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Para-Selective Gold-Catalyzed Direct Alkynylation of Anilines

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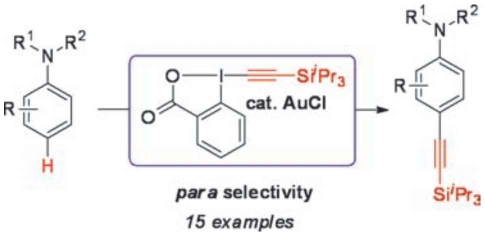
ABSTRACT



A method for the para-selective alkynylation of anilines is reported using AuCl as catalyst and tri*iso*propylsilylethynyl-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) as an electrophilic acetylene equivalent. Para-alkynyl anilines substituted at positions 2 or 3 were obtained in one step from simple anilines under mild conditions (room temperature to 60 °C) under air. The methodology could also be extended to the alkynylation of trimethoxybenzenes.

Heteroarylacetylenes are important structures in both organic synthesis and material sciences.[1] They are versatile building blocks thanks to the large number of transformations available based on the functionalization of the triple bond. In addition, both aromatics and acetylenes have been successfully used in extended π systems for organic electronic materials.[2] To access heteroarylacetylenes, the Sonogashira reaction is one of the most popular methods for sp^2–sp bond formation.[3] However, the main drawback of this method is the required prefunctionalization of the sp^2 carbon. Numerous methods have been developed in the field of C–H arylation to avoid this prefunctionalization of aromatics.[4] Surprinsingly, reports of direct alkynylations were scarce up to 2009.[5] Since then, important breakthroughs have been realized and several groups reported new C–H alkynylation methods.[6] Our group especially focused on the functionalization of electron-rich heterocycles such as indoles, pyrroles and thiophenes using tri*iso*propylsilylethynyl-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX (**1**)) as an electrophilic alkynylation reagent and AuCl as catalyst.[7] The focus on the synthesis of silylated acetylenes is motivated by their simple deprotection to access the synthetically highly versatile terminal alkynes.

Presently, there are only two reports for the alkynylation of anilines by Yamaguchi and Chatani,[5b,6j] with both

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(1) Diederich, F.; Stang, P. J.; Tykwinski, R. R. *Acetylene Chemistry: Chemistry, Biology and Material Science*; Wiley-VCH: Weinheim, 2005.

(2) (a) Tour, J. M. *Acc. Chem. Res.* **2000**, *33*, 791. (b) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537. (c) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (d) Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, *201*, 81. (e) Youngs, W. J.; Tessier, C. A.; Bradshaw, J. D. *Chem. Rev.* **1999**, *99*, 3153. (f) Haley, M. M. *Synlett* **1998**, 557. (g) Pinto, M. R.; Schanze, K. S. *Synthesis* **2002**, 1293. (h) Yamamoto, T. *Synlett* **2003**, 425. (i) Tobe, Y.; Sonoda, M. In *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley VCH: Weinheim, 2004; p 1. (j) Swager, T. M.; Semiconducting Poly(arylene ethylene)s. In *Acetylene Chemistry: Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005. (k) James, D. K.; Tour, J. M. *Top. Curr. Chem.* **2005**, *257*, 33.

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(5) (a) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528. (b) Amemiya, R.; Fujii, A.; Arisawa, M.; Yamaguchi, M. *J. Organomet. Chem.* **2003**, *686*, 94. (c) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. For non catalytic methods, see: (d) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. I.; Ushakov, I. A. *Tetrahedron Lett.* **2004**, *45*, 6513. (e) Kalinin, V. N.; Pashchenko, D. N.; She, F. M. *Mendeleev Commun.* **1992**, 60.

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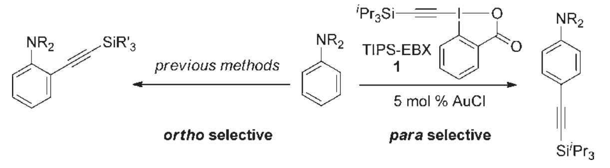
methods affording exclusively ortho-alkynylated products. This selectivity was rationalized by a mechanism involving a directing effect of the nitrogen functional group. As the gold-catalyzed alkynylation did not require a directing group, we hypothesized that para-selective functionalization could be realized (Scheme 1). Herein, we report the development of the first para-selective alkynylation of anilines using TIPS-EBX (**1**) as acetylene-transfer reagent, which proceeds under mild conditions (room temperature to 60 °C, ambient atmosphere).

Scheme 1. Direct Alkynylation of Anilines



Para-alkynyl anilines are widely used in material sciences, especially as strong electron donors in push–pull chromophores for applications in optoelectronic devices (Figure 1).[8] For example, tetraalkyne **2** has shown easily tunable photochromic properties.[8f] The tetraethynylene **3** (TEES) has molecular photoswitch properties.[8d] Furthermore, ethynylanilines are used as starting materials for the synthesis of chromophores based on core structure **4** via [2 + 2]-cycloaddition with tetracyanoethene followed by retro-electrocyclization.[8e] Consequently, an efficient access to para-alkynylated anilines would lead to a more straightforward synthesis of electronic organic materials.

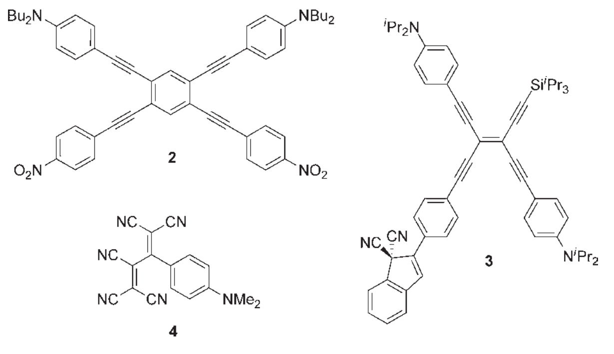


Figure 1. Para-alkynyl anilines in material sciences.

Gold catalysis has recently been investigated for the direct functionalization of benzene rings via amination,[9] alkylation,[10] hydroarylation,[11] and arylation.[12] Only one example of the catalytic use of gold for the alkynylation of benzene rings has been reported, but no anilines were used in that work.[6l,13] Moreover, there are only two single examples of gold-catalyzed direct functionalization of anilines for amination[9b] and hydroarylation.[11d] Consequently, the extension of the alkynylation reaction to anilines would constitute an important advance, not only in the field of acetylene chemistry but also for gold catalysis in general, especially in light of nitrogen-containing groups being reported to deactivate gold catalysts in several cases.[14]

To investigate the alkynylation of protected anilines with TIPS-EBX (**1**),[15] we decided to use *N*,*N*-benzylaniline (**5a**) as model compound since it is more nucleophilic than the corresponding carbamate and the benzyl groups are easily removed by hydrogenation. Unfortunately, the reaction conditions previously optimized for indoles[7a] only afforded a 14% yield employing *N*,*N*-dibenzylaniline (**5a**) as substrate (Table 1, entry 1) due to low conversion. The outcome of the reaction was highly dependent on the solvent, with ^{i}PrOH giving the best result (entries 2–4). No ortho alkynylation was observed for aniline **5a**. The use of 1.4 equiv of TIPS-EBX (**1**) was optimal (entries 4–6). The use of a higher concentration did not improve the yield (entry 7). Best results were obtained when the reaction was not pushed to full conversion to prevent the formation of

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(6) Reviews: (a) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem. Int., Ed.* **2010**, *49*, 2096. (b) Messaoudi, S.; Brion, J. D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495. Selected examples: (c) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. (d) Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 1764. (e) Kitahara, M.; Hirano, K.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 1772. (f) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358. (g) Besselievre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (h) Berciano, B. P.; Lebrequier, S.; Besselievre, F.; Piguel, S. *Org. Lett.* **2010**, *12*, 4038. (i) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868. (j) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (k) Gu, Y. H.; Wang, X. M. *Tetrahedron Lett.* **2009**, *50*, 763. (l) de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512. (m) Yang, L.; Zhao, L. A.; Li, C. J. *Chem. Commun.* **2010**, *46*, 4184.

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(8) Selected examples: (a) Kivala, M.; Diederich, F. *Acc. Chem. Res.* **2009**, *42*, 235. (b) Gobbi, L.; Elmaci, N.; Luthi, H. P.; Diederich, F. *ChemPhysChem* **2001**, *2*, 423. (c) Bosshard, C.; Spreiter, R.; Gunter, P.; Tykwinski, R. R.; Schreiber, M.; Diederich, F. *Adv. Mater.* **1996**, *8*, 231. (d) Gobbi, L.; Seiler, P.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 674. (e) Reutenauer, P.; Kivala, M.; Jarowski, P. D.; Boudon, C.; Gisselbrecht, J. P.; Gross, M.; Diederich, F. *Chem. Commun.* **2007**, 4898. (f) Marsden, J. A.; Miller, J. J.; Shirtcliff, L. D.; Haley, M. M. *J. Am. Chem. Soc.* **2005**, *127*, 2464.

(9) (a) Li, Z. G.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058. (b) Gu, L.; Neo, B. S.; Zhang, Y. *Org. Lett.* **2011**, *13*, 1872.

(10) Shi, Z. J.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596.

(11) Selected examples: (a) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. (b) Shi, Z. J.; He, C. *J. Org. Chem.* **2004**, *69*, 3669. (c) Reich, N. W.; Yang, C. G.; Shi, Z. J.; He, C. *Synlett* **2006**, 1278. (d) Jean, M.; van de Weghe, P. *Tetrahedron Lett.* **2011**, *52*, 3509.

(12) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, 386.

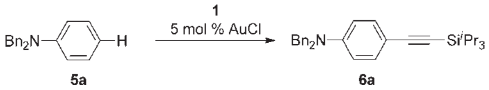
(13) For the stoichiometric use of gold, see: Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330.

(14) (a) Belot, S.; Vogt, K. A.; Besnard, C.; Krause, N.; Alexakis, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8923. (b) Monge, D.; Jensen, K. L.; Franke, P. T.; Lykke, L.; Jorgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 9478. (c) Loh, C. C. J.; Badorrek, J.; Raabe, G.; Enders, D. *Chem.—Eur. J.* **2011**, *17*, 13409.

(15) Our work has been focused on TIPS-EBX (**1**) to afford easy to deprotect silyl acetylenes. Furthermore, a bulky silyl group was shown to be essential for the success of the reaction, see ref 7. Indeed, no product was obtained using phenylethynyl-1,2-benziodoxol-3(1*H*)-one as acetylene transfer reagent.

side products. In this case, the starting material could easily be recovered. The obtained yields are in the same range as those obtained in the current state-of-the-art direct para-functionalizations of anilines.[16]

Table 1. Optimization of the Para-alkynylation of Anilines



entry	solvent	TIPS-EBX (**1**) equivalents	yield[a] (%)
1	Et$_2$O	1.2	14
2	CH$_2$Cl$_2$	1.2	49
3	CH$_3$CN	1.2	51
4	^{i}PrOH	1.2	58
5	^{i}PrOH	1.4	73 (84)[b]
6	^{i}PrOH	1.6	55
7[c]	^{i}PrOH	1.4	68 (81)[b]

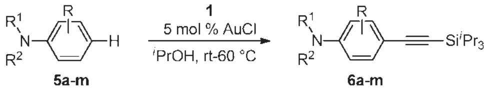
[a] Reaction conditions: 0.20 mmol *N*,*N*-dibenzylaniline (**5a**), 0.01 mmol AuCl in 4 mL ^{i}PrOH at 23 °C under air. Isolated yield after column chromatography. [b] Yield based on recovered starting material (brsm). [c] Two milliliters of ^{i}PrOH.

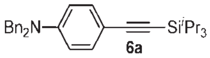
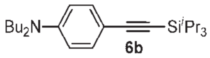
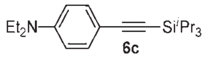
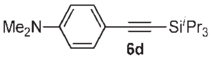
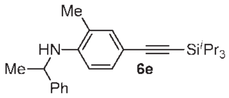
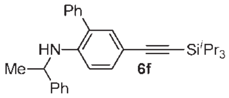
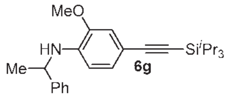
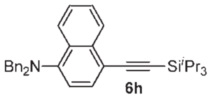
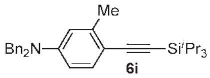
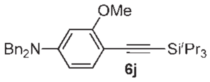
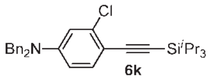
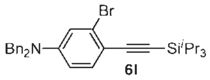
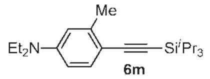
We then focused our attention on the scope of the reaction (Table 2). In addition to benzyl (entry 1), butyl, ethyl and methyl groups were tolerated as nitrogen substituents, but led to lower yields (entries 2–4). Smaller alkyl groups led to a complex mixture of side products, including 8% of the ortho–para disubstituted product for R = Me (entry 4). These results indicate that the process has the regioselectivity of an aromatic electrophilic substitution. It is in line with our previous highly SEAr regioselective methodologies for the alkynylation of indoles, pyrroles, and thiophenes.[7a,b]

Ortho-methyl, -phenyl, and -methoxy groups were tolerated for monoprotected anilines (entries 5–7).[17] This result also demonstrated that the method was tolerant toward a free NH bond on the aniline. The alkynylation reaction was even successful in the case of the less reactive dibenzyl 2-aminonaphthalene (**5h**), although full conversion could not be achieved in this case (entry 8).

Importantly, alkynylation was also possible for alkyl, methoxy, chloro and bromo groups in the meta position, giving more sterically hindered 1,3,4-substituted anilines (entries 9–13). In addition, the tolerance to chloro and bromo substituents demonstrated the orthogonality of the method to classical Pd cross-couplings. Low yields of ortho-alkynylated products were obtained using para-substituted anilines.[18] In the case of 4-methyl-*N*,*N*-dimethyl aniline (**5n**), one of the main products obtained was the sp^3 coupling product on the methyl substituent of the nitrogen (eq 1). This reaction can easily be achieved with free acetylenes and metal catalysts under oxidative conditions.[19] Consequently, it could indicate that this product results from the relatively high oxidation capacity of TIPS-EBX (**1**).

Table 2. Scope of the Para-alkynylation of Anilines[a]



entry	product	yield (%)[b]
1		73% (84%)[c]
2		63%
3		44%
4[d]		46% (8%)[c]
5		64%
6[d]		65%
7[d]		42% (70%)[c]
8[d]		35% (65%)[c]
9[d]		73%
10[d]		85%
11[d]		41% (72%)[c]
12[d]		35% (61%)[c]
13[d]		75%

[a] Reaction conditions: 0.40 mmol **5**, 0.56 mmol **1**, 0.02 mmol AuCl in 8 mL ^{i}PrOH at 23 °C under air. Isolated yields. [b] Yields based on recovered starting materials are given in parentheses. [c] At 60 °C in 2 mL of ^{i}PrOH. [d] Ortho–para disubstituted product.

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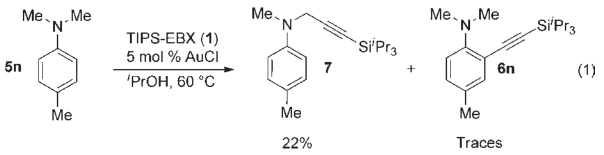
(16) Ciana, C. L.; Phipps, R. J.; Brandt, J. R.; Meyer, F. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458.

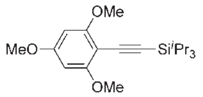
(17) Ortho substituted *N*,*N*-disubstituted anilines were not reactive, probably because of the deconjugation of the nitrogen for steric reasons.

(18) 4-Methyl-*N*,*N*-dibenzylaniline was ortho alkynylated in 18% yield.

(19) For sp^3 alkynylation of dimethylaniline (**5d**), see: (a) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701. (c) Liu, P.; Zhou, C. Y.; Xiang, S.; Che, C. M. *Chem. Commun.* **2010**, *46*, 2739. For cyanation of dimethylaniline (**5d**) using hypervalent iodine, see: (d) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, *36*, 7975. For sp^3 cyanation of dimethylaniline (**5d**) using a gold complexe, see: (e) Zhang, Y.; Peng, H.; Zhang, M.; Cheng, Y. X.; Zhu, C. J. *Chem. Commun.* **2011**, *47*, 2354.



In addition to anilines, the reaction could also be applied toward the alkynylation of trimethoxybenzenes (Figure 2). Up to now, the only report for the alkynylation of this class of substrates was limited to the use of more electron-deficient propiolic acid derivatives.[61] The use of TIPS-EBX (**1**) allowed access to an easily deprotectible nonelectron-deficient acetylene.


8a, 51% (80%)

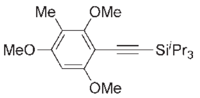

8b, 50% (79%)

Figure 2. Alkynylation of trimethoxybenzenes. Reaction conditions: 0.40 mmol trimethoxybenzene, 0.56 mmol **1**, 0.02 mmol AuCl in 2 mL ^{i}PrOH at 60 °C under air. Isolated yields. Yields based on recovered starting materials under parentheses.

In conclusion, we have developed the first para-selective direct alkynylation of anilines using gold chloride as catalyst and TIPS-EBX (**1**) as acetylene-transfer reagent. The method allowed a new and efficient access to important building blocks in synthetic chemistry and material sciences under mild reaction conditions and at ambient atmosphere. We demonstrated that a wide range of anilines could be alkynylated regioselectively using the developed methodology. Investigations toward the elucidation of the reaction mechanism are currently ongoing in our laboratory.

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

The authors declare no competing financial interest.