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# Characterization of Two Stable Degradants of Palladium $^{t}$BuXPhos Catalyst and a Unique Dearomatization Reaction

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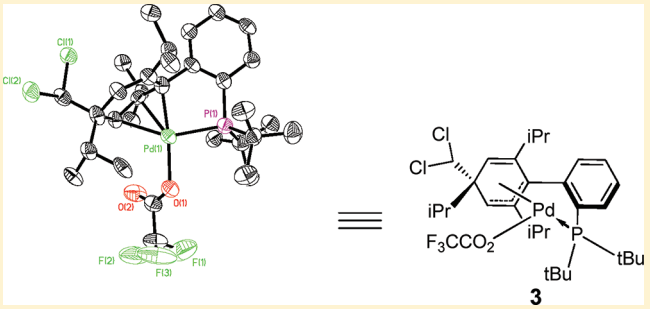
Supporting Information

**ABSTRACT:** Two stable degradants of palladium $^{t}$BuXPhos catalyst have been synthesized from $^{t}$BuXPhos and $Pd_2(dba)_3{\cdot}CHCl_3$, isolated, and fully characterized. Complex **2** augments the known literature examples of palladacycles from this ligand family but is present as a rare four-membered-ring palladacycle, having activated the top ring of the ligand. Complex **3** is an unusual case of palladium-mediated dearomatization, whereby chloroform functionalizes the bottom ring, generating a palladium allyl complex. The mechanism is assigned to an electrophilic carbene attack where palladium directs attack of dichlorocarbene to the anti face of the bottom arene. The structures have been confirmed by NMR and single-crystal X-ray diffraction.

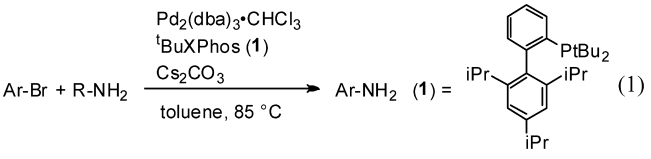



The utilization of electron-rich bulky dialkyl biphenyl phosphine ligands for cross-coupling reactions has significantly expanded the scope and practicality of these transformations.[1] Often the catalytically active species are described as L−Pd$^{0}$ complexes, formally 12-electron species,[2,3] but characterization of catalytically relevant intermediates or deactivation modes remains elusive. Computational methods have been employed to gain insight into the structure of reactive species,[2,4−6] when formation of pure components and characterization of single crystals present challenges to a study.[6]

The ligand 2-di-*tert*-butylphosphino-2′,4′,6′-tri-isopropylbiphenyl ($^{t}$BuXPhos, **1**) is an important member of the dialkyl biphenyl phosphine ligand family with utility in amidation reactions,[5,7] primary amine coupling,[8] aryl *tert*-butyl carbamate synthesis,[9] aryl sulfonamide synthesis,[10−12] and the coupling of hydroxide to Ar−X for phenol synthesis.[13] The high reactivity of Pd/$^{t}$BuXPhos enhances catalytic activity but may make it more challenging to isolate and characterize stable metal complexes. It may also encourage deactivation of L−Pd, as suggested for the coupling of aryl chlorides with carboxamides,[5] and contribute to the fact that there are no known crystal structures reported for palladium complexes of this ligand, though an isoelectronic Ag(I) complex has recently appeared.[14] A common entry into Pd/$^{t}$BuXPhos-catalyzed processes comprises use of $Pd_2(dba)_3$ as a precatalyst palladium source,[8,11,13] sometimes utilized as the crystalline chloroform solvate.[9] Activation of Pd−L precatalysts cannot be assumed to be a rapid and simple process; indeed, differences in coupling reaction rates are observed, depending upon the catalyst precursor.[15]

Herein, we report the formation and characterization of two unique palladium complexes of $^{t}$BuXPhos, which form during a cross-coupling process and represent deactivation modes of the active catalyst. One structure provides a highly unusual case of Pd-mediated dearomatization of a phenyl group and demonstrates a shortcoming of using $Pd_2dba_3{\cdot}CHCl_3$ as a precatalyst.

In the course of our development of cross-coupling reactions, heterogeneous metal scavengers have been employed to remove residual palladium from organic products, driven by the requirement to reduce concentrations of this potentially toxic metal in drug candidate molecules.[16,17] In one case, $Pd_2(dba)_3{\cdot}CHCl_3$ was combined with $^{t}$BuXPhos (**1**), $Cs_2CO_3$, and substrates in toluene under a nitrogen atmosphere before



(1)

heating to 85 °C (eq 1). After aqueous acidic workup the product solution was treated with Silicycle thiourea scavenger to reduce residual Pd content. Our work in removing metal from the product[16] revealed the resistance of certain Pd species to being cleared from the product by metal scavengers. These stable species clearly comprised a ligand field that was substitutionally resistant to the scavengers, prompting efforts to study and isolate the stable complexes by chromatographic techniques. Analysis by high-pressure liquid chromatography (HPLC) coupled with UV−vis detection, an inductively coupled plasma/mass spectrometer (ICP/MS), and an electrospray

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ionization mass spectrometer identified two palladium species with exact masses 529.222 and 613.175 Da (with a 530.230 Da fragment) (Figure 1), which were present in the product

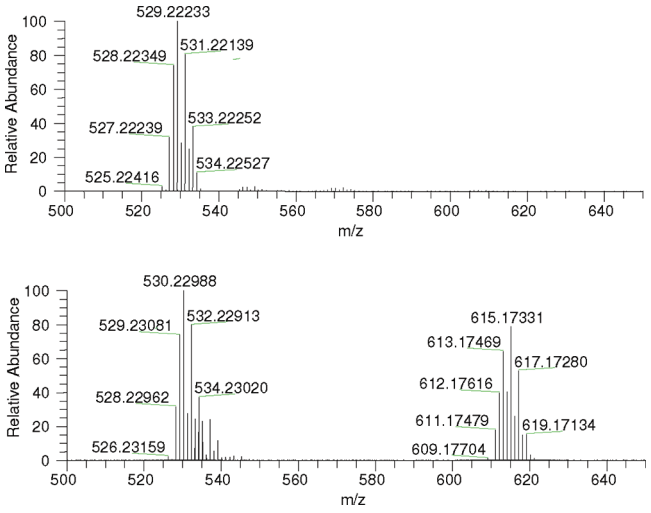



**Figure 1.** Mass spectra of species resistant to removal by metal scavenger.

solution even after treatment with Silicycle thiourea. The species at 529.222 Da was reduced in concentration ~85% from the untreated reaction mixture but not completely removed, and the 613.175 Da peak concentration was negligibly changed on treatment with scavenger, whereas most of the Pd present in other forms had cleared with the scavenger.

To better understand the two problematic complexes, an independent synthesis was attempted. The $Pd_2(dba)_3{\cdot}CHCl_3$ precursor was reacted with t-BuXPhos (L:Pd = 2.5) at 85 °C in deuterated toluene for 35 min in an air-free environment followed by filtration through Celite to remove insoluble black particles. Analysis by $^{31}P$ NMR showed a mixture of three phosphorus-containing molecules, including the free ligand (22.4 ppm) and peaks at 75.0 and −8.2 ppm, which were the largest peaks observed in solutions from the scavenging process (Figure 2b). LC/ICP-MS and LC/ESI-MS also confirmed that the solution comprised the two stable species that were resistant to scavenging. Notably, similar behavior and spectra were observed using L:Pd = 1.1 and no reaction was observed between tBuXPhos and $Pd_2(dba)_3{\cdot}CHCl_3$ at room temperature. Rigorous exclusion of light led to no change in the product distribution. Additionally, mixing an HPLC diluent (200 μL of 50% $H_2O$/50% MeCN) with 1 mL of the reaction mixture for 2 min led to no change in the spectrum and reaction mixtures held for 3 days were stable by $^{31}P$ NMR.

Intrigued by the stability, we attempted isolation by preparative chromatography. Using a semiprep HPLC system with a C18 stationary phase and gradient mobile phase (MPA, 0.1% TFA in water; MPB, 0.085% TFA in 25% ACN/75% MeOH), two peaks were isolated from multiple 110 μL injections of the toluene reaction mixture. When the isolated fractions were subjected back to the catalytic coupling reaction conditions, no coupling product was observed, suggesting that the complexes are degradants and are not catalytically active. The isolated fractions were dried to a residue in vacuo and analyzed by HPLC and NMR (toluene-$d_8$ or benzene-$d_6$; Figure 2). The fraction corresponding to $m/z$ 529 exhibited a single peak at −7.6 ppm in the $^{31}P$ NMR. In the $^1H$ NMR only

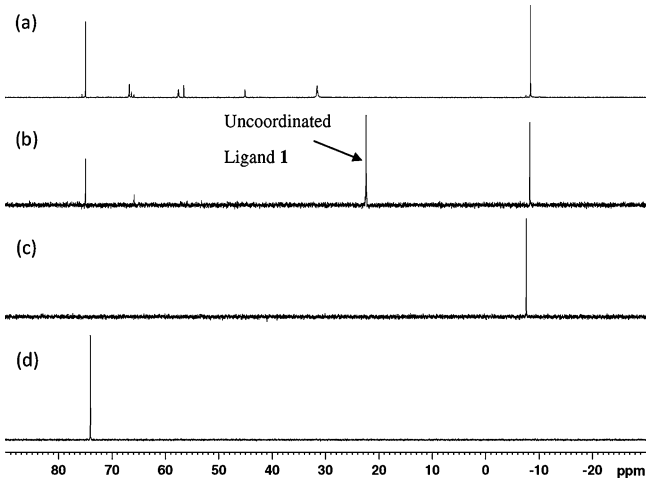
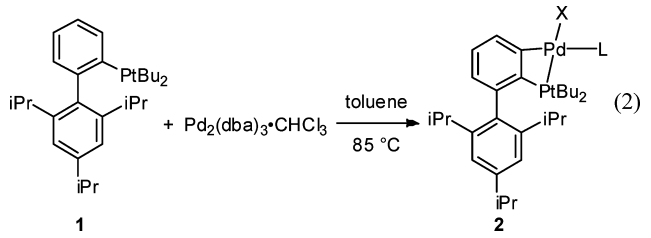



**Figure 2.** $^{31}P$ NMR spectra of (a) cross-coupling product solution before metal scavenger, (b) independent synthesis, (c) isolated $m/z$ 529 fraction, and (d) isolated $m/z$ 613 fraction.

three resonances corresponding to the top ring could be identified and unusually strong P−H coupling for hydrogens of the top ring were observed. No residual acetonitrile was detected by NMR. The spectra were consistent with activation of the ortho hydrogen of the top ring and formation of the palladacycle **2** (eq 2; see the Supporting Information for




chemical shift assignments). Similar to the case for many palladacycles in the literature,[18] no Pd−H signal was observed in the $^1H$ NMR spectrum of the isolated solid or the crude reaction mixture.

After recovery of the dried product residue of **2** from chromatography, crystals were grown by dissolution in and slow evaporation of acetonitrile. Single-crystal X-ray diffraction analysis confirmed the molecular structure of **2** (Figure 3) with

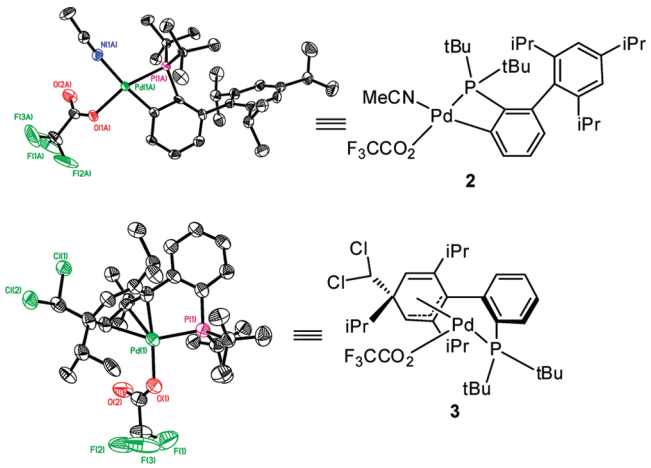



**Figure 3.** Molecular structures of complexes **2** and **3**.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acetonitrile and trifluoroacetate as stabilizing ligands. NMR studies of the dried product residue from chromatography in toluene-$d_8$ with >200 equiv of acetonitrile revealed no interaction of acetonitrile in the solution phase, suggesting the complex adopts a coordinatively unsaturated structure in solution or toluene served as the stabilizing ligand before crystallization from acetonitrile. Attempts to crystallize directly from toluene were not fruitful. During the synthesis of **2** and coupling reactions employing the catalyst, X may be halide present in the system (vida infra; **2** is never observed in the absence of **3**). Complex **2** adopts a distorted-square-planar geometry with a compressed P−Pd−C bond angle (68.4°) and an expanded N−Pd−P bond angle (105.2°). Palladacycle formation with bulky dialkylbiphenylphosphine ligands has been studied[19] for 2′-substituted biaryl ligands and 2′,6′-disubstituted biaryl ligands, but functionalization was limited to the bottom ring and not observed for the top ring as in complex **2.** Additionally, in the literature example, palladacycle formation was reversible in the presence of aliphatic amines with $\beta$-hydrides. In the present coupling, no such $\beta$-hydrides were accessible. The literature examples all utilized the $-PCy_2$ moiety. Here the $-P^tBu_2$ moiety enables activation of the top ring and the constrained four-membered palladacycle. Notably, successive generations of bulky dialkyl biphenyl phosphine ligands[5,20,21] have been constructed to block the $\alpha$ position of the phosphine-bearing aryl group to enhance reactivity. Structure **2** implies a further benefit by eliminating one mode of catalyst deactivation. It is notable that when complex **2** was subject to the cross-coupling conditions no coupling product was observed.

The second fraction isolated by chromatography corresponded to $m/z$ 613 and exhibited a single peak at 74.1 ppm in the $^{31}P$ NMR (toluene-$d_8$) and an intriguing group of peaks around 5.43 ppm and a shift of a C*H*$Me_2$ from 2.82 ppm in the free ligand to 1.75 ppm in the product fraction in the $^1H$ NMR (benzene-$d_6$). With lack of clarity on the structure, crystals were grown by dissolution in and slow evaporation of toluene that were suitable for single-crystal X-ray diffraction structure analysis, establishing the molecular structure of **3** (Figure 3). Consistent with this structure, the ESI/MS data revealed an ionization fragment with exact mass 530.230 Da, which corresponds to cleavage of a $Cl_2CH-$ fragment from **3** (Figure 1).

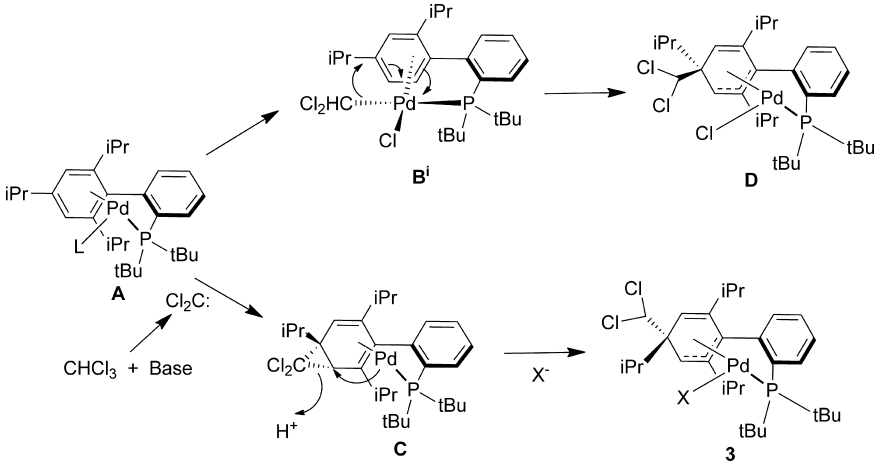
Complex **3** is a particularly striking example of dearomatization, in which chloroform has been activated and substituted onto the triisopropyl-bearing ring, which subsequently provides an allyl interaction with Pd. Examples of metal-mediated dearomatization are well-known[22] but are not common for the noble metals.[23] During the preparation of this paper, another Pd-mediated dearomatization reaction for this ligand family was reported.[24]

Two mechanistic possibilities were envisioned for the formation of complex **3**, each invoking a bonding interaction between Pd and the triisopropyl arene ring (**A**; Scheme 1). Such interactions have been well-established crystallographically for Pd(II)[20,25] and Pd(0).[26] Starting from common intermediate **A**, the two possibilities are (1) oxidative addition of chloroform to **B**, followed by migratory insertion of the arene double bond into the Pd alkyl to form the Pd(II) allyl complex, and (2) base-mediated dichlorocarbene formation followed by cyclopropanation and Pd oxidative insertion to form the Pd(II) allyl product **3** after protonation. In the oxidative addition manifold, the Pd−arene interaction of **A** should direct the placement of the dichloromethyl to the syn face for an intramolecular reaction, opposite of the orientation observed in the crystal structure. If the dichlorocarbene mechanism is operative, the electrophilic attack would favor the anti face. Consistent with this mechanism, addition of 5 equiv of triethylamine to the reaction mixture prevented formation of the palladacycle **2**; only free ligand and complex **3** were observed. Alternatively, addition of 0.8 equiv of $HBF_4$ relative to phosphine led to a 65% decrease in the production of **3** relative to **2**, likely through modulation of the basicity of the system. Uncoordinated phosphine may serve as the base promoting dichlorocarbene formation in the independent control synthesis, but in the case of the catalytic reaction, exogenous base could promote dichlorocarbene formation.

In light of the elucidated structures of **2** and **3**, it is reasonable that **2** would be more likely to react with a metal scavenger such as Silicycle thiourea because of the labile nature of one of its coordination sites, whereas **3** is coordinatively saturated and resistant to reaction with a metal scavenger. Consistent with these inferences, complex **2** was significantly but not completely cleared; about 15% remained after scavenger treatment. On the other hand, complex **3** was resistant to scavenging and its concentration was unchanged by the scavenger treatment.

In summary, we have demonstrated two degradation pathways for Pd/$^t$BuXPhos catalyst: palladacycle formation

**Scheme 1. Mechanistic Options for Formation of 3**





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via C−H activation of the top ring of the biphenyl system (compound **2**) and dearomatization of the bottom ring of the biphenyl system (compound **3**). The dearomatization reaction is thought to proceed via electrophilic dichlorocarbene attack. Complexes **2** and **3** were observed after acidic workup of a palladium-catalyzed cross-coupling reaction and independently synthesized. The formation of **2** bears similarity to palladacycles reported in the literature but is the first example of modification of the top ring of $^{t}$BuXPhos. The reactivity pattern for formation of **3** reveals the complications associated with utilizing $Pd_2(dba)_3{\cdot}CHCl_3$ as an entry point to cross-coupling but also lays the groundwork for extension of this work to other electrophiles and bases.

## ■ ASSOCIATED CONTENT

### Supporting Information

Text, figures, tables, and CIF files giving full experimental details, compound characterization data, NMR spectra, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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