°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.92 (dd, 1 H, J = 4.9 Hz, J = 1.4 Hz, minor), 8.90 (dd, 1 H, J = 4.9 Hz, J = 1.4 Hz, major), 7.37-6.99 (10 H major and 10 H minor), 6.91 (dd, 1 H, J = 8.7 Hz, J = 1.3 Hz, minor), 6.76 (dd, 1 H, J = 8.7 Hz, J = 1.3 Hz, major), 2.53 (s, 3 H, minor), 2.52 (s, 3 H, major), 2.34 (s, 3 H, minor), 2.31 (s, 3 H, major) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 160.3 (major), 160.2 (minor), 149.9 (minor), 149.8 (major), 148.6 (major), 148.4 (minor), 143.0 (major), 140.6 (minor), 140.3 (major), 139.9 (minor), 139.7 (major), 139.3 (minor), 138.8 (major), 136.4 (minor), 131.3 (major), 131.0 (minor), 130.2 (major), 129.9 (major), 129.8 (minor), 129.2 (minor), 128.9 (major), 127.6 (minor), 127.0 (major), 126.8 (minor), 126.6 (major), 126.5 (minor), 126.3 (major), 126.0 (minor), 125.9 (major), 125.8 (minor), 125.6 (major), 125.0 (minor), 21.4 (minor) 21.3 (major), 15.1 (major), 15.0 (minor) ppm. HRMS *m/z* [M+Na]$^{+}$ Calculated for $C_{20}H_{18}N_2NaS$: 341.10829; found 341.1084 (0 ppm), [M+H]$^{+}$ calculated for $C_{20}H_{19}N_2NaS$: 319.12635; found 319.1260 (1 ppm).

*(E)-3-(2-(4-(Methylthio)phenyl)-2-(p-tolyl)vinyl)pyridazine (**4g**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 70:30 to 60:40, *v*/*v*) as a brown solid (74 mg, 93%). Mp 119-120°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.91 (dd, 1 H, J = 4.8 Hz, J = 1.6 Hz, minor), 8.90 (dd, 1 H, J = 4.8 Hz, J = 1.4 Hz, major), 7.37-7.21 (8 H major and 8 H minor), 7.12 (d, 2 H, J = 8.3 Hz, minor), 7.08 (d, 2 H, J = 8.0 Hz, major), 6.90 (dd, 1 H, J = 8.7 Hz, J = 1.6 Hz, minor), 6.80 (dd, 1 H, J = 8.7 Hz, J = 1.6 Hz, major), 2.53 (s, 3 H, minor), 2.52 (s, 3 H, major), 2.39 (s, 3 H, major), 2.36 (s, 3 H, minor) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 160.3 (major and minor), 149.8 (minor), 149.7 (major), 148.4 (major), 146.4 (minor), 140.6 (major), 140.2 (minor), 140.2 (minor), 139.5 (major), 139.4 (minor), 139.0 (major), 136.9 (major), 136.5 (minor), 131.3 (major), 130.6 (major and minor), 130.0 (minor), 128.9 (major), 128.6 (minor), 127.0 (major), 126.8 (minor), 126.6 (major and minor), 126.0 (minor), 125.8 (major), 125.6 (minor), 125.5 (major), 21.3 (major), 21.1 (minor), 15.1 (major), 15.0 (minor) ppm. HRMS *m/z* [M+Na]$^{+}$ Calculated for $C_{20}H_{18}N_2NaS$: 341.10829; found 341.1084 (0 ppm), [M+H]$^{+}$ calculated for $C_{20}H_{19}N_2S$: 319.12635; found 319.1261 (1 ppm).

*(Z)-3-(2-(4-Methoxyphenyl)-2-(4-(piperidin-1-yl)phenyl)vinyl)pyridazine (**4h**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 60:40, *v*/*v*) as an orange solid (66 mg, 71%). Mp 122-124°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.86 (dd, 1 H, J = 4.9 Hz, J = 1.5 Hz, major), 8.85 (dd, 1 H, J = 4.9 Hz, J = 1.5 Hz, minor), 7.36 (d, 2 H, J = 8.9 Hz, major), 7.27 (d, 2 H, J = 8.9 Hz, minor), 7.23-6.93 (8 H major and 8 H minor), 6.87 (dd,

1 H, J = 8.8 Hz, J = 1.5 Hz, major), 6.75 (dd, 1 H, J = 8.8 Hz, J = 1.5 Hz, minor), 3.85 (s, 3 H, minor), 3.84 (s, 3 H, major), 3.33-3.23 (4 H major and 4 H minor), 1.69-1.61 (6 H major and 6 H minor) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 161.4 (minor), 161.1 (minor), 161.0 (major), 160.7 (major), 153.0 (minor), 152.8 (major), 149.4 (minor), 149.3 (major), 133.3 (major), 132.7 (minor), 132.5 (major), 132.4 (minor), 132.0 (major), 131.6 (minor), 130.1 (major), 129.5 (minor), 129.3 (minor), 126.7 (minor), 126.6 (major), 126.4 (major), 125.7 (major), 123.7 (minor), 122.8 (major), 118.6 (minor), 116.5 (major), 115.8 (minor), 115.2 (minor), 114.6 (major), 55.6 (major), 55.6 (minor), 50.2 (major), 50.1 (minor), 26.4 (major), 26.3 (minor), 25.1 (major), 25.0 (minor) ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{24}H_{25}N_3ONa$: 394.18898; found 394.1895 (1 ppm).

(Z)-4-(1-(6-Methoxynaphthalen-2-yl)-2-(pyridazin-3-yl)vinyl)-N,N-dimethylaniline ***(4i)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 70:30 to 60:40, *v/v*) as a yellow solid (80 mg, 84%). Mp 135-136°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.89 (dd, 1 H, J = 4.8 Hz, J = 1.5 Hz, minor), 8.80 (dd, 1 H, J = 4.8 Hz, J = 1.5 Hz, major), 7.86 (d, 1 H, J = 8.3 Hz, minor), 7.82-7.56 (3 H major and 3 H minor), 7.76 (d, 1 H, J = 8.9 Hz, major), 7.36 (d, 1 H, J = 2.4 Hz, major), 7.32-7.21 (2 H major and 3 H minor), 7.33 (d, 1 H, J = 2.4 Hz, minor), 7.28 (d, 2 H, J = 8.9 Hz, major), 7.17 (dd, 1 H, J = 9.0 Hz, J = 2.6 Hz, major), 7.16 (dd, 1 H, J = 9.0 Hz, J = 2.6 Hz, minor), 7.04 (d, 2 H, J = 8.9 Hz, minor), 6.94 (dd, 1 H, J = 8.8 Hz, J = 1.5 Hz, minor), 6.77 (d, 2 H, J = 8.3 Hz, minor), 6.74 (d, 2 H, J = 8.9 Hz, major), 6.68 (dd, 1 H, J = 8.8 Hz, J = 1.5 Hz, major), 3.95 (s, 3 H, major), 3.94 (s, 3 H, minor), 3.01 (s, 6 H, minor), 2.99 (s, 6 H, major) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 161.1 (major), 160.8 (minor), 159.3 (minor), 159.2 (major), 151.8 (major), 151.5 (minor), 149.6 (minor), 149.5 (major), 149.3 (minor), 149.2 (major), 139.0 (minor), 135.7 (minor), 135.6 (major), 135.3 (major), 131.8 (major), 130.8 (minor), 130.4 (major), 130.0 (minor), 129.6 (major), 129.5 (minor), 129.2 (major), 128.3 (major), 128.2 (minor), 127.6 (minor), 127.1 (major), 126.9 (minor), 126.7 (minor), 126.3 (major), 125.7 (minor), 125.6 (major), 124.9 (minor), 122.5 (major), 120.0 (major), 119.9 (minor), 113.1 (minor), 112.7 (major), 106.7 (major), 106.6 (minor), 58.8 (minor), 55.7 (major), 40.3 (major and minor) ppm. HRMS *m/z* $[M+H]^+$ Calculate d for$C_{25}H_{24}N_3O$: 382.19139; found 382.1912 (0 ppm), $[M+Na]^+$ calculated for $C_{25}H_{23}N_3ONa$: 404.17333; found 404.1728 (1 ppm).

3-(2,2-di-m-Tolylvinyl)pyridazine ***(4j)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 80:20 to 60:40, *v/v*) as a cream solid (69 mg, 96%). Mp 110-111°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.91 (br s, 1 H), 7.36 (s, 1 H), 7.31 (t, 1 H, J = 7.3 Hz), 7.29-7.17 (m, 6 H), 7.02 (s, 1 H), 6.98 (d, 1 H, J = 7.5 Hz), 6.77 (d, 1 H, J = 8.4 Hz), 2.33 (s, 3 H), 2.30 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 160.2, 149.8, 149.2, 142.9, 140.0, 139.6, 138.7, 131.0, 130.1, 129.8 (x 2), 129.1, 129.0, 127.6, 126.6, 126.2, 125.9, 125.8, 21.4, 21.3 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{20}H_{19}N_2$: 287.15427; found 287.1536 (2 ppm), $[M+Na]^+$ calculated for $C_{20}H_{18}N_2Na$ 309.13622; found 309.1360 (1 ppm).

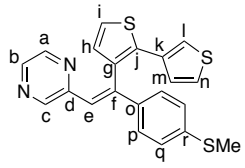
(Z)-3-(2-(m-Tolyl)-2-(o-tolyl)vinyl)pyridazine ***(4k)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 70:30, *v/v*) as a cream solid (62 mg, 86%). Mp 116-117°C. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 8.88 (d, 1 H, J = 3.8 Hz), 7.61 (s, 1 H), 7.34 (td, 1 H, J = 7.5 Hz, J = 1.0 Hz), 7.32-7.27 (m, 2 H), 7.27-7.25 (m, 1 H), 7.22 (d, 1 H, J = 7.4 Hz), 7.17-7.14 (m, 2 H), 7.12 (d, 1 H, J = 7.4 Hz), 7.02 (dd, 1 H, J = 8.6 Hz, J = 4.7 Hz), 2.34 (s, 3 H), 2.05 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 159.4, 148.8, 147.8, 140.5, 138.4, 138.2, 136.2, 130.9, 129.6, 129.4, 128.4 (x 2), 127.4, 126.7, 125.5, 125.4, 125.1, 124.2, 21.5, 19.6 ppm. HRMS *m/z* $[M+H]^+$ Calculaed for $C_{20}H_{19}N_2$: 287.1527; found 287.1537 (2 ppm), $[M+Na]^+$ calculated for $C_{20}H_{18}N_2Na$: 309.13622; found 309.1360 (1 ppm).

(E)-3-(2-(m-Tolyl)-2-(o-tolyl)vinyl)pyridazine ***(4l)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 70:30, *v/v*) as a cream solid (66 mg, 92%). Mp 123-124°C. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 8.94 (br s, 1 H), 7.27 (td, 1 H, J = 7.2 Hz, J = 1.5 Hz), 7.24-7.07 (m, 6 H), 6.98-6.93 (m, 4 H), 2.23 (s, 3 H), 2.15 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 159.8, 149.5, 149.1, 142.6, 139.0, 138.4, 136.1, 130.6, 129.9, 129.8, 129.0, 128.5, 128.0, 127.3, 126.9, 126.7, 125.7, 124.9, 21.3, 20.5 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{20}H_{19}N_2$: 287.15427; found 287.1538 (2 ppm), $[M+Na]^+$ calculated for $C_{20}H_{18}N_2Na$: 309.13622; found 309.1362 (0 ppm).

3-(2,2-di-o-Tolylvinyl)pyridazine ***(4m)***. Purified by silica gel column chromatography (petroleum ether/AcOEt, 70:30, *v/v*) as a cream solid (32 mg, 44%). Mp 121-123°C. ^1H NMR (400.1 MHz, acetone-d_6): δ = 8.93 (dd, 1 H, J = 4.9 Hz, J = 1.6 Hz), 7.30-7.18 (m, 8 H), 7.12-7.10 (m, 1 H), 7.07 (s, 1 H), 6.79 (dd, 1 H, J = 8.6 Hz, J = 1.6 Hz), 2.38 (s, 3 H), 2.04 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 160.0, 150.0, 148.2, 142.8, 140.2, 136.7, 136.5, 132.0, 131.8, 131.0, 130.7, 130.5, 129.1, 128.7, 127.2, 126.6, 126.2, 126.1, 21.0, 20.0 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{20}H_{19}N_2$: 287.15427; found 287.1533 (3 ppm), $[M+Na]^+$ calculated for $C_{20}H_{18}N_2Na$: 309.13622; found 309.1360 (1 ppm).

Synthesis and Characterization of 3oo. Substrate **1h** (0.25 mmol, 0.057 g, 1 eq.), 3-bromothiophene (1.25 mmol, 0.2038 g, 0.12 mL, 5 eq.), K_2CO_3 (1.5 mmol, 0.207 g, 6 eq.), KOAc (0.025 mmol, 0.0025 g, 0.1 eq.), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol, 0.0077 g, 0.05 eq.) and NMP (2 mL) were introduced in a dry Schlenk tube under Argon atmosphere. The reaction mixture was stirred at 150 °C during 12 h. Then, the reaction mixture was cooled down to room temperature and poured into 30 mL of water. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extract was dried with $MgSO_4$. After solvents evaporation, **3oo** was purified by silica gel column chromatography with mixtures of petroleum ether and ethyl acetate containing 1% of triethylamine as the eluent.

*(Z)-2-(2-([2,3'-bithiophen]-3-yl)-2-(4-(methylthio)phenyl) vinyl)pyrazine (**3oo**).*



Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 70:30, *v*/*v*) as an orange solid (87 mg, 89%). Mp 121-122°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ (assignment by COSY) = 8.40 (dd, 1 H, J = 2.4 Hz, J = 1.7 Hz; H_b), 8.23 (d, 1 H, J = 2.4 Hz; H_a), 8.00 (d, 1 H, J = 1.2 Hz; H_c), 7.58 (d, 1 H, J = 5.2 Hz; H_h), 7.46 (d, 2 H, J = 8.6 Hz; H_p), 7.34-7.30 (m, 2 H; H_l and H_n), 7.27 (d, 2 H, J = 8.6 Hz; H_q), 7.22 (s, 1 H; H_e), 7.11 (dd, 1 H, J = 4.9 Hz, J = 1.4 Hz; H_m), 6.92 (d, 1 H, J = 5.2 Hz; H_i), 2.51 (s, 3 H, Me) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ (assignment by HMQC and HMBC) = 152.9 (C_d), 144.8 (C_b), 144.7 (C_c), 142.5 (C_a), 142.2 (C_f), 140.8 (C_r), 137.6 (C_o), 136.5 (C_j), 135.6 (C_g), 134.8 (C_k), 131.2 (C_i), 128.2 (C_p), 127.6 (C_e), 127.5 (C_m), 127.0 (C_n), 126.7 (C_q), 125.9 (C_h), 122.6 (C_l), 15.0 (Me) ppm. HRMS *m/z* $[M+Na]^+$ Calculated for $C_{21}H_{16}N_2S_3Na$: 415.03678; found 415.0371 (1 ppm).

General Procedure for the Ruthenium-Catalyzed double-Arylation and Characterization of Products (5). The corresponding substrate **1** (0.25 mmol, 1 eq.), the corresponding arylbromide (1 mmol, 4 eq.), K_2CO_3 (1.5 mmol, 0.207 g, 6 eq.), KOAc (0.025 mmol, 0.0025 g, 0.1 eq.), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol, 0.0077 g, 0.05 eq.) and NMP (2 mL) were introduced in a dry Schlenk tube under Argon atmosphere. The reaction mixture was stirred at 150 °C during 6 h. Then, the reaction mixture was cooled down to room temperature and poured into 30 mL of water. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extract was dried with $MgSO_4$. After solvents evaporation, the desired product **5** was purified by silica gel column chromatography with mixtures of petroleum ether and ethyl acetate containing 1% of triethylamine as the eluent.

*4,6-bis(2,2-bis(4-(Methylthio)phenyl)vinyl)pyrimidine (**5a**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 70:30, *v*/*v*) as a yellow solid (116 mg, 75%). Mp dec. >250°C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.92 (s, 1 H), 7.16 (s, 8 H), 7.13 (d, 4 H, J = 8.3 Hz), 6.88 (d, 4 H, J = 8.3 Hz), 6.73 (s, 2 H), 6.27 (s, 1 H), 2.47 (s, 6 H), 2.47 (s, 6 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.6, 158.6, 148.6, 139.8, 138.8, 138.6, 135.1, 130.2, 128.4, 126.4, 125.8, 125.6, 119.2, 15.6, 15.4 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{36}H_{33}N_2S_4$: 621.15211; found 621.1521 (0 ppm), $[M+Na]^+$ calculated for $C_{36}H_{32}N_2NaS_4$: 643.13406; found 643.1330 (2 ppm). Crystals suitable for single crystal X-ray diffraction studies were grown by slow diffusion of *n*-hexane into a concentrated solution of **5a** in ethyl acetate at room temperature.

*4,4',4'',4'''-(Pyrimidine-4,6-diylbis(ethene-2,1,1-triyl))tetrakis(N,N-dimethylaniline) (**5b**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 80:20 to 60:40, *v*/*v*) as a yellow solid (105 mg, 69%). Mp dec. >250°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.73 (d, 1 H, J = 1.0 Hz), 7.14 (d, 4 H, J = 8.9 Hz), 6.77 (d, 4 H, J = 8.8 Hz), 6.66-6.70 (m, 8 H), 6.51 (s, 2 H), 6.26 (d, 1 H, J = 0.7 Hz), 2.97 (s, 12 H), 2.95 (s, 12 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 164.0, 159.0, 151.8, 151.3, 150.6, 131.7, 131.3, 129.9, 127.8, 122.7, 119.7, 113.2, 112.5, 40.5, 40.3 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{40}H_{45}N_6$: 609.37002; found 609.3702 (0 ppm).

*4,6-bis(2,2-bis(4-(Piperidin-1-yl)phenyl)vinyl)pyrimidine (**5c**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as an orange solid (117 mg, 61%). Mp dec. >250°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.76 (d, 1 H, J = 1.0 Hz), 7.15 (d, 4 H, J = 8.7 Hz), 6.88 (d, 4 H, J = 8.7 Hz), 6.86 (d, 4 H, J = 8.7 Hz), 6.77 (d, 4 H, J = 8.7 Hz), 6.55 (s, 2 H), 6.09 (d, 1 H, J = 1.0 Hz), 3.17-3.24 (m, 16 H), 3.60-3.65 (m, 24 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 163.8, 159.0, 153.0, 152.6, 150.3, 132.8, 131.6, 129.8, 129.7, 123.5, 120.2, 116.5, 115.7, 50.6, 50.2, 26.3, 25.1 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{52}H_{61}N_6$: 769.49522; found 769.4963 (1 ppm).

*4,6-bis(2,2-bis(4-Methoxyphenyl)vinyl)pyrimidine (**5d**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 70:30, *v*/*v*) as a brown solid (109 mg, 78%). Mp dec. >250°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.81 (d, 1 H, J = 1.0 Hz), 7.22 (d, 4 H, J = 8.9 Hz), 6.88-6.92 (m, 12 H), 6.66 (s, 2 H), 6.22 (d, 2 H, J = 1.0 Hz), 3.82 (s, 12 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 163.7, 161.2, 160.6, 159.2, 149.5, 135.6, 132.7, 131.9, 130.1, 125.2, 120.0, 115.0, 114.6, 55.6 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{36}H_{33}N_2O_4$: 557.24348; found 557.2439 (1 ppm).

*4,6-bis(2,2-di-m-Tolylvinyl)pyrimidine (**5e**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v*/*v*) as a cream solid (103 mg, 84%). Mp dec. >250°C.^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.83 (d, 1 H, J = 1.0 Hz), 7.24-7.13 (m, 10 H), 7.03 (d, 2 H, J = 7.5 Hz), 6.83 (s, 2 H), 6.77 (s, 2 H), 6.76 (d, 2 H, J = 7.5 Hz), 6.29 (br s, 1 H), 2.28 (s, 6 H), 2.26 (s, 6 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 163.5, 159.0, 150.3, 142.9, 139.8, 138.8, 138.6, 131.0, 130.1, 129.5, 129.2, 129.1, 129.0, 127.7, 126.9, 125.9, 120.6, 21.4, 21.3 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{36}H_{33}N_2$: 493.26382; found 493.2631 (2 ppm), $[M+Na]^+$ calculated for $C_{36}H_{32}N_2Na$: 515.24577; found 515.2455 (0 ppm).

General Procedure for the Ruthenium-catalyzed monoarylation/hydrogenation and Characterization of Products (6). The corresponding substrate **1** (0.25 mmol, 1 eq.), the corresponding arylbromide (0.5 mmol, 2 eq.), K_2CO_3 (0.75 mmol, 0.104 g, 3 eq.), KOAc (0.0125 mmol, 0.0012 g, 0.05 eq.), $[RuCl_2(p\text{-cymene})]_2$ (0.00625 mmol, 0.0038 g, 0.025 eq.) and NMP (1 mL) were introduced in a dry Schlenk tube under Argon atmosphere. The reaction mix-

ture was stirred at 150 °C during 3 h. Then, the reaction mixture was cooled down to room temperature and flushed with vacuum/hydrogen over 3-5 cycles. The Schlenk tube was connected to a balloon filled with H_2 (1 bar) and the reaction mixture was stirred at 150 °C during 12 h. Then, the reaction mixture was cooled down to room temperature and poured into 30 mL of water. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extract was dried with $MgSO_4$. After solvents evaporation, the desired product **6** was purified by silica gel column chromatography with mixtures of petroleum ether and ethyl acetate containing 1% of triethylamine as the eluent.

*4-(2-(4-(Methylthio)phenyl)-2-phenylethyl)pyrimidine (**6a**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 80:20, *v*/*v*) as a colourless solid (67 mg, 87%). Mp 119-120°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 9.00 (s, 1 H), 8.49 (d, 1 H, J = 5.0 Hz), 7.33 (d, 2 H, J = 8.0 Hz), 7.29-7.22 (m, 5 H), 7.18-7.12 (m, 3 H), 4.70 (t, 1 H, J = 8.1 Hz), 3.54 (d, 2 H, J = 8.1 Hz), 2.66 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 169.2, 159.3, 157.4, 145.0, 141.9, 137.3, 129.3, 129.2, 128.7, 127.3, 127.1, 122.3, 50.2, 43.7, 15.5 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{19}H_{18}N_2NaS$: 329.10829; found 329.1083 (0 ppm).

*N,N-Dimethyl-4-(1-phenyl-2-(pyrimidin-4-yl)ethyl)aniline (**6b**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a colourless solid (57 mg, 75%). Mp 124-125°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 9.00 (s, 1 H), 8.47 (d, 1 H, J = 4.9 Hz), 7.30 (d, 2 H, J = 7.8 Hz), 7.25-7.21 (m, 3 H), 7.19 (dd, 1 H, J = 5.0 Hz, J = 0.9 Hz), 7.14 (d, 2 H, J = 8.7 Hz), 7.13-7.09 (m, 1 H), 6.63 (d, 2 H, J = 8.7 Hz), 4.58 (t, 1 H, J = 8.1 Hz), 3.49 (d, 2 H, J = 8.1 Hz, J = 2.4 Hz), 2.85 (s, 6 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 169.7, 159.2, 157.2, 150.2, 146.0, 132.5, 129.2, 129.1, 128.6, 126.8, 122.3, 113.4, 50.0, 44.2, 40.6 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{20}H_{21}N_3Na$: 326.16277; found 326.1630 (1 ppm). Crystals suitable for single crystal X-ray diffraction studies were grown by slow diffusion of *n*-hexane into a concentrated solution of **6b** in ethyl acetate at room temperature.

*2-(2-(4-(Methylthio)phenyl)-2-(p-tolyl)ethyl)pyrazine (**6c**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 80:20, *v*/*v*) as a colourless solid (57 mg, 71%). Mp 99-101°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.48 (dd, 1 H, J = 2.4 Hz, J = 1.5 Hz), 8.34 (d, 1 H, J = 1.0 Hz), 8.32 (d, 1 H, J = 2.4 Hz), 7.27 (d, 2 H, J = 8.3 Hz), 7.21 (d, 2 H, J = 7.9 Hz), 7.16 (d, 2 H, J = 8.3 Hz), 7.06 (d, 2 H, J = 7.9 Hz), 4.61 (t, 1 H, J = 8.1 Hz), 3.56 (d, 2 H, J = 8.1 Hz), 2.42 (s, 3 H), 2.23 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 156.6, 146.0, 144.9, 143.1, 142.2, 142.0, 137.1, 136.5, 129.9, 129.3, 128.5, 127.3, 50.5, 41.5, 20.9, 15.5 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{20}H_{20}N_2NaS$: 343.12394; found 343.1239 (0 ppm).

*3-(2-(4-Methoxyphenyl)-2-(4-(piperidin-1-yl)phenyl)ethyl) pyridazine (**6d**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10 to 60:40, *v*/*v*) as an orange solid (49 mg, 52%). Mp 114-115°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.94 (dd, 1 H, J = 4.8 Hz, J = 1.3 Hz), 7.37 (d, 1 H, J = 8.3 Hz, J = 4.8 Hz), 7.30 (d, 1 H, J = 8.3 Hz, J = 1.5 Hz), 7.22 (d, 2 H, J = 8.7 Hz), 7.16 (d, 2 H, J = 8.6 Hz), 6.82 (d, 2 H, J = 8.6 Hz), 6.79 (d, 2 H, J = 8.7 Hz), 4.53 (t, 1 H, J = 8.2 Hz), 3.72 (s, 3 H), 3.65 (d, 2 H, J = 8.2 Hz), 3.07 (t, 4 H, J = 5.3 Hz), 1.66-1.60 (m, 4 H), 1.55-1.51 (m, 2 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 163.1, 159.0, 151.6, 150.3, 137.6, 135.6, 129.6, 129.1, 127.5, 126.6, 117.0, 114.5, 55.4, 51.1, 50.2, 43.0, 26.6, 25.0 ppm. HRMS *m/z* [M+Na]$^+$ Calculated for $C_{24}H_{27}N_3ONa$: 396.20463; found 396.2048 (0 ppm).

Procedure for the Ruthenium-catalyzed double-arylation/hydrogenation and Characterization of 7. Substrate **1u** (0.25 mmol, 0.093 g, 1 eq.), 1-bromo-4-*tert*-butylbenzene (1 mmol, 0.213 g, 0.17 mL, 4 eq.), K_2CO_3 (1.5 mmol, 0.207 g, 6 eq.), KOAc (0.025 mmol, 0.0025 g, 0.1 eq.), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol, 0.0077 g, 0.05 eq.) and NMP (2 mL) were introduced in a dry Schlenk tube under Argon atmosphere. The reaction mixture was stirred at 150 °C during 6 h. Then, the reaction mixture was cooled down to room temperature and flushed with vacuum/hydrogen over 3-5 cycles. The Schlenk tube was connected to a balloon filled with H_2 (1 bar) and the reaction mixture was stirred at 150 °C during 12 h. Then, the reaction mixture was cooled down to room temperature and poured into 30 mL of water. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extract was dried with $MgSO_4$. After solvents evaporation, the desired product **7** was purified by silica gel column chromatography with mixtures of petroleum ether and ethyl acetate containing 1% of triethylamine as the eluent.

*4,4'-(Pyrimidine-4,6-diylbis(1-(4-(tert-butyl)phenyl)ethane-2,1-diyl))bis(N,N-dimethylaniline) (**7**).* Purified by silica gel column chromatography (petroleum ether/AcOEt, 90:10, *v*/*v*) as a yellow solid (107 mg, 67%). Mp dec. >250°C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.91 (br. s, 1 H), 7.26 (d, 4 H, J = 8.1 Hz), 7.10 (d, 4 H, J = 8.1 Hz), 7.03 (dd, 4 H, J = 8.7 Hz, J = 1.1 Hz), 6.68 (s, 1 H), 6.65 (d, 4 H, J = 8.7 Hz), 4.31 (t, 2 H, J = 7.9 Hz), 3.32 (d, 4 H, J = 7.9 Hz), 2.91 (s, 12 H), 1.29 (s, 18 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 168.3, 157.9, 149.0, 148.8, 141.1, 131.8, 128.5, 127.3, 125.2, 121.0, 112.7, 48.9, 43.9, 40.7, 34.3, 31.3 ppm. HRMS *m/z* [M+H]$^+$ Calculated for $C_{44}H_{55}N_4$: 639.44212; found 639.4414 (1 ppm).

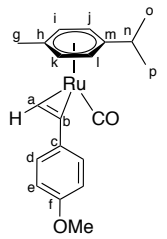
Synthesis and Characterization of 8. To a solution of **2b** (0.22 mmol, 0.076 g, 1 eq.) in dichloromethane (1.8 mL) was added anhydrous $FeCl_3$ (0.77 mmol, 0.124 g, 3.5 eq.) under Argon atmosphere. The reaction solution was stirred at room temperature under Argon atmosphere for 8 h, and then quenched with methanol. Then, the reaction mixture was poured into 30 mL of water. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined

organic extract was dried with $MgSO_4$. After solvents evaporation, product **8** was purified by silica gel column chromatography with mixtures of petroleum ether and ethyl acetate containing 1% of triethylamine as the eluent.

*4,4'-(2-Chloro-2-(pyrimidin-4-yl)ethene-1,1-diyl)bis(N,N-dimethylaniline) (**8**)*. Purified by silica gel column chromatography (petroleum ether/AcOEt, 80:20 to 60:40, *v*/*v*) as an orange solid (38 mg, 45%). Mp 236-237°C. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 9.08 (d, 1 H, J = 1.1 Hz), 8.47 (d, 1 H, J = 5.2 Hz), 7.24 (d, 2 H, J = 8.9 Hz), 7.03 (dd, 1 H, J = 5.2 Hz, J = 1.3 Hz), 6.77 (d, 2 H, J = 8.9 Hz), 6.74 (d, 2 H, J = 8.9 Hz), 6.52 (d, 2 H, J = 8.9 Hz), 3.00 (s, 6 H), 2.91 (s, 6 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 166.7, 159.5, 157.2, 151.4, 151.2, 147.1, 132.7, 132.2, 129.2, 128.9, 123.2, 122.1, 112.2, 111.9, 40.3, 40.1 ppm. HRMS *m/z* $[M+H]^+$ Calculated for $C_{22}H_{24}N_4{}^{35}Cl$: 379.16840; found 379.16800 (1 ppm), $[M+Na]^+$ calculated for $C_{22}H_{23}N_4{}^{35}ClNa$: 401.15034; found 401.1500 (1 ppm). Crystals suitable for single crystal X-ray diffraction studies were grown by slow diffusion of *n*-hexane into a concentrated solution of **8** in ethyl acetate at room temperature.

Synthesis and Identification of Ru-1. Substrate **1e** (0.25 mmol, 0.053 g, 1 eq.), $[RuCl_2(p\text{-cymene})]_2$ (0.125 mmol, 0.077 g, 0.5 eq.), KOAc (1 mmol, 0.098 g, 4 eq.), LiCl (2.5 mmol, 0.106 g, 10 eq.), and MeOH (5 mL) were introduced under argon atmosphere in a dry Schlenk tube and stirred at room temperature. After 2 h, a NMR spectrum was recorded indicating the presence of substrate **1e**, ruthenium-coordinated substrate (**Ru-1e**) and traces of ruthenacycles (see Fig. S36). The reaction was stirred at room temperature for 3 weeks. Then, the solvents were removed under vacuum and dichloromethane (3 x 10 mL) was added to reaction mixture followed by filtration over celite. After solvents evaporation under vacuum and heptane washing, the crude mixture was analysed by ^{1}H NMR spectroscopy (see Fig. S36) indicating the disappearance of the starting material (i.e. no singlet at 9.13 ppm and no doublet at 8.63 ppm) and some peaks belonging to chloride- and acetate-containing ruthenacycle complexes (see Fig. S37).[27] HRMS *m/z* $[M+H]^+$ Calculated for $C_{23}H_{26}N_2O^{35}Cl^{102}Ru$: 483.07716; found 483.0773 (0 ppm), $[M+Na]^+$ calculated for $C_{23}H_{25}N_2O^{35}Cl^{102}RuNa$: 505.05911; found 505.0591 (0 ppm), $[M+K]^+$ calculated for $C_{23}H_{25}N_2O^{35}Cl^{102}RuK$: 521.03305; found 521.0329 (0 ppm), $[M-Cl]^+$ calculated for $C_{23}H_{25}N_2O^{102}Ru$: 447.10049; found 447.1004 (0 ppm).

Synthesis and Characterization of Ru-2. Substrate **1e** (0.25 mmol, 0.053 g, 1 eq.), $[RuCl_2(p\text{-cymene})]_2$ (0.125 mmol, 0.077 g, 0.5 eq.), KOAc (1 mmol, 0.098 g, 4 eq.), LiCl (2.5 mmol, 0.106 g, 10 eq.), and MeOH (5 mL) were introduced under argon atmosphere in a dry Schlenk tube and stirred for 12 h at 60 °C. Then, solvents were removed under vacuum and the crude reaction mixture was purified by silica gel column chromatography with 1% of triethylamine (petroleum ether/AcOEt, 30:70 to 20:80, *v*/*v*) affording **Ru-2** as an orange solid (41 mg, 39%).



^{1}H NMR (400.1 MHz, $CDCl_3$): δ (assignment by COSY, HMQC and HMBC) = 7.54 (d, 2 H, J = 8.7 Hz; H_d), 6.91 (d, 2 H, J = 8.7 Hz; H_e), 6.70 (s, 1 H; H_a), 5.58 (d, 1 H, J = 5.8 Hz; H_l), 5.20 (d, 1 H, J = 5.6 Hz; H_j), 5.15 (d, 1 H, J = 5.8 Hz; H_k), 4.66 (d, 1 H, J = 5.6 Hz; H_i), 3.87 (s, 3 H; OMe), 2.36 (sept, 1 H, J = 6.9 Hz; H_n), 2.12 (s, 3 H; H_g) 0.96 (d, 3 H, J = 6.9 Hz; H_o), 0.93 (d, 3 H, J = 6.9 Hz; H_p) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (assignment by COSY, HSQC and HMQC) = 18.7 (C_g), 22.0 (C_o), 22.2 (C_p), 30.8 (C_n), 55.3 (OMe), 82.8 (C_i), 85.3 (C_k), 88.5 (C_j), 92.8 (C_l), 102.8 (C_m), 103.5 (C_h), 113.2 (C_e), 125.7 (C_a), 127.7 (C_d), 145.1 (C_c), 159.5 (C_f), 172.1 (C_b), 222.8 (CO) ppm. Due to the lack of stability of the complex, HRMS and elemental analysis were not successful. Although DOSY is not the ideal technique to determine exactly the volume of small species, it is enough accurate to qualitatively differentiate between monomers and higher aggregates (dimers, trimmers, etc.).[33] For **Ru-2**, an experimental diffusion value of D ($CDCl_3$) = $1.43\text{x}10^{-9}$ m^2s^{-1} was found, which corresponds to r_h = 2.8 Å applying the Stokes-Einstein equation at 298 K with a viscosity for $CHCl_3$ of $5.42\text{x}10^{-4}$ $Nm^{-2}s$. Molecular modelling (PM3-minimized) indicates that a monomeric structure such as **Ru-2** has a radius of *ca.* 5.5 Å. This data enables to qualitatively discard the presence of dimers or higher aggregates.

■ ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI.

Determination of isomeric ratio of products, mechanistic investigations, NMR spectral data and cartesian coordiantes (PDF)

Single-crystal X-ray diffraction data for **2a** (CIF)

Single-crystal X-ray diffraction data for **3b** (CIF)

Single-crystal X-ray diffraction data for **3e** (CIF)

Single-crystal X-ray diffraction data for **4b** (CIF)

Single-crystal X-ray diffraction data for **4e** (CIF)

Single-crystal X-ray diffraction data for **5a** (CIF)

Single-crystal X-ray diffraction data for **6b** (CIF)

Single-crystal X-ray diffraction data for **8** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*rafael.gramage-doria@univ-rennes1.fr

Notes

The authors declare no competing financial interest.

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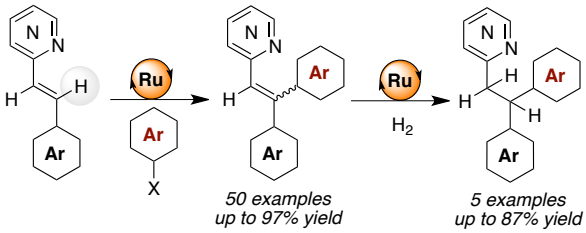
TOC



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