

Enantioselective α -Arylation of *N*-Acyloxazolidinones with Copper(II)-bisoxazoline Catalysts and Diaryliodonium Salts

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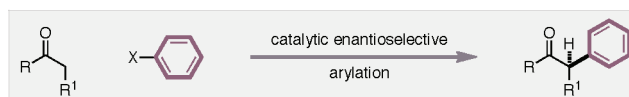
Supporting Information

ABSTRACT: A new strategy for the catalytic enantioselective α -arylation of *N*-acyloxazolidinones with chiral copper(II)-bisoxazoline complexes and diaryliodonium salts is described. The mild catalytic conditions are operationally simple, produce valuable synthetic building blocks in excellent yields and enantioselectivities, and can be applied to the synthesis of important nonsteroidal anti-inflammatory agents and their analogues.

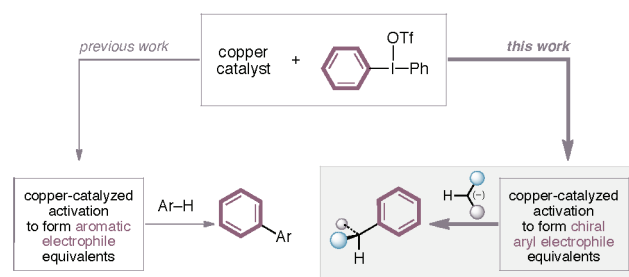
The arylation of enolate derivatives is a strategic C–C bond-forming process that has found widespread application in organic synthesis (eq 1).¹ While transition metal catalysts have facilitated major breakthroughs in enolate arylation, the development of corresponding catalytic enantioselective methods remains a significant challenge. Pioneering studies from the Buchwald and Hartwig laboratories have resulted in transition metal-catalyzed enantioselective enolate arylations which form all-carbon stereogenic centers.² Conversely, related processes to generate tertiary α -aryl carbonyl compounds have not been forthcoming, presumably due to problems of product racemization under the necessary basic reaction conditions. Fu and co-workers realized an alternative solution to this problem with their mild nickel-catalyzed cross coupling of α -halocarbonyls with aryl-organometallic reagents to deliver α -aryl carbonyls in high enantioselectivity.³ Aryl-boranes,^{3a} aryl-zinc,^{3b} aryl-silane,^{3c} and aryl Grignard reagents^{3d} can all be used with certain types of α -halocarbonyl to deliver the enantioenriched products. Despite these pioneering advances, the demonstrated importance 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 (eq 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 (eq 2).⁶ Koser et al. had reported an α -arylation of an enolsilane with diaryliodonium fluorides, a reaction that we speculated might be compatible with our enantioselective copper-catalyzed arylation blueprint (eq 3).⁷ Herein, we describe a copper-catalyzed enantioselective arylation of an enolate equivalent with diaryliodonium triflates (eq 4). This mild and operationally simple process delivers versatile α -arylcarbonyl products in excellent yields and enantioselectivities, is tolerant of a range of functionality, and

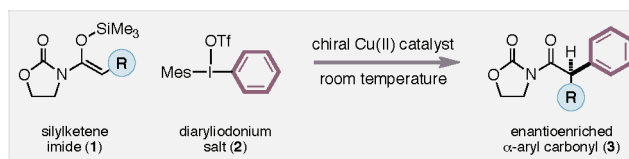
Challenging strategic bond formation – catalytic enantioselective arylation (1)



Copper catalyzed arylation of arenes with diaryliodonium salts (2)



Koser's reaction between enolsilanes and diphenyliodonium fluoride (3)

This study – Cu(II)-catalyzed enantioselective arylation of *N*-acyl oxazolidinones (4)

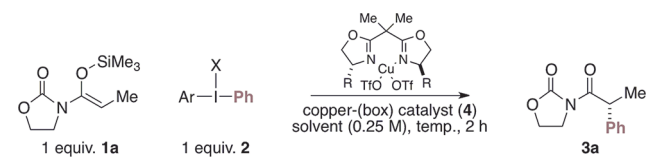
can be applied to the enantioselective synthesis of important therapeutic agents. During the course of our investigations, an elegant report by MacMillan and Allen described a related catalytic enantioselective process, which arylates aldehydes through the intermediacy of a chiral enamine.⁸

At the outset of our studies, we selected silylketenimides **1**, derived from *N*-acyloxazolidinones, as appropriate substrates for our designed catalytic enantioselective arylation process.⁹ *N*-acyloxazolidinones 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 stabilizing interactions with a

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Table 1. Optimization of Catalytic Enantioselective Arylation

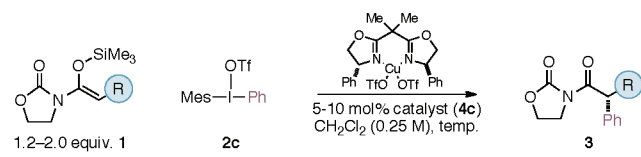


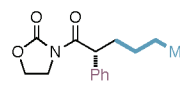
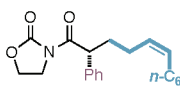
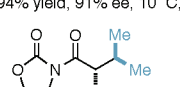
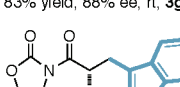
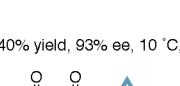
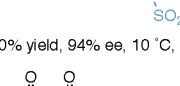
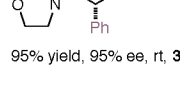
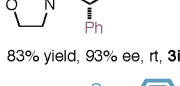
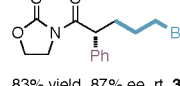
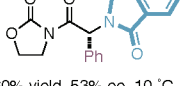
entry	Ar	X	mol % catalyst, R	solvent	temp (°C)	yield (%) ^a	ee 3a (%)
1	Ph, 2a	OTf	—	CH ₂ Cl ₂	rt	—	—
2	Ph, 2a	OTf	—	CH ₂ Cl ₂	50	—	—
3	Ph, 2a	OTf	10, Cu(OTf) ₂	CH ₂ Cl ₂	rt	55	—
4	Ph, 2a	OTf	10, <i>i</i> -Pr, 4a	CH ₂ Cl ₂	rt	38	44
5	Ph, 2a	OTf	10, <i>t</i> -Bu, 4b	CH ₂ Cl ₂	rt	—	—
6	Ph, 2a	OTf	10, Ph, 4c	CH ₂ Cl 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 ₂ Cl ₂	rt	71	70
12	Mes, 2c	OTf	10, Ph, 4c	CH ₂ Cl ₂	rt	82	93
13	Mes, 2c	OTf	10, Ph, 4c	CH ₂ Cl ₂	0	14	95
14	Mes, 2c	OTf	5, Ph, 4c	CH ₂ Cl ₂	rt	90	91
15 ^b	Mes, 2c	OTf	5, Ph, 4c	CH ₂ Cl ₂	rt	94	92

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

chiral copper complex, (3) α -functionalized *N*-acyloxazolidinones are less susceptible to postreaction racemization 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. The seminal studies of Evans and co-workers provided a fundamental understanding of related α,β -unsaturated systems and demonstrated their utility as electrophiles in a rich variety of copper(II)-bisoxazoline-catalyzed processes.¹⁰ In contrast, our proposed copper-catalyzed enantioselective arylation would require silylketenimide 1 to function as the nucleophile. To the best of our knowledge, silylketenimides derived from *N*-acyloxazolidinones have not previously been used as enolate equivalents in enantioselective copper-catalyzed transformations.

Before commencing our investigations into an enantioselective arylation, we first had to establish the viability of copper catalysts in this process. 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 (Table 1, entries 1, 2). However, in the presence of 10 mol % Cu(OTf)₂, a moderate yield of the desired arylated product 3a was observed at room temperature (entry 3), confirming our hypothesis that copper salts could catalyze this transformation. When we conducted the same experiment with a preformed chiral catalyst, generated from Cu(OTf)₂ and (*S,S*)-diisopropyl-bisoxazoline (to form 4a, entry 4), we were delighted to find that the reaction gave 38% yield of product 3a in a 44% enantiomeric excess. This prompted us to assess other bisoxazoline catalysts, and we found that both yield and enantioselectivity were significantly improved by changing the catalyst to Cu(OTf)₂·(*R,R*)-diphenyl-bisoxazoline (4c, entry 6), resulting in the formation of 3a in 75% yield and

Table 2. Scope of *N*-Acyloxazolidinone Component^{a,b}


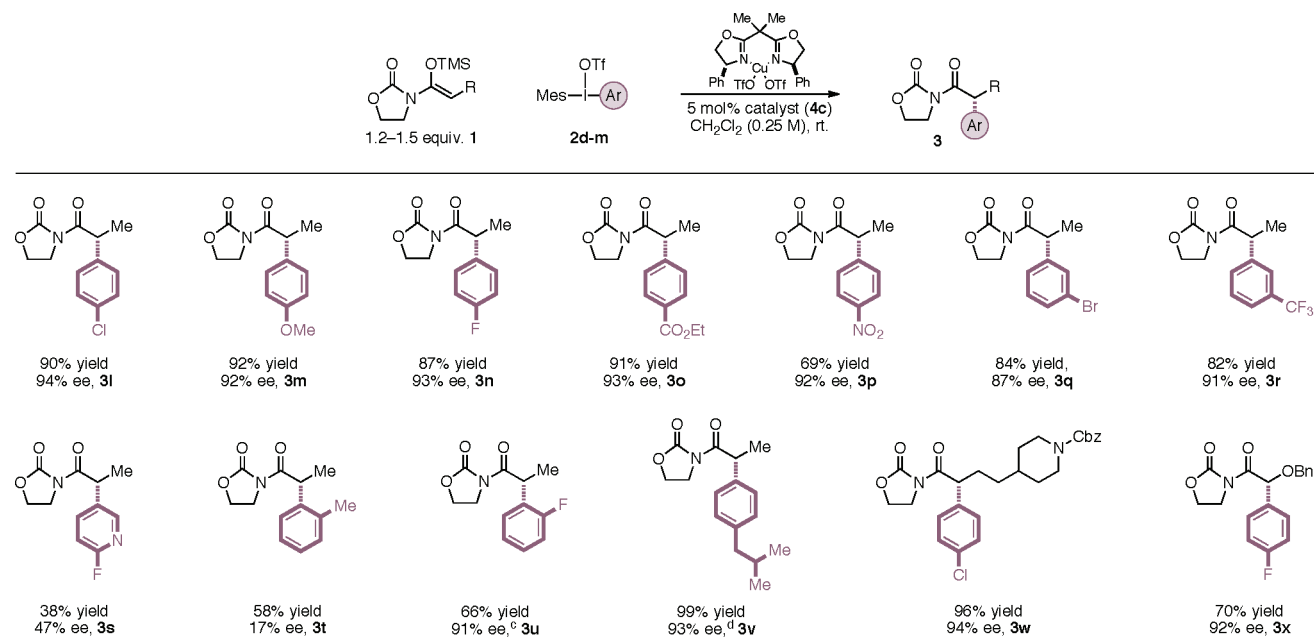
 94% yield, 91% ee, 10 °C, 3b	 83% yield, 88% ee, rt, 3g
 40% yield, 93% ee, 10 °C, 3c	 80% yield, 94% ee, 10 °C, 3h
 95% yield, 95% ee, rt, 3d	 83% yield, 93% ee, rt, 3i
 83% yield, 87% ee, rt, 3e	 60% yield, 53% ee, 10 °C, 3j
 95% yield, 94% ee, rt, 3f	 77% yield, 59% ee, 0 °C, 3k 50% yield, 92% ee after crystallization

^a See Supporting Information for details. ^b Yield and ee of isolated product are quoted as an average over two experiments.

91% ee.¹¹ Intriguingly, the enantioselectivity remained high across a range of solvents, although reactivity was greatly affected compared to the original dichloromethane reaction medium (entries 7–10). Notably, the enantiomeric excess was reduced when the counterion of the diphenyliodonium salt was changed from triflate to tetrafluoroborate (entry 11). Further assessment of the reaction conditions (entries 12–15) showed that using (Ph–I–Mes)OTf (2c) led to higher conversion, presumably owing to the increased solubility of this salt, compared to symmetric salt 2a.

The use of the nontransferring mesityl ligand is also advantageous as only one equivalent of the transferring aryl group is required, an important feature if valuable aryl coupling partners are employed.^{4,8,12} Our optimized reaction involved treatment of 1.2 equiv of 1a with 5 mol % of Cu(OTf)₂·diphenyl-bisoxazoline (4c) and 1 equiv of (Ph–I–Mes)OTf (2c) in dichloromethane at room temperature for 2 h to afford 3a in 94% yield and 92% ee (entry 15).¹³

We next explored the capacity of this new reaction (Table 2). Modified alkyl substrates (1b–d) performed well, although isopropyl derivative 1c gave only a moderate yield, presumably owing to a greater steric impact when compared to the cyclopropyl unit (1d). 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

Table 3. Scope of Diaryliodonium Salt Component in the Copper-Catalyzed Enantioselective Arylation^{a,b}

^a See Supporting Information for details. ^b Yield and ee of isolated product are quoted as an average over at least two experiments. ^c Reaction with 10 mol % catalyst **4c** at 10 °C for 20 h. ^d Reaction on 2 g scale with 2 mol % catalyst **4c** for 6 h.

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. Surprisingly, in comparison to other substrates, the sense of enantioinduction is reversed in the arylation of silylketenimide **1k**.¹⁴ To the best of our knowledge, this is the first example of a catalytic enantioselective arylation to install an α -carbonyl tertiary stereogenic center bearing two different aryl groups. We believe that these compounds may find broad utility as building blocks in drug discovery.

The catalytic enantioselective arylation reaction produces analogues of nonsteroidal anti-inflammatory drugs, an important class of pharmaceuticals for the treatment of pain and associated inflammation,¹⁵ as well as being implicated in other disease areas.¹⁶ 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 The unsymmetric diaryliodonium salts that are used in this process can be readily prepared in a one-pot procedure from the corresponding aryl iodide and mesitylene^{5,17} and are bench stable solids. 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, suggesting that the enantiodetermining step is influenced

by the steric properties of the aryl group. 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 affording **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.¹⁸ 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.¹⁹ The reaction proceeds in high yield and enantioselectivity and is catalyzed 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.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental details and full characterization are provided for all compounds, and crystallographic information for **3k** (PDF, CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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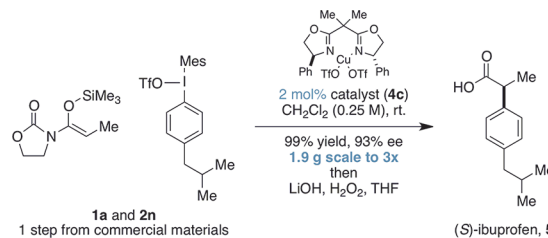
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REFERENCES

- (1) For metal-catalyzed α -arylation of enolates, see: (a) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, 40, 2355. (b) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, 46, 7236. (c) Vo, G. C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, 47, 2127. For a review, see: (d) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, 49, 676.
- (2) (a) Garcia-Fortanet, J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, 47, 8108. (b) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, 131, 9900. (c) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, 130, 195.
- (3) For Suzuki-type coupling with α -chloroamides, see: (a) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, 132, 11027. For Negishi-type coupling with α -haloketones, see: (b) Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, 48, 154. For Hiyama-type coupling with α -haloesters, see: (c) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, 130, 3302. For Kumada-type coupling with α -haloketones, see: (d) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, 132, 1264.
- (4) (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, 130, 8172. (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, 323, 1593. (c) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2010**, 50, 457. (d) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2010**, 50, 463.
- (5) For reviews on diaryliodonium salts, see: (a) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, 48, 9052. (b) Vavogliss, A. *The Organic Chemistry of Polycordinated Iodine*; VCH Publishers: New York, 1992. (c) Grushin, V. V. *Chem. Rev.* **2000**, 29, 315.
- (6) (a) Beringer, F. M.; Forgione, P. S.; Yudis, M. D. *Tetrahedron* **1960**, 8, 49. (b) Beringer, F. M.; Galton, S. A.; Huang, S. J. *J. Am. Chem. Soc.* **1962**, 84, 2819. (c) Beringer, F. M.; Forgione, P. S. *Tetrahedron* **1963**, 19, 739. (d) Beringer, F. M.; Forgione, P. S. *J. Org. Chem.* **1963**, 28, 714. (e) Beringer, F. M.; Daniel, W. J.; Galton, S. A.; Rubin, G. J. *Org. Chem.* **1966**, 31, 4315. (f) Chen, Z.; Jin, Y.; Stang, P. J. *J. Org. Chem.* **1987**, 52, 4115. (g) Hampton, K. G.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1964**, 29, 3511. (h) Gao, P.; Portoghese, P. S. *J. Org. Chem.* **1995**, 60, 2276. (i) Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, 64, 1338. For asymmetric examples, see: (j) Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1999**, 121, 9233. (k) Aggarwal, V. K.; Olofsson, B. *Angew. Chem., Int. Ed.* **2005**, 44, 5516.
- (7) Reactions with silyl enol ethers require the diaryliodonium fluoride in the absence of other additives; see: (a) Chen, K.; Koser, G. F. *J. Org. Chem.* **1991**, 56, 5764. (b) Iwama, T.; Birman, V. B.; Kozman, S. A.; Rawal, V. H. *Org. Lett.* **1999**, 1, 673.
- (8) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, 133, 4260.
- (9) For an example of the use of silylketenimides, derived from *N*-acyloxazolidinones, in palladium-catalyzed arylation reactions, see: Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, 126, 5182.
- (10) For the use of copper(II) bisoxazoline catalysts, see: (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, 113, 726. (b) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, 71, 1407. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, 33, 325.
- (11) Hydrolysis of the oxazolidinone in **3a** with LiOH, H₂O₂ gave 2-phenylpropionic acid. Comparison of its optical rotation with an authentic sample enabled us to establish the absolute configuration of the arylation products. We found that Cu(OTf)₂·(R,R)-Ph-bisoxazoline gave the (*R*)-stereocenter in **3a**; by analogy we base the absolute stereochemistry of arylated products **3a**–**3x** on this assignment.
- (12) Sanford and co-workers also used this approach in the Pd-catalyzed arylation of C–H bonds, see: (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, 127, 7330. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, 131, 11234.
- (13) We also found that no formation of products was observed in the absence of the chiral copper catalyst **4c** when the reaction was conducted at 50, 70, or 90 °C.
- (14) The absolute configuration was determined by X-ray diffraction: CCDC 831502.
- (15) Mack, D. J.; Brichacek, M.; Plichta, A.; Njardarson, J. T. *Top 200 Pharmaceutical Products by Worldwide Sales in 2009*; Department of Chemistry, University of Arizona; <http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster>.
- (16) Woodman, T. J.; Wood, P. J.; Thompson, A. S.; Hutchings, T. J.; Steel, G. R.; Jiao, P.; Threadgill, M. D.; Lloyd, M. D. *Chem. Commun.* **2011**, 47, 7332.
- (17) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, 349, 2610.
- (18) The gram-scale synthesis of (*S*)-ibuprofen using the highly modular copper(II)-catalyzed enantioselective arylation highlights the utility of the process for the preparation of useful quantities of drug-like molecules of potential use in medicinal chemistry programmes.



(19) We became aware that the MacMillan laboratory at Princeton University was engaged in related studies towards a copper-catalyzed arylation of enolsilane derivatives with diaryliodonium salts. We are grateful to the MacMillan group for kindly agreeing to publish their results in a back-to-back fashion with our own studies, and we thank them for their generosity and collegiality.