

A Facile and Modular Synthesis of Phosphinooxazoline Ligands

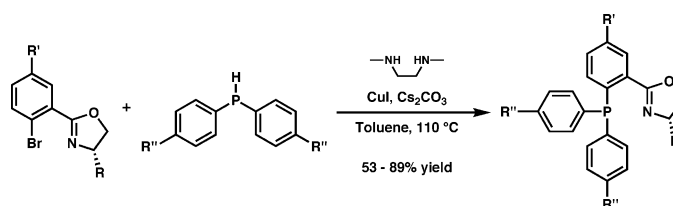
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ABSTRACT



The copper(I) iodide catalyzed phosphine/aryl halide coupling procedure of Buchwald et al. provides modular, robust, and scaleable access to phosphinooxazoline (PHOX) ligands. The advantages of this method are highlighted by the convenient synthesis of PHOX ligands with varied steric and electronic properties, which would be challenging to synthesize by other protocols.

Phosphinooxazoline (PHOX) ligands, pioneered by Pfaltz, Helmchen, and Williams,¹ have become a preeminent class of N/P ligands in organometallic transformations, such as allylic alkylation² and amination,³ Heck reactions,⁴ Diels–Alder⁵ and [3+2] dipolar cycloadditions,⁶ Ru-based transfer hydrogenation,⁷ and Ir-catalyzed hydrogenation.⁸ During our recent research into enantioselective Tsuji allylation and

decarboxylative protonation,⁹ we desired ready access to PHOX ligands of varied structure and in substantial quantity. Herein, we demonstrate the utility of Buchwald's P–C bond-forming reaction for the synthesis of a wide range of sterically and electronically varied PHOX ligands.¹⁰

Despite the broad utility of PHOX ligands and the multitude of known derivatives, access to certain substitution patterns on the ligand framework was challenging using the common synthetic methods for uniting the diarylphosphine and phenyloxazoline fragments.¹¹ Most commonly, the P–C bond was formed by anionic displacement, with a phosphine anion displacing an aryl fluoride, or by organometallic (e.g., Grignard or organolithium) displacement of a chlorophosphine (Scheme 1). In our hands, both routes had significant

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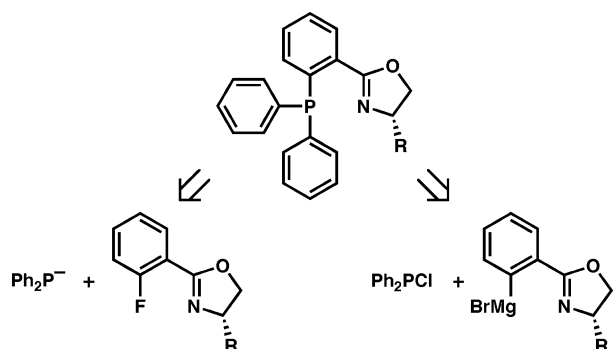
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Scheme 1. Common Syntheses of PHOX Ligands



drawbacks, particularly for certain PHOX analogues that we were pursuing. Specifically, the S_NAr route prohibited electron-withdrawing groups on the phosphine anion and often produced chromatographically tedious impurities. The organometallic route was often hampered by the sluggish reactivity of, and difficulty in generating hindered ortho-substituted Grignard reagents. More recently, two reports of palladium-catalyzed cross-coupling to these hindered ligands have appeared.¹² While promising, the generality of this approach over a range of sterically and electronically different substrates has not been demonstrated.

Recently, Buchwald developed a mild and effective method to perform Ullmann-type couplings of diaryl- and dialkylphosphines with aryl iodides and bromides.¹⁰ We were pleased to observe that Buchwald's protocol, with only slight modification, overcame the problems of the classical routes to the PHOX ligand class and allowed coupling of diphenylphosphine with a variety of ortho-substituted aryl bromides. As shown in Table 1, the coupling affords good yields of phosphines regardless of the bulk of the oxazoline substituent with yields ranging from 54% to 89%. The only byproduct observed was a small amount of reduced arene. Gratifyingly, the procedure scales well to give multigram quantities of (S)-*t*-Bu PHOX (entry 2). The reaction also tolerates a range of functional groups including alkyl ethers (entry 6), silyl ethers (entry 7), and heterocycles (entries 15 and 16).

Importantly, this protocol also allows the synthesis of electronically diverse PHOX ligands (Table 2). Electron-rich and electron-poor phosphines perform equally well in the reaction (entries 1 and 2). The electronics of the aryl bromides have little effect on the coupling reaction. Reactions of the *p*-methoxy (entry 5) and *p*-trifluoromethyl (entry 7) aryl bromides proceed with diphenylphosphine at similar rates and furnish comparable yields of PHOX ligands. Entry 8 demonstrates the synthesis of an extremely electron deficient PHOX ligand, while entry 6 is an excellent example of a ligand that would be difficult to synthesize by either Grignard or S_NAr chemistry.

In addition to coupling diarylphosphines, we have also adapted the reaction to utilize the HBF_4 salts of air-sensitive

Table 1. Buchwald Coupling with Diphenylphosphine

entry	substrate R group	time (h)	yield ^a (%)
1	<i>t</i> -Bu	8	81 ^b
2	<i>t</i> -Bu	6	81 ^c
3 ^d	cyclohexyl	8	68
4	1-adamantyl	3	71
5	CH ₂ (<i>t</i> -Bu)	8	73
6 ^d		12	75
7 ^{d,e}		9	84
8	CH ₂ (1-naphthyl)	12	54
9	CH ₂ (2-naphthyl)	23	71
10	CH ₂ CH ₂ Ph	8	64
11		8	72
12		6	70
13 ^d	CHPh ₂	20	89
14 ^d		11	55
15		6	69
16		20	53 (63) ^f

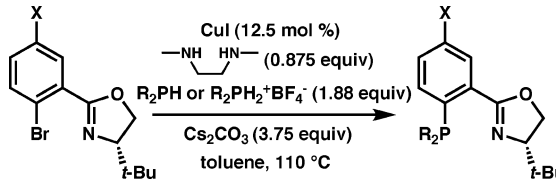
^a Isolated yield for 0.17 to 1.8 mmol reactions unless otherwise stated. ^b 3.5 mmol scale. ^c 14.2 mmol scale. ^d Performed on the enantiomeric *R* series. ^e 2.0 equiv of Ph₂PH used. ^f Yield in parentheses is based on recovered aryl bromide.

dialkylphosphines (Table 2, entries 3 and 4). Fu has demonstrated the in situ deprotection and use of similar trialkylphosphine salts in transition metal mediated reactions.¹³ These HBF_4 salts are stable to the atmosphere and are usually crystalline solids. The incorporation of an additional 1.25 equiv of cesium carbonate to the reaction allows the in situ generation of the free dialkylphosphine, which is competent in the coupling reaction. These dialkyl phosphinoxazolines are most conveniently isolated as their borane adducts in good yield. However, these borane adducts can be easily converted to the corresponding PHOX ligands in near quantitative yield by using the conditions reported by Hiyama (i.e., MS4Å-THF-MeOH).¹⁴

As an example of the utility of the electronically and sterically modified PHOX ligands available from this

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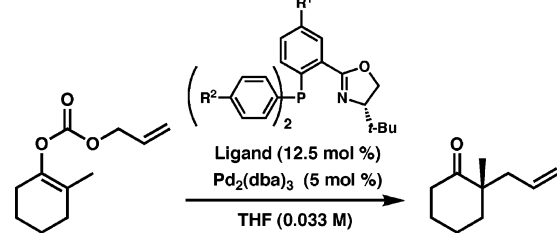
Table 2. Varying Electronics of Coupling Partners


entry	aryl bromide	phosphine	time (h)	yield ^a (%)
1	X = H	(<i>p</i> -Tol) ₂ PH	4	73
2	X = H	(<i>p</i> -CF ₃ Ph) ₂ PH	2	75
3	X = H	Cy ₂ PH ₂ ⁺ BF ₄ ⁻	27	63 ^b
4	X = H	<i>i</i> -Bu ₂ PH ₂ ⁺ BF ₄ ⁻	24	79 ^b
5	X = OMe	Ph ₂ PH	4	72
6	X = OMe	(<i>p</i> -CF ₃ Ph) ₂ PH	6	66
7	X = CF ₃	Ph ₂ PH	6	77
8	X = CF ₃	(<i>p</i> -CF ₃ Ph) ₂ PH	4	74

^a Isolated yield for 0.65 to 1.2 mmol reactions, see Table 1 for conditions.
^b 5.0 equiv of Cs₂CO₃ used. Isolated as borane adduct, see the Supporting Information for details.

procedure, we have found that the *p*-trifluoromethyl appended (*S*)-*t*-Bu PHOX ligands, when utilized in our asymmetric allylation reaction, afford reaction times that are 10-fold shorter than reactions employing unmodified (*S*)-*t*-Bu PHOX (Table 3). Additionally, the bis(*p*-trifluoromethyl) PHOX allowed allylation to proceed at temperatures where no reaction was observed with (*S*)-*t*-Bu PHOX and with improved ee.

PHOX ligands are finding ever-increasing use in catalytic asymmetric processes. The ability to readily fine-tune the sterics and electronics of these catalysts is expedient for reaction development. The Ullmann-type coupling developed by Buchwald et al. provides consistently good yields of PHOX ligands even in demanding steric and electronic cases. This method allows the most truly modular synthesis of PHOX ligands yet reported. Finally, this highly practical method uses an inexpensive copper(I) catalyst system and avoids the discrete preparation of anionic reagents. We

Table 3. Use of Fluorinated PHOX Ligands in Asymmetric Allylation


entry ^a	ligand	temp (°C)	time (min)	yield ^b (%)	ee ^c (%)
1	R ¹ = R ² = H	25	120	96	88
2	R ¹ = R ² = CF ₃	25	10	99	87
3	R ¹ = H, R ² = CF ₃	25	10	99	89
4	R ¹ = R ² = H	0	150	0	
5	R ¹ = H, R ² = CF ₃	0	150	54	92

^a Reactions performed on a 0.1 mmol scale. ^b GC yield relative to an internal standard (tridecane). ^c Enantiomeric excess measured by chiral GC. See ref 9 for details.

believe this experimentally convenient PHOX synthesis will find wide application.

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Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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