EurJIC European Journal of Inorganic Chemistry

ChemPubSoc Europe

FULL PAPER

DOI:10.1002/ejic.201402149

C–H Activation at a Bidentate Ligand Coordinated to Palladium(II) – an Electrophilic Attack Supported by an External Base

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Keywords: C–H activation / Palladium / Reaction mechanisms / Kinetics / Nitrogen heterocycles

2-(2-Phenylaminopyrimidin-4-yl)pyridines undergo C–H activation at the phenyl ring in the *ortho* position to the amine nitrogen atom when reacted with $(PhCN)_2PdCl_2$ and finally form *N*,*N*,*C*-coordinated palladium(II) complexes in high yields. Five differently substituted complexes were synthesized and characterized by spectroscopy and X-ray structure analysis. The reaction mechanism for the formation of these complexes was elucidated by kinetic experiments, which allowed the calculation of the activation parameters of the complex formation.

Introduction

The discovery of palladium-catalyzed C–C cross-coupling reactions has given a further dynamic impulse to the development of palladium chemistry.[1] Most of these reactions are nowadays well-established as tools in organic synthesis and follow a sequence wherein an aryl or alkyl halide undergoes an oxidative addition to the catalytically active palladium(0) species to generate a palladium(II) intermediate of the type $RPd^{II}X(L)_n$, which allows the transfer of the R group to the substrate. However, during the last decade, palladium-mediated C–H activation came into the focus of research to generate the palladium(II) intermediate $RPd^{II}X(L)_n$ from nonfunctionalized starting materials.[2] This type of substrate activation often occurs with high efficiency as soon as cyclic products are formed.[3] Although cyclopalladation reactions have been studied extensively, only some of the proposed mechanisms have been supported by kinetic measurements.[4]

Recently, we reported the synthesis and application of 2-(2-aminopyrimidin-4-yl)pyridines as ligands for a base-free hydrogen transfer reaction catalyzed by ruthenium complexes.[5] By spectroscopic investigations supported by quantum chemical calculations, we proved that such ligands can undergo intramolecular C–H activation at the 5-position of the 2-aminopyrimidin-4-yl site and that this process is the crucial step for the formation of the active species. For this to happen, a tertiary 2-amino group is required. In this manuscript, we report on the *ortho* C–H activation of phenyl groups attached to the amino moiety of 2-(2-aminopyrimidin-4-yl)pyridine ligands that occurs spontaneously after the formation of *N*,*N*′-coordinated palladium(II) complexes. The palladium-centered C–H activation was investigated by a kinetic study that allowed the elucidation of the kinetic parameters of this reaction. Similar C–H activation processes have been reported as primary steps in a series of palladium-catalyzed and pyridine-directed reactions, namely, for carbazole[6] and indole[7] syntheses as well as arene–alkyne[8] and arene–allene[9] couplings.

Results and Discussion

Complex Synthesis and Characterization

A multitude of different routes to functionalized pyrimidines have been reported.[10] For the synthesis of the 2-(2-arylaminopyrimidin-4-yl)pyridines **2a**–**2e**, the condensation of the appropriate arylated guanidinium salt **1a**–**1e** with (*E*)-3-(dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one in the presence of base proceeded best and provided moderate-to-good yields (45–70%) of the desired products (Scheme 1).[11] The corresponding phenylguanidinium salts **1a**–**1e** can be prepared from substituted anilines and cyanamide in the presence of nitric acid.[12] By following this strategy, five 2-(2-phenylaminopyrimidin-4-yl)pyridines **2a**–**2e** were obtained. Ligands **2a**–**2e** bear different functional

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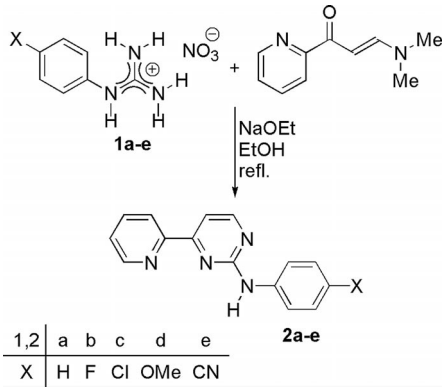
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejic.201402149.

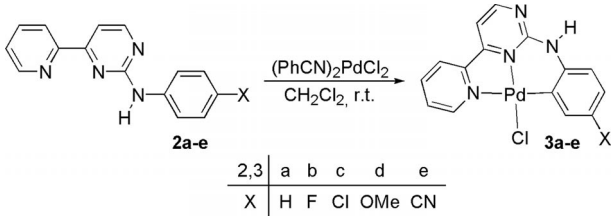
groups at the *para* position of the phenyl group and, therefore, allow the elucidation of their electronic influence on the C–H activation step.



Scheme 1. Synthesis of the ligands **2a**–**2e**.

Although the chemical shift of the pyridine protons is hardly affected by the substitution pattern of the phenyl ring, the ^{1}H NMR resonances of the pyrimidine protons reflect the influence of the different substituents. As expected, the electron-donating methoxy group (**2d**) leads to a shift of the pyrimidine ^{1}H NMR resonances to higher field and the electron-withdrawing cyanide group (**2e**) causes a shift to lower field. This effect is even more pronounced for the NH resonances [δ = 9.76 (**2a**), 9.79 (**2b**), 9.92 (**2c**), 9.56 (**2d**), and 10.34 (**2e**) ppm].

The reactions of **2a**–**2e** with $(PhCN)_2PdCl_2$ in dichloromethane at room temperature furnished the tetracoordinate palladium complexes **3a**–**3e** with a chelating N,N,C ligand in almost quantitative yields (Scheme 2).



Scheme 2. Synthesis of the palladium complexes **3a**–**3e**.

Complexes **3a**–**3e** precipitated from the reaction mixture as yellow to deep orange solids. Optimized yields were obtained by adding a large excess of diethyl ether to the reaction mixture. For further purification, **3a**–**3e** were redissolved in dimethyl sulfoxide (DMSO) and a very small amount of ethanol and subsequently reprecipitated by the addition of diethyl ether.

Single crystals of **3a** and **3d** suitable for X-ray diffraction studies were obtained by slow diffusion of diethyl ether into DMSO solutions. The solid-state molecular structures of **3a** and **3d** and characteristic structural parameters are presented in Figure 1.

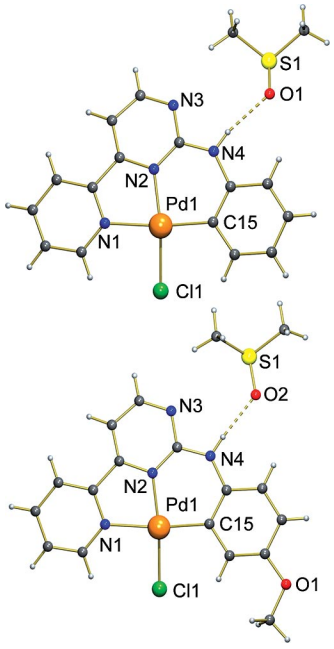


Figure 1. Solid-state molecular structures of the palladium complexes **3a** (top) and **3d** (bottom). Characteristic bond lengths [Å] and angles [°]: **3a**: Pd1–Cl1 2.3192(7), Pd1–N1 2.111(2), Pd1–N2 2.015(2), Pd1–C15 1.990(3), S1–O1 1.496(2), Cl1–Pd1–N1 92.03(7), Cl1–Pd1–N2 169.37(7), Cl1–Pd1–C15 94.75(7), N1–Pd1–N2 80.28(9), N1–Pd1–C15 172.29(10), N2–Pd1–C15 93.45(9), N4–O1 0.85(3), H4N···O1 2.09(3), N4···O1 2.931(3), N4–H4N···O1 168(3); **3d**: Pd1–Cl1 2.3226(5), Pd1–N1 2.1163(19), Pd1–N2 2.0068(18), Pd1–C15 1.993(3), S1–O2 1.511(2), Cl1–Pd1–N1 92.71(5), Cl1–Pd1–N2 168.76(6), Cl1–Pd1–C15 94.84(6), N1–Pd1–N2 79.97(7), N1–Pd1–C15 171.25(8), N2–Pd1–C15 93.20(8), N4–H4N 0.85(2), H4N···O2 2.00(2), N4···O2 2.848(3), N4–H4N··· O2 175(3).

The X-ray structure analyses proves that the C–H activation occurs at the phenyl ring and proceeds here without the addition of any external base or the use of basic ligands (e.g., CH_3COO^-) coordinated to the palladium center. Both complexes show the typical distorted square-planar geometry of palladium(II) compounds. The palladium center is coordinated by a chlorido ligand and a tridentate NNC-type ligand through the nitrogen atom of the pyridine moiety, the nitrogen atom at the 3-position of the pyrimidine ring, and one of the *ortho* carbon atoms of the phenyl group. The distances Pd–N1 (**3a**: 2.111; **3d**: 2.116 Å), Pd–N2 (**3a**: 2.015; **3d**: 2.007 Å), Pd–C15 (**3a**: 1.990; **3d**: 1.993 Å), and Pd–Cl1 (**3a**: 2.319; **3d**: 2.323 Å) are similar to those of related structures.[5,13] Owing to steric restrictions caused by the tridentate coordination mode, the Pd–N2 bond is considerably shorter than the Pd–N1 bond, and the aromatic rings are not completely coplanar. In both structures, an additional molecule of DMSO forms a hydrogen bond with the N–H moiety of the C–H-activated 2-(2-phenylaminopyrimidin-4-yl)pyridine ligand.

The NMR spectra of **3a**–**3e** further confirm that the C–H activation occurs at the phenyl ring. All resonances of the N–H protons are shifted to lower field; however, the clear correlation for the free ligands between the electronic impact of the substituent at the *para* position and the chem-

ical shift is lost [δ = 11.10 (**3a**), 11.03 (**3b**), 11.19 (**3c**), 11.02 (**3d**), and 11.51 (**3e**) ppm]. The ^{1}H and ^{13}C NMR resonances of the phenyl moieties now show the typical patterns of 1,2- (**3a**) or 1,2,4-substituted phenyl groups (**3b**–**3e**). The ^{13}C NMR chemical shift of the quaternary, palladium-bound carbon atom C-11 that possesses anionic character is typical for all complexes [δ =125.0 (**3a**), 126.5 (**3b**), 126.4 (**3c**), and 125.8 (**3d**) ppm]. As expected, the influence of the substituent at the *meta* position to this site on the chemical shift of C-11 is small. Compound **3e** was not soluble enough to allow measurement of a ^{13}C NMR spectrum.

Kinetic Studies

The kinetics of the formation of the cyclometalated (NNC)PdCl complexes in a CH_2Cl_2/DMSO (1:1) solution were followed by monitoring the spectral changes by UV/Vis spectroscopy (Figure 2). Although **3a**–**3e** were synthesized in neat CH_2Cl_2, DMSO was added for the kinetic studies to assure the complete solubility of even the rather poorly soluble, cyano-functionalized complex **3e**. Some changes of the UV/Vis spectrum with isosbestic points at 383 and 345 nm occur within the first 60 s after the addition of equimolar amounts of the NNC ligand precursor to a 0.66 mM solution of $(PhCN)_2PdCl_2$ in CH_2Cl_2/DMSO (1:1) at 40 °C (see Figure S1). This is followed by a much slower second phase of the reaction, which is characterized by isosbestic points at 433 and 355 nm (Figure 2; first spectrum 90 s after mixing). We attribute the fast initial phase to the binding of the bidentate pyrimidinylpyridine part of the ligand to the palladium center; the subsequent cyclometalation occurs in a slower second step.

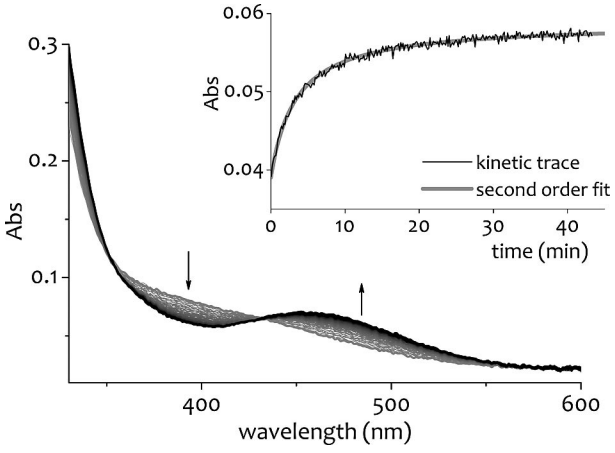


Figure 2. Absorption spectral changes for the reaction of $(PhCN)_2PdCl_2$ (0.66 mM) with **2a** (X = H) in CH_2Cl_2/DMSO (1:1) at 40 °C. Curves: bold grey, t = 0 min (90 s after mixing); bold black, t = 40 min; 15 s steps. Inset: kinetic trace at 490 nm (black line) with second-order fit (grey line). The isosbestic points are at 433 and 355 nm.

The spectral changes during the slow cyclometalation step follow second-order kinetics (see inset of Figure 2; a linearized form of the kinetic trace is shown in Figure S2). For the differently substituted ligand precursors **2a**–**2e**, the second-order reaction rate constants k increase as the electron donor ability of the *meta* substituent of the ligands increases. This is a clear indication that the reaction builds a positive charge during the rate-determining step and of the electrophilic nature of the intermediate. Further support for this conclusion came from the Hammett analysis [plot of $\log(k/k_H)$ vs. Hammett constants σ_{meta}] shown in Figure 3.[14] A good linear correlation (R^2 = 0.982) was obtained with a Hammett parameter ρ of –1.21 ± 0.09 for the reactions at 25 °C. The investigation of the reaction rates at different temperatures gave ρ constants of ca. –1 over the investigated temperature range.[15] Thus, an electrophilic aromatic substitution mechanism such as that depicted in Scheme 3 can be assumed. In that scenario, the palladium center serves as the electrophile and a proton is liberated from the ligand precursor; a chloride anion probably acts as the base. Second-order kinetics indicate an intermolecular reaction during proton abstraction. The alternative scenario of a σ-bond metathesis reaction is usually characterized by a positive value for the Hammett parameter ρ and can, thus, be excluded in the present case.[16]

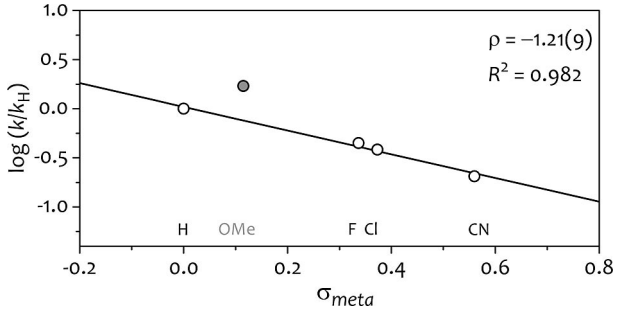
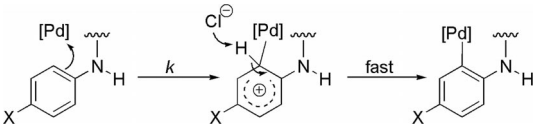


Figure 3. Hammett plot for the formation of the cyclopalladated complexes **3a**–**3e** at 25 °C based on rate constants taken from linear fits as exemplarily shown in Figure 2. The linear regression gives the Hammett parameter ρ = –1.21 ± 0.09. The grey dot for X = OMe represents the average of four measurements. This value was not included in the fit owing to the large deviations between the different measurements.



Scheme 3. Proposed mechanism for the formation of the cyclometalated complexes **3a**–**3e**.

In addition to the Hammett analysis, a full kinetic investigation was performed in the temperature range –10 to +45 °C. The activation parameters for the rate-limiting step were determined from the temperature dependence of the respective rate constants (Eyring plots shown in Figure 4) and are compiled in Table 1.

The slopes of the linear fits in the Eyring plots are roughly equal and give enthalpies of activation $\Delta H^{\ddagger}$ in the narrow range 12.5–15.3 kcal mol^{-1}. The entropies of activation $\Delta S^{\ddagger}$ are quite small (3.4 to –8.0 cal K^{-1} mol^{-1}). Although $\Delta H^{\ddagger}$ shows only a minor trend towards smaller values with the more-electron-withdrawing substituents, such

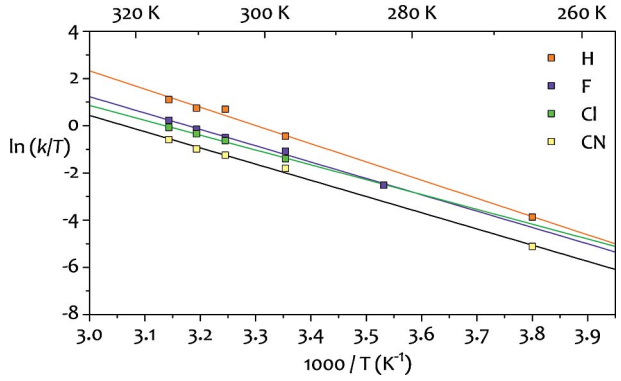


Figure 4. Eyring plots, $\ln(kT^{-1})$ vs. T^{-1}, of the second-order rate constants k for the formation of cyclopalladated complexes **3a**–**3e** with linear regressions (see Table 1 for kinetic parameters).

Table 1. Activation parameters for the reaction of $Pd(PhCN)_2Cl_2$ with the ligands **2a**–**2e**.

X	k_{298}[a] [M^{-1} min^{-1}]	$\bar{R}^2$	$\Delta H^{\ddagger}$ [kcal mol^{-1}]	$\Delta S^{\ddagger}$ [cal K^{-1} mol^{-1}]	$\Delta G^{\ddagger}_{298}$ [kcal mol^{-1}]
OMe[b]	335.4[c]	–	–	–	–
H	197.5	0.993	15.32 ± 0.65	3 ± 2	14.31 ± 0.93
F	88.1	0.993	13.76 ± 0.60	–4 ± 2	14.79 ± 0.84
Cl	75.7	0.993	12.48 ± 0.65	–8 ± 2	14.88 ± 0.91
CN	40.5	0.995	13.64 ± 0.49	–5 ± 2	15.25 ± 0.69

[a] Rate constants at 25 °C from the linear regressions in the Eyring plots in Figure 4. [b] No determination of activation parameters for X = OMe, see the Exp. Section for details. [c] Average of four measurements at 25 °C.

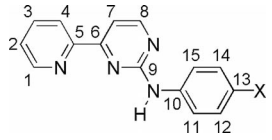
a trend is more obvious for $\Delta S^{\ddagger}$. Regarding the Eyring plot, the almost parallel linear fits decrease to lower values with more-electron-withdrawing substituents. This results in more-negative entropies, which render the reactions less entropically favored, and more-ordered transition states are indicated. Entropies around zero are difficult to interpret;[17] however, as the entropies are mostly negative, an associative mechanism in the rate-determining step is likely, in accordance with the mechanism outlined above.

Conclusions

We have presented the synthesis and characterization of new palladium complexes with N,N,C coordination, which were obtained by C–H activation at the phenyl group of a 2-(2-phenylaminopyrimidin-4-yl)pyridine ligand. The reaction was investigated by kinetic methods, which clearly suggested that it follows a mechanism similar to an electrophilic aromatic substitution at the aniline site with the palladium center as the electrophile.

Experimental Section

General Information: All chemicals for the syntheses of the ligands were purchased from Sigma–Aldrich or Acros Organics; $(PhCN)_2PdCl_2$ was obtained from STREM Chemicals. Solvents for the ligand syntheses were used without further purification; solvents for the syntheses of the palladium complexes and for the kinetic experiments were dried by standard methods prior to use. The elemental analyses were performed at the Fachbereich Chemie of the TU Kaiserslautern. Infrared spectra with a resolution of ±2 cm^{-1} were recorded with a PerkinElmer FT-ATR IR 1000 spectrometer equipped with a diamond-coated ZnSe window. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Spectrospin device with resonance frequencies of 400.1 and 100.6 MHz for the ^{1}H and ^{13}C nuclei, respectively. The NMR resonances of the ligands **2a**–**2e** and of the palladium complexes **3a**–**3e** are assigned according to Scheme 4.



Scheme 4. Assignment of the NMR resonances (14 and 15 are only relevant for the palladium complexes).

Kinetic Measurements: The reactions were followed by UV/Vis spectroscopy, and measurements of the reaction solutions were performed directly with an all-quartz immersion probe in a custom-made reaction tube (transmission measurement with 1 mm optical path, Hellma Analytics). Time-dependent UV/Vis spectra were recorded approximately every 15 s with a Cary 50 Bio spectrometer through the use of a fiber-optical connection. Temperature control of the solutions was accomplished with a Lauda ECO RE 630 cryostat. CH_2Cl_2/DMSO (1:1, 0.66 mM) solutions were prepared, and five different temperatures were applied, depending on the ligand. Single-wavelength kinetic traces were then obtained from the spectra and fitted by applying second-order kinetics with Cary Win UV and OriginLab OriginPro 8.5.1 software. All measurements yielded consistent results. However, in the case of experiments with ligand X = OMe, the determined rate constants were barely reproducible and showed only a weak linear temperature-dependent correlation. Therefore, only the rate constants obtained at 25 °C have been considered in the further evaluation.

General Procedure for the Synthesis of the Guanidinium Salts 1a–1e:[7] Concentrated nitric acid was added to a solution of the appropriate arylamine in ethanol followed by a 50% aqueous solution of cyanamide (1.5 equiv.). The reaction mixture was heated under reflux for 16 h and then cooled to 0 °C, diethyl ether was then added. This solution was kept in the refrigerator for 12 h. The resulting solids were collected by filtration to afford the products in good yield.

Phenylguanidinium Sulfate (1a): This compound was prepared according to a previously published procedure (yield 35%).[18] $C_{14}H_{20}N_6O_4S$ (368.41): calcd. C 45.64, H 5.47, N 22.81, S 8.70; found C 45.06, H 5.36, N 23.02, S 8.66. ^{1}H NMR (400 MHz, D_2O): δ = 7.49–7.46 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, *m*-H), 7.40–7.37 (t, 1 H, *p*-H), 7.29 (d, 2 H, *o*-H) ppm. ^{13}C NMR (100.6 MHz, D_2O): δ = 156.3 (CN_3), 134.1 (C-*i*), 129.9 (C-*m*), 128.0 (C-*p*), 125.8 (C-*o*) ppm.

(4-Fluorophenyl)guanidinium Nitrate (1b): Prepared from 4-fluoroaniline according to the general procedure (yield 63%). $C_7H_9FN_4O_3$ (216.17): calcd. C 38.89, H 4.20, N 25.92; found C 39.04, H 4.49, N 26.02. ^{1}H NMR (400 MHz, D_2O): δ = ppm 7.35–7.29 (m, 2 H, *o*-H), 7.25–7.16 (m, 2 H, *m*-H) ppm. ^{13}C NMR (100.6 MHz, D_2O): δ = 161.8 (d, $^1J_{F,C}$ = 245.5 Hz, C-*p*), 156.6 (CN_3), 130.0 (C-*i*), 128.5 (d, $^3J_{F,C}$ = 9.1 Hz, C-*o*), 116.7 (d, $^2J_{F,C}$ = 23.2 Hz, C-*p*) ppm.

(4-Chlorophenyl)guanidinium Nitrate (1c): Prepared from 4-chloroaniline according to the general procedure (yield 58%). $C_7H_9ClN_4O_3$ (232.62): calcd. C 36.14, H 3.90, N 24.08; found C 36.05, H 3.96, N 24.04. ^{1}H NMR (400 MHz, D_2O): δ = 7.48 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *m*-H), 7.28 (d, 2 H, *o*-H) ppm. ^{13}C NMR (100.6 MHz, D_2O): δ = 156.3 (CN_3), 133.0, 132.9 (C-*i*, C-*p*), 129.9 (C-*m*), 127.4 (C-*o*) ppm.

(4-Methoxyphenyl)guanidinium Nitrate (1d): Prepared from *para*-anisidine according to the general procedure (yield 82%). $C_8H_{12}N_4O_4$ (228.21): calcd. C 42.11, H 5.30, N 24.55; found C 42.05, H 5.31, N 24.43. ^{1}H NMR (400 MHz, DMSO): δ = 9.40 (s, 1 H, NH), 7.23 (br, 4 H, NH), 7.18 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, *o*-H), 7.00 (d, 2 H, *m*-H), 3.77 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100.6 MHz, DMSO): δ = 158.2 (C-*p*), 156.3 (CN_3), 127.5 (C-*i*), 127.3 (C-*o*), 114.9 (C-*m*), 55.4 (OCH_3) ppm.

(4-Cyanophenyl)guanidinium Nitrate (1e): Prepared from 4-aminobenzonitrile according to the general procedure (yield 33%). $C_8H_9N_5O_3$ (223.19): calcd. C 43.05, H 4.06, N 31.38; found C 43.07, H 3.75, N 30.92. ^{1}H NMR (400 MHz, DMSO): δ = 10.04 (s, 1 H, NH), 7.88 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *m*-H), 7.66 (br, 4 H, NH), 7.40 (d, 2 H, *o*-H) ppm. ^{13}C NMR (100.6 MHz, DMSO): δ = 155.3 (CN_3), 140.7 (CN), 133.9 (C-*m*), 123.4 (C-*o*), 118.6 (C-*i*), 107.5 (CN) ppm.

General Procedure for the Synthesis of Ligands 2a–2e: Sodium (0.5 g, 22 mmol) was dissolved in a solution of the appropriate guanidinium salt **1a**–**e** (11 mmol) in dry EtOH (50 mL) under an atmosphere of dinitrogen. As soon as the evolution of dihydrogen ceased, (*E*)-3-(dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one (1.80 g, 10 mmol) was added, and the mixture was heated to reflux for 24 h. The solution was cooled to 0 °C, and the precipitated solid was collected by filtration; unreacted salt and the excess base were washed out with water, and the product was dried in vacuo.

2-(*N*-Phenylamino)-4-(pyridine-2-yl)pyrimidine (2a): From **1a** according to the general procedure (yield 50%). $C_{15}H_{12}N_4$ (248.29): calcd. C 72.56, H 4.87, N 22.57; found C 72.35, H 5.21, N 22.47. ^{1}H NMR (400.1 MHz, [D$_6$]DMSO): δ = 9.76 (br, 1 H, NH), 8.75 (d, $^3J_{H,H}$ = 4.3 Hz, 1 H, 1-H), 8.65 (d, $^3J_{H,H}$ = 5.1 Hz, 1 H, 8-H), 8.41 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 4-H), 8.05 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H, 3-H), 7.85 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H, 11-H), 7.73 (d, 1 H, 7-H), 7.57 (dd, 1 H, 2-H), 7.33 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, 12-H), 6.98 (t, 1 H, 13-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.8 (C-9), 160.1 (C-6), 159.5 (C-8), 153.7 (C-5), 149.6 (C-1), 140.5 (C-10), 137.6 (C-3), 128.6 (C-12), 125.7 (C-2), 121.5 (C-4), 121.0 (C-13), 119.0 (C-11) 108.0 (C-7) ppm.

2-(*N*-4-Fluorophenylamino)-4-(pyridine-2-yl)pyrimidine (2b): From **1b** according to the general procedure (yield 53%). $C_{15}H_{11}FN_4$ (266.28): calcd. C 67.66, H 4.16, N 21.04; found C 67.49, H 4.28, N 20.90. ^{1}H NMR (400.1 MHz, [D$_6$]DMSO): δ = 9.79 (br, 1 H, NH), 8.74 (d, $^3J_{H,H}$ = 4.3 Hz, 1 H, 1-H), 8.63 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 8-H), 8.39 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 4-H), 8.03 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H, 3-H), 7.85–7.81 (m, 2 H, 12-H), 7.81 (d, 1 H, 7-H), 7.58 (dd, 1 H, 2-H), 7.17 (t, $^4J_{F,H}$ = $^3J_{H,H}$ = 8.0 Hz, 2 H, 11-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.8 (C-9), 160.0 (C-6), 159.5 (C-8), 158.4 (d, $^1J_{C,F}$ = 237.7 Hz, C-13), 153.6 (C-5), 149.6 (C-1), 137.6 (C-3), 136.9 ($^4J_{C,F}$ = 2.8 Hz, C-10), 125.7 (C-2), 121.1 (C-4), 120.7 (d, $^3J_{C,F}$ = 7.4 Hz, C-11), 115.2 (d, $^2J_{C,F}$ = 22.2 Hz, C-12), 108.0 (C-7) ppm.

2-(*N*-4-Chlorophenylamino)-4-(pyridine-2-yl)pyrimidine (2c): From **1c** according to the general procedure (yield 45%). $C_{15}H_{11}ClN_4$ (282.73): calcd. C 63.72, H 3.92, N 19.82; found C 63.46, H 4.10, N 19.75. ^{1}H NMR (400.1 MHz, [D$_6$]DMSO): δ = 9.93 (br, 1 H, NH), 8.75 (d, $^3J_{H,H}$ = 3.9 Hz, 1 H, 1-H), 8.66 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 8-H), 8.40 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 4-H), 8.04 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H, 3-H), 7.89 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 12-H), 7.75 (d, 1 H, 7-H), 7.58–7.55 (m, 1 H, 2-H), 7.39 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 11-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.9 (C-9), 159.8 (C-6), 159.6 (C-8), 153.5 (C-5), 149.6 (C-1), 139.5 (C-10), 137.6 (C-3), 128.4 (C-11), 125.8 (C-2), 124.9 (C-13), 121.1 (C-4), 120.3 (C-12) 108.3 (C-7) ppm.

2-(*N*-4-Methoxyphenylamino)-4-(pyridine-2-yl)pyrimidine (2d): From **1d** according to the general procedure (yield 70%). $C_{16}H_{14}N_4O$ (278.31): calcd. C 69.05, H 5.07, N 20.13; found C 69.36, H 4.81, N 19.70. ^{1}H NMR (400.1 MHz, [D$_6$]DMSO): δ = 9.56 (br, 1 H, NH), 8.74 (d, $^3J_{H,H}$ = 4.3 Hz, 1 H, 1-H), 8.59 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 8-H), 8.37 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 4-H), 8.03 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H, 3-H), 7.73 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 12-H), 7.66 (d, 1 H, 7-H), 7.57–7.54 (m, 1 H, 2-H), 6.94 (d, 2 H, 11-H), 3.74 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.7 (C-9), 160.2 (C-6), 159.5 (C-8), 154.3 (C-5), 153.8 (C-13), 149.6 (C-1), 137.5 (C-3), 133.6 (C-10), 125.6 (C-2), 121.0 (C-4), 120.7 (C-11), 113.8 (C-12) 107.4 (C-7), 55.2 (OCH_3) ppm.

2-(*N*-4-Cyanophenylamino)-4-(pyridine-2-yl)pyrimidine (2e): From **1e** according to the general procedure (yield 47%). $C_{16}H_{11}N_5\cdot(H_2O)_{0.2}$ (276.90): calcd. C 69.40, H 4.15, N 25.29; found C 69.70, H 4.14, N 25.01. ^{1}H NMR (400.1 MHz, [D$_6$]DMSO): δ = 10.34 (br, 1 H, NH), 8.77 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 1-H), 8.74 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 8-H), 8.42 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 4-H), 8.06–8.04 (m, 3 H, 3-H, 12-H), 7.85 (d, 1 H, 7-H), 7.8 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 11-H), 7.61–7.58 (m, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 163.1 (C-9), 159.9 (C-6), 159.5 (C-8), 153.3 (C-5), 149.7 (C-1), 144.9 (C-10), 137.7 (C-3), 133.1 (C-11), 126.0 (C-2), 121.2 (C-4), 119.6 (C-13), 118.4 (C-12), 109.4 (C-7), 102.5 (CN) ppm.

General Procedure for the Synthesis of the Palladium Complexes 3a–3e: A solution of the appropriate ligand **2a**–**2e** (0.50 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of [$(PhCN)_2PdCl_2$] (192 mg, 0.50 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 16 h. The precipitated products were collected by filtration and washed with CH_2Cl_2. The complexes can be recrystallized from DMSO.

3a: From **2a** according to the general procedure (yield 93%). $C_{15}H_{11}ClN_4Pd\cdot(CH_2Cl_2)_{0.25}$ (410.36): calcd. C 44.64, H 2.82, N 13.65; found C 44.58, H 2.90, N 13.73. ^{1}H NMR (400.1 MHz, [D$_6$]DMSO): δ = 11.10 (br, 1 H, NH), 9.33 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 1-H), 9.00 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 8-H), 8.67 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 4-H), 8.37 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 12-H), 8.28 (t, $^3J_{H,H}$ = 7.0 Hz, 1 H, 3-H), 7.99 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 7-H), 7.89–7.86 (m, 1 H, 2-H), 7.19 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, 15-H), 7.04 (t, $J_{H,H}$ = 7.0 Hz, 1 H, 14-H), 6.71 (t, $^3J_{H,H}$ = 7.0 Hz, 1 H, 13-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.1 (C-6), 161.1 (C-8), 152.5 (C-5), 150.0 (C-9), 149.2 (C-1), 140.3 (C-10), 139.8 (C-3), 136.6 (C-11), 128.0 (C-2), 125.0, 124.5 (C-12, C-14), 123.9 (C-4), 120.6 (C-13), 116.2 (C-15), 108.8 (C-7) ppm.

3b: From **2b** according to the general procedure (yield 94%). $C_{15}H_{10}ClFN_4Pd\cdot DMSO$ (485.25): calcd. C 42.08, H 3.32, N 11.55; found C 41.80, H 3.42, N 11.46. ^{1}H NMR (400.1 MHz, [D$_6$]DMSO): δ = 11.07 (br, 1 H, NH), 9.21 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H, 1-H), 8.93 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 8-H), 8.59 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 4-H), 8.23 (t, $^3J_{H,H}$ = 8.2 Hz, 1 H, 3-H), 8.07 (dd, $^3J_{F,H}$ = 11.4 Hz, $^5J_{H,H}$ = 2.9 Hz, 1 H, 12-H), 7.91 (d, 1 H, 7-H), 7.82 (dd, 1 H, 2-H), 7.15 (dd, $^4J_{F,H}$ = 5.5 Hz, 1 H, 15-H), 6.86 (m, 1 H, 14-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.0 (C-6), 161.2 (C-8), 156.2 (d, $^1J_{F,C}$ = 240 Hz, C-13), 152.6 (C-5), 150.0 (C-

9), 149.2 (C-1), 139.8 (C-3), 133.5 (C-10), 128.0 (C-2), 126.5 (d, $^3J_{C,F}$ = 5.0 Hz, C-11), 124.9 (d, $^2J_{C,F}$ = 20.6 Hz, C-12), 123.9 (C-4), 116.8 (d, $^3J_{C,F}$ = 7.7 Hz, C-15), 112.0 (d, $^2J_{C,F}$ = 23.4 Hz, C-14), 108.7 (C-7) ppm.

3c: From **2c** according to the general procedure (yield 88%). $C_{15}H_{10}Cl_2N_4Pd\cdot(CH_2Cl_2)_{0.30}$ (449.06): calcd. C 40.92, H 2.38, N 12.48; found C 40.95, H 2.41, N 12.70. ^{1}H NMR (400.1 MHz, [D$_6$]-DMSO): δ = 11.19 (br, 1 H, NH), 9.27 (d, $^3J_{H,H}$ = 5.1 Hz, 1 H, 1-H), 9.00 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 8-H), 8.66 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 4-H), 8.32 (s, 1 H, 12-H), 8.28 (dd, $^3J_{H,H}$ = 8.2 Hz, 1 H, 3-H), 7.99 (d, $^3J_{H,H}$ = 4.70 Hz, 1 H, 7-H), 7.88 (dd, 1 H, 2-H), 7.16 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 15-H), 7.07 (d, 1 H, 14-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.1 (C-6), 161.3 (C-8), 152.6 (C-5), 150.1 (C-9), 149.3 (C-1), 139.9 (C-3), 138.6 (C-13), 135.9 (C-10), 128.0 (C-2), 126.4 (C-11), 124.7, 124.0, 123.9 (C-4, C-12, C-14), 117.3 (C-15), 109.1 (C-7) ppm.

3d: From **2d** according to the general procedure (yield 95%). $C_{16}H_{13}ClN_4OPd$ (419.16): calcd. C 45.85, H 3.13, N 13.37; found C 45.30, H 3.30, N 13.15. ^{1}H NMR (400.1 MHz, [D$_6$]DMSO): δ = 11.02 (br, 1 H, NH), 9.33 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 1-H), 8.95 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 8-H), 8.66 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 4-H), 8.28 (t, $^3J_{H,H}$ = 8.3 Hz, 1 H, 3-H), 8.00 (d, $^4J_{H,H}$ = 2.7 Hz, 1 H, 12-H), 7.91 (d, 1 H, 7-H), 7.88 (dd, 1 H, 2-H), 7.14 (d, $^1J_{H,H}$ = 8.0 Hz, 1 H, 15-H), 6.69 (dd, 1 H, 14-H), 3.68 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 161.9 (C-6), 160.9 (C-8), 152.6 (C-5), 152.0 (C-13), 149.7 (C-9), 149.2 (C-1), 139.7 (C-3), 130.6 (C-10), 127.9 (C-2), 125.8 (C-11), 124.1 123.8 (C-4, C-12), 116.4 (C-14), 111.5 (C-15), 108.2 (C-7), 54.9 (OCH_3) ppm.

3e: From **2e** according to the general procedure (yield 90%). $C_{16}H_{10}ClN_5Pd\cdot$DMSO (492.27): calcd. C 43.92, H 3.28, N 14.23; found C 44.04, H 3.33, N 14.47. ^{1}H NMR (400.1 MHz, [D$_6$]-DMSO): δ = 11.54 (br, 1 H, NH), 9.32 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 1-H), 9.11 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 8-H), 8.74 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 4-H), 8.73 (s, 1 H, 12-H), 8.35 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, 3-H), 8.13 (d, 1 H, 7-H), 7.93 (dd, 1 H, 2-H), 7.47 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 14-H), 7.29 (d, 1 H, 15-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO): **3e** was not soluble enough to obtain a ^{13}C NMR spectrum.

X-ray Structure Analyses: The crystal data and refinement parameters for **3a** and **3d** are collected in Table 2. The structures were solved by direct methods (SIR92[19]), completed by subsequent difference Fourier syntheses, and refined by full-matrix least-squares procedures.[20] Semi-empirical absorption corrections from equivalents (multiscan) were applied.[21] The hydrogen atom bound to the nitrogen atom N-4 was located in the difference Fourier synthesis and was refined semifreely with the help of a distance restraint, and its U value was constrained to 1.2 times the U_{eq} value of N-4. All the other hydrogen atoms were placed in calculated positions and refined by using a riding model.

CCDC-999071 (for **3a**) and -999072 (for **3d**) 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/data_request/cif.

Supporting Information (see footnote on the first page of this article): UV/Vis spectral changes in the first 60 s after the addition of **2a** to $(PhCN)_2PdCl_2$, second-order kinetic trace for the second step of the reaction of **2a** with $(PhCN)_2PdCl_2$, NMR spectra of all compounds.

Table 2. Summary of the crystallographic data and details of data collection and refinement.

	3a	**3d**
Empirical formula	$C_{17}H_{17}ClN_4OPdS$	$C_{18}H_{19}ClN_4O_2PdS$
Formula weight	467.26	497.28
Crystal size /mm	0.32 × 0.15 × 0.14	0.26 × 0.07 × 0.06
T /K	150(2)	150(2)
λ /Å	1.54184	1.54184
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/n$
a /Å	11.3161(2)	9.0633(2)
b /Å	20.3112(4)	16.6341(3)
c /Å	7.6539(1)	13.2038(3)
α /°	90	90
β /°	97.815(2)	109.739(2)
γ /°	90	90
V /Å^3	1742.86(5)	1873.64(7)
Z	4	4
$\rho_{calcd.}$ /g cm^{-3}	1.781	1.763
μ /mm^{-1}	11.233	10.534
θ range /°	3.94–62.62	4.44–62.62
Reflections collected	10892	13076
Independent reflections	2777 [R(int) = 0.0293]	3004 [R(int) = 0.0304]
Data/restraints/parameters	2777/1/232	3004/1/250
Final R indices [$I > 2\sigma(I)$][a]	0.0229, 0.0636	0.0211, 0.0521
R indices (all data)	0.0258, 0.0745	0.0230, 0.0527
GooF[b]	1.189	1.069
$\Delta\rho_{max./min.}$ /e Å^3	0.509/–0.854	0.316/–0.677

[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 = $[\Sigma\omega(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) through funding for the transregional collaborative research centre 3MET (Project B2) and by the International PhD program "Catalysis for Sustainable Synthesis (CaSuS)" funded by the German Federal State of Lower Saxony (see www.casus.uni-goettingen.de).

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Received: March 7, 2014
Published Online: April 30, 2014

