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Intramolecular Redox-Active Ligand-to-Substrate Single-Electron Transfer: Radical Reactivity with a Palladium(II) Complex

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Supporting Information

ABSTRACT: Coordination of the redox-active tridentate *NNO* ligand $\mathbf{L^{H2}}$ to Pd^{II} yields the paramagnetic iminobenzosemiquinonato complex **3**. Single-electron reduction of **3** yields diamagnetic amidophenolato complex **4**, capable of activating aliphatic azide **5**. Experimental and computational studies suggest a redox-noninnocent pathway wherein the redox-active ligand facilitates intramolecular ligand-to-substrate single-electron transfer to generate an open-shell singlet "nitrene-substrate radical, ligand radical", enabling subsequent radical-type C−H amination reactivity with Pd^{II}.

Redox-active ligands are highly relevant for many metalloenzymatic transformations, supplying electrons and facilitating selective atom transfer reactivity.[1] Synthetic analogues have recently also shown remarkable potential in enabling two-electron redox processes for bond activation and formation processes, either acting as an electron reservoir or directing radical-type reactivity when combined with transition metals.[2] Single-electron transfer (SET) from a redox-active ligand to a substrate without metal oxidation state change is very rare.[3] Transformations mediated by palladium are dominated by two-electron processes,[4] whereas ligand-to-substrate SET might allow selective substrate activation via a controlled radical-type mechanism while benefiting from favorable Pd-substrate coordination.

In order to induce and control this ligand-to-substrate electron transfer reactivity on a suitable stable Pd platform and to avoid ligand dissociation during the redox-state shuttling events, we integrated the redox-active 2-aminophenol[5] (N^HO^H) unit within a tridentate NN^HO^H pincer[6] scaffold. Upon double deprotonation, this ligand may coordinate to Pd^{II} as a 2-amidophenolato dianion (NNO^{AP}), iminobenzosemiquinonato radical monoanion (NNO^{ISQ}), or a neutral iminobenzoquinone (NNO^{IBQ}, Figure 1), without formal redox changes occurring at Pd.[7] Single-electron transfer reactivity from such an *NO*-fragment to exogenous electron acceptors is not described to date for any of its redox states. We envisioned that the (NNO^{AP}) state might be ideally suited to establish intramolecular ligand-to-substrate electron shuttling and to perform radical-type reactions with Pd^{II}.

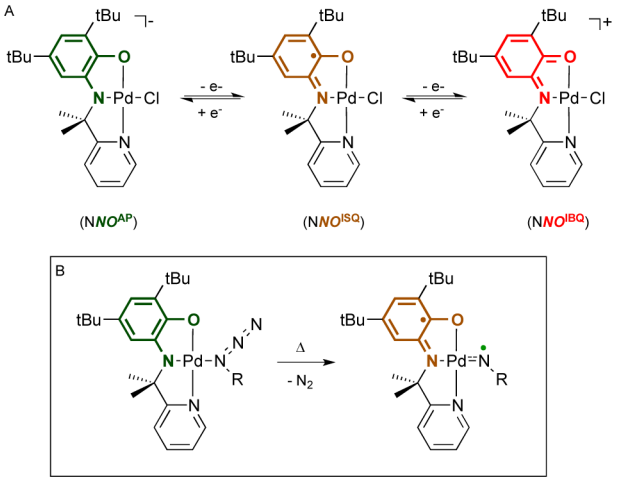

Figure 1. (A) Redox states of Pd^{II}-coordinated *NNO* ligand. (B) Concept of ligand-to-substrate single-electron transfer demonstrated for an azide substrate, generating a "nitrene-substrate radical, ligand radical" on Pd^{II}.

We herein report the synthesis of this new redox-active NN^HO^H pincer ligand, bearing an additional pyridine donor to impart coordinative stability, the resulting air- and moisture-stable paramagnetic Pd^{II} complex ($S = 1/2$) **3**, and its one-electron reduced diamagnetic derivative **4**. The ligand-centered redox behavior of this one-electron reduced species was probed experimentally and computationally (DFT). The combined data indicate that single-electron transfer from the redox-active ligand to an organic azide occurs under thermal activation to produce a "nitrene-substrate radical, ligand-radical" Pd^{II} intermediate with an open-shell singlet (singlet diradical) ground state. As proof-of-principle reactivity with this ligand-based electron transfer concept, this unusual intermediate undergoes intramolecular sp^3 C−H amination to generate a pyrrolidine species.

The two-step synthesis of NN^HO^H ligand $\mathbf{L^{H2}}$ involves double addition of $MeCeCl_2$ on 2-cyanopyridine[8] to form amine **1** (Scheme 1), followed by condensation with 1,3-di(*tert*-

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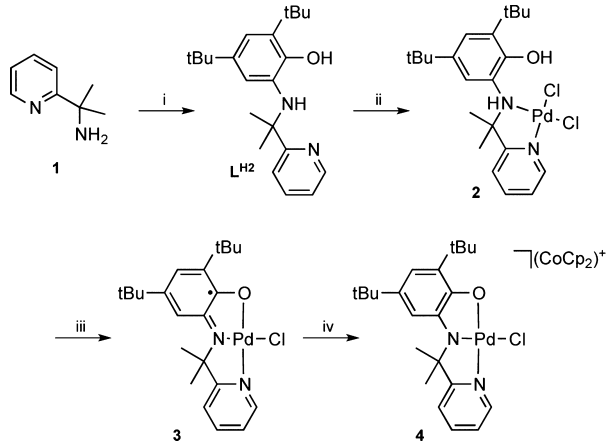
Scheme 1. Synthesis of L^{H2}, 2, 3, and 4[a]



[a]Reagents: (i) DTBQ, DTBC, neat; (ii) $PdCl_2(NCMe)_2$; (iii) NEt_3, air; (iv) $CoCp_2$.

butyl)quinone to produce an iminoquinone intermediate that is reduced *in situ* by 1,3-di(*tert*-butyl)catechol.[9] The geminal methyl and *tert*-butyl groups are incorporated in the framework to prevent β-H elimination and to stabilize the NNO^{ISQ} oxidation state upon coordination, respectively. Colorless solid $\mathbf{L^{H2}}$ is bench-stable for months but susceptible to oxidation in solution under air, concomitant with a color change to green and broadening of the NMR signals. For reference, we also synthesized $\mathbf{L'^{H2}}$ bearing no *gem*-dimethyl groups.[10]

Ligand $\mathbf{L^{H2}}$ reacts as a neutral ligand with $PdCl_2(MeCN)_2$ to give orange $PdCl_2(\mathbf{L^{H2}})$ (**2**) in high yield. NMR analysis suggests pyridine and −NH coordination to Pd (diastereotopic $-CH_3$ groups; δ 6.58 (N*H*)), with no interaction of the −OH group (δ 6.53).[10] Addition of NEt_3 in MeOH under aerobic conditions resulted in brown paramagnetic compound **3**, characterized as $PdCl(\mathbf{L^{\bullet}})$ ($\mathbf{L^{\bullet}}$ = NNO^{ISQ}). Magnetic susceptibility measurement of **3** at 298 K using Evans' method[11] gave an effective magnetic moment (μ_{eff}) of 1.78 μ_B, indicating an S = 1/2 ground state. X-band EPR spectroscopy in toluene at 298 K (Figure 2, left) revealed hyperfine couplings with ^{105}Pd, ^{15}N, and two ^{1}H nuclei. The simulated spectrum and calculated hyperfine couplings correlate well with the experimental data. The g_{iso} value of 2.0055 supports an NNO^{ISQ} ligand radical coordinated to Pd^{II}. The calculated spin-density plot for **3** (93% total spin density, 34% on the iminosemiquinonato nitrogen) is in agreement with EPR data (Figure 2, right).

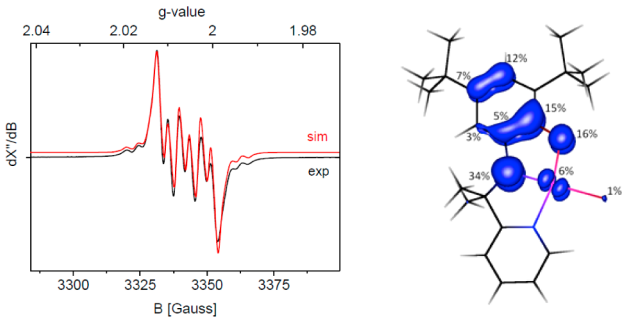


Figure 2. Left: Experimental and simulated EPR spectrum of **3**. Microwave frequency = 9.382892 GHz. Power = 2 mW. Modulation amplitude = 0.1 G. Simulated (DFT) g value and hyperfine couplings A (MHz): g_{iso} 2.0055 (2.0059); A^{Pd}_{iso} +12.8 (+10.7); A^{N}_{iso} +22.8 (+17.1); A^{H1}_{iso} −10.6 (−7.9); A^{H2}_{iso} −2.8 (−2.4). DFT parameters: ORCA (b3-lyp/def2-TZVP). Right: DFT (b3-lyp/def2-TZVP) calculated spin-density plot for **3**.

The molecular structure of **3** (Figure 3) shows metric parameters that are characteristic for the $(N)NO^{ISQ}$ ligand

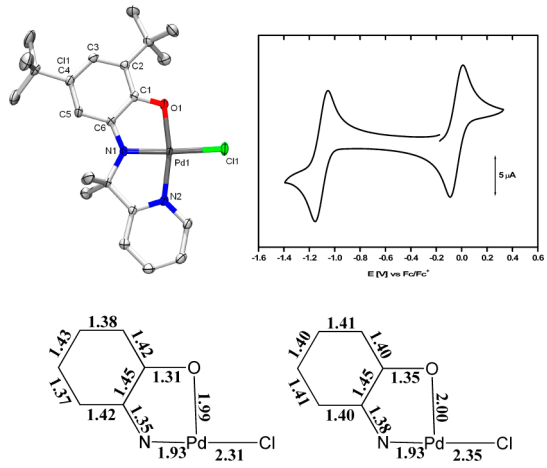


Figure 3. Top left: Displacement ellipsoid plot (50% probability level) of **3**. H atoms and solvent omitted for clarity.[11] Top right: Cyclic voltammogram of **3** in CH_2Cl_2 (10^{-3} M); scan rate 200 mV s^{-1}; referenced to Fc/Fc^+. Bottom: Relevant XRD metric parameters of **3** (left) and **4** (right).

oxidation state.[12] DFT (b3-lyp/def2-TZVP) calculated optimized geometric parameters for the doublet NNO^{ISQ} ground state matched well with the experimentally found values.[10] Cyclic voltammetry of **3** in CH_2Cl_2 solution revealed fully reversible one-electron oxidation and reduction events at +0.04 V and −1.11 V vs Fc/Fc^+, respectively (Figure 3, right). Chemical reduction of **3** with $CoCp_2$ in CH_2Cl_2 furnished $[CoCp_2][PdCl(NNO^{AP})]$ as soluble, air-sensitive diamagnetic species **4**. Single crystals were obtained by reactive diffusion of a $CoCp_2$ solution into a solution of **3** in benzene. The anionic portion of this complex is almost isostructural to **3** (Figure 3), showing an elongated Pd−Cl bond and characteristic bond lengths for the $(N)NO^{AP}$ oxidation state that matched well with DFT calculated metric parameters. Synthesis of the neutral analogue $\mathbf{4PPh_3}$ was achieved by addition of 1 equiv of PPh_3 to either the *in situ* reduction of **3** or preformed **4**.[10]

We anticipated that the reduced nature of the NNO^{AP} scaffold in species **4** could be utilized to generate an unpaired electron at a coordinated substrate by unprecedented intramolecular ligand-to-substrate SET on Pd^{II}. To support this hypothesis, we performed DFT calculations on **4** with model azide $\mathbf{N_3^{Et}}$. MO plot analysis showed that loss of N_2 concomitant with SET from the NNO^{AP} ligand to the nitrene substrate is indeed accessible, generating a rare "nitrene-substrate radical,[13,14] ligand-radical" Pd^{II} species $\mathbf{5N^R}$ with an open-shell singlet (singlet diradical) ground state. $\mathbf{5N^R}$ bears 87% α-spin density at the nitrene N-atom (Figure 4; left: HOMO for $\mathbf{4N_3^R}$, right: spin density distribution for $\mathbf{5N^R}$).

To exploit this concept of ligand-based single-electron transfer to generate a substrate radical, we investigated the reactivity of these Pd(*NNO*) complexes in radical-type sp^3 C−H amination.[15] These reactions often proceed via a radical-type mechanism involving C−H abstraction followed by a radical-

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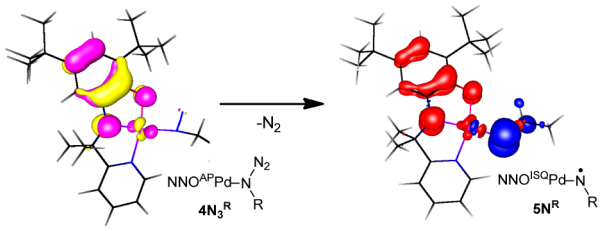
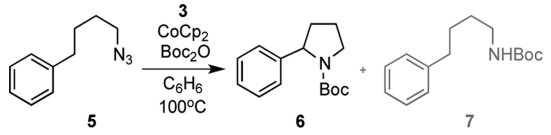


Figure 4. DFT (b3-lyp/def2-TZVP) calculated HOMO plot for model complex $\mathbf{4N_3^R}$ (left) and spin-density plot for model diradical $\mathbf{5N^R}$ (right) with blue: positive (α) and red: negative (β) spin density. **R** = ethyl.

rebound step, or alternatively via direct insertion of the radical nitrene fragment in the C–H bond. The Fe-mediated C–H amination of unactivated alkyl azides occurs via a radical pathway involving metal-based redox chemistry,[16] but a ligand-induced radical pathway for this reaction has never been disclosed. Upon reduction of **3** to **4** with cobaltocene in the presence of unactivated azide **5** and Boc_2O, pyrrolidine **6** (~1 equiv with respect to **4**), and the reduced Boc-protected amine **7** were observed (Scheme 2). Use of **4PPh$_3$**, $Pd^0_2(dba)_3$,

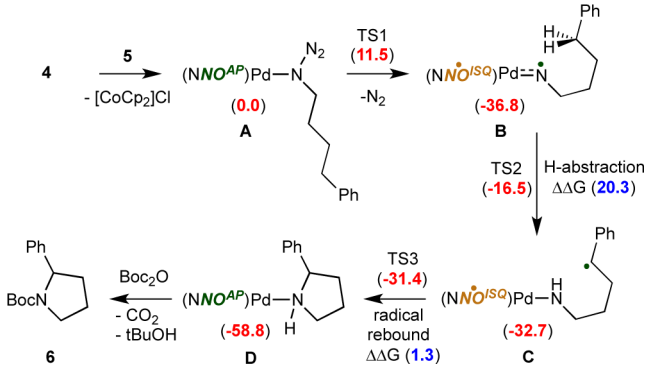
Scheme 2. Conversion of Azide 5 into Pyrrolidine 6



$Pd^{II}Cl_2(NCMe)_2$, complex **2** (with and without $CoCp_2$), complex **3** (with and without $AgPF_6$ or $TlPF_6$), $CoCp_2$, or $CoCp_2^+$ did not result in the formation of product **6**.[17] The analogous PdCl-complex of $\mathbf{L'^{H2}}$ was inactive, likely due to formation of iminopyridyl ligand $\mathbf{L'^{H}}$ via facile β-H elimination, which prohibits redox activity of the *NO*-fragment. Notably, in the presence of TEMPO-H, reaction of *in situ* generated **4** with azide **5** did not lead to any pyrrolidine formation, and the detection of TEMPO$^\bullet$ by EPR spectroscopy[10] supports the trapping of an active radical intermediate.

Based on these data and supported by DFT calculations, we propose the following mechanism for the intramolecular cyclization using **4** (Scheme 3). Initial chloride substitution by azide **5** gives closed-shell singlet (CSS) species **A** with an

Scheme 3. OSS Pathway from Azide 5 into 6 via Radical-Type *sp*^{3} C–H Amination with 4; calculated free energies ΔG for species A–D and transition states (red) and relative barriers $\Delta\Delta G$ (blue) in kcal mol^{-1}



NNO^{AP} ligand. Loss of N_2 generates Pd-nitrene intermediate **B** that can exist in three plausible electronic states. The open-shell singlet diradical (OSS) is more stable than the CSS and triplet states by 10.6 and 5.8 kcal/mol, respectively. Furthermore, the OSS nitrene diradical **B** is most effectively generated from **A** (lowest barrier of 11.5 kcal mol^{-1}) via electron transfer from the *NNO*-ligand, with no redox chemistry occurring at Pd. Subsequent intramolecular H-atom abstraction forms intermediate **C** for the OSS and triplet states with barriers of 20.3 and 19.4 kcal mol^{-1}, respectively. A subsequent low barrier transition state for the radical rebound step (1.3 kcal mol^{-1}) to form **D** was found on the OSS surface. For the CSS species, direct C–H insertion of the nitrene fragment in **B** to form **D** has a higher absolute barrier than the stepwise radical process on the OSS surface (Figure 5). Reaction of intermediate **D** with

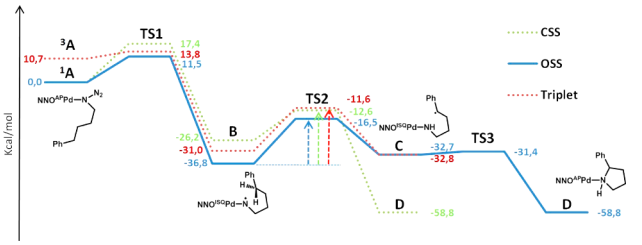


Figure 5. DFT (b3-lyp/def2-TZVP) calculated free energy profile $\Delta G^\circ_{298\ K}$ (in kcal mol^{-1}) for C–H amination of azide complex **A** derived from **4** for the three possible spin states.

Boc_2O gives **6** and an unidentified paramagnetic Pd complex. Reaction of independently prepared **D**, by addition of pyrrolidine to **4**, with Boc_2O also generated product **6**. Using an isotopically labeled analogue of azide **5**, selectively monodeuterated at the benzylic position,[10] we established a kinetic isotope effect (KIE) of 3.35 ± 0.1 for formation of **6**, which is reproduced very well by DFT calculations (KIE of 3.65). Attempts to trap a rare Pd(organo-azide) complex or a hitherto elusive (quasi)stable Pd-nitrene analogue of **B** using e.g. PhI=NNs, AdN_3, or $C_6F_5N_3$ did not provide a clear indication for the formation of such species.[10]

In conclusion, a new redox-active *NNO* pincer ligand $\mathbf{L^{H2}}$ has been synthesized and coordinated to Pd^{II}, affording paramagnetic (S = 1/2) complex **3** bearing the ligand-centered radical *NNO*^{ISQ} (**L**$^\bullet$), as supported by spectroscopic, X-ray crystallographic, and computational data. Reduction of **3** generates diamagnetic complex **4**, $[CoCp_2][PdCl(NNO^{AP})]$, which is able to activate azide **5** for intramolecular C–H bond amination to produce pyrrolidine **6**. DFT calculations, isotopic labeling, and trapping experiments support a process that involves intramolecular single-electron transfer from the redox-active ligand to the substrate upon thermal activation of the organic azide, thus producing an unusual 'nitrene-substrate radical, ligand-radical' Pd^{II} intermediate **B** with an open-shell singlet (singlet diradical) ground state. The noninnocent *NNO* ligand is proposed to dictate single-electron reactivity onto Pd^{II}, enabling radical-type pathways using a metal that is normally involved in two-electron processes. This concept is likely more broadly applicable with group 8–10 metals, including for cooperative bond activation processes and catalysis.

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■ ASSOCIATED CONTENT

Supporting Information

General methods, experimental data for new compounds, NMR spectra, crystallographic details and cif files for **3** and **4**, computational data. 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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(17) Pd_2dba_3 did lead to full conversion, but only to **7**. Pd-black is observed after reaction; we propose that a decomposition product of **4** is responsible for the formation of **7**.