Atropo-Enantioselective Oxidation-Enabled Iridium(III)-Catalyzed C–H Arylations with Aryl Boronic Esters
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Abstract: Atropo-enantioselective biaryl coupling through C–H bond functionalization is an emerging technology allowing direct construction of axially chiral molecules. This approach is largely limited to electrophilic coupling partners. We report a highly atropo-enantioselective C–H arylation of tetralone derivatives paired with aryl boronic esters as nucleophilic components. The transformation is catalyzed by chiral cyclopentadienyl (Cp*) iridium(III) complexes and enabled by oxidatively enhanced reductive elimination from high-valent cyclometalated Ir-species.

Atropisomerism is a fundamental property of a variety of organic molecules having a profound effect on their properties and biological activity.[1] The chiral axis arising from restricted bond rotation is a key stereochemical element existing in many natural products[2] and drugs.[3] Notably, atropisomerism has an increasing impact on medicinal chemistry where atropisomers of drug candidates may significantly differ in biological activity.[6] Developments of efficient methods for the stereocontrolled assembly of biologically relevant atropichiral molecules are therefore highly desirable.[7] In this respect, atropo-enantioselective C–H functionalization is a promising emerging technology enabling their direct and atom efficient construction.[6] Most current atroposelective C–H functionalization methodologies base on de novo syntheses of an aromatic ring[9] or use biaryl substrates having a pre-existing axis.[10] Functionalization of C–H bonds then locks the axis by (dynamic) kinetic resolution[11] or creates chirality via desymmetrization processes.[12] Less explored, but retrosynthetically straightforward, is the direct coupling of two aryl fragments. This strategy directly forges the chiral axis from simple precursors. However, the hefty steric requirements to form stable atroposomers is a challenge for the catalyst performance and requires a very high efficiency to accommodate such hindered substrates. We and others reported capable Pd-[13] Ir-,[14] and Rh-catalysts.[15] An important aspect of this disconnection strategy is the choice of a suitable coupling partners. Electrophilic partners like aryl halides used in Pd-catalysis,[13a,b] and quinone diazides suitable for Rh,[15] and Ir-based[14] systems do not require external oxidant to close the catalytic cycle (Scheme 1a).[16] The versatility and wide availability of aryl boronic esters and silanes would make their use as carbon nucleophiles under oxidative conditions[17] an attractive complementary choice for direct atroposelective couplings. Besides a single moderately enantioselective example under Pd-catalysis,[13c,d] this approach is largely underdeveloped.

We were intrigued by recent reports of Chang et al. detailing C–H arylations enabled by oxidatively induced reductive elimination from high-valent metal centers.[18] Further oxidation of the iridium(III) center by an external oxidant increased the driving force for the C–C bond-forming reductive elimination, enabling direct C–H arylations with nucleophilic donors like aryl silanes[18d] and aryl boronic

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We hypothesized that this boosted reductive elimination from the high-valent iridium complex is advantageous for the conversion of sterically demanding substrates to axially-chiral products in Scheme 1b. This would overcome the high stability of cyclometalated Cp*Ir(III) complexes. Complexes with alkylxoy groups similar to I are stable under acidic conditions and exploitable as powerful hydrogenation catalysts. Herein, we demonstrate a highly enantioselective C–H arylation of tetralone derivatives with boronic esters giving access to atropochiral biaryls.

We investigated the feasibility of the transformation with oxime 1a derived from 7-benzoxy tetralone and naphthalen-1-ylboronic ester 2a in the presence of iodium catalyst [Cp*IrCl2] under oxidative conditions. Silver trifluoromethanesulfonate was used as a halide abstractor of the starting Ir-complex. Hydrated copper(II) trifluoroacetate was expected to facilitate transmetallation, and silver(I) fluoride was used to accelerate the reaction. We hypothesized that high stereocontrol but as well improve the efficiency of the process. We next evaluated the scope of the atrop-enantioselective biaryl formation with respect to diversely substituted aryl boronic esters in Scheme 2. A variety of naphthyl boronic esters were smoothly converted to their corresponding enantoenriched products in good yield and excellent selectivity.

Table 1: Optimization of the Ir-catalyzed atropo-enantioselective C–H arylation of oxime 1a.

| Entry | [Cp*IrCl2] | Temp. [°C] | yield [%] | ee [%] |
|-------|------------|------------|-----------|--------|
| 1     | I         | 40         | 13        | –      |
| 2     | Ir1       | 23         | 49        | 95.5   |
| 3     | Ir1       | 40         | 77        | 92.5:7.5 |
| 4     | Ir2       | 40         | 78        | 91.5:8.5 |
| 5     | Ir3       | 40         | 57        | 95.5   |
| 6     | Ir4       | 40         | 76        | 95.5:4.5 |
| 7     | Ir5       | 40         | 72        | 97.3   |
| 8     | Ir5       | 45         | 84 (84)   | 97.3   |
| 9     | Ir5       | 45         | 71        | 97.3   |

[a] Conditions: 50 μmol 1a, 100 μmol 2a, 2.5 μmol [Ir], 15 μmol AgNTf2, 50 μmol Cu(CO)2F2, 100 μM AgF in PhCF3 (0.2 M) for 14 h; [b] yields determined by 1H-NMR with an internal standard; [c] enantioselective ratio determined by chiral HPLC; [d] isolated yield at 0.1 mmol scale; [e] 25 μmol Cu(CO)2F2·H2O; MBn = 4-methyl benzyl, Bn = benzyl.

![Scheme 2](https://www.angewandte.org/comm/int/2021/1/06/S2.png)
lent selectivities up to 97.5:2.5 er. Besides naphthyl type-substrates, we investigated ortho-substituted aryl boronic esters. The yields for aryl substrates with axis-locking substituents 2-iPr (3ae), 2-Pr (3af) was slightly lower whereas very high selectivity levels were maintained. Product 3ag having a 2-trifluoromethoxy group locking the chiral axis was formed in 83% yield albeit slightly lower selectivity. However, aryl boronic esters with 2-MeO or 2-CF3 groups did not engage in a productive pathway, leaving oxime 1a untouched (see SI for unreactive substrates). In contrast, trisubstituted aryl boronic esters with an ortho-chlorine substituent and an additional functional group (CF3, OMe, F) reacted smoothly giving products 3ah-3aj in high yields and selectivities between 94.5:5.5 and 96.5:3.5 er. Notably, probing the atropo-enantioselective C–H arylation at 2.8 mmol scale yielded 1.17 g of biaryl 3aa in 84% yield and 97.3 er, indicated neither an efficiency nor a selectivity erosion at 28-fold scale-up.

The scope with respect to the oxime substrates 1 was investigated using naphthalen-1-ylboronic ester 2a (Scheme 3). The transformation provided efficient access to biaryl products having different ether substituents R1 including methyl cyclobutyl (3ba, 80% yield, 96:4 er), isopropyl (3ca, 80%, 95:5 er), and methyl (3da, 88% yield, 92:8 er). Suitable crystals of 3da unequivocally revealed the absolute configuration of the chiral axis to be (R) by single crystal X-ray diffraction analysis. Substrates with different oxime substituents R2 reacted smoothly with boronic ester 2a regardless of their size. For instance, methyl cyclobutyl oxime 3ea was formed in 82% yield and 96:4 er. Methyl and benzyl substituted oximes led to the products 3fa and 3ga in similar yields and selectivity. The C–H arylation of a chromane-derived oxime 3i gave product 3ia in 66% yield and 92.5:7.5 er. In addition, flavone-derived substrate 1j was converted at 23 °C to its corresponding product 3ja with 85:15 er using complex Ir1. The oxime-directing group is not a prerequisite for the directed C–H functionalization. In this respect, ketone 1h could be converted to the expected biaryl product, providing 3ha in 93:7 er. In this case, the less sterically demanding Ir1 complex was superior to Ir5.

The reactivity profile of atropochiral oxime 3aa, in particular with respect to its variety of reducible positions was investigated (Scheme 4). For instance, hydrogenation in the presence of Pearlman catalyst resulted in a selective cleavage of the phenolic benzyl group without a reduction of any other group. Phenol 4 displayed the same enantioenrichment as the starting material. In contrast, reduction of 3aa with sodium cyanoborohydride selectively reduced the C=N bond without cleavage of the sensitive N–O bond, affording without epimerization protected alkoxy amine 5 in 80% yield and with an excellent dr of 15:1. The chiral axis dictated the diastereoselectivity of the reduction resulting in a selective hydride delivery from the less hindered face giving diastereomer 5. A further reduction to phenol 6 and subsequent conversion to its 4-nitrobenzenesulfonate salt 6-H+ gave products 3aa.

In summary, we reported a highly atropo-enantioselective, CpxIr(III)-catalyzed C–H arylation of α-tetralone derivatives with boronic esters as nucleophilic coupling partners. Facile reductive elimination from high valent Ir-complexes and the use of fine-tuned disubstituted Cp ligands enabled the stereoselective synthesis of highly substituted biaryls. The method provides an efficient access to unexplored atropochiral oxime-derived α-tetralones, as well as chromane and...
flavone products. Moreover, this exemplifies that oxidation-induced eliminations are suitable to improve catalytic performance of otherwise relatively stable chiral cyclometalated Cp–iridium(III) complexes.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · atroposelectivity · C-H functionalization · chiral cyclopentadienyl - iridium

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