Asymmetric Catalysis

DOI: 10.1002/anie.201205805

Chiral Aryl–Copper(III) Electrophiles: New Opportunities in Catalytic Enantioselective Arylations and Domino Processes**

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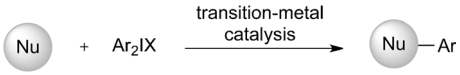
arylation · asymmetric catalysis · copper · domino reactions · iodonium salts

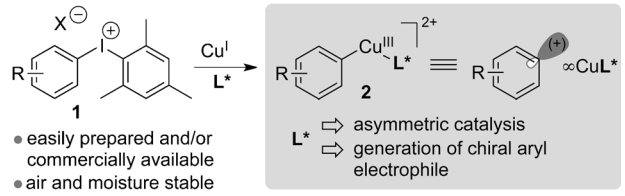
First isolated in the late 19th century, diaryliodonium salts (Ar_2IX) have undergone a rebirth as highly electrophilic alternatives to traditional arylating reagents in organic synthesis. This growing interest is not only due to their electrophilic character, but may also be explained by their ease of preparation, their air and moisture stability, and their lack of toxicity. Very recently, their ability to participate in transition-metal-catalyzed transformations has been uncovered, providing new perspectives and opportunities in this area (Scheme 1).[1]



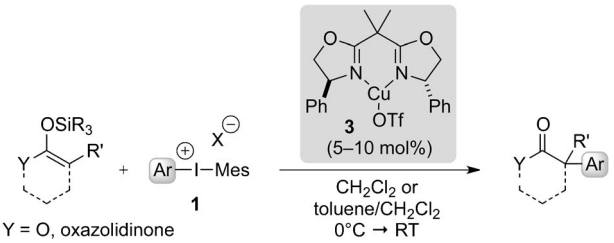
Scheme 1. Metal-catalyzed arylations employing diaryliodonium salts.

Gaunt and co-workers have pioneered the use of copper catalysts in combination with Ar_2IX to catalytically generate an electrophilic arylating reagent under mild conditions.[2] Its highly reactive nature enables the arylation of various latent nucleophiles, including (hetero)arenes,[2,3] alkenes,[4] enamines,[5] and silyl enol ethers.[6] It has been proposed that the reaction occurs via an aryl–Cu^{III} electrophile with aryl-cation-like properties.[3] The mechanism of these copper-catalyzed arylation reactions has been a subject of debate. However, a recent theoretical mechanistic study (supported by experimental results) has shed light on this topic.[7] Importantly, based on the intimate role of the copper species, the use of chiral ligands may provide access to chiral aryl "cation" synthons (**2**, Scheme 2).

The first example to validate this concept has been simultaneously reported by the groups of MacMillan and Gaunt, who accomplished challenging enantioselective α arylation reactions involving carbonyl derivatives.[6] Employing Cu^{I}–PhBox catalyst **3**, which is readily generated from commercially available materials, valerolactone and various N-acyl oxazolidinones were arylated in good to excellent yields and generally excellent enantioselectivity (Scheme 3). Based on Gaunt's previous work, nonsymmetrical aryl mesityl iodonium salts **1** were employed to allow the selective transfer of the desired arene, thus avoiding the loss of potentially elaborated reactant as ArI side product.



Scheme 2. Generation of chiral aryl electrophiles.



Scheme 3. Copper-catalyzed enantioselective α arylation of valerolactone and N-acyl oxazolidinones. Mes = 2,4,6-trimethylphenyl, Tf = trifluoromethanesulfonyl.

This α arylation reaction proceeds via an electrophilic (oxonium) intermediate that spontaneously decomposes to afford the desired carbonyl product. Alternatively, in a broader context, the ability to generate similar key asymmetric electrophilic intermediates **4** (Scheme 4) with this methodology may provide a wealth of opportunity for the design of a wide variety of subsequent transformations. For example, these arylated transient intermediates **4** may be exploited for cation-induced diastereoselective processes, such as cyclizations, cascade events, multicomponent reactions, etc. (Scheme 4).[8] Consequently, this approach could lead to

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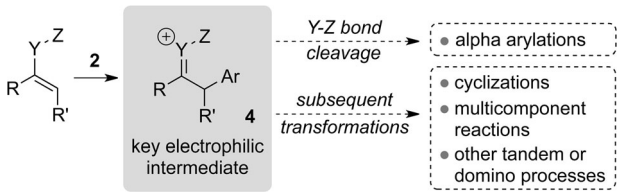
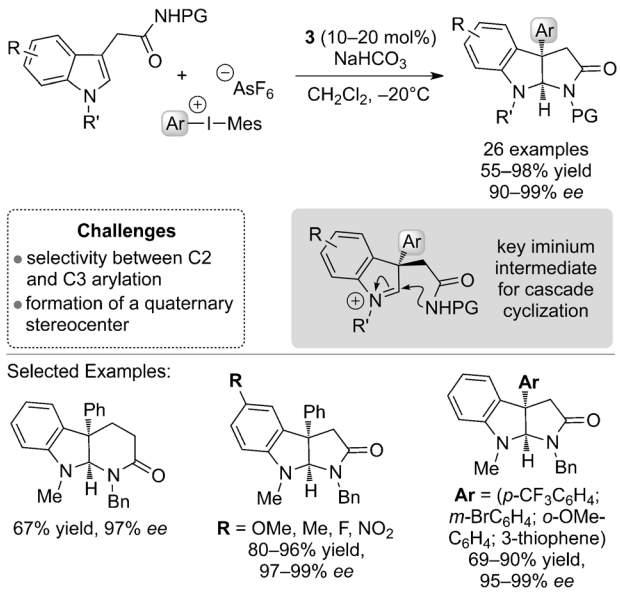
[**] We thank ANR Copenol for financial support.



Scheme 4. Potential applicability of the key transient intermediate **4** arising from Cu^{I}–PhBox-catalyzed arylation reactions.

promising opportunities for the selective generation of molecular complexity from simple prochiral building blocks.

As an initial proof of concept,[9] Zhu and MacMillan have investigated this strategy for the synthesis of aryl pyrroloindolines, a very important class of biologically active natural products (Scheme 5). The challenge in preparing these complex alkaloid structures lies in the design/elaboration of rapid synthetic routes that allow the efficient stereocontrol of



Scheme 5. Enantioselective synthesis of pyrroloindolines through an arylation/cyclization domino process. Bn = benzyl, PG = protecting group.

the quaternary center. With this objective in mind, the authors employed an enantioselective copper-catalyzed electrophilic arylation of indole nucleophiles at C3 to generate an asymmetric quaternary center for the first time using this chemistry. The presence of a pendant nucleophile enables a subsequent diastereoselective cyclization by addition to the transient iminium intermediate. Thus, this strategy not only allows the highly efficient formation of the quaternary center, but also the diastereoselective construction of a saturated heterocycle through a one-pot domino process.

At the outset of their studies, the authors evaluated the effect of the copper ligand on both regio- and enantioselectivity. Ligand-free conditions led to the exclusive arylation at the C2 position whereas the introduction of Box-type ligands had a significant influence on both C2/C3 selectivity and enantioselectivity. Similar to the previously developed α arylation processes, Cu^{I}–PhBox **3** proved optimal. Further improvement was noticed when the counterion (X) of the Ar_2IX salt was changed from OTf to AsF_6 and the temperature lowered to −20 °C (ratio of C2/C3 up to 1:40, 96 % yield, > 99 % *ee*). It should be noted that the reaction conditions are mild and operationally simple. Catalyst loadings of 10–20 mol % are typically required. The reaction appears to be broad in scope. Indeed, various aryl electrophiles are successfully transferred, including *ortho*-, *meta*-, and *para*-substituted electron-rich and electron-deficient arenes as well as thiophene. These can contain a wide range of functional groups, including ethers, esters, chlorides, and bromides. The presence of electron-rich and electron-deficient substituents at the C4 and C5 positions of the indole derivatives is well tolerated (80–96 % yield, 97–99 % *ee*). Interestingly, a piperidinyl indoline analogue can also be efficiently prepared under these conditions.

The generation of highly electrophilic chiral aryl "cation" equivalents provides novel opportunities for asymmetric arylation reactions that may initiate further domino processes. The possibility of using novel iodonium salt reagents[10] as well as more complex latent nucleophiles should offer interesting perspectives for the rapid and selective construction of intricate molecular structures.[11]

Received: July 23, 2012
Published online: September 23, 2012

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