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A Robust and Efficient Catalyst Possessing an Electron-Deficient Ligand for the Palladium-Catalyzed Direct Arylation of Heteroarenes

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Keywords: C-H activation / Palladium / Fluorinated ligands / Biaryls / Electron-deficient compounds

The exploration of the direct arylation capacity of a unique, thermally stable, and air-stable Pd^0 -phosphine catalyst is reported. Besides decisively contributing to catalyst robustness, the electron-deficient trifluoromethyl-substituted triphenylphosphine ligands make the palladium center more electron-deficient and accelerate the direct arylation step. The combination of only 0.5–2 mol-% of the catalyst and a

Introduction

Generally recognized as a privileged structure, the biaryl motif has received increased attention by both academic and industrial chemists having pharmaceutical, agrochemical, and materials science interests.^[1] Accordingly, its synthesis has been a perpetual focus of activity, which has resulted in the discovery and development of several efficient synthetic routes. Among the myriad of catalytic reactions to afford biaryls, the transition-metal-catalyzed direct arylation of aryl (pseudo)halides is an appealing approach.^[2] This non-oxidative, catalytic C-C bond-forming methodology represents one of the most elegant and straightforward synthetic pathways, as it eliminates the need to synthesize organometallic coupling partners, and only 1 equiv. of the halide salt is produced as a side product. Accordingly, a growing number of studies have been directed toward the development of suitable catalyst and catalytic conditions to effect this transformation. Despite these focused efforts, several practical challenges still remain to be solved. The reported procedures generally employ a relatively high (5-10 mol-%) catalyst load^[2b,3] or a stoichiometric amount of a quaternary ammonium salt additive,^[4] presumably as a result of thermal decomposition of the applied palladium catalysts at the elevated reaction temperature. This synthetic problem has been partially relieved by the utilization of phosphine-free catalysts for a limited class of substrates.^[5] However, most of the methods developed to date utilize one

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substoichiometric quantity of pivalic acid generates an efficient system to promote biaryl-forming reactions of a broad range of electronically varied hetarenes and aryl bromides. The observed regioselective arylations suggest that a concerted metalation-deprotonation pathway is involved in the C-H activation step.

of the coupling partners in excess amount and require prolonged reaction times (typically >12 h). Further practical deficiency of these methodologies is that the utilization of a different set of reaction conditions for each class of substrates has really caught on and has remained the norm.

Whereas catalyst development has been centered on the study of electron-rich and sterically bulky ligands, there is recent evidence by Fagnou,^[6] Gevorgyan,^[7] and Baudoin^[8] that shows that electron-deficient phosphine ligands can be used effectively for palladium-catalyzed C–H functionalization reactions, as they can accelerate the concerted metalation–deprotonation step.^[6]

Recently, we developed unprecedentedly thermo- and airstable Pd⁰ complex 1, the stability of which is associated with enhanced ligand dispersion interaction between the trifluoromethylated phenylphosphine ligands (Figure 1).^[9] Contrary to the electron-poor nature of the ligand, this complex proved to be an efficient and robust catalyst for Suzuki reactions. As a subsequent step to chart its synthetic utility, we became interested in exploring the applicability of this catalyst toward C–H activation reactions, as the thermal robustness of the complex combined with the presence of the electron-poor ligand was expected to be advantageous for the direct arylation processes. Herein, we report the results of catalyst 1 promoting direct arylation of a broad variety of heteroarenes.



Figure 1. Superstable Pd⁰ catalyst.

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Results and Discussion

Since the seminal work of $Ohta^{[10]}$ in 1990, many palladium-catalyzed methodologies have been developed for the direct arylation of (het)arenes. In 2006, Fagnou and coworkers discovered enabling reaction conditions for this type of reaction by using a combination of a substoichiometric pivalate additive with *N*,*N*-dimethylacetamide (DMA) as the solvent.^[11]

At the outset of our study, the direct arylation of benzene under the "Fagnou-type" reaction conditions was taken as a model reaction to investigate the efficiency of previously developed "superstable" Pd catalyst 1 (Table 1). Under these reaction conditions, catalyst 1 gave the biaryl product in 61% yield within 12 h at 120 °C (Table 1, Entry 1). The utilization of pivalic acid and DMA (Table 1, Entries 2–4) proved to be indispensable, as no biaryl formation was found in their absence.^[12] These trends suggested that a concerted metalation–deprotonation pathway was operating during this direct arylation process. In accordance with the suggested mechanism,^[5d] there was no beneficial effect of the utilization of phosphine additives (Table 1, Entries 5 and 6).^[13] Finally, employing more forcing conditions resulted in a slightly improved yield (Table 1, Entry 7).

Table 1. Influence of the reaction conditions in the palladium-catalyzed direct arylation of benzene with 4-bromotoluene by using Pd^0 complex 1.^[a]

| + 2 | | Br J 3a | 1 (3 mol-%) χ_2CO_3 (2.5 equiv.) PivOH (30 mol-%) | |
|---------------------|--------|-----------------------|--|--------------------------|
| Entry | Ligand | Solvent | Conv. ^[b] [%] | Yield ^[c] [%] |
| 1 | none | DMA | >99 | 61 |
| 2 | none | DMF | 65 | (6) |
| 3 | none | MeOH/H ₂ O | 0 (10:1) 33 | (<5) |
| 4 | none | <i>n</i> BuOH | >99 | (<5) |
| 5 | SPhos | DMA | 44 ^[d] | (<5) |
| 6 | dppb | DMA | 33 ^[d] | (<5) |
| 7 ^{[e][f]} | none | DMA | >99 | 64 |

[a] Reaction conditions: Catalyst 1 (3 mol-%), ligand (3 mol-%), K_2CO_3 (2.5 equiv.), additive (30 mol-%), 4-bromotoluene (0.6 mmol), benzene (3 mL), solvent (3.5 mL), 120 °C, 12 h. SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, dppb = 1,4-bis(diphenylphosphino)butane. [b] Conversion of 4-bromotoluene was determined by GC–MS. [c] Yield of isolated product. Yields determined by GC–MS are given in parentheses. [d] The reaction was conducted at 140 °C. [e] Reaction time was 72 h. [f] The employment of 52 equiv. of benzene was critical; the use of only 26 equiv. resulted in a dramatic drop in the yield (<5%).

To gauge the synthetic potential of catalyst 1 in direct arylation reactions, a survey of a broad range of heteroarenes and bromobenzene derivatives was performed by utilizing a strict 1:1 cross-coupling partner stoichiometry (Table 2). Gratifyingly, the direct arylation proceeded smoothly within 2–12 h in the presence of catalyst 1 to afford the products in synthetically useful yields. Molecules containing furan, thiazole, and benzothiophene rings resulted in biaryl products in moderate to good yields, similar to previously reported direct arylation methodologies (Table 2, Entries 1–12).^[3c,14] Nevertheless, these reactions indicated the strength and practical merit of catalyst 1 in direct arylation. Owing to its robustness, the employment of catalyst 1 did not necessitate strictly inert conditions and allowed the catalyst loading (0.5 mol-%) and the reaction time to be reduced significantly without compromising the yield. Next, a more challenging hetarene was selected to test the utility of catalyst 1. 1-Methylimidazole, previously recognized as a poor substrate,^[14a] reacted smoothly to give biaryl 8 regioselectively in excellent yield. In a similar manner, the direct arylation of oxazole occurred regioselectively in favor of the C5 position and in accordance with the presumed concerted metalation-deprotonation mechanism.^[3b] Although the cross-coupling of electron-rich and electrondeficient aryl bromides proceeded smoothly, the reaction failed if sterically congested 2-bromo-1,3,5-triisopropylbenzene (3n) or the less reactive 4-chloroacetophenone (3m) was used as the coupling partner.

Conclusions

We demonstrated the capacity and synthetic utility of superstable Pd^0 catalyst **1** in the direct arylation of benzene and heteroaryl molecules. Owing to the robustness of the catalyst at higher temperatures, there was no need to run the reaction under a strictly inert atmosphere, and the catalyst loading could be reduced without compromising the yields. Applying "Fagnou-type" conditions, a wide range of heteroaromatic biaryls were obtained within reasonable times and with high regioselectivity. Efforts are underway to further study the applicability of catalyst **1** in additional palladium-catalyzed reactions.

Experimental Section

General Procedure for the Direct Arylation of Heteroarenes: A mixture of K_2CO_3 (207 mg, 1.5 mmol), catalyst 1 (0.5–2 mol-%), pivalic acid (31 mg, 30 mol-%), aryl halide (1 mmol) and heteroarene (1 mmol) dissolved in DMA (3 mL) was stirred and heated in a screw-cap vial at 140 °C for the indicated time. After cooling to room temperature, the mixture was diluted with ethyl acetate (7 mL), washed with water (2 × 10 mL), and dried with Na₂SO₄. The solvent was evaporated in vacuo, and the crude product was further purified by flash chromatography (hexane/ethyl acetate) to provide the desired product.

Supporting Information (see footnote on the first page of this article): Experimental procedures and copies of the ¹H NMR and ¹³C NMR spectra for all biaryl products.

Acknowledgments

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Palladium-Catalyzed Direct Arylation of Heteroarenes

Table 2. Palladium-catalyzed arylation of heteroarenes with aryl halides.^[a]

| | | | A. D | 1-44-11 | 1 (C | 1 (0.5–2 mol-%) K ₂ CO ₃ (1.5 equiv.) PivOH (30 mol-%) DMA, 140 °C | | | | | |
|-------|---------------------------|---------------------------|---------------------------|-------------|--------------------------------|---|--|---------|---------------------|-------------|-----------------------------|
| | | | аг—вг + н 3а –п | ietAr-H | K ₂ CO PivC D | | | | | | |
| Entry | Aryl halide | Product | Catalyst [mol-%] | Time [h] | Yield ^[b] [%] | Entry | Aryl halide | Product | Catalyst [mol-%] | Time [h] | Yield ^[b] [%] |
| 1 | Ph Br | Рһ СНО | 2 | 12 | 68 | 9 | Br | | 2 | 4 | 63 |
| 2 | Br | S S | 2 | 2 | 78 | 10 | CI Br | | 2 | 4 | 62 |
| 3 | 3a Br | 6a | 0.5 | 3 | 47 | 11 | MeO Br 3i | | 2 | 4 | 58 |
| | 3c | 6b | | | | 12 | F 3j | | 0.5 | 3 | 66 |
| 4 | 3d | 6c | 1 | 3 | 55 | 13 | MeO 3k | MeO 8 | 2 | 12 | 90 |
| 5 | CI | CI | 2 | 3 | 67 | 14 ^[c] | Br 3I | Ph 9a | 2 | 12 | 54 |
| 6 | 3e | 6d S | 1 | 22 | 54 | 15 ^[c] | Br 3a | 9b | 2 | 4 | 57 |
| 7 | 3f F ₃ C Br | 6c F ₃ C 6f | 1 | 3 | 78 | 16 | CI 3m | 6c | 2 | 24 | _ |
| 8 | tBu tBu | tBu tBu | 1 | 20 | 53 | 17 | <i>i</i> Pr <i>B</i> r <i>i</i> Pr | | 2 | 24 | _ |
| | 3h | 6g | | | | | 3n | 6h | | | |

[a] Reaction conditions: Catalyst 1 (0.5–2 mol-%), K₂CO₃ (1.5 equiv.), pivalic acid (30 mol-%), aryl halide (1 equiv.), heteroarene (1 mmol), 140 °C, 2–12 h. [b] Yield of isolated product. [c] 1.5 equiv. of oxazole was used.

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C–H Activation

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H PivOH (30 mol-%), K₂CO₃ (1.5 equiv.) furan, oxazole, dimethylacetamide

the Pd⁰ complex possessing an electron-

Palladium-Catalyzed Direct Arylation of Heteroarenes

imidazole, thiazole, benzothiophene Application of a unique, thermally stable, and air-stable Pd^0 catalyst for the direct arylation of heteroarenes is described. The combination of only 0.5–2 mol-% of

superstable Pd⁰ (0.5-2 mol-%)

Ar Ar Ar' 16 examples 53–90 % yield

deficient fluorinated phosphine ligand with a substoichiometric quantity of pivalic acid (PivOH) generates an efficient system to promote the C–H activation of a broad range of heteroarenes. A. Jakab, Z. Dalicsek, T. Soós* 1-5

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