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Copper-Catalyzed Oxidative Ring Closure and Carboarylation of 2-Ethynylanilides

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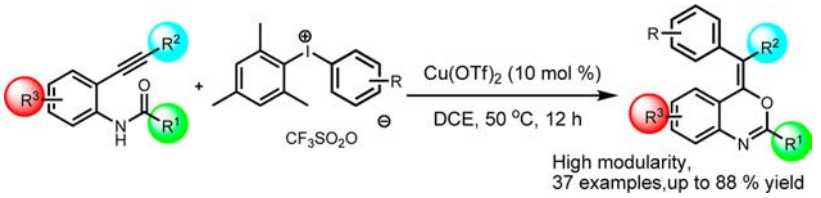
ABSTRACT



A new copper-catalyzed oxidative ring closure of ethynyl anilides with diaryliodonium salts was developed for the highly modular construction of benzoxazines bearing a fully substituted exo double bond. The oxidative transformation includes an unusual 6-*exo-dig* cyclization step with the formation of C−O and C−C bonds.

Synthesis and functionalization of aromatic and heteroaromatic systems through oxidative couplings are one of the most important areas of current organic syntheses.[1] Iodonium salts[2] are useful coupling partners, and their use enables the introduction of ethynyl[3] and aryl[4] moieties into the aromatic and heteroaromatic substrates via transition-metal-catalyzed oxidative transformations. In the presence of directing groups with the appropriate choice of metal catalyst, the incoming functional group can be directed selectively into the aromatic ring. As described by Daugulis, the palladium-catalyzed arylation of anilides gives *o*-arylacetanilides,[5] while copper-triflate catalyzed arylation of pivalanilides provides selectively meta-directed arylpivalanilides, as demonstrated by Gaunt and Phipps.[6] In most cases of the meta selective arylation, the pivalanilides bear

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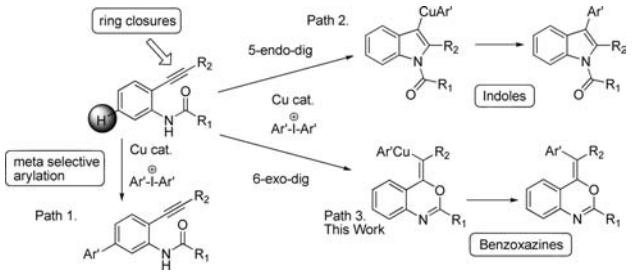
functional groups in the ortho position next to the protected amino group.

We aimed to examine the chemoselective functionalization of *o*-alkynylanilides with iodonium salts via copper-catalyzed oxidative coupling. The alkynylanilide motif offers multiple sites of reactivity, either with the anilide aromatic system or using the triple bond (Scheme 1). Considering the available synthetic pathways, meta-selective arylation[6] would provide meta-arylated ethynyl anilides (path 1) while the copper-catalyzed electrophilic carbofunctionalization of alkynes with diaryl iodonium triflates would form 2,3-diarylindoles (path 2) or benzoxazines with fully substituted exo double bond (path 3). A similar carboarylation strategy has been described by Gaunt and utilized for the synthesis of highly functionalyzed tetrasubstituted alkenyl triflates[7] and the construction of heterocycles and carbacycles.[8]

Transition-metal-accelerated ring closure with the participation of the triple bond can occur through two possible pathways: the preferred 5-*endo-dig* cyclization provides indoles[9] while in the presence of Au,[10] Pd,[11] or iodine[12] catalysts the relatively rare 6-*exo-dig* ring closure affords benzoxazines,[13] which have been shown to possess significant biological activity.[14]

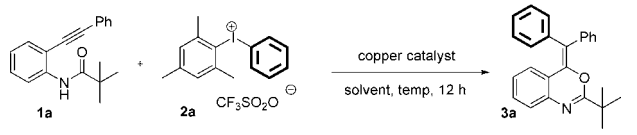
As a model substrate, 2-phenylethynylpivalanilide **(1a)** was reacted with phenylmesityliodonium triflate **(2a)** in the presence of transition-metal catalysts in various solvents (Scheme 2.). We found that the alkyne was transformed

Scheme 1. Possible Functionalization Modes of Alkynylanilides



with full conversion in the presence of 10 mol % of $Cu(OTf)_2$ in dichloroethane at 50 °C.[15] The reaction product was isolated in 59% yield and determined to be benzoxazine **3a** through NMR analysis. Other solvents (DCM, chloroform, DMF, dioxane, THF) and other catalysts ($Pd(OAc)_2$, AuCl, $CuSO_4$, CuI, $Cu(MeCN)_4OTf$) proved to be unsuitable for the efficient transformation of the pivalanilide.[16]

Scheme 2. Model Reaction for Optimization Studies



To examine the scope and limitation of the developed methodology, we reacted different alkynylanilides with phenylmesityliodonium triflate in the presence of 10 mol % of $Cu(OTf)_2$ in DCE at 50 °C (Scheme 3). The presence of a methyl group in any position of the arylethynyl part caused lower efficiency compared to the unsubstituted phenylethynyl derivative, but we obtained the desired compounds (**3b**–**d**) in 65%, 63%, and 44% yields, respectively. Arylethynylpivalanilides substituted with halogens (Br, Cl, F) were also transformed to the appropriate benzoxazines (**3e**–**i**) in 40–63% yield. Both strongly electron-withdrawing and -donating groups are compatible with the reaction. In the case of nitro and methoxy group we obtained the appropriate products (**3j** and **3k**) in 34 and 48% yield.

However, when the arylethynyl reactant was substituted with an ester group, benzoxazine **3l** was obtained in 65% yield. When an extended aromatic ring system such as naphthalene was present in the substrate, the appropriate benzoxazine (**3m**) was prepared in good yield (79%). In the case of these nonsymmetrically substituted diaryl derivatives, the NMR measurements showed the presence of mixture of geometric isomers.[17] Careful analysis revealed that the products undergo light-induced isomerization in solution.[18]

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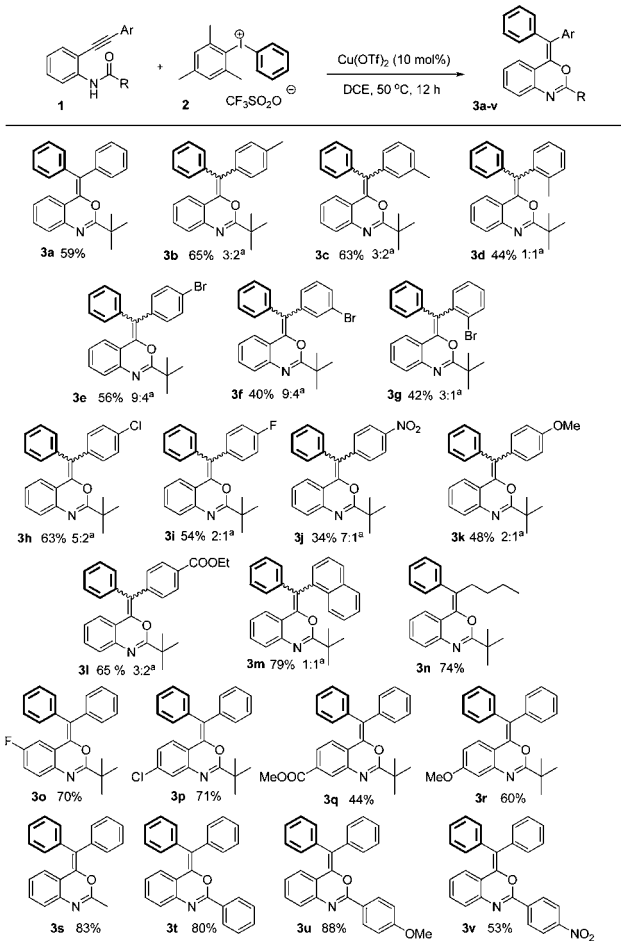
(15) 50 °C is the optimal temperature. For further details of optimization studies, see the Supporting Information.

(16) $Cu(OTf)_2$–DCE was found to be the optimal catalyst–solvent combination. For further details of optimization studies, see the Supporting Information.

Scheme 3. Copper-Catalyzed Coupling of Ethynylanilides with Phenyl Mesityl Iodonium Triflate[a]



[a] Reaction conditions: arylethynylanilide (0.3 mmol), iodonium salt (0.36 mmol), $Cu(OTf)_2$ (0.03 mmol), DCE (3 mL) at 50 °C. Percent yields of isolated product. (a) Molecular structure of the major isomers. Value refers to the major/minor ratio obtained from the NMR analysis of freshly prepared samples.[18]

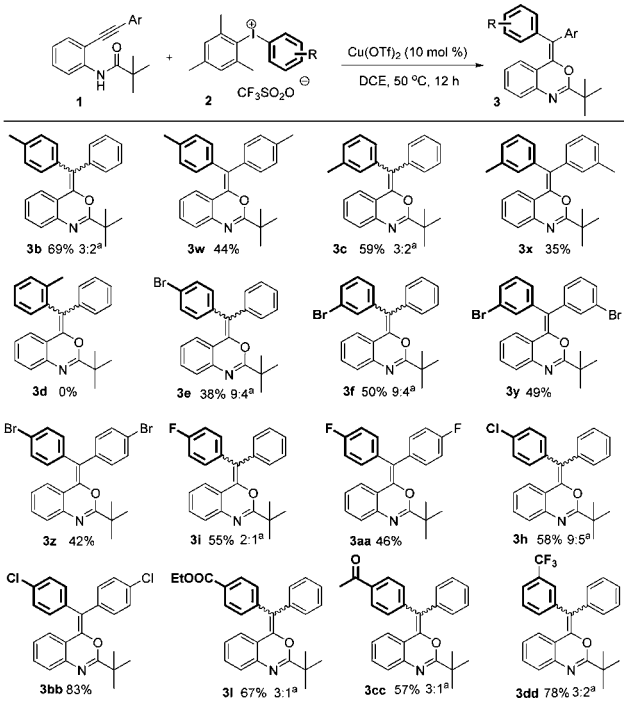
Exchanging the aryl group in the ethynyl substituent to a butyl group had no deleterious consequences on reactivity, and benzoxazine formation took place smoothly to afford the desired alkyl substituted product **3n** in good yield (74%) as single isomer.

The ring closure and the C−C bond formation were also performed with substrates bearing substituents on the anilide. The presence of halogens on the aromatic ring such as fluoro- and chloro- groups are well tolerated under the reaction conditions, and the reaction provides the products **3o** and **3p** in high yield (70% and 71%). The transformation also worked with functional groups with different electronic properties. With an electron-withdrawing ester functionality present in the anilide part, benzoxazine **3q** was isolated in 44% yield, and the methoxy derivative **3r** was obtained in 60% yield. When the *tert*-butyl group of the amide moiety was replaced with methyl, phenyl, *p*-methoxyphenyl, and *p*-nitrophenyl groups the reactions provided the appropriate benzoxazine products (**3s**−**v**) with efficiency similar to that pivalanilide **3a** (53−88%).

After examining the applicability of different ethynyl anilides we studied the reactivity of different arylmesityliodonium triflates in the transformation (Scheme 4). Utilizing the developed conditions, reaction of *m*- and *p*-tolyliodonium triflates with alkynylpivalanilides gave the products **3b**, **3c**, **3w**, and **3x** in 35−69% yields. However, ortho-substituted tolylethynyliodonium salt did not provide benzoxazine **3d**.[19] Iodonium salts with halogen (F, Cl, Br)-substituted aromatic rings reacted with similar efficiency and provide the appropriate products in 38−83% yields. The benzoxazines were obtained in good yield when ester (**3l**), acetyl (**3cc**), and trifluoromethyl (**3dd**) groups were present in the aryl part of the iodonium salt.

While NMR studies supported the formation of a benzoxazine product, unambiguous identification of

Scheme 4. Copper-Catalyzed Coupling of Arylethynyl Pivalanilides with Different Aryl Mesityl Iodonium Triflates[a]



[a] Reaction conditions: arylethynyl pivalanilide (0.3 mmol), iodonium salt (0.36 mmol), $Cu(OTf)_2$ (0.03 mmol), DCE (3 mL) at 50 °C. Percent yields of isolated product. (a) Molecular structure of the major isomers. Value refers to the major/minor ratio obtained from the NMR analysis of freshly prepared samples.[18]

(17) Structure and geometry of the major isomer of compound **3j** were determined by single-crystal X-ray diffraction measurements. See the Supporting Information. We found that the aryl groups originating from the acetylene derivative were in a cis position to the oxygen of the oxazine ring.

(18) Effects of time, temperature, light, and presence of acid on isomerization have been examined with NMR. For results of preliminary studies of the isomerization, see the Supporting Information.

(19) It is of note that the deleterious effect of any kind of ortho substituent on the aryl ring of the iodonium salt was observed in five additional cases (F, Cl, Br, CF_3, COOEt, not shown in Scheme 5).

product was achieved through a single-crystal X-ray diffraction study of a benzoxazine derivative (**3aa**) (Figure 1). X-ray analysis confirmed that benzoxazine derivatives are formed through 6-*exo-dig* ring closure and subsequent C−C bond formation on the exo double bond.

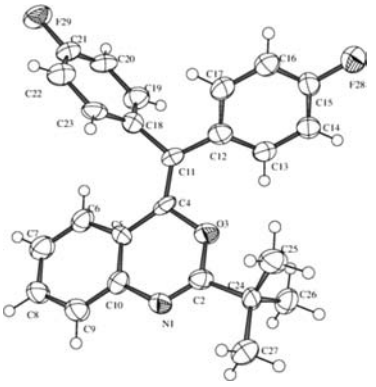
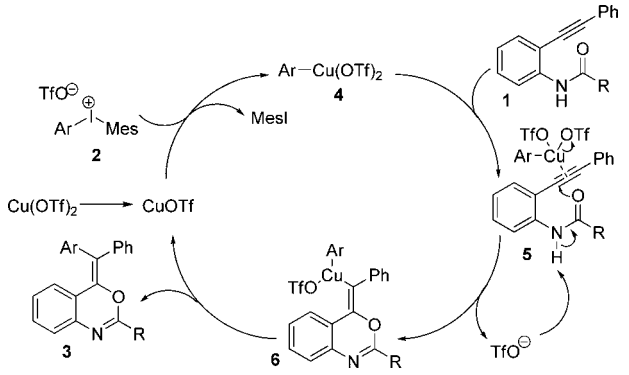


Figure 1. Molecular structure of compound **3aa**. The displacement ellipsoids are drawn at the 50% probability level, and heteroatoms are shaded.

Scheme 5. Proposed Mechanism for the Formation of the Major Geometric Isomer



Regarding a possible mechanism of the transformation, on the basis of similar copper-catalyzed oxidative couplings, we propose that the reaction starts with the formation of the Cu(I) species from $Cu(OTf)_2$ (Scheme 5). In the following step, the Cu(I) catalyst is oxidized by the iodonium salt (**2**) resulting the formation of $Ar-Cu(OTf)_2$ intermediate **(4)**. We suppose that this highly electrophilic Cu(III) species coordinates to the triple bond from the outer sphere and induces the ring closure.The lone pair of the amide nitrogen serves as the electron source, and the oxygen attacks to the sp carbon atom next to the aromatic ring of the anilide. With the lost of triflate anion from **5** alkenylcopper intermediate (**6**) forms, which is able to undergo reductive elimination providing the CuOTf catalyst and the benzoxazine product **3**.The overall transformation includes 6-*exo-dig* cyclization which is accompanied by the formation of new C−O and C−C bonds. This mechanistic path provides the major geometric isomers formed during the transformation where the aryl group derived from the arylacetylene is in the cis position to the oxygen atom of the benzoxazine ring.[20]

In conclusion, we have developed a new copper-catalyzed oxidative transformation for the construction of benzoxazine derivatives from substituted *o*-ethynylanilides and diaryliodonium salts. We determined that the oxidative transformation includes an unusual 6-*endo-dig* cyclization with the formation of a C−O bond, followed by C−C bond coupling in the exo double bond. The developed methodology enables the versatile synthesis of a new class of benzoxazines with high modularity due to the easily variable functional groups built in through the reaction sequence. Examination of the isomerization, detailed mechanistic studies, and the expansion of the principle of an *endo-dig* cyclization−C−C bond formation sequence catalyzed by copper for substrates containing a triple bond and nucleophilic sites are in progress in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Although the products could isomerize during the workup process, we cannot exclude completely the possibility of the formation of the minor isomer during the oxidative coupling. We suppose that the reaction would also take place via the inner sphere coordination of copper to the triple bond providing the minor geometric isomer or via vinyl cation formation as has been proposed very recently: see ref 8b.

The authors declare no competing financial interest.