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Ethynyl Benziodoxolones for the Direct Alkynylation of Heterocycles: Structural Requirement, Improved Procedure for Pyrroles, and Insights into the Mechanism

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Abstract: This report describes a full study of the gold-catalyzed direct alkynylation of indoles, pyrroles, and thiophenes using alkynyl hypervalent iodine reagents, especially the study of the structural requirements of alkynyl benziodoxolones for an efficient acetylene transfer to heterocycles. An improved procedure for the alkynylation of pyrroles using pyridine as additive is also reported. Nineteen alkynyl benziodoxol(on)es were synthesized and evaluated in the direct alkynylation of indoles and/or thiophenes. Bulky silyl groups as acetylene substituents were optimal. Nevertheless, transfer of aromatic acetylenes to thiophene was achieved for the first time. An accelerating effect of a methyl substituent in both the 3- and 6-position of triisopropylsilylethynyl-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) on the reaction rate was observed. Competitive experiments between substrates of different nucleophilicity, deuterium labeling experiments, as well as the regioselectivity observed are all in agreement with electrophilic aromatic substitution. Gold(III) 2-pyridinecarboxylate dichloride was also an efficient catalyst for the reaction. Investigations indicated that gold(III) could be eventually reduced to gold(I) during the process. As a result of these investigations, a π activation or an oxidative mechanism are most probable for the alkynylation reaction.

Keywords: alkynylation · gold · heterocyclic compounds · iodine · reactivity

Introduction

(Hetero)aryl acetylenes are widespread structures in organic synthesis, both as synthetic intermediates and targets.[1] The unique reactivity of acetylenes allows a wide range of synthetic modifications through nucleophilic addition, cycloaddition, cycloisomerisation, reduction, oxidation, and cross-coupling. In addition, heteroaryl acetylenes find application in the material sciences. Both oligomeric[2] and polymeric[3] heteroaryl acetylenes can be used as molecular wires, liquid crystals, sensors, and have many other important applications.

Two of the most frequently used methods for alkyne synthesis are triple bond formation from carbonyl compounds[4] and acetylene transfer using cross-coupling reactions such as the Sonogashira reaction.[5] Despite the widespread use of these reactions, both need pre-functionalization of the heterocyclic ring, which could be challenging in complex structures where achieving high chemo- and regioselectivity is difficult. Furthermore, the number of linear steps required to reach the target is also increased. As a result, more direct methods to access heteroaryl acetylenes through C–H bond alkynylation would be highly desirable.

Numerous strategies for aryl–aryl bond formation directly from unactivated C–H bonds have been developed.[6] In contrast, catalytic direct alkynylation methods were scarce up to 2009.[7] In 2002, Yamaguchi et al. first reported the *ortho* alkynylation of phenols and anilines using $GaCl_3$ and chloroacetylenes.[8] In 2007, Gevorgyan and co-workers developed the first palladium-catalyzed direct alkynylation of N-heterocycles using bromoacetylenes.[9] However, since 2009, the situation has radically changed[10] and alkynylation of azoles,[11] electron-rich aromatics[12,13] and pentafluoroarenes[11d,14] have subsequently been reported. Nevertheless, there still exists a paucity of general methods that can be applied to a range of different classes of aryl substrates. Most of the strategies are based on the use of halogenoacetylenes (mostly bromoacetylenes). Additionally, there are a few examples of reactions using directly terminal acetylenes but these processes have usually a limited scope.[11d,12c,d,14] In order to develop more efficient and general methodologies, we decided to focus on more reactive alkynyl iodonium salts, which were studied intensively 20 to 30 years ago.[15] Due to the excellent leaving group ability of PhI, alkynyl iodonium salts proved to be strongly electrophilic and reacted with keto esters, cuprates and heteroatom nucleophiles. However, alkynyliodonium salts were never used for the alkynylation of nucleophilic (hetero)aromatics.

In 2009, we reported the first example of the use of a hypervalent iodine reagent for the gold-catalyzed direct alkynylation of indoles and pyrroles (Scheme 1).[13a] Classical al-

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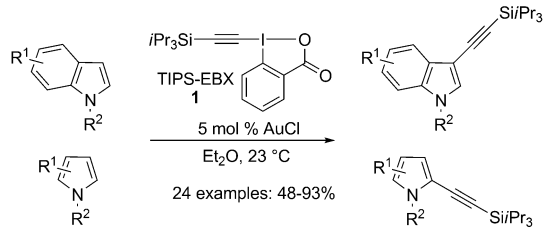
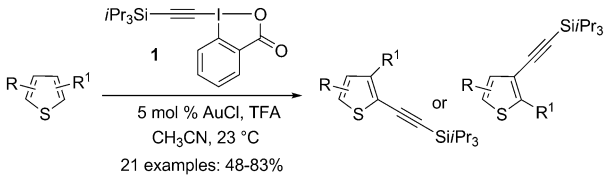


Scheme 1. Direct alkynylation of indoles and pyrroles.

kynyl iodonium salts derived from iodobenzene were not successful in this transformation, and we introduced triisopropylsilylethynyl-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **1**) as an efficient acetylene transfer reagent.[16,17] In the case of indoles, the process showed good to excellent yields, high C3 regioselectivity, a broad functional group tolerance and afforded easily deprotectable silyl acetylenes. For pyrroles, C2-alkynylated products were obtained in moderate to good yields. Importantly, this report was the first example of the combination of gold and hypervalent iodine for direct alkynylation.[18]

Building upon this work, we later reported the first direct alkynylation of thiophenes using TIPS-EBX (**1**) (Scheme 2).[13b] Primary investigation using the conditions



Scheme 2. Direct alkynylation of thiophenes.

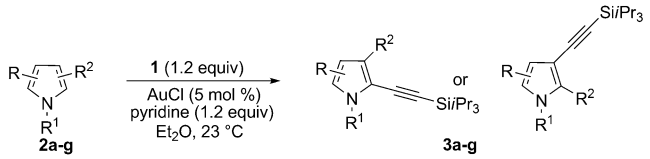
for indole alkynylation afforded only low yields. This is in accordance with the lower nucleophilicity of thiophene. Fine tuning of reaction conditions was not successful to improve the yields, but the discovery of a cooperative effect between the gold catalyst and a Brønsted acid (trifluoroacetic acid (TFA)) allowed the direct alkynylation of a broad range of thiophenes in 48–83% yield. The reaction was applied to a wide range of building blocks for material sciences.

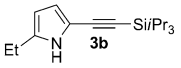
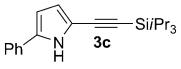
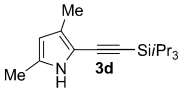
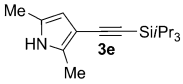
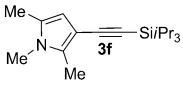
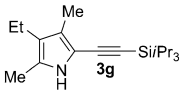
Herein, we would like to report a further expansion of our work, including 1) Improved conditions for the alkynylation of pyrroles, resulting in enhanced yields (from 48–79% to 56–97%); 2) The first in depth studies of the influence of the reagent structure on reaction rate and efficiency. In the course of these studies, many unprecedented benziodoxolone reagents were synthesized and their structures studied by X-ray crystallography. Several reagents with reactivity superior to TIPS-EBX were discovered, and 3) Finally, further investigations toward the elucidation of the reaction mechanism are reported, including qualitative structure–reactivity relationships, kinetic isotope effects, intermediate-trapping experiments, and studies on Au^{III} versus Au^{I} catalysis.

Results and Discussion

Improved procedure for pyrrole alkynylation: In our previous work in the AuCl-catalyzed alkynylation of indoles and pyrroles, yields were usually lower for the latter (48–79%).[13a] In particular, for applications in the functionalization of more complex valuable pyrroles, a more efficient protocol would be highly desirable. Pyrroles are very electron-rich heterocycles, and are sensitive to strong Lewis and Brønsted acids. We hypothesized that a competitive degradation of pyrroles by traces of HCl generated from AuCl during the reaction was at the origin of the lower yields observed. The mild base pyridine was consequently added to quench adventitious acid in the reaction mixture. In fact, the addition of 1.2 equivalents of pyridine led to a significant increase in product yields (Table 1). The yield of the C2 alkynylation of *N*-methylpyrrole (**2a**) was increased from 48 to 71% (entry 1, Table 1). Interestingly, the C2/C3 selectivity was increased from 1.9:1 to 4.2:1. The yield with 2-ethyl (**2b**) and 2-phenyl (**2c**) pyrrole were enhanced from 58 and 60%, to 81 and 84%, respectively (entries 2–3, Table 1). Of note, the alkynylation of 2,4-dimethylpyrrole (**2d**) did not

Table 1. Improved alkynylation of pyrroles.



Entry	Product	Yield [%][a]
1[b]		71–17 (48–25)
2		81 (58)
3		84 (60)
4		56[c]
5		73 (59)
6		97
7		83 (48)

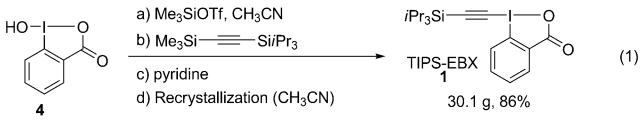
[a] Reaction conditions: pyrrole **2** (0.20 mmol), TIPS-EBX (**1**) (0.24 mmol), pyridine (0.24 mmol) and AuCl (0.01 mmol) in Et_2O (4 mL) at 23 °C under air for 12–15 h. Isolated product yields after column chromatography. Yields without addition of pyridine are given in parenthesis. [b] Yields based on TIPS-EBX (**1**) with three equivalents of *N*-methylpyrrole (**2a**). [c] 15% of bis-alkynylated product was isolated. 73% yield of bis-alkynylated product could be obtained when three equivalents of TIPS-EBX (**1**) were used.

only afford 56% of monoalkynylated product but also 15% of bis alkynylation product (entry 4, Table 1). In this case, 73% yield of the bis-alkynylated product was obtained using three equivalents of TIPS-EBX (**1**).

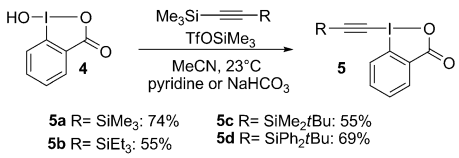
2,5-Disubstituted pyrroles were also efficiently alkynylated (entries 5 and 6, Table 1). A nearly quantitative transformation was obtained with 1,2,5-trimethylpyrrole (**2f**; entry 6, Table 1). In our previous work, trisubstituted pyrrole **2g** was a particularly challenging substrate and the desired product was obtained only in 48% yield, probably due to the three electron-donating substituents on the heterocycle. In the presence of pyridine, however, the alkynylation product was obtained in 83% yield (entry 7, Table 1), which is very promising for the use of the method for especially challenging electron-rich pyrroles. Our original motivation for the use of pyridine was its basic properties. However, pyridine is also a potential ligand for gold. To distinguish between these two possible effects, we then examined di-*tert*-butylpyridine as additive. To our surprise, no increase in yield was observed. This result might indicate that pyridine is acting as a ligand and not as a base, and the lower yields obtained in the absence of pyridine was due to a higher Lewis acidity of the gold catalyst.

Synthesis and study of alkynyl benziodoxolones: Essential for the success of the alkynylation reaction was the replacement of established alkynyliodonium salts by EBX-type reagents. In fact, in presence of Au catalysts, alkynyliodonium salts only yielded diyne products, and the desired alkynylation was not observed. When considering the key role of the reagent structure, we decided to realize a more precise structure–reactivity relationship study of the alkynyl benziodoxolone reagents. One important goal for these studies was to further understand the unique reactivity of alkynyl benziodoxolones in the quest of even more efficient reagents. We were also motivated by the recent report of Fujii and Ohno on the favorable effect of a nitro group *para* to the iodine in a Cu-catalyzed annulation reaction,[19] and wanted to see if such an effect would also be observed in Au-catalyzed reactions. A second important objective of this work was to examine if the method could also be extended to the transfer of alkynes without a silyl protecting group. In this context, the goal was to examine the potential of the reagents in a broad sense, and not yet to develop truly efficient processes.

Alkynyl benziodoxolones were first reported and structurally characterized by Ochiai and co-workers in 1991.[20] In 1996, Zhdankin and co-workers published an improved synthesis of this class of reagents and also synthesized silyl alkynyl benziodoxolones, including TIPS-EBX (**1**) for the first time.[17] Nevertheless, these compounds did not find application in organic synthesis despite the utility of the parent alkynyliodonium salts. We optimized the synthesis of TIPS-EBX (**1**) to afford the reagent in 86% yield on a 30 g scale without column chromatography from iodosyl benzoic acid (**4**) [Eq. (1)]. On a large scale, acidic work-up to remove pyridine followed by a basic work-up to remove iodobenzoic acid were crucial to obtain reproducible yield and purity.

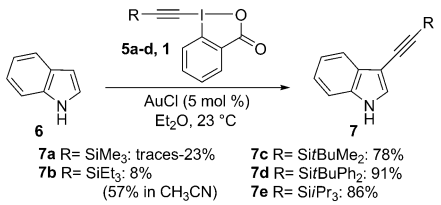


For both indoles and thiophenes, TIPS-EBX (**1**) had proven a superior alkynylation reagent over TMS-EBX (**5a**). To better quantify the importance of steric bulk on the silicon atom, further silylated EBX reagents of increasing size were synthesized (Scheme 3). A first difference was already apparent during the preparation of the reagents: the Zhdankin protocol worked well for sterically hindered silyl groups, but a problem with yield reproducibility was observed for smaller protecting groups, especially TMS. We then discovered that partial decomposition of the reagent often occurred upon treatment with pyridine. A milder neutralization using sodium bicarbonate led to a more reproducible synthesis of the desired reagents.



Scheme 3. Synthesis of silylethynyl benziodoxolones.

All new reagents were first tested in the alkynylation of indole (**6**) (Scheme 4). Reagents with bulky silyl groups such as $SiMe_2tBu$ (**5c**) and $SiPh_2tBu$ (**5d**) gave similar results as TIPS-EBX (**1**). However, both TMS-EBX (**5a**) and $SiEt_3$EBX (**5b**) gave poor results in Et_2O (as well as low reproducibility for TMS-EBX (**5a**)). Due to their low solubility, the reaction was carried out in CH_3CN. TMS-EBX (**5a**) still did not afford any product, whereas the $SiEt_3$ reagent **5b** afforded 57% of the alkynylated product.

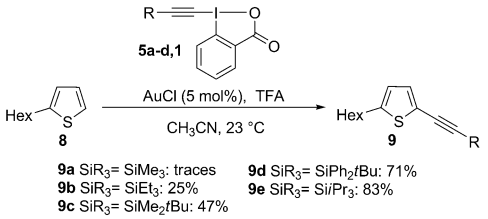


Scheme 4. Alkynylation of indole (**6**) using silylethynyl benziodoxolones.

To investigate the reason for the low yield obtained for small groups, we investigated the stability of the catalyst in the presence of TMS-EBX (**5a**). When TIPS-EBX (**1**) and indole (**6**) were added to a premixed solution of AuCl and TMS-EBX (**5a**), a low yield was obtained (8%). On the

contrary, premixing of TIPS-EBX (**1**) and AuCl did not lead to a decrease of yield. This result may indicate the degradation of AuCl by TMS-EBX (**5a**).

When TMS-EBX (**5a**) was used for the alkynylation of 2-hexylthiophene (**8**), only traces of product were observed (Scheme 5). In contrast to what had been observed for



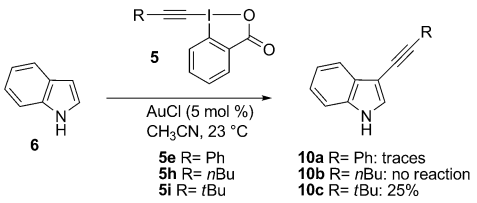
Scheme 5. Alkynylation of 2-hexylthiophene (**8**) using silylethynyl benziodoxolones. Hex = Hexyl.

indole alkynylation, no TMS-EBX (**5a**) was remaining. This result is probably due to the degradation of the reagent under acidic conditions. A steady improvement of the yield was observed by increasing the size of the silyl group ($SiEt_3$, $SiMe_2tBu$ and $SiPh_2tBu$). Importantly, whereas the triisopropylsilyl product was difficult to separate from the starting material, the *tert*-butyldiphenylsilyl group allowed an easier separation.

The high efficiency observed for the transfer of silyl acetylenes is important for practical applications, as easy deprotection of the products gave access to terminal acetylenes, which can then be further functionalized. Nevertheless, the transfer of aryl and alkyl acetylenes directly would allow a more convergent synthesis of complex compounds. For this reason, we decided to investigate acetylene transfer using aryl and alkyl EBX reagents.

Again, the use of $NaHCO_3$ instead of pyridine for neutralization and benziodoxole ring closure led to a reproducible synthesis of Ph-EBX (**5e**) in 46% yield. To examine steric and electronic effects on the aryl acetylene, the synthesis of mesitylene, *para*-nitrobenzene and *para*-methoxybenzene reagents was then attempted. None of these reagents have been previously reported. Mesitylene (**5f**) and *para*-nitrophenyl EBX (**5g**) were obtained in moderate yields (30 and 59%, respectively). Unfortunately, no product was obtained for *para*-methoxybenzene due to the fast degradation of the product under the reaction conditions. In addition to aromatic groups, alkyl acetylenes were also investigated. Gratifyingly, the conditions developed for Ph-EBX (**5e**) proved to be efficient for the very sensitive *n*Bu-EBX (**5h**) (28% yield). In contrast to other reagents, this product was not purified by recrystallization but by flash chromatography. *t*Bu-EBX (**5i**) was synthesized using the procedure reported by Zhdankin and co-workers.[17]

When Ph- (**5e**) and *n*Bu- (**5h**) EBX were submitted to the reaction conditions with indole (**6**), only traces of product were obtained (Scheme 6). In the case of *t*Bu-EBX, the alkynylated product was obtained in 25% yield. Although

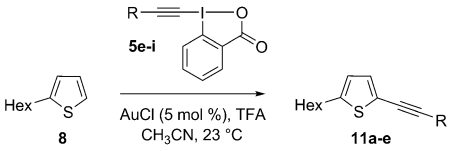


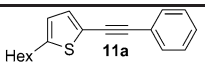
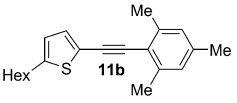
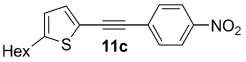
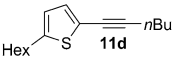
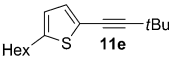
Scheme 6. Alkynylation of indoles using phenyl and alkyl ethynyl benziodoxolones.

this yield is still low, it constituted the first example of the transfer of alkyl acetylene by using gold catalysis.

In the case of 2-hexyl-thiophene (**8**), aromatic EBX reagents afforded products in moderate yields (Table 2, entries 1–3). These results are promising, and future work will be directed towards the optimization of this highly convergent synthesis of arylated alkynyl thiophenes. Alternatively, arylacetylenes can also be obtained in higher yields from the TIPS-acetylene products in a one-pot deprotection-Sonogashira sequence.[21] *n*Bu-EBX (**5h**) was unsuccessful for the alkynylation of thiophene (Table 2, entry 4), but *t*Bu-EBX (**5i**) gave 36% yield (entry 5).

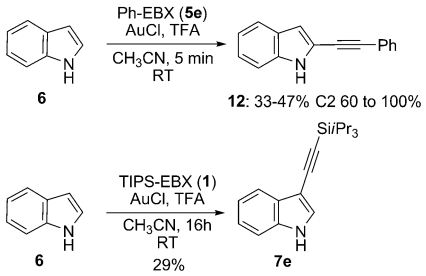
Table 2. Alkynylation of 2-hexylthiophene (**8**) using phenyl and alkyl ethynyl benziodoxolones.



Entry	Product	Yield [%][a]
1		23
2		27
3		35
4		n.r.[b]
5		36

[a] Reaction conditions: **8** (0.40 mmol), benziodoxolone (0.48 mmol), AuCl (5 mol%), TFA (0.48 mmol, 0.2 M), RT, 14–36 h. Isolated product yield after column chromatography. [b] n.r.: no reaction. Hex = Hexyl.

The difference in reactivity of aromatic alkynyl benziodoxolones between indoles and thiophenes was intriguing, because generally indoles were the most reactive substrates in our methodology. We wondered if the relative success obtained with 2-hexylthiophene (**8**) was due to the presence of TFA. In fact, when indole (**6**) was submitted to thiophene alkynylation conditions with Ph-EBX (**5e**), a mixture of C2 and C3 alkynylated indoles **12** was observed by ^1H NMR spectroscopy in only 5 min (Scheme 7). Unfortunately, sig-



Scheme 7. Alkynylation of indole (**6**) using ethynyl benziodoxolones and TFA.

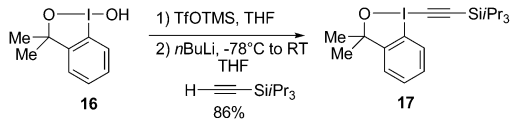
nificant batch to batch variations in both yield (33 to 47%) and regioselectivity (C2/C3 60 to 100%) were observed.

To investigate whether this lower regioselectivity was due to the reaction conditions or the structure of the reagent, we used TIPS-EBX (**1**) with indole (**6**) under the same conditions. In this case however, substitution at position 3 only was obtained in 29% yield. The lower yields obtained with indole (**6**) in presence of acids can be rationalized by the higher acid-sensitivity of this electron-rich heterocycle. The change of regioselectivity with Ph-EBX (**5e**) is more intriguing, and perhaps indicates a change of mechanism depending on the reagent and the addition of acid.

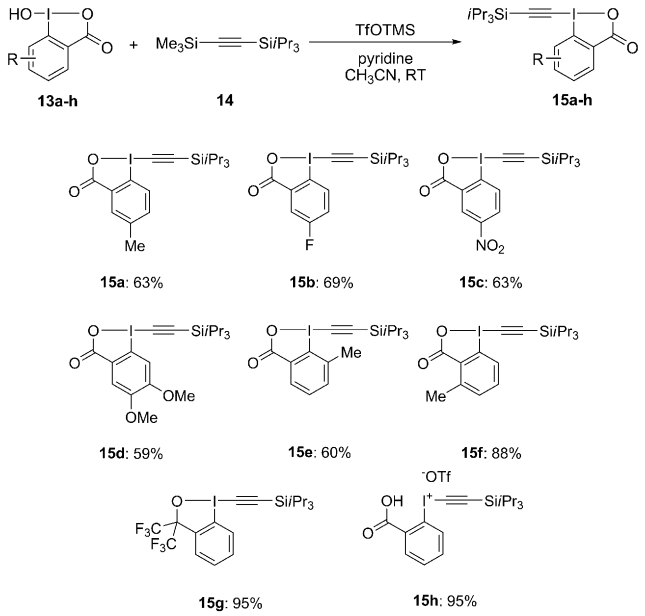
This investigation on the variation of the alkynyl substituent clearly showed the superiority of bulky silyl groups. It can be hypothesized that the improved solubility and stability of bulky silyl EBX reagents can explain their higher efficiency in the alkynylation of heterocycles. Furthermore, the more electron-rich C–Si bonds could also play a role to explain the exceptional reactivity of these reagents. Preliminary results were also obtained for the transfer of aryl acetylenes in the case of 2-hexylthiophene (**8**), but further improvement is required in this case.

The influence of substituents on the benziodoxolone aromatic ring was then investigated to increase the reactivity of TIPS-EBX (**1**). A range of EBX reagents bearing electron-donating or electron-withdrawing groups as well as bistrifluoromethyl-substituted benziodoxole **15g** were synthesized in moderate to good yields using Zhdankin procedure (Scheme 8).[17] In addition, a protonated benziodoxolone **15h** was also synthesized using a known method.[17]

Togni reported the efficiency of dimethyl benziodoxole structure in CF_3 transfer.[22] In contrast to bistrifluoromethyl-substituted benziodoxole, alkynyl dimethyl benziodoxole **17** has never been synthesized. Unfortunately, no product was obtained when Zhdankin's method was used. However, we discovered that the addition of lithiated triisopropylsilylacetylene to benziodoxole **16** activated by TMSOTf led to **17** in 86% of yield [Eq. (2)]. **17** represents a highly interesting new electrophilic acetylene due to the higher *trans* effect present in dimethyl benziodoxole.[23]



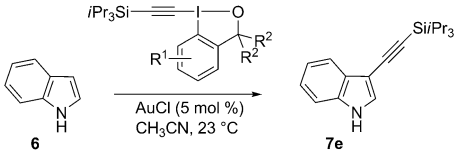
(2)



Scheme 8. Synthesis of analogues of TIPS-EBX (**1**).

Under standard reaction conditions with indole (**6**), all substituted benziodoxolones gave the product in yields comparable to TIPS-EBX (**1**) (86%, entries 1–7, Table 3). Interestingly, bis CF_3 benziodoxole **15g** afforded a mixture of the C3-alkynylated (43%) and C2-alkynylated (15%) products (Table 3, entry 8). Protonated benziodoxolone **15h** did not form any product and degradation of indole (**6**) was observed (Table 3, entry 9). Dimethyl benziodoxole **17** only afforded traces of product (Table 3, entry 10). This result showed the highly different properties of compounds **1**, **15g** and **17**. The reaction was consequently only minimally influ-

Table 3. Alkynylation of indole (**6**) using analogues of TIPS-EBX (**1**).

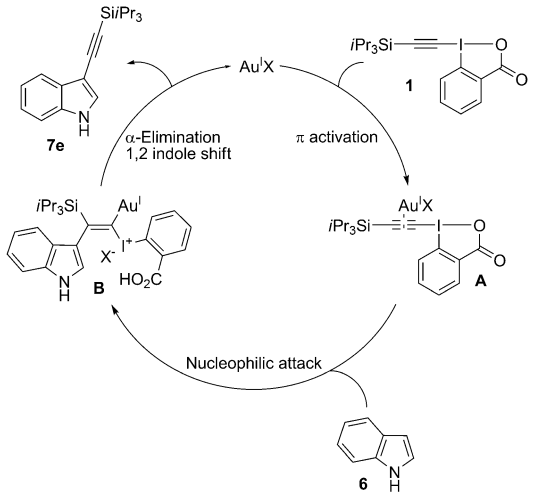


Entry	Benziodoxol(on)e	Yield [%][a]
1	**1**	85
2	**15a**	83
3	**15b**	84
4	**15c**	84
5	**15d**	81
6	**15e**	80
7	**15f**	77
8	**15g**	43 (15)[b]
9	**15h**	0
10	**17**	traces

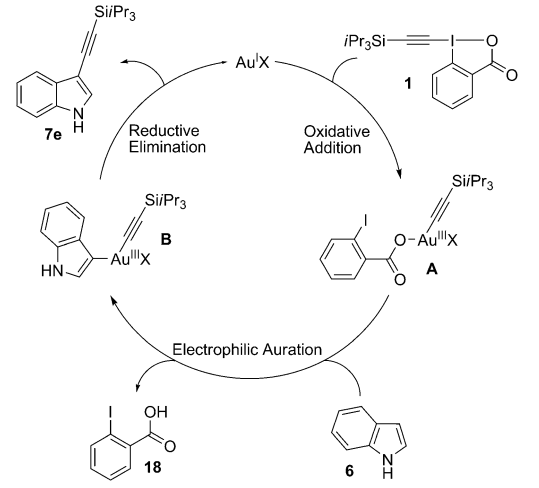
[a] Reaction conditions: indole **6** (0.10 mmol), benziodoxol(on)e (0.12 mmol), and AuCl (0.01 mmol) in a 0.025 M solution of undecylcyanide in CH_3CN (2 mL) at 23 °C under air for 14 h. GC/MS yield using undecylcyanide as internal reference. [b] C2-alkynylation product.

enced by substitution on the benzene ring, but the carbonyl group was an essential component of the reagent for an efficient alkynylation.

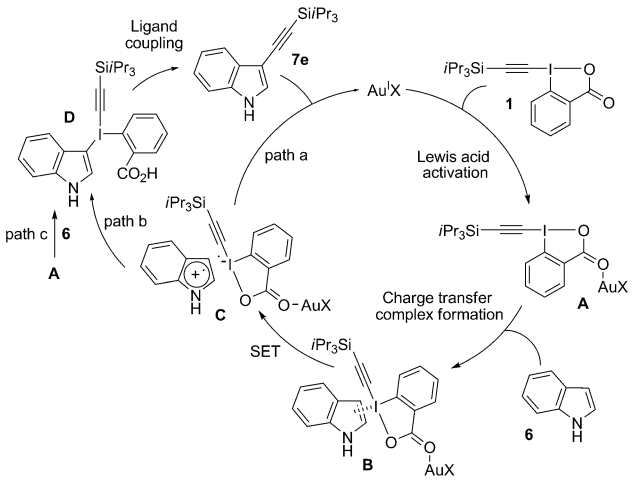
Mechanistic investigations: The reactivity and properties of both gold and hypervalent iodine have recently attracted broad interest. Gold complexes have been first established as excellent catalysts for the activation of π systems.[24] More recently, other types of reactions involving changes in the oxidation state of the gold catalyst have also incited a strong interest in the scientific community.[25] Conversely, hypervalent iodine reagents are involved in oxidative and atom transfer processes, which have been proposed to proceed either through two electrons or SET mechanisms.[26,27] Based only on these results in the literature, several pathways are possible for the Au-catalyzed alkynylation reaction. The three main mechanisms envisaged are the π activation mechanism (Scheme 9), the Au^{I}/Au^{III} mechanism (Scheme 10), and the Lewis acid activation of the benziodoxolone, which can be followed either by a SET mechanism or by a direct attack on the iodine (Scheme 11).



Scheme 9. π Activation mechanism.



Scheme 10. Oxidative mechanism.



Scheme 11. Lewis acid activation mechanism

The first step of the π activation mechanism involves coordination of the triple bond by gold chloride, which leads to an increased electrophilicity (Scheme 9).[24] A Friedel–Craft-type reaction of indole (**6**) at the most electrophilic β position of the alkynyl benziodoxolone would then be in accordance with the inherent reactivity of alkynyl iodonium ions.[28] This step is expected to follow an electrophilic aromatic substitution mechanism. The vinyl gold intermediate **B** can then undergo an α elimination to generate a carbene, which then rearranges to form the triple bond (Fritsch–Buttenberg–Wiechell-type rearrangement).

An alternative mechanism involves an oxidative addition of gold in the C–I bond to form the Au^{III} intermediate **A** (Scheme 10).[25,29] The highly electrophilic gold(III) species can then undergo indole auration through electrophilic aromatic substitution. A reductive elimination then affords alkynylated indole **7e**.

AuCl could also act as a Lewis acid and increase the electrophilicity of the iodine atom (Scheme 11).[22] The activated hypervalent iodine **A** can then form a charge transfer complex **B** with the electron-rich heterocycle. According to Kita,[26c] a single electron transfer can occur to form **C**, which can then either directly rearrange to **7e** through alkyne transfer (path a) or form the iodine(III) intermediate **D** and give **7e** by a subsequent ligand coupling (path b). A direct nucleophilic attack of indole (**6**) on **A** can also generate **D** through a two electron transfer (path c).

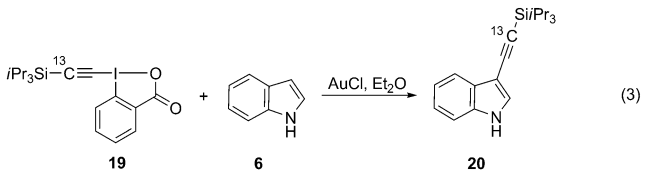
In the three mechanisms, an attack of unactivated indole (**6**) as nucleophile has been proposed. Another possible alternative would be the nucleophilic activation of indole (**6**) by auration on the three position.[30] The formed Au complex would then act as nucleophile instead of indole (**6**) in the described catalytic cycles.

Unfortunately, the study of the mechanism of the gold-catalyzed alkynylation with TIPS-EBX (**1**) is made more difficult by the characteristics of the reaction. First, reproducible kinetics measurements are very difficult due to the het-

erogenous nature of gold chloride. Second, electron-rich ligands like phosphines or carbenes inhibit the reaction, even if the more reactive cationic gold complexes are used. In our previous communication, we used only simple triphenylphosphine cationic complexes, but when the screen was extended to other ligands recently introduced in gold catalysis, no better results were obtained.[31] This is a major drawback for mechanistic investigations, because well-defined metal complexes would potentially allow the characterization of reactive intermediates, which is particularly challenging for gold species. In fact, vinyl gold species could be recently isolated, but this was only possible using N-heterocyclic carbene ligands or phosphines.[32] Furthermore, phosphine NMR spectroscopy is a valuable tool for studying the structure and oxidation state of metal complexes. Consequently, mostly indirect evidence had to be used to better understand the reaction.

Prior to describing new experiments, it is important here to briefly summarize the knowledge gathered through our previous work on the alkynylation of indoles and thiophenes:[13a,b]

1) The alkynylation method showed a regioselectivity consistent with an electrophilic aromatic substitution (C3 of indole, C2 of pyrrole and thiophene).
2) AuCl was always the best catalyst, but with indole moderate yields could also be obtained with $AuCl_3$.[33]
3) An isolated gold thiophene complex did not react with TIPS-EBX (**1**). Protonated benziodoxole **15h** was also not able to transfer an acetylene to 2-hexylthiophene (**8**).
4) Reaction with a ^{13}C-labeled EBX reagent **19** showed that no silicium shift occurred during the reaction [Eq. (3)]. Ochiai reported that the addition of α-ketoester nucleophile on alkynyliodonium proceeds via carbene formation followed by 1,2-shift of the best migrating group,[28] often silicium or hydrogen. As a result, addition of indole (**6**) in α position followed by TIPS 1,2 shift can be ruled out. On the other hand, a 1,2-shift of indole cannot be excluded as aromatic groups are known to be prone to this type of rearrangement.



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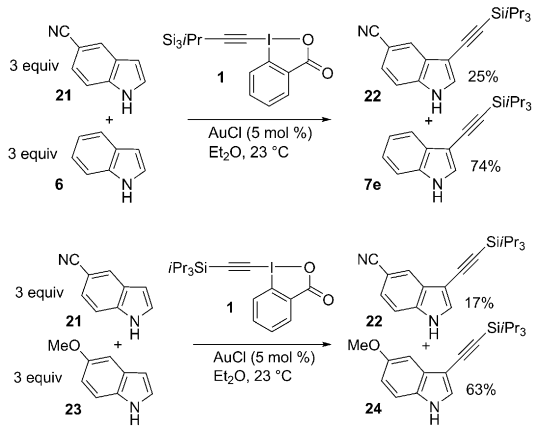
The regioselectivity results obtained are in agreement with what would be expected for an electrophilic aromatic substitution. Nevertheless in this study we discovered that the regioselectivity for the alkynylation of indole was dependent on the structure of the reagent (benziodoxole vs. benziodoxolone), which seemed to indicate that several mechanisms could be possible. On the other hand, substitution of the benzene ring of the reagents showed surprisingly little effect on the yield.

In this section, we will first present further experiments which indicated that a Lewis Acid or a SET mechanism was less probable. To further investigate the mechanism, we decided then to concentrate our efforts on semi-quantitative competitive experiments to gain a better insight into the kinetics of the reaction. Furthermore, the fact that Au^{III} was also a catalyst for the reaction was highly interesting, as it could be better rationalized by a π activation mechanism: we consequently decided to investigate Au^{III} catalysts in more detail.

SET and Lewis acid mechanisms: Single-electron-transfer pathways are less likely for two reasons. First, the high electrophilic aromatic substitution regioselectivity observed with indoles would not be in agreement with SET processes, for which C2 substitution would be expected.[26c] The case is less clear for thiophenes, as in this case both electrophilic aromatic substitutions and SET processes give C2 functionalization. Second, no formation of heterocyclic dimers was observed, which is a frequent process for heterocyclic radical cations.[26c] Furthermore, the reaction was also done in the presence of one equivalent of $TMSN_3$ which has been demonstrated to react rapidly with indole or thiophene radical cations.[26b] For both indole (**6**) and 2-hexylthiophene (**8**), no addition of azide on the heterocycle was observed. However, it is difficult to exclude the presence of a tight radical pair, which would react too rapidly to be trapped. Direct attack on iodine, Lewis acid-catalyzed or not, also appeared less probable for us, although it is often proposed for trifluoromethylation using benziodoxolone reagents.[22] In fact, no alkynylation was observed for indole (**6**) and/or 2-hexylthiophene (**8**) in an extended screening of Lewis and Brønsted acids including HCl, TsOH, TFA, $FeCl_3$, $AlCl_3$, $Zn(OTf)_2$, $Yb(OTf)_3$, and $In(OTf)_3$. The unique reactivity of AuCl would be very difficult to explain, as simple Lewis and Brønsted acids should be even more efficient to promote the reaction. In addition, control experiments at high temperature without the gold catalyst did not afford any product, although this has been observed for arylation reactions using iodonium salts.[34] A first important conclusion of these mechanistic studies is consequently that an activation of the I–O bond followed by reaction on iodine is not probable. Consequently, the Au-catalyzed alkynylation reaction seems to be mechanistically distinct from other reactions using benziodoxolone reagents, in particular trifluoromethylation.

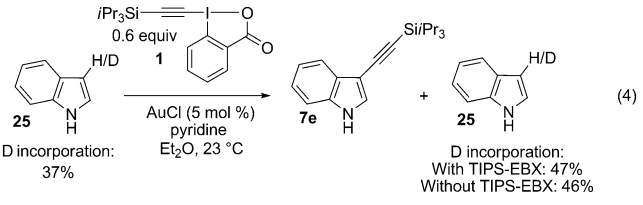
Competitive experiments: As complete kinetic studies were difficult because of the heterogenous nature of AuCl, we then turned to competitive experiments to gain a semi-quantitative insight into the reaction rate. The alkynylation was carried out with mixtures of indole (**6**) ($N=5.55$), 5-cyanoindole (**21**) ($N=2.83$) and 5-methoxyindole (**23**) ($N=6.22$), as the nucleophilicity of these substrates has been described quantitatively (Scheme 12).[35] The reactivity pattern observed is correlated with the nucleophilicity according to the Mayr's scale, as the ratio of products was 3.0:1 between



Scheme 12. Competitive experiments with indoles.

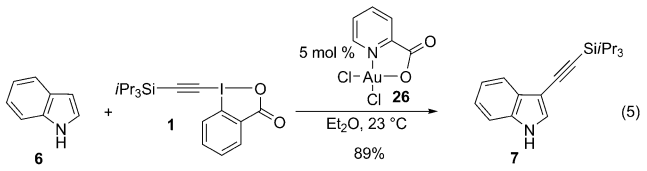
indole (**6**) and 5-cyanoindole (**21**), and 3.7:1 between 5-methoxyindole (**23**) and 5-cyanoindole (**21**), respectively. Although the differences of reactivity are lower than in Mayr's model reaction for the reaction of nucleophile with an electrophile, this result certainly confirms that an electrophilic attack on the indole is part of the rate determining step of the reaction. This result is in agreement with the high regioselectivity observed for the most electron-rich position of the functionalized heterocycles.

A qualitative determination of a potential kinetic isotope effect was then achieved by reaction of 37% deuterated indole **25** with 0.6 equivalents of TIPS-EBX (**1**) [Eq. (4)]. When **25** was submitted to the reaction conditions, a slight enrichment in deuterium was observed. However, performing the reaction in the absence of TIPS-EBX (**1**) showed a significant loss of deuterium even without reaction, making interpretation of this result impossible (not shown). We hypothesized that this outcome could be due to traces of acid or reversible auration of indole **25**. Based on our previous results, we repeated these reactions in the presence of pyridine. In this case, the same deuterium enrichment was observed both with and without TIPS-EBX (**1**). Although the reason for this effect is not clear, the same result obtained in both cases demonstrated that there is no significant kinetic deuterium effect in the alkynylation reaction itself. Consequently, it appears that cleavage of the C–H bond is not occurring during the rate-limiting step. This would be in agreement with a rate-limiting electrophilic attack on the indole, followed by a fast proton transfer and re-aromatization. In the case of thiophene, as it is not possible to slow down proton–deuterium exchange by the addition of pyridine, no conclusive results could be obtained.



(4)

Au^{III} catalysis: At this point, we decided to re-investigate Au^{III} catalysts for the reaction, as we hoped it could help us exclude a mechanism involving redox catalysis. In particular, we found that gold 2-pyridinecarboxylate dichloride (**26**) was a good catalyst for the alkynylation of indole (**6**) [Eq. (5)]. Furthermore, this catalyst is much better defined



(5)

than AuCl and clear solutions were obtained during the reaction. Despite the fact that we cannot be sure that both reactions have the same mechanism, this cleaner reaction profile motivated us to compare the reactivity of the different synthesized alkynyl benziodoxolones (Figure 1). In particular, substitution on the benzyl ring of the EBX reagents had led to no changes in yield. By studying the full profile of the reaction instead of just the yield, we hoped to be able to detect subtle effects that we had missed in the preparative reactions.

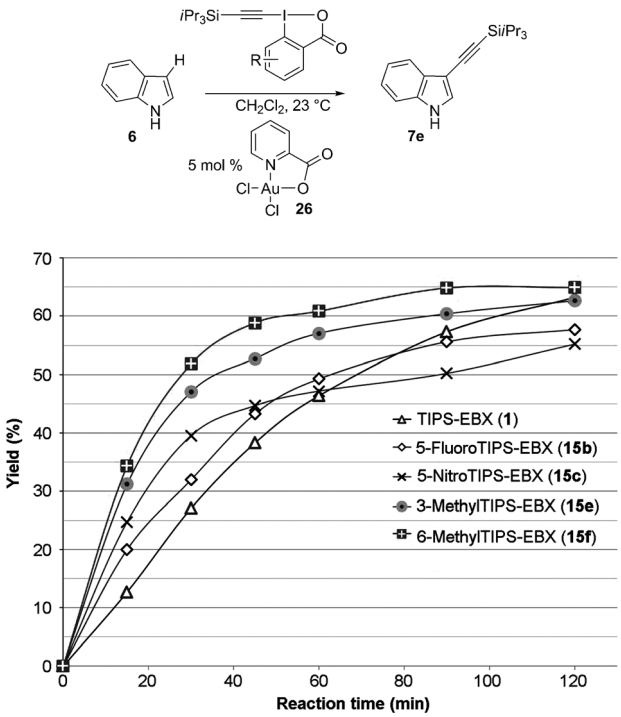


Figure 1. Kinetic profile for the alkynylation of indole (**6**) using triisopropyl ethynyl benziodoxolones.

5-MethylTIPS-EBX (**15a**) and 4,5-dimethoxyTIPS-EBX (**15d**) gave similar kinetics as TIPS-EBX (**1**).[36] In contrast, 5-fluoro (**15b**) and 5-nitroTIPS-EBX (**15c**) have higher initial rates, even if they gave slightly lower final yields

(Figure 1). Interestingly, 3-methylTIPS-EBX (**15e**) and 6-methylTIPS-EBX (**15f**) led to the highest reaction rates.

The observed kinetics are difficult to explain: an accelerating effect of the *para* electron-withdrawing group would be in accordance with a rate-limiting step involving electrophilic attack of the reagent (π activation mechanism, Scheme 9). However, the effect is weak, and could eventually also be explained by a ligand effect during the auration step in the oxidative mechanism (Scheme 10). The even stronger effect observed by the introduction of a methyl group in 3 or 6 positions is startling. To better understand the reactivity, we decided to analyze the structure of the reagents by X-ray crystallography. First, high-quality crystals of TIPS-EBX (**1**) were obtained by recrystalization from CH_3CN. In accordance with previously published X-ray structures of alkynyl benziodoxolones,[17,20] the T-shape of the hypervalent iodine was confirmed. Furthermore, the alkyne is nearly in the same plane as the benziodoxolone (torsion angle C8-I1-C7-C6: −8.33°; Figure 2).

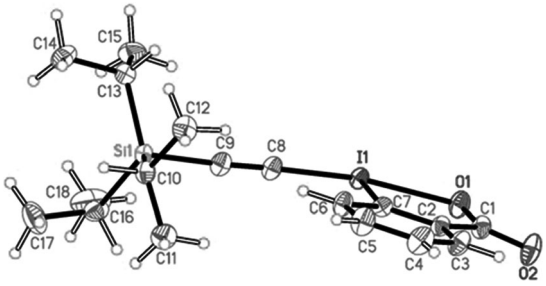


Figure 2. X-ray structure of TIPS-EBX (**1**). Selected bond lengths [Å] and angles [°]: C8−I1: 2.0539(19), I1−O1: 2.3379(13); C8-I1-C7: 91.37(7), C8-I1-C7-C6: −8.33(16).

The structure of TIPS-EBX (**1**) was then compared with the two methyl-substituted reagents **15e** and **15f**. In the case of 3-methylTIPS-EBX (**15e**), the steric bulk of the methyl group forces the alkyne substituent outside the plane of the ring (torsion angle C8-I1-C7-C6: 34.6°) (Figure 3). In this case, a weaker 3-center-4-electron hypervalent bond can

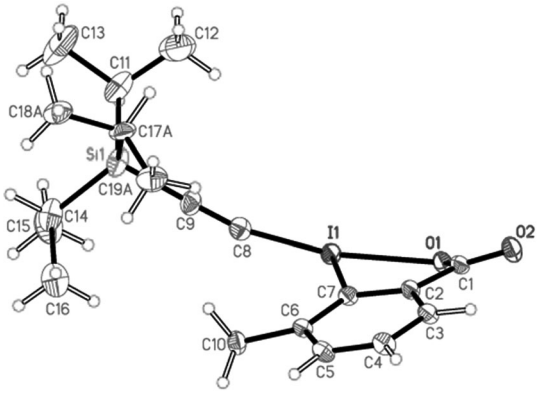


Figure 3. X-ray structure of 3-methylTIPS-EBX (**15e**). Selected bond lengths [Å] and angles [°]: C8−I1: 2.043(7), I1−O1: 2.385(4); C8-I1-C7: 95.2(2), C8-I1-C7-C6: 34.6(5).

be expected, and consequently a more reactive reagent.[37] 6-MethylTIPSEBX (**15f**), however, displayed a nearly perfectly planar structure (torsion angle C8-I1-C7-C6: −0.72°) (Figure 4). In this case, the accelerating effect is more diffi-

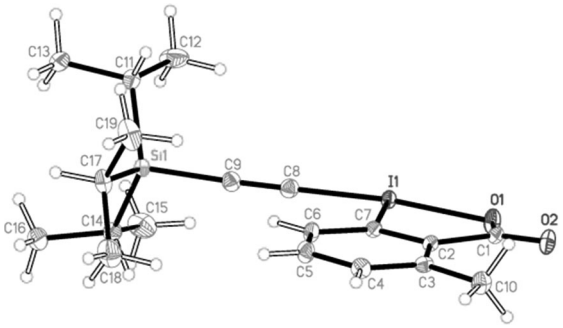


Figure 4. X-ray structure of 6-methylTIPS-EBX (**15f**). Selected bond lengths [Å] and angles [°]: C8−I1: 2.0733(12), I1−O1: 2.3088(9); C8-I1-C7: 91.58(5), C8-I1-C7-C6: −0.72(10).

cult to rationalize. Nevertheless, it is interesting to observe that the I1−O1 bond is shorter than in TIPS-EBX (**1**) (2.3088 vs. 2.3379 Å) and the C8−I1 bond longer (2.0733 vs. 2.0539 Å), which could tentatively be used to rationalize the different reactivity of this reagent.

With the more reactive reagent **15f**, a higher yield was obtained both for indole **27** and pyrrole **28** (Figure 5).

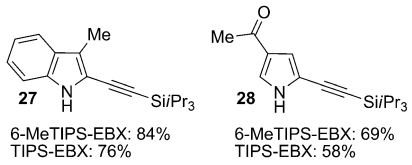
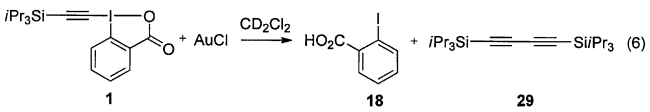


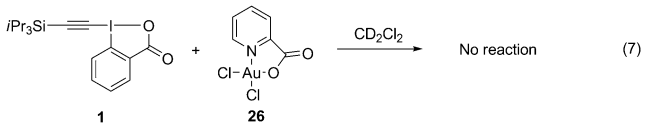
Figure 5. Improved yield using 6-methylTIPS-EBX (**15f**).

The fact that gold(III) is active for the reaction is mechanistically highly interesting. It seems to indicate that a π activation mechanism is more probable. Nevertheless, in situ reduction of Au^{III} to Au^{I} can be envisaged.[38] When TIPS-EBX (**1**) was mixed with a stoichiometric amount of AuCl, the reagent was transformed into iodobenzoic acid (**18**) and bisalkyne **29** [Eq. (6)].

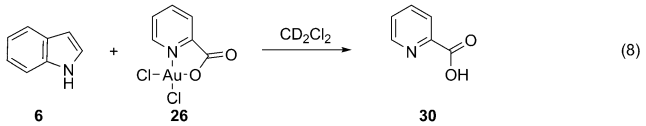


On the contrary, when complex **26** was used, no reaction was observed [Eq. (7)]. When **26** was mixed up with indole (**6**), the fast precipitation of a solid was observed, which was identified as 2-pyridine carboxylic acid (**30**) [Eq. (8)]. Interestingly, the resulting reaction mixture gave product when

TIPS-EBX (**1**) was added, indicating that the reaction between Au^{III} complex **26** and indole (**6**) indeed formed an active catalyst. A possible explanation is that indole (**6**) is electron-rich enough to reduce Au^{III} to Au^{I} in situ. Up to now, no product resulting from the oxidation of indole (**6**), such as indole dimers could be observed by NMR spectroscopy, and further investigations will be required to understand what is happening in this reaction. Furthermore, gold 2-pyridinecarboxylate dichloride (**26**) gave no product in the case of 2-hexylthiophene (**8**), which would be in accordance with the lower reduction potential of thiophenes.



1 **26** (7)



6 **26** **30** (8)

With the results of these control experiments, the fact that Au^{III} is active for the alkynylation of indole unfortunately does not allow the conclusion that a redox mechanism is improbable, as reduction to Au^{I} could occur in situ.

Conclusion

In this full account, we have reported a more efficient protocol for the alkynylation of pyrroles, which gave high yields even in the case of challenging tetrasubstituted pyrroles. The structure of the ethynyl benziodoxolone has been systematically modified, and in the case of thiophene, the transfer of arylacetylenes has been achieved for the first time. Important conclusions could already be drawn on the reaction mechanism: 1) A mechanism involving attack on iodine or SET processes is less probable, 2) Electrophilic attack on the indole is rate limiting, as demonstrated by competitive experiments, and 3) Re-aromatization through proton transfer is fast, as no significant kinetic isotope effect could be observed. We further demonstrated that the alkynylation of indole (**6**) could also be catalyzed by Au^{III} complex **26**, and in this case a more reproducible reaction kinetic was observed. Electron-withdrawing groups and a methyl group in 3- and 6 positions accelerated the reaction. Control experiments showed that the Au^{III} catalyst reacted with indole (**6**) to form a potentially reduced, not yet identified gold species. This last result does not permit to exclude a mechanism involving changes of oxidation state on gold. In conclusion, the results obtained concerning the influence of the reagent structure, the reaction kinetics and the oxidation state of gold can be used to further support both a redox cycle or a simple π activation mechanism. An in-depth investigation will be required to distinguish definitively these two alternatives and further develop this promising research area.

Experimental Section

General procedure for pyrrole alkynylation using pyridine: AuCl (2.3 mg, 0.010 mmol, 0.05 equiv) was added to a stirring solution of pyridine (19 μL, 0.24 mmol, 1.2 equiv), TIPS-EBX (**1**) (103 mg, 0.240 mmol, 1.2 equiv) and the corresponding pyrrole (0.200 mmol, 1.0 equiv) in Et_2O[39] (4 mL) under air. The reaction was sealed and stirred at room temperature for 15 h. Et_2O (10 mL) was added, the organic layer was washed twice with 0.1 M NaOH (15 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography.

1-(Phenylethynyl)-1,2-benziodoxol-3(1*H*)-one (Ph-EBX, 5e): Trimethylsilyltriflate (7.50 mL, 41.5 mmol, 1.1 equiv) was added to a suspension of compound **4** (10.0 g, 37.7 mmol, 1 equiv) in CH_2Cl_2 (100 mL) at RT. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(phenylethynyl)silane (8.10 mL, 41.5 mmol, 1.1 equiv) (slightly exothermic). The resulting suspension was stirred for 6 h at RT, during this time a white solid was formed. A saturated solution of $NaHCO_3$ (100 mL) was then added and the mixture was stirred vigorously. The resulting suspension was filtered on a glass filter of porosity 4. The two layers of the mother liquors were separated and the organic layer was washed with sat. $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting mixture was combined with the solid obtained by filtration and boiled in CH_3CN (300 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **5e** (6.08 g, 17.4 mmol, 46%) as a colorless solid. Mp (Dec.) 155–160 °C (lit 153–155 °C); ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 0.03 mmol mL^{-1}): $\delta = 8.46$ (m, 1H, ArH), 8.28 (m, 1H, ArH), 7.80 (m, 2H, ArH), 7.63 (m, 2H, ArH), 7.48 ppm (m, 3H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 163.9$, 134.9, 132.9, 132.5, 131.6, 131.3. 130.8, 128.8, 126.2, 120.5, 116.2, 106.6, 50.2 ppm.[17]

3-Methyl-1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (15e): Trimethylsilyltriflate (2.10 mL, 11.6 mmol, 1.1 equiv) was added dropwise to a stirred solution of compound **4** (2.93 g, 10.5 mmol, 1.0 equiv) in acetonitrile (45 mL). After 20 min, compound **14** (2.94 g, 11.6 mmol, 1.1 equiv) was then added dropwise, followed, after 30 min, by the addition of pyridine (934 μL, 11.6 mmol, 1.1 equiv). The mixture was stirred 20 min. The solvent was then removed under reduced pressure and the yellow crude oil was dissolved in dichloromethane (30 mL). The organic layer was washed with 1 M HCl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (40 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (ca. 10 mL) and washing with pentane afforded **15e** (2.79 g, 6.31 mmol, 60%) as colorless crystals. Mp (Dec.) 138–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 0.04 mmol mL^{-1}): $\delta = 8.21$ (dd, 1H, $J =$ 6.8, 2.5 Hz, ArH), 7.50 (m, 2H, ArH), 2.87 (s, 3H, CH_3), 1.10 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.8$, 140.3, 138.0, 133.3, 131.7, 130.8, 119.1, 112.5, 66.9, 24.0, 18.5, 11.2 ppm. IR: $\tilde{\nu} = 2946$ (w), 2867 (w), 2244 (w), 1649 (m), 1562 (w), 1464 (w), 1326 (w), 1281 (w), 998 (w), 907 (s), 884 (w), 763 (w), 728 (s), 687 (s), 647 cm^{-1} (m). HRMS (ESI): *m/z* calcd for $C_{19}H_{28}O_2ISi^+$: 443.0903 [*M*+H]; found: 443.0893.

6-Methyl-1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (15f): Trimethylsilyltriflate (1.50 mL, 8.27 mmol, 1.1 equiv, freshly distilled) was added dropwise to a stirred solution of compound (**4**) (2.09 g, 7.52 mmol, 1.0 equiv) in acetonitrile (30 mL). After 20 min, compound **14** (2.10 g, 8.27 mmol, 1.1 equiv) was then added dropwise, followed, after 20 min, by the addition of pyridine (667 μL, 8.27 mmol, 1.1 equiv). The mixture was stirred 20 min. The solvent was then removed under reduced pressure and the yellow crude oil was dissolved in dichloromethane

(150 mL). The organic layer was washed with 1 M HCl (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (150 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (150 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile and wash with cold acetonitrile afforded **15 f** (2.84 g, 6.60 mmol, 88%) as colorless crystals. Mp: 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.25$ (m, 1H, ArH), 7.53 (d, 2H, $J = 5.2$ Hz, ArH), 2.90 (s, 3H, CH_3), 1.15 ppm (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.8$, 146.7, 135.0, 133.3, 128.7, 124.2, 118.3, 113.3, 68.7, 22.4, 18.5, 11.2 ppm; IR: $\tilde{\nu} = 3055$ (w), 2938 (m), 2873 (m), 2865 (m), 2244 (w), 2089 (w), 1626 (s), 1612 (s), 1586 (m), 1550 (m), 1450 (m), 1382 (w), 1329 (m), 1276 (w), 1253 (w), 1157 (w), 1076 (w), 1018 (w), 998 (w), 911 (w), 884 (m), 846 (m), 817 (m), 770 (m), 706 (s), 679 (s), 649 cm^{-1} (m); HRMS (ESI): *m/z* calcd for $C_{19}H_{28}IO_2Si^+$: 443.0898 $[M+H]^+$; found: 443.0896.

1-[(Triisopropylsilyl)ethynyl]-3,3-dimethyl-3(1*H*)-1,2-benziodoxole (23): Trimethylsilyltriflate (250 μL, 1.38 mmol, 1 equiv) was added to a stirring solution of **4** (408 mg, 1.38 mmol, 1 equiv) in THF (40 mL) at RT. The solution was stirred at RT for 20 min and then cooled to −78 °C. In the meantime, *n*BuLi (2.5 M in hexanes, 550 μL, 1.38 mmol, 1 equiv) was added to a stirring solution of triisopropylacetylene (310 μL, 1.38 mmol, 1 equiv) in THF (10 mL) at −78 °C. The solution was stirred for 30 min at −78 °C and then added via cannula to the first solution. The reaction was stirred for 1 h at −78 °C, warmed to RT and stirred 4 h. The reaction was quenched with saturated NH_4Cl (20 mL). The layers were separated and the aqueous layers were extracted with CH_2Cl_2 (20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and reduced under vacuum. The resulting oil was then purified by column chromatography (PET/Et_2O 6:4) to afford **23** (524 mg, 1.18 mmol, 86%) as a yellow oil which crystallized at −18 °C. R_f (PET/Et_2O 6:4) = 0.15; Mp 59–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 0.16 mmol mL^{-1}): $\delta = 8.23$ (dd, 1H, $J = 8.2$, 0.9 Hz, ArH), 7.52 (td, 1H, $J = 7.3$, 1.0 Hz, ArH), 7.41 (ddd, 1H, $J = 8.6$, 7.2, 1.5 Hz, ArH), 7.35 (dd, 1H, $J = 7.5$, 1.5 Hz, ArH), 1.44 (s, 6H, Me), 1.12 ppm (s, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 148.0$, 130.4, 129.2, 127.4, 126.5, 111.0, 105.8, 80.8, 75.7, 31.5, 18.6, 11.4 ppm; IR: $\tilde{\nu} = 2945$ (m), 2864 (m), 2064 (w), 1690 (w), 1562 (w), 1462 (m), 1436 (m), 1355 (w), 1244 (w), 1162 (w), 1116 (w), 1073 (w), 999 (m), 968 (m), 883 (m), 756 (m), 691 cm^{-1}(s); HRMS (ESI): *m/z* calcd for $C_{20}H_{32}OISi^+$: 443.1267 $[M+H]$; found: 443.1276.

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