Zinc–gold cooperative catalysis for the direct alkynylation of benzofurans

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Abstract
The direct alkynylation of benzofurans was achieved for the first time using the hypervalent iodine reagent 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (TIPS-EBX) based on the cooperative effect between a gold catalyst and a zinc Lewis acid. High selectivity was observed for C2-alkynylation of benzofurans substituted with alkyl, aryl, halogen and ether groups. The reaction was also successful in the case of the more complex drug 8-methoxypsoralen (8-MOP).

Introduction
Benzofurans are important heterocycles frequently encountered in both bioactive compounds and organic materials (Figure 1). For example, members of the furocoumarin class of natural products including psoralen (1), 8-methoxypsoralen (2) and angelicin (3) can cross-link with DNA upon light irradiation. They have consequently been used for the treatment of skin diseases such as cancer or psoriasis [1-4]. The natural product coumestrol (4) is found especially in soy beans and has estrogenic activity [5]. Synthetic bioactive compounds containing benzofurans are also important, as exemplified by amiodarone (5), as antiarrhythmic drug [6,7]. Finally, benzofurans have also emerged recently as important structural elements for organic materials, such as the organic transistor 6 [8].

Due to the importance of benzofurans, the discovery of new efficient methods for their synthesis and functionalization is an intensive field of research [9-11]. Especially interesting would be methods allowing the direct and regioselective C–H functionalization of benzofurans [12]. In this context, the introduction of an alkyne would be particularly useful, as acetylenes are important building blocks in synthetic chemistry, chemical biology and materials science [13]. Nevertheless, to the best of our knowledge, the direct alkynylation of benzofurans is still an unknown process.

Since 2009, our group has developed a mild gold-catalyzed [14-17] method for the alkynylation of electron-rich aryls such as...
Scheme 1: Zinc–gold catalyzed C2-alkynylation of benzofurans.

Table 1: Optimization of the alkynylation of benzofuran (7a).

| Entry | Equiv 8 | Additive 8 | T [°C] | Yield 8 |
|-------|---------|------------|--------|---------|
| 1     | 1.2     | –          | 23     | <5%     |
| 2     | 1.2     | –          | 60     | <5%     |
| 3     | 1.2     | TFA        | 60     | 42%     |
| 4     | 1.2     | Zn(OTf)2  | 60     | 56%     |
| 5     | 1.2     | Zn(OTf)2c | 60     | <5%     |
| 6     | 1.2     | Zn(OTf)2d | 40     | 48%     |
| 7     | 1.2     | Zn(OTf)2  | 82     | 36%     |
| 8     | 2       | Zn(OTf)2  | 60     | 75%     |
| 9     | 2       | Zn(OTf)2d | 60     | 37%     |
| 10    | 2       | Zn(OTf)2g | 60     | 0%      |
| 11    | 2       | Zn(NTf)2  | 60     | 57%     |
| 12    | 2       | Yb(OTf)3  | 60     | 62%     |

8Reaction conditions: 7a (0.20 mmol) and AuCl (0.01 mmol) in acetonitrile (0.8 mL) under air for 26 h, isolated yield; a same amount as 8; b without gold catalyst; d0.2 equiv; d4.0 equiv.
The scope of the reaction was then investigated (Scheme 2). Substitution by diverse functional groups was first examined on the C5 position. An electron-rich methoxy group was well tolerated, giving the desired alkynylation product 9b in 73% yield. The reaction was also successful with a bromide substituent (product 9c), making the method orthogonal to classical cross-coupling chemistry [30]. In presence of an aryl or an alkyl substituent, alkynylation was also obtained in 72% and 50% respectively (products 9d and 9e). Benzofurans substituted at the C7 position could also be used, as demonstrated by the efficient formation of alkynes 9f and 9g. In contrast, when 7-methoxybenzofuran (7j) was used, no C2 alkynylation product could be isolated. Instead, a mixture of C4 and C6 alkynyated benzofurans 9j and 9j' was obtained (Scheme 3) [31]. Substitution on the furan ring was also possible at the C3 position (product 9h), but the use of 2-methylbenzofuran (7i) led to very a low yield in the alkynylation reaction.

Finally, we wondered if the alkynylation method could also be successful in the case of more complex benzofuran-containing natural products and drugs. We were pleased to see that the alkynylation of 8-methoxypsoralen (2) was indeed possible. The major product 10 bearing the acetylene group at the C5’ position was obtained in 37% yield (Scheme 4) [32]. Although the yield was still moderate, this was one of the first examples of direct alkynylation of a marketed drug. It also gave access in a single step to an interesting furocoumarin derivative with an extended chromophore, which could be important for phototherapy.

Mechanistically, the reaction could proceed either via π-activation of the triple bond by the gold catalyst followed by conjugate addition of the benzofuran, α-elimination and 1,2-shift, or oxidative addition of TIPS-EBX (8) onto the gold catalyst (either at the Au(I) or Au(0) oxidation level) followed by elec-
trophilic auration and reductive elimination [33]. The role of the zinc Lewis acid is not completely clear at this stage, but it may act by complexing the carboxylate group of the hypervalent iodine reagent, enhancing its electrophilic reactivity [19,34]. In fact, a complete shift of the $^1$H NMR signals of TIPS-EBX (8) was observed when Zn(OTf)$_2$ was added, whereas no signal shift was observed when mixing the Lewis acid and benzofuran (7a) [35].

In conclusion, the first direct alkylation method of benzofurans has been developed. Key for success was a cooperative effect between a gold catalyst and a zinc Lewis acid, together with the use of the hypervalent iodine reagent TIPS-EBX (8). Preliminary results obtained with 8-methoxypsoralen (2) demonstrated that the reaction could also be applied to more complex furcoumarin natural products.

**Experimental**

General procedure for the alkylation of benzofurans: TIPS-EBX (8, 342 mg, 0.800 mmol, 2.0 equiv), AuCl (4.6 mg, 0.020 mmol, 0.050 equiv), Zn(OTf)$_2$ (289 mg, 0.800 mmol, 2.0 equiv) and benzofuran 7 (0.40 mmol, 1.0 equiv) were added into CH$_3$CN (2.0 mL) under air. The mixture was stirred for 26 hours at 60 °C. Then the mixture was concentrated in presence of silica gel and purified directly by column chromatography.

Supporting Information

Supporting Information File 1
Experimental part.
[http://www.beilstein-journals.org/bioc/content/supporting/1860-5397-9-204-S1.pdf]

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   See for a review on electrophilic alkynylation.
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   See for a recent example of cooperative gold-zinc catalysis.
29. No product was obtained with strongly electron-withdrawing substituents, such as cyanide.
30. A 5:1 mixture of non-separable products was obtained, which prevented complete assignment of the structure of the major regioisomer.
31. The regiochemistry of the alkynylation was determined by 2D NMR experiments after removal of the silyl protecting group on alkyne 10.
   One other non-identified isomer was observed in the crude mixture by 1H NMR (yield < 5%).
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34. See Figure S1 in the Supporting Information File 1.

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