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Evidence for Metal–Ligand Cooperation in a Pd–PNF Pincer-Catalyzed Cross-Coupling

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Supporting Information

ABSTRACT: The first Pd–pincer complex bearing a halogen (fluorine) arm has been prepared via the base-assisted dearomatization of a phosphine–quinoline (P∼N) ligand. This dearomatization is reversible and has been used to facilitate catalytic Sonogashira-type cross-coupling that, contrary to the typical mechanistic approach, is based on a metal–ligand cooperation mode.

Late transition metal pincer complexes have long become ubiquitous in a great variety of synthetic and mechanistic studies.[1−4] Initially introduced in 1970s as unusually robust cyclometalated structures bearing two fused chelates (**A** in Figure 1),[5−7] metal–pincer complexes have become invaluable

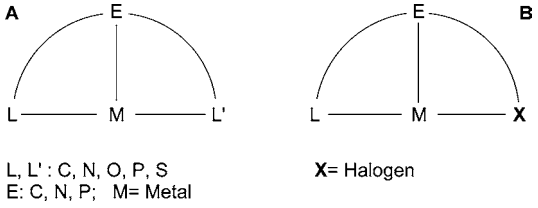

Figure 1. Schematic representation of metal–pincer complexes.

for the activation of strong bonds[8−10] and catalysis.[11−17] As the initial work on the catalytic behavior of pincer complexes focused on the metal-based bond activation properties, Milstein and co-workers recently elevated the metal–pincer catalysts to a new level by introducing the metal–ligand cooperation mechanism, which involves reversible dearomatization of the ligand's aromatic core.[18−20] For example, this approach allowed for a variety of synthetically challenging catalytic transformations that require the activation of O–H and N–H bonds to take place under mild conditions with very high selectivity.[21,22]

The significant interest in the metal–pincer ligand chemistry led to the development of a myriad of pincer structures with group 4–6 donors in various oxidation states placed at either the central or side-arm positions (**A** in Figure 1). However, to the best of our knowledge, there is only one example of a metal (Ru) complex where a halogen atom (F) is incorporated as a donor in a tridentate pincer system (**B** in Figure 1),[23] and there are no reports on the chemical reactivity of such complexes. In addition to the fundamental interest in exploring the properties of halogen-containing pincer complexes, a relatively weak coordinating halogen ligand would be expected to be labile, providing an empty site for the incoming substrate during the catalytic cycle. Herein we present the first example of a palladium pincer complex that contains a fluorine atom as a side arm. We also show cross-coupling catalytic activity of this complex that is based on metal–ligand cooperation, which is unprecedented in cross-coupling chemistry.

Since organic halogen atoms are not expected to form strong bonds with late transition metals, we designed a rigid system that would pitch the metal center against the fluorine atom upon the coordination of the former to a chelating donor system. Thus, we prepared the 8-fluoroquinoline-based chelated Pd(II) complex **1**,[24] which could be used as a precursor to a new PNF-type pincer system. Upon removal of the iodo ligand with silver tetrafluoroborate ($AgBF_4$), cationic complex **2** was obtained in a high yield (Scheme 1). The $^{19}F\{^1H\}$ NMR signal of the 8-fluorine atom shifted significantly upfield, which could be indicative of the Pd---F interaction (vide infra), but no other evidence for such an interaction could be obtained. On the other hand, stronger ligands, such as acetone or pyridine, readily coordinated to the Pd atom, giving the new cationic complexes **3** (Scheme 1). As the reaction of **1** with excess sodium methoxide (NaOMe) cleanly produced **4**, the dearomatized product of the OCH_3-for-F substitution,[24] we decided to investigate the reactivity of **1** toward bulkier, less nucleophilic alkoxides that could remove HI from the complex without replacing the fluorine atom of the 8-fluoroquinoline core.

Although the reaction between **1** and 2–5 equiv of sodium ethoxide (NaOEt) in benzene resulted in the fluorine substitution to give complex **5**, which was characterized crystallographically (Scheme 1), the addition of the bulkier sodium *tert*-butoxide (NaOt-Bu) to **1** cleanly produced the new PNF-type pincer complex **6** (Scheme 1). Deep-red crystals of **6** were subjected to X-ray structural analysis, which showed that the Pd center is located in a distorted square-planar environment. The coordination of the fluorine atom of the 8-fluoroquinoline moiety is evident from the relatively short Pd–F distance of 2.4076(18) Å, which is well below the sum of the van der Waals radii of the two elements (3.10 Å). This distance is noticeably longer than covalent Pd–F bonds, which generally have lengths of 1.947–2.090 Å.[25] However, it compares well to the Ru–F distance of 2.367(3) Å in the only other known metal–PNF pincer system.[23] Importantly, in the few reported examples of late transition metal–fluorine interactions in nonpincer systems, the metal–F distances are significantly longer [cf. the Pd–F distance of 3.0690(17) Å[26] and the Ir–F

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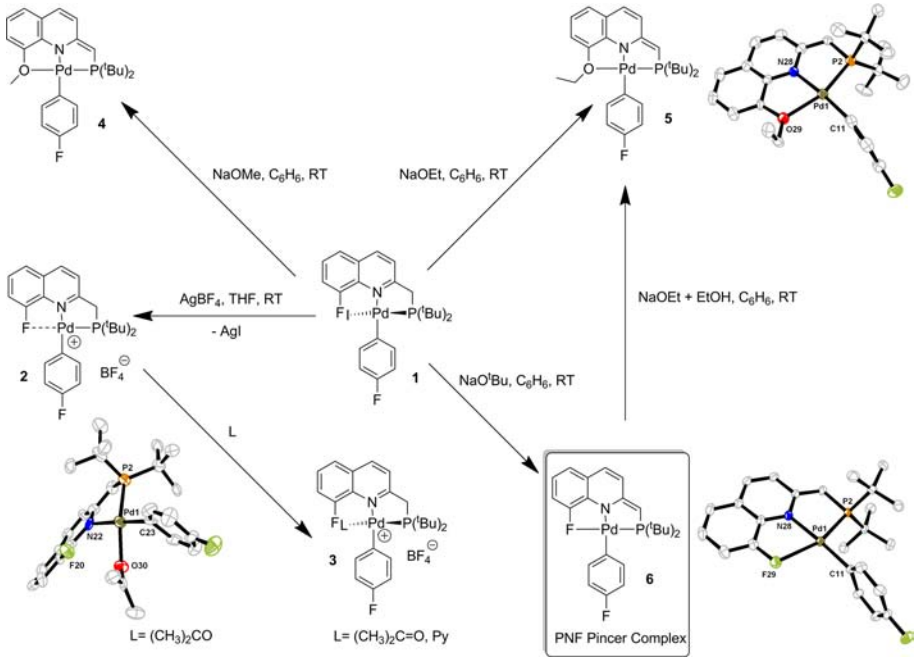
Scheme 1. Formation of the Pd−PNF Pincer Complex



distance of 2.514 (8) Å[27]]. Because of the rigid ligand core and the smaller size of the F atom compared with O, the Pd−F distance is also longer than the Pd−O distances in related PCO-type pincer complexes **4** and **5** [2.232(4) and 2.229(4) Å, respectively], indicating weaker coordination of the fluorine arm of the new pincer system. In addition, the pincer chelates are now more distorted, as the trans P−Pd−F angle of 158.89(5)° is slightly smaller than the trans P−Pd−O angles in **4** [160.95(12)°] and **5** [160.84(11)°].

Fluorine coordination to the palladium in **6** in solution was also evident from its NMR spectra. In particular, the $^{19}F\{^1H\}$ NMR signal of the 8-fluoroquinoline moiety shows a dramatic upfield shift of over 30 ppm relative to that in the starting complex **1** and appears at −144.3 ppm as a doublet (J_{PF} = 51 Hz) due to splitting with the trans phosphine ligand (Figure S1 in the Supporting Information). An upfield chemical shift is expected for fluorine atoms coordinated to late transition metals. For example, fluorine atoms trans to the phosphine ligand in Pd(II) fluoro complexes show chemical shifts lower than −230 ppm.[28] The $^{31}P\{^1H\}$ NMR spectrum of **6** exhibits a doublet at 97 ppm due to the coupling to the fluorine side arm. To study the effect of the electron density at the Pd center on the fluorine complexation, we prepared complexes **7a** and **7b**, which are similar to **1** but bear aryl groups of opposing electronic properties (*p*-$MeOC_6H_4$ and C_6F_5, respectively). Upon reaction with NaOt-Bu, the corresponding new PNF-type pincer complexes **8a** and **8b** were obtained. Interestingly, the electronic property of the aryl ligand had a noticeable effect on the fluorine signal in the $^{19}F\{^1H\}$ NMR spectrum. With the electron-donating *p*-$MeOC_6H_4$ group (**8a**), the signal appeared downfield at −143.1 ppm with a smaller J_{PF} of 45 Hz, while with the electron-accepting C_6F_5 group (**8b**), it appeared upfield (−147.7 ppm) with a larger J_{PF} of 67 Hz (Figure S1).

As both EtONa and t-BuONa should be capable of deprotonating **1** to give the dearomatized quinoline complex, it seemed likely that the pincer complex **6** served as the intermediate in the nucleophilic substitution of the 8-fluoro substituent to give **5**. Indeed, when 1 equiv of EtONa was added to **6** formed in situ from **1** and t-BuONa in benzene, the formation of **5** was observed within a few minutes. Surprisingly, when 1 equiv of EtONa was added to a sample of *pure* **6**, the formation of **5** was not observed; instead, the reaction gave free fluorobenzene and a new complex, **9**, within ca. 30 min. Although there is presently no X-ray structure of **9**, NMR suggested that the complex contains two 2-(di-*tert*-butyl)-phosphinomethyl-8-fluoroquinoline ligands coordinated to a single Pd center.[29] Thus, it is clear that the nucleophilic substitution reaction to give **5** requires the presence of an alcohol molecule formed during the deprotonation of **1**. Indeed, the addition of 1 equiv of EtONa *and* 1 equiv of EtOH to a solution of pure **6** in benzene resulted in the instantaneous formation of **5** (Scheme 1).

With these results in hand, we decided to explore the reactivity of **6** toward less nucleophilic hydrogen donors. We found that the reaction of **6** with 1 equiv of phenylacetylene (PhC≡CH) cleanly gave the C−C coupling product 4-$FC_6H_4C{\equiv}CPh$ and **9**, with the acetylenic hydrogen atom moving to the CH_2−P group with concomitant ligand aromatization. To trap the Pd(0) species prior to the formation of **9**, we added *p*-FC_6H_4I to a solution of **6** and then added PhC≡CH. In this case, the quantitative formation of 4-$FC_6H_4C{\equiv}CPh$ was accompanied by the regeneration of complex **1** (Scheme 2). When PhC≡CD was used, incorporation of the deuterium into the $-CH(D)P(t\text{-}Bu)_2$ group of **1** was observed by ^2H NMR spectroscopy (Figure S3).[29]

The above reactivity suggested that complex **1** could serve as a precursor for the catalytic copper-free Sonogashira-type cross-coupling reaction. Unlike the typical Sonogashira reaction, the cycle incorporating complexes **1** and **6** operates via metal−ligand cooperation utilizing the consequent dearomatization and aromatization steps (Scheme 3).[30] To verify the validity of this catalytic cycle, we treated **6** with 1 equiv of 4-FC_6H_4I, PhC≡CH, and t-BuONa. While 1 equiv of 4-$FC_6H_4C{\equiv}CPh$ was formed, **6** remained present in the reaction mixture.

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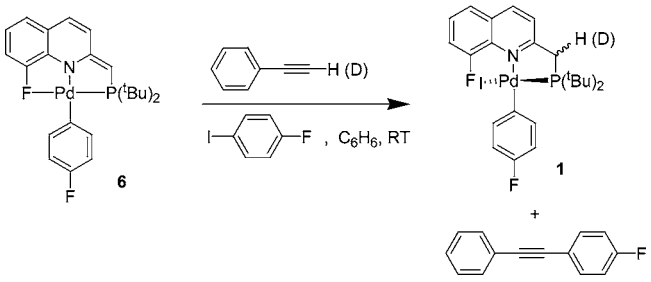
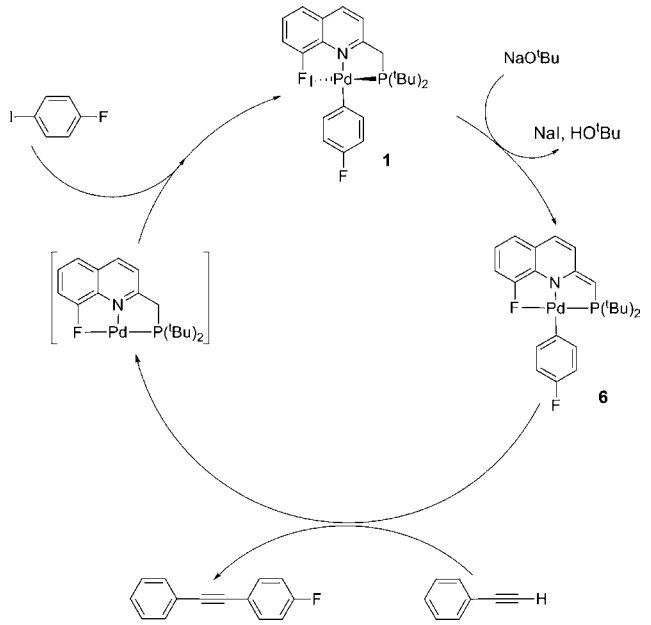
Scheme 2. C−C Coupling at the PNF Pincer Complex 6



Scheme 3. Proposed Catalytic Cycle for the Sonogashira Cross-Coupling Reaction



Under the catalytic conditions, 70% conversion to 4-$FC_6H_4C{\equiv}CPh$ was observed after 7 h at room temperature using 1 mol % **1** as the catalyst. At 55 °C, the reaction was complete within 1 h. In addition to 4-FC_6H_4I, other aryl iodides could be efficiently coupled with phenylacetylene, giving the corresponding Sonogashira reaction products in very high yields (Table 1). Both electron-donating and electron-withdrawing substituents on the aromatic ring were tolerated, without the formation of byproducts. Sterically hindered 2-iodotoluene was also converted to the Sonogashira reaction product in an excellent yield under very mild conditions (entry 7), and even iodomesitylene was active in the catalytic reaction, albeit at a lower rate (entry 8). Aryl bromides were also successfully employed in the cross-coupling reaction (entries 11 and 12). The reaction also tolerates sulfur-based heterocycles, giving the cross-coupling product between 2-bromothiophene and PhC≡CH in an excellent yield (entry 6). The use of less acidic i-$Pr_3SiC{\equiv}CH$ resulted in ca. 50% conversion to the cross-coupling product (entry 10). Only 17% of conversion was obtained with the significantly more challenging chlorobenzene.

Vigorous stirring with mercury or addition of triphenylphosphine did not affect the catalytic reaction, indicating that the formation of Pd particles during the catalysis is unlikely.[31] Also, performing the reaction in the dark or adding radical scavenger such as butylated hydroxytoluene (BHT) did not reduce the reaction yield or selectivity, suggesting that no radicals are

Table 1. Sonogashira Cross-Coupling of Ar−X and RC≡CH Catalyzed by 1[a]

entry	Ar	X	R	yield (%)
1	4-FC_6H_4	I	Ph	96 (92[b])
2	4-$MeOC_6H_4$	I	Ph	96 (93[b])
3	2-naphthyl	I	Ph	96 (91[b])
4	Ph	I	Ph	92 (75[b])
5	4-$CF_3C_6H_4$	I	Ph	98 (92[b])
6	2-C_4H_3S	Br	Ph	96 (92[b])
7	2-MeC_6H_4	I	Ph	93 (72[b])
8	2,4,6-MeC_6H_2	I	Ph	43 (87[c])
9[d]	4-FC_6H_4	I	Ph	46
10	4-FC_6H_4	I	i-Pr_3Si	48 (47[b])
11	4-FC_6H_4	Br	Ph	80
12	4-MeC_6H_4	Br	Ph	78 (72[b])

[a]Typical conditions: To a solution of PhC≡CH (33 mg, 0.31 mmol), 4-FC_6H_4I (77 mg, 0.35 mmol), and 1 mol % **1** (2 mg, 0.0031 mmol) in C_6H_6 was added NaOt-Bu (36 mg, 0.37 mmol), and the mixture was stirred at 55 °C for 1 h. The reaction progress was monitored by GC and NMR spectroscopy. [b]Isolated yield. [c]Yield after 24 h. [d]The reaction was performed at room temperature.

formed in the catalytic cycle.[32] Without complexes **1** or **6**, no catalytic reaction was observed, while the common cross-coupling catalyst $(Ph_3P)_2PdCl_2$ gave only ca. 40% conversion under our reaction conditions. Following the catalytic reaction between 4-FC_6H_4I and PhC≡CH by NMR spectroscopy at a catalyst loading of ca. 20% showed that **6** was the only complex present in solution regardless of whether **1** or **6** was initially employed (Figure S4). When PhC≡CD was used, incorporation of the deuterium in the $-CDP(t\text{-}Bu)_2$ group was observed as the reaction progressed. Conversely, when partially isotope-enriched **6-D** was used as the catalyst, the catalytic reaction between 4-FC_6H_4I and PhC≡CH regenerated **6-H** in high yield (Figure S5). However, the isotope incorporation rate was slower than the reaction rate, suggesting that a parallel catalytic path, likely involving direct nucleophilic attack at **1**, also operates under the reaction conditions. Importantly, no catalysis was observed when complex **4** or **5** was applied instead of **1**, demonstrating that the stronger coordination of an alkoxy arm is detrimental to the overall transformation.

In summary, we have prepared the first pincer-type Pd complex with a halogen atom (fluorine) as a side arm. We have also provided strong evidence for a mechanism that operates via a reversible dearomatization of the ligand core, which is unprecedented in cross-coupling chemistry. We are presently exploring the mechanism and scope of this and other cross-coupling reactions based on this operation mode.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental details for all new compounds and X-ray data (CIF) for **3-acetone**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 1 was incorrect in the version published ASAP December 28, 2012. The corrected version was re-posted on January 7, 2013.