Cooperative Catalysis

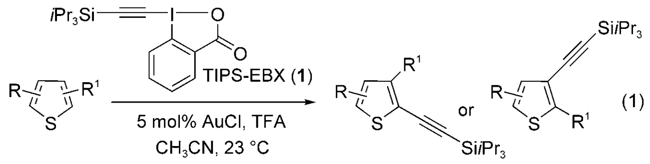
DOI: 10.1002/anie.201003179

Direct Alkynylation of Thiophenes: Cooperative Activation of TIPS–EBX with Gold and Brønsted Acids**

*Jonathan P. Brand and Jérôme Waser**

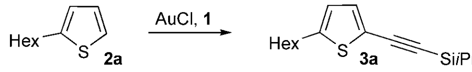
Thiophene is a ubiquitous heterocycle in both medicinal chemistry and materials science.[1] Oligo- and polythiophenes play a crucial role in organic electronic materials.[2] For most applications, extended π-electron systems are required, which are usually prepared by cross-coupling methods.[3] Direct arylation has recently emerged as a more step- and atom-economic alternative.[4] However, no direct alkynylation of thiophenes has been reported to date, even though oligo- and poly(arylene ethynylene)s are an important class of organic materials.[5] Consequently, more direct methods to access ethynylthiophenes in particular would be highly desirable.

The direct alkynylation of (hetero)aromatic compounds has become an active research area.[6,7] The direct alkynylation of thiophenes, however, remains elusive. In fact, the extension of known alkynylation methodologies to thiophene is not easy, because of its low reactivity.[4,8] Herein, we report the alkynylation of thiophenes by using 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS–EBX; **1**). The reaction proceeded at room temperature under air [Eq. (1)]. The discovery of a cooperative effect between a gold catalyst and a Brønsted acid allowed the development of the direct silylethynylation of thiophenes.



(1)

Table 1: Reaction optimization and discovery of the Brønsted acid activation.



Entry	Solvent	Conc. **2a** [M]	Additive[b]	Yield [%][a]
1	Et_2O	0.05	–	2
2	CH_3CN	0.4	–	14[c]
3	CH_3CN	0.4	$Zn(OTf)_2$	62
4	CH_3CN	0.4	CH_3CO_2H	18
5	CH_3CN	0.4	$ClCH_2CO_2H$	53
6	CH_3CN	0.4	Cl_3CCO_2H	73
7	CH_3CN	0.4	TFA	84
8	CH_3CN	0.4	TsOH	0
9	CH_3CN	0.4	TFA[d]	50
10	CH_3CN	0.2	TFA	94 (83)[e]

[a] Reaction conditions: 0.20 mmol **2a**, 0.24 mmol **1**, and 0.01 mmol AuCl under N_2 for 12–15 h; yields determined by GC using pentadecane as reference. [b] 1.2 equiv additive. [c] Reaction run at 60 °C. [d] 0.1 equiv TFA. [e] Isolated yield; Hex = hexyl; Tf = trifluoromethanesulfonic ; Ts = toluene-4-sulfonyl.

Recently, our research group reported the direct alkynylation of indoles and pyrroles by using AuCl and TIPS-EBX.[7,9] Unfortunately, when the reaction was applied to thiophenes only traces of **3a** were observed under the reaction conditions (Table 1, entry 1). An increased concentration, use of acetonitrile as solvent, and higher reaction temperatures led to only slightly better results (Table 1, entry 2), thus demonstrating the challenges associated with the less reactive thiophenes. Inspired by recent examples on the activation of benziodoxole reagents,[9g–h] we then attempted the reaction in presence of Lewis or Brønsted acids (Table 1, entries 3–8). The best result (84 % yield) was obtained with trifluoroacetic acid (TFA; 1 equivalent with respect to **1**). A correlation between the yield and the acid strength was observed, but no product was obtained with acids stronger than TFA; in this case the starting material decomposed (Table 1, entry 8). TFA could also be used catalytically, but the yield was lower (Table 1, entry 9). The alkynylation reaction did not occur in the absence of AuCl. To the best of our knowledge, this result is the first example of the cooperative activation of a benziodoxolone reagent with a gold catalyst and a Brønsted acid.[10] In contrast to most direct arylation methods of thiophenes, the alkynylation did not require heating. A reaction under more dilute conditions (0.2 M) gave the product in 94 % yield (83 % isolated compound; Table 1, entry 10). Other solvents or gold catalysts gave lower yields.[11] No product was afforded when alkynyliodonium salts and bromo- or iodoalkynes were used, hence showing the unique properties of TIPS-EBX **1**.[12] On a 2 mmol scale, **3a** was obtained in 84 % yield by using only 1 mol % AuCl under air without drying the solvents.[13] 2-Iodobenzoic acid could be recovered in 86 % yield by a simple basic workup and could be recycled for the synthesis of TIPS–EBX (**1**).[14]

---

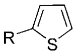
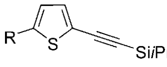
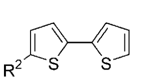
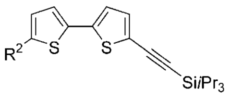
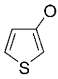
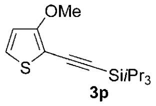
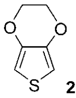
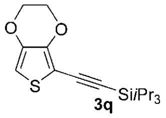
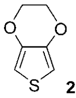
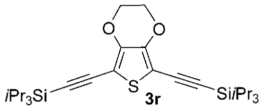
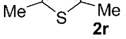
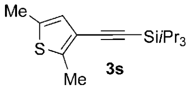
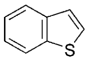
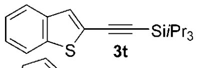
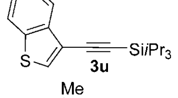
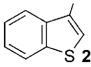
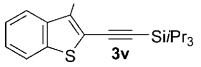
[*] J. P. Brand, Prof. Dr. J. Waser
Laboratory of Catalysis and Organic Synthesis
Ecole Polytechnique Fédérale de Lausanne
EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne (Switzerland)
Fax: (+41) 21-693-9700
E-mail: jerome.waser@epfl.ch
Homepage: http://isic.epfl.ch/lcso

[**] EPFL is acknowledged for financial support, Prof. Holger Frauenrath and Jan Gebers (LMOM, EPFL) for fruitful discussions, and Prof. Xile Hu (LSCI, EPFL) for proofreading this manuscript. TIPS–EBX = [(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201003179.

The scope of the reaction was then examined. 2-Alkyl-substituted thiophenes were alkynylated in good yields (Table 2, entries 1–2). Monoalkynylation of thiophene (**2c**) was achieved when thiophene was used as a solvent without TFA (Table 2, entry 3). 2-Methoxythiophene (**2d**) was also alkynylated without TFA (Table 2, entry 4).[15] The reaction was tolerant towards functional groups such as alcohols, carbamates, esters, and amides, including a protected amino acid (Table 2, entries 5–9). The reaction was slower in the presence of protected amines or esters, and full conversion could not be achieved under standard conditions. Fortunately, the use of 10 mol% of catalyst, two equivalents of TIPS–EBX, and a higher concentration of TFA afforded the desired products in moderate to good yields (Table 2, entries 7–9). Only traces of product were observed for less nucleophilic substrates with electron-withdrawing groups directly attached to the thiophene.[16]

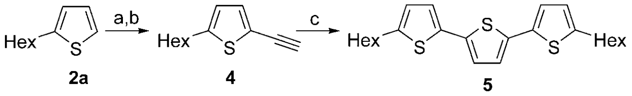
Table 2: Scope of the ethynylation of thiophenes.

Entry	Substrate	Product	Yield [%][a]
			
1	R = Hexyl **2a**	**3a**	83
2	R = Methyl **2b**	**3b**	80
3[b,c]	R = H **2c**	**3c**	73
4[c]	R = OMe **2d**	**3d**	68
5	R = CH_2OH **2e**	**3e**	50
6	R = CH_2CH_2OH **2f**	**3f**	65
7[d]	R = CH_2NHCbz **2g**	**3g**	81
8[d]	R = CH_2CO_2Et **2h**	**3h**	55
9[d]	R = C_2H_4NH(CbzVal) **2i**	**3i**	62
10[d]	R = Phenyl **2j**	**3j**	70
11[d]	R = 4-BrPhenyl **2k**	**3k**	67
12	R = 4-MeOPhenyl **2l**	**3l**	67
			
13	R^2 = Hexyl **2m**	**3m**	68
14[e]	R^2 = Methyl **2n**	**3n**	73
15[d]	R^2 = Bromo **2o**	**3o**	61
16	 **2p**	 **3p**	63
17[f]	 **2q**	 **3q**	70
18[g]	 **2q**	 **3r**	71
19	 **2r**	 **3s**	48
20[h]	 **2s**	 **3t**  **3u**	65
21[h]	 **2t**	 **3v**	73

[a] Reaction conditions: 0.40 mmol **2** (0.2 M in CH_3CN), 0.48 mmol **1**, 5 mol% AuCl, 0.48 mmol TFA, RT, 12–60 h. Yields of isolated products are shown.[b] Thiophene used as solvent. [c] Without TFA. [d] 2 equiv **1** and TFA, 10 mol% AuCl, **2** (0.4 M in CH_3CN). [e] Product was shown to be 85% pure by NMR spectroscopy. [f] Without TFA, 1 equiv **1**, 3 equiv **2q**. [g] 2.2 equiv **1** and TFA. [h] 1.5 equiv **1** and TFA; Cbz = carboxybenzyl; Val = valine.

We then turned to 2-aryl thiophenes, because substrates with extended π systems are more useful for applications in materials science (Table 2, entries 10–12). Gratifyingly, full conversion could be achieved (Table 2, entries 10–11). 4-Bromophenylthiophene (**2k**) could be successfully alkynylated, thus demonstrating the orthogonality of the method to classical cross-coupling reactions (Table 2, entry 11). The alkynylation of 2,2′-bithiophenes gave useful building blocks for the elaboration of oligothiophenes (Table 2, entries 13–15).[2] 3-Methoxythiophene (**2p**) was selectively alkynylated at the 2 position (Table 2, entry 16). 3,4-Ethylene-dioxythiophene (EDOT, **2q**) could be either mono- or bisalkynylated, depending on the reaction stoichiometry (Table 2, entries 17–18). Reaction of 2,5-methylthiophene (**2r**) furnished the 3-substituted alkynylated product **3s** in 48% yield (Table 2, entry 19). Less reactive benzothiophenes were then investigated; gratifyingly, full conversion was obtained with 5 mol% of AuCl for benzothiophene (**2s**), but no regioselectivity was observed (Table 2, entry 20).[17] Finally, reaction of 3-methylbenzothiophene (**2t**) afforded **3v** in 73% yield (Table 2, entry 21).

Our methodology allowed rapid access to oligothiophenes (Scheme 1). 2-Hexylthiophene (**2a**) was alkynylated under standard conditions and deprotected to afford acetylene **4** in 78% yield. Instead of the reported two-step sequence,[18] we developed a one-pot procedure that involves a copper-mediated dimerization and cyclization with Na_2S to give terthiophene **5** in 86% yield.



Scheme 1. Straightforward synthesis of terthiophene **5**. Reaction conditions: a) **1** (1.2 equiv), TFA (1.2 equiv), 5 mol% AuCl, CH_3CN, RT; b) tetra-*n*-butylammonium fluoride (TBAF; 1.2 equiv)), THF, 0°C, 78% over 2 steps; c) $Cu(OAc)_2$, (2 equiv), CH_3CN, 80°C, then $Na_2S{\cdot}3H_2O$ (4 equiv), 80°C, 18 h, 86%.

Our research group[7] and others[6k] have proposed that the gold-catalyzed alkynylation could proceed either through an Au^{III} acetylide complex or by π activation of the triple bond. A mechanism that involves a reaction at the iodine atom or a single-electron transfer[19] (SET) appeared less probable, as it would be difficult to rationalize the role of the metal catalyst. However, this possibility cannot be excluded at this stage. The cooperative effect observed here with Brønsted acids is particularly intriguing. TFA could promote the 2-auration of thiophene.[20] However, no product was obtained when 2-[(triphenylphosphine)gold]thiophene[21] was treated with **1** in the presence or absence of TFA. TIPS-EBX could also be activated by TFA.[9g–h] No product was observed when using the trifluoromethanesulfonic acid (TfOH) adduct of TIPS-EBX, but a 54% yield (determined by GC) was obtained when using the TFA adduct.[22] At this point, it is not clear if the latter TFA adduct represented an activated form of the reagent, or just served as a source of TFA during the reaction. Stoichiometric mixtures of AuCl and **1** gave 2-iodobenzoic acid and 1,4-bis(tri*iso*propylsilyl)buta-1,3-diyne; no strong effect of the TFA was observed.[23] No gold-containing intermediate could be detected, hence these results did not allow us to discriminate with certitude between an oxidative or a π-activation mechanism. Further investigations will be needed to understand the mechanism of the reaction and the Brønsted acid effect.

In summary, we have reported the first direct alkynylation of thiophenes mediated by gold and TFA at room temperature. The scope of the reaction included deactivated conjugated systems, such as aryl thiophenes, bithiophenes, and benzothiophenes, which are important for organic materials. The unique reactivity of TIPS-EBX is crucial for the success of the reaction. Activation by both the gold catalyst and the Brønsted acid was required; the discovery of this cooperative effect is expected to significantly expand the scope of benziodoxolone-based alkynylation reactions. Investigations on the mechanism and the extension of the scope of the reaction are currently under way in our laboratory.

Received: May 26, 2010

Keywords: alkynes · cooperative catalysis · direct alkynylation · heterocycles · hypervalent iodine

---

[1] *The Chemistry of Heterocyclic Compounds*, *Vol. 44*, Wiley-Interscience, New York, **1994**.

[2] a) A. R. Murphy, J. M. J. Frechet, *Chem. Rev.* **2007**, *107*, 1066; b) S. Allard, M. Forster, B. Souharce, H. Thiem, U. Scherf, *Angew. Chem.* **2008**, *120*, 4138; *Angew. Chem. Int. Ed.* **2008**, *47*, 4070; c) A. Mishra, C. Q. Ma, P. Bäuerle, *Chem. Rev.* **2009**, *109*, 1141.

[3] *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. De Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[4] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; b) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; c) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; For selected examples involving thiophenes, see: d) T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286; e) K. Masui, H. Ikegami, A. Mori, *J. Am. Chem. Soc.* **2004**, *126*, 5074; f) A. Battace, M. Lemhadri, T. Zair, H. Doucet, M. Santelli, *Adv. Synth. Catal.* **2007**, *349*, 2507; g) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622. For a metal-free approach, see: h) Y. Kita, K. Morimoto, M. Ito, C. Ogawa, A. Goto, T. Dohi, *J. Am. Chem. Soc.* **2009**, *131*, 1668.

[5] a) "Semiconducting Poly(arylene ethylene)s": T. M. Swager in *Acetylene Chemistry: Chemistry, Biology and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, **2005**; b) D. K. James, J. M. Tour, *Top. Curr. Chem.* **2005**, *257*, 33.

[6] For a review, see: a) A. S. Dudnik, V. Gevorgyan, *Angew. Chem.* **2010**, *122*, 2140; *Angew. Chem. Int. Ed.* **2010**, *49*, 2096. For selected examples, see: b) K. Kobayashi, M. Arisawa, M. Yamaguchi, *J. Am. Chem. Soc.* **2002**, *124*, 8528; c) M. Tobisu, Y. Ano, N. Chatani, *Org. Lett.* **2009**, *11*, 3250; d) I. V. Seregin, V. Ryabova, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 7742; e) N. Matsuyama, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 4156; f) F. Besselièvre, S. Piguel, *Angew. Chem.* **2009**, *121*, 9717; *Angew. Chem. Int. Ed.* **2009**, *48*, 9553; g) S. H. Kim, S. Chang, *Org. Lett.* **2010**, *12*, 1868; h) B. A. Trofimov, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, I. A. Ushakov, *Tetrahedron Lett.* **2004**, *45*, 6513; i) Y. H. Gu, X. M. Wang, *Tetrahedron Lett.* **2009**, *50*, 763; j) T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833; k) T. de Haro, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 1512; l) Y. Wei, H. Q. Zhao, J. Kan, W. P. Su, M. C. Hong, *J. Am. Chem. Soc.* **2010**, *132*, 2522.

[7] J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem.* **2009**, *121*, 9510; *Angew. Chem. Int. Ed.* **2009**, *48*, 9346.

[8] H. Mayr, A. R. Ofial, *J. Phys. Org. Chem.* **2008**, *21*, 584.

[9] For general reviews on hypervalent iodine, see: a) "Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis": T. Wirth, M. Ochiai, V. V. Zhdankin, G. F. Koser, H. Tohma, Y. Kita, *Topics of Current Chemistry*, *Vol. 224*, Springer, Berlin, **2003**; b) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; for selected examples of heterocycle functionalization using hypervalent iodine, see: c) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972; d) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593; e) E. A. Merritt, B. Olofsson, *Angew. Chem.* **2009**, *121*, 9214; *Angew. Chem. Int. Ed.* **2009**, *48*, 9052. For uses of benziodoxol(on)es, see: f) I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem.* **2007**, *119*, 768; *Angew. Chem. Int. Ed.* **2007**, *46*, 754; g) R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann, A. Togni, *Angew. Chem.* **2009**, *121*, 4396; *Angew. Chem. Int. Ed.* **2009**, *48*, 4332; h) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 4986; i) S. Nicolai, S. Erard, D. Gonzalez Fernandez, J. Waser, *Org. Lett.* **2010**, *12*, 384.

[10] The effect of the Brønsted acid described here is different from the reported acceleration of a proto-deauration step; see: A. S. K. Hashmi, *Catal. Today* **2007**, *122*, 211.

[11] See the Supporting Information.

[12] The success of TIPS-EBX **1** is probably caused by steric shielding, which prevents side reactions.

[13] For comparison, the corresponding TMS acetylene was obtained in two steps and 72% yield from 2-hexylthiophene (**2a**) by using a bromination–Sonogashira sequence: A. van Breemen, P. T. Herwig, C. H. T. Chlon, J. Sweelssen, H. F. M. Schoo, S. Setayesh, W. M. Hardeman, C. A. Martin, D. M. de Leeuw, J. J. P. Valeton, C. W. M. Bastiaansen, D. J. Broer, A. R. Popa-Merticaru, S. C. J. Meskers, *J. Am. Chem. Soc.* **2006**, *128*, 2336.

[14] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547. The synthesis of **1** proceeded in 79% yield over 2 steps from 2-iodobenzoic acid on a 30 g scale. This compound will soon be commercially available.

[15] For electron-rich thiophenes, the higher reactivity observed in presence of TFA is sometimes counterbalanced by the acid-mediated decomposition. In some cases, better yields are obtained without TFA. The optimal conditions are given in Table 2.

[16] 2-Bromo-3-hexyl-, 2-formyl- and 3-acetyl- thiophenes were tested.

[17] The low regioselectivity observed for benzothiophene could not yet be rationalized.

[18] J. Kagan, S. K. Arora, *J. Org. Chem.* **1983**, *48*, 4317.

[19] a) V. V. Grushin, *Acc. Chem. Res.* **1992**, *25*, 529; b) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka, Y. Kita, *Angew. Chem.* **2010**, *122*, 3406; *Angew. Chem. Int. Ed.* **2010**, *49*, 3334. When the reaction was carried out in the presence of 3,5-di-*tert*-butyl-4-hydroxytoluol (BHT), full conversion was observed, but the reaction was impeded by the addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). However, the result obtained with TEMPO could also be caused by the oxidative degradation of the catalyst.

[20] For selected examples of auration of aromatic C−H bonds, see: a) Z. G. Li, D. A. Capretto, R. O. Rahaman, C. He, *J. Am. Chem. Soc.* **2007**, *129*, 12058; b) P. F. Lu, T. C. Boorman, A. M. Z. Slawin, I. Larrosa, *J. Am. Chem. Soc.* **2010**, *132*, 5580. For examples of reactions of organogold intermediates with oxidants, see: c) A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *J. Organomet. Chem.* **2009**, *694*, 592 – 597. For a selected review on gold catalysis, see: d) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180.

[21] F. Bonati, A. Burini, B. R. Pietroni, R. Galassi, *Gazz. Chim. Ital.* **1993**, *123*, 691. [AuPPh$_3$Cl] itself was a viable catalyst for the reaction, although less efficient than AuCl (see the Supporting Information).

[22] The TfOH adduct of **1** is a well-behaved solid compound that could be fully characterized (see the Supporting Information). In contrast, the TFA adduct gave an oil upon evaporation of the solvent; further studies to determine its structure are under way.

[23] 1,4-Bis(triisopropylsilyl)buta-1,3-diyne and 2-iodo benzoic acid were detected as the major products by ^{1}H NMR spectroscopy and GC–MS, but could not be separated from other impurities formed during the reaction.