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Intramolecular Thiopalladation of Thioanisole-Substituted Propargyl Imines: Synthesis of Benzothiophene-Based Palladacycles

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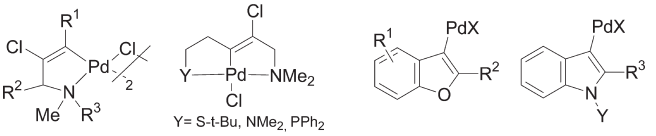
*Summary: A highly selective intramolecular thiopalladation has been achieved by the treatment of o-SMeC$_6$H$_4$C≡CC(CF$_3$)(=N-4-OCH$_3$C$_6$H$_4$), **1**, with PdCl$_2$(PhCN)$_2$ in THF at 0 °C to afford [(C$_8$H$_4$S-3-)C(CF$_3$)(=N-4-OCH$_3$C$_6$H$_4$)-Pd(μ-Cl)]$_2$, **4**. The mechanistic implications of the results with the aid of low-temperature ^{1}H NMR and ATR-IR spectroscopy are discussed.*

Palladacycles are a class of organometallic compounds of considerable interest due to their air- and moisture-tolerant character and also due to their variety of applications in catalysis, material science, and organic synthesis and in biological and medicinal chemistry as potential anticancer agents.[1] Among the known protocols,[1d] the synthesis of palladacycles derived from a C≡C bond has received great attention, as this method can also be used to derive various useful Pd-vinyl intermediate species in organic synthesis.[2] The previous reports for the synthesis of this type of palladacycles have been known only via intermolecular nucleophilic addition of the chloride anion onto the C≡C bond in which the heteroatom is incorporated in the ring system of the cyclopalladated product (Chart 1, type A).[3] On the other hand, when the reaction proceeds via an intramolecular pathway, the formation of a heterocyclic ring system is realized through the generation of organopalladium intermediate species (Chart 1, type B).[2a,2b,2j] The synthesis of 2,3-disubstituted indoles and benzofurans has been achieved via an intramolecular pathway in the presence of catalytic amounts of palladium and the corresponding 2-alkynyl anilines or 2-alkynyl phenols. However, in the case of 2,3-disubstituted benzothiophene, the 2-alkynyl thiophenol is not accessible by Songashira coupling of 2-halo benzenethiols with alkynes because the palladium-catalyzed reaction does not proceed due to poisoning by the mercapto group.[4] The synthesis of 2,3-disubstituted benzothiophene via organopalladium species is a challenging research area since the structural framework of the substituted benzothiophene is often seen in biologically active compounds.[5] Moreover, the isolation of the corresponding intermediary organopalladium compounds in the presence of a potentially coordinating group is likely to provide a new route for the synthesis of annulated benzothiophene-based palladium complexes. In this respect, we herein report the first synthesis and characterization of air- and moisture-stable perfluoroalkyl-substituted benzothiophene-based palladacycles starting from *ortho*-thioanisole-substituted perfluoroalkyl propargyl imines and palladium chloride salts via intramolecular thiopalladation reaction.

Chart 1. Palladacycles Derived from Alkynes via Nucleophilic Palladation



Type A: intermolecular palladation Type B: intramolecular palladation

In a continuation of our previous result on the synthesis of highly substituted 2-perfluoroalkyl quinolines via electrophilic iodocyclization of various perfluoroalkyl propargyl imines/amines, we started investigating the reaction of thioanisole-substituted perfluoroalkyl propargyl imines with a stoichiometric amount of palladium salts.[6] Accordingly, we prepared propargyl imines bearing an *o*-SMe unit in a single step, by Sonogashira coupling of perfluoroalkyl imidoyl iodides and the corresponding alkyne, in excellent yields according to the reported procedure (Chart 2).[6] We initiated the palladation reaction of a propargyl imine bearing an

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ortho-thioanisole unit, **2**, with a methanolic solution of Li_2PdCl_4/LiCl at 0 °C (Scheme 1). Initially, we observed the formation of a red solution, which gradually transformed into an air- and moisture-stable orange solid in 1 h. These observations prompted us to investigate the probable formation of palladacycles produced in the reaction mixture. The solid palladacycle **4** was isolated in good yield (62%) and characterized as given below.

The ^{13}C NMR and IR spectra of **1** show characteristic resonances of a C≡C bond at 85.5 and 97.3 ppm and a stretching frequency at 2189 cm^{-1}, respectively (see the Supporting Information), which are absent upon the cyclopalladation in **4**. Similarly, the ^1H NMR spectra of **5** clearly show the absence of a CH_3 signal from the *o*-$SCH_3C_6H_4$ group. Further, the change in chemical shift from 133 ppm to 166 ppm in the ^{13}C NMR of the imine carbon atom (C=N) suggests the interaction of the nitrogen lone pair with the palladium atom. The single crystal of **4** was obtained on slow evaporation of chloroform at room temperature. The structure of **4** was ascertained by means of X-ray diffraction. The crystallographic data of the dimeric compound **4** suggest that the Pd(II) center is coordinated in a square-planar fashion by the N1, an imine nitrogen atom, and the C3(sp^2) vinyl carbon atom on one side and two bridging Cl atoms on other side (Figure 1).

The stereochemistry of the palladacycle **4** was observed as a *transoid* dimeric form with the asymmetric unit containing one half-molecule and the other half generated by a crystallographic 2-fold axis of symmetry. We have also successfully isolated the pincer-type complexes **5** (yield 10%) and **7** (yield 4%) from the filtrate by column chromatography. A single crystal of **7** was obtained on slow evaporation of chloroform at room temperature. The structure of the palladacycle **7** was confirmed by ^1H and ^{13}C NMR, elemental analysis, and X-ray diffraction (Figure 2).

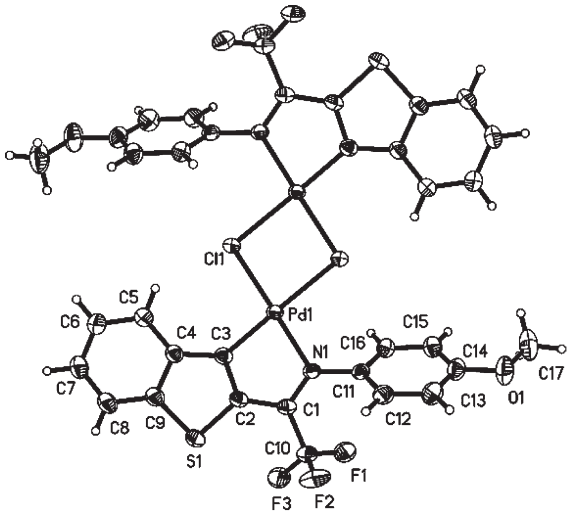


Figure 1. X-ray structure of dimeric thiopalladacycle **4**. Displacement ellipsoids are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radius. Unlabeled atoms are generated by the symmetry code (−*x*+1/2, −*y*+3/2, −*z*+1). Selected bond lengths [Å] and bond angles [deg]: N1−Pd1 = 2.0439(19); Cl1−Pd1 = 2.3152(6); C2−S1 = 1.747(2); C9−S1 = 1.729 (3); C14−O1 = 1.375(3); C3−Pd1−N1 = 81.16(9); N1−C1−C2 = 115.4(2); C9−S1−C2 = 90.03(12).

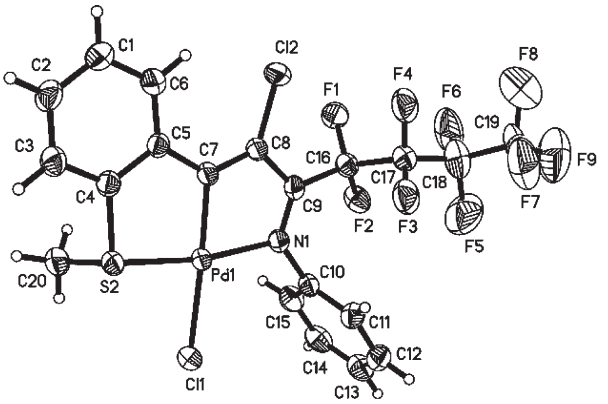
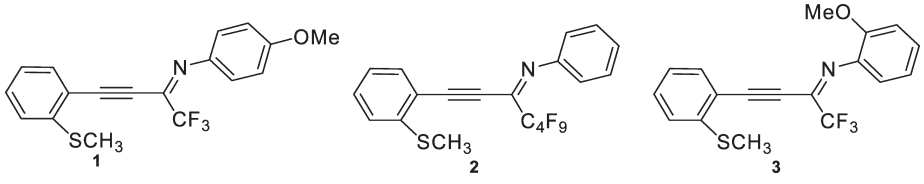
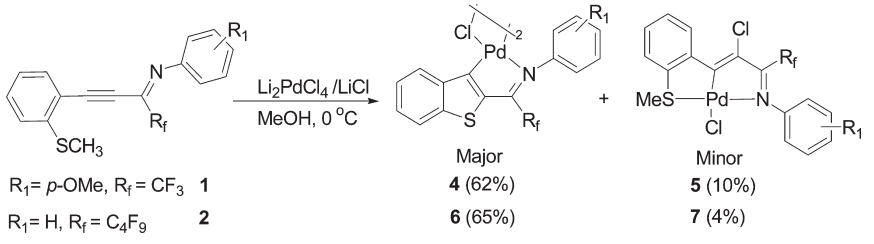


Figure 2. X-ray structure of SCN pincer-type chloropalladacycle **7**. Displacement ellipsoids are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radius. Selected bond lengths [Å] and bond angles [deg]: C7−Pd1 = 1.972(5); Cl1−Pd1 = 2.3775(14); N1−Pd1 = 2.052(4); Pd1−S2 = 2.2483(13); C8−Cl2 = 1.752(5); C4−S2 = 1.780(6); C20−S2 = 1.814(6); C7−Pd1−N1 = 81.86(18); N1−Pd1−S2 = 169.19(12); C7−Pd1−S2 = 87.42(15); C7−Pd1−S2 = 87.42(15); C7−Pd1−Cl1 = 177.17(14); N1−Pd1−Cl1 = 99.83(12); S2−Pd1−Cl1 = 90.93(5).

Chart 2. Various Perfluoroalkyl Propargyl Imines Investigated for the Cyclopalladation Reaction



Scheme 1. Synthesis of Dimeric Palladacycles and SCN Pincer-Type Palladacycles



R_1= *p*-OMe, R_f = CF_3 **1**
R_1= H, R_f = C_4F_9 **2**

4 (62%) **5** (10%)
6 (65%) **7** (4%)

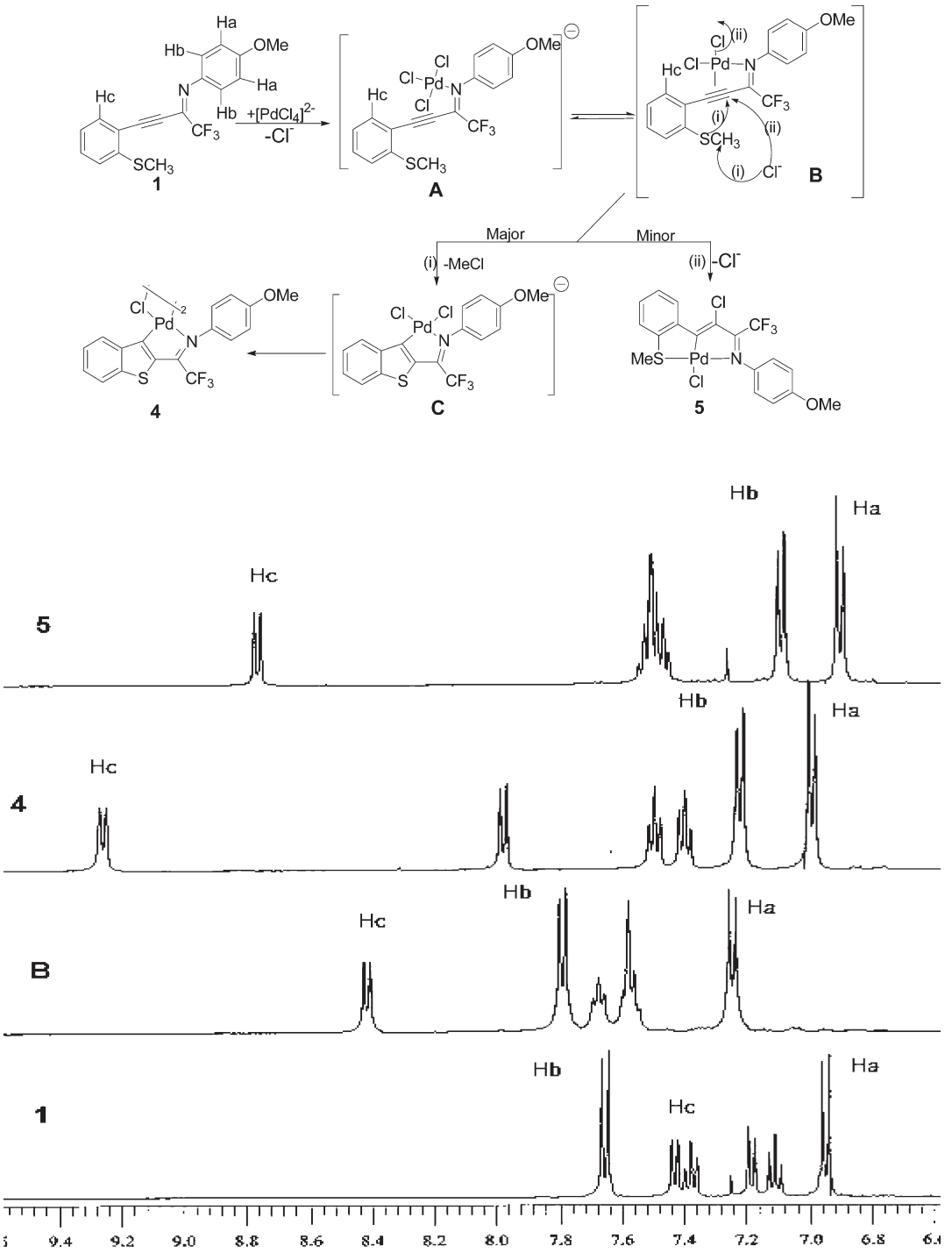


Figure 3. Possible mechanism for the formation of **4** and **5**. Reaction pathway for **4** and **5** investigated by ^{1}H NMR spectroscopy.

To the best of our knowledge, this is the first cyclopalladation reaction where intramolecular thiopalladation and intermolecular chloropalladation took place simultaneously to form a dimeric palladacycle as a major compound and a SCN pincer-type palladacycle as a minor compound from a single ligand precursor.

The possible reaction pathway for the formation of a benzothiophene-based palladacycle and a pincer-type complex has been monitored using ^{1}H NMR and ATR-IR spectroscopy. In the proposed mechanism, we speculate that the first step involves the coordination of the N atom followed by interaction of the triple bond to the electrophilic Pd center to give an intermediate **A** and **B**, respectively.[3d,7] The formation of **B**[8] is observed by the change in chemical shift for the *ortho*-proton of the phenyl ring to a triple bond after coordinating to a Pd center (Hc, 7.44 to 8.42 ppm; see Figure 3). The intermediate **B** can

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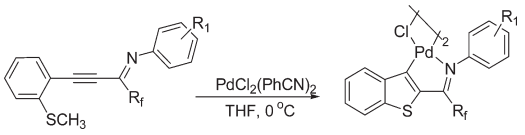
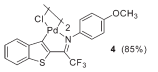
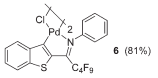
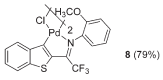
(8) Li_2PdCl_4 (0.03 mmol)/LiCl solution was prepared in CD_3OD (0.4 mL) and transferred to an NMR tube under N_2 atmosphere. Alkyne **2** (0.03 mmol) in CD_3OD (0.4 mL) was added to the NMR tube at −30 °C. The NMR tube was shaken well and subjected to ^{1}H NMR analysis at −5 °C (INOVA, 400 MHz).

Table 1. Intramolecular Thiopalladation of *ortho*-Thioanisole-Substituted Perfluoroalkyl Propargyl Imines



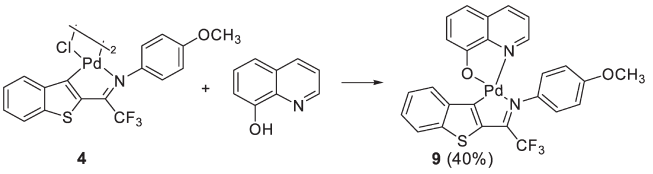
Entry	Ligand	R_1	R_f	Palladacycle (Iso.yield %)
1	1	*p*-OMe	CF_3	
2	2	H	C_4F_9	
3	3	*o*-OMe	CF_3	

Reaction conditions: alkyne (0.25 mmol), $PdCl_2(PhCN)_2$ (0.25 mmol), and THF (5 mL) at 0 °C, stirred for 2 h and warmed slowly to room temperature.

undergo either intramolecular thio addition or intermolecular chloride addition. The above experimental evidence indicates that intramolecular addition is a thermodynamically more favored process than the intermolecular addition. In intramolecular nucleophilic addition, the electronically rich thio group attacks the activated triple bond, followed by the removal of methyl group via SN_2 nucleophilic displacement by the Cl anion present in the reaction medium, resulting in the intermediate **C** (see the SI for ATR-IR experimentation for gradual disappearance of the triple bond). The anionic palladacycle is further stabilized into a thermodynamically favored dimeric cyclopalladated form.

In order to achieve high selectivity and high yield for compound **4**, we have optimized the thiopalladation reaction by screening the various palladium precursors, solvent systems, temperature, etc. To our delight, using $PdCl_2(PhCN)_2$ in THF with alkyne **1** at 0 °C, only the dimeric palladacycle was obtained in high yield (85%). The scope of the thiopalladation reaction was then extended to the alkynes **2** and **3** under the same optimized reaction conditions (Table 1). The dimeric palladacycles **6** and **8** were fully characterized by ^1H and ^{13}C NMR and IR (see the SI).

Scheme 2. Bridge Splitting of Dimeric Palladacycle 5



Finally, the bridge-splitting reaction of dimeric palladacycle **4** was examined with 8-hydroxyquinoline in ethanol at room temperature to afford monomeric palladacycle **9** in moderate yield (Scheme 2). The molecular geometry of **9** is expected as *N,N cis*- type, as confirmed by ^1H NMR.[9]

In conclusion, this work reports the first intramolecular thiopalladation of *ortho*-thioanisole-substituted propargyl imines to annulated benzothiophene-based palladacycles in a single step under mild reaction conditions with good yields. The method allows an easy access to heterocyclic-based palladacycles that does not require a heterocyclic ligand system. The new synthetic protocol can be extended to the synthesis of 2,3-disubstituted benzothiophenes using catalytic palladium and appropriate electrophiles (work is in progress). The application of other heteroatoms such as N, O, and Se for the synthesis of annulated heterocyclic-based palladacycles is also under active investigation.

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Supporting Information Available: Experimental procedures, characterization data for all ligands and palladacycles, and X-ray crystallography data for **4** (CCDC 718850) and **7** (CCDC 718851). This material is available free of charge via the Internet at http://pubs.acs.org.

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