Enantioselective and regiodivergent copper-catalyzed electrophilic arylation of allylic amides with diaryliodonium salts

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Supporting Information Placeholder

ABSTRACT: A catalytic enantioselective and regiodivergent method for the arylation of alkenes is described. Chiral copper(II)bioxazoline complexes catalyze the electrophilic addition of diaryliodonium salts to allylic amides in excellent ee. Moreover, the position of arylation can be controlled by the electronic nature of the diaryliodonium salt enabling the preparation of non-racemic diaryloxazines or \( \beta,\beta'^{\prime} \)-diaryl enamides.

The catalytic asymmetric addition of carbon-based electrophiles to simple alkenes represents a strategically important bond forming process that would find widespread use in chemical synthesis. Successful examples of this ideal have arisen from variations of the venerable Heck reaction, with Sigman’s enantioselective palladium-catalyzed addition of aryl diazonium salts and aryliboronic acids to simple alkenols most notable. Despite the remarkable nature of this transformation, catalytic enantioselective variants remain underdeveloped, and is in contrast to the burgeoning area of catalytic enantioselective halogenation and related transformations. Therefore, the identification of distinct strategies for the catalytic enantioselective addition of carbon electrophiles to unactivated alkenes remains an important challenge to the continued advance of chemical synthesis.

Over the last 7 years our laboratory has introduced the novel reactivity of a putative copper(III)-aryl species that behaves as an aromatic electrophile equivalent. This high oxidation state organometallic can be catalytically generated by the union of simple copper complexes and diaryliodonium salts, and we have shown that a range of latent nucleophiles undergo unique site-selective arylation reactions to form synthetically versatile products. An important facet of many of these reactions is the presence of a proximal carbonyl group that steers selectivity and influences the reactivity of the nucleophilic substrate. In addition to these studies, our group, as well as that of McMillan, have also shown that asymmetric copper-biosoaxazoline complexes can function as excellent catalysts for enantioselective arylation reactions between electron rich alkenes (such as indoles or enol silane derivatives) and diaryliodonium salts (eqn 1). A proposed pathway for these reactions involves the electrophilic Cu(III)-aryl center engaging the electron rich carbon-carbon double bond through a two-point binding model with a proximal carbonyl group, organizing the substrate for selective insertion to the Cu(III)-aryl bond. In light of these advances, we questioned whether these enantioselective arylation tactics could be merged with a carbonyl-directed oxy-arylation of simple alkenes (eqn 2).

Previous work – copper catalyzed arylation of enol silanes and alkenes (eqn 1)

\[
\begin{array}{c}
\text{Me}_2\text{N}O \rightarrow \text{Me}_2\text{N}O \rightarrow \text{Me}_2\text{N}O \\
\text{Me}_2\text{N}O \rightarrow \text{Me}_2\text{N}O \rightarrow \text{Me}_2\text{N}O \\
\end{array}
\]

This work – electronically controlled regiodivergent catalytic enantioselective arylation (eqn 3)

\[
\begin{array}{c}
\text{allylic amide} \\
\text{diaryliodonium salt} \\
\end{array}
\]

Here we report the successful realization of this idea through the development of a copper-catalyzed enantioselective arylation of allylic amides with diaryliodonium salts (eqn 3). Chiral copper(II)biosoaxazoline catalysts impart high levels of enantioselectivity as part of an electrophilic oxy-arylation process wherein arylation takes place at the carbon atom of the alkene most proximal to the carbonyl group to form 1,3-oxazine scaffolds. During our studies, we also discovered a remarkable...
electronic effect that enabled enantioselective arylation at the other position on the carbon-carbon double bond leading to a \(\beta,\beta'-\text{diaryl} \) enamide. Taken together, this represents an electronically controllable regiodivergent enantioselective alkene arylation which forms synthetically versatile non-racemic products from a single starting material.\(^9\)

At the outset of our studies, we focused on creating a catalytic enantioselective variant of an endo selective oxy-arylation of allylic amides, that we had recently published in racemic form using CuTC as the catalyst (see also eqn 2).\(^{60}\) Treatment of alkene \(1\) with the unsymmetrical diaryliodonium \(2\) salt in the presence of chiral copper(II) bisoxazoline catalyst \(3\) at room temperature, conditions similar to our enantioselective arylation of enol silane derivatives, disappointingly gave no product and returned only starting material. Pleasingly, reaction at 50 °C afforded a 70% assay yield (by \(^1\)H NMR) of the desired 1,3-oxazine product \(4a\) but with only a 6% enantiomeric excess (Scheme 1). The reaction of diaryliodonium triflates in such a reaction is accompanied by the formation of trifluoromethanesulfonic acid (TfOH), which we speculated might lead to a decomposition of chiral copper catalyst ultimately leading to a racemic (or near racemic) reaction. To counter this, we added two equivalents of the hindered base, 2,6-di-tert-butylpyridine (DTBP), to the reaction. Although we were pleased to observe the formation of the oxazine \(4a\), this time with 45% ee, we were surprised to find that the reaction also produced a second product that we determined to be the \(\beta,\beta'-\text{diaryl} \) enamide \(5a\) in 21% yield and 48% ee. While the 1,3-oxazine \(4a\) is constructed via arylation at the position proximal to the amide motif and is accompanied by concomitant carbon-oxygen bond formation, the \(\beta,\beta'-\text{diaryl} \) enamide \(5a\) is the result of arylation at the other end of the carbon-carbon double bond and accompanied by alkene transposition into conjugation with the amide group.

**Scheme 1.** Discovery of regiodivergent arylation.

![Scheme 1](https://example.com/scheme1.png)

In order to further investigate this unusual regioselective arylation, we first varied the counterion of the diaryliodonium reagent and found that changing from the OTf to the PF\(_6\) salt\(^{10}\) resulted in a small increase in the regioselectivity but huge improvement in enantioselectivity for both the oxazine (to 98%) and enamide (to 94%) products (Table 1, entries 1 and 2). A brief survey of solvents revealed consistently high ee for both products but a loss in both the regioselectivity and reactivity (entries 2-5), and so dichloromethane was retained as the optimum reaction media. The use of the symmetrical diphenyliodonium hexafluorophosphate salt did not significantly change the regioselectivity but the ee of the enamide dropped slightly (entry 6). However, when we changed the electronic nature of the transferring aryl group from phenyl to 4-methoxyphenyl (2d), we were surprised to find that only the 1,3-oxazine was formed exclusively in 93% assay yield and 95% ee (Scheme 2a). The remarkable selectivity observed in this result was further exemplified when we reversed the electron nature on the aryl group; the electron deficient diaryliodonium salt (2e) gave exclusively the \(\beta,\beta'-\text{diaryl} \) enamide product in 78% assay yield and 95% ee (Scheme 2b).\(^{11}\)

**Scheme 2.** Electronically controlled regiodivergent arylation.

![Scheme 2](https://example.com/scheme2.png)

Encouraged by these results, we next explored the regiodivergency of the arylation processes using a single, electronically unbiased alkene. Focussing initially on the catalytic enantioselective oxy-arylation of alkenes to form 1,3-oxazines, we found that a selection of electron rich aryl groups could be transferred from the corresponding unsymmetrical aryl(mesityl)diaryliodonium hexafluorophosphates salts (Table 2a). In most cases the yields of the oxy-arylation process were good and accompanied by excellent enantioselectivities in the products (4b–4f); only the oxazine product was observed. Although the transfer of a thiophene group proceeded in lower yield the ee was high (4g). Interestingly, the limit of the electronic control element in the diaryliodonium salt extended to the transfer of a phenyl moiety; here, we observed the formation of the oxazine product in high ee and 53% yield (4h), but the reaction was accompanied by the formation of 32% of the corresponding achiral \(\beta,\beta'-\text{diphenyl} \) enamide (product not shown). Importantly, oxazine \(4h\) was crystalline, enabling identification of the absolute configuration by single crystal X-ray diffraction.\(^{13}\)

When we examined the transfer of electron-deficient aryl groups to the unbiased alkene \(1b\), we found that the enamide was usually the exclusive product (Table 2b). Aryl groups displaying ester, halogens and trifluoromethyl groups in the para, and meta positions all worked well to produce the expected enamide products (5b–i). We did observe small amounts of the corresponding oxazine (4-8%) in the reactions that formed during the the aryl transfer of p-Cl(C\(_6\)H\(_5\)) and p-Br(C\(_6\)H\(_5\)) groups. o-Fluoroaryl groups could also be accommodated and proceeded with moderate yield but excellent ee to form 5j. Interestingly, transfer of the electron donating o-tolyl group also formed the enamide product in high ee 5k. This result is in contrast to other electron-rich salts that generate the oxazine products, and suggest there may also be a subtle steric effect involved in determining the reaction selectivity.

**Table 1.** Optimization of regiodivergent arylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>([\text{Ar}^-\text{I}^-\text{Ar}']\text{X} ) (2)</th>
<th>solvent</th>
<th>Yield %(^a)</th>
<th>ee %(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Mes-I-Ph]OTf</td>
<td>CH(_2_)Cl</td>
<td>40:21</td>
<td>45, 48</td>
</tr>
<tr>
<td>2</td>
<td>[Mes-I-Ph]PF(_6)</td>
<td>CH(_2_)Cl</td>
<td>65:26</td>
<td>98, 94</td>
</tr>
<tr>
<td>3</td>
<td>[Mes-I-Ph]PF(_6) 1,4-dioxane</td>
<td></td>
<td>5:0</td>
<td>90, 90</td>
</tr>
<tr>
<td>4</td>
<td>[Mes-I-Ph]PF(_6) 1,2-DCE</td>
<td></td>
<td>34:25</td>
<td>95, 94</td>
</tr>
<tr>
<td>5</td>
<td>[Mes-I-Ph]PF(_6) PhMe</td>
<td></td>
<td>27:33</td>
<td>93, 93</td>
</tr>
<tr>
<td>6</td>
<td>[Ph-I-Ph]PF(_6)</td>
<td></td>
<td>70:26</td>
<td>96, 88</td>
</tr>
</tbody>
</table>

\(^a\) Yield measured by \(^1\)H NMR against an internal standard. \(^b\) Measured by chiral HPLC.
We next investigated the scope of the alkene substrate in the regiodivergent process with a range of aryl substituted allylic amides and either an electron-rich or electron deficient aryl(mesityl)iodonium hexafluorophosphate. In general, substrates with electron-donating or neutral substituents on the aryl group of the alkene were highly reactive towards the 4-methoxyphenyl(mesityl)iodonium salt and gave oxazine products in high yields and high enantioselectivity (Table 3a). For example, the synthetically versatile methoxy and halogen substituents can be positioned at various points on the alkene motif to afford good yield of the oxazines in high enantiomeric excess (4a, 4i-k). 2-naphthyl, o-tolyl and the pharmaceutically common 1,3-benzodioxoxazole and 3-indole motifs also worked well to generate potentially interesting diarylated scaffolds in high ee (4l-o).

### Table 2a. Scope of enantioselective aryl transfer to form oxazines

<table>
<thead>
<tr>
<th>R</th>
<th>Ar</th>
<th>1b (R=CMe₂)</th>
<th>2 (electron poor aryl)</th>
<th>10mol % Cu catalyst</th>
<th>3 (equiv. DTBP)</th>
<th>4 (R=CMe₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>55%, 93% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>53%, 94% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>52%, 92% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>58%, 93% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2b. Enantioselective aryl transfer to β,β′-diaryl enamides

<table>
<thead>
<tr>
<th>R</th>
<th>Ar</th>
<th>1b (R=CMe₂)</th>
<th>2 (electron poor aryl)</th>
<th>10mol % Cu catalyst</th>
<th>3 (equiv. DTBP)</th>
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<tbody>
<tr>
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<td>55%, 93% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>53%, 94% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>52%, 92% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>58%, 93% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3b. Enantioselective arylation to β,β′-diarylaldehydes

<table>
<thead>
<tr>
<th>R</th>
<th>Ar</th>
<th>1b (R=CMe₂)</th>
<th>2 (electron poor aryl)</th>
<th>10mol % Cu catalyst</th>
<th>3 (equiv. DTBP)</th>
<th>4 (R=CMe₂)</th>
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</thead>
<tbody>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>55%, 93% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>53%, 94% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Me</td>
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<td>F</td>
<td>52%, 92% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>F</td>
<td>58%, 93% ee</td>
<td>R</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>
Particularly appealing about the enantioselective arylation to form the \( \beta,\beta' \)-diaryl enamides is their facile hydrolysis to the corresponding arylaldehyde; enantioenriched \( \beta,\beta' \)-diaryl aldehydes are useful building blocks that have a range of potential applications. For example, acidic hydrolysis of enamide 5i was performed in 84% yield and the resulting arylaldehyde (6) could be converted into indatraline 7, a non-selective monoamine transporter inhibitor that has shown promise in the treatment of cocaine addition.

![Scheme 3. Application of enantioenriched \( \beta,\beta' \)-diaryl enamides](image)

In summary, we have discovered an electronically controlled, regiodivergent copper-catalyzed enantioselective arylation of allicylic amides. The electronic properties of the diaryliodonium hexafluorophosphate salt can be used to affect the position of allicylic arylation leading to either 1,3-oxazines or \( \beta,\beta' \)-diaryl enamides with high enantioselectivity. The process uses readily available starting materials, commercial catalysts and bioxazoline ligand, and is operationally simple. Although at present, the factors that control the regio- and enantioselectivity of the arylation process remain unclear, work is currently ongoing to elucidate the fascinating selectivity that control these transformations, and will be reported in due course.

ASSOCIATED CONTENT

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES


(10) Reaction using Cu(I)OTf-bioxazoline catalysts gave comparable yield and ee (5h, 58% yield and 93% ee)

(11) Arylation products 4h and 5i were obtained as single crystals. Interestingly, the products 4h and 5i appear arise from arylation on different faces of the alkene using the same chiral catalyst. This suggests distinct regio- and enantiocontrol elements are operating for each arylation pathway.

(12) Species 4h and 5i appear arise from arylation on different faces of the alkene using the same chiral catalyst. This suggests distinct regio- and enantiocontrol elements are operating for each arylation pathway.
1,3-diaryl oxazine

[reaction diagram]

1,3-diaryl oxazine εlectron rich

Ar¹ εlectron deficient

[reaction diagram]

β,β'-diaryl enamide