Cross-Coupling

Controlling Regioselectivity in Palladium-Catalyzed C–H Activation/Aryl–Aryl Coupling of 4-Phenylamino[2.2]paracyclophane

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In memory of Dieter Enders

Abstract: Selective activation/functionalization of C–H bonds has emerged as an atom- and step-economical process at the forefront of modern synthetic chemistry. This work reports palladium-catalyzed exclusively *para*-selective C–H activation/aryl–aryl bond formation with a preference over *N*-arylation under the Buchwald–Hartwig amination reaction of 4-phenylamino[2.2]paracyclophane. This innovative synthetic strategy allows a facile preparation of [2.2]paracyclophane derivatives featuring disparate *para*-substitutions at C-4 and C-7 positions in a highly selective manner, gives access to a series of potential candidates for [2.2]paracyclophane-derived new planar chiral ligands. The unprecedented behavior in reactivity and preferential selectivity of C–C coupling over C–N bond formation via C–H activation is unique to the [2.2]paracyclophane scaffold compared to the non-cyclophane analogue under the same reaction conditions. Selective C–H activation/aryl–aryl bond formation and sequential C–N coupling product formation is evidenced unambiguously by X-ray crystallography.

Carbon-hydrogen (C–H) bond functionalization as an atom- and step-economical process have attracted tremendous attention owing to their exciting synthetic potential in complex molecules, such as natural products and pharmaceuticals.[1] Advanced metal catalysts design in combination with efficient versatile ligands have greatly improved the practical utilization of C–H bonds, enabling fast and efficient derivatization.[2] Direct functionalization of C–H bonds with controlled site selectivity is an appealing concept, yet the ability to effect selective functionalization of one specific C–H bond over the others within complex molecules remains a more formidable challenge.[3] In contrast to electron-rich arenes and their reactivity/selectivity patterns, [2.2]paracyclophane is a highly strained prevalent carbocycle bearing multiple C–H bonds of chemically very similar nature and laced with unexpected chemical reactivities and unique stereochemical features (planar chirality), but often resistant to chemical transformation and has been challenging scaffold for regioselective functionalization.[4] [2.2]Paracyclophane (PCP) scaffold has been largely investigated in planar chiral ligand design and development of asymmetric catalysts,[5] optoelectronic research,[6] π-stacked conjugated polymers,[7] parylene-derived thin films, and bioinstructive coatings via chemical vapor deposition that finds broad applications in bio- and materials science.[8] This rather unusual "bent and battered" strained scaffold (consists of two co-facially stacked strongly interacting benzene rings, held together by two ethylene "bridges" at the bridgehead carbon atoms in *para* position),[9] has fascinated chemists for decades since its discovery in 1949 by gas-phase pyrolysis.[10] The short distance between the two cyclophane decks causes distortion abnormalities, forcing the benzene rings out of their aromatic planarity, which in turn causes unusual chemical reactivity when compared to conventional aromatics.

Transforming [2.2]paracyclophane scaffolds at only one or both benzene rings poses hurdles and synthetic challenges of

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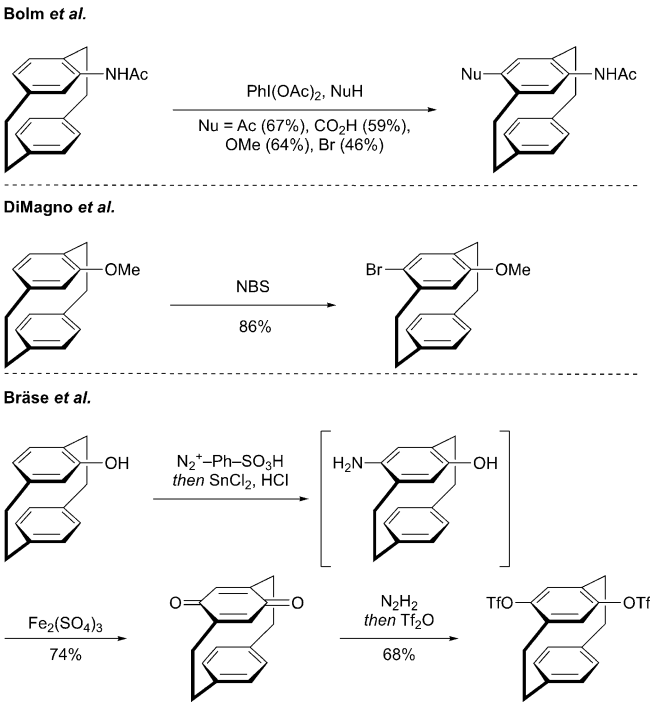
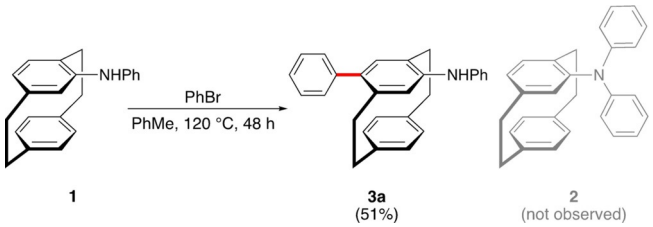
selectivity and unusual reactivity due to the transannular effects.[11] To functionalize PCP, the predominant synthetic strategies previously reported rely substantially on electrophilic substitution and subsequent transformations which offers the opportunity for improvements. Notable drawbacks and limitations are associated with conventional approaches, for instance, multiple pre-functionalization steps, low yields, an undesired mixture of side products, and a lack of selectivity due to the competing reactivity of the multiple C–H bonds of chemically very similar nature.[12] To overcome these hurdles, herein we report an atom-economical and minimal step-count process based on palladium-catalyzed selective C–H activation/aryl–aryl bond formation that offers many challenges to overcome and demonstrates significant practical advantages over previously reported other procedures for tailoring the [2.2]paracyclophane scaffold such as; 1) high regioselectivity control, 2) skips pre-functionalization steps and reducing tedious synthetic efforts, and 3) give access to a wide range of PCP-based products as potential candidates for new planar chiral ligands and other materials that would be otherwise difficult to prepare.

Our research group and others had a long-standing interest in the chemistry of [2.2]paracyclophane PCP scaffolds, from diverse application perspectives, including developing versatile, reliable, and commonly used practical PCP-based planar chiral ligands or catalysts employed most notably for synthetically important various enantioselective transformations.[13] Recent accomplishments include the direct introduction of substituents in pseudo-*ortho* and *ortho*-position using directing groups either for metalation[14] or Pd-mediated functionalization.[15] The synthesis of *meta*- difunctionalized derivatives on the other hand is particularly challenging so that de novo strategies are often inevitable.[16] Various synthetic approaches to access *para*-difunctionalized PCP-derivatives have been pursued (Scheme 1). The oxidative *para*- functionalization using phenyliodine(III) diacetate (PIDA) as oxidant,[17] as well as a *para*-directed bromination for a simple methoxy derivative have been developed.[18] Similarly, we have previously demonstrated a *para*-selective amination of hydroxy-PCP followed by subsequent oxidation to a quinone species and conversion to the versatile *para*-ditriflate derivative.[19]

Exploring selective C–H functionalization, in our preliminary trial, *N*-phenylamino[2.2]paracyclophane (**1**) was chosen as a model platform because of the significant application perspectives of the conceivable resulting products. PCP **1** was subjected to the palladium-catalyzed Buchwald–Hartwig amination reaction conditions employing bromobenzene as a coupling partner, Pd_2dba_3 (5 mol%) with SPhos (15 mol%) as ligand and potassium *tert*-butoxide as base in toluene at 120 °C. The *para* C–H activation/aryl–aryl coupling product **3a** was obtained in 51% yield (Scheme 2). After careful screening of different reaction conditions, (for detailed information, see Supporting Information, Tables S1–S7) including varying catalyst source, base, and temperature employing a series of chloro-, bromo- and iodobenzene derivatives as coupling partners, it was found that conducting strictly-controlled reaction at 60 °C, using $Pd(PPh_3)_4$ (5 mol%) in combination with KO*t*Bu (1.25 equiv) as a base in toluene, enables a highly preferential and exclusively *para*- C–H activation/aryl–aryl coupling. Enabling preferential selectivity in other settings, for instance, selective borylation and silylation of an aryl C–H bond in the presence of the more reactive aryl C-Halogen bonds (aryl chloride and iodide) via catalyst control by choosing Pd- over Ir-catalysts has been proved most crucial in the kilo-scale synthesis of doravirine,[20] In literature such preferential selectivity of C–C bond formation over C-N coupling under Buchwald–Hartwig amination reaction conditions is rarely reported.



Scheme 1. Previous accomplishments towards *para*-difunctionalized PCPs.



Scheme 2. Pd-catalyzed *para*-selective C–H activation/aryl–aryl coupling under classical Buchwald–Hartwig- amination of *N*-phenylamino[2.2]paracyclophane (0.5 mmol, 0.17 M): PhBr (0.6 mmol), Pd_2dba_3 (5.0 mol%), SPhos (5.0 mol%), KO*t*Bu (1.0 mmol), PhMe, 120 °C, 48 h.

Under Pd-catalyzed Buchwald–Hartwig amination, aryl halides couple with *N*-phenylamino[2.2]paracyclophane in a highly selective manner, and enable one-pot sequential C–C and C–N coupling product formation of compound **4**. The particular preferential *para*-selective C–H activation/C–C arylation coupling product **3** (Figure 1) and sequential C–N coupling product formation **4** (Figure 2), both were characterized by detailed spectroscopic techniques and unambiguously by single-crystal X-ray analysis.

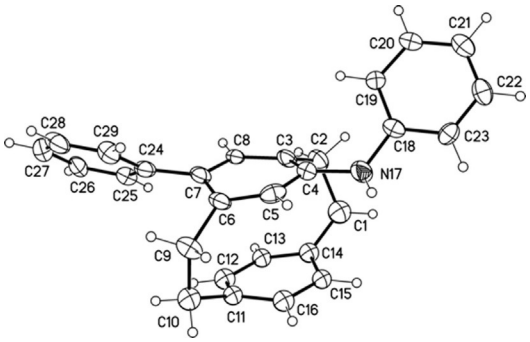


Figure 1. Molecular structure of *para*-phenyl *N*-phenylamino[2.2]paracyclophane **3a** (minor disordered parts omitted for clarity, displacement parameters are drawn at 50% probability level; the quality of the crystal only allows to collate the connectivity on the unsubstituted benzene unit).

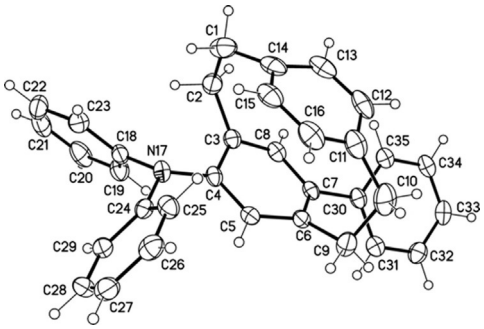
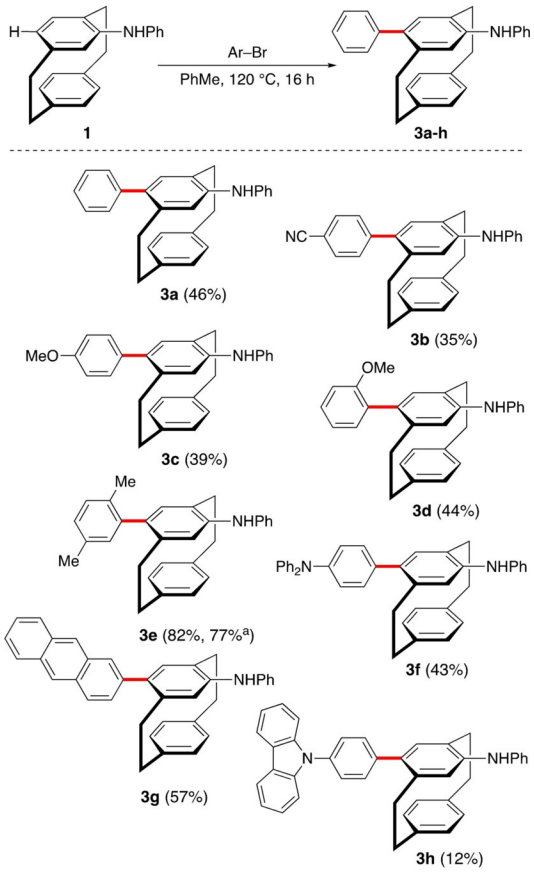


Figure 2. Molecular structure of *para*-phenyl *N*,*N*-diphenylamino[2.2]paracyclophane **4** (displacement parameters are drawn at 50% probability level).



Scheme 3. Generality, compatibility and synthetic scope of halo-arene derivatives as coupling partners: **1** (0.50 mmol, 0.17 M), Ar-Br (0.63 mmol), $Pd(PPh_3)_4$ (5.0 mol%), KO*t*Bu (0.63 mmol), PhMe, 120 °C, 16 h. [a] **1** (1.00 g, 3.34 mmol) was used; all yields refer to the isolated compound.

After careful screening of reaction conditions, the sequential C–N bond formation, initially observed and isolated in 9% yield, was completely oppressed (for detailed information see SI). In neither attempt, the diphenylamine PCP derivative **2** was detected. After having the optimized reaction conditions in hands, we investigated the generality and compatibility of this synthetic protocol (Scheme 3). Electron poor bromoarenes such as 4-nitro, 4-trifluoromethyl, 4-acetyl, and 4-diphenyltriazine did not give the desired products except for the 4-benzonitrile **3b**. Next, electron-donating bromoarenes were tested, which yielded the desired products in varying yields. While the 2-anthracenyl derivative **3g** and the diphenylamino derivative **3f** were isolated in moderate yields, respectively, the analogous carbazolyl derivative **3h** could only be obtained in a poor yield of 12%. Despite having an *ortho*-methyl group, which induces steric hindrance and should, therefore, hamper the performance of the reaction, the *para*-xylene derivative **3e** was formed with the best yield of 82% in this screening. Employing this synthetic protocol, Pd-catalyzed C–H activation/aryl–aryl coupling can be exploited on a gram scale while controlling preferential regioselectivity of C–C bond formation via C–H activation over *N*-arylation under the optimized Buchwald–Hartwig amination reaction conditions. The *para*-xylene derivative **3e** was formed with a 77% yield employing (1.00 g, 3.34 mmol) of *N*-phenylamino-PCP (**1**). To corroborate the marginal influence of steric effects on the yields, *para*-methoxy (**3c**, 39%) and *ortho*-methoxy (**3d**, 44%) derivatives were synthesized. In each case, the corresponding coupling product formation was verified either by single-crystal X-ray structure analysis or the presence of the N–H band in NMR/IR spectroscopy. For both the latter examples, the molecular structure was confirmed by crystallography (Figure 3 and Figure 4).

To compare the chemical reactivity and selectivity, the *para*-xylene moiety is commonly used as a non-strained [2.2]paracy-

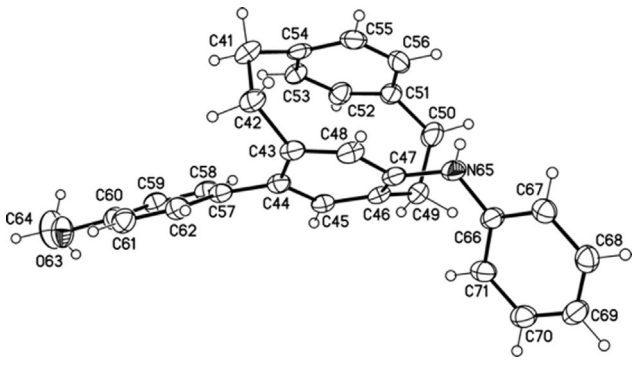


Figure 3. Molecular structure of **3c** (displacement parameters are drawn at 50% probability level).

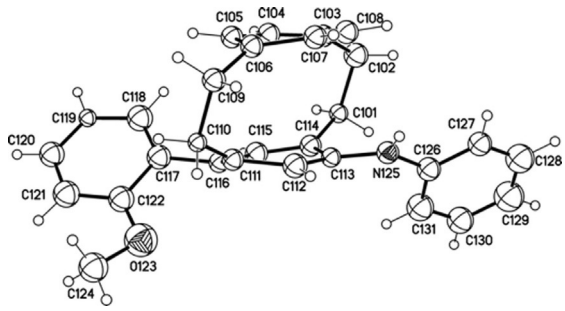
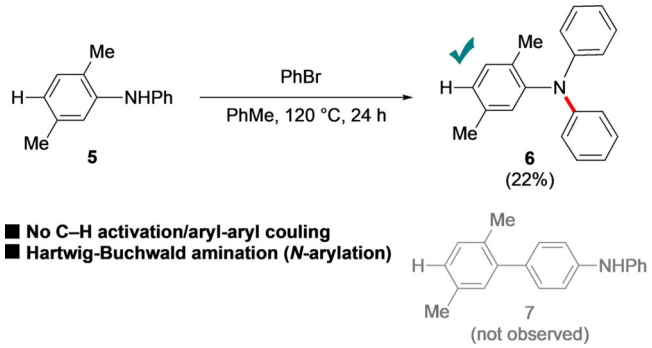


Figure 4. Molecular structure of **3 d** (due to the bad quality of the crystal and the date only constitution and conformation determined (see SI for details), one of the two crystallographic independent molecules shown, isotropic displacement parameters are drawn at 50 % probability level).

clophane analogue, hence we examined 2,5-dimethyl-*N*-phenylaniline (**5**) under the same Buchwald–Hartwig amination reaction conditions previously optimized for the PCP scaffold. Interestingly, it was found that substrate **5** predominantly yields the C–N coupling product **6** (Scheme 4), whereas no C–H bond functionalization was observed, at all. The C–N coupling product formation was verified by single-crystal X-rays analysis (Figure 5).



Scheme 4. Reactivity and selectivity of 2,5-dimethyl-*N*-phenylaniline (**5**) under Pd-catalyzed Buchwald–Hartwig amination reaction conditions initially optimized for the PCP core.

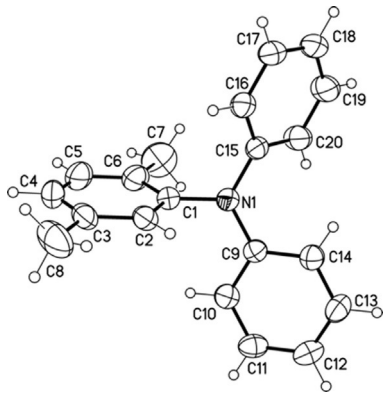


Figure 5. Molecular structure of **6** (one of the four crystallographic independent molecules shown, displacement parameters are drawn at 30 % probability level).

In the case of multiple C–H bonds, the origin of the regioselectivity in coupling processes is dominated by electronic effects, but steric effects do play an important role. Compared to other aromatic systems, PCP shows a peculiar reactivity and preferential selectivity of C–H bond activation/aryl–aryl coupling over C–N bond formation. The preliminary evidence suggests that this might arise from through-space conjugation/electronic communication of the PCP structural motif. Additional insights into the mechanism could be obtained from in silico computational studies. Experimental efforts are underway for the isolation and characterization of intermediates, which might serve as a rationale for the understanding of the mechanism.

In summary, we have developed a two-step one-pot sequential strategy combining a direct *para*-selective C–H activation/aryl–aryl coupling and subsequent C–N bond formation under Pd-catalyzed Buchwald–Hartwig amination reaction employing *N*-phenylamino[2.2]paracyclophane with a range of haloarenes for the preparation of synthetically useful PCPs. This process demonstrates a preferential selectivity of C–C bond formation over C-N coupling under the Buchwald–Hartwig amination reaction conditions. This preferential and exclusive *para*-site-selective C–H activation/aryl–aryl coupling enables selective substitution at previously inaccessible positions. Compared to the conventional synthetic strategies reported previously, this atom- and step-economical functionalization process based on selective C–H bond activation offers many challenges to overcome and demonstrates impressive practical advantages for tailoring PCP scaffolds such as 1) reducing tedious pre-functionalization steps, 2) highly preferential and site-controlled fashion, and 3) enables disparate substitution at previously inaccessible/challenging positions. In some cases, the yields of the C–H arylation products are low. During optimization, the particular role of catalyst/ligand combinations as well as the influence of the base were evaluated on the rate of the reaction and the yield of the C–H arylation products. A series of aromatic derivatives were used as coupling partners. However, for surmounting this problem, further studies on different C–H bond activation modes employing more sophisticated and versatile other complexes are needed.

The products can be readily transformed to showcase their utility in developing new planar chiral ligands or catalyst systems for stereo-controlled transformations.[21] Beyond ligand/catalyst design, besides, inspired by the recent reports exploiting PCP scaffolds in (deep) blue through-space conjugated thermally activated delayed fluorescence (TADF) emitters, circularly polarized luminescence (CPL),[22] and other PCP-based chemical vapor deposition (CVD) functional materials,[23] we believe this new methodology and as well as the corresponding products could diversify PCP applications in designing conceptually novel and efficient PCP-based materials.

Supporting Information

Deposition Number(s) 2009020 (for **3 a**), 2009021 (for **3 c**), 2009022 (for **4**) and 2009023 (for **6**) contain the supplementary crystallographic data for this paper. These data are provided

free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures. Due to the bad quality of the data of **3d** the data were not deposited with The Cambridge Crystallographic Data Centre (see Supporting Information for crystallographic data).

Experimental procedures and spectral data for all the new compounds are available in the Supporting Information.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: [2.2]paracyclophane · aryl–aryl coupling · Buchwald–Hartwig amination · C–H activation · cyclophanes · palladium

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