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Room Temperature Rapid Functionalization of E−H Bonds (E = O, N, S) via the Metal−Ligand Cooperation Mechanism

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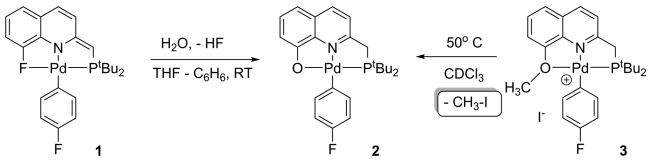
Supporting Information

ABSTRACT: An arylpalladium PNF-type pincer complex reacts with water and anilines under very mild conditions, providing access to new PNO- and PNN-pincer complexes with concomitant hydrogen transfer to the ligand core. Such a metal−ligand cooperation mode allows for the irreversible double activation of even highly sterically hindered aniline molecules. With thiols, the activation mode depends on the nature of the substituent at the sulfur atom, with thiophenols giving products of C−S elimination.

Late-transition-metal-assisted functionalization of E−H bonds (E = O, N, S) is a very active area of research because of its relevance to a broad spectrum of useful catalytic processes.[1] Although traditionally such functionalization was associated with the oxidative addition mechanism where the metal in the low oxidation state inserted into the E−H bond,[2] more recent findings, most notably from the Milstein group, demonstrated that metal−ligand cooperation-based activation can be a very powerful method of productive cleavage of such bonds.[3] In this mechanism, no change in the metal's oxidation states occurs during the bond activation step, with the hydrogen atom usually migrating to the pincer-type ligand. Still, productive cleavage of typical E−H bonds, particularly in unactivated amines and in water, remains a challenge.[4] In addition, to the best of our knowledge, no activation of *both* E−H bonds has been reported for water and primary amines.[5] Such an activation mode can be utilized to avert reversibility of the O−H and N−H bond cleavage in water and primary amines, respectively, which usually significantly hinders the functionalization efforts. Herein, we present the first examples of double activation of these bonds that take place rapidly at room temperature with very high selectivity.

Recently, we reported the first palladium PNF-type pincer complex **1** and its catalytic properties in the Sonogashira cross-coupling taking place via the metal−ligand cooperation mechanism.[6] While studying the reactivity of this complex toward various weakly acidic molecules, we treated **1** with 10 equiv of water in C_6H_6−THF. To our surprise, the activation of *both* O−H bonds was observed within 1 h at room temperature, resulting in quantitative formation of the PNO-pincer complex **2** (Scheme 1). The newly formed CH_2−P group gives rise to a doublet at 3.62 ppm (J_{PH} = 8.6 Hz, 2H) in the ^{1}H NMR spectrum. Using D_2O instead of regular water resulted in transfer of a deuterium atom at the CH(D)−P position, as confirmed by ^{1}H and ^{2}H NMR spectroscopy. Interestingly, replacement of the weakly coordinating fluoro substituent at the 8 position in **1** with the stronger anionic phenoxide ligand did not result in the expected elongation of the Pd−P distance in the X-ray structure of **2** [Figure 1a; 2.2344(7) vs 2.2214(7) Å in **1**]. It is worth noting that complex **2** can be quantitatively obtained by warming the iodo complex **3** in chloroform or THF. In that case, iodomethane was obtained as the organic product (Scheme 1), indicating that metal coordination makes the methoxy group highly susceptible to a S_N2-type attack by a weak nucleophile.

Scheme 1. Synthesis of 2 via Iodomethane Elimination



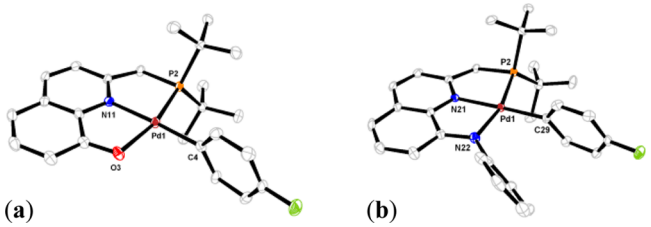


Figure 1. X-ray structures of complexes **2** (a) and **4a** (b). Selected bond distances (Å) and angles (deg) for **2**: Pd1−N11 2.033(2), Pd1−O3 2.0955(19), Pd1−P2 2.2344(7); O3−Pd1−N11 81.28(8), N11−Pd1−P2 84.20(7). Selected bond distances (Å) and angles (deg) for **4a**: Pd1−N21 2.047(2), Pd1−N22 2.068(2), Pd1−P2 2.2412(7); N22−Pd1−N21 80.27(8), N21−Pd1−P2 84.08(6).

Next, we decided to investigate the reactivity of **1** toward even less acidic unactivated aromatic amines. Unexpectedly, the addition of 1 equiv of aniline to a benzene solution of **1** resulted in a very rapid (*within seconds*!) reaction, giving a new product, **4a**, in quantitative yield (Scheme 2). ^{1}H NMR spectrum of **4a** showed a doublet centered at 2.98 ppm (2H), thus confirming rearomatization of the quinoline core. The X-ray analysis of **4a** revealed formation of the PNN-Pd complex, the product of double activation of the aniline N−H bonds (Figure 1b). Again, the strong trans influence of the diarylamido ligand in the 8 position does not lead to elongation of the Pd−P bond [2.2412(7) Å] compared with that in **1** or **2** [2.2344(7) and 2.2214(7) Å, respectively].

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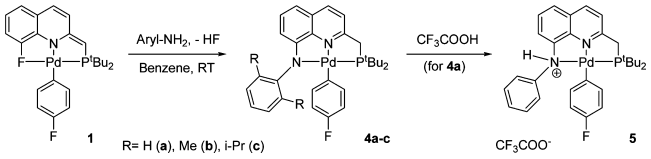
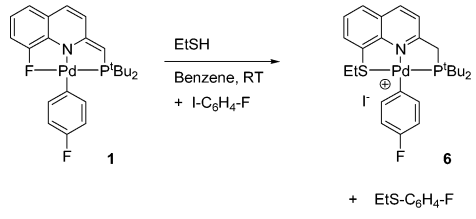
Scheme 2. Instantaneous Room Temperature Double Activation of Anilines



Considering the very low acidity of aniline, such a rapid cleavage of *both* N−H bonds is unexpected and unprecedented in late-transition-metal chemistry.[7] Unlike rare monodeprotonation of aniline with a rhodium complex via metal−ligand cooperation,[8] the C−F bond cleavage at the 8 position drives the reaction irreversible. The newly installed amido function at this position remains basic and can be protonated by acids. For example, the addition of 1 equiv of trifluoroacetic acid (H-TFA) to **4a** gives the PNN-Pd complex **5**, which has a diaryl*amino* group coordinated to the cationic metal center (Scheme 3 and

Scheme 3. Reaction of 1 with an Aliphatic Thiol



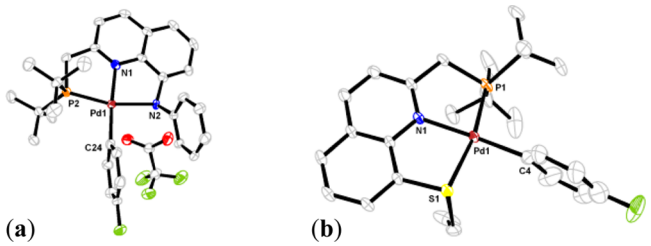


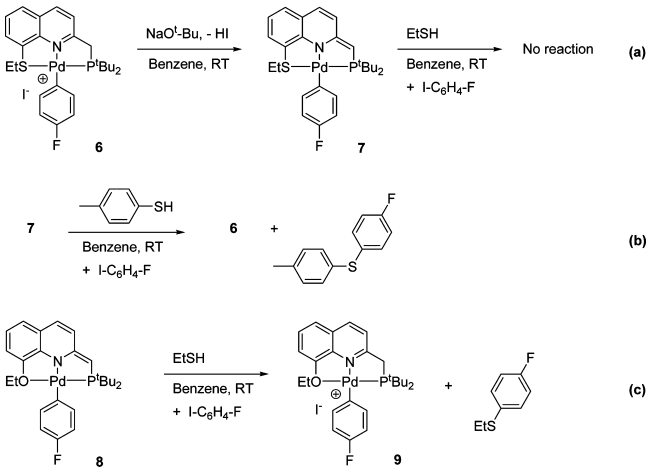
Figure 2. X-ray structures of complexes **5** (a) and **6** (b). Selected bond distances (Å) and angles (deg) for **5**: Pd1−N1 2.045(3), Pd1−N2 2.155(3), Pd1−P1 2.2417(10); N2−Pd1−N1 81.72(11), N1−Pd1−P1 84.61(9). Selected bond distances (Å) and angles (deg) for **6**: Pd1−S1 2.3414(13), Pd1−N1 2.072(4), Pd1−P1 2.2741(13); S1−Pd1−N1 84.66(11), N1−Pd1−P1 83.89(11).

Figure 2a). The distance between this group and the palladium center is significantly longer than that in the parent amido complex **4a** [2.155(3) and 2.184(3) Å (two molecules per unit cell in **5**) vs 2.068(2) Å in **4a**], while the distance between the metal and quinoline nitrogen atom remains unchanged. Similarly, there were no changes in the Pd−P distance despite the dramatic change in the nature of the ligand trans to the phosphine group.

Complex **1** also reacted with the sterically hindered 2,6-dimethyl- or even 2,6-diisopropylaniline giving products of double activation of the N−H bonds (**4b** and **4c**) upon stirring in benzene at room temperature (Scheme 2). Although longer times were required in those cases, no intermediates could be observed. Under typical conditions, no N−H bond activation was observed when **1** was reacted with aliphatic amines or secondary amines, with reactions resulting in amine coordination to the metal center. Similarly, ammonia was unreactive under the reaction conditions.

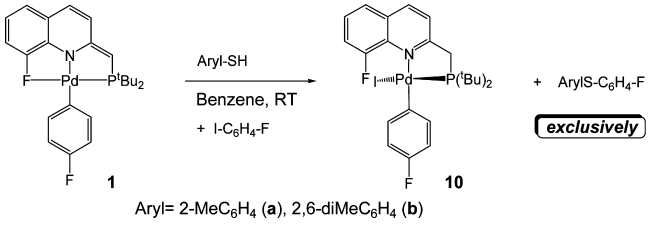
Because **1** showed very high reactivity toward the nonacidic N−H bonds, the activation of more reactive S−H bonds in thiols should be expected. Yet, because the activation of thiols via the metal−ligand cooperation mechanism has not been reported, we were interested in exploring this reaction with **1**. Interestingly, the reaction of **1** with ethylmercaptan in benzene in the presence of *p*-IC$_6$H$_4$F led to cleavage of the Pd−C bond and formation of EtS-C$_6$H$_4$F together with the PNS-Pd pincer complex **6** (Scheme 3). The crystal structure of **6** was also determined and is shown in Figure 2b. These results suggest that, unlike in the activation of O−H and N−H bonds, in the case of thiols, there is a competition between nucleophilic substitution of the 8-F atom and C−S bond elimination. Theoretically, the latter reaction leading to **6** can occur after installment of the EtS group in the 8 position. To explore this, we prepared the PNS-pincer complex **7** and treated it with an excess of EtSH (Scheme 4a). Under these

Scheme 4. Reactivity of the Dearomatized Palladium Pincer Complexes toward Thiols



conditions, no reaction was observed, suggesting that the fluorine substitution leading to complex **6** takes place *after* the initial elimination of EtS−C$_6$H$_4$F. Interestingly, complex **7** reacted with the more acidic *p*-thiocresol, giving, in the presence of I−C$_6$H$_4$F, complex **6** and *p*-CH$_3$C$_6$H$_4$−S−C$_6$H$_4$F (Scheme 4b). Also, complex **8**, the PNO-pincer analogue of **7**,[6] reacted with EtSH, giving **9** (analogous to **6**) and EtS−C$_6$H$_4$F (Scheme 4c). These observations suggest that the selectivity of the reaction between **1** and thiols can be finely tuned. Indeed, using the sterically hindered 2-Me and 2,6-diMe thiophenols gave exclusively diarylthioether and complex **8** (Scheme 5).

Scheme 5. Exclusive C−S Elimination in the Reaction with Sterically Hindered Aromatic Thiols



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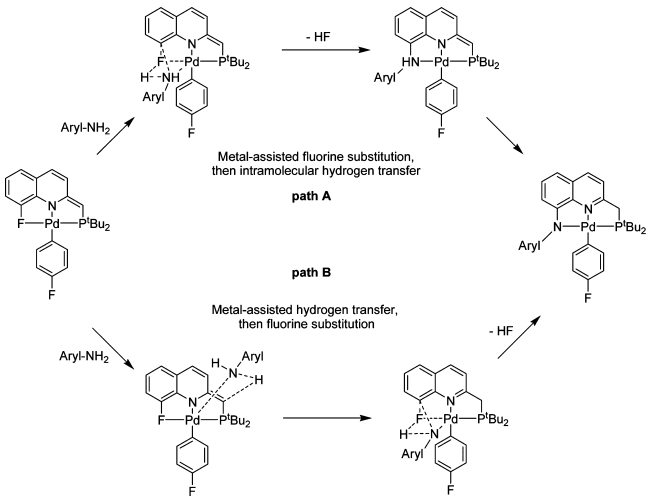
As this reactivity mode closes the postulated catalytic cycle, we explored the possibility of catalytic C−S coupling using **1** as the catalyst and NaO-*t*-Bu as the base. With only 1% of **1**, the reaction between 2,6-dimethylthiophenol and *p*-IC_6H_4F was complete within 30 min at room temperature. Although several systems are known to catalyze the C−S coupling of aromatic thiols,[9,10] the PNF-Pd pincer **1** is unusual because it shows high selectivity with sterically hindered substrates.

Overall, the results of E−H bond functionalization studies demonstrate that there are two competing pathways by which these bonds can be activated in the PNF-pincer system. These pathways are tentatively presented for the activation of aniline in Scheme 6. Simultaneous coordination of the nucleophilic

Scheme 6. Proposed Mechanistic Pathways for the Activation of N−H Bonds in Aniline



heteroatom and fluorine "arm" can facilitate the fluorine substitution, which is followed by a rapid *intra*molecular hydrogen transfer to the ligand recovering the aromatic quinoline core (path A). Alternatively, concerted metal-assisted *inter*molecular hydrogen transfer to the ═CH−P group can take place initially, thus activating the nucleophile toward the C−F activation reaction (path B). Experimental evidence for the concerted activation of N−H and O−H bonds by the metal and ═CH−P group has been provided in related ruthenium systems and corroborated by density functional theory studies.[7a,11] In any case, metal coordination seems to be essential in the activation of E−H bonds by **1** because fairly acidic noncoordinating C−H acids, such as nitromethane or acetylacetone, did not react under these conditions. With the softer more acidic thiols, reaction initially takes place at the metal center, leading to S−aryl elimination. When sterically encumbered thiols are used, no fluorine replacement at the 8 position takes place, allowing for catalytic cross-coupling reactions to occur.[6] Although, in the case of aromatic thiols, such cross-coupling does not necessarily involve the aromatization−dearomatization mechanism, our studies suggest that with less acidic E−H bonds it should be possible to direct cross-coupling chemistry to proceed via such a pathway when the organic molecule is a poor nucleophile.

In conclusion, we reported the first examples of irreversible double activation of water and unactivated aromatic amines that involve the metal−ligand cooperation mechanism, with reactions taking place under very mild conditions. In addition, the activation of S−H bonds is dependent on the nature of the thiol reagent, with bulky aromatic thiols strongly favoring the C−S coupling pathway. Further studies of bond functionalization via metal−ligand cooperation in **1** and similar systems are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental details for all new compounds and X-ray crystallographic data (CIF) for **2**, **4a**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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