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# An efficient catalyst system for diaryl ether synthesis from aryl chlorides

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**Abstract**—The combination of 2-phosphino-substituted *N*-arylpyrroles or related indoles (cata*CX*ium®P) and $Pd(OAc)_2$ allows for efficient cross-coupling reactions of aryl chlorides and phenols to give diaryl ethers. A variety of aryl and heteroaryl chlorides can be coupled with substituted phenols showing unprecedented catalyst turnover numbers.

The diaryl ether moiety is present in numerous naturally occurring and biologically active compounds. Important medicinal products having this structural motif include polycyclic glycopeptide antibiotics like vancomycin[1] or teicoplanin,[2] and the antineoplastic agent combretastatin D-2.[3] Until recently, the most general method for the synthesis of diaryl ethers was the classic copper-mediated Ullmann coupling of aryl bromides/iodides and phenols with the drawback of harsh reaction conditions and the need of a stoichiometric amount of metal.[4] Due to these problems significant efforts have been undertaken in the last decade to develop more efficient and environmentally benign coupling processes of phenols. For example, an interesting copper-catalyzed Ullmann coupling has been described by Buchwald and co-workers.[5] Palladium-catalysts have also been used for the synthesis of diaryl ethers.[6–10] Important contributions to that came mainly from Buchwald and co-workers[6,7] and Hartwig and co-workers.[8,9] So far it has been shown that electron-poor arylphosphines give good results for the coupling of activated aryl bromides with phenols.[8] On the other hand it has been demonstrated that electron-rich and bulky phosphines are more suitable ligands for palladium-catalyzed C–O bond forming reactions of deactivated aryl bromides and aryl chlorides.[7,9] Until now only little attention has been paid to the efficiency (productivity) of the respective palladium catalysts in such reactions. Hence, in general catalyst turnover numbers (TON) in the range 5–80 are obtained,[11] although it is well known that TONs of around 1000 are required to consider further practical application.[12]

Here, we report for the first time successful C–O coupling reactions of aryl chlorides, which fulfil the requirements for fine chemical syntheses and work in general at comparatively low catalyst concentration (0.1–0.5 mol % Pd).

For some time we have been interested in catalytic refinement reactions of aryl chlorides, which are often economically more attractive substrates than similar bromides and iodides.[13] Very recently, we reported on

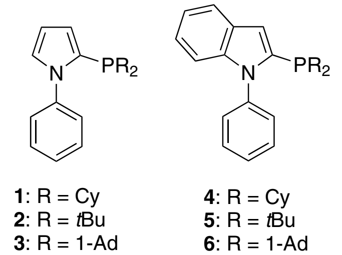

**Figure 1.** Selected examples of 2-phosphino-*N*-arylpyrroles and -indoles (cata*CX*ium®P ligands).

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*Keywords*: Aryl chlorides; Aryl ethers; Etherification; Palladium; Phosphines.

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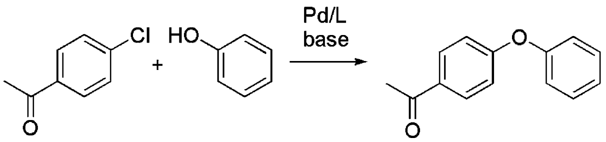
the synthesis of novel monophosphine ligands based on 2-phosphino-*N*-arylpyrrole and -indole structures (so-called cata*CX*ium®P ligands, e.g., **1**–**6**, Fig. 1).

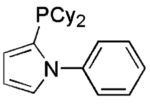
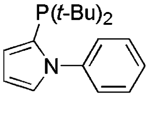
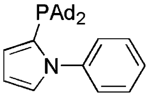
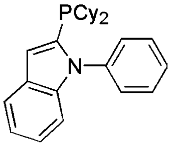
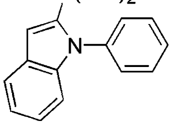
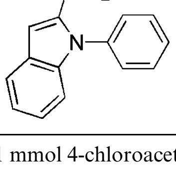
These ligands lead to efficient catalysts for Suzuki and Sonogashira cross-couplings as well as Buchwald–Hartwig aminations of aryl chlorides and bromides.[14] Because of the performance, the easy synthesis and tunability of this class of ligands we became also interested in testing them in the reaction of aryl chlorides and phenols. As a starting point of our investigation we examined the reaction of 4-chloroacetophenone (activated aryl chloride) and phenol as a model system (Scheme 1, Table 1).

At first the influence of the ligand structure was studied in the presence of 2 mol % $Pd(OAc)_2$ and 4 mol % ligand with $K_3PO_4$ as the base in toluene at 120 °C. These are typical reaction conditions, which have been used previously for C–O coupling reactions. Selected results are summarized in Table 1. In general, an increasing steric bulk of the electron-rich ligand facilitates the coupling reaction. For example, ligands having *tert*-butyl and 1-adamantyl groups on the phosphorus atom gave best results (Table 1, entries 2, 3, 5 and 6), while ligands bearing cyclohexyl groups provided significant conversions but almost no expected product (Table 1, entries 1 and 4).[15] Interestingly, when we started to decrease the catalyst concentration to 0.1 mol % $Pd(OAc)_2$ similarly good results were obtained, which led to the highest turnover numbers obtained for this type of reaction.



**Scheme 1.** Coupling reaction of 4-chloroacetophenone and phenol.

**Table 1.** Variation of ligands for the coupling reaction of 4-chloroacetophenone and phenol[a]

| Entry | Ligand | Conv. [%][b] | Yield [%][b] |
|---|---|---|---|
| 1 |  | 63 | 0 |
| 2 |  | 99 | 91 |
| 3 |  | 99 | 92 |
| 4 |  | 67 | 0 |
| 5 |  | 99 | 95 |
| 6 |  | 99 | 96 |

[a] Conditions: 1 mmol 4-chloroacetophenone, 1.2 mmol PhOH, 2 mmol $K_3PO_4$, 2 mol % $Pd(OAc)_2$, 4 mol % ligand, 3 mL toluene, 120 °C, 20 h.

[b] Average of 2 runs, determined by GC using hexadecane as internal standard.

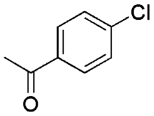
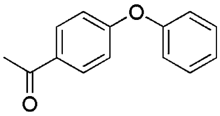
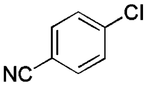
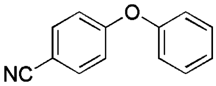
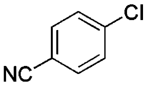
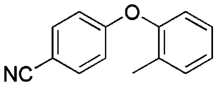
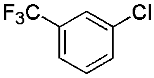
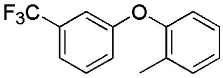
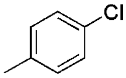
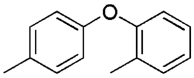
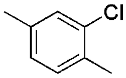
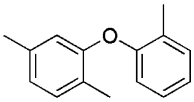
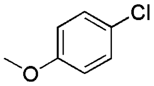
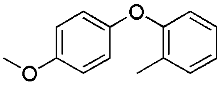
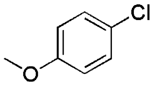
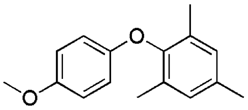
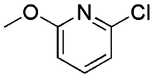
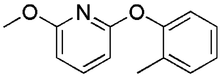
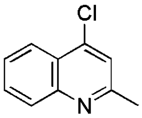
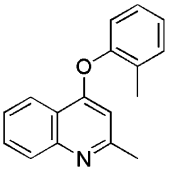
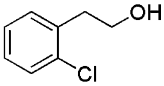
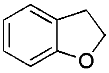
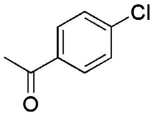
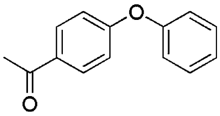
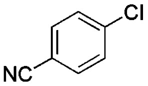
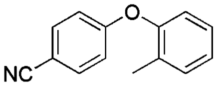
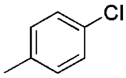
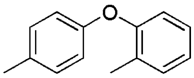
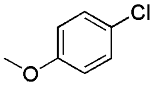
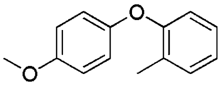
Next, the general usefulness of our ligands was examined and is shown in Table 2. Activated (electron deficient) aryl chlorides such as 4-chloroacetophenone, 4-chlorobenzonitrile and 1-chloro-3-(trifluoromethyl)-benzene react with phenol or *o*-cresol at 0.1 mol % $Pd(OAc)_2$ and 1 mol % ligand giving good to excellent yields (84–99%) of the corresponding diaryl ethers and unprecedented turnover numbers up to ca. 1000 (Table 2, entries 1–4). Nonactivated and electron-rich aryl chlorides require somewhat higher catalyst concentrations (0.5 mol % $Pd(OAc)_2$, 1 mol % ligand) in order to get high yields. Hence, 4-chlorotoluene and *o*-cresol provided the desired diaryl ether in 93% yield (Table 2, entry 5), while 4-chloroanisole gave 87% of the corresponding product (Table 2, entry 7). Again, to the best of our knowledge the obtained TON is the highest ever reported for a C–O coupling reaction of a deactivated aryl chloride. Even sterically more hindered 2,2′-dimethyl substituted diaryl ethers can be obtained in the presence of 0.5 mol % palladium catalyst (Table 2, entry 6).

Furthermore, heteroaryl chlorides reacted well, and the diaryl ether products were obtained in >80% yield (Table 2, entries 9 and 10). Apart from intermolecular coupling reactions, intramolecular C–O bond formation is also possible. For example, 2,3-dihydrobenzofuran can be synthesized in moderate yield at low temperature (60 °C).

In most cases the *tert*-butyl-substituted phosphine **5** proved to form the most productive catalyst. However, in few cases the 1-adamantyl-substituted pyrrole ligand **3** gave slightly higher yields in the tested reactions. A comparison of **5** and the commercially available 'standard' Buchwald ligand 2-(di-*tert*-butylphosphino)-biphenyl for the reaction of 4-chloroacetophenone, 4-chlorobenzonitrile, 4-chlorotoluene and 4-chloroanisole with phenol or *o*-cresol (0.1–2.0 mol % $Pd(OAc)_2$, Table 2, entries 12–15) demonstrates the increased efficiency of our novel ligands.

In summary, we have shown that the cata*CX*ium®P ligand family allows for an efficient diaryl ether synthesis from aryl chlorides and phenols. Good to excellent yields are obtained at low catalyst concentration. The catalyst productivities are the best ever reported for any metal-catalyzed C–O coupling reaction: turnover numbers up to 1000 have been observed. Due to the

**Table 2.** Palladium-catalyzed coupling of aryl chlorides and phenols[a]

| Entry | Aryl chloride | $Pd(OAc)_2$ [mol %] | Ligand | Product | Yield [%][b] | TON |
|---|---|---|---|---|---|---|
| 1 |  | 0.1 | **5** |  | 96 | 960 |
| 2 |  | 0.1 | **5** |  | 86 | 860 |
| 3 |  | 0.1 | **5** |  | 99 | 990 |
| 4 |  | 0.1 | **5** |  | 84 | 840 |
| 5 |  | 0.5 | **5** |  | 93 | 186 |
| 6 |  | 0.5 | **3** |  | 92 | 184 |
| 7 |  | 0.5 | **3** |  | 87 | 174 |
| 8[c] |  | 2.0 | **5** |  | 68 | 34 |
| 9 |  | 0.1 | **5** |  | 84 | 840 |
| 10[c] |  | 2.0 | **5** |  | 82 | 41 |
| 11[c] |  | 2.0 | **5** |  | 51 | 25 |
| 12[c] |  | 2.0 | **L** |  | 96 | 48 |
| 13 |  | 0.1 | **L** |  | 76 | 760 |
| 14 |  | 0.5 | **L** |  | 4 | 8 |
| 15 |  | 0.5 | **L** |  | <2 | <4 |

[a] Conditions: 1 mmol aryl chloride, 1.2 mmol ArOH, 2 mmol $K_3PO_4$, 1 mol % ligand, 3 mL toluene, 120 °C, 20 h. **L** = 2-(di-*tert*-butylphosphino)biphenyl.

[b] Average of 2 runs, determined by GC using hexadecane as internal standard.

[c] 4 mol % ligand.

modular synthesis of cata*CX*ium®P ligands[14] a fine tuning of the ligand properties for other substrates is easily possible and should lead to further improved catalyst performance.

## Acknowledgements

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## Supplementary data

Supplementary data with a general procedure for C–O coupling reactions and the analytical data of the newly synthesized ethers (Table 2, entries 4 and 9) is available online and with this article can be found in the online version, at doi:10.1016/j.tetlet.2005.03.033.

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11. To the best of our knowledge there is only one example reported using 4-bromoacetophenone as substrate in the presence of 0.1 mol % $Pd(OAc)_2$, for details see Ref. 7a.
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14. Cata*CX*ium®P ligands are commercially available at Strem and Degussa Homogeneous Catalysts (DHC). (a) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38–39; (b) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983–2990; (c) Harkal, S. F.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742–1748.
15. Small amounts of side-products observed by GC–MS are acetophenone and 4,4′-diacetylbiphenyl (<5% each).