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Enantioselective and Regiodivergent Copper-Catalyzed Electrophilic Arylation of Allylic Amides with Diaryliodonium Salts

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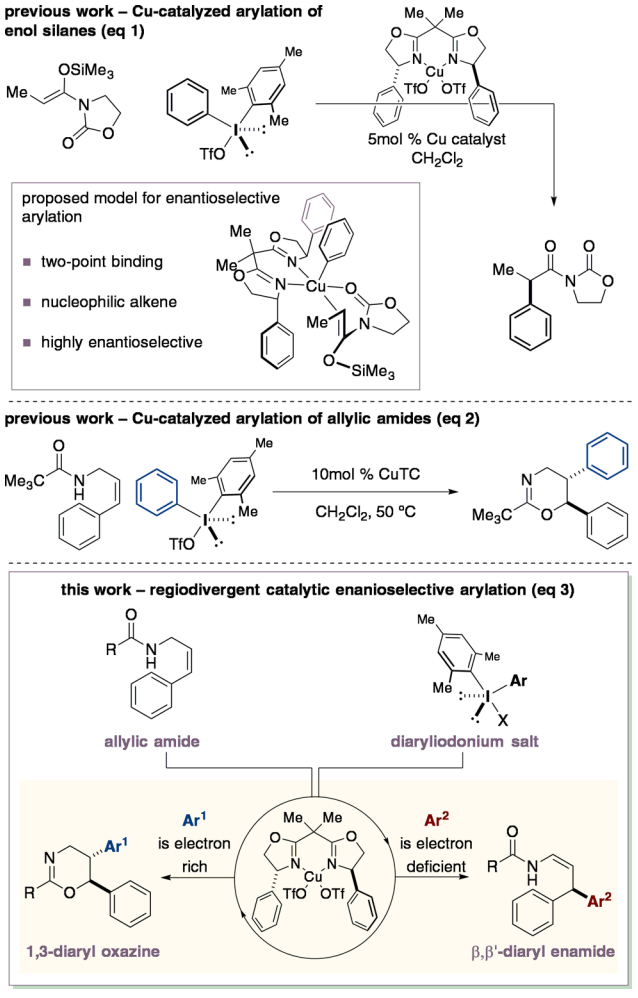
Supporting Information

ABSTRACT: A catalytic enantioselective and regiodivergent arylation of alkenes is described. Chiral copper(II)-bisoxazoline complexes catalyze the addition of diaryliodonium salts to allylic amides in excellent ee. Moreover, the arylation can be controlled by the electronic nature of the diaryliodonium salt enabling the preparation of nonracemic diaryloxazines or β,β'-diaryl enamides.

The catalytic asymmetric addition of carbon electrophiles to alkenes represents a strategically important bond-forming process. Successful examples of this have arisen from variations of the venerable Heck reaction,[1] with Sigman's enantioselective palladium-catalyzed addition of aryl diazonium salts and arylboronic acids to alkenols most notable.[2] Despite this remarkable transformation, catalytic enantioselective variants remain underdeveloped[3] and are in contrast to the burgeoning area of catalytic enantioselective halogenation.[4] Therefore, the identification of distinct strategies for the catalytic enantioselective addition of carbon electrophiles to unactivated alkenes remains an important challenge.

Over the last 7 years our laboratory has explored the novel reactivity of a putative copper(III)-aryl species as an aromatic electrophile equivalent.[5−7] These high oxidation state organometallics can be catalytically generated by the combination of simple copper complexes and diaryliodonium salts, and we have shown that a range of latent nucleophiles undergo 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 reaction of the substrate. In addition to these studies, our group,[6d] as well as that of MacMillan,[7b,c] has also shown that copper−bisoxazoline complexes can function as excellent catalysts for enantioselective arylation reactions between electron-rich alkenes and diaryliodonium salts (eq 1). A proposed pathway for these reactions involves the electrophilic Cu(III)-aryl center engaging the carbon−carbon double bond through a two-point binding mode 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 alkenes (eq 2).[6f]

Here we report the successful realization of this idea through a copper-catalyzed enantioselective arylation of allylic amides with diaryliodonium salts (eq 3). Chiral copper(II)bisoxazoline catalysts impart high enantioselectivity in an oxy-arylation process wherein arylation takes place at alkene position proximal



to the carbonyl, to form 1,3-oxazines. During our studies, we also discovered a remarkable electronic effect that enabled enantioselective arylation at the other position on the double bond leading to a β,β'-diaryl enamide. Together, this represents an electronically controllable regiodivergent enantioselective alkene arylation which forms synthetically versatile nonracemic products from a single starting material.[8,9]

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 using CuTC as the

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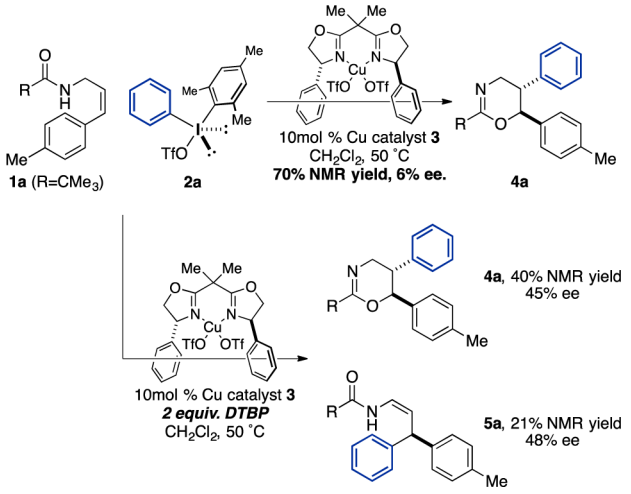
catalyst (eq 2).[6f] Treatment of alkene **1a** with the diaryliodonium salt **2a** in the presence of copper(II) bisoxazoline catalyst **3** at room temperature,[6d] conditions similar to our enantioselective arylation of enol silanes, disappointingly returned only starting material. Pleasingly, reaction at 50 °C afforded a 70% 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, which we speculated might lead to decomposition of the chiral catalyst ultimately leading to a racemic reaction. To counter this, we added 2 equiv of the hindered base, 2,6-ditertbutylpyridine (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 determined to be *β,β′*-diarylenamide **5a** in 21% yield and 48% ee. While 1,3-oxazine **4a** is constructed via arylation at the alkene carbon atom proximal to the amide motif and is accompanied by concomitant carbon−oxygen bond formation, *β,β′*-diaryl enamide **5a** is the result of arylation at the other end of the double bond, accompanied by alkene transposition into conjugation with the amide group.

Scheme 1. Discovery of Regiodivergent Arylation



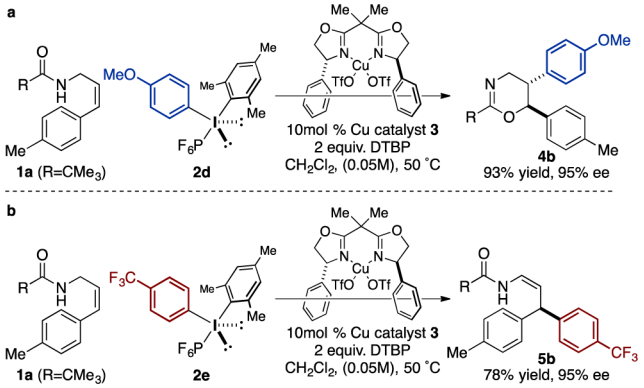
In order to further investigate this unusual regioselective arylation, we varied the counteranion of the diaryliodonium reagent and found changing from the OTf to the PF_6 salt[10] resulted in a small increase in the regioselectivity but huge improvement in enantioselectivity for both the oxazine (to 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 regioselectivity and reactivity (entries 2−5), and so dichloromethane was retained as the optimum reaction medium. Use of the symmetrical diphenyliodonium hexafluorophosphate salt did not significantly change the regioselectivity, but the ee of the enamide was lower (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 the 1,3-oxazine was formed exclusively in 93% assay yield and in 95% ee (Scheme 2a). This selectivity was further exemplified when we reversed the electron nature of the aryl group; the electron-deficient diaryliodonium salt **2e** gave exclusively the *β,β′*-diaryl enamide product in 78% assay yield and 95% ee (Scheme 2b).[11]

Table 1. Optimization of Regiodivergent Arylation

entry	[Ar−I−Ar′]X (**2**)	solvent	yield %[a] **4a**:**5a**	ee %[b] **4a**, **5a**
1	[Mes−I−Ph]**OTf**	CH_2Cl_2	40:21	45, 48
2	[Mes−I−Ph]$\mathbf{PF_6}$	CH_2Cl_2	65:26	98, 94
3	[Mes−I−Ph]$\mathbf{PF_6}$	1,4 dioxane	5:0	90, −
4	[Mes−I−Ph]$\mathbf{PF_6}$	1,2-DCE	34:25	95, 94
5	[Mes−I−Ph]$\mathbf{PF_6}$	PhMe	27:33	93, 93
6	[Ph−I−Ph]$\mathbf{PF_6}$	CH_2Cl_2	70:26	96, 88

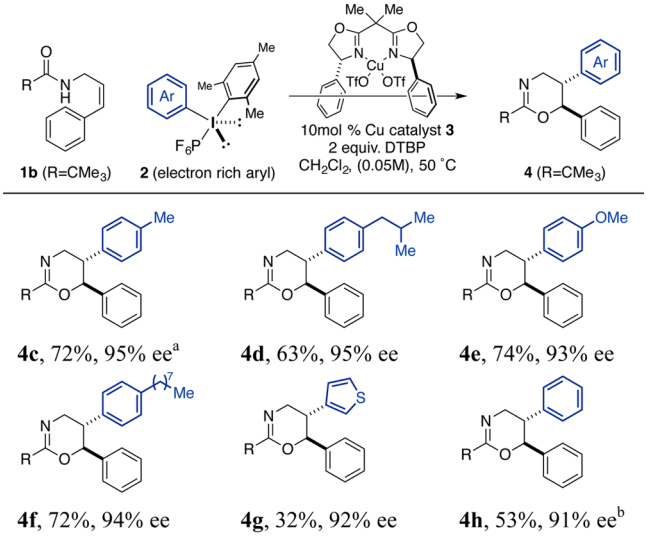
[a]Yield measured by 1H NMR against an internal standard. [b]Measured by chiral HPLC.

Scheme 2. Electronically Controlled Regiodivergent Arylation



Encouraged by these results, we next explored the regiodivergency of the arylation process using a single, electronically unbiased alkene. Focusing initially on the 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 hexafluorophosphate salts (Table 2a). In most cases the yields of the oxy-arylation process were good and accompanied by excellent enantioselectivities in the products (**4b−f**); only the

Table 2a. Enantioselective Aryl Transfer to Form Oxazines



[a]15 mol % **3** employed. [b]28% diphenyl enamide is isolated.

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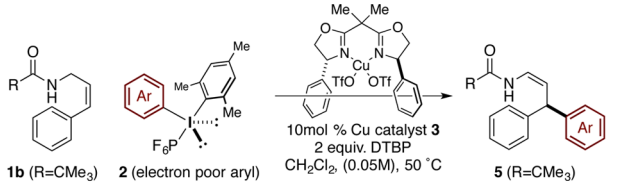
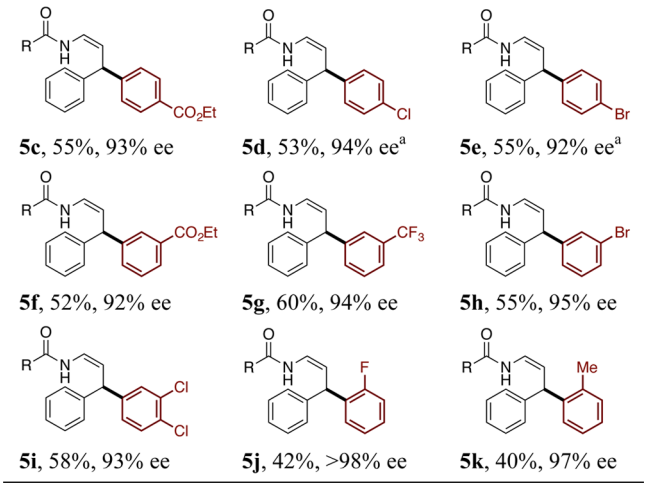
Table 2b. Enantioselective Aryl Transfer to *β,β′*-Diaryl Enamides





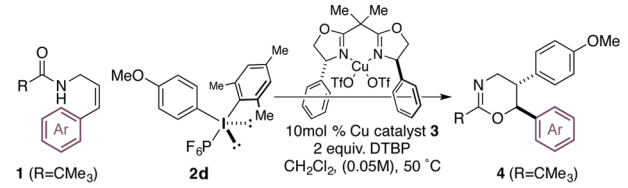
[a]4–8% (by NMR) of the corresponding oxazine product is observed.

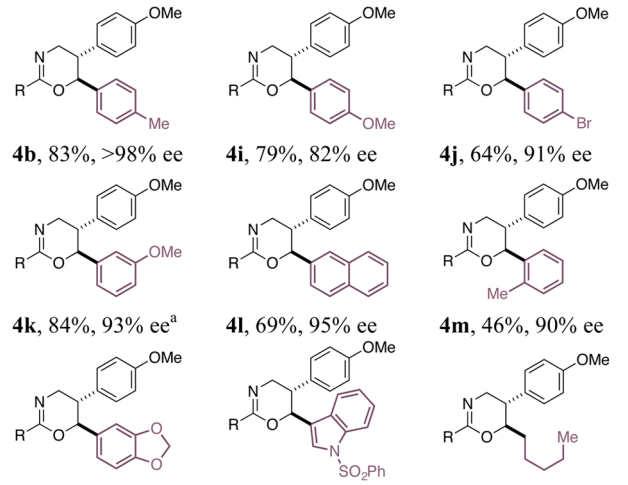
oxazine product was observed. Although the transfer of a thiophene group proceeded in lower yield the ee was high (**4g**). Interestingly, the limit of the electronic control of the diaryliodonium salt extended to the transfer of a phenyl moiety; here, we observed the formation of the oxazine product in high ee and 53% yield (**4h**), but the reaction was accompanied by the formation of 32% of the corresponding achiral *β,β′*-diphenyl enamide (product not shown). Oxazine **4h** was crystalline, enabling identification of the absolute configuration by single crystal X-ray diffraction.[12]

When we examined the transfer of electron-deficient aryl groups to 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**). Small amounts of the corresponding oxazine (4–8%) were observed in the reactions transfering of *p*-Cl(C_6H_5) and *p*-Br(C_6H_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 suggests there may be a subtle steric effect involved in determining the reaction selectivity.

We next investigated the scope of the alkene substrate in this 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 toward the 4-methoxyphenyl(mesityl)-iodonium salt (**2d**) and gave oxazine products in high yields and enantioselectivities (Table 3a). Synthetically versatile methoxy and halogen substituents can be positioned at various points on the aryl motif to afford oxazines in high yield and enantiomeric excess (**4a**, **4i–k**). 2-naphthyl, *o*-tolyl, and the pharmaceutically

Table 3a. Alkene Scope in the Enantioselective Oxy-Arylation



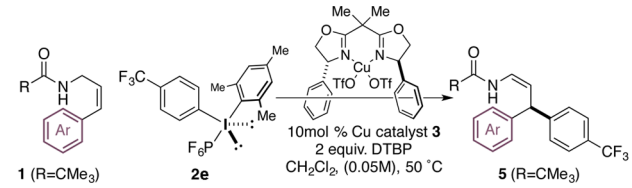


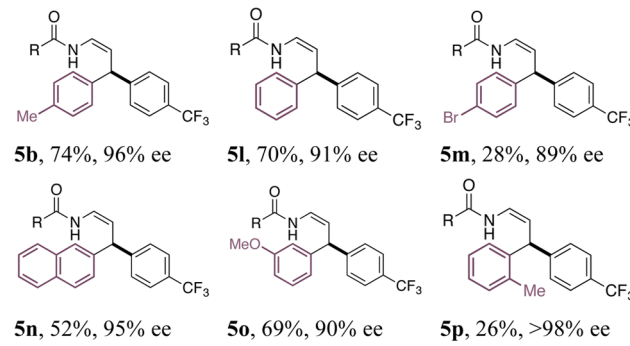
[a]15 mol % **3** employed.

common 1,3-benzodioxozole and 3-indole motifs also worked well to generate potentially interesting diarylated scaffolds in high ee (**4l–o**). Alkenes substituted with alkyl groups did not react in the oxy-arylation process (**4p**).

Using electron-deficient diaryliodonium salt **2e**, a similar set of allylic amides underwent arylation to *β,β′*-diaryl enamides (Table 3b). Here we observed that the allylic amide needed an electron-donating alkene substituent to impart sufficient reactivity. Despite this, a number of alkenes performed well in the reaction to form the *β,β′*-diaryl enamides with high enantioselectivity. *β,β′*-Diaryl enamide **5l** was crystalline, enabling identification of the absolute configuration by single crystal X-ray diffraction.[12]

Table 3b. Enantioselective Arylation to *β,β′*-Diarylaldehydes





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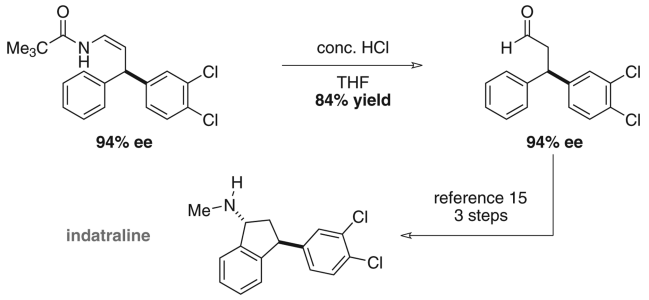
Scheme 3. Application of *β,β*-diaryl enamides



Particularly appealing about the enantioselective arylation to form the *β,β′*diaryl enamides is their hydrolysis to the corresponding aldehyde; enantioenriched *β,β′*-diaryl aldehydes are useful building blocks that have a range of potential applications.[13] Acidic hydrolysis of enamide **5i** was performed in 84% yield. The resulting aldehyde **6** could be converted into indatraline **7**, a nonselective monoamine transporter inhibitor that has shown promise in the treatment of cocaine addition (Scheme 3).[14,15]

In summary, we have discovered an electronically controlled, regiodivergent copper-catalyzed enantioselective arylation of allylic amides. The electronic properties of the diaryliodonium salt can be used to affect the position of alkene arylation leading to either 1,3-oxazines or *β,β′*-diaryl enamides with high enantioselectivity. The process uses readily available starting materials, commercial catalyst and bisoxazoline ligand and is operationally simple. Although at present, the factors that control the regio- and enantioselectivity of the arylation process remain unclear, work is ongoing to elucidate the fascinating selectivity that control these transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03937.

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Notes

The authors declare no competing financial interest.

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(11) Reaction using Cu(I)OTf·bisoxazoline catalysts gave comparable yield and ee (**5h**, 58% yield and 93% ee)

(12) Interestingly, the products **4h** and **5l** appear arise from arylation on different faces of the alkene using the same chiral catalyst. This suggests distinct regio- and enantiocontrol elements could be operating for each arylation pathway.

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