Copper-Catalyzed Oxidative Ring Closure and Carboarylation of 2-Ethynyl-Anilides

Ádám Sinai, Ádám Mészáros, Tamás Gáti,[†] Veronika Kudar,[‡] Anna Palló,[‡] Zoltán Novák*

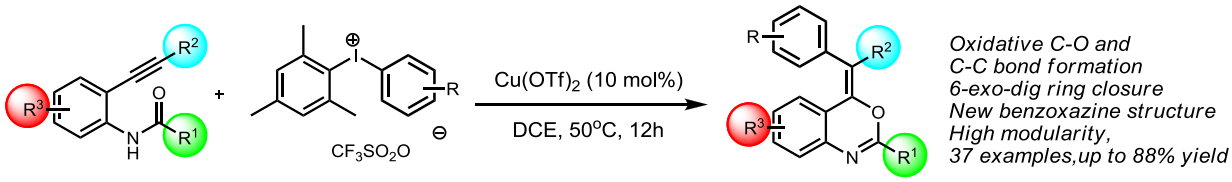
MTA-ELTE „Lendület" Catalysis and Organic Synthesis Research Group, Institute of Chemistry, Eötvös University, Pázmány Péter stny. 1/a H-1117 Budapest, Hungary

[†] *Servier Research Institute of Medicinal Chemistry, Záhony utca 7. H-1031 Budapest, Hungary*

[‡] *Research Centre for Natural Sciences, Hungarian Academy of Sciences, Pusztaszeri út 59-67. H-1025 Budapest, Hungary*

novakz@elte.hu

Received Date (will be automatically inserted after manuscript is accepted)



A new copper catalyzed oxidative ring closure of ethynyl anilides with diaryliodonium salts were developed for the highly modular construction of benzoxazines bearing 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 bond.

Synthesis and functionalization of aromatic and heteroaromatic systems through C-H activation and oxidative coupling are 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 it was described by Daugulis the palladium catalyzed arylation of anilides gives ortho aryl acetanilides,[5] while copper-triflate catalyzed arylation of pivalanilides provide selectively meta

[1] (a) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (b) Mei, T.-S.; Kou, L. Ma, S. Engle, K. M. Yu, J.-Q. *Synthesis* **2012**, *44*, 1778. (c) Liu, C. Zhang, H. Shi, W. Lei, A. *Chem. Rev.* **2011**, *111*, 1780; (d) Lyons, T. W.; Sanford, M. S *Chem. Rev.* **2010**, *110*, 1147–1169; (e) Daugulis, O.; Do, H.-Q.; Shabashov, O. *Acc. Chem. Res*. **2009**, *42*, 1074. (f) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (g) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (h) S. R. Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (i) Wencel-Delord, J.; Glorius, F. *Nature Chemistry* **2013**, *5*, 369.(j) Johnson, K. R. D.; Hayes, P. G. *Chem. Soc. Rev.* **2013**, *42*, 1947.

[2] (a) Hypervalent Iodine Chemistry in *Topics in Current Chemistry*, Vol 224 (Ed. Wirth, T. Springer, **2003**, pp.1-265); (b) Merritt, E. A.; Olofsson, B. *Angew. Chem. Int Ed.* **2009**, *48*, 9052. (c) Bouma, J. M.; Olofsson, B. *Chem. Eur. J.* **2012**, *18*, 14242. d) Merritt, E. A.; Carneiro, V. M. T.; Silva Jr., L. F.; Olofsson, B. *J. Org. Chem.* **2010**, *75*, 7416. e) Merritt, E. A.; Malmgren, J.; Klinke, F. J.; Olofsson, B. *Synlett* **2009**, 2277. (f) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602. (g) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett*, **2008**, 592. (h) Bielawski, M.; Zhu, M.; Olofsson, B.; *Adv. Synth. Catal.* **2007**, *349*, 2610.

[3] _(a) Li, Y.; Brand, J. P.; Waser, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 6743. (b) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112. (d) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165. (e) Brand, J. P.; Waser, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 7304. (f) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9346.

[4] (a) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 458. (b) Duong, H. A.; Gilligan, R. E.; Cooke, M. J.; Phipps, R. J.; Gaunt, M .J. *Angew. Chem. Int. Ed.* **2011**, *50*, 463. (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (d). Hickman, A. J ; Sanford, M. *ACS Catalysis*, **2011**, *1*, 170. (e) Storr, T. E.; Greaney, M. F. *Org. Lett*. **2013**, *15*, 1410. (f) Kalyani, D.; Deprez, N. R.; Desai, L. V. Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (g) Bedford, R. B.; Mitchell, C. J.; Webster, R. L. *Chem. Commun.* **2010**, *46*, 3095. (h) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 468.

[5] Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046.

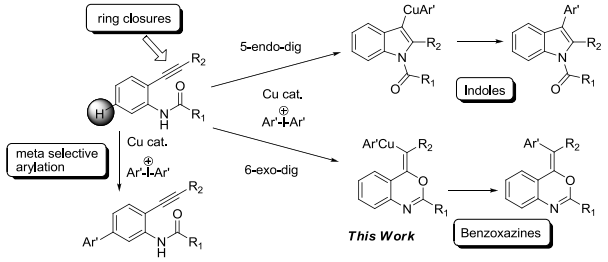
directed arylpivalanilides, as it was demonstrated by Gaunt and Phipps.[6] In most cases of the meta selective arylation, the pivalanilides bear functional groups in ortho position next to the protected amino group.

We aimed to examine the chemoselective functionalization of ortho 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.). Meta selective arylation would provide meta arylated anilides,[6] while the copper catalyzed electrophilic carbofunctionalization of alkynes with diaryl iodonium triflates forms highly functionalyzed tetrasubstituted alkenyl triflates or induce ring closure, which were demonstrated by Gaunt very recently.[7]

Transition metal-accelerated ring closure with the participation of the triple bond can induce the formation of heterocycles. The ring closure can occur through two possible pathways: the preferred 5-endo-dig cyclization provides indoles[8] while in the presence of Au,[9] Pd[10] or iodine[11] catalysts the relatively rare 6-exo-dig ring closure affords benzoxazines,[12] which have been shown to possess significant biological activity.[13]

Beyond economic reasons a copper-catalyzed site selective formation of benzoxazines would offer the additional advantage through the formation of a copper σ-complex during the ring closure, which may enable the

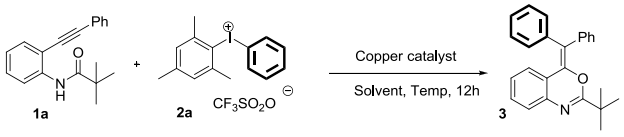
Scheme 1. Functionalization modes of alkynylanilides



formation of an additional C-C bond between the heterocycle and an aryl group via reductive elimination.

As a model substrate we chose 2-phenylethynyl-pivalanilide **(1a)** and reacted with phenyl-mesytyl iodonium triflate **(2a)** in the presence of transition metal catalysts in various solvents (Scheme 2.). We found that the alkyne was transformed with full conversion in the presence of 10 mol% $Cu(OTf)_2$ in dichloroethane at 50°C.[14] Other solvents (DCM, chloroform, DMF, dioxane, THF) and other catalysts ($Pd(OAc)_2$, AuCl, $CuSO_4$, CuI, $Cu(MeCN)_4OTf$) proved to be not suitable for the efficient transformation of the pivalanilide.[15] After isolation of the reaction product **(3a)** with 79% yield in the $Cu(OTf)_2$-catalyzed reaction we examined its structure using NMR and were able to exclude formation of a biaryl system via meta selective arylation and indole formation.

Scheme 2. Model reaction for optimization studies



[6] Phipps, R. J.; Gaunt, M. J. *Science,* **2009**, *323*, 1593.

[7] (a) Suero, M. G.; Bayle, E. D.; Collins, S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332. (b) Walkingshaw, A. J. Xu, W.;Suero, M. G. Gaunt M. J. *J. Am. Chem. Soc.* DOI: 10.1021/ja405972h.

[8] (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, 104, 2285. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. g) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.

[9] Hashmi, A. S. K.; Schuster, A. M.; Schmuck, M.; Rominger, F. *Eur. J. Org. Chem.* **2011**, 4595.

[10] (a) Saito, T.; Ogawa, S.; Takei, N.; Katsumura, N.; Otani, T. *Org. Lett.* **2011**, *13*, 1098. (b) Costa, M.; Cà, N. D.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 2469.

[11] Lee, W.-C.; Shen, H.-C.; Hu, W.-P.; Lo, W.-S.; Murali, C.; Vandavasi, J. K.; Wang, J.-J. *Adv. Synth. Catal.* **2012**, *354*, 2218.

[12] for synthesis of 4-alkylidene-4H-3,1-benzoxazines see: (a) Fresneda, P. M.; Bleda, J. A.; Sanz, M. A.; Molina P. *Synlett*, **2007**, 1541. (b) Kobayashi, K.; Okamura Y.; Konishi H. *Synthesis*, **209**, *41*, 1494. (c) Kobayashi, K. Okamura, Y.; Fukamachi, S.; Konishi, H. *Heterocycles,* **2010**, *81,* 1253.

[13] (a) Fensome, A.; Bender, R.; Chopra, R.; Cohen, J.; Collins, M. A.; Hudak, V.; Malakian, K.; Lockhead, S.; Olland, A.; Svenson, K.; Terefenko, E. A.; Unwalla, R. J.; Wilhelm, J. M.; Wolfrom, S.; Zhu, Y.; Zhang, Z.; Zhang, P.; Winneker, R. C.; Wrobel, J. *J. Med. Chem.* **2005**, *48*, 5092. (b) Hays, S. J.; Caprethe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpali, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060. (c) Patel, M.; Ko, S. S.; McHugh, R. J.; Markwalder, J. A.; Srivasta, A. S.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Seitz, S. P. *Bioorg. Med. Chem Lett.* **1999**, *9*, 2805. (d) Dias, N. ; Goossens, J. F.; Baldeyrou, B.; Lansiaux, A.; Colson, P.; Di Salvo, A.; Bernal, J.; Turnbull, A.; Mincher, D. J.; Bailly, C. *Bioconjugate Chem*. **2005**, *16*, 949. (e) Zhang, P.; Terefenko, T. A.; Fensome, A.; Zhang, Z.; Zhu, Y.; Cohen, J.; Winneker, R.; Wrobel, J.; Yardley, *J. Bioorg. Med. Chem. Lett.* **2002**, 12, 787.

[14] 50°C is the optimal temperature. Further details of optimization studies see Supporting Information

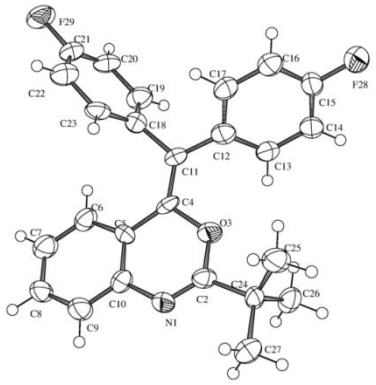
[15] $Cu(OTf)_2$-DCE was found to be the optimal catalyst-solvent combination. For further details of optimization studies see Supporting Information.

While NMR studies supported the formation of a benzoxazine product, unambiguous identification of product was achieved through a single crystal X-ray diffraction study of 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.

To examine the scope and limitation of the developed methodology, we reacted different alkynylanilides with phenylmesytyliodonium triflate in the presence of 10 mol% $Cu(OTf)_2$ in DCE at 50°C (Scheme 4).

The presence of methyl group in any position of the arylethynyl part caused lower efficiency compared to

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

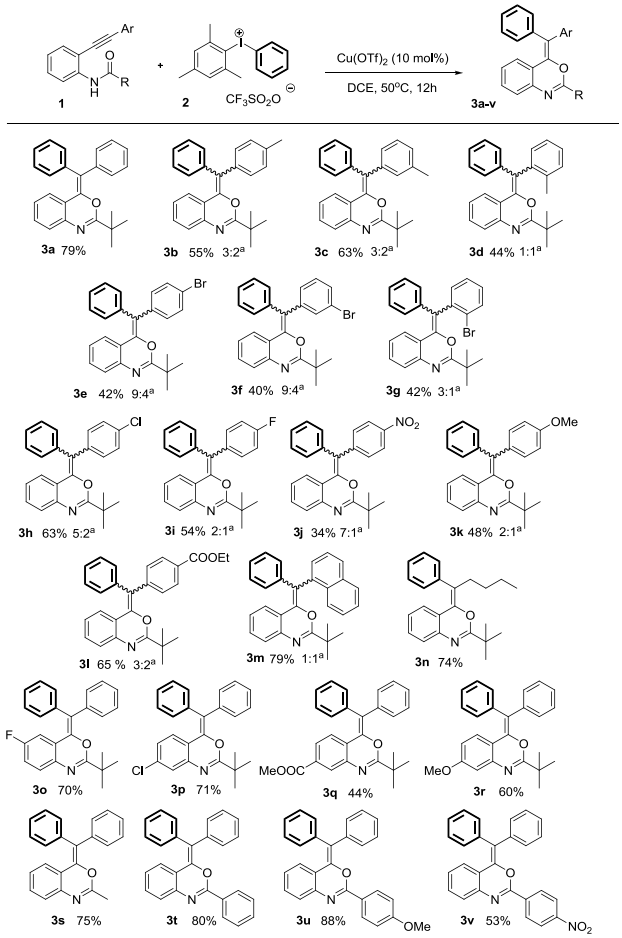


the unsubstituted phenylethynyl derivative, but we obtained the desired compounds **(3b, 3c, 3d)** in 55%, 63% and 44% yields respectively. Arylethynyl pivalanilides substituted with halogens (Br, Cl, F) were also transformed to the appropriate benzoxazines **(3e-i)** in 40-63% yield. Both strongly electron 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 ester group, benzoxazine **3l** was obtained with 65% yield. When an extended aromatic ring system such as naphthalene was present in the substrate, the appropriate benzoxazine **(3m)** was prepared with good yield (79%). Exchanging the aryl group in the ethynyl substituent to a butyl group had no deleterious consequences on reactivity, and benzoxazine formation took place smoothly affording the desired alkyl substituted product **3n** in good yield (74%).

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 was also worked with functional groups with different electronic properties. In case of electron withdrawing ester functionality present in the anilide part, benzoxazine **3q** was isolated in 44% yield, and the methoxy derivative **3r** was obtained with 60% yield. When the t-butyl group of the amide moiety was replaced with methyl, phenyl, p-methoxyphenyl and p-nitrophenyl group the reactions provided the appropriate benzoxazine products **(3s-v)** with the similar efficiency to pivalanilide **3a** (53-88%).

After examining the applicability of different ethynyl anilides we studied the reactivity of different aryl-mesityl iodonium triflates in the transformation (Scheme 5.). Utilizing the developed conditions, reaction of meta and para tolyliodonium triflates with alkynyl pivalanilides gave the products **3b, 3c, 3w** and **3x** with 35%-69% yields. However, ortho substituted tolylethynyl iodonium salt did not provide benzoxazine **3d**.

Scheme 4. Copper catalyzed coupling of ethynylanilides with phenyl mesityl iodonium triflate.

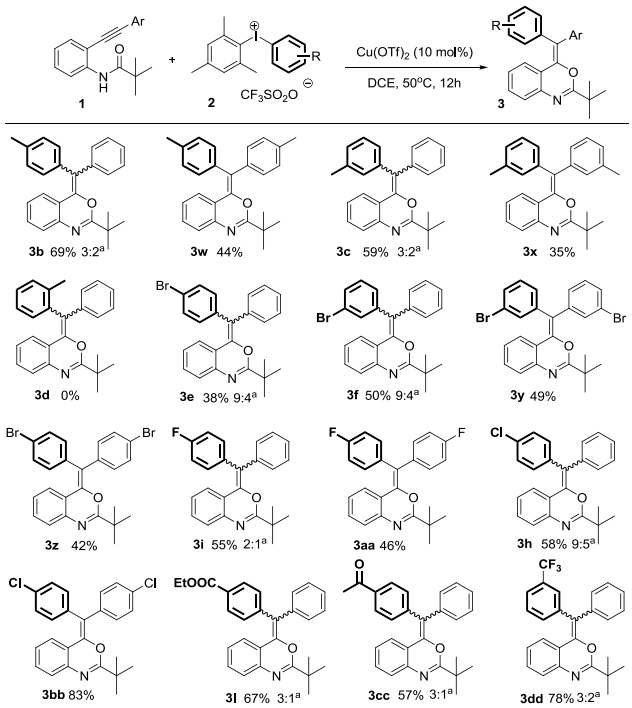


Reaction conditions: Arylethynylanilide (0.3 mmol), iodonium salt (0.36 mmol), $Cu(OTf)_2$ (0.03 mmol), DCE (3 ml) at 50°C. % Yields of isolated product. [a] The scheme indicates the molecular structure of the major isomers. Value refers to the time dependent major:minor ratio obtained from the NMR analysis of freshly prepared samples. Isomerization was observed in the NMR solvent.

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 5 additional cases (F, Cl, Br, CF_3, COOEt, not shown in Scheme 5.). Iodonium salts with halogen (F, Cl, Br) substituted aromatic rings reacted with similar efficiency and provide the appropriate products with 38%-83%. The benzoxazines were obtained with good yield when ester **(3l)**, acetyl **(3cc)** and trifluoromethyl **(3dd)** groups were present in the aryl part of the iodonium salt.

After the exploration of the substrate scope, we considered the product structure with regard to the

Scheme 5. Copper catalyzed coupling of arylethynyl pivalanilides with different aryl mesityl iodonium triflates.

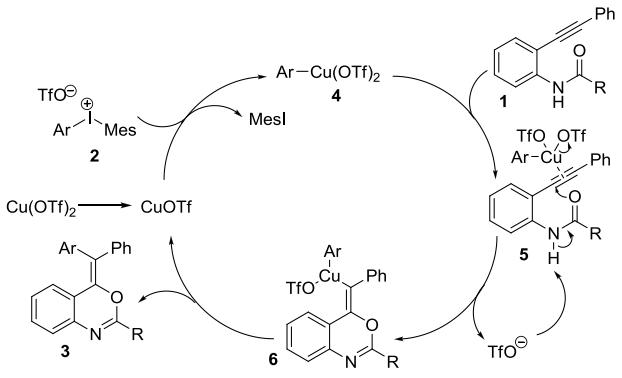


Reaction conditions: Arylethynyl pivalanilide (0.3 mmol), iodonium salt (0.36 mmol), $Cu(OTf)_2$ (0.03 mmol), DCE (3 ml) at 50°C. % Yields of isolated product. [a] The scheme indicates the molecular structure of the major isomers. Value refers to the time dependent major:minor ratio obtained from the NMR analysis of freshly prepared samples. Isomerization was observed in the NMR solvent.

geometry of the substituted double bond. In case of all the non-symmetrically substituted diaryl derivatives the NMR measurements showed the presence of mixture of geometric isomers.[16] Careful analysis revealed that the products are isomerizing in NMR solvents.[17]

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 Cu(I) species from $Cu(OTf)_2$ (Scheme 6.). 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 group from copper intermediate **6** forms, which is able to undergo

Scheme 6. Proposed mechanism for the formation of the major geometric isomer



reductive elimination providing the Cu(I) 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 bond. This mechanistic path provides the

[16] . Structure and geometry of compound **3j** we were determined single crystal X-ray diffraction measurements. See Supporting Information We found that the aryl group originated from the acetylene derivative were in Z position to the oxygen of the oxazine ring.

[17] During the storage of compound **3j** in $CDCl_3$ for 24 hours the isomeric ratio was changed from 10:1 to 2:1. The isomerization phenomenon was also observed in case of all the non-symmetrically substituted products.

major geometric isomers formed during the transformation where the aryl group derived from the arylacetylene is in *Z* position to the oxygen atom of the benzoxazine ring.[18]

In conclusion we have developed a new copper-catalyzed oxidative transformation for the construction of benzoxazine derivatives from substituted ortho ethynyl anilides and diaryl iodonium salts. We determined that the oxidative transformation includes an unusual 6-endo-dig cyclization with the formation of 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. Detailed mechanistic studies and the expansion of the principle of endo-dig cyclization-C-C bond formation sequence catalyzed by copper for substrates containing triple bond and nucleophilic sites are in progress in our laboratory.

Acknowledgment This project was supported by the "Lendület" Research Scholarship of the Hungarian Academy of Sciences, and by OTKA-NKTH (CK 80763). The Authors also thank to Prof. Tim Peelen for the proofreading of this manuscript.

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

[18] Although, there are strong proof of the isomerization of the products after the isolation 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 it is proposed very recently: Walkingshaw, A. J. Xu, W.;Suero, M. G. Gaunt M. J. *J. Am. Chem. Soc.* DOI: 10.1021/ja405972h