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Secondary Phosphine Oxide Preligand for Palladium-Catalyzed C–H (Hetero)Arylations: Efficient Access to Pybox Ligands

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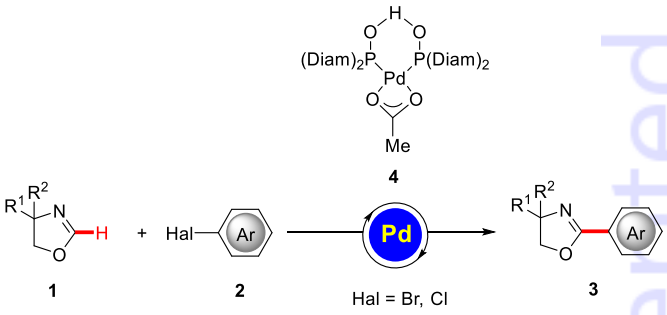
Abstract. C–H arylations of oxazolines were accomplished with a well-defined palladium catalyst derived from a secondary bisdiamantyl phosphine oxide. The single-component secondary phosphine oxide (SPO)-palladium complex enabled C–H activations with aryl bromides and challenging aryl chlorides in the absence of directing groups, setting the stage for the step-economical synthesis of pybox ligands under racemization-free reaction conditions.

Keywords: C–H activation; heteroarylation; pybox ligands; oxazolines, palladium; secondary phosphine oxides

Introduction

The arylation of otherwise inert C–H bonds[1] has emerged as an environmentally benign and economically attractive alternative to traditional cross-coupling chemistry,[2] because C–H arylations avoid tedious multi-step syntheses and reduce undesired by-product formation.[3] Thereby, the step-[4] and atom-economy[5] of molecular transformations are significantly improved. In particular, palladium(0) catalysis has proven to be instrumental for the development of novel C–H arylations.[6] In this context, we have previously disclosed a novel catalyst design based on air- and moisture-stable secondary phosphine oxide (SPO) preligands[7] for efficient C–H arylations of heteroarenes.[8] To unravel the influence of repulsive steric and attractive dispersion[9] interactions exerted by the ligand backbone, we became attracted to probing SPO[10] precursors with sterically differentiated substituents in the palladium-catalyzed C–H arylation[8, 11] regime. As a result of our efforts, we herein report on the development of a particularly powerful palladium catalyst for C–H functionalizations on synthetically useful oxazolines **1**. Notable features of our findings include (i) effective C–H functionalizations on decorated oxazolines **1**[12] with aryl bromides and challenging chloride **2**, (ii) the design of a well-defined single component palladium(II) catalyst **4** with improved catalytic efficacy (iii) and high-yielding double C–H arylations to deliver chiral pybox ligands in a step-economical fashion (Scheme 1).



Scheme 1. C–H arylation with SPO-palladium catalyst **4**.

Results and Discussion

At the outset of our studies we prepared the novel palladium(II) complex **4**, using air-stable bisdiamantyl-substituted SPO **5**[13] through the tautomerization equilibrium[14] between the SPO **5** and its phosphinous acid (PA) **6** (Scheme 2).

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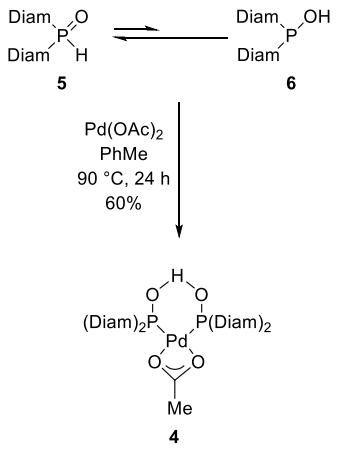


Scheme 2. Preparation of SPO-derived palladium(II) complex **4**.

The connectivity of the SPO-derived palladium(II) complex **4** was unambiguously established by single crystal X-ray diffraction crystallography, as depicted in Figure 1.

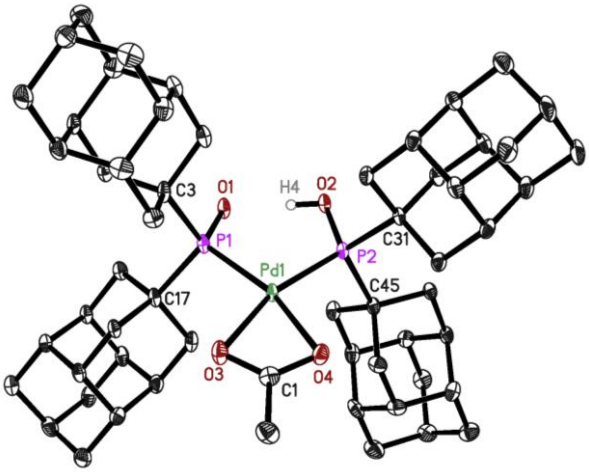
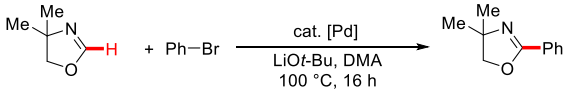
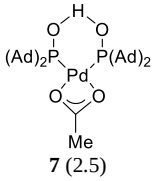
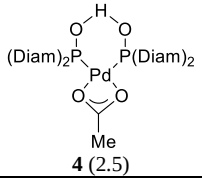


Figure 1. Molecular structure of complex **4** with anisotropic displacement parameters at the 50% probability level. The hydrogen atoms except to the OH group are omitted for clarity. Selected bond distances [Å] and angles [°] for the main position: Pd1-P1 2.2563(12), Pd1-P2 2.2709(16), Pd1-O3 2.196(2), Pd1-O4 2.187(2), P1-C3 1.883(3), P1-C17 1.881(3), P2-C31 1.864(3), P2-C45 1.876(3), P1-O1 1.557(2), P2-O2 1.558(2), O2-H4 0.816(19), O1-H4-O2 171(4).

Subsequently, we compared the activities of in-situ generated palladium catalysts with the one of well-defined SPO-derived complexes **4** and adamantyl derivative **7**[8,10s] in the C–H arylation of oxazoline **1a** (Table 1, and Table S-1 in the Supporting Information). Among a set of representative ligands, SPOs showed considerable efficacy (entries 1–7), with optimal results being accomplished with the (4-Diam)$_2$P(O)H preligand **5** (entry 7). A comparable observation was made, when single-component catalysts were employed. Thus, the diamantyl-substituted complex **4** provided best results and clearly outperformed the adamantyl-based complex **7** (entries 8 and 9).

Table 1. Palladium-catalyzed C–H arylation of oxazoline **1a**.[a]



entry	[Pd] (mol %)	ligand (mol %)	**3a** (%)[b]
1	---	---	---
2	$Pd(OAc)_2$ (5.0)	---	8
3	$Pd(OAc)_2$ (5.0)	dppf (5.0)	58
4	$Pd(OAc)_2$ (2.5)	$(n\text{-Hex})_2P(O)H$ (5.0)	30
5	$Pd(OAc)_2$ (2.5)	$(t\text{-Bu})_2P(O)H$ (5.0)	68
6	$Pd(OAc)_2$ (2.5)	$(1\text{-Ad})_2P(O)H$ (5.0)	64
7	**$Pd(OAc)_2$ (2.5)**	**$(4\text{-Diam})_2P(O)H$ (5.0)**	**73**
8	 **7** (2.5)	---	69
9	 **4** (2.5)	---	**80**

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), cat. [Pd], LiO*t*-Bu (2.5 equiv), DMA (1.0 mL), 100 °C, 16 h. [b] Yield of isolated product.

Thereafter, we explored the versatility of single-component complex **4** in the C–H arylation of oxazolines **1** (Scheme 3). Here, palladium catalyst **4** proved amenable to various aryl bromides **2** with substituents in the *para*-, *meta*-, and even *ortho*-position. Oxazolines **1** with *gem*-disubstitution as well as their mono-substituted derivatives were identified as viable substrates. Furthermore, even the C–H arylation with a pyrene electrophile enabled the synthesis of the desired product **3m**, which bears great potential for future applications to fluorescence labelling strategies.

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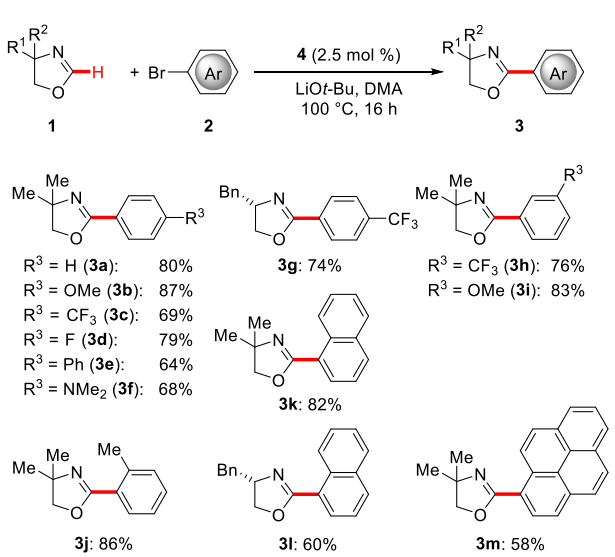
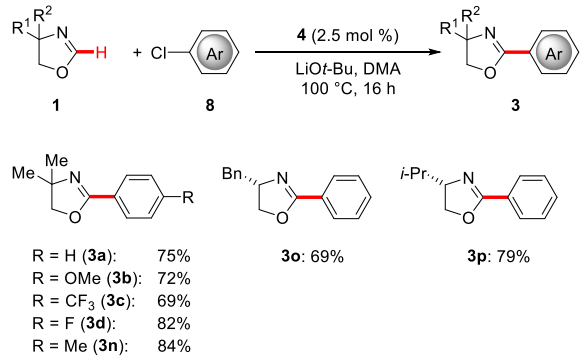


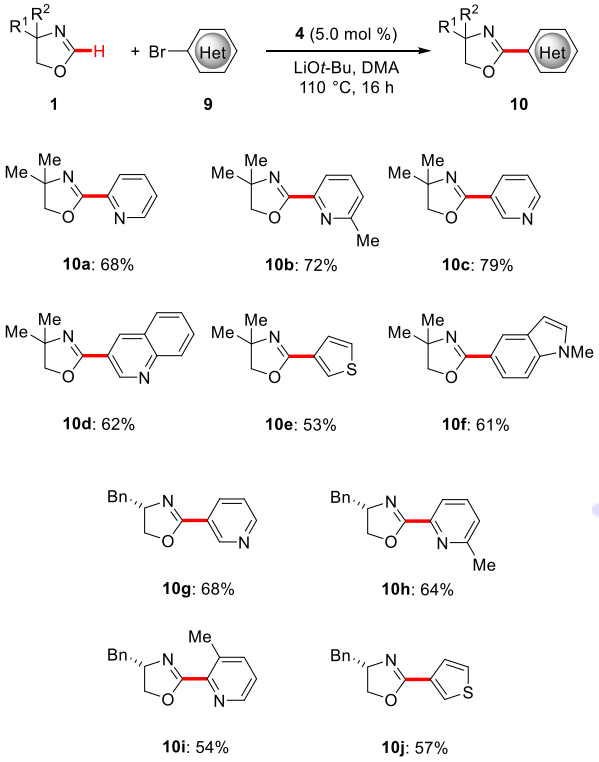
Scheme 3. C–H arylation of oxazolines **1**.

The powerful diamantyl-derived complex **4** was not limited to the conversion of aryl bromides **2**. Indeed, less-expensive, yet more difficult to activate aryl chlorides **8** could also be efficiently utilized within the challenging C–H arylation regime, even when being electron-rich and, thus, deactivated for the elementary oxidative addition step (Scheme 4).



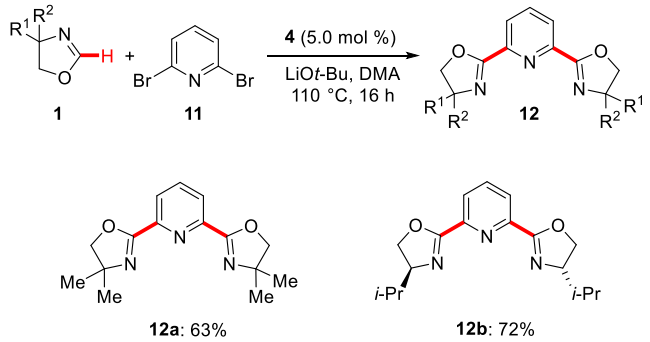
Scheme 4. C–H arylation with aryl chlorides **8**.

Heterocycles are omnipresent structural motifs in compounds of relevance to biology and drug discovery.[15] Thus, we were pleased to find that the optimized palladium catalyst **4** enabled the C–H arylation[16] using differently decorated heteroaryl halides with ample substrate scope (Scheme 5). Thereby, a variety of synthetically meaningful Lewis-basic heteroarenes, including pyridine, indole quinoline, and thiophene, were fully tolerated by the chemo-selective palladium catalyst **4**.



Scheme 5. C–H arylations with heteroaryl halides **9**.

In consideration of the importance of pyridine-bisoxazolines (pybox)[17] **12** as ligands in stereo-selective transition metal catalysis, we explored the catalyst **4** in the challenging twofold C–H arylation with the pyridyl dihalides **11** (Scheme 6). While the previously used dppe-based palladium catalysts delivered only unsatisfactory results,[11] the phosphinous acid palladium(II) complex **4** set the stage for the step-economical assembly of pybox ligands in high yields. It is particularly noteworthy that product inhibition was not observed despite of the tridentate nature of the generated pybox ligand products **12**. Furthermore, the double C–H activation occurred without racemization of the stereogenic centers, which should prove useful for the step-economical synthesis of chiral ligands for asymmetric catalysis.



Scheme 6. Twofold C–H arylation: Access to pybox ligands **12**.

Conclusion

In summary, we have reported on the design of a novel palladium complex derived from a bulky, diamondoid-derived SPO preligand and its use in versatile C–H arylations of oxazolines. The powerful palladium catalysis manifold enabled C–H functionalizations of aryl bromides and chlorides without the need for directing groups. The user-friendly single-component palladium catalyst proved particularly tolerant of challenging N- and S-heterocycles, which was exploited for the high-yielding synthesis of chiral pybox ligands in a step-economical fashion.

Experimental Section

General Procedure: C–H Arylation of Oxazolines 1 Catalyzed by SPO-Palladium Complex 4.
Catalyst **4** (13 mg, 2.5 mol %), LiO*t*-Bu (100 mg, 1.25 mmol), bromobenzene (**2a**) (105 µl, 1.0 mmol) and 4,4-dimethyl-2-oxazoline (**1a**) (50 mg, 0.5 mmol) were stirred in DMA (2.00 mL) at 100 °C for 16 h. H_2O (30 mL) was added at ambient temperature, and the resulting mixture was extracted with Et_2O (3 × 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) to yield **3a** (70 mg, 80%) as a colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (dd, J = 8.3, 1.3 Hz, 2H), 7.45 (d, J = 7.4 Hz, 1H), 7.39 (dd, J = 8.3, 7.4 Hz, 2H), 4.10 (s, 2H), 1.38 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.2 (C_q), 131.3 (CH), 128.4 (CH), 128.3 (CH), 128.2 (C_q), 79.2 (CH_2), 67.7 (C_q), 28.5 (CH_3). IR (ATR): 2966, 1649, 1351, 1319, 1190, 1059, 1025, 966, 780, 693 cm^{-1}. MS (EI) *m/z* (relative intensity): 175 [M$^+$] (10), 160 (100), 145 (25), 132 (30), 104 (70), 77 (27). HR-MS (EI): *m/z* calcd for $C_{11}H_{13}NO$ 175.0997, found 175.1004. The analytical data are in accordance with those reported in the literature.[8]

Preparation of Palladium Complex 4:
A mixture of $Pd(OAc)_2$ (56 mg, 0.25 mmol) and di-4-diamantylphosphine oxide (**5**) (211 mg, 0.5 mmol) was stirred in dry toluene (5.0 mL) at 90 °C for 24 h. The reaction mixture was cooled to ambient temperature and the solvent was removed *in vacuo*. The resulting residue was dissolve in CH_2Cl_2 (3 × 25 mL) at 40 °C and filtered through short celite pad. Evaporation of the solvent, afforded **4** (152 mg, 60%) as a pale yellow solid.
Crystal data for complex **4** at 100(2) K: $C_{79}H_{104}O_4P_2Pd$, Mr = 1285.96 g/mol, 0.2 x 0.2 x 0.1 mm, triclinic, *P*-1, a = 13.497(7) Å, b = 15.447(8) Å, c = 17.008(8) Å, α = 97.43(3)°, β = 104.16(3)°, γ = 105.94(4)°, V = 3232(3) Å^3, Z = 2, μ(Ag Kα) = 0.213 mm-1, θ_{max} = 19.8°, 95889 reflections measured, 11829 independent (R_{int} = 0.0975), R_1 = 0.0370 [I > 2σ(I)], wR_2 = 0.0832 (all data), res. density peaks: 0.774 to -0.470 eA^{-3}, CCDC:1550696
The data were integrated with SAINT.[18] A multi-scan absorption correction was applied using SADABS.[19] The structures were solved by SHELXT[20] and refined on F^2 using SHELXL[21] in the graphical user interface SHELXLE.[22]

Acknowledgments

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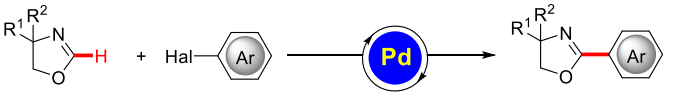
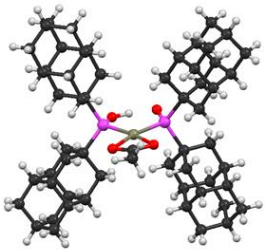
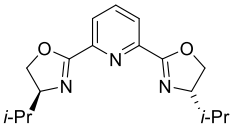
FULL PAPER

Secondary Phosphine Oxide Preligand for Palladium-Catalyzed C–H (Hetero)Arylations: Efficient Access to Pybox Ligands







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