Access to *P*- and Axially-Chiral Biaryl Phosphine Oxides by Enantioselective Cp^xIr^{III}-Catalyzed C-H Arylations

Yun-Suk Jang,[a] Łukasz Woźniak,[a] Julia Pedroni[a] and Nicolai Cramer*[a]

Abstract: An enantioselective C-H arylation of phosphine oxides with *o*-quinone diazides catalyzed by an iridium(III) complex bearing an atropchiral cyclopentadienyl (Cp^x) ligand and phthaloyl *tert*-leucine as co-catalyst is reported. The method allows access to (a) *P*-chiral biaryl phosphine oxides, (b) atropo-enantioselective construction of sterically demanding biaryl backbones as well as (c) selective assembly of axial and *P*-chiral compounds in excellent yields, diastereo- and enantioselectivities. Enantiospecific reductions provide monodentate chiral phosphorus(III) compounds having structures and biaryl backbones with proven importance as ligands in asymmetric catalysis.

Chiral biaryl phosphines are a critically important cornerstone of asymmetric transition-metal catalysis.[1] Besides classical chelating diphosphines,[2] chiral monodentate biaryl phosphines have gained tremendous importance as ligands for a very broad range of different enantioselective transformations (Figure 1).[3] The most exploited chiral element of these ligands is a very stable chiral axis of the binaphthyl backbone.[4] Archetypical members are the MOP[5] and Kenphos ligands.[6] Complementary elements of chirality proved to be highly valuable as well. For instance, ligands having a C_2-symmetric point chiral phospholane unit such as Sagephos[7] or *P*-chiral center as found in the BI-DIME ligand have been introduced.[8] For an increasing number of catalytic applications, combinations of the different chiral elements have proven advantageous.[9] For instance, ligand **A**, featuring a chiral axis and a *P*-chiral phosphorus atom.[9a] However, accessing these ligands requires elaborate synthetic routes.[9, 10] Despite their utility, these shortcomings hamper full exploitation of their application potential. Hence, the development of modular and straightforward catalytic enantioselective procedures, providing access to these structural motifs is a highly desirable goal.

Over the past years, the phosphorous(V) compounds have emerged as a competent directing group[11] for enantioselective C-H functionalizations.[12, 13] We recently disclosed an Ir(III)-catalyzed enantioselective C-H amidation of phosphine oxides,[12h] capitalizing on synergistic effects of a chiral cyclopentadienyl (Cp^X) ligand[14] and a chiral carboxylic acid. Herein, we report highly selective C-H arylations of phosphine oxides with *o*-quinone diazides providing access to highly sought-after *P*- and atrop-chiral biaryl phosphine oxides. Recent report by Yang *et al.*[15] indicated the suitability of trapping an iridacycle with quinone diazides.[16]

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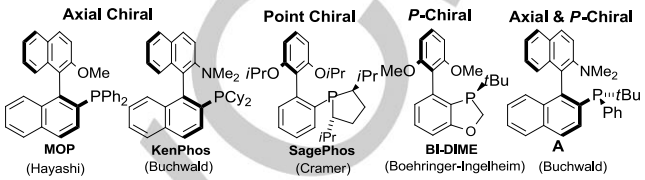
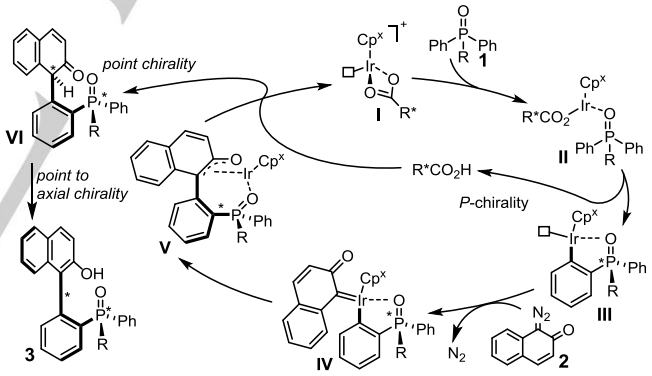


Figure 1. Typical chiral biaryl monophosphines with different chiral elements.

The asymmetric phosphine oxide C-H arylation offers a unifying efficient approach to construct a variety of different chiral elements (Scheme 1). First, an enantioselective C-H activation of **II** desymmetrizes the phosphorus atom (**III**) yielding *P*-chirality.[13] Subsequent trapping of the iridacycle with an *o*-quinone diazide forges the biaryl axis (**V**). Usage of a bulky *o*-quinone diazides result in stable atropisomers with a locked chiral axis (**3**)[14f, 17, 12g, 18] that is either formed directly or by point-to-axial chirality transfer[19] upon aromatization (**VI**).

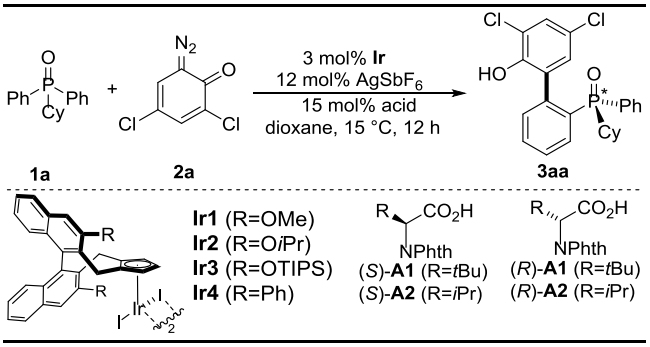


Scheme 1. Different possible stereo-determining steps of the enantioselective phosphine oxide C-H arylation.

Initially, the different catalysts and reaction parameters were evaluated with diphenylcyclohexylphosphine oxide (**1a**) and quinone diazide **2a**. A small set of Ir^{III}-catalysts bearing our most common chiral Cp^x ligands, were tested in combination with *tert*-leucine derived acid (*S*)-**A1** (table 1, entries 1-4). **Ir1** bearing the MeO-substituted Cp^x ligand,[14d] performed best in terms of reactivity and enantioselectivity, giving desired *P*-chiral product **3aa** in 73 % isolated yield and 95:5 er (entry 1). Bulkier Cp^x ligands were less reactive and selective. The opposite enantiomer (*R*)-**A1** caused a drop in enantioselectivity, while the overall reactivity was maintained (entry 5). Valine-derived acid (*S*)-**A2** provided a slightly lower enantiomeric ratio of **3aa** (entry 6). A reaction using (*R*)-**A2** confirmed the observed matched/mismatched trend (entry 7). Achiral 2,4,6-trimethylbenzoic acid

resulted in poor conversion and low enantioselectivity (entry 8). Control experiments confirmed the importance of each ingredient of the reaction protocol. Omitting the carboxylic acid additive shut down the reaction completely (entry 9). Along the same lines, no reaction occurred without $AgSbF_6$, confirming the requirement of an intermediate cationic Ir^{III} species (entry 10). Finally, the combination of achiral Cp^*Ir^{III} with (*S*)-**A1** gave **3aa** in a very poor yield and negligible enantioselectivity (entry 11).

Table 1. Optimization of the enantiotopic C-H arylation.[a]

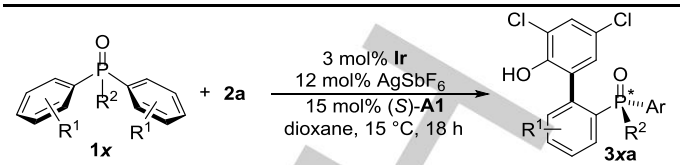


Entry	Ir	Acid	Yield [%][b]	er[c]
1	**Ir1**	(*S*)-**A1**	73 (79)[d]	95:5
2	**Ir2**	(*S*)-**A1**	46	92.5:7.5
3	**Ir3**	(*S*)-**A1**	30	87.5:12.5
4	**Ir4**	(*S*)-**A1**	0	-
5	**Ir1**	(*R*)-**A1**	77	83.5:16.5
6	**Ir1**	(*S*)-**A2**	88	91:9
7	**Ir1**	(*R*)-**A2**	67	70.5:29.5
8	**Ir1**	2,4,6-Me-$C_6H_2CO_2H$	12	38:62
9	**Ir1**	-	0	0
10	**Ir1** (no $AgSbF_6$)	(*S*)-**A1**	0	0
11	$[Cp^*IrCl_2]_2$	(*S*)-**A1**	<5	45.5:54.5

[a] Conditions: 0.1 mmol **1a**, 0.05 mmol of **2a**, 1.5 µmol **Ir**, 6.0 µmol $AgSbF_6$, 7.5 µmol acid, 0.1 M in dioxane, 15 °C for 12 h; [b] NMR yield with internal standard; [c] determined by chiral HPLC; [d] Isolated yield on doubled scale.

With the aforementioned optimized conditions, we evaluated a range of phosphine oxides **1*x*** (Table 2). A variety of different substituents R^1 on different positions on the aryl groups were found to have little influence on the reaction outcome. Very good yields and enantioselectivities of C-H arylation products **3*x*a** were obtained.[20] Variation of R^2 revealed that in particular, bulky groups such as *tert*-butyl or adamantyl, which are of high value for later applications as phosphine ligands were well suited (entries 1-9). Nevertheless, smaller (entry 10) or heteroatom substituents R^2 (entry 11) were tolerated and provided the arylation product **3ka** and **3la** in good yields, albeit with reduced enantioselectivities. X-Ray crystal structure analysis of **3ba** allowed for the determination of the absolute configuration of the arylation products.[21]

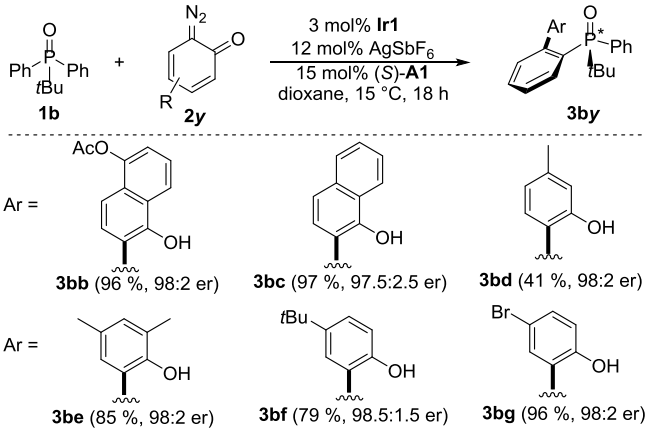
Table 2. Scope of the enantioselective phosphine oxide arylation.[a]



Entry	3*xy*	R^1	R^2	Yield [%][b]	er[c]
1	**3ba**	H	*t*Bu	98	97.5:2.5
2	**3ca**	4-Me	*t*Bu	85	98:2
3	**3da**	3-Me	*t*Bu	96	94.5:5.5
4	**3ea**	4-MeO	*t*Bu	92	98.5:1.5
5	**3fa**	3-MeO	*t*Bu	60	94.5:5.5
6	**3ga**	4-NMe_2	*t*Bu	89	97.5:2.5
7	**3ha**	4-Cl	*t*Bu	69	95.5:4.5
8	**3ia**	H	Ad	94	98:2
9	**3ja**	H	*i*Pr	96	94.5:5.5
10	**3ka**	H	Me	74	68.5:31.5
11	**3la**	H	$N(iPr)_2$	69	85.5:14.5

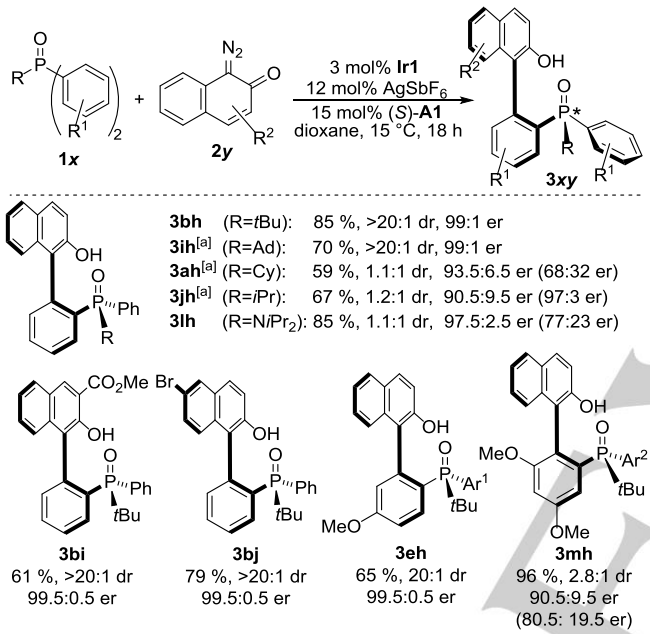
[a] Conditions: 0.2 mmol **1*x***, 0.1 mmol of **2a**, 3.0 µmol **Ir1**, 12 µmol $AgSbF_6$, 15 µmol (*S*)-**A1**, 0.1 M in dioxane, 15 °C for 18 h; [b] Isolated yield; [c] determined by chiral HPLC.

Furthermore, a range of diazo components **2*y*** was studied in the transformation (Scheme 2). *o*-Quinone diazides having just a 4-methyl (**2d**), a 5-*t*Bu (**2f**) or a 5-Br substituent (**2g**) proved to be sufficiently stable and underwent smooth transformation. In addition, 2-naphthyl derived quinone diazides such as **2b** and **2c** performed equally well. A uniformly high enantioselectivity of 98:2 er was achieved as quinone diazides intersect the catalytic cycle after the enantiodetermining step and trapping occurs faster than erosion of the selectivity of iridacycle **III**.



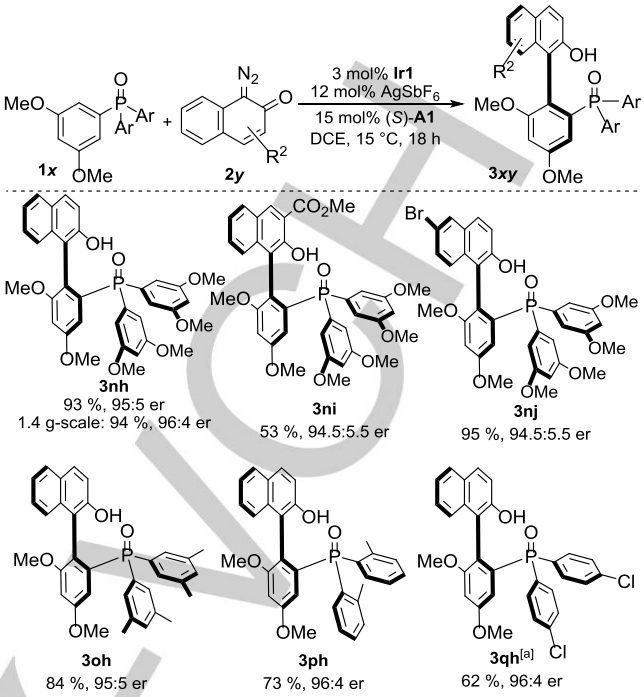
Scheme 2. Scope of the C-H arylation with different diazo compounds **2**.

Diazo reactants with increased bulk in the ortho position such as 1-diazonaphthalen-2(1*H*)-one **2h**, generated a stable chiral axis in addition to the point chirality at the phosphorus atom (Scheme 3). Single diastereomers and an excellent er of 99:1 to 99.5:0.5 were observed for bulky phosphine oxides **1b**, **1e**, **1i** and **1m**. Smaller groups R^1 lead to lower dr values, but still maintain high enantioselectivities for the major diastereomers. Isolated diastereoisomers did not undergo isomerization even at elevated temperature, indicating a high rotational barrier of the biaryl axis (See SI). This feature, in addition to the arrangement of the modifiable hydroxyl group makes these structures attractive precursors for the corresponding phosphine ligands.



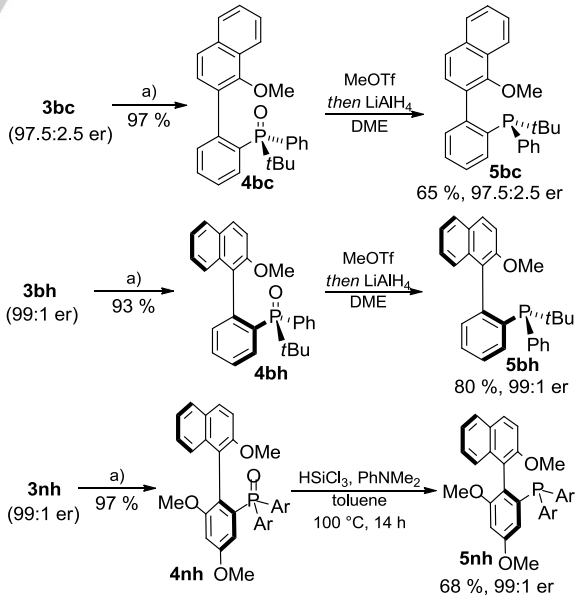
Scheme 3. Scope of the C-H arylation for the axial and *P*-chiral phosphine oxides **3*xy***. [a] reaction at 25 °C. Ar^1=PMP, Ar^2=3,5-MeO-C_6H_3.

The observation that the chiral Cp^x ligand enables enantiotopic C-H activation, but also has a bearing on the formation of the atropchiral biaryl axis, prompted us to further investigate this intriguing aspect. We exploited our methodology for the synthesis of purely axial chiral phosphine oxides possesing the basis structural feature of the MOP ligand. In this respect, *tris*-3,5-dimethoxy-phenylphosphine oxide **1n** was used as a substrate (Scheme 4). Smooth arylations with different napthoquinone diazides occurred in dichloroethane and formed products **3nh**, **3ni** and **3nj** in high enantioselectivities. To underscore the application potential, the transformation was perfomered at gram-scale giving **3nh** in 94 % yield and 96:4 er. Trituration with *i*PrOH/hexane increased the optical purity to >99.5:0.5 er (87 % yield). The superior reactivity of the 3,5-dimethoxyphenyl allowed the highly selective preparation of products **3oh**, **3ph** and **3qh** featuring sterically and electronically different triaryl phosphines. No activation of other possible C_{aryl}-H bonds was observed.



Scheme 4. Scope for the atropo-enantioselective C-H arylation. [a] with 5 mol% **Ir1**, 20 mol% $AgSbF_6$, 25 mol% (*S*)-**A1**.

Subsequently, reductions of representative members for all three phosphine oxide classes to the corresponding desired phosphine ligands were performed (Scheme 5). Alkylation of the free hydroxyl group with MeI gave the corresponding products **4** in excellent yields. Reduction using Imamoto's method[22] provided P^{III}-chiral phosphine **5bc** and **5bh** with complete enantiospecificity. **4nh** could be reduced under classical conditions with trichlorosilane to **5nh** without erosion of enantiopurity.



Scheme 5. Enantiospecific reduction to the corresponding phosphines: a) MeI, K_2CO_3, acetone, 60 °C.

In summary, we disclosed efficient and highly enantioselective C-H arylations of phosphine oxides with *o*-quinone diazides enabled by chiral $Cp^{x}Ir^{III}$ complexes in cooperation with phthaloyl *tert*-leucine as co-catalyst. This technology is suitable to access biaryl phosphine oxides with point chirality at phosphorus as well as to construct axial chirality of sterically demanding biaryl backbones. Moreover, compounds containing both axial and *P*-chirality, which are otherwise cumbersome to obtain, are synthesized in highly enantioselective and diastereoselective fashion. Enantiospecific reductions complete access to monodentate chiral phosphorus(III) compounds with proven biaryl ligand backbones in asymmetric catalysis.

Acknowledgements

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Keywords: Asymmetric Catalysis • C–H Activation • Iridium • Chiral Cp Ligand • P-Chirality

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[20] Compounds **3aa**-**3la** and **3ba**-**3bg** appear as a set of rotamers by NMR spectroscopy.

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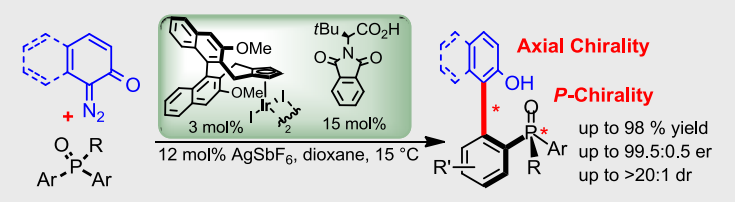

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Access to *P*- and Axially-Chiral Biaryl Phosphine Oxides by Enantioselective Cp^xIr^{III}-Catalyzed C-H Arylations

An enantioselective C-H arylation of phosphine oxides with *o*-quinone diazides is catalyzed by a $Cp^xIr(III)$ complex and chiral carboxylic acid co-catalyst. It provides a unifying access to *P*-chiral phosphine oxides, atropo-enantioselective construction of sterically demanding biaryl backbones and a selective assembly of axial and *P*-chiral compounds in excellent yields, diastereo- and enantioselectivities.