RESEARCH ARTICLE

The Multifaceted Chemistry of [2.2]Paracyclophane-Based Thioethers with Palladium(II) Complexes

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Dedication ((optional))

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Abstract: The reactions of chiral planar [2.2]paracyclophane-4-yl)methyl thioethers ([2.2]PCP-CH_2-SR^1) with various palladium(II) sources (PdL_2) were studied. Unexpectedly, with most of the sulfur substrates investigated (SR^1 = Ph, 2-pyridyl, Me, *n*-dodecyl), and independently of the PdL_2 salt employed (L = TFA, OAc, OPiv, Cl, Br), loss of the SR^1 sulfanyl unit, along with incorporation of one palladium L ligand to the lateral benzylic position of the [2.2]PCP core, has been observed. In contrast, the precursor featuring a *t*-butylsulfanyl group (R^1 = *t*-Bu) exhibited a distinct reactivity. An *ortho* C(sp^2)–H activation took place, and allowed the formation of a [2.2]paracyclophane-based *SC*-palladacycle, in an efficient and highly diastereoselective manner (83% yield, single diastereoisomer).

Introduction

[2.2]Paracyclophane ([2.2]PCP) is the parent hydrocarbon for a fascinating family of organic scaffolds (Figure 1).[1] It involves a robust and compact arrangement of two co-facially stacked and strongly interacting aryl rings, linked together at the *para* positions by ethylene groups. Following the pioneering investigations of Brown, Farthing and Cram more than sixty years ago,[2] the unique structural, physical and electronic characteristics of [2.2]PCP derivatives have been the focus of increasing attention. They have been successfully applied in various fields,[3,4] including catalysis, polymer science, advanced materials, and medicinal chemistry.[5] An important aspect of [2.2]PCP chemistry is related to the inherent planar chirality of these systems.[6] Indeed, introduction of a substituent on the [2.2]PCP skeleton removes the plane of symmetry of the molecule and leads to the generation of enantiomers.

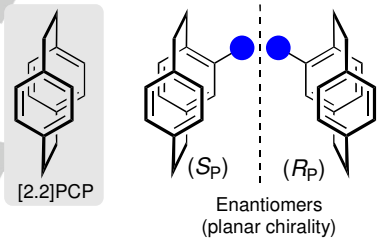
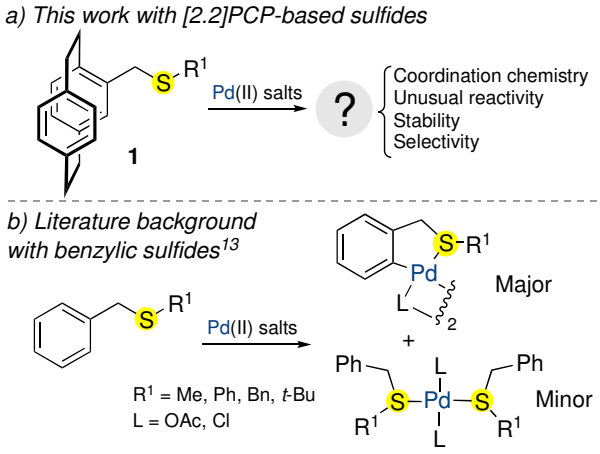


Figure 1. Parent [2.2]PCP and planar chiral monosubstituted derivatives.

Despite the fact that functionalized planar chiral [2.2]paracyclophanes have received a lot of attention, the chemistry of their transition metal complexes remains largely unexplored.[7,8] In the context of our continuous interest in sulfur chemistry,[9] we already described the synthesis and the applications of various monosubstituted sulfur-based [2.2]paracyclophanes.[10,11] We wish to give here an account of the reactivity of the planar chiral [2.2]PCP sulfides **1** in the presence of various palladium(II) complexes (Scheme 2a). To the best of our knowledge, such studies have not been reported yet. This investigation is linked to the fact that organosulfur compounds have various applications as ligands in palladium chemistry.[12] Literature background reveals that the reaction of analogous benzylic aryl/alkyl sulfides ($PhCH_2$–S–R^1) with Pd(II) salts has been thoroughly examined (Scheme 2b).[13,14] Cyclometallation of the sulfur ligand is invariably observed, as a result of C–H activation, thus providing *SC*-palladacycles. In some cases, mononuclear chelates are also detected as side-products. Furthermore, such sulfur-containing palladacycles have been recently successfully involved in C–H functionalization processes.[15]



Scheme 2. Reaction of [2.2]PCP and benzylic sulfides with palladium sources.

Results and Discussion

Five [2.2]PCP-based thioethers **1** possessing distinct sulfanyl substituents (R^1 = aryl, hetaryl, alkyl) in terms of steric hindrance and electronic nature were selected for our study (Figure 2). They were conveniently prepared (yields > 72%) from the 4-formyl or 4-bromomethyl [2.2]PCP precursors **2** and **3** and the appropriate thiol. The carbon-sulfur bond was created at the benzylic position of the [2.2]PCP, through a reductive sulfanylation reaction[11] (from **2**) or by nucleophilic substitution (from **3**) (see the Supporting Information).

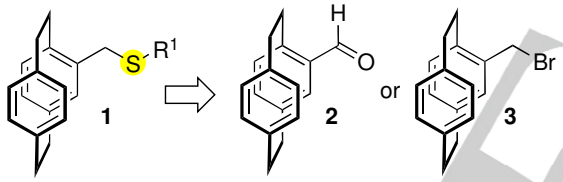
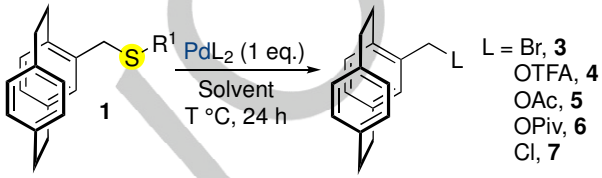


Figure 2. Structures and precursors of the [2.2]PCP sulfides **1** investigated in this study.

With the [2.2]PCP sulfides **1** in hands, we then examined their chemical behavior with various palladium(II) salts. In a first experiment, a stoichiometric amount of the phenylsulfanyl derivative **1a** (R^1 = Ph) and palladium trifluoroacetate $Pd(TFA)_2$ was heated at a temperature of 60 °C in toluene as solvent (Table 1, entry 1). After 24 h of reaction, TLC analysis revealed a total disappearance of the starting material. Purification of the dark brown crude product on silica gel led to the isolation of a [2.2]PCP compound in a 52% yield. Analysis of the ^{1}H NMR spectrum rapidly indicated that the initial aromatic sulfur substituent has disappeared, whereas the lateral methylene motif was preserved. A diagnostic, but intriguingly deshielded AX pattern was observed for these diastereotopic protons (δ = 5.30 and 5.12 ppm, ^2J = 12.2 Hz). Combination of other spectral data (^{13}C NMR, IR, HRMS) allowed us to unambiguously identify the product as the unexpected [2.2]PCP trifluoroacetic acid ester **4** (entry 1).[16] A similar transfer of the trifluoroacetate group was observed from the 2-pyridylsulfanyl (R^1 = 2-pyridyl, entry 2) and the methylsulfanyl (R^1 = Me, entry 3) [2.2]PCP precursor **1b** and **1c**.

The isolated yields in trifluoroacetate **4** are in the same range (33 and 30%), even if both reactions were conducted under different scales (60 µmol and 0.933 mmol, respectively). A control experiment was then carried out with benzyl phenyl sulfide. Upon treatment with $Pd(TFA)_2$ under similar reaction conditions, no formation of benzyl trifloroacetate was detected (see the Supporting Information). These preliminary results highlighted the original reactivity of the three [2.2]PCP sulfides **1a-c** investigated, compared to that previously reported in the classical aromatic series (Scheme 2b).[13]

Table 1. Reaction of [2.2]PCP sulfides **1** with various Pd(II) sources.[a]



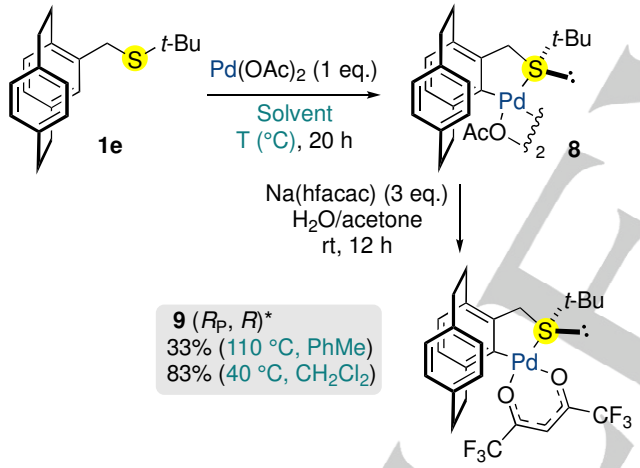
Entry	Sulfide	R^1	Conditions Solvent, T (°C)	Ligand of PdL_2	Product [b],[c]
1	**1a**	Ph	PhMe, 60	TFA	**4** (52)
2	**1b**	2-pyridyl	PhMe, 60	TFA	**4** (33)
3[d]	**1c**	Me	PhMe, 60	TFA	**4** (30)
4	**1a**	Ph	PhMe, 110	OAc	**5** (17)
5	**1b**	2-yridyl	PhMe, 110	OAc	**5**[e]
6	**1c**	Me	PhMe, 110	OAc	**5**[e]
7	**1d**	*n*-odecyl	PhMe, 110	OAc	**5**[e]
8	**1a**	Ph	PhMe[f], 110	OAc	**5** (48)
9	**1a**	Ph	AcOH, 110	/[g]	NR[h]
10	**1a**	Ph	PhMe, 110	OPiv	**6** (30)
11	**1a**	Ph	PhMe, 110	Cl	**7** (66)
12	**1a**	Ph	PhMe, 110	Br	**3** (22)

[a] Reactions performed on a 60 µmol scale, in 3 mL of solvent. [b] Determined by analysis of the ^{1}H spectrum of the crude product. [c] Isolated yields in brackets. [d] Reaction carried out on a 0.933 mmol scale (250 mg of **1c**), in 8 mL of solvent. [e] Non optimised reaction. Yield not calculated. [f] With 30 eq. of AcOH. (g) Without the presence of a palladium complex. [h] NR = No reaction.

To get more information on this original C–S bond cleavage, we pursued our study with a switch to palladium acetate $Pd(OAc)_2$ (L = OAc) in the presence of precursor **1a**. Upon heating the reaction mixture in toluene at 110 °C for 24 h, replacement of the sulfur substituent by the palladium acetate ligand was observed (entry 4). The process was however less efficient than with $Pd(OTFA)_2$. The starting [2.2]PCP sulfide **1a** was still detected in the crude mixture and [2.2]PCP acetate **5** was produced in a rather low 17% yield. In a similar manner, [2.2]PCP acetate **5** was produced, starting from the other [2.2]PCP sulfanyl precursors **1b-d,** with respectively 2-pyridyl, methyl and *n*-dodecyl pendants (entries 5–

7).[17] To improve the yield of the transformation, we then tested the introduction of glacial acetic acid (30 eq.) with the phenylsulfanyl derivative **1a** (R^1 = Ph). Pleasingly, a significant enhancement to a 48% yield was obtained (entry 8). Worthy of note is that no reaction occurred, upon heating at 110°C, a solution of **1a** in acetic acid without $Pd(OAc)_2$ (entry 9). This control experiment indicates that the transition metal is essential for the conversion. The screening of the palladium salts was then pursued with palladium pivalate (L = OPiv) in the presence of precursor **1a** (entry 10). Accordingly, the isolated product was the [2.2]PCP pivalate **6** (30% yield). Finally, the process was extended to the transfer of halogen atoms. Indeed, palladium chloride (L = Cl) allowed transformation of **1a** into the corresponding [2.2]PCP chloride **7** in a satisfactory 66% yield (entry 11), while the related bromo derivative **3** was produced in a 22% yield employing palladium bromide (L = Br, entry 12).

To sum up, with [2.2]PCP thioethers **1a-d** (R^1 = Ph, 2-pyridyl, Me and *n*-dodecyl), and independently of the palladium source PdL_2 employed, a formal replacement of the SR^1 sulfanyl unit for one L ligand, was observed in each case providing the [2.2]PCP products **3-7**.[18] Even if one can easily speculate that the reaction proceeds through an initial coordination of the sulfide center (Lewis base) on the palladium center (Lewis acid), followed by a substitution process by the nucleophilic L ligand, a more sophisticated pathway is probably involved to fully rationalize the obtained results[19] and is currently under study in our group.



Scheme 3. Reaction of [2.2]PCP sulfide **1e** with $Pd(OAc)_2$.

The investigation was then pursued with the sterically encumbered *t*-butylsulfanyl [2.2]PCP derivative **1e** in the presence of a stoichiometric amount of $Pd(OAc)_2$ (Scheme 3). In this case, only trace amounts of the [2.2]PCP acetate derivative **5** have been detected in the crude product. A quick NMR analysis led us to presume that an *ortho* C–H activation might have occurred. However, the complexity of the NMR spectrum did not allow us to fully characterized the species formed. It was however assumed that the crude product contains the acetato-bridged dimeric palladium species **8**, as a complex mixture of isomers. Consequently, conversion into a monomeric species was then performed through ligand exchange, upon treatment with sodium (hexafluoroacetyl)acetonate Na(hfacac) in an acetone/H_2O solution. After column chromatography, the resulting monomeric derivative **9** was isolated in a 33% yield, calculated from the starting [2.2]PCP ligand **1e**. We were rapidly aware that the initial C–H activation process was the limiting step of the sequence. Consequently, an optimization of the reaction conditions was undertaken, through the variation of the solvent and the temperature. Best results were obtained by heating a stoichiometric mixture of the thioether **1e** overnight (20 h) at 40 °C in a CH_2Cl_2 solution, followed by ligand exchange on reaction with Na(hfacac). Pleasingly, the resulting monomeric derivative **9** was isolated in an excellent overall 83% yield. Interestingly, it was obtained as a single diastereoisomer, according to the single set of signals observed in the ^1H and ^{13}C NMR spectra. It is important to point out that in contrast to the [2.2]PCP sulfide precursor **1e** which is only planar chiral, the palladium complex **9** displays two stereochemical elements, *ie* planar chirality inherent to the [2.2]PCP skeleton and central chirality of the metal-coordinated sulfur center. The structure and the configuration of palladacycle **9** was assessed by single-crystal X-ray analysis (see later on in the manuscript for the description, Figures 3 and 4). Worth noting is that very few planar chiral [2.2]PCP-based palladacycles have already been reported in the literature. Most examples concern *NC*–complexes,[8,20] in which the palladium is coordinated to the nitrogen center of an oxazoline, an imine, a pyridine or an amino group, whereas a single example has been described in the phosphorus series[21] with a phosphinite function (see the Supporting Information). To the best of our knowledge, there is no precedent involving a sulfur atom as the donor atom.

The complex **9** is air and moisture stable, and no decomposition occurs after storage for several months in the freezer. A full analytical description is reported hereafter. Analysis of the ^1H NMR spectrum of **9**, and especially the peak integration in the region of the aryl hydrogens, clearly indicated that an *ortho* C(sp^2)–H-activation had occurred. There are signals of 6 hydrogens for the [2.2]PCP backbone, ranging from 6.67 to 6.12 ppm (instead of 7H for the sulfide precursor **1e**). Furthermore, the 8 hydrogens of the ethylene group are detected (3.51–2.82 ppm), thus excluding the option of a C(sp^3)–H bond activation. Indeed, a competition between a C–H activation in aromatic or benzylic positions of a [2.2]PCP has already been demonstrated by the group of Bolm[20a] in the case of an oxazolinyl ligand.[22] Furthermore, the single set of signals observed allowed to assess that the cyclopalladated complex **9** was formed as a single diastereoisomer. The full diastereoselectivity of the palladacycle formation was supported by additional NMR data. The ^{13}C {^1H} NMR spectrum displays 24 discrete signals (for the 24 chemically inequivalent carbon atoms of **9**), four of them being quartets as the result of $J(^{13}C–^{19}F)$ couplings. Furthermore, a single ^{19}F signal was observed for each diastereotopic CF_3 group at δ = –75.0 and –75.8 ppm. The palladacycle was further characterized by IR spectroscopy, and high-resolution mass spectrometry (HRMS).

A single crystal of **9** suitable for X-ray diffraction analysis crystallography was obtained by slow diffusion of pentane in a CH_2Cl_2 solution. This confirmed the molecular structure of **9** and established the stereochemistry and the relative configuration as (R_P, R)*, as depicted in Figure 3.

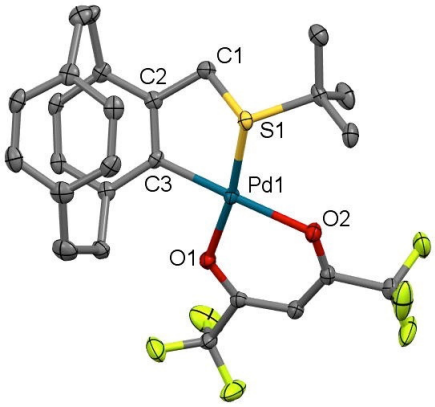


Figure 3. X-ray crystal structure of complex **9** (CCDC 1909567). All H atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): C3–Pd1 1.998(2), O1–Pd1 2.0783(18), O2–Pd1 2.1336(18), S1–Pd1 2.2449(7), C3–Pd1–O1 91.56(9), O1–Pd1–O2 88.07(7), C3–Pd1–S1 80.54(7), O2–Pd1–S1 99.80(5).

The C3–Pd1 and S1-Pd1 bond lengths, respectively of 1.998 and 2.2449 Å, are in perfect agreement with the values reported for other 5-membered palladacycles isolated in the classical aromatic series.[13b,23] Additional structural information on the spatial arrangement of the palladacycle **9** in the solid state showed a distorted geometry of the square planar arrangement around the Pd center. The O(1)–Pd–O(2) and C(3)–Pd–O(1) angles are close to ideal with values of 88.07° and 91.56°, respectively. On the other hand, the C(3)–Pd–S angle has a value of 80.54°, while the S–Pd–O(2) angle, is significantly more obtuse (99.80°). As exemplified in Figure 4, the five-membered chelate ring displays an envelope conformation, in which the C(1), C(2), C(3) and Pd atoms are almost coplanar (torsion angle of 171.69°). The sulfur atom is orientated above this plane, pointing towards the [2.2]PCP deck. Finally, the *tert*-butyl group is located in a pseudo-equatorial position, probably to minimize steric interactions with the [2.2]PCP unit.

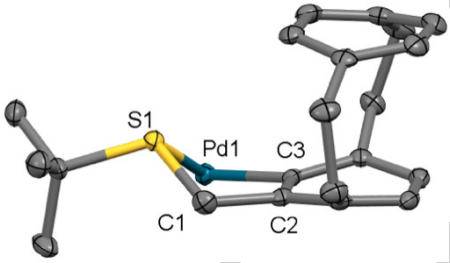


Figure 4. Relevant view of the X-ray crystal structure of palladacycle **9**. The (hfacac) fragment has been omitted for clarity.

For a better understanding of this diversity in reactivity of [2.2]PCP sulfides (**1a-d** versus **1e**) with palladium salts, further studies both from an experimental and theoretical point of view are currently run.

Conclusion

This paper described the chemical behavior of [2.2]paracyclophanes **1** possessing a CH_2SR^1 group on one aromatic ring with palladium(II) complexes. Unexpectedly, in most cases (**1a-d**), removal of the sulfanyl substituent SR^1, in favor of the transfer in the benzylic position of an L ligand of the palladium source, was observed (L = TFA, OAc, OPiv, Cl, Br) leading to variously functionalized [2.2]PCP **3-7**. To the best of our knowledge, this original reactivity has never been mentioned in previous investigations with the analogous benzyl sulfides. Interestingly, a regioselective *ortho* C–H bond activation took place with the precursor **1e** displaying a *t*-butylsulfanyl group in the presence of $Pd(OAc)_2$ to provide unprecedented planar chiral [2.2]PCP derived *SC*-palladacycle species. The study has been carried out with racemic planar chiral [2.2]PCP precursors **1**. It could be easily extended in the enantiopure series.[24] We believe that these preliminary results could diversify [2.2]PCP applications and serve as a guide in designing conceptually novel and efficient [2.2]PCP-based compounds with various functional groups in the benzylic position of the [2.2]PCP skeleton, beyond carboxylates and halogen atoms. A better understanding of the mechanism is however required. Research in this area is currently being run and will be published in due course. Another attractive extension is also to demonstrate the synthetic utility of the SC-palladium complexes 8 and 9[25] and to further develop the functionalization of the notoriously challenging *ortho*-position[26] of [2.2]paracyclophanes.

Experimental Section

*General procedure for the reaction of [2.2]PCP sulfides **1a-d** with palladium sources:* In a Schlenk tube, equipped with a condenser and an argon inlet, [2.2]PCP-based sulfide **1** (60 µmol, 1 equiv) and PdL_2 salt (60 µmol, 1 equiv) was dissolved in dry toluene (3 mL). The reaction mixture was heated under argon atmosphere at 60 °C or 110 °C for 24 h. After concentration under vacuum, the resulting crude product was purified by column chromatography on silica gel to afford the [2.2]PCP derivatives **3**–**7**.

*Synthesis of the acetato-bridged dimer **8** from [2.2]PCP sulfide **1e**:* In a flamed Schlenk tube, under an argon atmosphere, [2.2]PCP sulfide **1e** (70 mg, 0.225 mmol) and $Pd(OAc)_2$ (50.5 mg, 0.225 mmol, 1 equiv) were heated in anhydrous CH_2Cl_2 (8.5 mL) at 40 °C for 20 h. The resulting mixture was diluted in water (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and evaporated to dryness to afford the dimer **8** which was directly engaged in the next step without further purification.

*Conversion of **8** into monomer **9** through ligand exchange:* In a round bottomed flask, the crude dimer **8** previously prepared from sulfide **1e** (0.225 mmol, 1 equiv) was dissolved in acetone/H_2O (2:1, 20 mL) and sodium hexafluoroacetylacetonate (156 mg, 0.675 mmol, 3 equiv) was introduced. The reaction mixture was stirred at room temperature for 12 h, after which time it was diluted in water (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was then purified by column chromatography on silica gel (pentane/CH_2Cl_2, 70:30 as eluent) to afford the palladacycle **9**. Yield over 2 steps 83% (117 mg, 0.188 mmol). Yellow solid, mp: 214–215 °C (decomposition). TLC (pentane/CH_2Cl_2, 70:30) R*f* = 0.54. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.67 (d, *J* = 8.1 Hz, 1H), 6.60–6.58 (m, 3H), 6.20 (d, *J* = 7.7 Hz, 1H), 6.12 (d, *J* = 7.7 Hz, 1H), 6.07 (s, 1H), 4.11 (d, *J* = 13.1 Hz, 1H), 3.87 (d, *J* = 13.1 Hz, 1H), 3.51 (ddd, *J* = 13.9, 10.1 and 5.6 Hz, 1H), 3.28 (ddd, *J* = 13.2, 10.0 and 3.2 Hz, 1H), 3.17–3.11 (m, 3H), 2.98 (ddd, *J* = 13.2, 10.1 and 6.1 Hz, 1H), 2.92 (ddd, *J* = 13.2, 10.0 and 5.6 Hz, 1H), 2.82 (ddd, *J* = 13.9, 11.0 and 6.1 Hz, 1H), 1.63 (s, 9H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$) δ 175.4 (q, J_{CF} = 28 Hz), 175.2 (q, J_{CF} = 28 Hz), 146.0, 145.7, 142.7, 140.6, 138.5, 133.5, 133.2, 133.0, 132.9, 132.8, 132.1, 129.3, 118.0 (q, J_{CF} = 285 Hz), 117.9 (q, J_{CF} = 285 Hz), 89.8, 49.8, 39.9, 36.1, 35.5, 34.4, 34.3, 28.8. ^{19}F {^{1}H} NMR (565.8 MHz, $CDCl_3$) δ –75.0 (3F), –75.8 (3F). IR (cm^{-1}) ν: 732, 793, 907, 1099, 1143, 1198, 1254, 1479, 1550, 1636 (C=O), 2862, 2928, 3031. HRMS (ESI) calcd for $C_{26}H_{26}F_6NaO_2PdS$ with ^{106}Pd isotope $[M+Na]^+$: 645.0490; Found: 645.0486.

Supporting Information

The authors have cited additional references within the Supporting Information.[27-35]

Acknowledgements

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Keywords: sulfur • palladium • [2.2]paracyclophane • C–H activation • palladacycle • ligand exchange • functionalization

[1] *Modern Cyclophane Chemistry* (Eds: R. Gleiter, H. Hopf), Wiley-VCH:Weinheim, **2004**.

[2] C. J. Brown, A. C. Farthing, *Nature* **1949**, *164*, 915-916.

[3] For reviews dedicated to the synthesis of [2.2]PCP derivatives: (a) Z. Hassan, E. Spuling, D. M. Knoll, S. Bräse, *Angew. Chem. Int. Ed.* **2020**, *59*, 2156-2170. (b) Y. Morisaki, Y. Chujo, *Bull. Chem. Soc. Jpn.* **2019**, *92*, 265-274. (c) O. R. P. David, *Tetrahedron* **2012**, *68*, 8977-8993.

[4] For reviews dedicated to the applications of [2.2]PCP derivatives: (a) J. M. Teng, D. W. Zhang, C. F. Chen, *ChemPhotoChem* **2022**, *6*, e202100228. (b) K.-i. Sugiura, *Front. Chem.* **2020**, *8*, doi: 10.3389/fchem.2020.00700.

[5] D. N. Tran, A. Zhdanko, S. Barroso, P. Nieste, R. Rahmani, J. Holan, R. Hoefnagels, P. Reniers, F. Vermoortele, S. Duguid, L. Cazanave, M. Figlus, C. Muir, A. Elliott, P. Zhao, W. Paden, C. H. Diaz, S. J. Bell, A. Hashimoto, A. Phadke, J. A. Wiles, I. Vogels, V. Farina, *Org. Process Res. Dev.* **2022**, *26*, 832-848.

[6] (a) S. Felder, S. Wu, J. Brom, L. Micouin, E. Benedetti, *Chirality* **2021**, *33*, 506-527. (b) G. J. Rowlands, *Org. Biomol. Chem.* **2008**, *6*, 1527-1534.

[7] Z. Hassan, S. Bräse, *Chem. Eur. J.* **2021**, *27*, 15021-15027.

[8] For a previous investigation reported by us, using an *N,N*-dimethylamino substituent as coordinating group, see: N. Dendele, F. Bisaro, A.-C. Gaumont, S. Perrio, C. J. Richards, *Chem. Commun.* **2012**, *48*, 1991-1993.

[9] See, for example: (a) T. Martzel, J.-F. Lohier, A.-C. Gaumont, J.-F. Brière, S. Perrio, *Eur. J. Org. Chem.* **2018,** 5069-5073. (b) T. Martzel, J.-F. Lohier, A.-C. Gaumont, J.-F. Brière, S. Perrio, *Adv. Synth. Catal.* **2018**, *360*, 2696-2706. (c) F. Gelat, J.-F. Lohier, A.-C. Gaumont, S. Perrio, *Adv. Synth. Catal.* **2015**, *357*, 2011-2016.

[10] (a) J.-F. Lohier, F. Foucoin, P.-A. Jaffrès, J.-I. Garcia, J. Sopková–de Oliveira Santos, S. Perrio, P. Metzner, *Org. Lett.* **2008**, *10*, 1271-1274. (b) L. Beqa, D. Deschamps, S. Perrio, A.-C. Gaumont, S. Knoppe, T. Bürgi, *J. Phys. Chem. C* **2013**, *117*, 21619-21625. (c) A. Vincent, D. Deschamps, T. Martzel, J.-F. Lohier, C. J. Richards, A.-C. Gaumont, S. Perrio, *J. Org. Chem.* **2016**, *81*, 3961-3966.

[11] D. Deschamps, J.-F. Lohier, C. J. Richards, A.-C. Gaumont, S. Perrio, *J. Org. Chem.* **2021**, *86*, 507-514.

[12] As representative example, see: (a) D. Sharma, A. Bahuguna, S. Rawat, A. Kumar, A. K. Singh, *Appl. Organomet. Chem.* **2023**, *37*, e7106. (b) R. Naskar, P. Ghosh, C. K. Manna, N. Murmu, T. K. Mondal, *Inorg. Chim. Acta* **2022**, *534*, 120802. (c) M. Zábranský, A. Machara, I. Císařová, P. Štěpnička, *Eur. J. Inorg. Chem.* **2017**, 4850-4860. (d) F. Saleem, G. K. Rao, S. Kumar, M. P. Singh, A. K. Singh, *RSC Adv.* **2014**, *4,* 56102-56111. (e) J. R. Lamb, V. A. Stepanova, I. P. Smoliakova, *Polyhedron* **2013** *53*, 202-207. (f) Y. Fuchita, H. Maruyama, M. Kawatani, K. Hiraki, *Polyhedron* **1991**, *10*, 561-566. (g) Y. Fuchita, K. Hiraki, Y. Kamogawa, M. Suenaga, K. Tohgoh, Y. Fujiwara, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1081-1085.

[13] See for example: (a) G. G. Flores-Rojas, L. González-Sebastián, R. Reyes-Martínez, B. A. Aguilar-Castillo, S. Hernández-Ortega, D. Morales-Morales, *Polyhedron* **2020**, *185*, 114601. (b) M. Yu, Y. Xie, C. Xie, Y. Zhang, *Org. Lett.* **2012**, *14*, 2164-2167. (c) J. E. Kukowski, J. R. Lamb, V. A. Stepanova, I. P. Smoliakova, *Inorg. Chem. Commun.* **2012**, *26*, 64-65. (d) R. Bhawmick, P. Bandyopadhyay, *Polyhedron* **1996**, *15*, 2923-2926. (e) J. Dupont, N. Beydoun, M. Pfeffer, *J. Chem. Soc. Dalton Trans.* **1989**, 1715-1720. (f) K. Hiraki, Y. Fuchita, T. Maruta, *Inorg. Chim. Acta* **1980**, *45*, L205-L206. (g) R. L. Bennett, M. I. Bruce, I. Matsuda, *Aust. J. Chem.* **1975**, *28*, 2307-2310.

[14] For substituted benzylic sulfides, see: A. S. Gruber, D. Zim, G. Ebeling, A. L. Monteiro, J. Dupont, *Org. Lett.* **2000**, *2*, 1287–1290.

[15] (a) X. Q. Feng, H. C. Wang, Z. Li, L. Tang, X. Sun, K. Yang, *RSC Adv.* **2022**, *12*, 10835-10845. (b) K. X. Tang, C. M. Wang, T. H. Gao, L. Chen, L. Fan, L. P. Sun, *Adv. Synth. Catal.* **2019**, *361*, 26-38.

[16] This structural assignment was further confirmed by comparison with a sample prepared by trifluoroacetylation of [2.2]paracyclophan-4-yl methanol (see Supporting Information).

[17] According to ^{1}H NMR analyses, a substantial amounts of starting materials **1b-d** was detected in the crude products. Additional experiments based on treatment of the crude products with Na(hfacac), indicated that these reactions did not result in any cyclometallation.

[18] For a literature precedent with allylic sulfides as substrates, in the presence of copper salts, see: D. Uguen, *Tetrahedron Lett.* **1984**, *25*, 541-542.

[19] A. Joshi, Z. Iqbal, P. Kandwal, S. R. De, *Asian J. Org. Chem.* **2022**, *11*, e202200400.

[20] (a) C. Bolm, K. Wenz, G. Raabe, *J. Organomet. Chem.* **2002**, *662*, 23-33. (b) V. V. Dunina, E. I. Turubanova, M. V. Livantsov, K. A. Lyssenko, N. V. Vorontsova, D. Y. Antonov, Y. K. Grishin, *Tetrahedron Asymmetry* **2009**, *20*, 1661-1671. (c) J. E. Glover, P. G. Plieger, G. J. Rowlands, *Aust. J. Chem.* **2014**, *67*, 374-380. (d) V. V. Dunina, E. I. Turubanova, O. N. Gorunova, M. V. Livantsov, K. A. Lyssenko, D. Y. Antonov, Y. K. Grishin, *Polyhedron* **2012**, *31*, 413-421. (e) C. Zippel, T. Bartholomeyzik, C. Friedmann, M. Nieger, Z. Hassan, S. Bräse, *Eur. J. Org. Chem.* **2021**, 5090-5093. (f) M. Stahlberger, N. Schwarz, C. Zippel, J. Hohmann, M. Nieger, Z. Hassan, S. Bräse, *Chem. Eur. J.* **2022**, *28*, e202103511.

[21] V. V. Dunina, E. I. Turubanova, M. V. Livantsov, K. A. Lyssenko, Y. K. Grishin, *Tetrahedron Asymmetry* **2008**, *19*, 1519-1522.

[22] There is another possible cyclometallation product, which could arise from CH insertion onto the second aromatic ring of the [2.2]PCP, to form an additional bridge between the two aryl decks. For a precedent with PhanePhos in the iridium series: L. A. Schwartz, M. Holmes, G. A. Brito, T. P. Gonçalves, J. Richardson, J. C. Ruble, K.-W. Huang, M. J. Krische, *J. Am. Chem. Soc.* **2019**, *141*, 2087-2096.

[23] N. Takeda, D. Watanabe, T. Nakamura, M. Unno, *Organometallics* **2010**, *29*, 2839-2841.

[24]] For reliable resolution protocols of 4-formyl [2.2]PCP **2** and of a pivotal sulfur-based [2.2]PCP, see ref. 6a and 11.

[25] A possible investigation could focus on Suzuki-Miyaura and Heck coupling reactions. See for example, ref. 13a and 14.

[26] P. Lennartz, G. Raabe, C. Bolm, *Adv. Synth. Catal.* **2012**, *354*, 3237-3249.

[27] C. J. Friedmann, S. Ay, S. Bräse, *J. Org. Chem.* **2010**, *75*, 4612-4614.

[28] D. J. Cram, L. A. Singer, *J. Am. Chem. Soc.* **1963**, *85*, 1075-1079.

[29] M.-L. Delcourt, S. Turcaud, E. Benedetti, L. Micouin, *Adv. Synth. Catal.* **2016**, *358*, 1213-1218.

[30] M. T. Rispens, A. Manfredi, G. Pozzi, S. Banfi, S. Quici, *J. Mol. Catal. A: Chem.* **1998**, *136*, 13-22.

[31] J. Lahann, R. Langer, *Macromolecules* **2002**, *35*, 4380-4386.

[32] F. Roncaglia, A. F. Parsons, F. Bellesia, F. Ghelfi, *Synth. Commun.* **2011**, *41*, 1175-1180.

[33] L. I. Zakharkin, V. A. Ol'shevskaya, L. E. Vinogradova, *Russ. Chem. Bull.* **1997**, *46*, 1158-1163.

[34] J. Limwongyut, Y. Liu, G. S. Chilambi, T. Seviour, J. Hinks, Y. Mu, G. C. Bazan, *RSC Adv.* **2018**, *8*, 39849-39853.
[35] M. Hitt, A. N. Vedernikov, *Org. Lett.* **2022**, *24*, 7737-7741.
[36] S. J. Coles, P. A. Gale, *Chem. Sci.* **2012**, *3*, 683-689.

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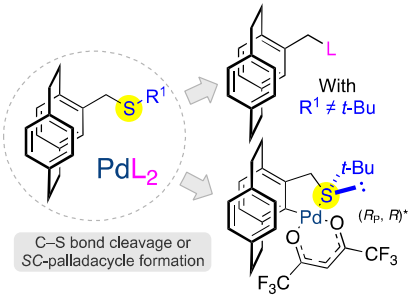

This work explores the reactivity of [2.2]paracyclophanes displaying a CH_2SR^1 group on one aromatic ring with various PdL_2 salts. In most cases (R^1 = Ph, 2-pyridyl, Me, *n*-dodecyl), an unexpected cleavage of the carbon-sulfur, along with incorporation of one L ligand (L = TFA, OAc, OPiv, Cl, Br), occurred. In contrast, the *t*-butylsulfanyl derivative (R^1 = *t*-Bu) underwent a regioselective *ortho* C–H bond activation to furnish a *SC*-palladacycle species as a single diastereoisomer.