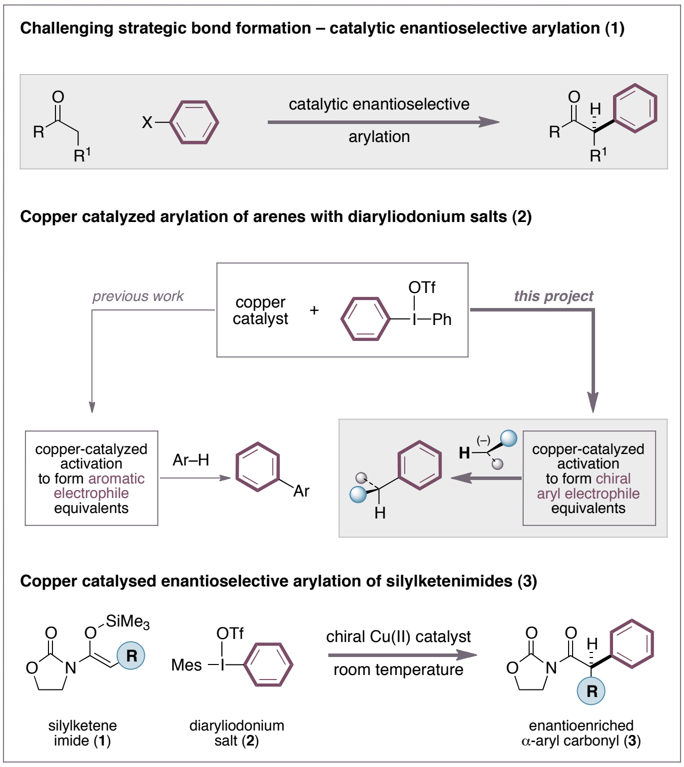
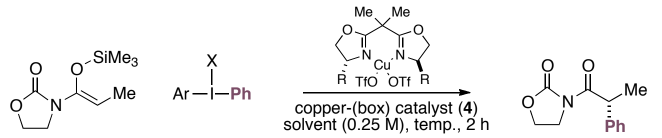
The use of catalysts to control the synthesis of architecturally complex and enantiopure molecules is a key aspect for the future of organic chemistry. Not only does this concept impact strongly on the area of natural product synthesis but also the continued development of chemical biology, medicinal chemistry and materials science. The challenge for the synthetic chemist is to develop novel strategies for complex molecule synthesis, that combine the factors of atom economy, catalysis and stereocontrol.



One such challenge is represented by the arylation of enolate derivatives; a strategic C–C bond-forming process that has found widespread application in organic synthesis (eqn. 1).[1] While transition metal catalysts have facilitated major breakthroughs in enolate arylation, the development of corresponding catalytic enantioselective methods remains a significant challenge. Pioneering studies from the Buchwald and Hartwig laboratories have resulted in transition metal–catalysed enantioselective enolate arylations which form all-carbon stereogenic centres.[2] Conversely, related processes to generate tertiary α-aryl carbonyl compounds have not been forthcoming, presumably due to problems of product racemisation under the necessary basic reaction conditions. Despite some important advances,[3] the demonstrated significance of the α-aryl carbonyl motif (in both pharmaceutical molecules and chiral building blocks) necessitates the development of new catalytic enantioselective methods for their preparation. Recently, our laboratory discovered that copper catalysts facilitate regioselective biaryl bond formation between diaryliodonium salts and simple arenes (eqn. 2).[4,5] While the mechanism of these reactions remains unclear, we consider the reactive species to be a copper-activated aromatic electrophile. As a logical extension of this catalyst activation mode, we questioned whether the action of a chiral copper catalyst on a diaryliodonium salt would form an aryl electrophile species suitable for participation in an enantioselective arylation.[6] Herein, we describe a copper-catalysed enantioselective arylation of an enolate equivalent with diaryliodonium triflates (eqn. 3). This mild and operationally simple process delivers versatile α-arylcarbonyl products in excellent yields and enantioselectivities, is tolerant of a range of functionality, and can be applied to the enantioselective synthesis of important therapeutic agents.

At the outset of our studies we selected silylketenimides **1**, derived from *N*-acyl oxazolidinones, as appropriate substrates for our designed catalytic enantioselective arylation process.[7] *N*-acyl oxazolidinones possess several favorable features: (1) the derived silylketenimides can be formed as single (*Z*)-isomers; (2) the presence of the Lewis basic carbonyl oxygen of the oxazolidinone could rigidify a transition state via stabilising interactions with a chiral copper complex; (3) α-functionalised *N*-acyl oxazolidinones are less susceptible to post-reaction racemisation than other carbonyl compounds; and (4) the products resulting from arylation can be readily transformed into useful intermediates – including carboxylic acids, esters, ketones, aldehydes, and alcohols – in a single step.

Table 1. Optimisation of the catalytic enantioselective arylation.



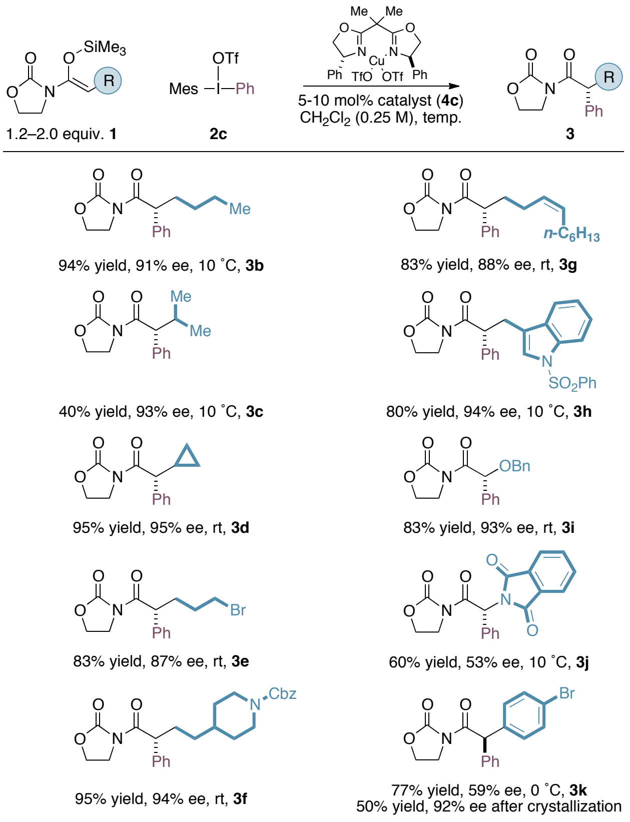
1 equiv. **1a** 1 equiv. **2** **3a**

entry	Ar	X	mol % catalyst, R	solvent	temp. ˚C	yield %[a]	ee **3a** %
1	Ph, **2a**	OTf	–	CH_2Cl_2	rt	–	–
2	Ph, **2a**	OTf	–	CH_2Cl_2	50	–	–
3	Ph, **2a**	OTf	10 mol% $Cu(OTf)_2$	CH_2Cl_2	rt	55	–
4	Ph, **2a**	OTf	10, *i*-Pr, **4a**	CH_2Cl_2	rt	38	44
5	Ph, **2a**	OTf	10, *t*-Bu, **4b**	CH_2Cl_2	rt	–	–
6	Ph, **2a**	OTf	10, Ph, **4c**	CH_2Cl_2	rt	75	91
7	Ph, **2a**	OTf	10, Ph, **4c**	dioxane	rt	15	91
8	Ph, **2a**	OTf	10, Ph, **4c**	EtOAc	rt	28	93
9	Ph, **2a**	OTf	10, Ph, **4c**	hexane	rt	33	87
10	Ph, **2a**	OTf	10, Ph, **4c**	PhMe	rt	60	90
11	Ph, **2b**	BF_4	10, Ph, **4c**	CH_2Cl_2	rt	71	70
12	Mes, **2c**	OTf	10, Ph, **4c**	CH_2Cl_2	rt	82	93
13	Mes, **2c**	OTf	10, Ph, **4c**	CH_2Cl_2	0	14	95
14	Mes, **2c**	OTf	5, Ph, **4c**	CH_2Cl_2	rt	90	91
15[b]	Mes	OTf	5, Ph, **4c**	CH_2Cl_2	rt	94	92

[a] NMR yields based on 1,3,5-trimethoxybenzene as internal standard.
[b] 1.2 equivalents of **1a** used, yield of isolated product after chromatography.

Before commencing our investigations into an enantioselective arylation, we first had to establish the viability of copper catalysts in this process (Table 1). A control reaction between silylketenimide **1a** and diphenyliodonium triflate **2a**, in the absence of a copper salt, failed to produce any arylation product **3a** at both room temperature and 50 ˚C. However, in the presence of 10 mol% $Cu(OTf)_2$, a moderate yield of the desired arylated product **3a** was observed at room temperature. We then assessed various preformed chiral catalysts generated from $Cu(OTf)_2$ and bisoxazoline ligands together with other reaction parameters such as solvent, temperature, nature of the electrophile and catalyst loading. After optimisation we were delighted to find that treatment of 1.2 equivalents of **1a** with 5 mol% of $Cu(OTf)_2$•(*R,R*)–diphenylbisoxazoline **4c** and 1 equivalent of (Ph–I–Mes)OTf **2c** in dichloromethane at room temperature for 2 hours afforded **3a** in 94% yield and 92% ee.[2]

Table 2. Scope of *N*-Acyloxazolidinone component



94% yield, 91% ee, 10 ˚C, **3b**

83% yield, 88% ee, rt, **3g**

40% yield, 93% ee, 10 ˚C, **3c**

80% yield, 94% ee, 10 ˚C, **3h**

95% yield, 95% ee, rt, **3d**

83% yield, 93% ee, rt, **3i**

83% yield, 87% ee, rt, **3e**

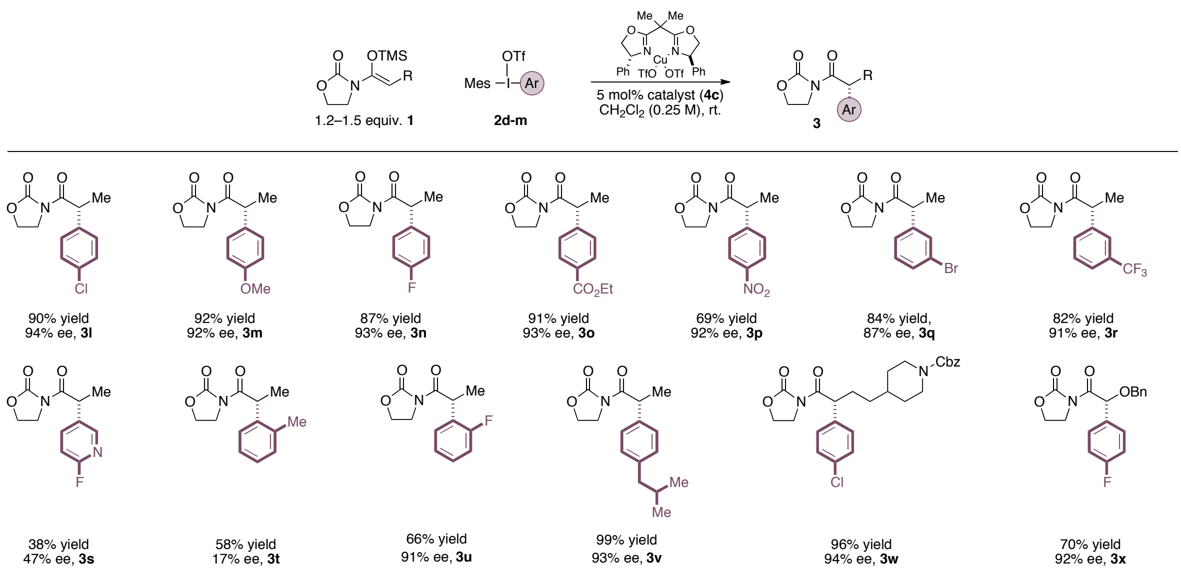
60% yield, 53% ee, 10 ˚C, **3j**

95% yield, 94% ee, rt, **3f**

77% yield, 59% ee, 0 ˚C, **3k**
50% yield, 92% ee after crystallization

We next explored the capacity of this new reaction (Table 2). Modified alkyl substrates (**1b-d**) performed well. Substrates displaying remote functionality, such as alkyl bromides, protected nitrogen functionality, alkenes and heterocyclic substituents, afforded the products in high yield and ee (**3e**–**h**). Reaction of benzyloxy-substituted silylketenimide **1i** gave the arylated mandelic acid derivative **3i** in excellent yield and ee. We were also able to generate the protected arylglycine product **3j** in moderate ee (53%). While we have not yet been able to improve this result, it provides a new entry into an important class of amino acids. Notably, these results demonstrate that our new methodology can be extended to *N*-acyloxazolidinones containing α-heteroatoms; valuable functionality for a range of synthetic applications. Finally, we also showed that aryl-substituted silylketenimide **1k** undergoes the reaction in good yield (77%) and moderate ee (59%). The ee can be upgraded by crystallization from methanol to produce **3k** in 50% yield and 92% ee. To the best of our knowledge, this is the first example of a catalytic enantioselective arylation to install an α-carbonyl tertiary stereogenic centre bearing two different aryl groups. We believe that these compounds may find broad utility as building blocks in drug discovery.

Table 3. Scope of Diaryliodonium Salt Component in the Copper-Catalyzed Enantioselective Arylation



90% yield
94% ee, **3l**

92% yield
92% ee, **3m**

87% yield
93% ee, **3n**

91% yield
93% ee, **3o**

69% yield
92% ee, **3p**

84% yield,
87% ee, **3q**

82% yield
91% ee, **3r**

38% yield
47% ee, **3s**

58% yield
17% ee, **3t**

66% yield
91% ee, **3u**

99% yield
93% ee, **3v**

96% yield
94% ee, **3w**

70% yield
92% ee, **3x**

The catalytic enantioselective arylation reaction affords products that are analogues of non-steroidal anti-inflammatory drugs, an important class of pharmaceuticals for the treatment of pain and associated inflammation,[8] as well as being implicated in other disease areas.[9] Furthermore, enantioenriched α-aryl carbonyl compounds are versatile building blocks for a wide range of synthetic applications. Therefore, we next examined the compatibility of the reaction with other diaryliodonium salts (Table 3).[5] Aryl groups displaying halogens, electron-rich and electron-deficient substituents, and useful functionality could all be introduced through this simple arylation process (**3l**–**r**). Transferring a fluoropyridine group proved challenging, with only moderate yield and ee observed under a range of reaction conditions (**3s**). We found that aryl groups bearing ortho-methyl substituents gave a moderate yield of arylated product **3t**, but in low ee. Pleasingly, however, the less sterically encumbered ortho-fluorophenyl group was transferred in excellent ee (**3u**). When the new arylation process was conducted on a larger scale, between silylketenimide **1a** and diaryliodonium salt **2n**, we found that the catalyst loading could be reduced to 2 mol% while still producing the product **3v** in 99% yield and 93% ee. Hydrolysis of the oxazolidinone **3v** completed a short synthesis of (*S*)-ibuprofen in just three chemical transformations from commercial materials, and provides a versatile strategy for the preparation of related molecules of therapeutic interest. We also demonstrated the compatibility of different silylketenimides (**1f**, **1i**) with other diaryliodonium salts, forming the versatile products **3w** and **3x** in high yield and ee.

In summary, we have developed a new transformation that enables the α-arylation of *N*-acyloxazolidinones with diaryliodonium salts. The reaction proceeds in high yield and enantioselectivity and is catalysed by a chiral copper(II)-complex derived from a commercially available bisoxazoline ligand. We have demonstrated that the catalytic enantioselective arylation has a broad substrate scope, is operationally simple and scalable, and can be applied to the synthesis of pharmaceuticals and their novel analogues. In line with our original hypotheses,[4] we currently favor a copper(III)-mediated aryl transfer, although at this stage we cannot rule out other mechanisms. Further investigations into the mechanism and extension of this asymmetric catalytic activation mode are ongoing and will be reported in due course.

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