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An Efficient Catalyst System for Pd-Catalyzed Amination of [2.2]Paracyclophanyl Bromides

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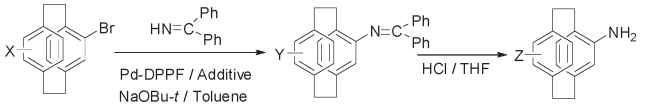

A practical Buchwald−Hartwig amination of [2.2]paracyclophanyl bromides with benzhydrylideneamine is developed. The method provides a facile route to a variety of imino and amino [2.2]paracyclophanes that are otherwise not readily synthesized.

Planar chiral [2.2]paracyclophane-based ligands possess a rigid [2.2]paracyclophanyl unit, which provides a versatile platform for designing different types of chiral ligands.[1] Examples of [2.2]paracyclophane-based ligands include diphosphanes,[2] oxazoline-phosphanes,[3] imidazoliums,[4] oxazoline-alcohols,[5] and imine ligands.[6] Recently, a series of planar chiral [2.2]paracyclophanyl dihydroimidazoliums have been prepared by our group[7] and their applications as rhodium[7a] or ruthenium complexes[7b] in highly enantioselective transformations have also been demonstrated. [2.2]Paracyclophanyl amines are important intermediates for the synthesis of [2.2]paracyclophanyl carbene precursors and imine ligands.[8,9c] Their synthesis has been a topic of interest in organic chemistry, and although several methods are available,[9] the discovery of new and improved methodology is still of interest. Herein, we present a study on palladium-mediated substituted [2.2]paracyclophanyl amination dealing with ligand effects and functional group tolerance.

The Buchwald−Hartwig palladium-catalyzed amination of aryl halides/triflates has emerged in the last decades as a powerful tool for the synthesis of arylamines.[10] Hartwig and Buchwald previously reported that benzhydrylideneamine can function as an effective ammonia equivalent,[11] and Connick adopted this strategy for Pd(BINAP)-catalytic amination of 4,16-dibromo[2.2]paracyclophane.[9c] To our knowledge, this is the only reported example of palladium-catalyzed amination of [2.2]paracyclophanyl halides with benzhydrylideneamine as an ammonia equivalent. Although Pd(BINAP) catalyst is capable of coupling benzhydrylideneamine with 4,16-dibromo[2.2]paracyclophane, reaction with this catalyst has several limitations: the catalyst has a short lifetime and a limited scope, needs a long reaction time, and requires large amounts of catalyst.

We now report on catalysts that overcome these limitations. Our approach, which is based upon the selection of ligands that combine steric hindrance, strong electron donation, and tight chelation, leads to a catalyst system that simultaneously possesses long lifetimes and displays

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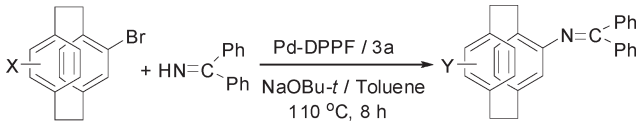
TABLE 1. Substrate Scope of the 3a-Promoted Amination[a]



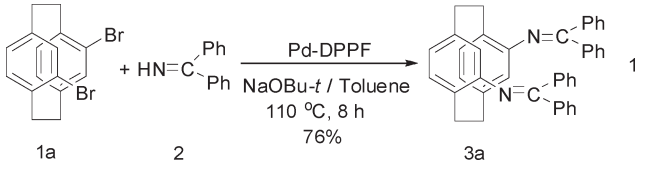
1 2 3

entry	X	catalyst (mol %)	Y	yield (%)
1	**1b**, H	Pd-dppf (0.5)	**3b**, H	15
2	**1b**, H	Pd-dppf (0.5) **3a** (0.25)	**3b**, H	64
3	**1b**, H	Pd-dppf (0.5) **3a** (0.5)	**3b**, H	79
4	**1b**, H	Pd-dppf (0.5) **3a** (1.0)	**3b**, H	80
5	**1a**, 12-Br	Pd-dppf (0.2)	**3aa**, 12-Br	52
6	**1c**, 16-Br	Pd-dppf (0.5) **3a** (0.5)	**3c**, 16-imino	94
7	**1d**, 15-Br	Pd-dppf (0.5) **3a** (0.5)	**3d**, 15-Br	41
8	**1e**, R_p-12-MeO	Pd-dppf (0.5) **3a** (0.5)	**3e**, R_p-12-MeO	84
9	**1f**, S_p-12-*i*-PrO	Pd-dppf (0.5) **3a** (0.5)	**3f**, S_p-12-*i*-PrO	62
10	**1g**, S_p-12-AcO	Pd-dppf (0.5)**3a** (0.5)	**3g**, S_p-12-OH	75
11	**1h**, 12-NH_2	Pd-dppf (0.5) **3a** (0.5)	**3h**, 12-NH_2	55
12	**1i**, R_p-12-NMe_2	Pd-dppf (0.5) **3a** (0.5)	**3i**, R_p-12-NMe_2	96
13	**1j**, 12-imino	Pd-dppf (5)	**3j**, 12-imino	93
14	**1k**, 4R_p,13S_p-13-MeO	Pd-dppf (5) **3a** (5)	**3k**, 4R_p,13S_p-13-MeO	98
15	**1 L**, 4R_p,13S_p-13-*i*-PrO	Pd-dppf (5) **3a** (5)	**3 L**, 4R_p,13S_p-13-*i*-PrO	63[b]
16	**1m**, 7,12,15-tribromo	Pd-dppf (0.5) **3a** (0.5)	**3m**, 7,12,16-tribromo	20
17	**1m**, 7,12,15-tribromo	Pd-dppf (5) **3a** (5)	**3ma**, 7,12,16-triimino	23

[a]All reactions were carried out in the presence of catalyst, benzhydrylideneamine (1.5 equiv/Br), and NaOBu-*t* (1.5 equiv/Br) in toluene at 110 °C for 8 h. [b]Product is 4R_p,13S_p-4-amino-13-isopropoxy[2.2]paracyclophane.

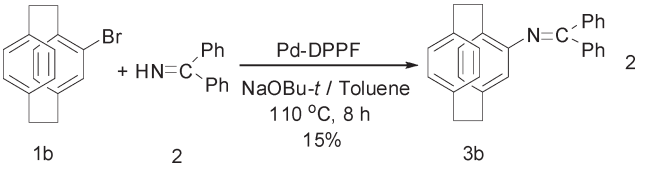
high activity for reactions of benzhydrylideneamine with [2.2]paracyclophanyl bromides.

In an initial set of experiments, we studied the reaction of 4,12-dibromo[2.2]paracyclophane **1a** with the benzhydrylideneamine **2** and chose $Pd(dba)_2$ as the precatalyst, NaOBu-*t* as the base, and toluene as the solvent. The reactions were carried out in toluene at 110 °C for 8 h with Pd (0.5 mol %) in the presence of different ligands ($P(t\text{-}Bu)_3$, BINAP, $P(o\text{-}Tol)_3$, IPrHCl, and SIPrHCl); however, only the unaltered starting material was recovered. Only, when the commercially available Pd-DPPF was used as catalyst, under our standard reaction conditions, was the corresponding imine **3a** obtained in good yield (eq 1).



1a 2 3a

In a different series of experiments with 4-bromo-[2.2]paracyclophane **1b** and **2**, under the same reaction conditions as described above, however, it was observed that the reaction provided the coupling product **3b** in merely 15% yield (eq 2). This transformation works well with **1a**, but is unsuccessful when **1b** is employed. Clearly, the difference in the structure alone cannot explain the significantly different characteristics of the two substrates (**1a** and **1b**). We postulated that the benzhydrylideneamine **2** or product imine **3b** binds too strongly to the resulting palladium[II] complexes and inhibits catalyst turnover by retarding the reductive elimination step of the cycle.[12] In contrast, the product imine **3a** appears to achieve a balancing act that renders it near perfect for its role as an accelerator of the amination catalysis. It binds strongly enough to the resulting palladium[II] complexes to accelerate reductive elimination of product imines, but not so tightly to the palladium[0] that it interferes with subsequent stages of the catalytic cycle. We considered the possibility that formation of an in situ protected "catalyst" prevents **2** or **3b** from binding to the palladium[II] (preventing catalyst deactivation).[12] Thus, we decided to examine the properties of **3a** as an additive in palladium-catalyzed substituted [2.2]paracyclophanyl amination.



1b 2 3b

Under our standard reaction conditions, varying the ratio of Pd-DPPF and **3a** from 1.0/0 to 1.0/2.0, to our great surprise, the yield was dramatically increased from 15% to 80% (entries 1−4, Table 1). Clearly, this result suggested that the reaction has the features of "ligand-accelerated catalysis". As defined by Sharpless, the phenomenon arises when the addition of a ligand increases the rate of an already existing catalytic transformation.[13] To the best of our knowledge, there are no examples of a successful "ligand-accelerated catalysis" in the palladium-catalyzed cross-coupling reaction of nitrogen nucleophiles with aryl bromides.

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We explored the reaction parameters in order to gain a deeper insight into this unexpected result.

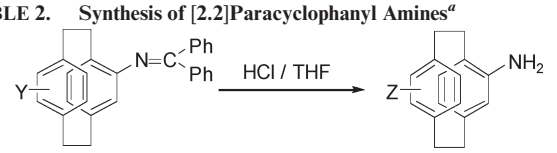
With the ligand in hand, we examined the generality in scope of the combination of **3a** and the other palladium source in the corresponding Pd-catalyzed amination. Unfortunately, catalyst systems based on the combination of $PdCl_2(PPh)_2$ or $Pd(PPh)_4$ and **3a** provided only trace amounts of product **3b**. Other palladium precatalysts such as $Pd(dba)_2$, $Pd(OAc)_2$, and $PdCl_2$ failed to produce the desired product. These results, taken together, reveal a cooperative effect between the **3a** and the Pd-DPPF and demonstrate that both are required for the observed reactivity in the above catalytic reactions employing Pd-DPPF.

Having defined an efficient catalytic system, the scope of [2.2]paracyclophanyl bromide coupling reactions was explored. Highlighted in Table 1, the benzhydrylideneamine **2** was successfully reacted with both electron-rich and electron-deficient [2.2]paracyclophanyl bromides in good to excellent yields. Particularly, we found that the combination of **3a** and Pd-DPPF was the most effective for the transformation of 4,16-dibromo[2.2]paracyclophane **1c** at 110 °C, thus providing the product **3c** in 94% yield in 3 h (Table 1, entry 5). While the same reaction catalyzed by $Pd_2(dba)_3$/BINAP at 130 °C for 4 days gave the corresponding product in 68% yield,[9c] its efficiency was far less than that of our catalyst system. In addition to [2.2]paracyclophanyl bromides, other simple aryl bromides were successfully combined with benzhydrylideneamine **2** in high yields.[14]

Due to the variety of methods available for imine cleavage,[15] substituted [2.2]paracyclophanyl imines **3** were easily converted into its amino analogue **4** by acid hydrolysis in good to high yields (Table 2).

In conclusion, we have developed highly reactive catalyst systems based on the combination of Pd-DPPF and **3a** ligand. These provide unprecedented reactivity and selectivity in palladium-catalyzed substituted [2.2]paracyclophanyl amination processes. The optimized catalyst system was effective for the reaction of [2.2]paracyclophanyl bromides bearing various functional groups and benzhydrylideneamine. We hypothesize that the efficacy of catalyst systems based on the combination of Pd-DPPF and **3a** is attributed to a successful "ligand-accelerated catalysis".

TABLE 2. Synthesis of [2.2]Paracyclophanyl Amines[a]



3 4

entry	Y	Z	yield (%)
1	**3a**, 12-imino	**4a**, 12-NH_2	86
2	**3aa**, 12-Br	**4aa**, 12-Br	97
3	**3b**, H	**4b**, H	98
4	**3c**, 16-imino	**4c**, 16-NH_2	83
5	**3e**, R_p-12-MeO	**4e**, R_p-12-MeO	96
6	**3f**, S_p-12-*i*-PrO	**4f**, S_p-12-*i*-PrO	91
7	**3h**, 12-NH_2	**4a**, 12-NH_2	86
8	**3i**, R_p-12-NMe_2	**3i**, R_p-12-NMe_2	91
9	**3k**, 4R_p,13S_p-13-MeO	**4k**, 4R_p,13S_p-13-MeO	68

[a]Reaction conditions: 1 equiv of **3** and 3 equiv of concentrated HCl in THF (4 mL/mmol imine) at rt or 65 °C for 4 h.

Experimental Section

General Procedure A for Pd-Catalyzed Amination of 4-Bromo-[2.2]paracyclophane 1b. In a glovebox, an oven-dried Schlenk flask was charged with Pd-DPPF (4.1 mg, 5.0×10^{-3} mmol), 4,12-bis(benzhydrylideneamino)[2.2]paracyclophane **3a** (2.8 mg, 5.0×10^{-3} mmol), 4-bromo[2.2]paracyclophane **1b** (287 mg, 1.0 mmol), benzhydrylideneamine (271 mg, 1.5 mmol), sodium *tert*-butoxide (144 mg, 1.5 mmol), and toluene (0.60 mL). The mixture was stirred at 110 °C under nitrogen for 8 h. After the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (15.0 mL), HOAc was added to the mixture until the stirred solution tested acidic (pH 6). The acidic solution was washed with water (3 × 10.0 mL) and saturated aqueous NaCl solution (3 × 10.0 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate = 10:0−10:5) to give 4-benzhydrylideneamino-[2.2]paracyclophane **3b** as a yellow solid (304 mg, 79%). Mp 208−210 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 7.89−7.87 (m, 2H), 7.50−7.48 (m, 3H), 7.37−7.35 (m, 1H), 7.17−7.14 (d, 3H), 7.01−7.00 (m, 2H), 6.55−6.46 (m, 3H), 6.25 (m, 2H), 5.48 (br, 1H), 3.29 (m, 2H), 3.07−2.89 (m, 4H), 2.76 (m, 1H), 2.51−2.46 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, rt) δ 165.2, 148.7, 140.0, 139.9, 139.9, 138.9, 136.7, 134.3, 133.2, 132.4, 131.9, 131.4, 130.4, 129.5, 129.3, 129.2, 128.2, 128.2, 128.0, 127.6, 126.7, 35.3, 35.1, 34.0, 33.0. Anal. Calcd for $C_{29}H_{25}N$ (387.52): C, 89.88; H, 6.50; N, 3.61. Found: C, 89.92; H, 6.48; N, 3.60.

General Procedure B for Cleavage of 4-Benzhydrylideneamino-[2.2]paracyclophane 3b. To a solution of 4-benzhydrylideneamino-[2.2]paracyclophane (387 mg, 1.0 mmol) in THF (4.0 mL) was added concentrated hydrochloric acid (12.0 M, 0.25 mL, 3.0 mmol). The mixture was stirred at room temperature for 4 h. After the yellow color of the mixture faded, the white precipitate was collected by filtration, washed with ether (3 × 5.0 mL), and dried in vacuo. The remaining solid in ethanol (4.0 mL) was stirred, then saturated NaOH was added dropwise until the stirred mixture tested basic (pH 9). The solvent was removed, and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate = 10:1) to afford 4-amino[2.2]paracyclophane **4b** as a white solid (219 mg, 98%). Mp 243−245 °C. ^{1}H NMR (300 MHz, $CDCl_3$, rt) δ 7.19−7.15 (dd, 1H), 6.60−6.57 (dd, 1H), 6.40−6.37 (dd, 2H), 6.28−6.25 (d, 1H), 6.14−6.11 (dd, 1H), 5.38−6.37 (d, 1H), 3.49 (br, 2H), 3.18−2.84 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, rt) δ 144.2, 140.6, 138.5, 138.4, 134.7, 132.9, 131.9, 131.0, 126.3, 124.1, 122.5, 121.8, 34.9, 34.4, 32.5, 31.7. Anal. Calcd for $C_{16}H_{17}N$ (223.31): C, 86.05; H, 7.67; N, 6.27. Found: C, 86.28; H, 7.44; N, 6.09.

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Supporting Information Available: Experimental procedures and characterization data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) In general, the rates for amination of bromobenzene, 1-bromonaphthalene, and 3-bromopyridine were faster than those for amination of brominated [2.2]paracyclophanes. The reaction of 3-bromopyridine with benzhydrylideneamine in toluene occurred to completion after 2 h at 110 °C in 96% yield with the catalytic system (0.5% Pd-DPPF and 0.5% **3a**). Under the same reaction condition, reaction of benzhydrylideneamine with bromobenzene and 1-bromonaphthalene occurred to completion in 93% and 94% yield within only 3 and 5 h.

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