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Enantioselective α -Arylation of Carbonyls via Cu(I)-Bisoxazoline Catalysis

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Abstract

The enantioselective α -arylation of both lactones and acyl oxazolidones has been accomplished using a combination of diaryliodonium salts and copper catalysis. These mild catalytic conditions provide a new strategy for the enantioselective construction and retention of enolizable α -carbonyl benzylic stereocenters, a valuable synthon for the production of medicinal agents.

The enantioselective α -arylation of carbonyls has become a mainstay transformation in chemical synthesis, primarily driven by the research efforts of Buchwald and Hartwig.^{1,2} These seminal studies have delivered a number of transition metal-catalyzed protocols that directly produce quaternary carbon stereocenters adjacent to a series of carbonyl moieties including ketones, lactones, esters, imides and amides. Slower to develop, however, have been methods that enable the enantioselective production of enolizable α -carbonyl benzylic stereocenters (methine stereocenters), presumably due to the propensity for post-reaction racemization when elevated temperatures or basic conditions are employed.³ Notable recent progress has been made, however, through the work of (i) Fu and coworkers,⁴ who have shown that nickel-catalyzed Kumada and Negishi couplings can afford α -aryl carbonyl products with excellent enantiocontrol (eq 1) and (ii) our own laboratory's combined use of copper and organic catalysis with iodonium salts for the direct asymmetric α -arylation of aldehydes (eq 2).⁵

Fu Coupling: Dynamic Enantioselective α -Carbonyl Arylation (Eq 1)

Metal–Organocatalysis Merger: Enolizable α -Arylation Adducts (Eq 2)

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Supporting Information Available. Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

General Carbonyl Approach: Enantioselective α -Arylation (Eq 3)

As an outgrowth of these latter studies, we postulated that a broadly expanded array of carbonyl systems might be readily accessible using chiral copper catalysts in the presence of iodonium salts with silylketene acetals (eq 3). As a critical advantage, this new mechanistic approach would allow access to a range of carbonyl adducts that contain enolizable benzylic stereocenters, a significant challenge for asymmetric arylation chemistry. Herein, we describe the successful execution of these ideals and present an operationally trivial protocol to generate α -carbonyl methine-bearing stereogenicity without post-reaction racemization.

Design Plan

We elected to employ silylketene acetals and *N,O*-aminals as suitable enolic substrates, given their synthetic accessibility⁶ and well-established capacity to combine with electrophilic coupling partners.⁷ As outlined in Scheme 1, we proposed that oxidative insertion of a ligand-bound copper(I) complex into a suitable diaryliodonium salt⁸ would result in a highly electrophilic chiral copper(III) species,^{9,10} which would be intercepted by the silylated nucleophile. Subsequent reductive elimination and silyl hydrolysis yields the desired α -arylated carbonyl product and regenerates the copper(I) catalyst. As was the case with our previous organocatalytic studies, we recognized that aryliodonium salts are non-toxic, readily accessible, and air and moisture stable, valuable characteristics with respect to the development of a broadly useful transform.^{8c}

From the outset, we rationalized that bidentate coordination at copper would be important to facilitate high levels of enantioselectivity. As such, we sought to incorporate an *N*-acyl oxazolidone into our substrates that would both act as a directing group for copper and as a latent source of functionality for further transformations.¹¹

As shown in Table 1, we were delighted to find that exposure of the propyl oxazolidone-derived silylketene *N,O*-aminal to diphenyliodonium triflate in the presence of 5 mol% (CuOTf)₂PhMe produced the corresponding α -arylation adduct in high yield (entry 2, 77% yield).¹² Although previous reports have demonstrated that silylenol ethers can undergo direct arylation using non-catalytic conditions with iodonium salts, we observed no detectable reaction when our protocol was performed in the absence of copper salts.¹³ With this validation of our catalysis proposal in hand, we next turned our attention to the development of an enantioselective variant via the examination of a series of well known

chiral ligand sets.¹⁴ As revealed in Table 1, both the isopropyl and phenyl substituted bisoxazoline (Box)¹⁵ derived Cu(I) complexes (**2** and **3** respectively) produced the desired α -arylation product with useful efficiency (60–77% yield); however, notably superior levels of enantiocontrol were observed with catalyst **3** (87% ee). Changing the iodonium salt to the corresponding PF₆ counterion, using a mixed medium (CH₂Cl₂/toluene), and lowering the reaction temperature to 0 °C resulted in further improvements to provide the α -phenyl oxazolidone product in 98% yield and 93% ee, a protocol that was employed in subsequent scope studies.

As outlined in Table 2, we have found that a broad range of aryl and heteroaryl rings can be enantioselectively coupled with silylketene acetals using this Cu(I)Box-mediated technology. While symmetrical diaryliodonium triflates can be successfully employed in this context, we have found that the more practical approach of Gaunt to generate Ar-Cu(III)-XY systems from non-symmetrical aryl-mesityl reagents is preferred.^{9b} Both electron-deficient (entries 2–3 and 11, 80–96% yield, 91–95% ee) and electron-rich arenes (entries 4–5 and 10, 89–96% yield, 90–94% ee) were found to be suitable coupling partners. Moreover, a broad range of meta- and para-substituted aryl rings with diverse steric and electronic properties (ethers, esters, and halides) can be readily exploited in this protocol (entries 2–4, 6, 10–11, 80–96% yield, 90–95% ee). It is important to note that the iodonium moiety is chemoselectively targeted by the copper catalyst in preference to other halogen substituents (entry 6). In addition to aryl rings, we were delighted to find that heteroaromatic systems such as thiophenes and indoles were suitable coupling partners (entries 9 and 12, 75–88% yield, 90–94% ee), a useful outcome given the utility of these systems within the realm of medicinal agent discovery.

We have also found that this α -arylation protocol is tolerant of enolic coupling partners that display a wide range of functional groups, including arenes and olefins (Table 3, entries 7–11, 83–95% yield, 88–95% ee) as well as ethers, esters and carbamates (entries 3, 9–11, 91–94% yield, 91–93% ee). Notably, our mild α -arylation strategy is fully selective for the enolic α -position in the presence of other nucleophilic heterocycles such as indoles (entry 13, 65% yield, 89% ee), a system that has previously been shown to undergo arylation in the presence of similar Cu(III)aryl intermediates.^{9a} Importantly, sterically demanding β -branched substrates are accommodated with little effect on yield or enantioselectivity (entry 4–6, 74–90% yield, 84–92% ee). Finally, other non-oxazolidone-based nucleophiles readily undergo coupling via this procedure in high yield and selectivity (entries 12, 14–15, 76–89% yield, 88–91% ee).

To further demonstrate the value of this new α -arylation strategy, we implemented this technology in a unique and expeditious route to a known oral non-steroidal anti-inflammatory medicinal agent ((*S*)-naproxen, See Supporting Information). This demonstration reveals that a variety of similar drug-like molecules could be produced in a rapid and enantioselective fashion for the purposes of medicinal agent testing.¹⁶

In conclusion, we have developed a new technology that allows the direct and enantioselective α -arylation of enolate equivalents using a readily available catalyst from commercial sources. Further investigations into (i) the mechanism of this transformation and (ii) developing models for induction are currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. For racemic α -arylation of carbonyl compounds using Pd catalysis see: (a) Muratake H, Nakai H. *Tetrahedron Lett.* 1999; 40:2355.(b) Martín R, Buchwald SL. *Angew Chem, Int Ed.* 2007; 46:7236. (c) Vo GC, Hartwig JF. *Angew Chem, Int Ed.* 2008; 47:2127.
2. For asymmetric α -arylation of carbonyl compounds, see: (a) García-Fortanet J, Buchwald SL. *Angew Chem, Int Ed.* 2008; 47:8108.(b) Taylor AM, Altman RA, Buchwald SL. *J Am Chem Soc.* 2009; 131:9900. [PubMed: 19580273] (c) Liao X, Weng Z, Hartwig JF. *J Am Chem Soc.* 2008; 130:195. [PubMed: 18076166] Hartwig and Liu have constructed α -methine stereogenic centers using a chiral auxiliary: (d) Liu X, Hartwig JF. *J Am Chem Soc.* 2004; 126:5182. [PubMed: 15099101]
3. Alemán J, Cabrera S, Maerten E, Overgaard J, Jørgensen KA. *Angew Chem, Int Ed.* 2007; 46:5520.
4. (a) Dai X, Strotman NA, Fu GC. *J Am Chem Soc.* 2008; 130:3302. [PubMed: 18302392] (b) Lundin PM, Esquivias J, Fu GC. *Angew Chem, Int Ed.* 2009; 48:154.(c) Lou S, Fu GC. *J Am Chem Soc.* 2010; 132:1264. [PubMed: 20050651] (d) Lundin PM, Fu GC. *J Am Chem Soc.* 2010; 132:11027. [PubMed: 20698665]
5. (a) Allen AE, MacMillan DWC. *J Am Chem Soc.* 2011; 133:4260. [PubMed: 21388207] For examples of α -carbonyl arylation via SOMO catalysis see: (b) Conrad JC, Kong J, Laforteza BN, MacMillan DWC. *J Am Chem Soc.* 2009; 131:11640. [PubMed: 19639997]
6. (a) Yu J-Q, Wu H-C, Corey EJ. *Org Lett.* 2005; 7:1415. [PubMed: 15787520] (b) Denmark SE, Beutner GL, Wynn T, Eastgate MD. *J Am Chem Soc.* 2005; 127:3774. [PubMed: 15771512]
7. Kobayashi S, Sugiura M, Kitagawa H, Lam WL. *Chem Rev.* 2002; 102:2227. [PubMed: 12059268]
8. For reviews on diaryliodonium salts, see: (a) Merritt EA, Olofsson B. *Angew Chem, Int Ed.* 2009; 48:9052.(b)Varvoglis A. *The Organic Chemistry of Polycoordinated Iodine.* VCH PublishersNew York1992(c) Grushin VV. *Chem Soc Rev.* 2000; 29:315.
9. For examples of copper-catalyzed arylation reactions, see: (a) Phipps RJ, Grimster NP, Gaunt MJ. *J Am Chem Soc.* 2008; 130:8172. [PubMed: 18543910] (b) Phipps RJ, Gaunt MJ. *Science.* 2009; 323:1593. [PubMed: 19299616] (c) Duong HA, Gilligan RE, Cooke ML, Phipps RJ, Gaunt MJ. *Angew Chem, Int Ed.* 2010; 50:463.(d) Ryan JH, Stang PJ. *Tetrahedron Lett.* 1997; 38:5061.
10. For studies on the mechanism of copper-catalyzed arylation, see: (a) Lockhart TP. *J Am Chem Soc.* 1983; 105:1940.(b) Beringer FM, Geering EJ, Kuntz I, Mausner M. *J Phys Chem.* 1956; 60:141.
11. Boyd E, Coulbeck E, Coumbarides GS, Chavda S, Dingjan M, Eames J, Flinn A, Motevalli M, Northen J, Yohannes Y. *Tetrahedron Asymm.* 2007; 18:2515.
12. A range of other Lewis acids including Pd(OAc)₂, AuCl.PPh₃, AgOTf, Ni(OTf)₂, Sc(OTf)₃, and Zn(OTf)₂ gave < 2% product.
13. Typically non-catalytic processes require the use of fluoride ion or equivalent, see: (a) Chen K, Koser GF. *J Org Chem.* 1991; 56:5764.(b) Iwama T, Birman VB, Kozman SA, Rawal VH. *Org Lett.* 1999; 1:673. [PubMed: 10823199]
14. A range of other chiral ligands were employed all of which resulted in lower selectivity and or reactivity than bisoxazoline derived ligands e.g. BINOL (41% yield, 25% ee), DIOP (< 2% yield)
15. (a) Johnson JS, Evans DA. *Acc Chem Res.* 2000; 33:325. [PubMed: 10891050] (b) Evans DA, Scheidt, Johnston JN, Willis MC. *J Am Chem Soc.* 2001; 123:4480. [PubMed: 11457234] (c) Evans DA, Johnston JN. *Org Lett.* 1999; 1:865. [PubMed: 10823215] (d) Evans DA, Johnson DS. *Org Lett.* 1999; 1:5985.
16. By demonstrating a new and rapid route to (S)-naproxen via enantioselective catalysis, we do not intend to infer that this would be a competitive process for the known manufacturing route. Instead we illustrate this synthesis as a useful strategy to generate α -aryl carbonyl containing drug-like molecules for implementation in medicinal-agent testing programs.

17. During the course of this work we became aware that the Gaunt lab at Cambridge University were involved in similar studies. The Gaunt group graciously agreed to publish their results in a back-to-back format with our own results. We thank them for their collegiality and generosity.

Scheme 1.
Proposed Mechanism for Carbonyl α -Arylation

Table 1

Evaluation of CuBox Catalysts and Iodonium Counterions

entry	catalyst	X	Temp. (°C)	yield (%) ^a	ee (%) ^b
1	None	OTf	23	0	--
2	(CuOTf) ₂ PhMe	OTf	23	77	--
3	1	OTf	23	< 2	--
4	2	OTf	23	60	59
5	3	OTf	23	77	87
6	3	PF ₆	23	98	89
7	3	PF ₆	0	98	91
8 ^c	3	PF ₆	0	98	93

^a NMR yield.^b Determined by chiral HPLC analysis, absolute configuration determined by chemical correlation or by analogy.^c Performed with 1:1 toluene/CH₂Cl₂, Ox = oxazolidone.

Table 2

Scope of the Iodonium Aryl-Coupling Component^{a,b} ^a Absolute configuration assigned by chemical correlation or by analogy.^b Enantiomeric excess determined by chiral HPLC analysis of the isolated product.^c Performed at 0 °C.^d Symmetrical diaryliodonium hexafluorophosphate was used. Ox = oxazolidone.

Table 3

Scope of the Silylketene Acetal Coupling Component^{a,b}

$ \begin{array}{c} \text{OTBS} \\ \\ \text{X}-\text{C}=\text{C}-\text{Y} \\ \text{silylketene} \end{array} + \begin{array}{c} \text{PF}_6^- \\ \\ \text{Ph}-\text{I}-\text{Ph} \\ \text{diaryliodonium} \end{array} \xrightarrow[24 \text{ h, } 0^\circ\text{C}]{10 \text{ mol\% } \mathbf{3}, \text{ toluene/CH}_2\text{Cl}_2} \begin{array}{c} \text{O} \\ \\ \text{X}-\text{C}-\text{CH}(\text{Y})-\text{Ph} \\ \alpha\text{-aryl carbonyl} \end{array} $		
<p>1^c</p> <p>86% yield, 93% ee</p>	<p>2^d</p> <p>76% yield, 90% ee</p>	<p>3</p> <p>91% yield, 91% ee</p>
<p>4^{e,f}</p> <p>84% yield, 87% ee</p>	<p>5^e</p> <p>90% yield, 92% ee</p>	<p>6^{d,f}</p> <p>74% yield, 84% ee</p>
<p>7^g</p> <p>95% yield, 92% ee</p>	<p>8^f</p> <p>89% yield, 88% ee</p>	<p>9</p> <p>94% yield, 93% ee</p>
<p>10^h</p> <p>93% yield, 91% ee</p>	<p>11</p> <p>91% yield, 95% ee</p>	<p>12^{i,j}</p> <p>79% yield, 90% ee</p>
<p>13^k</p> <p>65% yield, 89% ee</p>	<p>14^{i,j}</p> <p>76% yield, 91% ee</p>	<p>15^{i,k}</p> <p>89% yield, 88% ee</p>

^a Absolute configuration assigned by chemical correlation or analogy.^b Enantiomeric excess determined by chiral HPLC analysis.^c Performed at 23 °C.^d Reaction performed at −5 °C with CH₂Cl₂/toluene (2:1) as solvent.^e Performed at −10 °C with CH₂Cl₂/toluene (2:1).^f 25 mol% **3** employed at 10 °C.^g Performed at −10 °C.^h Performed at 5 °C with CH₂Cl₂/toluene (2:1).ⁱ Performed at −20 °C.

^j Mesityl iodonium hexafluorophosphate was employed.

^k Performed at -10°C . Ox = oxazolidone.