Nickel-Catalyzed Atroposelective *Cross*-Electrophile Coupling of Aryl Halides: A General and Practical Route to Diverse MOP-type Ligands

Raphael S. Kim, Lebogang O. Kgoadi, Jacob C. Hayes, Derek P. Rainboth, Catherine M. Mudd, Glenn P. A. Yap, Donald A. Watson*

Department of Chemistry and Biochemistry, University of Delaware, Newark, DE, 19716, United States.

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ABSTRACT: We report a highly cross- and atroposelective coupling between *ortho*-(chloro)arylphosphine oxides and *ortho*-(bromo)arylethers. This previously unknown asymmetric nickel-catalyzed reaction offers a direct route to highly enantioenriched axially chiral biaryl monophosphine oxides that are difficult to access by other means. These products can be readily reduced to generate chiral MOP-type ligands bearing complex skeletal backbones. The utility of these chiral ligands in asymmetric catalysis is also demonstrated.

Recently, significant progress has been achieved in the development of cross-electrophile coupling reactions, leveraging a diverse array of transition metal catalysts.[1] Particularly noteworthy is the emergence of asymmetric variants between C_{sp3} and C_{sp2} electrophiles, providing potent methods for constructing intricate chiral molecules.[2] In addition, numerous groups have independently reported progress on the reductive coupling of aryl electrophiles to make achiral or racemic biaryls (Figure 1a).[3,4] However, despite these advancements, the asymmetric reductive cross-coupling of two different aryl electrophiles to form axially chiral biaryl compounds has not been reported.

Simultaneously, C_1-symmetric axially chiral biaryl monophosphines have emerged as highly effective chiral inducers for various metal-catalyzed transformations.[5] Examples of widely utilized monophosphines include MOP, KenPhos, and QUINAP (Figure 1b).[6] Typically, this class of privileged ligands is prepared either via chiral resolution to separate the atropisomers or via the use of commercially available enantiopure biaryl starting materials, such as BINOL (Figure 1b). Chiral resolutions are often difficult to optimize for new compounds, and in some cases require stoichiometric precious metals,[7] making resolution generally unappealing for novel ligand synthesis. Likewise, in the latter case, the requirement for enantiopure biaryls as starting materials, which have limited commercial access, severely limits the types of new ligands that can be prepared.

Notably, while atroposelective Suzuki-Miyaura and other redox-neutral cross-coupling reactions have been known for many years,[8] only recently have conditions been reported that are able to access tetra-*ortho*-substituted biaryl products and they remain limited in scope.[9] To date, Suzuki-Miyaura couplings to prepare biaryl monophosphine ligands have been limited to the preparation of tri-*ortho*-substituted monophosphobiarenes, and cannot access ligands such as MOP and KenPhos.[6d, 10, 11] Other approaches to fully substituted chiral biaryl phosphine ligands have been developed,[12,13,14,15] but are less general than cross-coupling strategies. These factors severely limit the development and design of new ligands.

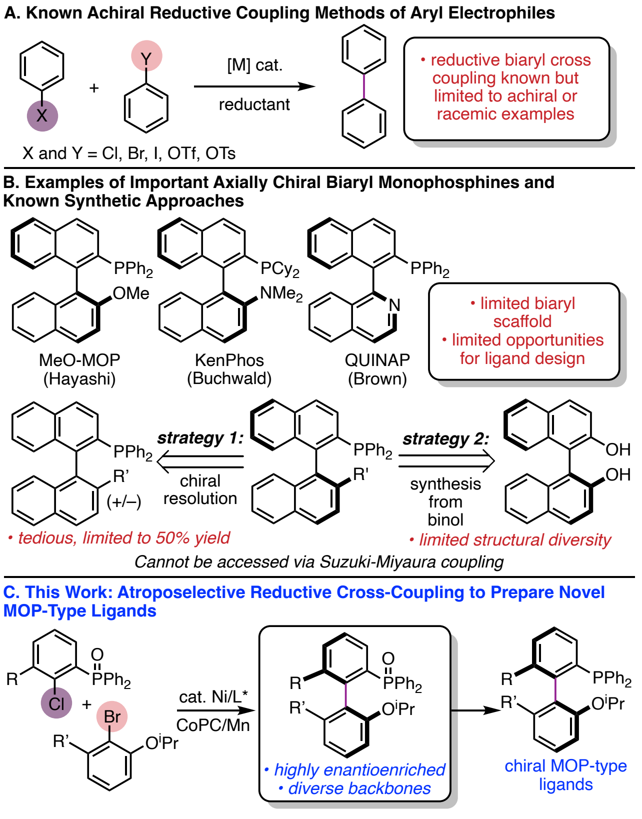


Figure 1. Methods for the preparation of biaryl compounds

Recently, we and others have developed nickel-catalyzed methods for preparing C_2-symmetric axially chiral biaryl compounds via the atroposelective reductive *homocoupling* reaction.[16] In particular, we demonstrated the synthesis of highly enantioenriched tetra-*ortho*-substituted bisphosphobiarenes, as well as other C_2-symmetric biaryl products.

Encouraged by our success in the homocoupling reaction, we envisioned the possibility of an atroposelective reductive coupling of two different aryl halides. Herein, we present the successful development of a nickel-catalyzed atroposelective cross-electrophile coupling reaction involving *ortho*-(chloro)arylphosphine oxides and *ortho*-(bromo)arylethers (Figure 1c).[17] This reaction yields chiral biaryl monophosphine oxides in good yields with high levels of enantioselectivity and requires approximately equimolar amounts of each coupling partner. Furthermore, we demonstrate that these products can be reduced to access chiral MOP-type ligands, and show successful application in asymmetric catalysis. In addition to its potential impact in the synthesis of chiral biaryl monophosphines, this transformation also represents the first enantioselective reductive cross-coupling of aryl halides, and is a rare example of a cross-coupling that can provide a tetra-*ortho*-substituted biarene with four unique *ortho*-substituents.[18]

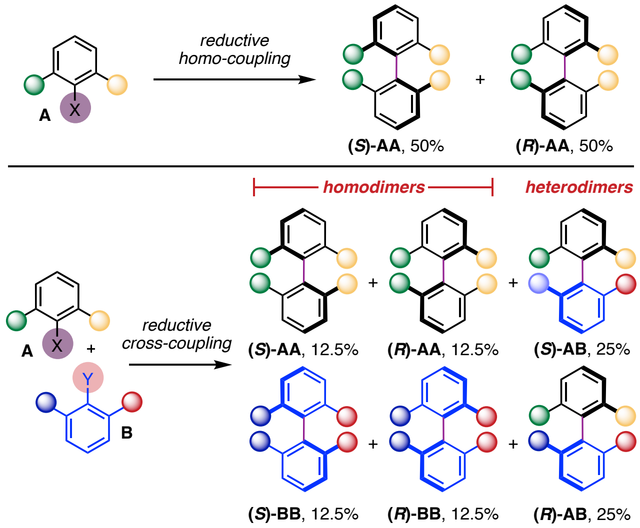
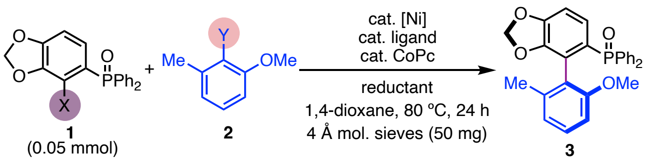


Figure 2. Statistical product distribution from the reductive coupling between two similar aryl halides.

In asymmetric reductive homocoupling, as only a single aryl halide is involved, only a single biaryl product is expected (Fig 2, top). Thus, control of stereochemistry is the only major obstacle. Enantioselective aryl halide reductive *cross-coupling* presents a considerably higher challenge. Assuming similar reactivity from the two aryl electrophiles, six stereochemically unique products are expected (Fig 2, bottom). In the absence of a large excess of one of the coupling partners, either enantiomer of the desired heterodimer is statistically expected in only 25% yield. Achieving success in this area necessitates not only a highly organized and selective enantiodetermining step but also selective sequencing of the reactivity of the two aryl electrophiles.

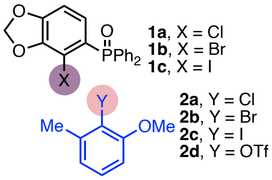
We began our study by addressing the challenge of cross-selectivity. By leveraging the known oxidative addition rates of aryl electrophiles towards low-valent nickel complexes,[3a, 3d-f, 19] we hypothesized that cross-selectivity could be achieved by varying the electronic properties and leaving groups of the two electrophiles. With aryldiphenylphosphine oxide **1** and aryl methylether **2** as model substrates, which we anticipated would provide electronic differentiation in rates of reaction, we prepared each with a variety of halides and pseudohalides. The cross-couplings of these partners were evaluated using catalytic Ni(COD)$_2$/**L1**, cobalt phthalocyanine (CoPc) additive, and Mn as the reductant with added 4Å mol. sieves (Scheme 1a).[16b] We found that a combination of *ortho*-(chloro)arylphosphine oxide **1a** and *ortho*-(bromo)arylether **2b** provided the best results, providing product **3** in 53% yield and 76% ee. Notably, conditions employing aryl iodide **1c**, were particularly ineffective and resulted in significant levels of homo-coupling. In other cases, proto-dehalogenation was the major byproduct.

Scheme 1. Optimization of Reaction Conditions[a]



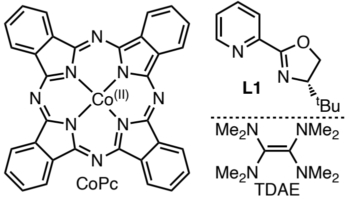
A. Optimization of Aryl Electrophiles[b]

	2a (Cl)	**2b** (Br)	**2c** (I)	**2d** (OTf)
1a (Cl)	0% (ee n.d.)	53% (76% ee)	2% (ee n.d.)	0% (ee n.d.)
1b (Br)	2% (ee n.d.)	34% (71% ee)	35% (71% ee)	1% (ee n.d.)
1c (I)	0% (ee n.d.)	0% (ee n.d.)	1% (ee n.d.)	0% (ee n.d.)

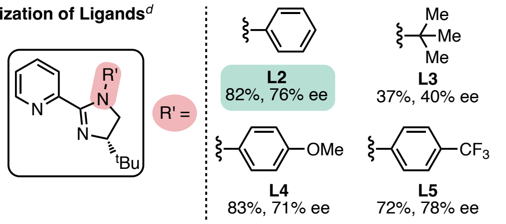


B. Optimization of Reaction Parameters[c]

entry	[Ni] / ligand	2b (equiv)	reductant	additive	yield (ee)
1	NiCl$_2$•DME/**L1**	2	Mn	CoPc	68%, 78% ee
2	NiCl$_2$•DME/**L1**	1.1	Mn	CoPc	68%, 78% ee
3	NiCl$_2$•DME/**L1**	1.1	Zn	CoPc	12%, 77% ee
4	NiCl$_2$•DME/**L1**	1.1	TDAE	CoPc	0%, n.d. ee
5	—	1.1	Mn	CoPc	0%, n.d. ee
6	NiCl$_2$•DME/**L1**	1.1	Mn	—	16%, 48% ee



C. Optimization of Ligands[d]

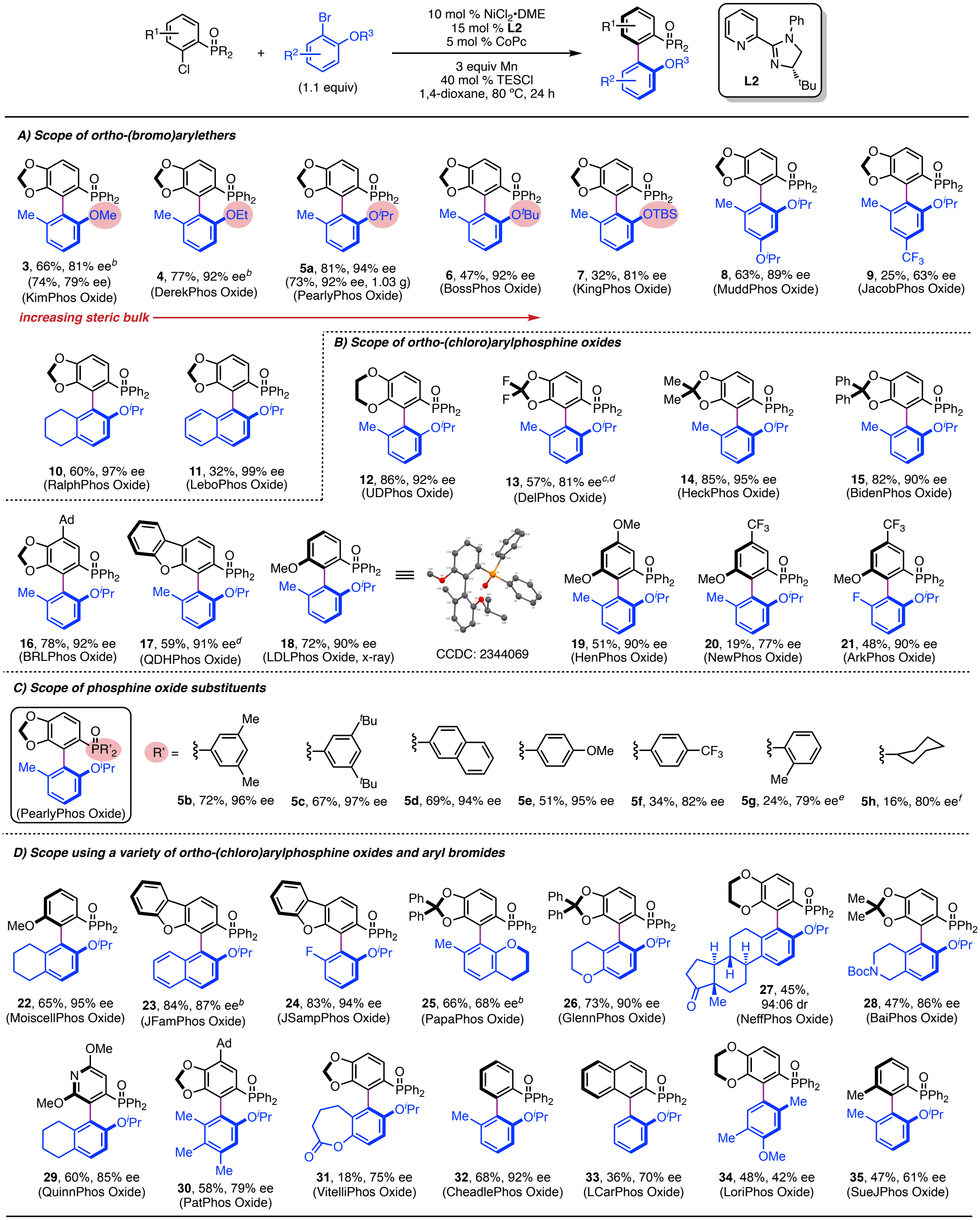


D. Source of Manganese[e]

mechanically activated Mn	82%, 76% ee
non-mechanically activated Mn + 40 mol % TESCl (no 4 Å MS)	88%, 76% ee

[a] Yields determined by ^{1}H NMR using an internal standard. Ee's determined by HPLC or SFC analysis using purified samples. [b] 2 equiv **2**, 10 mol % Ni(COD)$_2$, 15 mol % **L1**, 5 mol % CoPc, 3.0 equiv Mn. [c] 10 mol % NiCl$_2$·DME, 15 mol % **L1**, 5 mol % additive, 3.0 equiv reductant. [d] 1.1 equiv ArBr, 10 mol % NiCl$_2$·DME, 15 mol % **L2**-**L5**, 5 mol % CoPc, 3.0 equiv Mn. [e] 1.1 equiv ArBr, 10 mol % NiCl$_2$·DME, 15 mol % **L2**, 5 mol % CoPc, 3.0 equiv Mn.

Scheme 2. Scope of Atroposelective Cross Electrophile Coupling.[a]



[a] 1.0 mmol scale. Yield and ee's of isolated products. [b] 60 °C for 48 h. [c] 2.0 equiv of ArBr. [d] 20 mol % $NiCl_2$•DME, 30 mol % **L2**. [e] 0.2 mmol scale. [f] 100 °C.

Further improvements were observed using NiCl₂·DME in place of Ni(COD)₂ (Scheme 1b, entry 1). Surprisingly, an equimolar amount of each aryl halide component could be used without negative influence on cross-selectivity (entry 2). This is particularly notable since many previous non-atroposelective methods have relied on using excess of one coupling partner.[1a] Other classes of stoichiometric reductants were also examined, but failed to give more than trace product (entries 3 and 4). The nickel catalyst was essential for reactivity, and removing CoPc dramatically lowered yield and ee (entries 5-6).[20] Additional solvents and additives were evaluated, but none led to further improvements.[21]

Other pyridine-oxazoline (PyOx) ligands were examined, but none proved better than **L1**.[21] However, pyridine-imidazoline (PyIm) ligands were superior (Scheme 1C).[21] When *N*-phenyl substituted PyIm ligand **L2** was used, 82% yield of the cross-coupling product was observed, while maintaining enantioselectivity. Evaluation of other *N*-substituted PyIm ligands were less fruitful.

Finally, we investigated the activation of the manganese reducing agent. To this point, the manganese had been activated mechanically (continuous stirring in a glovebox). However, to develop a more robust set of reaction conditions that could be conducted without the use of a glovebox, we investigated the use of chlorotriethylsilane (TESCl), which has been shown to activate reducing metal *in situ*.[22] We found that the use of 40 mol % TESCl as an additive in the reaction successfully activated the manganese (as purchased) and led to product **3** in comparable yield and ee. This activation approach allowed the reaction to be set-up in a fume hood without need for a glovebox. We also found that under these condition molecular sieves were not needed.

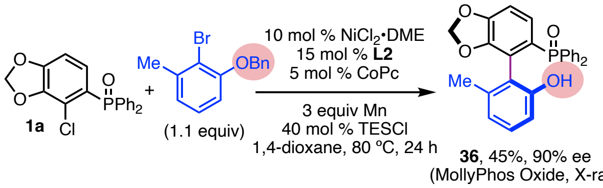
We next explored the scope of the reaction on a 1 mmol scale using the bench-top protocol. We began by investigating the role of the aryl bromide structure on the outcome of the reductive coupling (Scheme 2A). First, we found that the size of the ether substituent had significant impact on the enantioselectivity, with larger alkyl groups leading to a marked increase in selectivity. With isopropyl ethers, 81% yield and 94% ee of the cross-coupling product was observed (**5a**). On gram scale, similar yield and ee were observed. Notably, for the smaller ethers, conducting the reaction at lower temperature (60 °C) led to improved ee's, albeit at lower yield (**3**). In contrast, with O^{t}Bu ethers, the ee remained high, but the yield was suppressed (**6**), and with silyl ethers (**7**) both yield and ee were lower. As isopropyl ethers have been employed in MOP-type ligands,[6a, 6c, 23] we selected this group to move forward in the remainder of the study.

Electron-rich aryl bromides provided higher yield and ee compared to electron-poor aryl bromides (**8** vs. **9**). With electron-poor aryl bromides, more homo-coupling of the aryl chloride is observed. Larger, bicyclic aryl bromides were also tolerated in the reaction and provided products with high ee and reasonable cross-selectivity (**10** and **11**).

The scope of the aryl chloride also proved to be broad (Scheme 2B). Ring expansion (**12**) and various ring substitutions (**13**-**17**) are tolerated. Similar to the aryl bromide scope studies, electron-donating groups proved beneficial (**18**-**19** vs. **20**).[24] Evaluation of the crude reaction mixture with electron-poor substrates revealed higher amounts of homocoupling side products. Unfortunately, higher loading of each aryl halide component did not lead to better results. However, electron-deficient aryl chlorides could be utilized to provide products in good yield and high ee when matched with small aryl bromides containing π-donors (**21**).

Various phosphorus substitutions are tolerated (Scheme 2C), including those with moderately bulky (**5b**-**5d**), electron-donating (**5e**) and electron-withdrawing (**5f**) groups. Very bulky aryl (**5g**), as well as alkyl (**5f**), phosphine oxides could also be used albeit with lower yield and ee.

As previously mentioned, chiral biaryl monophosphines bearing complex biaryl scaffolds are often challenging to access. As a result, explored whether our method could be utilized to prepare chiral biaryl monophosphine oxides bearing structurally diverse backbones (Scheme 2D). In addition to various coupling combinations, complex natural products (**27**) and heterocycles such as dibenzofurans (**23** and **24**), chromanes (**25** and **26**), piperidines (**28**), pyridines (**29**), and lactones (**31**) are tolerated. Functional groups such as carbamates (**28**), distal ketones (**27**), and esters (**31**) are also compatible. This reaction enjoys diverse substitution patterns with generally high selectivity for cross-coupled products and high enantioselectivity, resulting in a wide variety of potential new monophosphine ligands. In addition to tetra-substituted products, tri-*ortho*-substituted biaryl phosphine oxides could also be prepared (**32**, **33** and **34**), as well as those lacking an ether meta to the phosphine oxide (**35**).



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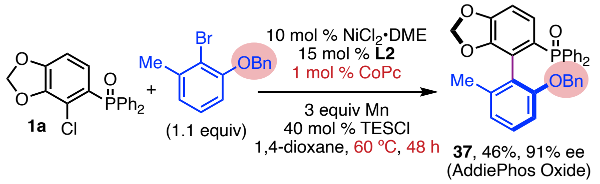
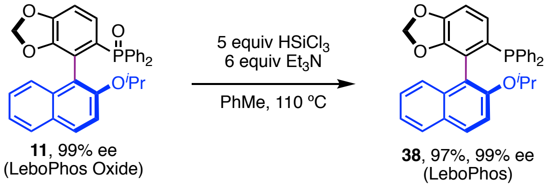
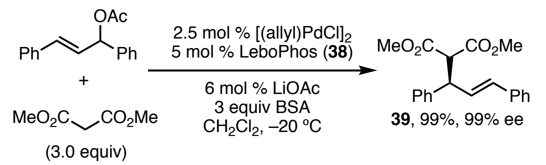


(2)

Interestingly, when a benzyl ether substrate was used under our standard conditions, high yield and ee were observed, but the product that resulted was phenol **36** resulting from debenzylation (eq 1).[25] This result potentially provides access to a variety of ether products via further manipulation of the phenol. We hypothesize a low-valent CoPc species generated in-situ is responsible for the dealkylation.[21, 26] Consistent with this, lowering the temperature and loading of CoPc, the debenzylation was prevented, and good yield and ee of product **37** was observed.



(3)



(4)

To showcase the utility of our products, the chiral biaryl monophosphine oxide **11** was reduced using known conditions to access biaryl monophosphine **38** in high yield with retention of enantiopurity (eq 3). This chiral monophosphine was then applied as a ligand for the Tsuji-Trost reaction, previously described using various chiral ligands.[27] Excitingly, high yield and enantioselectivity were observed using this novel ligand (eq 4). This finding underscores the potential importance of biaryl phosphine oxides that result from this reaction.

A possible mechanism to account for cross-selectivity in this reaction is shown in Figure 3. Pre-coordination of the phosphine oxide, in combination with its electron-withdrawing capability, facilitates oxidative addition to the aryl chloride.[11, 28] After reduction to Ni(I), oxidative addition to a second aryl chloride is likely slow due to steric encumbrance, resulting in slow homo-dimerization. In contrast, oxidative addition to the smaller aryl bromide is likely faster, resulting in cross-selectivity. Detailed mechanistic studies are currently underway.

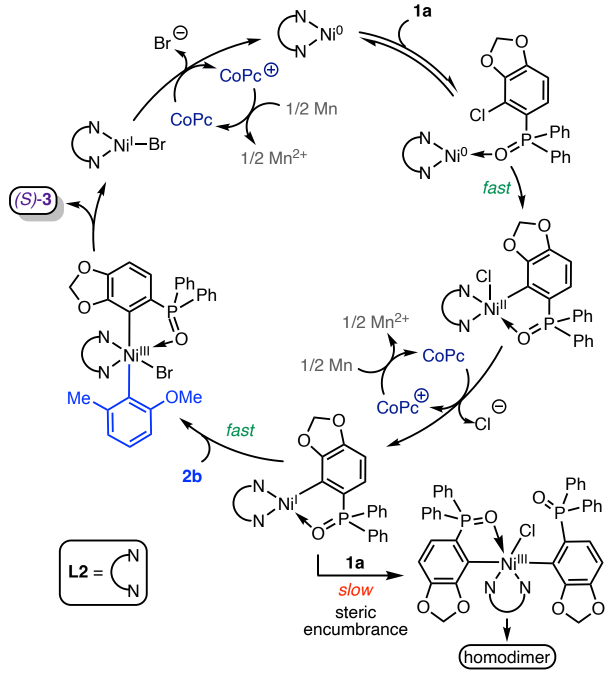


Figure 3. Possible mechanism.

In conclusion, we have demonstrated the first example of an atroposelective reductive cross-coupling of two aryl halides. By developing conditions for the enantioselective union of *ortho*-(chloro)arylphosphine oxides and *ortho*-(bromo)arylethers via nickel catalysis, we have developed a method for the synthesis of highly enantioenriched axially chiral biaryl monophosphine oxides. The reaction proceeds under mild conditions, using bench-top procedures, and is compatible with a range of functional groups. The resulting chiral biaryl monophosphine oxide products can be easily reduced using known conditions to access novel biaryl monophosphine (MOP-type) ligands in high ee's. To showcase the utility of these products, a newly developed ligand was applied to an asymmetric Tsuji-Trost reaction, yielding product in high yield and high enantiopurity. Current studies are focused on better understanding of the mechanism of this reaction and the unique role of CoPc in obtaining high levels of atroposelectivity. We hope that this method will open up new avenues for designing and developing enantioenriched biaryl monophosphine ligands.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional details from optimization studies, detailed experimental procedures, spectral and X-ray data (PDF and CIF).

NMR FID files (ZIP)

AUTHOR INFORMATION

Corresponding Author

Donald A. Watson – Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, 19716, United States
Email: dawatson@udel.edu

Authors

Raphael S. Kim – Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, 19716, United States
Lebogang O. Kgoadi – Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, 19716, United States
Jacob C. Hayes – Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, 19716, United States
Derek P. Rainboth – Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, 19716, United States
Catherine M. Mudd – Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, 19716, United States
Glenn P. A. Yap – Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, 19716, United States

Notes

The authors declare no competing financial interest.

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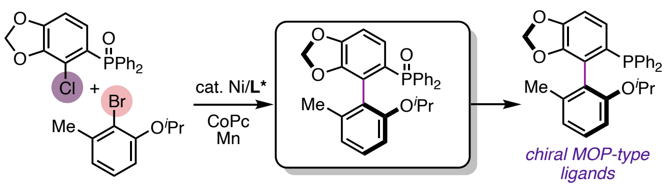
TOC Graphic



- *reductive cross-coupling of two aryl halides*
- *highly enantioenriched biaryl monophosphine oxides in a single-step*
- *diverse backbones and novel ligands*
- *scalable, glovebox-free reaction conditions*