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Pyridinium Amidate Ligands for Efficient Pd-Catalyzed Reductive Nitroarene Cyclization Using Formate as CO Surrogate

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Abstract

The field of reductive cyclization of substituted nitroarenes by CO is dominated by the use of palladium complexes with phenanthroline ligands due to their, up to now, unrivalled combination of resistance to oxidation by the nitroarene and ability to stabilize both Pd(II) and Pd(0) complexes. Recently developed pyridinium amidate and pyridinium amide (PYA) ligands are shown here to play the same role. We tested several *N,N*-bidentate PYAs in the reductive cyclization of methyl *o*-nitrocinnamate to 2-carbomethoxyindole using either phenyl formate or the formic acid/acetic anhydride combination as a suitable CO surrogate. This approach avoids high-pressure setups for CO handling, allowing the reactions to be performed in standard pressure tubes. Two of the tested ligands, *viz.* a quinoline-substituted *para*-pyridinium amide and a pyridine-functionalized *ortho*-pyridinium amidate gave excellent results that were comparable to those achieved using phenanthroline, even at a low catalyst loading (0.25 mol%). However, the results obtained with the pyridyl-PYA ligand strongly depend on the acidity of the reaction mixture and the reason was identified as its protonation in an acidic environment. Lower activity observed with other ligands was attributed to either an *ortho*-palladation of the pyridinium N-Me moiety or to an insufficient stabilization of key palladium(0) intermediates.

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Introduction

In homogeneous catalysis, the field of reductive carbonylation of nitroarenes[1–5] and of related reductive cyclization of substituted nitroarenes by CO[6–10] to form N-heterocycles such as indoles are dominated by the use of palladium complexes with 1,10-phenanthroline (Phen) or its substituted derivatives as ligands (Fig. 1a). Phosphines can and have also been employed as ligands, but it has long been known that under the typical reaction conditions, they are oxidized by nitroarenes to phosphinoxides,[11] which severely limits the lifetime of the catalytic system and undermines their suitability for industrial scale applications . Reports on the use of N-heterocyclic carbene (NHC) complexes as catalysts for these reactions are absent, and also our own experience indicates that NHC ligands are indeed unsuitable for these processes. Among the various nitrogen ligands, bipyridine (Bipy) and its substituted analogues induce markedly lower catalytic activity than Phen (Fig. 1b).[12] Likewise, other chelating bis-imines were shown to stabilize the key palladium(0) intermediates only insufficiently.[11] Therefore, Phen has remained unrivalled as ligand in this field so far.

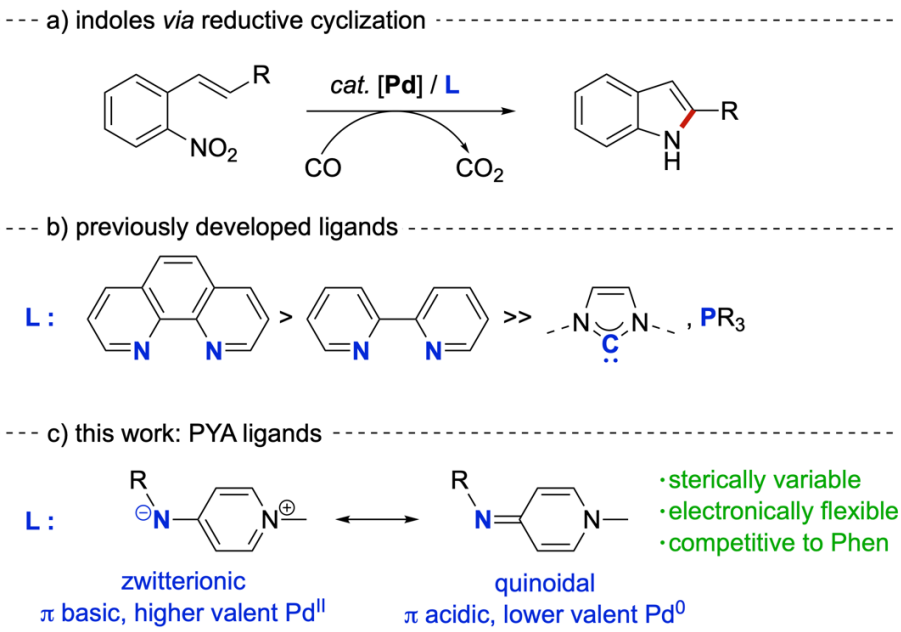

Figure 1. a) General reaction scheme of the palladium-catalyzed reductive cyclization of nitroarenes using CO as reducing agent; b) ligands used in reductive cyclization in combination with a palladium source; c) limiting resonance forms of pyridinium amidate ligands used in this work for palladium-catalyzed reductive cyclization.

The recent development of pyridinium amides and pyridinium amidates (PYAs)[13–15] has introduced a new class of *N*-donors that are formally neutral, yet characterized by a significant contribution from a

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zwitterionic resonance form, resulting in an enhanced anionic character of the *N*-donor site (Fig. 1c).[16] Their strong σ-donating ability,[13,17,18] combined with electronic flexibility,[16,19] enables an effective stabilization of metal centers throughout different stages of catalytic cycles, particularly by supporting both high- and low-valent oxidation states. As a consequence, PYAs have gained wide application as supporting ligands in various areas of homogeneous catalysis.[16,20–24] Notably, when applied as ligands for Pd catalysis including cross-couplings, PYAs have produced highly active systems,[15,25,26] which has been attributed to their ability to stabilize both palladium(0) and palladium(II) complexes. These unique properties prompted us to investigate their competence in substituting Phen for the reductive cyclization of nitroarenes by CO.

An advantage of PYAs compared to other strong σ-donors like NHCs or anionic amido ligands, consists in their stability in deprotonated form. This stability allows catalysts to be formed *in situ* and avoids any handling of typically air- and moisture-sensitive intermediates as well as the use of a strong base. Moreover, it substantially broadens the range of catalytic conditions compatible with PYA systems, including neutral and acidic environments. The latter is particularly relevant when considering formic acid as a green and renewable CO surrogate[27–30] Here we demonstrate that appropriate substitution of the PYA ligand yields *N,N'*-bidentate chelating palladium complexes that catalyze the reductive cyclization of nitroarenes with activities that are competitive with those induced by Phen.

Results and Discussion

Ligands **A**–**H** were prepared by straightforward deprotonation of their corresponding pyridinium salts[14,25,31,32] with a NaOH solution and subsequent extraction with CH_2Cl_2 (Fig. 2). The preparation of ligand **D** is a notable exception and requires DBU to generate the fully deprotonated ligand. Successful deprotonation is indicated by a marked >1 ppm up-field shift of the PYA protons. In **E**, for example, the α and β resonances shifted from δ = 8.10 and 7.39 in the pyridinium salt to 7.04 and 5.90 ppm in the deprotonated ligand.

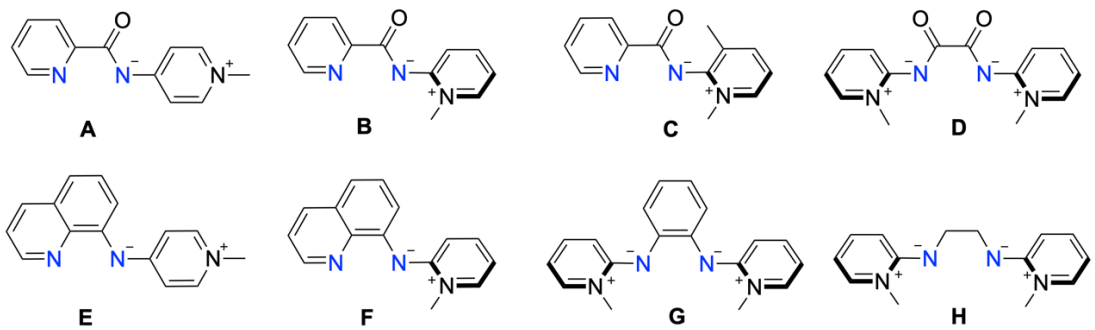

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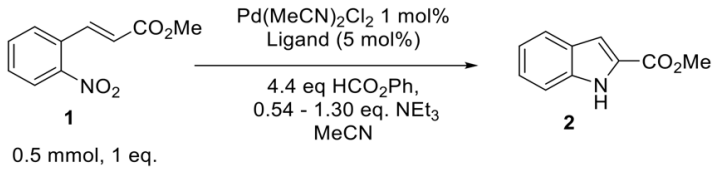
Figure 2. Deprotonated pyridinium amidate and pyridinium amide ligands **A–H** used in the reductive cyclization of nitroarenes. Note that pyridinium amidate ligands **A–D** have also been termed pyridylidene amides, while pyridinium amide ligands **E–H** have originally been termed pyridylidene amines (with reference to their neutral resonance structures). Earlier work distinguished these two subclasses as PYA and PYE ligands, respectively. Here we use PYA as an all-encompassing abbreviation of both, pyridinium amidates and pyridinium amides.

The broad range of neutral PYA ligands offers a large degree of steric and electronic modulation of the ligand properties. For example, the σ-donor properties and electronic flexibility are dependent on the PYA isomers,[16] with the donor strength increasing in the order *o*-PYA < *p*-PYA < *m*-PYA (*cf.* **A** *vs.* **B**, **E** *vs.* **F**).[20] Furthermore, the introduction of *o*-methyl substituents affects the flexibility and steric shielding of the coordinated metal center with obvious consequences on reactivity (*cf.* **B** *vs.* **C**).[25,33] In addition, the linker in bidentate bis-PYA systems allows the rigidity of the ligand to be fine-tuned and the donation to be adjusted (*cf.* **D** *vs.* **G** *vs.* **H**).

As mentioned in the introduction, many reactions have been reported in the literature where a suitably substituted nitroarene is deoxygenated by CO to give a heterocyclic compound. Among these, we chose to investigate the reductive cyclization of methyl *ortho*-nitrocinnamate (**1**) to 2-carbomethoxy-indole (**2**) because we have previously shown that it proceeds efficiently in the presence of either phenyl formate[34,35] or formic acid [30] as CO surrogates. Initially, phenyl formate was chosen as the CO surrogate because it does not alter the pH of the reaction mixture. Ligand screening was performed under standard conditions as previously optimized for the Pd/phen catalyzed reaction (Table 1).[34]

Table 1. Activity of PYA ligands **A–H** in the catalytic reductive cyclization of nitrostyrene **1** [a]



Entry	Ligand	Conditions	Yield (%) [b]	Conversion (%) [b]	Selectivity (%)
1	**A**	I	54	61	89
2	**B**	I	69	73	95
3	**C**	I	>99	>99	>99
4	**D**	I	5	5	>99
5	**E**	I	>99	>99	>99
6	**F**	I	68	70	98
7	**G**	I	<1	13	--
8	**H**	I	<1	10	--
9 [c]	Phen	I	99	99	99

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10	**C**	II	>99	>99	>99
11	**E**	II	>99	>99	>99
12	Phen	II	99	99	99

[a] General reaction conditions I: **1** (104 mg, 0.50 mmol), $Pd(CH_3CN)_2Cl_2$ 1 mol%, ligand 5.0 mol%, HCOOPh (240 µL, 2.2mmol), NEt_3 (40 µL, 0.29 mmol), in CH_3CN (10 mL), 140 °C for 3 h; reaction conditions II identical to I except for NEt_3 (90 µL, 0.65 mmol), in CH_3CN/DMF (9:1 mL), 100 °C for 6 h; [b] yields and conversions determined by GC analysis using biphenyl as internal standard; [c] 2.5 mol% ligand used.

Ligand screening revealed excellent activity and selectivity with essentially quantitative yields of **2** with both ligands **C** and **E** that rival the state-of-the-art catalytic system based on Phen (entries 3, 5, 9). The catalytic performance of pyridyl-functionalized PYA ligands increases in the series *p*-PYA< *o*-PYA << *o,o*-PYA (ligands **A–C**, entries 1–3), hinting at a beneficial effect of the added steric bulk near the Pd center. The more pronounced zwitterionic character of ligand **C** arising from the hindered rotation about the C–N_{PYA} bond also appears beneficial, though electronic rather than steric factors must account for the higher activity and selectivity of ligand **E** compared to **F** (entries 5, 6).[36]

Generally, the presence of two strongly donating PYA units drastically reduces the yield (entries 4, 7, 8). This might be due to the increased flexibility of the ligand for **D** and, especially, for **H** as these flexible ligands may not coordinate strongly enough to palladium to sufficiently stabilize catalytically active intermediates. For example, it is known that substitution of Phen for more flexible Bipy leads to a marked drop in catalytic activity.[8] In support of this hypothesis, formation of palladium black was observed shortly after the start of the reaction with ligands **D** and **H**. Alternatively, the deprotonation of the relatively acidic N–CH_3 protons might also play a role in the deactivation of the catalytic system since the rigid fully conjugated ligand **G** did not afford any measurable amount of **2** (entry 7).

The high selectivity of ligands **C** and **E** at elevated temperature (140 °C) was also maintained under milder conditions in reactions performed at 100 °C, without losing significant activity and competitive with Phen (entries 10–12). Such performance is particularly relevant for targeting substrates with thermally sensitive functional groups like pyrroles or aldehydes, which require mild conditions.[34]

Since all reactions involving ligands **C**, **E**, and Phen reported in Table 1 gave a complete conversion of the starting nitrostyrene in the allotted time, the data do not allow for distinguishing which ligand imparts the highest activity or how the reaction proceeds over time. To better differentiate the ligand-induced catalytic performance, a series of reactions were performed with a lower catalyst loading of 0.25 mol% and shorter reaction times for both ligands **C** (Table 2, entries 1–4) and Phen (entries 5–8). In contrast to any other ligand investigated thus far, the PYA ligand **C** and Phen feature the same conversion profile within the reproducibility limits of the reaction (Fig. 3). Moreover, after an initial period, the reaction proceeds with zero-order kinetics with respect to nitrocinnamate **1** (R^2 = 0.999 for **C**, R^2 = 0.998 for Phen). This rate

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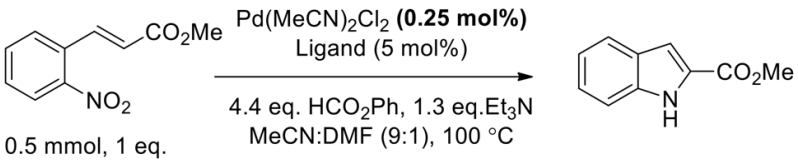
dependence is remarkable, because all related cyclization reactions that were kinetically investigated have been identified as first-order in nitroarene.[37–41] Also relevant to the reaction kinetics is the fact that the selectivity in indole is virtually quantitative all over the reaction course. This implies that any intermediate, whether organic or metallorganic, during the reaction must be short-lived. Since the palladium center is supposed to shuttle between the zero and the +2 oxidation states,[8] the only catalytic step that is substrate-independent under the present conditions is the palladium reduction. Moreover, since the reaction does not slow down over time, decomposition of phenyl formate must be slow under the reaction conditions and the actual CO concentration in the reaction mixture has to be essentially constant, at least within the 2 to 6 hour reaction time interval. Such a model also rationalizes the identical performance of ligands **C** and Phen. While this hypothesis is plausible, an unambiguous verification is prohibited as our set-up does not allow for measuring CO liberation and consumption inside a pressure tube. In support of the model proposed here, previously obtained kinetic data for phenyl formate decomposition under experimental conditions close to those employed in this work[34,42] indicate that formate decomposition proceeds at a rate comparable to that observed for our catalytic reaction.

Table 2. Time-dependent activity induced by ligands **C** and Phen[a]



Entry	Ligand	Time (h)	Conversion (%) [b]	Selectivity (%)[b]
1	**C**	2	46	97
2	**C**	3	59	>99
3	**C**	4	72	>99
4	**C**	6	99	>99
5	Phen	2	45	>99
6	Phen	3	60	99
7	Phen	4	71	98
8	Phen	6	100	>99

[a] General reaction conditions: **1** (104 mg, 0.50 mmol), $Pd(CH_3CN)_2Cl_2$ 0.25 mol%, ligand 5.0 mol%, HCOOPh (240 µL, 2.2 mmol), NEt_3 (90 µL, 0.65 mmol), in CH_3CN/DMF (9:1 mL), 100 °C; [b] selectivity and conversion determined by GC analysis using biphenyl as an internal standard.

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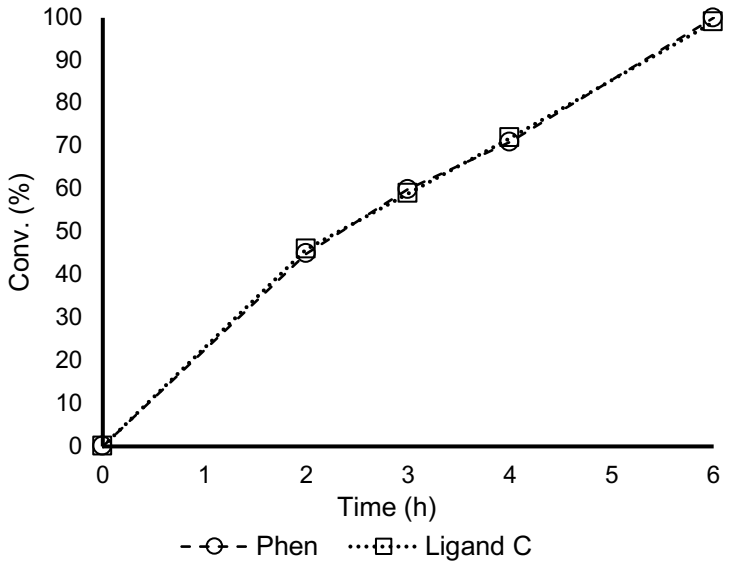

Figure 3. Comparison of the activity of ligands **C** and Phen over time in the palladium-catalyzed reductive cyclization of **1** to **2**. Data from Table 2.

Formic acid (FA) offers considerable advantages over phenyl formate as a CO surrogate in terms of cost, atom economy and bioavailability compared to phenyl formate. Thus, the best performing ligands **C** and **E** were evaluated in the synthesis of **2** mediated by FA and using two sets of previously optimized conditions (Table 3).[43] Under neutral conditions (1:1 NEt_3/FA ratio), $Pd(acac)_2$ with ligand **C** achieves 88% yield of **2** with a low 0.5 mol% palladium loading, similar to Phen as the current state-of-the art ligand for this transformation (entries 1 *vs.* 3). Again, the relatively low reaction temperature of 110 °C permits the use of temperature-sensitive substrates. In contrast, ligand **E** induced only very poor performance with only 8% yield (entry 2). Similar results were obtained when the catalytic reactions were performed in MeCN instead of acetone or with $Pd(CH_3CN)_2Cl_2$ instead of $Pd(acac)_2$ as palladium precursor (Table S4), indicating that neither solvent incompatibility nor the metal precursor plays a significant role.

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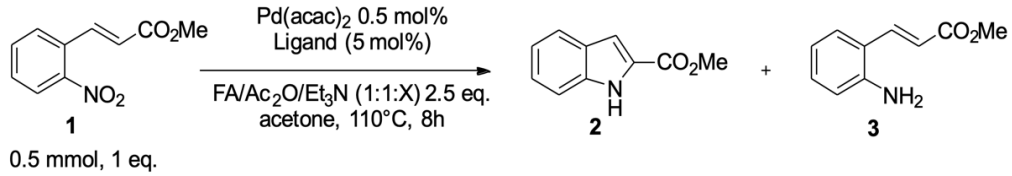
Table 3. Activity of ligands **C**, **E**, and Phen in the catalytic reductive cyclization of nitrostyrene **1** to indole **2** using formic acid (FA) [a]



Entry	Ligand	NEt_3/FA ratio	Yield **2** (%)[b]	Conversion (%)	Selectivity **2** (%)	Yield **3** (%) [b]
1	**C**	1	88	>99	88	8
2	**E**	1	8	9	89	1
3	Phen	1	93	>99	93	n.d.
4	**C**	2	88	>99	88	7
5	**E**	2	33	43	77	2
6	**E**	4	44	55	80	2
7	**E**	9	87	97	90	3

[a] Reaction conditions III: **1** (104 mg, 0.50 mmol), $Pd(acac)_2$ (0.5 mol%), ligand 5.0 mol%, HCOOH (47 µL, 1.25 mmol), NEt_3 (174 µL – 1.5 mL, 1.25 – 10.75 mmol), Ac_2O (118 µL, 1.25 mmol) in acetone (10 mL), 110 °C for 8 h; [b] yields determined by GC analysis using biphenyl as an internal standard.

While an excess of base did not affect the productivity of ligand **C** (entry 4), a substantial impact was noted for the performance of ligand **E**, with increasing NEt_3/FA ratios, both the activity and selectivity of the previously inefficient ligand **E** markedly improved (entries 5–7) and reached essentially equal activity as ligand **C** when NEt_3 was present in a 9-fold excess (entry 7).

These catalytic data disclose a different acid-base sensitivity of the two ligands and call for a rationale as to why productivity of ligand **E** is much worse than that of **C** when formic acid is employed as a CO surrogate, even though they perform almost equally when the surrogate is phenyl formate. Since the CO-releasing step is thought to take place outside of the catalytic cycle and independent of the ligand ― FA dehydration takes place readily at room temperature in the presence of Ac_2O and bases[44] ― the observed reactivity differences therefore ought to originate from distinct ligand behavior at different pH. Three hypotheses for this diverging behavior were considered in more detail: (i) Does protonation and dissociation of the ligand take place under acidic conditions? (ii) Does cyclometalation of a *N*–CH_3 group play a role? And (iii) Are deprotonated ligand species, *e.g., N*-ylides involved in catalysis?

Synthesis and Catalytic Activity of Preformed Complexes. In order to probe these hypotheses, specific complexes were prepared that are presumed to be relevant during catalysis, including [Pd(**C**)Cl_2], **4a**, and the analogue [Pd(**E**)Cl_2], **5a**, as the products from simple ligand exchange with the Pd precursor $PdCl_2$(cod)

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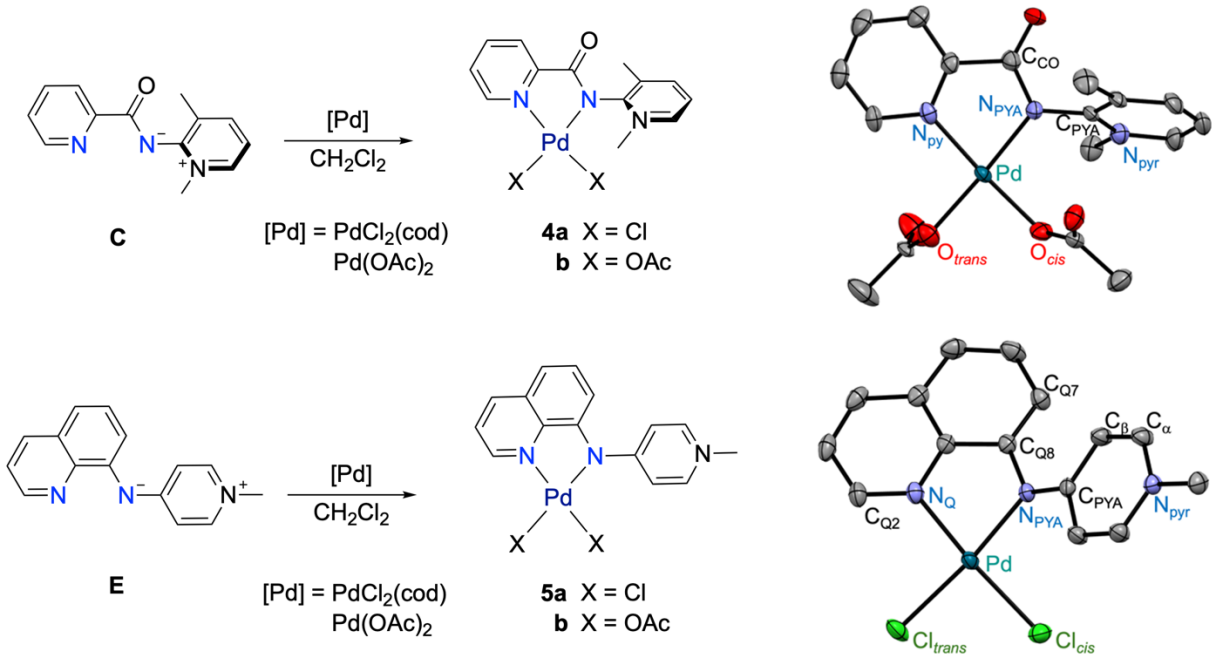
(Scheme 1). In addition to these complexes, the acetate analogues [Pd(**C**)(OAc)$_2$], **4b**, and [Pd(**E**)(OAc)$_2$], **5b**, were prepared, which are thought to form upon hydrolysis of acetic anhydride and subsequent anion metathesis under catalytic conditions.



Scheme 1. Synthesis of well-defined Pd complexes **4a,b** and **5a,b**, and crystallographically determined molecular structures of **4b** and **5a** (50% probability ellipsoids, hydrogen atoms and co-crystallized solvent molecules omitted for clarity).

Complex **4a** was prepared according to the literature,[25] while for **5a**, the deprotonated ligand **E** was reacted with [PdCl$_2$(cod)] to afford the desired complex as an air and moisture stable yellow solid in good yield (87%).[15] Successful metalation was evidenced by the characteristic downfield shift of the ligand protons and especially the quinoline proton in the 2-position (δ = 9.06 ppm) due to the characteristic interaction with the chloride anion in square planar complexes.[45,46] Also, the resonance of the *N*-methyl protons, which has been used as a proxy for the donor properties of the PYA unit, [47] shifted from 3.42 to 3.76 ppm. Single crystal X-ray diffraction analysis of **5a** revealed a considerably distorted square-planar geometry around the palladium center with significant deviation from planarity (Scheme 1, Table S9),[48] which was attributed to the highly rigid nature of the quinoline ligand. As a consequence, C_{PYA} and N_Q are located above and below the palladium coordination plane defined by the metal center, the two chlorides and N_{PYA} (Fig. S39), and the quinoline is twisted out this plane. Likewise, the PYA ring is positioned entirely out of the palladium coordination plane. Despite this distortion, the two Pd–N bonds are essentially identical in length (2.031(6) Å), and so are the two Pd–Cl bonds (2.307(5) Å). The hydrogen in the 2-position of quinoline is close to

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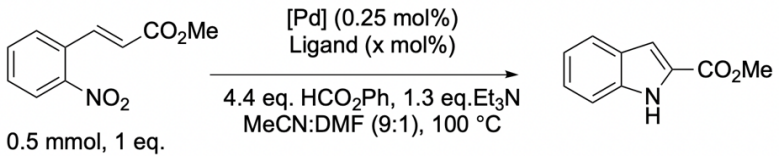
the adjacent chloride (H_{Q2}…Cl_{trans} = 2.7013(5) Å), in agreement with the large deshielding observed in solution (see above). The N_{PYA}–C_{PYA} bond is short for a single bond (1.3494(15) Å), suggesting at least a partial quinoidal contribution of the ligand in **5a**.[15,47] Also, the C_α–C_β bonds are notably shorter than the C_{PYA}–C_β bonds (average 1.362(5) *vs.* 1.424(3) Å), in agreement with considerable double bond localization.

Notably, reaction of [$PdCl_2$(cod)] and an excess of ligand **C** as used under catalytic conditions afforded a NMR spectrum that revealed the superimposition of complex **4a** and ligand **C**. Similar results were obtained when exposing complex **4a** to ligand **C** (Fig. S8), without forming any detectable amounts of a complex containing two ligands bound to palladium of the type [Pd(**C**)$_2$]$^{2+}$, thus justifying the choice of complexes [PdX_2(L)] as the starting point for catalytically relevant reactivity studies.

In order to check the relevance of preformed complexes **4a** and **5a** in the reductive cyclization, they were both tested as catalyst precursors under standard experimental conditions (*cf* Table 2), yet only for 4 h. This shorter reaction time avoided complete conversion that would hide the real catalytic activity. The results were compared with those obtained by employing the *in situ* formed catalysts and those obtained by employing the preformed complexes, but in the presence of an excess free ligand so that total amount of ligand added is the same as for the *in situ* generated complex (Table 4).

Table 4. Comparison of the catalytic activity of preformed and *in situ* generated complexes[a]



Entry	[Pd]	Ligand (mol%)	Yield (%)[b]	Conversion (%) [b]	Selectivity (%)[b]
1	$Pd(MeCN)_2Cl_2$	**C** (5)	72	72	>99
2	**4a**	**C** (4.75)[c]	93	95	98
3	**4a**	-	6	15	37
4	$Pd(MeCN)_2Cl_2$	**E** (5)	69	80	86
5	**5a**	**E** (4.75)[c]	58	68	86
6	**5a**	-	1	4	29

[a] General reaction conditions: **1** (104 mg, 0.50 mmol), [Pd] 0.25 mol%, HCOOPh (240 µL, 2.2 mmol), NEt_3 (90 µL, 0.65 mmol), in CH_3CN/DMF (9:1 mL), 100 °C, 4 h; [b] determined by GC analysis using biphenyl as internal standard; [c] 4.75 mol% was used to ensure a consistent total ligand amount.

The results clearly show that the preformed complexes have a similar activity to the *in situ* generated system when excess ligand is present (entry 1 *vs* 2, and entry 4 *vs* 5), but their activity and selectivity drops when

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no extra ligand is added (entries 3, 6). Whereas the results in the presence of extra ligand support the formation of **4a** and **5a** at some stage during the reaction, the low activity observed when no additional **C** or **E** are added is consistent with the well-known fact that nitrogen ligands are quite labile, especially when bound to a palladium(0) center. Indeed, for all carbonylation reactions of nitroarenes catalyzed by palladium supported by phenanthroline-type ligands, excess ligand is always necessary to stabilize the catalytic system, with the molar ligand to metal ratio exceeding sometimes 100:1 especially when a very low palladium loading is employed.[49] Furthermore, the requirement for a large excess of ligand disfavors the formation of nanoparticles as active species, as the ligand/metal ratio is lower than 1 even for ligand-stabilized nanoparticles.

Reaction of **C** and **E** with $Pd(OAc)_2$ afforded complexes **4b** and **5b** in good yields (89% and 79%, respectively) as air and moisture stable orange solids. Again, metalation was indicated spectroscopically by the downfield shifts of the ligand protons, especially those belonging to the PYA unit. For instance, the N-CH_3 signal was shifted from δ_H = 3.86 to 4.32 ppm for **4b** and from 3.42 to 3.85 ppm for **5b**. Another distinctive feature of these complexes is the presence of two inequivalent acetate ligands. In **4b**, the chemical shift difference between the two ligands was 0.70 ppm, i.e. δ_H = 1.91 *vs.* 1.21 ppm. The more deshielded signal was attributed to the acetate *trans* to the strongly donating PYA unit via ^{1}H NOE spectroscopy. For **5b**, the limited solubility prevented ^{1}H NOE assignment of the acetate resonances. Notably the chemical shift difference between the two signals was lower, 0.11 ppm, i.e. δ = 1.87 *vs* 1.76 ppm. Moreover, neither the *ortho* protons of the pyridine nor the quinoline fragment were deshielded, in contrast to the chloride complexes **4a** and **5a**. Crystallographic analysis of **4b** revealed a square-planar geometry with two κ^1-bound acetate ions (Scheme 1, Table S8). Bond length analysis of the PYA moiety revealed a typical zwitterionic type configuration of the ligand supported by the long N_{PYA}–C_{PYA} bond (1.395(4) Å), similar to the 1.401(4) Å for the same bond in the protonated ligand precursor **[C-H][PF$_6$]**.[25] Despite the different metrics in the PYA ligand, the bond lengths and angles around Pd are essentially identical to those in **5a** (Tables S8, S9). Notably, the palladium square plane is much less distorted with all four coordinating nuclei and C_{PYA} located in the coordination plane. However, the PYA heterocycle is rotated out of this plane as represented by the dihedral angle Pd–N_{PYA}–C_{PYA}–N_{pyr} = 76.1(3)°. This quasi-orthogonal arrangement is imposed by the two *ortho*-methyl substituents and was observed previously also for **4a**. This conformation also induces a ring current effect of the PYA ring on the *cis*-located acetate, thus rationalizing its considerable shielded resonance (δ_H = 1.21).

Acid-Sensitivity of Complexes with Ligands C and E. Protonolysis was investigated with $[HNEt_3]Cl$, as this is the acid expected to prevail under catalytic conditions due to the presence of NEt_3.[50] Complex **4a** does not react at all when exposed for 48 h to 10 eq. $[HNEt_3]Cl$ under catalytically relevant conditions

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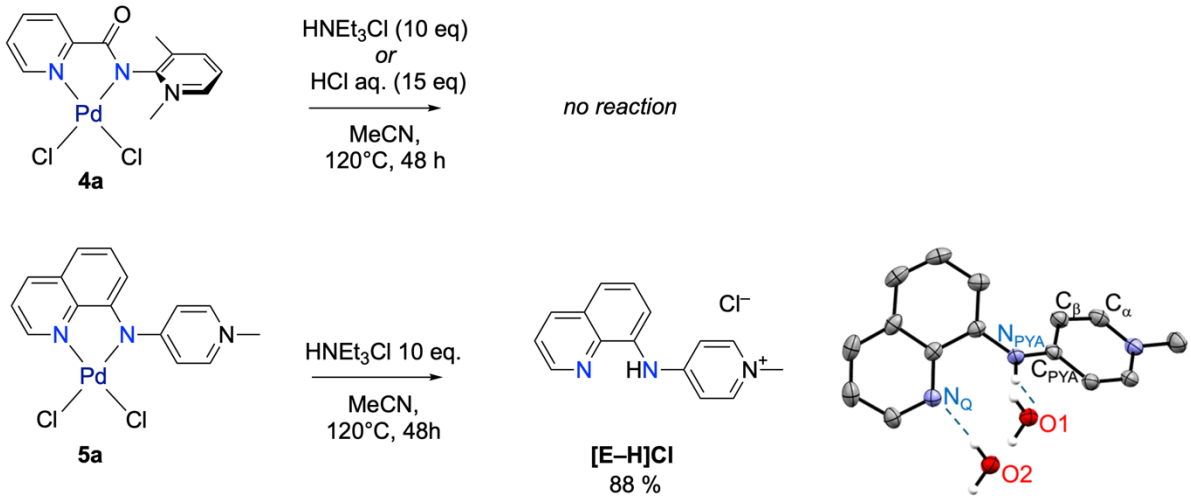
(MeCN, 120 °C; Scheme 2). Even under harsh conditions using 15 eq. HCl, complex **4a** is completely stable, indicating a remarkable robustness of the N–Pd bonds in this complex (Fig. S19, S20).



Scheme 2. Reactivity of complexes **4a** and **5a** towards acids with formation of the ligand precursor salt **[E–H]X** and molecular structure of the **E–H** cation (50% probability ellipsoids, carbon-bound hydrogen atoms, non-bonding water molecules and counteranion omitted for clarity).

In contrast, **5a** is much less stable and after 16 h at catalytic reaction temperature, the presence of 10 eq [HNEt$_3$]Cl led to 54% ligand protonolysis and formation of **[E–H]Cl** (Scheme 2) and up to 88% after extended periods of time together with a black deposit attributed to palladium(0) formation.[51] Even at milder temperatures such as 70 °C, signals attributed to ligand protonation start to appear after 16 h.

It is worth noting that **[E–H]Cl** is spectroscopically distinct from the protonated ligand precursor **[E-H]OTf** with aromatic signals shifted by 0.2–0.7 ppm (Fig. S21, S22). Crystals grown from diffusion of THF into a solution of **[E–H]Cl** from the reaction mixture confirmed, however, the identity of the pyridinium chloride and revealed hydrogen-bonded water molecules (Scheme 2). Such hydrogen bonding is expected to depend strongly on the counterion and may cause the chemical shift differences observed in the NMR spectra of [E–H]$^+$ with OTf$^-$ as better hydrogen bond acceptor than Cl$^-$.[52]

The high sensitivity of **5a** towards acids may thus rationalize the poor activity of ligand **E** under acidic conditions and also plausibly explains the recovery of catalytic activity when formic acid is buffered with sufficient NEt$_3$. In contrast, **4a** is remarkably stable, even under strongly acidic conditions and, therefore, ligand **C** remains operative in the presence of large quantities of formic acid even in the absence of excess NEt$_3$.[53]

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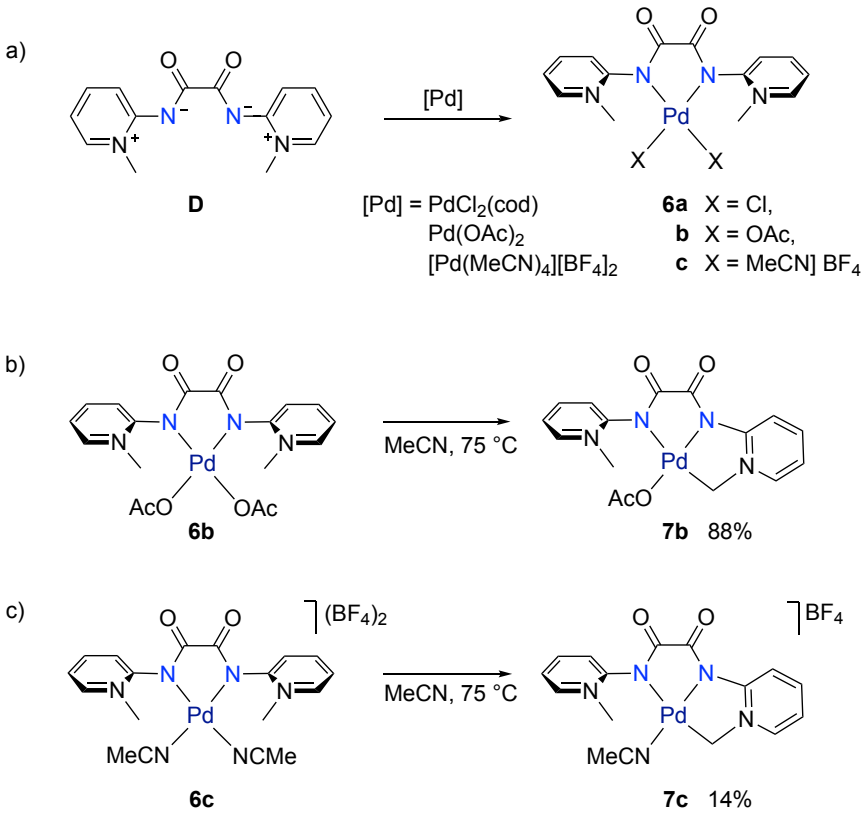
The Impact of Cyclometallated PYA Complexes. Cyclometalation via C–H bond activation of the *ortho*-positioned *N*-methyl group was first tested with ligand **D,** which is assumed to feature the most acidic methyl C–H bonds due to the presence of the carbonyl linker**.** To this end, ligand **D** was complexed with various commercially available palladium(II) precursors to afford complexes **6a–c** containing anionic ligands that may potentially be present under catalytic conditions (Scheme 3a). No thermally induced cyclometalation of chloride complex **6a** was observed when stirring the complex at 75 °C for 48 h. In contrast, the acetate analogue **6b** readily cyclometallated under these conditions, with 75% conversion to the palladacycle **7b** within 16 h, and full conversion in 48 h (Scheme 3b). Complex **7b** was isolated as an air-stable yellow solid in high yield (88%). Cyclometalation was readily identified by the appearance of a new *N*–CH_2 singlet at 5.08 ppm together with a complete desymmetrization of the aromatic signals (Fig. 4, S31).



Scheme 3. a) Synthesis of well-defined palladium(II) complexes **6a**–**6c**; b) Thermally induced cyclometalation of **6b** to give complex **7b**; c) Thermally induced cyclometalation of **6c** to yield partial conversion to **7c**.

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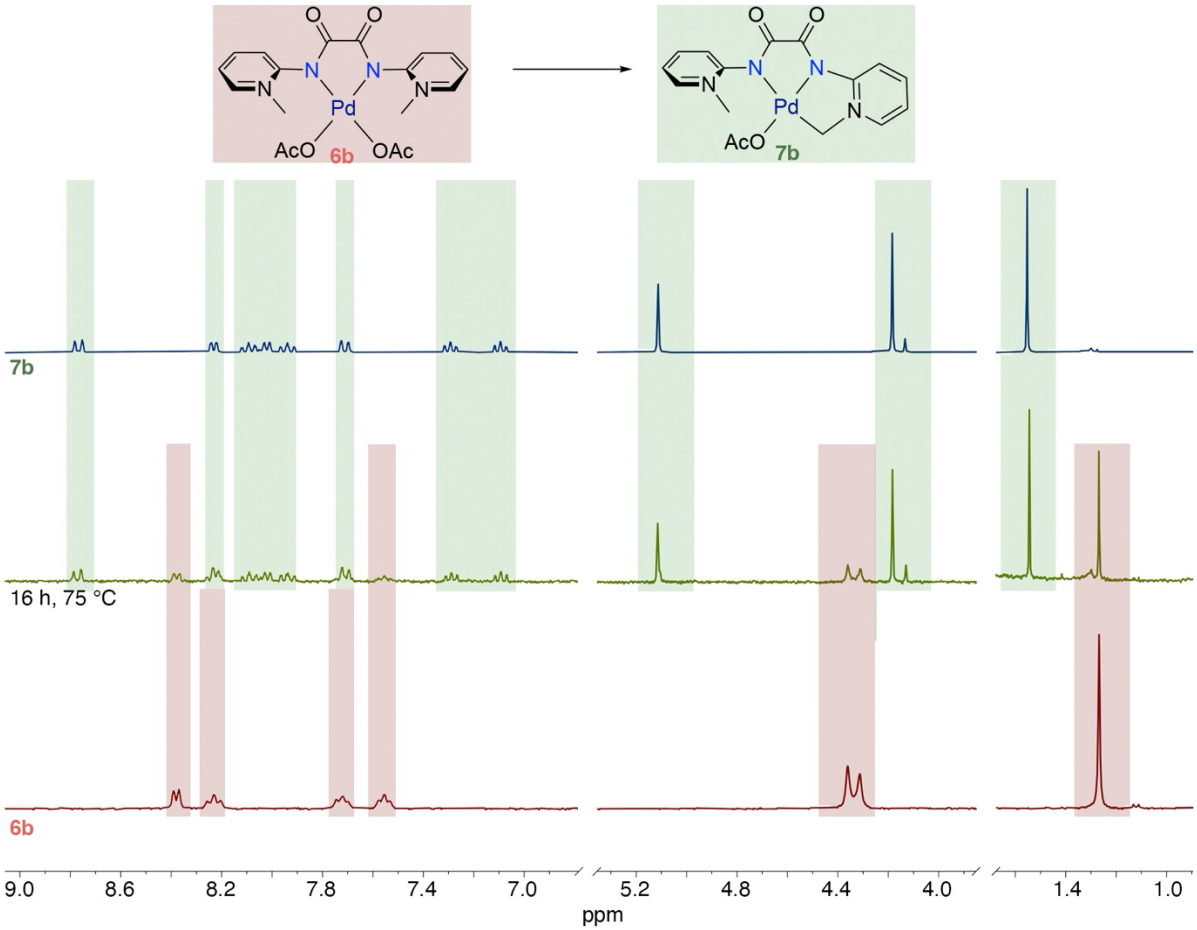

Figure 4. ^{1}H NMR spectra (CD_3CN, 298 K, 300 MHz) of **6b** (bottom), **6b** after heating to 75 °C for 16 h (middle) showing 75% conversion to **7b** (middle), and **7b** isolated after 48 h. Aliphatic signals belonging to **6b** are highlighted in red, and those belonging to **7b** in green. The PYA N-CH_3 resonances appear as two signals in a 5:4 ratio due to mutual *syn* and *anti* orientation of the two PYA heterocycles in **6b** (only *syn* shown), while in **7b** the signals were split in a 10:1 ratio between two configurational isomers.

The cationic bis(acetonitrile) complex **6c** also underwent cyclometalation under these conditions, though the conversion was very slow and reached a modest 7% after 16 h and just 14% after 48 h (Scheme 3c, Fig. S29). The conversion increased to 41% when the reaction temperature was raised from 75 to 90 °C, though extending the reaction time beyond 48 h did not improve the yield any further. Presumably, an equilibrium was reached due to the release of HBF_4, which may be prone to ring-open the metallacycle when present in sufficiently high concentration. Notably, this anion-dependence of the cyclometalation may be less relevant under catalytic conditions, as anion exchange is dynamic and fast. For example, adding 10 eq. NaOAc to the chloride complex **6a** instantaneously yielded a mixture of acetate complex **6b**, starting material, and the mixed anion complex [Pd(**D**)Cl(OAc)] (Fig. S35). Since anion metathesis occurs readily at room

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temperature, a large excess of acetate ions is expected to provide access to complex **6b** under catalytic conditions for mild and efficient cyclometalation.

While cyclometalation is feasible with ligand **D** and induced already at moderate temperatures, ligand **C** is much more resistant to cyclopalladation. Heating the acetate complex **4b** to 75 °C did not change the spectrum at all. [54] Only at elevated temperatures of 120 °C, traces of a new species appeared after 16 h, which was attributed to the cyclopalladated complex based on the characteristic CH_2 resonance at $\delta_H = 5.65$ in the NMR spectrum. However, conversion reached only 7% after a week, together with the formation of unidentified species (Fig. S30). This cyclometalation rate is presumably too small to be relevant in the 4–6 h time window of the catalytic reaction with ligand **C**. Moreover, the low catalytic activity imparted by ligand **D** hints to a deactivating role of cyclopalladation.

Relevance of Ligand Deprotonation for Catalyst Activation. To assess the potential role of the base in deprotonating the N-methyl group of the PYA ligand and to form *N*-ylide species, complexes **4a** and **5a** were exposed to 20 eq. NEt_3. Both complexes were stable and did not react at RT (Fig S36, S37), though upon heating to 75°C, new signals appeared around $\delta_H = 10$ together with the formation of a Pd mirror. Extending the reaction time to 16 h did not increase conversion to the newly formed species. When the temperature was increased to 120 °C, the ligand was the only species in solution after 16 h, indicating full degradation of the complex and for complex **4a** due to apparent reduction, in contrast to the high robustness towards acids. According to these results, deprotonation of the coordinated ligand may constitute a pathway for catalyst deactivation, yet it does not provide access to the active species.

Conclusions

For the first time, this work presents ligands that are competitive with Phen for the palladium-catalyzed reductive cyclization of nitroarenes using *in situ* generated CO. Key to these ligands is a pyridinium amidate (PYA) donor site, together with a supporting imine donor site. Electronically and structurally diverse variation is facilitated by the synthetic versatility of the amino-pyridine core of the PYA ligand. The most competent ligands are comprised of a quinolyl-PYA or a pyridine-acyl-PYA system. While their activity is high when using phenyl formate as CO surrogate, only the pyridine-acyl-PYA system shows excellent performance also when formic acid is used as CO source. Mechanistic work indicates a higher basicity of the quinolyl system, which results in ligand dissociation and loss of catalytic activity, while the pyridine-acyl-PYA is highly robust, even under harshly acidic conditions such as HCl. Moreover, cyclometallation

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involving the *N*-methyl group of the pyridinium fragment has been demonstrated and may constitute another pathway for catalyst deactivation. The synthetic flexibility of the best-performing ligand system, both at the pyridinium amidate site as well as the pyridine unit, offers vast opportunities for further optimization of the catalytic performance and may lead to activities that surpass Phen as a benchmark system. In addition, such work may further support our mechanistic model including palladium reduction as the turnover-limiting step.

Experimental Section

General: The pyridinium amides **[D-H]PF$_6$**,[S1] **[E-H]OTf**,[S2] pyridinium amidates **A**,[S3] **B**,[S3] **C**,[S3] **F**,[S4] **G**,[S5] and **H**,[S6] complexes **4a**,[S3] and **5a**,[S2] phenyl formate,[S7] and methyl-2-nitrocinnamic-carboxylate[S7] were prepared according to previously reported procedures. MeCN and CH_2Cl_2 were dried by passage through a solvent purification column. All other reagents and solvents were commercially available and used as received. Unless otherwise stated all the reactions were run under exclusion of air using standard Schlenk techniques under an atmosphere of dry nitrogen. Unless otherwise specified, NMR spectra were recorded at 25 °C on Bruker spectrometers operating at 300 or 400 MHz (^{1}H NMR) and 75 or 100 MHz (^{13}C{^{1}H} NMR), respectively. Chemical shifts (δ) are expressed in ppm downfield from $SiMe_4$ using the residual protonated solvent as an internal standard and coupling constants in Hz. Assignments are based on homo- and heteronuclear shift correlation spectroscopy and NOE measurements. High resolution mass spectrometry was carried out with a Thermo Scientific LTQ Orbitrap XL (ESI-TOF). All the MS data were collected by the mass spectrometry group in the DCBP. Elemental analyses were performed on a Thermo Scientific Flash 2000 CHNS-O elemental analyzer by the microanalytic laboratory at the DCBP.

Synthesis of Complex 4b: Pyridinium amidate **C** (130 mg, 0.57 mmol) and [Pd(OAc)$_2$] (128 mg, 0.57 mmol) were dissolved in CH_2Cl_2 (10 mL) under N_2 and the resulting solution was stirred at 23 °C for 2 h. The reaction mixture was then filtered over celite, concentrated and dried at 90 °C for 4 days to yield 4b as an orange solid (230 mg, 89%). Crystals suitable for XRD were obtained by slow diffusion of Et_2O into a CH_2Cl_2 solution of **4b**. ^{1}H NMR (300 MHz, CD_3CN, 298K) δ = 8.33 (d, J_{HH} = 6.2 Hz, 1H, H_α), 8.23–8.06 (m, 3H, H_γ + 2H_{pyr}), 7.84 (d, J_{HH} = 7.8 Hz, 1H, H_{pyr}), 7.68–7.59 (m, 1H, H_{pyr}), 7.59–7.52 (m, 1H, H_β), 4.32 (s, 3H, NCH_3), 2.60 (s, 3H, C–CH_3), 1.91 (s, 3H, *trans*-CH_3COO), 1.21 (s, 3H, *cis*-CH_3COO) ppm. ^{13}C{^{1}H} NMR (101 MHz, CD_3CN , 298K) δ = 177.50 (*trans*-MeCOO), 176.90 (*cis*-MeCOO), 168.99, (NCO), 157.33 (C_{PYA}), 152.84 (C_{pyr}), 149.48(C_{pyr}), 146.72 (C_γ), 143.05 (C_α), 141.34 (C_{pyr}), 138.83 (C_δ), 129.19 (C_{pyr}), 126.57 (C_{pyr}), 123.76 (C_β), 45.57 (NCH_3), 23.65 (*trans*-*C*H_3COO), 21.79 (*cis*-*C*H_3COO), 18.61

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($C_{\delta}CH_3$) ppm. ^{1}H NMR (400 MHz, CD_2Cl_2, 298K) δ = 8.27 (d, $^3J_{HH}$ = 6.3 Hz, 1H, H_{α}), 8.19 (dd, J_{HH} = 5.5, 1.5 Hz 1H, H_{pyr}), 8.09 (d, $^3J_{HH}$ = 7.8 Hz, 1H, H_{γ}), 8.05 (td, J_{HH} = 7.7, 1.5 Hz 1H, H_{pyr}), 7.87 (dd, J_{HH} = 7.8, 1.5 Hz 1H, H_{pyr}), 7.55 (ddd, J_{HH} = 7.3, 5.5, 1.5 Hz 1H, H_{pyr}), 7.51 (dd, J_{HH} = 7.8, 6.3, Hz 1H, H_{β}), 4.32 (s, 3H, NCH_3), 2.60 (s, 3H, C–CH_3), 1.91 (s, 3H, *trans*-CH_3COO), 1.21 (s, 3H, *cis*-C*H*$_3$COO) ppm. HR-ESI-MS (m/z): calculated for $C_{15}H_{16}N_3O_3Pd$ [M–OAc]$^+$ = 392.0226; found: 392.0218. Elemental analysis calculated for $C_{17}H_{19}B_2N_3O_5Pd$ ´ 0.3 CH_2Cl_2: C 43.54; H 4.14; N 8.80, found: C 43.78; H 4.26; N 8.48%.

Synthesis of Complex 5b: Pyridinium amidate **E** (75 mg, 320 µmol) and $Pd(OAc)_2$ (72 mg, 320 µmol) were dissolved in CH_2Cl_2 (10 mL) under N_2 and the solution was stirred at 23 °C for 2 h. The formed red suspension was filtered, and the residue was washed with CH_2Cl_2 and dried at 90 °C for 4 days to yield **5b** as an orange solid (115 mg, 79%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 298 K): δ = 8.59 (dd, J_{HH} = 8.4, 1.3 Hz, 1H, H_{quin}^4), 8.07 (dd, J_{HH} = 5.1, 1.3 Hz, 1H, H_{quin}^2), 8.02 (d, $^3J_{HH}$ = 7.6, 2H, H_{α}), 7.75–7.58 (m, 2H, H_{quin}^3 + H_{quin}), 7.56–7.42 (m, 4H, H_{β} + 2H_{quin}), 3.85 (s, 3H, NCH_3), 1.87 (s, 3H, *trans*-CH_3COO), 1.76 (s, 3H, *cis*-C*H*$_3$COO). ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$, 298 K): δ = 175.5 (*trans*-MeCOO), 174.9 (*cis*-MeCOO), 163.5 (C_{PYA}), 150.7 (C_Q), 148.43 (C_{quin}^2), 145.0 (C_{quin}), 142.01 (C_{α}), 138.86 (C_{quin}^4), 128.41, 122.20, 119.40 (3 × C_{quin}H), 116.47 (C_{quin}^3), 115.97 (C_{β}), 44.07 (NCH_3), 24.11 (*trans*-*C*H$_3$COO), 23.83 (*cis*-*C*H$_3$COO) ppm. Quaternary C_{quin} chemical shifts estimated from HMBC spectra. HR-MS (m/z): calculated for $C_{17}H_{16}N_3O_2Pd$ [M–OAc]$^+$ = 400.0277; found: 400.0272. Elemental analysis calculated for $C_{19}H_{19}N_3O_4Pd$ ´ 0.2 CH_2Cl_2: C 48.37, H 4.10, N 8.81; found: C 48.41, H 3.98, N 8.61%.

Typical Catalytic Procedure for Reductive Nitroarene Cyclization with Phenyl Formate: A pressure tube was charged with **1** (104 mg, 0.5 mmol) and placed under an atmosphere of dry N_2. The appropriate amount of catalyst and ligand was added from stock solutions and the mixture was stirred for 10 min. Then HCOOPh (240 µL, 2.2 mmol) was added and the reaction volume was adjusted to 10 mL by adding CH_3CN (conditions I) or CH_3CN/DMF (9:1, conditions II). Finally, NEt_3 (40 µL, 0.29 mmol for conditions I, 90 µL, 0.65 mmol for conditions II) was added, the reaction vessel plugged and the mixture was stirred for 10 min at 23 °C. The tube was placed in a preheated aluminum block at 140 °C (conditions I) or 100 °C (conditions II). After the indicated reaction time, the reaction mixture was cooled to room temperature, carefully opened, and the content was analyzed by GC after adding biphenyl (50 mg) as internal standard.

Typical Catalytic Procedure for Reductive Nitroarene Cyclization with Formic Acid: A pressure tube was charged with **1** (104 mg, 0.5 mmol) and placed under an atmosphere of dry N_2. The appropriate amount of catalyst and ligand was added from stock solutions and the mixture was stirred for 10 min. Subsequently, NEt_3 (1.74 µL, 1.25mmol) and acetic anhydride (118 µL, 1.25mmol) were added, and the corresponding solvent was layered to a total volume of 10 mL. Finally, formic acid (47 µL, 1.25 mmol) was added, and the pressure tube was sealed under dinitrogen and heated while stirring to 110 °C (conditions III) or 120 °C

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(conditions IV). After the indicated reaction time, the pressure tube was cooled to room temperature, carefully opened, and the content analyzed by GC after adding 50 mg of biphenyl as internal standard.

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Supporting Information available: synthetic procedures including NMR spectra, catalytic procedures, precatalyst reactivity studies, and crystallographic data (pdf), see DOI: **XXXX**. Deposition Numbers <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/cctc.202401933">2404744 (for **4b**), 2404745 (for **5a**), 2404746 (for **[E–H]Cl**)</url> contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href="http://www.ccdc.cam.ac.uk/structures">Access Structures service</url>.

Competing Interests: The authors declare no competing financial interest.

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however, an order of magnitude smaller than the one observed between quinoline H^6 and H^7, suggesting hindered rotation about the exocyclic C–N bond and an orthogonal conformation of the pyridinium heterocycle with the quinoline fragment. The same features were observed with ligand **E**, with a correlation between PYA H_β and quinoline H^7 that is substantially smaller than the one observed between the quinoline protons, suggesting an orthogonal arrangement also with the *para*-PYA (Fig. S5, S6).

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[50] To mimic catalytic conditions, **3a** and **4a** were initially exposed to the acid formed by the in-situ reaction of FA and NEt_3, *i.e.* $[HNEt_3][HCOO]$. However, rapid anion metathesis with the formate anion followed by palladium-catalyzed formic dehydrogenation leading to ligand hydrogenation at elevated temperatures complicated a straightforward evaluation of the precatalysts acid robustness (Fig S23–S25). Since under catalytically relevant conditions, HCOOH is readily decomposed to CO and H_2O, the innocent chloride anion was chosen instead for a better evaluation of the precatalyst behavior.

[51] It was noted that the same species was quantitatively obtained upon reacting **4a** with 3 eq. of $[HNEt_3][HCOO]$ at 23 °C for 16 h.

[52] The **[E–H]X** products formed upon degradation of **5a** in the presence of various $[HNEt_3]X$ salts (X = Cl^-, $HCOO^-$) or aqueous HCl display a high-field ^1H NMR resonance for the NCH_3 protons at about 4 ppm, similar to that of the parent protonated ligand **[E–H]OTf**, though they show differences in the aromatic region (Fig. S22, S26). These different chemical shifts in the aromatic region of **[E–H]X** salts may be rationalized by ion pairing and H-bonding effects. Such behavior is further supported by the gradual shifts observed for the aromatic resonances of both the PYA and the quinoline units upon addition of aliquots of D_2O to a solution of **[E–H]OTf** in CD_3CN (Fig. S27). Likewise, the species obtained by treatment of **[E–H]OTf** with NEt_3 shows such variation, and the spectrum is distinctly different from that of the deprotonated ligand **E** (Fig. S26, S37). The former features PYA β proton

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resonances at 7.3 ppm (cf. 5.9 ppm in **E**) and a NCH_3 singlet at 3.96 (cf. 3.45 ppm in **E**). These data suggest that the ligand is protonated even in the presence of an excess of NEt_3.

[53] In agreement with the higher basicity of **E**, the ligand precursor pyridinium ion **[E-H]**$^+$ remains unchanged in the presence of 20 eq. NEt_3, whereas **[C–H]**$^+$ is fully deprotonated under these conditions to afford ligand **C** exclusively (Fig. S37).

[54] When **4a** was treated with 10 eq. NaOAc at 23 °C, anion metathesis was induced to give a 65:10:25 distribution of **4a**, [Pd(**C**)Cl(OAc)], and **4b**. Notably this ratio was not affected by temperature and remained equal when the reaction mixture was heated at 120 °C for 16 h (Fig. S33). No decomposition to palladium(0) was observed either, further confirming the highly stabilizing nature of ligand **C**.

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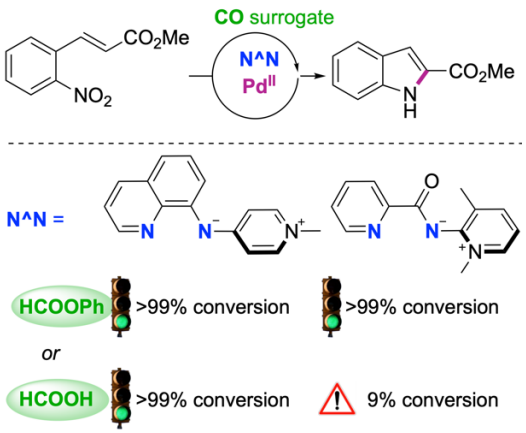

Pyridinium amidate ligands can do it: while phenanthrolines have been the only ligands suitable for palladium-catalyzed reductive cyclization of nitroarenes so far, we demonstrate that pyridinium amidates are competitive and provide high conversion. With tailored ligands, even formic acid is a suitable CO surrogate for efficient cyclization with high selectivity. Acid-labile ligands are poorly performing, unless sufficient NEt_3 is provided.

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