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# A novel class of amide-derived air-stable P,O-ligands for Suzuki cross-coupling at low catalyst loading

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**Abstract**—The benzamide-derived P,O-ligands efficiently promoted the Pd-catalyzed Suzuki cross-coupling reactions of aryl bromides with phenylboronic acid at 0.01 mol% of Pd loading at 60–80 °C to form biaryls in excellent yields. A sterically hindered arylboronic acid gave a quantitative yield of the coupling product at 110 °C with 1 mol% Pd.
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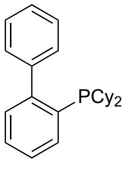
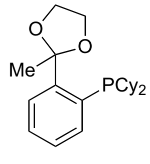
The palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with arylboronic acids is a powerful method for accessing structurally diversified biaryls.[1,2] With recent successful development of bulky and electron-rich phosphines, the Suzuki cross-coupling reaction has significantly advanced to include aryl chlorides,[3] fluorides,[4] and tosylates[5] and alkyl tosylates[6] as the substrates. For example, *o*-(dicyclohexylphosphino)biphenyl **1** was reported to promote the Suzuki cross-coupling of hindered substrates. It also effected the formation of biaryls from aryl bromides at very low catalyst loading (0.001–0.005 mol% of Pd) at 100 °C.[7] The ether-type P,O-ligand **2** was reported to form monophosphine–Pd intermediates featuring both P and O coordinations. Its combination with $Pd(dba)_2$ provides an efficient catalyst system for the Suzuki cross-coupling of a variety of aryl chlorides at 100–110 °C.[8] Moreover, the Suzuki cross-coupling reaction of aryl bromides in the absence of transition metal was reported to take place in hot water (150 °C) under microwave irradiation.[9] Recently, we disclosed a novel class of 1-naphthamide-derived atropisomeric P,O-ligands for the Pd-catalyzed asymmetric allylic alkylation in up to 94.7% ee.[10] We report here on the Suzuki cross-coupling reaction of aryl bromides using the benzamide-derived air-stable P,O-ligands **3** and **4** at low catalyst loading (0.01 mol% of Pd) at 60–80 °C.

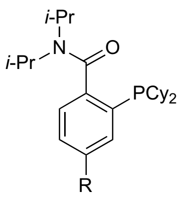
The P,O-ligands **3** and **4** were readily prepared from the benzamides in one operation via the amide-directed *ortho* lithiation[11] followed by quenching with $(Cy)_2PCl$. The tertiary amide moiety in **3** and **4** is considered to deliver two functions: (a) it provides the necessary bulkiness to prevent formation of bisphosphine–Pd complexes as it was noted for the methyl group in **2**;[8b] and (b) the amide carbonyl oxygen acts as a coordinating atom to Pd.[12] Our initial experiments with **3** showed that a 1:2 Pd:ligand ratio[13] gave the best yields of the biaryl products. Therefore, the reactions shown in Scheme 1 were carried out with 0.005 mol% of $Pd_2(dba)_3$ (0.01 mol% of Pd), 0.02 mol% of the P,O-ligand **3**, and 3 equiv of $KF{\cdot}2H_2O$ or $K_3PO_4$ as the base in toluene at 60–80 °C. The results are summarized in Table 1.



**1**



**2**



**3**: R = H
**4**: R = Ph

We first attempted the Suzuki reaction of 3-bromotoluene **7** with phenylboronic acid at room temperature using 0.5 mol% of $Pd_2(dba)_3$ (1 mol% of Pd). The

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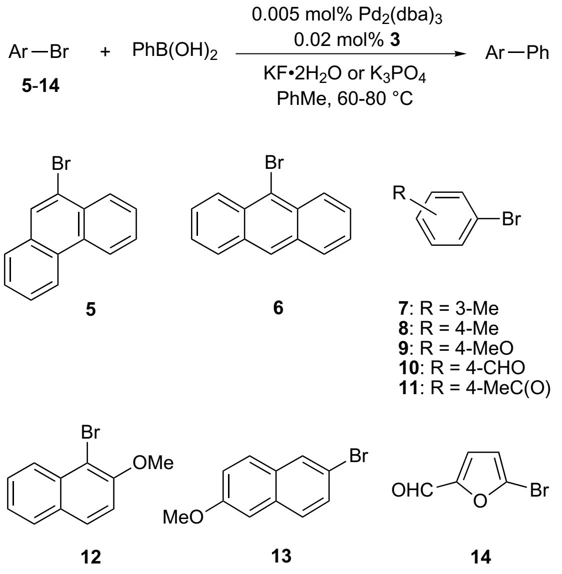


**Scheme 1.** The Suzuki cross-coupling reaction of aryl bromides.

reaction proceeded initially but almost stopped after 24 h to give the product in 24% yield (entry 6). In contrast, the same reaction carried out at 60 °C completed within 1 h to give the product in 99% yield in the presence of 1 mol% of Pd or the product was obtained in 95% yield after 18 h with 0.01 mol% of Pd (entries 7 and 8). In another set of experiments of 9-bromophenanthrene **5**, the effect of Pd loading on the reaction was examined. At 60 °C, the coupling of **5** with phenylboronic acid afforded a 99% yield of the biaryl after 4 h using 1 mol% of Pd whilst a 96% yield was obtained at 80 °C for 26 h using 0.01 mol% of Pd (entries 1 and 2). Further reduction of Pd to 0.0005 mol%, however, significantly diminished the yield of the product to 32% (entry 3). We found that either $KF{\cdot}2H_2O$ or $K_3PO_4$ could be used as the base without remarkable differences. An electronic effect on the reactivity of 4-substituted phenyl bromides **8–11** was observed. For the phenyl bromides **10** and **11** possessing a C4 electron-withdrawing group, the Suzuki reactions with phenylboronic acid took place at 60 °C with 0.01 mol% of Pd, affording the biaryl products in 95% and 99% yields, respectively (entries 11 and 12). For the electron-rich phenyl bromides **8** and **9**, a higher reaction temperature at 80 °C was required for the coupling reactions with 0.01 mol% of Pd, giving excellent yields of 93–99% (entries 9 and 10).

The steric effect also plays an important role on the efficiency of the Suzuki cross-coupling reaction. The reaction of 9-bromoanthracene with $PhB(OH)_2$ at 60 °C for 40 h in the presence of 0.01 mol% Pd gave the product in 84% yield, which could be improved to 97% using a slightly increased Pd loading of 0.015 mol% (60 °C, 26 h) (entries 4 and 5). More significantly, two naphthalene substrates **12** and **13** gave very different results. With 0.01 mol% of Pd loading at 80 °C for 40 h, 1-bromo-2-methoxynaphthalene **12** gave the product in only 57% yield compared to 2-bromo-6-methoxynaphthalene **13**, which afforded the biaryl in 98% yield under the identical reaction conditions (entries 13 and 15). The yield of the reaction of **12** was improved to 86% when 0.1 mol% of Pd was employed (entry 14). Finally, the heterocyclic aryl bromide **14** underwent the Suzuki reaction with phenylboronic acid at 80 °C for 30 h to furnish the product in 90% yield (entry 16). The P,O-ligand **4** acts in a similar manner as **3** and gave slightly better results in some cases (data not shown).

Cross-coupling of sterically hindered substrates via the Suzuki reaction is an attractive method for accessing biaryl atropisomers.[7b,14] It forms the basis for development of the asymmetric version of this catalytic process.[15] We performed the coupling reaction of **5** with 2,6-dimethylphenylboronic acid using the P,O-ligand **4**

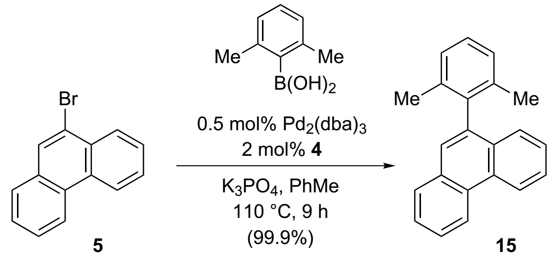
**Table 1.** Suzuki cross-coupling of aryl bromides with phenylboronic acid using amide-derived P,O-ligand **3**[a]

| Entry | ArBr | Pd loading (%) | Base | Temperature (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **5**: 9-bromophenathrene | 1 | $KF{\cdot}2H_2O$ | 60 | 4 | 99 |
| 2 | **5**: 9-bromophenanthrene | 0.01 | $KF{\cdot}2H_2O$ | 80 | 26 | 96 |
| 3 | **5**: 9-bromophenanthrene | 0.0005 | $K_3PO_4$ | 80 | 24 | 32 |
| 4 | **6**: 9-bromoanthracene | 0.01 | $KF{\cdot}2H_2O$ | 60 | 40 | 84 |
| 5 | **6**: 9-bromoanthracene | 0.015 | $KF{\cdot}2H_2O$ | 60 | 26 | 97 |
| 6 | **7**: 3-bromotoluene | 1 | $K_3PO_4$ | rt | 24 | 24 |
| 7 | **7**: 3-bromotoluene | 1 | $K_3PO_4$ | 60 | 1 | 99 |
| 8 | **7**: 3-bromotoluene | 0.01 | $KF{\cdot}2H_2O$ | 60 | 18 | 95 |
| 9 | **8**: 4-bromotoluene | 0.01 | $KF{\cdot}2H_2O$ | 80 | 20 | 99 |
| 10 | **9**: 4-bromoanisole | 0.01 | $KF{\cdot}2H_2O$ | 80 | 24 | 93 |
| 11 | **10**: 4-bromobenzaldehyde | 0.01 | $KF{\cdot}2H_2O$ | 60 | 40 | 95 |
| 12 | **11**: 4-bromoacetophenone | 0.01 | $KF{\cdot}2H_2O$ | 60 | 12 | 99 |
| 13 | **12**: 1-bromo-2-methoxynaphthalene | 0.01 | $KF{\cdot}2H_2O$ | 80 | 40 | 57[c] |
| 14 | **12**: 1-bromo-2-methoxynaphthalene | 0.1 | $KF{\cdot}2H_2O$ | 80 | 24 | 86[c] |
| 15 | **13**: 2-bromo-6-methoxynaphthalene | 0.01 | $KF{\cdot}2H_2O$ | 80 | 40 | 98 |
| 16 | **14**: 5-bromo-2-furaldehyde | 0.01 | $KF{\cdot}2H_2O$ | 80 | 30 | 90 |

[a] Reactions were carried out with 1.0 equiv of aryl bromide, 1.5 equiv of phenylboronic acid, and 3.0 equiv of base in toluene. $Pd_2(dba)_3$ was used as the catalyst precursor with a Pd:ligand ratio of 1:2.

[b] Isolated yield.

[c] Debromonation by-product was noted on TLC analysis of the reaction mixture.



**Scheme 2.** The Suzuki cross-coupling of hindered arylboronic acid.

at 110 °C for 9 h to produce the product **15** in 99.9% yield (Scheme 2).

In summary, we have developed a novel class of amide-derived P,O-ligands **3** and **4**, which are air-stable and readily available, for the Suzuki cross-coupling of structurally versatile aryl bromides with phenylboronic acid at low Pd loading of 0.01 mol% at 60–80 °C. The P,O-ligands are also effective for cross-coupling of sterically hindered substrates. In our previous work on asymmetric allylic alkylation, enantiomerically pure version of the P,O-ligands has been prepared.[10] Our results presented here form the basis for designing an asymmetric Suzuki cross-coupling employing the 1-naphthamide-derived atropisomeric P,O-ligands. Study on the asymmetric Suzuki cross-coupling is in progress in our laboratories.

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