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Structure-dependent regioselectivity of a roll-over cyclopalladation occuring at 2,2′-bipyridine-type ligands

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ABSTRACT

In this work, different bipyridine-analogue ligands bearing a dimethylamino group in the *meta*-position of one of the heterocyclic rings were synthesized and reacted with palladium(II) acetate under identical conditions. Cyclometallated palladium(II) complexes with *C,N*- or *C,N,N*'-coordinating chelate ligands are formed which were characterized by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, and single crystal X-ray diffraction analysis. In the case of the mononuclear, *C,N,N*'-coordinated complex, which is formed by an attack of the palladium(II) site at of the N-methyl groups, the primarily coordinating acetato ligand is exchanged against a chlorido ligand, which is liberated from the solvent dichloromethane by a nucleophilic substitution reaction. In contrast, cyclometallation occurring at one of the six-membered heterocycles leads to dinuclear acetato-bridged palladium(II) complexes.

1. Introduction

In 1973 Trofimenko defined a cyclometallation reaction as a chemical transformation leading to a (small) ring system that contains a metal site and a carbon atom directly bound to each other [1]. However, cyclometallation reactions have been known much longer. Bähr and Müller for example described a first cyclometallated aluminum compound in 1955 [2]. In this early synthesis, the M–C bond was formed by activation of a C–X bond (X = halogen). However, the activation of a C-H bond is also possible and in particular this strategy has led to a multitude of cyclometallated systems during the last decades [3–5].

The situation may become complicated in case there is more than one position in a ligand molecule where a cyclometallation can occur. While the activation of aromatic units is usually considered to be easier achievable than the activation of aliphatic groups [6], there are electronic as well as steric effects leading to some modifications of this general rule. Friedrich and Cope for example established that five-membered metallacyclones usually exhibit particularly high stabilities [7].

Some time ago, we started to investigate a special type of cyclometallation reactions in more detail, the so-called roll-over cyclometallation. Herein, a chelating ligand such as 2,2′-bipyridine plays the central role, which kinetically will provide access to a *N,N*'-chelate complex. However, thermodynamically a cyclometallated species may be favored. To achieve this with our example, one of the M-N bonds of 2,2′-bipyridine has to be broken and a rotation around the C-C bond between the two pyridyl rings has to occur, allowing the metal to attack at the *ortho*-C-H unit of the ligand. This often enables a direct comparison of the properties of classical chelate complexes with those of their cyclometallated congeners. During the last years, we were able to show that roll-over cyclometallation may provide profound benefits for homogeneous catalysis [8]. A common feature of the ligand systems we used for these studies is the presence of a 2-aminopyrimidin-4-yl ring, that undergoes a type of roll-over cyclometallation reaction which is mechanistically closely related to an electrophilic aromatic substitution reaction. A series of studies that combined deuterium-labeling experiments with ESI-MS studies in combination with DFT calculations supported this mechanism [9].

In case there are different sites in one ligand where a cyclometallation can occur, it is important to be able to predict the regioselectivity of the attack. This is in particular true for the application of cyclometallated transition metal complexes in catalysis. We here report on the regioselectivity of cyclopalladation reactions occurring at a series of structurally closely related *N*-donor ligands.

2. Results and discussion

A common feature of the ligands **1–3** (Scheme 1) we applied in this study is a six-membered nitrogen containing heterocycle bearing a dimethylamino group next to the nitrogen atom. This

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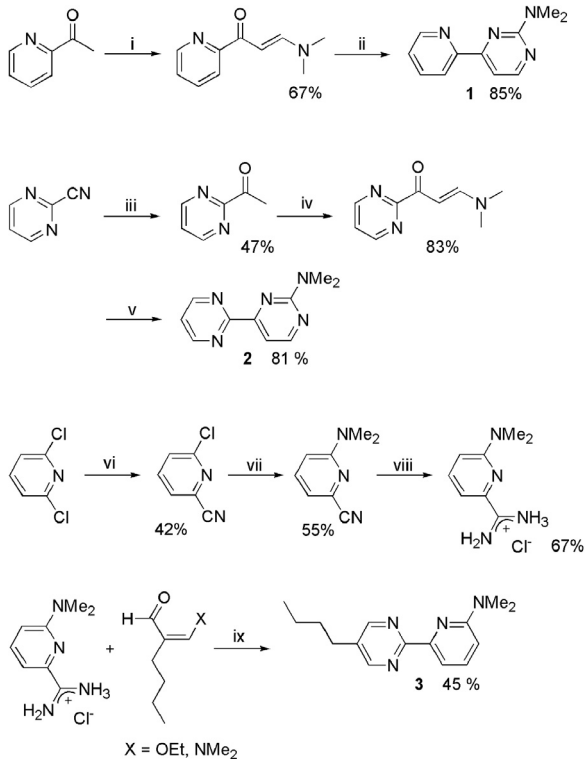
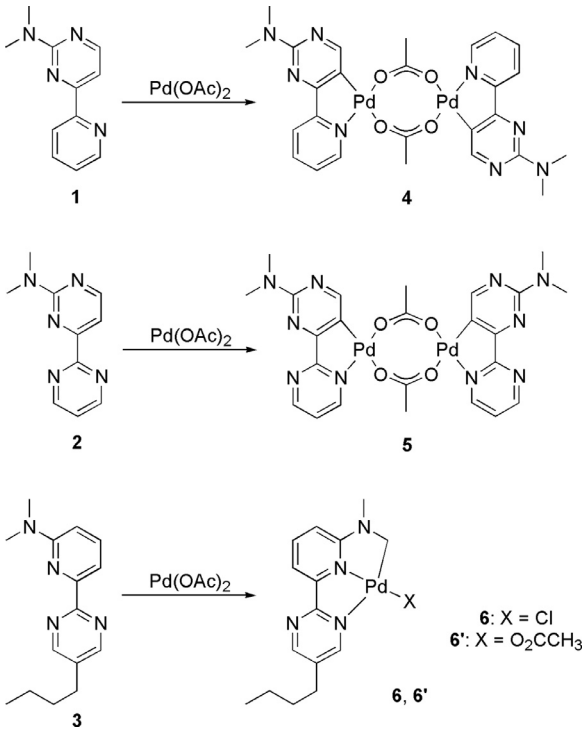


Scheme 1. Synthesis routes leading to ligands **1–3**. i) and iv) $HC(NMe_2)(OMe)_2$, 6 h, reflux; ii) and v) $[(Me_2N)C(NH_2)_2]_2(SO_4)$, EtOH, reflux, 24 h; iii) MeMgBr in Et_2O, THF, 18 h, 0 °C; vi) CuCN, DMF, 18 h, 150 °C; vii) DMF, 72 h, 160 °C; viii) NaOMe then NH_4Cl, MeOH, 3 h, reflux then EtOH, 1 h, reflux; ix) NaOMe, toluene, 18 h, reflux.

fragment is combined with either a second pyrimidine or a pyridine ring. Using a simple primary amino (NH_2) instead of a tertiary dimethylamino group (NMe_2) leads to stable *N,N*-coordinated systems, which do not undergo roll-over cyclometallation at all. From our mechanistic studies it is clear, that the dimethylamino substituent is beneficial for a roll-over cyclometallation in different ways: 1) it is sterically more demanding than a primary amino group, which weakens the N-M bond at the *N,N*'-coordinated intermediate, 2) it is not able to undergo any intramolecular hydrogen bonding e.g. to a halogenido ligand coordinated at the metal site which would strongly stabilize the *N,N*'-coordinated species, and 3) it is a substituent with a strong +M effect (stronger than the +M effect of a NH_2 group), which allows the cyclometallation to occur as a S_NAr reaction. Scheme 1 summarizes all information about the ligand synthesis.

Ligands **1** and **2** are synthesized following the same strategy: The dimethylaminopyrimidine ring is closed by a cyclisation reaction between an appropriate 3-aminoprop-2-en-1-one and dimethylaminoamidinium sulfate [8f,10]. 1-(2-Pyridinyl)- respectively 1-(2-pyrimidinyl)-3-aminoprop-2-en-1-one are obtained from the corresponding acetyl derivatives by treatment with dimethylformamide dimethylacetale in high yields [8f,10,8b]. While 2-acetyl pyridine is commercially available, the pyrimidine derivative was synthesized by reacting 2-cyanopyrimidine with methylmagnesium bromide [8b]. The access to ligand **3** is different, since it bears a 2-dimethylaminopyridin-6-yl instead of a 2-dimethylaminopyrimidin-6-yl ring. An appropriate starting material is not commercially available. We therefore decided not to construct the 2-dimethylaminopyridin-6-yl ring but the pyrimidin-2-yl ring. The primary intention to introduce the butyl group in the 4-position of the pyrimidin-2-yl ring was to enhance the solubility of the derived transition metal complexes in organic solvents. To achieve ligand **3** from simple starting materials, 2,6-dichloropyridine was converted into 2-chloro-6-cyanopyridine, which gave 2-dimethylamino-6-cyanopyridine after treatment with DMF at elevated temperatures [11,12]. 1-(6-(Dimethylamino)pyridin-2-yl)amidinium chloride is obtained by treating 6-dimethylamino-2-cyanopyridine with sodium methanolate and ammonium chloride [13]. The final closure of the pyrimidine entity was done by treating the guanidinium intermediate with a mixture of appropriate prop-1-enals which was generated by reacting 1,1-diethoxyhexane [14] with phosphoroxytrichloride in dimethylformamide [15]. All ligands and intermediates were fully characterized by NMR and infrared spectroscopy (see the Supporting Information) and by elemental analysis.



Scheme 2. Synthesis of the palladium complexes **4–6**.

To get a deeper insight in the regioselectivity of the roll-over cyclometallation reactions occurring with ligands **1–3**, they were treated with palladium(II) acetate under identical conditions in refluxing dichloromethane. The results are summarized in Scheme 2.

While ligands **1** and **2** are undergoing roll-over cyclometallation at the dimethylamino functionalized heterocycle, one of the methyl groups of the dimethyl amino substituent is activated with ligand **3**. This leads to a trident *C,N,N*'-coordination mode in the derived palladium(II) complex **6** (for a detailed structural discussion see below) while *C,N*-coordination is observed in compounds **4** (from ligand **1**) and **5** (from ligand **2**) leading to acetato-bridged dinuclear palladium(II) complexes. At a first glance, it seems strange that instead of the expected acetato complex **6'**, the chlorido complex **6** is obtained. The chlorido ligand probably origins from the solvent, which undergoes nucleophilic substitution by acetate. The trident *C,N,N*'-coordination mode is proved by ^1H and ^{13}C NMR spectroscopy and elemental analysis as well as an X-ray structure analysis on compound **6'** which is present in the raw product in traces and could be isolated in crystalline form (see below).

The most striking difference between the ^1H NMR spectra of ligands **1** and **2** and their palladium(II) complexes **4** and **5** is that the resonance of H5 (for the numbering see the Supporting Information) at the aminopyrimidinyl ring is no longer present in the spectra of these complexes. By metalation of this ring, the

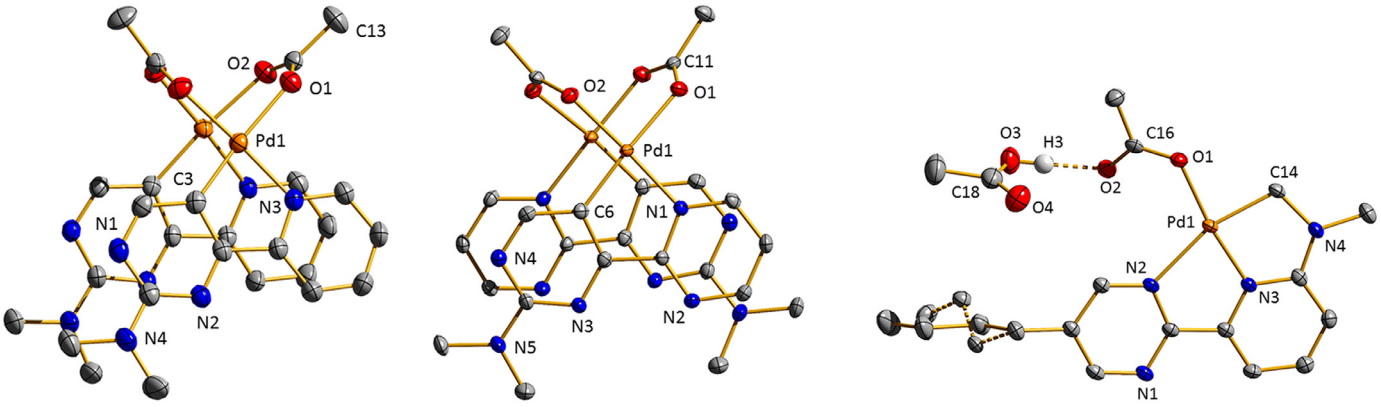


Fig. 1. Molecular structures of compounds **4** (left), **5** (middle) and **6′** (right) in the solid state. Hydrogen atoms are omitted for clarity. The ellipsoids are at the 50% level.

Table 1
Characteristic bond lengths [Å] and angles [°] of the palladium(II) complexes **4, 5** and **6′**.

	Bond lengths			
4	Pd1-C3 1.965(2)	Pd1-N3 2.016(2)	Pd1-O2 2.128(2)	Pd1-O1A 2.052(2)
5	Pd1-C6 1.951(3)	Pd1-N1 2.016(2)	Pd1-O1 2.140(2)	Pd1-O2 2.048(2)
6	Pd1-C14 1.995(2)	Pd1-N3 1.943(2)	Pd1-N2 2.190(2)	Pd1-O1 2.050(1)
	Bond angles			
4	C3-Pd1-N3 81.50(9)	C3-Pd1-O2 95.04(8)	N3-Pd1-O1 93.65(7)	O1-Pd1-O2 89.70(7)
	C3-Pd1-O1 174.39(8)	N3-Pd1-O2 176.01(8)		
5	C6-Pd1-N1 81.1(1)	C6-Pd1-O2 95.3(1)	N1-Pd1-O1 94.9(1)	O1-Pd1-O2 89.5(1)
	C6-Pd1-O1 171.0(1)	O2-Pd1-N1 173.3(1)		
6	C14-Pd1-N3 82.36(7)	C14-Pd1-O1 90.27(6)	N2-Pd1-O1 108.87(6)	N2-Pd1-N3 78.60(6)
	C14-Pd1-N2 160.81(7)	N3-Pd1-O1 171.98(6)		

two doublets at about 8.5 (H6) and 7.4 ppm (H5) have disappeared and one singlet is observed at about 8.1 ppm (H6). The resonances of H8 (in **4**) respectively H7 (in **5**) are shifted to higher field due to the carbanionic nature of metallated carbon next to their position. The resonance of the formerly magnetically equivalent protons next to the nitrogen atoms of the pyrimidin-2-yl ring (9.00 ppm) in palladium complex **5** splits into two doublets of doublets at 8.74 and 8.29 ppm. At this point it has to be mentioned, that according to the X-ray structures of compounds **4** and **5** (see below) two different orientations of the C,N donors are possible in the dimeric, acetato-bridged arrangements leading either to a C_2 symmetric or a C_S symmetric structure. In both cases, no trace of a second isomer could be detected in the NMR spectra, which suggests that the observed structures are the energetic minima. There is one case in the literature where a C_2 symmetric and a C_S symmetric structure are present in the reaction mixture of a cyclometallation: Zucca *et al.* reported this for the unsymmetrical precursor 6-methoxy-2,2′-bipyridine [16].

In contrast, the number of aromatic protons does not change for complex **6**. As in compound **5**, the two protons of the pyrimidine ring are no longer chemically equivalent due to the coordination of one of the pyrimidine nitrogen atoms to the palladium(II) center. The resonances of the pyrimidine protons appear at 8.72 and 8.70 ppm (AB spin system), which is close to the value being measured for these protons in ligand **3**. This is different to complex **5**, where the proton next to the nitrogen atom that coordinates to the palladium site is shifted strongly to lower field compared to the other one (see above). The absence of this effect indicates one rather weak Pd–N bond in compound **6**. This is due to the steric consequences of the strong Pd–C bond in the trans-position, which is formed with one of the methyl groups of the former dimethylamino moiety. In the ^{1}H NMR spectrum the new situation at this site of the ligand is clearly reflected: The resonance of the methylene group is observed at 4.46 and the resonance of the methyl group at 2.97 ppm, which demonstrates the withdrawing of electron density by the palladium(II) center. The same effect is observed in the ^{13}C NMR spectrum of compound **6** (N-CH_2-Pd: 50.8, N-CH_3: 36.6 ppm).

While the complexes **4** and **5** crystallized without any problems, crystallization of complex **6** led to microcrystalline powders in most attempts. Compound **4** was achieved crystalline by layering a chloroform solution with *n*-hexane, while single crystals of compound **5** were obtained by slow diffusion of diethyl ether into a dichloromethane solution. A few crystals from a crystallization experiment with compound **6** were of sufficient quality for single crystal X-ray diffraction. The solution and refinement process however derived the expected *C,N,N′*coordination but the forth coordination site was occupied by a η^1-coordinating acetato instead of a chlorido ligand. We believe that the acetato complex **6′** is the primary product of the cyclometallation reaction, whereby one equivalent of acetic acid is liberated. Most of this compound, which is not accessible in larger amounts, is in the following converted into the chlorido complex **6**, by chloride that is liberated from the solvent dichloromethane via a nucleophilic substitution reaction as discussed above. Nevertheless, the molecular structure found for **6′** is fully consistent with the ^{1}H and ^{13}C NMR data of **6**. Compound **6′** crystallizes with one additional molecule of acetic acid, which undergoes hydrogen bonding to the free oxygen atom of the acetato ligand. The solid-state structures **4, 5** and **6′** are presented in Fig. 1. Table 1 summarizes the relevant bond parameters.

The most striking difference between the molecular structures of complexes **4** and **5** is the relative orientation of the *C,N*-donor ligands. While complex **4** occupies a C_2 symmetrical geometry, complex **5** is C_S symmetric. At a first glance, C_2 symmetry should be preferred with respect to some steric repulsion of the dimethylamino groups. Additionally, the C_2 symmetric arrangement should be preferred since it allows for π-stacking of more and less electron-rich π-systems. It therefore might be that

the electronic difference between the pyridine rings and the cyclometallated aminopyrimidine rings in compound **5** is small and that attractive interactions of the dimethylamino methyl groups are stabilizing the C_S symmetric arrangement. Aside these differences, the bond parameters of complexes **4** and **5** are rather similar and found in the range of related structures, which have been reported in the literature [17]. Labinger *et al.* have for example studied in detail the electronic structures of acetato-bridged dimeric palladium(II) complexes bearing cyclometallated 2-phenylpyridine ligands in combination with acetate and trifluoro acetate [18]. As expected, the largely covalent Pd–C bonds are shorter than the Pd–N bonds. The Pd–O bonds in *trans*-position to the Pd–C bonds are by about 0.1 Å shorter than those in the *trans*-position to the Pd–N bonds indicating a stronger *trans*-influence of the carbanion compared to the nitrogen donor site. Due to the tridentate *C*,*N*,*N*'-coordination mode of the chelating ligand, the bond parameters of complex **6′** are different. The strong Pd–C bond in combination with the steric strain of the two five-membered rings that are annulated to one pyridine ring leads to a pronounced elongation of the Pd–N bond in the *trans*-position to the Pd–C bond (see NMR discussion), which is by almost 0.2 Å longer than the Pd–N bonds in complexes **4** and **5**. The Pd–N bond in *trans*-position to the acetato ligand is in contrast shorter than the Pd–N bonds in complexes **4** and **5**, which can be explained by the weak *trans*-influence of the acetato ligand and again with the steric strain of the two five-membered rings. The Pd–C bond in complex **6′** is slightly longer than in complexes **4** and **5**, which can be explained by the different hybridizations of the involved carbanionic carbon atoms. In the literature, there is a series of structurally characterized C,N,N' coordinated palladium(II) complexes with bond parameters similar to those of compound **6′** [19].

At the end arises the question on the stereoelectronic reasons that are responsible for the different regioselectivities of the roll-over cyclometallation. A few years ago, Cinellu *et al.* published the roll-over cyclometallation of 6,6′-dimethoxy-2,2′-bipyridine with palladium(II) acetate and found, depending on the reaction conditions, cyclometallation at one of the heterocycles (like in compounds **4** and **5**) as well as at the methoxy group, which is comparable to the process leading to **6′** [16]. The corresponding platinum(II) complexes were also obtained. Here the regioselectivity of the roll-over cyclometallation depends on the reaction conditions and on the applied palladium(II) precursors.

At this point it is helpful to remember the mechanism that explains the roll-over cyclometallation of an aromatic ring system as it occurs with complexes **4** and **5**. This reaction can be considered as an electrophilic aromatic substitution with the metal cation acting as the electrophile and one of its ligands acting as a base that takes the proton that is substituted during the cyclometallation. In the course of the roll-over cyclometallation it is known that the chelating ligand coordinates first with its two nitrogen atoms. To allow the metal site to attack the carbon atom, one of the M–N bonds has to be broken. Therefore, the strength of this bond is critical. The σ-donor ability of the nitrogen donor is lowered by σ-accepting fragments such as additional nitrogen atoms that are located in the heterocycle or directly bound to it. In addition, the dimethylamino group next to the donating nitrogen atom weakens the M-N bond by steric repulsion with the ligand in the *cis*-position at the metal site. This explains why the 2-dimethyaminopyrimidin-4-yl ring is undergoing cyclometallation so easily. However, the dimethyamino group is also a strong π-donor, which is favorable in the sense of an electrophilic aromatic substitution, since it stabilizes the intermediate where the metal site is σ-bound to the ring. Astonishingly, the second ring, that does not undergo cyclometallation, also has an influence on the cyclometallation of the first ring. Ligand **1** e.g. reacts spontaneously with $[Cp^*IrCl_2]_2$ to give the cyclometallated product, while ligand **2** requires elevated temperatures and the presence of a base [8b,9d]. The Lewis-acidic metal cation requires the deliverance of a certain amount of electron density from the chelating ligand. In case of the weaker donating pyrimidin-2-yl ring in ligand **2** (poorer compared to the pyridine-2-yl ring in ligand **1**) the M-N bond to the 2-dimethylaminopyrimidin-4-yl ring therefore has to become stronger, which hinders the cyclometallation of this ring. The understanding of these subtle effects allows to explain the reactivity of ligand **3**: Here the pyrimidin-2-yl ring is a weaker donor, which strengthens the Pd–N bond to the 6-dimethyaminopyridin-2-yl ring in a way that the cyclometallation of the pyridine ring is impossible. However, there are basic acetato ligands not only at the palladium(II) site, but also in close proximity to the *N*-methyl groups, which are already activated for deprotonation by the electronegative nitrogen atom. The role of the acetato groups is crucial! We never observed any cyclopalladation with palladium dichloride. In the case of compound **6**, we therefore believe that the cyclometallation occurs first followed by a slower substitution reaction at the solvent dichloromethane that delivers the chlorido ligand for the formation of **6** from the acetato intermediate **6′**.

3. Conclusion

Three different bipyridine-analogue ligands bearing dimethylamino units and their cyclometallated palladium(II) complexes were synthesized and structurally as well as spectroscopically characterized. Despite of closely related ligand structures, the cyclopalladation reaction occurs either at the heteroaromatic fragment or at the dimethylamino moiety. The regioselectivity of the product formation depends on subtle effects, in particular on the Pd–N bond strengths of the intermediately formed *N*,*N*'-adducts. A profound knowledge of these effects in the future will allow for a prediction of cyclometallation reactivity, which is of importance, e.g. for the design of a series of catalysts.

4. Experimental section

4.1. General remarks

All reactions were carried out under an atmosphere of dinitrogen. The solvents were dried and degassed before use according to standard techniques. Other reagents were obtained from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on BRUKER Spectrospin Avance 400 and 600 spectrometers at room temperature (unless otherwise denoted). The chemical shifts are referenced to internal solvent resonances and the assignment of the resonances refers to the numbering schemes provided Scheme 3 and in the Supporting Information to this manuscript. Infrared spectra were recorded on a Perkin Elmer FT-ATR-IR spectrometer Spectrum 100 equipped with a diamond coated ZnSe window. Elemental analyses (C,H,N) were carried out with a vario MICRO cube elemental analyzer at the Analytical Laboratory of the Fachbereich Chemie. All commercially available starting materials were purchased from Sigma Aldrich and used without any further purification. Toluene and dichloromethane were dried in a MB-SPS solvent dryer. Tetrahydrofurane was dried over potassium/benzophenone, acetonitrile was dried over CaH_2. 2-(2-Dimethylaminopyrimidin-4-yl)pyridine (**1**) and 2-(2-dimethylaminopyrimidin-4-yl)pyrimidine (**2**) were synthesized according to published procedures [8b,f].

4.2. 6-Chloro-2-picolylnitrile

50.0 g of 2,6-dichloropyridine (338 mmol) and 15.3 g of copper(I) cyanide (169 mmol) were added to 100 mL of dry DMF. The

mixture was heated to 160 °C for 18 h. After cooling to room temperature, the resulting suspension was poured onto 400 mL of a saturated aqueous solution of Na_2CO_3 and extracted three times with 300 mL of ethyl acetate. The combined organic phases were dried over $MgSO_4$. After filtration of the drying agent, the solvent was removed under reduced pressure and the raw product was purified by column chromatography (ethyl acetate/*n*-hexane 1:4 v/v). Yield: 9.84 g (42%) of a colorless solid. Elemental analysis calcd. for $C_6H_3ClN_2$ (138.55): C 52.01, H 2.18, N 20.22; found: C 52.01, H 2.25, N 20.30%.^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (dd, $^3J_{HH}$ = 8.6, $^3J_{HH}$ = 7.1 Hz, H3, 1H), 7.65 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.9 Hz, H4, 1H), 7.58 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 0.9 Hz, H2, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 152.9 (C5), 139.8 (C3), 133.6 (C1), 128.6 (C4), 127.3 (C2), 116.0 (CN). IR (ATR, cm^{-1}): $\nu\tilde{}$3081 w, 3059 w, 2240 w ($\nu_{C\equiv N}$), 1570 m, 1553 m, 1430 m, 1143 m, 985 m, 805 s, 678 m.

4.3. 6-(Dimethylamino)-2-picolylnitrile

5.00 g (36.1 mmol) of 6-chloro-2-picolylnitrile were dissolved in 20 mL of DMF and heated to 160 °C for 48 h. After cooling to room temperature, the solvent was removed under vacuum and the resulting solid was in a first step purified by column chromatography (ethyl acetate/*n*-hexane 1:5 v/v). Final purification was carried out by subliming off residuals of 6-chloro-2-picolylnitrile. Yield: 2.94 g (55 %) of a colorless solid. Elemental analysis calcd. for $C_8H_9N_3$ (147.18): C 65.29, H 6.16, N 28.55; found: C 65.07, H 6.19, N 28.51%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (dd, $^3J_{HH}$ = 8.8, $^3J_{HH}$ = 7.2 Hz, H3, 1H), 6.86 (d, $^3J_{HH}$ = 7.2 Hz, H4, 1H), 6.66 (d, $^3J_{HH}$ = 8.8 Hz, H2, 1H), 3.06 (s, 6H, NMe_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 159.0 (C5), 137.3 (C3), 131.5 (C1), 118.3 (CN), 116.2 (C4), 109.8 (C2), 37.8 (NMe_2). IR (ATR, cm^{-1}): $\nu\tilde{}$ = 2915 w, 2230 m, 1739 m, 1599 s, 1550 m, 1380 s, 1186 s, 784 s.

4.4. 6-(Dimethylamino)pyridin-2-yl)amidinium chloride

89.2 mg (3.9 mmol) of sodium were dissolved in 15 mL of methanol. 2.94 g (19.4 mmol) of 6-(dimethylamino)-2-picolylnitrile were added and the mixture was stirred for 18 h at room temperature. Then 1.25 (23.3 mmol) of ammonium chloride were added and the resulting solution was stirred under reflux for 3 h. After cooling to room temperature the solvent was stripped off under reduced pressure, the remaining solid was treated with 20 mL of ethanol and heated to reflux for another hour. After filtration of the hot solution, the solvent was removed under vacuum and the resulting rw product was recrystallized from a 1:1 mixture of *n*-hexane and isopropanol. Yield: 2.61 g (67%) of a colorless solid. Elemental analysis calcd. for $C_8H_{13}ClN_4\bullet(NH_4Cl)_{0.4}$ (200.67): C 43.27, H 6.63, N 27.75; found C 43.11, H 6.75, N 27.90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.31 (br. s, NH_2, 4H), 7.75 (dd, $^3J_{H,H}$ = 8.7 Hz, 7.3 Hz, 1H, H3), 7.51 (d, $^3J_{H,H}$ = 7.3 Hz, H2, 1H), 7.00 (d, $^3J_{H,H}$ = 8.5 Hz, H4, 1H), 3.10 (s, 6H, NMe_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 162.5 (C6), 158.2 (C5), 141.4 (C1), 138.5 (C3), 111.4 (C4), 110.4 (C2), 37.7 (C7). IR (ATR, cm^{-1}): $\nu\tilde{}$3360 m, 3053 s, 1686 m, 1599 s, 1513 s, 1383 m, 1190 m, 799 m, 740 m.

4.5. 2-Butyl-1-ethoxyprop-1-enal and 2-Butyl-1-dimethylamino-prop-1-enal [15]

12.9 mL (21.3 g, 139.0 mmol) of phosphoroxytrichloride were cooled to 0 °C. 14.2 mL (13.4 g, 183.0 mmol) of dimethylformamide were added dropwise over a period of 30 min. 11.0 g (63.3 mmol) of 1,1-diethoxyhexane were added drop-wise over a period of 30 min at 0 °C. The mixture was stirred for another 20 min at 0 °C. It was heated to 75 °C for 2 h and then poured onto 150 g of crushed ice. By addition of K_2CO_3 the mixture was brought to pH = 9. The aqueous phase was extracted four times with 4 × 30 mL of dichloromethane and 4 × 30 mL of diethyl ether. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under vacuum. According to the ^{1}H NMR spectrum a 2:3 mixture of 2-butyl-1-ethoxyprop-1-enal and 2-butyl-1-dimethylamino-prop-1-enal was obtained, which was nor further purified. The two components were not separated because they react in the same way in the next step. Yield: 95% of a brown oil. ^{1}H NMR ($CDCl_3$, 600 MHz) of the minor ethoxy derivative: δ 9.18 (s, 1H, H1), 6.92 (s, 1H, H3), 4.14 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H8), 2.20 (t, $^3J_{HH}$ = 7.7 Hz, 3H, H9), 1.34 (m, 6H, H4, H5, H6), 0.88 (t, $^3J_{HH}$ = 7.2 Hz, 3H, H7). ^{1}H NMR ($CDCl_3$, 600 MHz) of the major dimethylamino derivative: δ 8.72 (s, 1H, H1), 6.46 (s, 1H, H3), 3.09 (s, 6H, H8), 2.35–2.29 (m, 2H, H4), 1.35–1.17 (m, 4H, H5, H6), 0.88–0.80 (m, 3H, H7). For the $^{13}C\{^1H\}$ NMR spectrum of the product mixture see the Supporting Information.

4.6. 5-Butyl-2-(6-dimethylaminopyridin-2-yl)pyrimidine (3)

316 mg (13.8 mmol) of sodium were dissolved in 25 mL of methanol. The solvent was removed under reduced pressure and the remaining solid was suspended in 30 mL of toluene. 2.50 g (12.5 mmol) of 6-(dimethylamino)pyridin-2-yl)guanidinium chloride were added and the mixture was stirred for 30 min at room temperature. Then 1.95 g (ca. 12.5 mmol) of the mixture of 2-butyl-1-ethoxyprop-1-enal and 2-butyl-1-dimethylamino-prop-1-enal described above were added and the reaction mixture was heated to reflux for 18 h. After cooling to room temperature, 20 mL of saturated brine and 10 mL of water were added. The organic phase was separated and the aqueous phase was extracted with 3 × 30 mL of dichloromethane. The combined organic solutions were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The raw product obtained this way was purified by column chromatography (ethyl acetate / *n*-hexane, 1:5). Yield: 897 g (28%) of a pale yellow solid. Elemental analysis calcd. for $C_{15}H_{20}N_4 \times (C_4H_8O_2)_{0.25}$ (256.35): C 69.03, H 7.97, N 20.13; found: C 69.16, H 8.02, N 20.15%. ^{1}H NMR (400.1 MHz, $CDCl_3$): C 69.03, H 7.97, N 20.13; found: C 69.16, H 8.02, N 20.15%. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 8.69 (s, 2H, H7), 7.66 (d, $^3J_{HH}$ = 7.2 Hz, 1H, H2), 7.62–7.56 (m, 1H, H3), 6.63 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H4), 3.20 (s, 6H, $N(CH_3)_2$), 2.64 (t, $^3J_{HH}$ = 7.6 Hz, 2H, H9), 1.63 (p, $^3J_{HH}$ = 7.7 Hz, 2H, H10), 1.38 (m, 2H, H11), 0.94 (t, $^3J_{HH}$ = 7.3 Hz, 3H, H12). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 162.9 (C6), 159.61 (C5), 157.4 (C7), 153.3 (C1), 138.0 (C3), 133.8 (C8), 111.7 (C2), 107.23 (C4), 38.2 ($N(CH_3)_2$), 33.0 (C9), 30.1 (C10), 22.2 (C11), 13.9 (C12) IR (ATR, cm^{-1}): IR (ATR, cm^{-1}): $\nu\tilde{}$2957 w, 2929 w, 2858 w, 1594 m, 1414 s, 983 m, 783 s.

4.7. General method for the synthesis of the palladium complexes 4–6

Palladium(II) acetate (1.0 equiv.) and the appropriate ligand (1.05 equiv.) were filled into a crimp-cap vial. The vial was closed and the atmosphere was exchanged against nitrogen. Then 5.0 mL of dichloromethane were added and the vial was heated to 60 °C for 18 h. After this time, the solvent was removed under reduced pressure. Single crystals for x-ray were obtained either by ether diffusion into a dichloromethane solution (**5**) or by layering a chloroform solution with *n*-hexane (**4** and **6**).

4.8. Bis[μ^2-acetato(2-(2-dimethylaminopyrimidin-4-yl)pyridine)palladium(II)] (4)

124 mg (617 µmol) of **1**, 132 mg (588 µmol) of palladium(II) acetate, yield: 156 mg (73%) of a red solid. Elemental analysis calcd. for $C_{26}H_{28}N_8O_4Pd_2$ (729.39): C 42.81, H 3.87, N 15.36; found: C 42.84, H 3.60, N 15.62%. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 8.00 (d, $^3J_{HH}$ = 5.3 Hz, 1H, H5), 7.88 (s, 1H, H8), 7.57 (m, 2H, H3, H4), 6.86

Table 2
Crystallographic data, data collection and refinement.

	4	**5**	**6′**
Empirical formula	$C_{26}H_{28}N_8O_4Pd_2$	$C_{12}H_{13}N_5O_2Pd$	$C_{17}H_{22}N_4O_2Pd(C_2H_4O_2)$
Formula weight	729.36	365.67	480.84
Crystal size [mm]	0.04 × 0.14 × 0.16	0.20 × 0.33 × 0.44	0.08 × 0.21 × 0.36
T [K]	150	150	100
λ [Å]	1.54184	1.54184	0.71073
Crystal system	monoclinic	monoclinic	triclinic
Space group	$P2_1/n$	$C2/c$	$P\bar{1}$
a [Å]	10.7994(2)	16.8803(3)	8.0745(4)
b [Å]	16.8431(2)	12.8934(2)	8.6118(4)
c [Å]	14.9851(2)	11.9995(2)	15.0409(8)
α [°]	90	90	81.143(2)
β [°]	98.579(2)	92.034(1)	78.060(2)
γ [°]	90	90	88.612(2)
V [Å^3]	2695.22(7)	2609.98(8)	1011.02(9)
Z	4	8	2
$\rho_{calcd.}$ [g cm^{-3}]	1.798	1.861	1.579
μ [mm^{-1}]	11.184	11.574	0.950
θ-range [°]	3.974–62.775	4.316–62.720	2.394–30.506
Refl. coll.	19,003	8074	63,494
Indep. refl.	4318	2097	6177
Data/restr./param.	4318/0/367	2097/0/184	6177/130/289
Final R indices [$I>2\sigma(I)$] [a]	0.0196, 0.0488	0.0284, 0.0726	0.0298, 0.0636
R indices (all data)	0.0220, 0.0496	0.0288, 0.0730	0.0386, 0.0668
$GooF$ [b]	1.012	1.115	1.068
$\Delta\rho_{max/min}$ (e•Å^{-3})	0.590/-0.378	0.516/-1.126	1.298/-0.941

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $\omega R2 = [\Sigma\omega(F_o^2 - F_c^2)^2/\Sigma\omega F_o^2]^{1/2}$. [b] $GooF = [\Sigma\omega(F_o^2 - F_c^2)^2/(n\text{-}p)]^{1/2}$.

(s, 1H, H2), 3.08 (s, 6H, NMe_2), 2.21 (s, 3H, O_2CCH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 182.4 (O_2CCH_3), 167.7 (C9), 162.1, 160.2 (C5, C8), 159.3, 150.1 (C1, C6), 138.1 (C7), 125.2, 124.3, 120.9 (C2, C3, C4), 37.3 ($N(CH_3)_2$), 24.4 (O_2CCH_3). IR (ATR, cm^{-1}): IR (ATR, cm^{-1}): $\tilde{\nu}$2926 w, 2853 w, 1547 s, 1517 s, 1393 s, 981 m, 773 s.

4.9. Bis[μ^2-acetato(2-(2-dimethylaminopyrimidin-4-yl)pyrimidine)palladium(II)] (5)

94.0 mg (467 µmol) of **2**, 100 mg (445 µmol) of palladium(II) acetate, yield: 120 mg (74%) of a reddish-brown solid. Elemental analysis calcd. for $C_{24}H_{26}N_{10}O_4Pd_2$ (731.38): C 39.41, H 3.58, N 19.15; found: C 39.26, H 3.88, N 18.85%. ^1H NMR (400.1 MHz, $CDCl_3$): δ 8.74 (dd, $^3J_{HH}$ = 4.8, $^4J_{HH}$ = 2.2 Hz, 1H, H4), 8.29 (dd, $^3J_{HH}$ = 5.6, $^4J_{HH}$ = 2.2 Hz, 1H, H2), 8.06 (s, 1H, H10), 6.89 (dd, $^3J_{HH}$ = 5.5, $^3J_{HH}$ = 4.9 Hz, 1H, H3), 3.15 (s, 6H, $N(CH_3)_2$), 2.22 (s, 3H, O_2CCH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 182.8 (O_2CCH_3), 169.1 (C8), 164.1 (C1), 160.9 (C5), 159.8, 158.7, 156.6 (C2, C4, C7), 124.8 (C6), 119.8 (C3), 37.5 (NMe_2), 24.4 (O_2CCH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$3039 w, 2857 w, 1584 w, 1547 vs, 1462s, 1401 vs, 1386 vs, 1336 s, 1267 m, 1225 m, 1195 m, 1163s, 1070 m, 1020 m, 983 m, 951 m, 840 w, 816 m, 780 s, 734 s, 686 m.

4.10. Chlorido(N-(6-(2-(5-butyl-pyrimidin-2-yl)pyridyl)))(N-methyl)amino)methylpalladium(II) (6)

68.1 mg (166 µmol) of **2**, 56.8 mg (253 µmol) of palladium(II) acetate, yield: 81 mg (76%) of a red solid. Elemental analysis calcd. for $C_{15}H_{19}ClN_4Pd \times (C_4H_{10}O)_{0.3} \times (H_2O)_{0.8}$ (433.85): C 44.85, H 5.48, N 12.91; found C 44.80, H 5.21, N 12.66%. ^1H NMR (400.1 MHz, $CDCl_3$): δ 8.72, 8.70 (2 × d, $^4J_{HH}$ = 2.8 Hz, 2H, H7, H7'), 7.58 (dd, $^3J_{HH}$ = 8.8, 7.3 Hz, 1H, H3), 7.38 (dd, $^3J_{HH}$ = 7.3, $^4J_{HH}$ = 0.6 Hz, 1H, H2), 6.41 (d, $^3J_{HH}$ = 8.5 Hz, 1H, H4), 4.49 (s, 2H, H14), 3.03 (s, 3H, H13), 2.71–2.65 (m, 2H, H9), 1.67–1.60 (m, 2H, H10), 1.38 (sextett, $^3J_{HH}$ = 7.5 Hz, 2H, H11), 0.94 (t, $^3J_{HH}$ = 7.4 Hz, 3H, H12). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.9, 160.1 (C5, C6), 157.9, 155.4 (C7, C7'), 149.9 (C1), 137.9, 137.1 (C2, C3), 110.2, 109.5 (C4, C8), 50.8 (C14), 36.6 (C13), 32.8 (C9), 30.3 (C10), 22.4 (C11), 13.8 (C12). IR (ATR, cm^{-1}): $\tilde{\nu}$2955 m, 2928 m, 2871 m, 1586 s, 1560 s, 1361s, 1013 m, 766 s.

4.11. X-ray structure analyses

Crystal data and refinement parameters are collected in Table 2. All structures were solved using direct method, completed by subsequent difference Fourier syntheses, and refined by full-matrix least-squares procedures based on F^2 [20]. Analytical numeric absorption correction was carried out to compounds **4** and **5**, while semi-empirical absorption correction (multi-scan) was applied to complex **6′** [21]. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms except hydrogen atom H3 (complex **6′**) were placed in calculated positions and refined by using a riding model. The position of H3 was located in the difference Fourier synthesis, and was refined semi-freely with the help of a distance restraint, while constraining its U-value to 1.5 times the $U(eq)$ value of the bonded oxygen atom O3. CCDC 2061925–2061927 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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