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

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Supporting Information

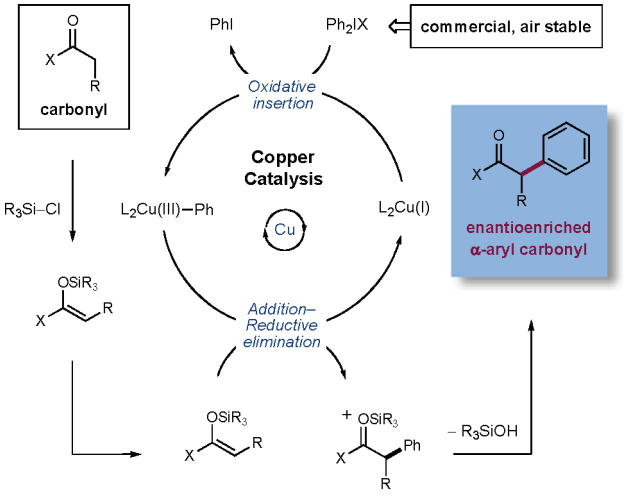
ABSTRACT: The enantioselective α-arylation of both lactones and acyl oxazolidones has been accomplished using a combination of diaryliodonium salts and copper catalysis. These mild catalytic conditions provide a new strategy for the enantioselective construction and retention of enolizable α-carbonyl 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 postreaction racemization when elevated temperatures or basic conditions are employed.[3] Notable recent progress has been made, however, through the work of (i) Fu and co-workers,[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]

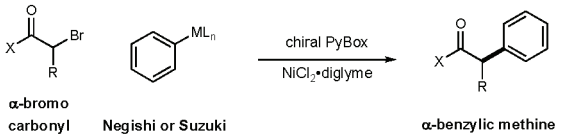
As an outgrowth of these latter studies, we postulated that a broadly expanded array of carbonyl systems might be readily accessible using chiral copper catalysts in the presence of iodonium salts with silylketene acetals (eq 3). As a critical advantage, this new mechanistic approach would allow access 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 postreaction racemization.

Design Plan. We elected to employ silylketene acetals and *N*, *O*-aminals as suitable enolic substrates, given their synthetic accessibility[6] 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 salt[8] 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

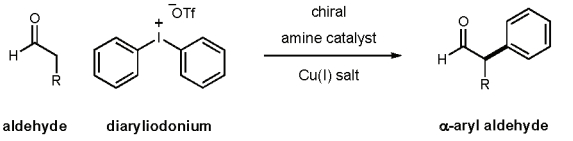
Scheme 1. Proposed Mechanism for Carbonyl α-Arylation



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



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



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

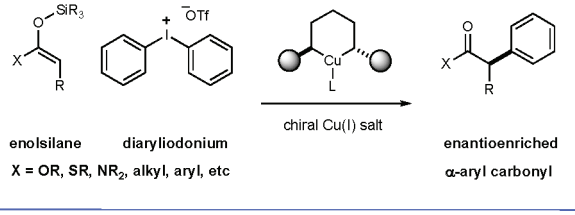


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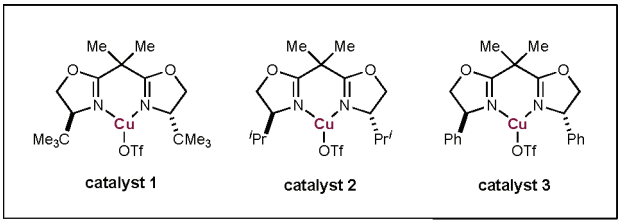
Table 1. Evaluation of CuBox Catalysts and Iodonium Counterions



entry	catalyst	X	temp (°C)	yield (%)[a]	ee (%)[b]
1	none	OTf	23	0	
2	$(CuOTf)_2PhMe$	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

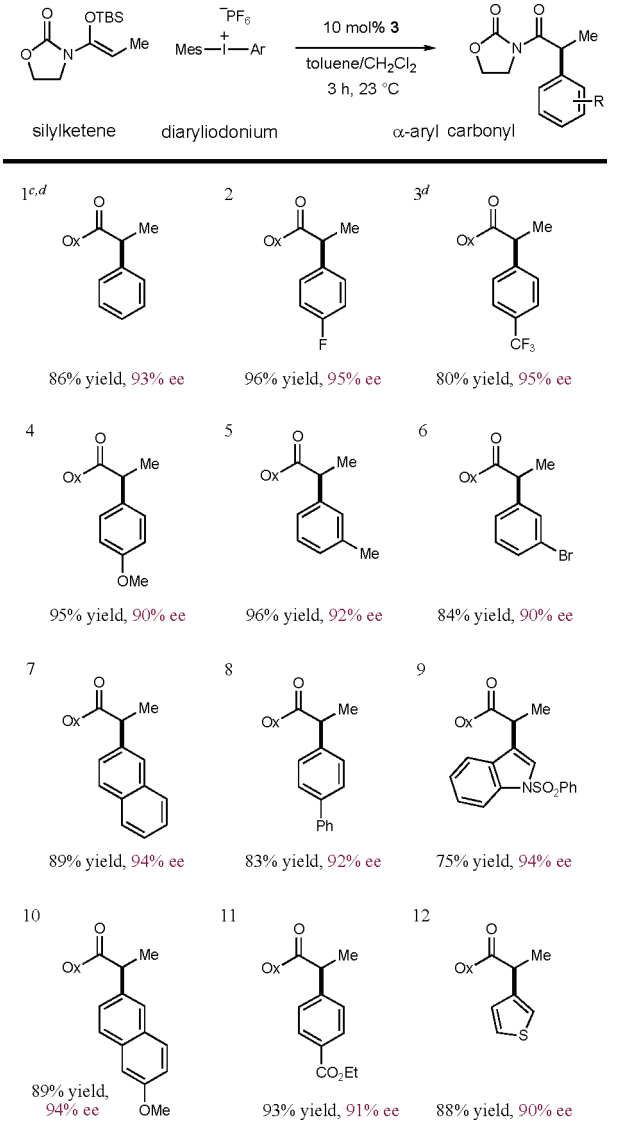
[a] NMR yield. [b] Determined by chiral HPLC analysis, absolute configuration determined by chemical correlation or by analogy. [c] Performed with 1:1 toluene/CH_2Cl_2. Ox = oxazolidone.

carbonyl product and regenerates the copper(I) catalyst. As was the case with our previous organocatalytic studies, we recognized that aryliodonium salts are nontoxic, 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 % $(CuOTf)_2$-PhMe, 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 noncatalytic 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 PF_6 counterion, using a mixed medium (CH_2Cl_2/toluene) and lowering the reaction temperature to 0 °C, resulted in further improvements to provide the α-phenyl

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.

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 nonsymmetrical 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,

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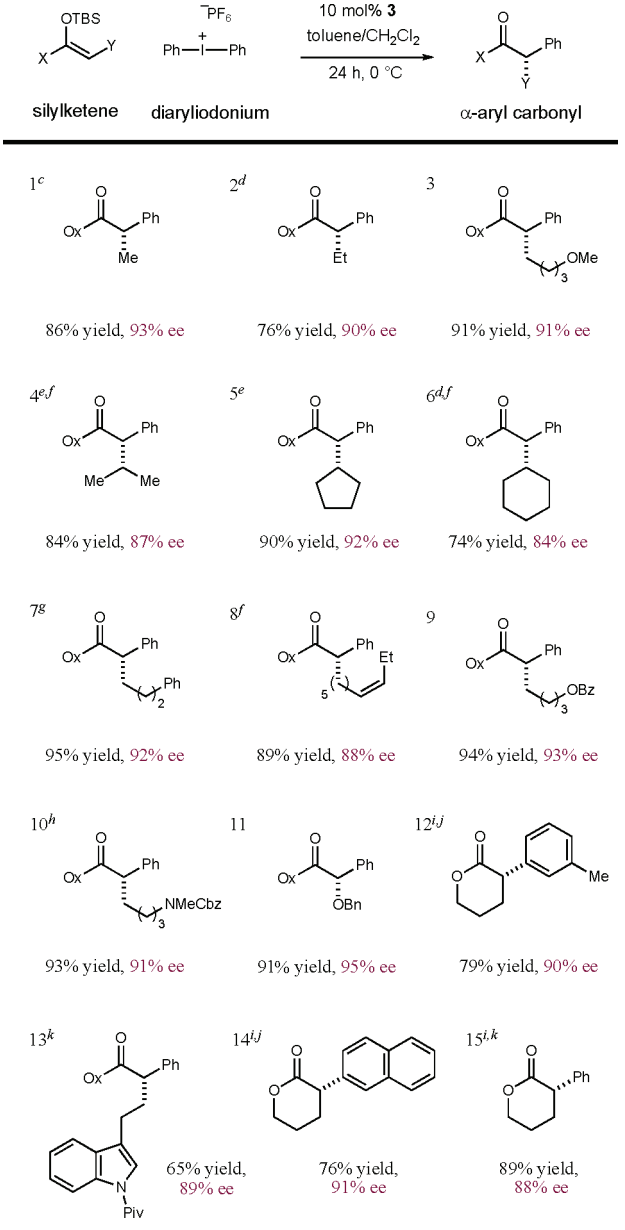
Table 3. Scope of the Silylketene Acetal Coupling Component[a,b]



[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 CH_2Cl_2/toluene (2:1) as solvent. [e] Performed at −10 °C with CH_2Cl_2/toluene (2:1). [f] 25 mol % **3** employed at 10 °C. [g] Performed at −10 °C. [h] Performed at 5 °C with CH_2Cl_2/toluene (2:1). [i] Performed at −20 °C. [j] Mesityl iodonium hexafluorophosphate was employed. [k] Performed at −10 °C. Ox = oxazolidone.

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 nonoxazolidone-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 nonsteroidal 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.

■ ASSOCIATED CONTENT

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

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(12) A range of other Lewis acids including $Pd(OAc)_2$, $AuCl \cdot PPh_3$, AgOTf, $Ni(OTf)_2$, $Sc(OTf)_3$, and $Zn(OTf)_2$ gave <2% product.

(13) Typically noncatalytic processes require the use of fluoride ion or equivalent, 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.

(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)

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(16) By demonstrating a new and rapid route to (*S*)-naproxen via enantioselective catalysis, we do not to 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.