

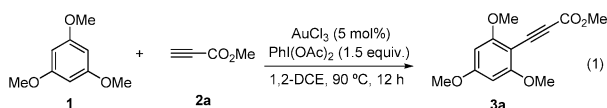
Gold-Catalyzed Ethynylation of Arenes

Teresa de Haro and Cristina Nevado*

Organic Chemistry Institute, University of Zürich, Winterthurerstrasse 190, CH-8057, Zürich, Switzerland

Received November 16, 2009; E-mail: nevado@oci.uzh.ch

The introduction of acetylenic groups in organic molecules is an important synthetic transformation. Among all available methods,¹ the Sonogashira cross-coupling reaction is the most widely spread.² Due to its versatility, the palladium-catalyzed C_{sp^2} – C_{sp} reaction between aryl halides (particularly iodides) and terminal alkynes, with or without the presence of a copper cocatalyst, efficiently produces aryl-alkynes, which are precursors for bioactive natural molecules, pharmaceuticals, and molecular organic materials.³ Nevertheless, several drawbacks still limit the scope of this ubiquitous transformation: first, alkynes containing electron-withdrawing groups directly attached to the ethynyl carbon poorly react with aryl halides.⁴ Second, if the aromatic halide is “deactivated”, that is, electron-rich, oxidative addition is more difficult making any cross-coupling reaction extremely challenging.⁵ Activation of aromatic C–H bonds followed by C–C bond formation constitutes a conceptually attractive methodology since it avoids the otherwise necessary prefunctionalization of the aromatic counterpart.⁶ Described here is the first ethynylation of “deactivated” arenes with electron-deficient alkynes via a gold-catalyzed C–H functionalization of both aromatic and acetylenic counterparts.⁷



The reaction of 1,3,5-trimethoxybenzene (**1**) with methyl propiolate (**2a**) in the presence of $AuCl_3$ (5 mol %) and $PhI(OAc)_2$ (1.5 equiv.) in 1,2-dichloroethane at 90 °C afforded 3-(2,4,6-trimethoxyphenyl)propiolate (**3a**) in 45% yield (eq 1). Neither previously described hydroarylation of the alkyne⁸ nor homocoupling of the aromatic counterpart was detected in the reaction mixture.⁹ This result prompted us to optimize the reaction conditions and study its scope.¹⁰

We first examined the influence of the gold source on the reaction: cationic gold complexes such as $Ph_3PAuNTf_2$ or $Ph_3PAuOTf$ afforded **3a** in 43 and 70% yield respectively (Table 1, entries 1–2). Surprisingly, when neutral PPh_3AuCl was used, 72% yield of **3a** was obtained becoming the catalyst of choice for the reaction (entry 3). Other metals such as Pd(II) or Cu(I) did not effect the above-mentioned transformation (Table 1, entries 4 and 5). Next, we studied the sensitivity of the reaction to both solvent polarity and coordinating ability: toluene afforded **3a** in 28% yield, whereas polar nitromethane or acetonitrile delivered the product in trace amounts (entry 6). The presence of water totally inhibited the desired reactivity (Table 1, entry 7). Addition of different bases was also examined:¹⁰ MgO and K_2CO_3 showed moderate improvement (entry 8), whereas $NaHCO_3$ afforded **3a** in an optimized 85% yield (entry 9). Finally, the key role of the oxidant was unravelled. $PhIO$ gave **3a** in 55% yield (entry 10), whereas neither selectfluor nor *tert*-butylhydroperoxide, well-known oxidants for gold catalysts,¹¹ effects any conversion of **1** (Table 1, entries 11–12). Thus, we decided to use conditions from entry 9 to study the reaction scope.

Table 1. Optimization for the Au-Catalyzed Ethynylation of **1**

entry	reaction conditions ^a	yield % ^b
1 ^c	$Ph_3PAuNTf_2$ (5 mol %), 1,2-DCE	43
2 ^c	$Ph_3PAuOTf$ (5 mol %), 1,2-DCE	70
3 ^c	Ph_3PAuCl (5 mol %), 1,2-DCE	72
4 ^d	$Pd(OAc)_2$ (5 mol %), 1,2-DCE	—
5 ^d	CuI (5 mol %), 1,2-DCE	—
6 ^c	Ph_3PAuCl (5 mol %), Toluene/ CH_3NO_2 / CH_3CN	28/7/6
7 ^c	Ph_3PAuCl (5 mol %), 1,2-DCE/ H_2O (100:1)	—
8 ^c	Ph_3PAuCl (5 mol %), MgO / K_2CO_3 (1.5 equiv), 1,2-DCE	64/77
9 ^c	Ph_3PAuCl (5 mol %), $NaHCO_3$ (1 equiv), 1,2-DCE	85 (81%)^e
10	Ph_3PAuCl (5 mol %), $NaHCO_3$ (1 equiv), $PhIO$	55
11	Ph_3PAuCl (5 mol %), $NaHCO_3$ (1 equiv), Selectfluor	—
12	Ph_3PAuCl (5 mol %), $NaHCO_3$ (1 equiv), <i>t</i> -BuOOH	—

^a Reaction conditions: **1** (2 equiv), **2a** (1 equiv), 0.5 M at 90 °C in a sealed tube for 12 h. ^b Determined by GC-MS (isolated yield in brackets). ^c $PhI(OAc)_2$ (1.5 equiv). ^d With and without $PhI(OAc)_2$. ^e 2-Iodo-1,3,5-trimethoxybenzene **4** could be isolated in 20% yield in entries 1–10.¹²

Table 2. Scope of Au-Catalyzed Ethynylation of **1**^a

entry	substrate	product (yield %) ^b
1	2b , Z = CO_2Et	3b (75)
2	2c , Z = CO_2tBu	3c (60)
3	2d , Z = $COPh$	3d (72)
4	2e , Z = $CO(3,5\text{-dimethoxy-phenyl})$	3e (68)
5	2f , Z = $CO(p\text{-}CF_3C_6H_4)$	3f (70)
6	2g , Z = $COtBu$	3g (31) ^c
7	2h , Z = $CO(C_7H_{12})$	3h (66)
8	2i , Z = $(CH_3)_2C=CH_2$	3i (48)
9	2j , Z = Ph	3j (25)

^a Reactions carried out with **1** (2 equiv), **2b–j** (1 equiv), 0.5 M in a sealed tube. ^b Isolated yield after column chromatography. ^c Microwave reactor: 62% yield based on recovered starting material (**1**).

The ethynylation reactions of **1** with various terminal alkynes have been summarized in Table 2. Ethyl and *tert*-butyl propiolates **2b–c** showed a comparable reactivity to **2a** (Table 2, entries 1–2). Aromatic as well as aliphatic acetylenic ketones (**2d–h**) could also be efficiently coupled with this method to give arylated products **3d–h** in moderate to good yields (entries 3–7). The reaction of **1** with methyl enyne **2i** afforded aryl-substituted enyne **3i** in 48% yield (entry 8). Finally, phenyl acetylene **2j** produced the expected ethynylated product (**3j**) in low yield due to homocoupling of the alkyne (entry 9).

We have extended this reaction to other electron-rich aromatic rings. The presence of groups such as benzyl, *iso*-propyl, and methoxymethyl (MOM) ethers (**5a–d**) was well tolerated affording the corresponding ethynylation products **6a–d** as regiomeric mixtures in good yields (Table 3). Substrates such as **5e–h** were transformed into single regioisomers **6e–h** in moderate yields, revealing that *para*/*ortho*- is

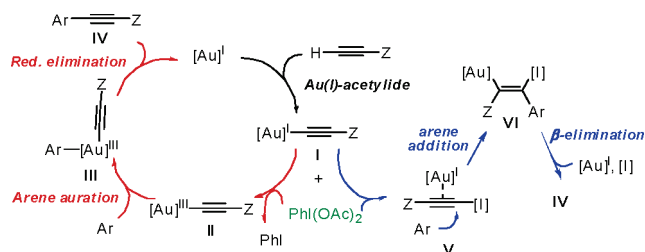
Table 3. Scope of Au-Catalyzed Ethynylation of Arenes^a

Substrate ^b	products, yield(%) ^c	Substrate ^b	products, (yield %) ^c
 5a: R ¹ =R ³ =OMe, R ⁵ =OBn 5b: R ¹ =R ³ =OMe, R ⁵ =O <i>i</i> Pr 5c: R ¹ =R ³ =OMe, R ⁵ =OMOM 5d: R ¹ =R ³ =R ⁵ =OBn 5e: R ¹ =R ² =R ⁴ =OMe 5f: R ¹ =R ² =R ³ =OMe 5g: R ¹ =R ³ =OMe 5h: R ³ =OMe, R ⁵ =R ⁶ =OCH ₂ O 5i: R ¹ =R ³ =OMe, R ⁵ =Me 5j: R ¹ =R ³ =R ⁵ =OMe, R ² =Me 5k: R ¹ =R ² =R ⁶ =OMe, R ⁴ =Me	 6a+6a': (R ^{2/4} =Z), 75 ^d 6b+6b': (R ^{2/4} =Z), 62 ^d 6c+6c': (R ^{2/4} =Z), 75 ^d 6d (R ² =Z), 42 6e (R ⁵ =Z), 56 6f (R ⁴ =Z), 25 6g (R ⁴ =Z), 52 6h (R ² =Z), 40 6i (R ⁴ =Z), 70 6j (R ⁴ =Z), 60 6k (R ³ =Z), 51	 7	 8a (43)
		 9	 10a (60)
		 11	 12a (48)
			 12b (22)

^a Reaction conditions: arene (2 equiv), **2a** (1 equiv), Ph₃PAuCl (5 mol %), PhI(OAc)₂ (1.5 equiv) in 1,2-DCE (0.5 M) at 90 °C in a sealed tube. ^b Undefined substituents: R³=H; Z = -C≡C(CO₂Me). ^c Isolated yield after column chromatography. ^d Ratio 2:1. ^e PhI(OAc)₂ (1 equiv), preheated oil bath.

preferred over *ortho/ortho*-activation in the arene. The presence of inductive donating groups as in the case of **5i–k** was also well accommodated although mesomeric activation seemed to be preferred. Heteroaromatic rings are also suitable substrates for this reaction:¹³ *N*-benzyl pyrrole (**7**) delivered ethynylated regioisomers **8a** and **8b** in 43 and 26% yield respectively. *N*-Benzyl indole **9** afforded **10a** in 60% yield together with acetoxy derivative **10b**. Finally, conjugated system **11** produced the cross-coupling products in both the chromene (**12a**) and aromatic ring (**12b**) in 48 and 22% yield respectively. In all cases, no hydroarylation products could be detected in the reaction mixtures.

Scheme 1. Mechanistic Proposal for the Au-Catalyzed Ethynylation of Arenes



NMR experiments were conducted to elucidate the reaction mechanism. ³¹P NMR analysis of the reaction of **2a** with a stoichiometric amount of Ph₃PAuCl in CD₂Cl₂ showed a sharp peak at 34.2 ppm, which corresponds to the pure complex. Upon heating to 90 °C, a new signal at 42.3 ppm was observed. This peak is attributed to the formation of gold(I)-acetylide **I** (see Scheme 1, Z = CO₂Me) by comparison with a pure sample of this complex synthesized independently.¹⁴ Interestingly, in the catalytic reaction of compound **5i** with **2a**, the formation of complex **I** could also be detected by ¹H and ³¹P NMR.¹⁰

Reaction kinetics were also studied, showing this transformation to be first-order in both alkyne and arene reactants.¹⁰ The rates of the reactions of **1** vs **1-d₃** and **2d** vs **2d-d₁** were compared to determine if C–H/C–D bond breaking was involved in the rate-determining step. The rate constants were found to be 1.2 × 10^{−4} and 1.3 × 10^{−4} s^{−1} for **2d** and **2d-d₁** and 2.3 × 10^{−5} s^{−1} and 2.0 × 10^{−5} s^{−1} for **1** and **1-d₃** respectively. The lack of primary effect in these intermolecular isotope effect experiments clearly indicated that neither the C_{sp} nor the C_{sp}²–H bond breaking is involved in the rate-determining step of this ethynylation reaction.

With these results in hand, two possible reaction pathways can be envisioned starting with the formation of the gold(I)-acetylide complex (**I**). In the presence of PhI(OAc)₂, **I** can be oxidized to a gold(III)-alkynyl intermediate (**II**).¹⁵ The reaction of the arene with complex **II** might occur via electrophilic aromatic substitution to give complex **III**.¹⁶ Finally, upon reductive elimination, the new C_{sp}²–C_{sp} bond is formed and the alkynylated products (**IV**) are obtained (Scheme 1, red path). Alternatively, the reaction of **I** with PhI(OAc)₂ could afford an electrophilic alkynyl-iodonium complex (**V**). A gold-mediated addition of the aromatic ring to the triple bond in **V** affords a vinyl gold intermediate **VI**, which upon β-elimination would deliver the arylated alkynes **IV** (Scheme 1, blue path).

In summary, we report here the first gold-catalyzed ethynylation of arenes with electron-deficient alkynes via gold catalyzed C–H activation of both C_{sp} and C_{sp}²–H bonds. This transformation provides aromatic propiolates difficult to prepare by other methods. Further studies to expand the reaction scope and gain a deeper insight into the reaction mechanism are currently underway and will be reported in due course.

Acknowledgment. The Organic Chemistry Institute of the University of Zürich is kindly acknowledged for financial support.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, p 271.
- (2) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Sonogashira, K. In *Metal-Catalyzed Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York 1998, p 203.
- (3) (a) *Modern Acetylene Chemistry*; Stang, P. J.; Diederich, F., Eds.; VCH: Weinheim, 1995. (b) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: Berlin, 1998; p 198.
- (4) (a) Yoneda, N.; Matsuoka, S.; Miyaura, N.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1990**, 63, 2124. (b) Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y.; Yamanaka, H. *Synthesis* **1992**, 746. (c) Kundu, N. G.; Dasgupta, S. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2657. For exceptions, see: (d) Eckert, T.; Ipaktschi, J. *Synth. Commun.* **1998**, 28, 327.
- (5) Hegedus, L. S. In *Organometallics in Synthesis*; Schlosser, M., Eds.; Wiley-VCH: New York, 2002; p 1150.
- (6) (a) Ru: Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, 366, 529. (b) Pd: Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, 287, 1992.
- (7) For a stoichiometric version of this reaction, see: Fuchita, Y.; Utsonomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330.
- (8) (a) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. (b) Shi, Z.; He, C. *J. Org. Chem.* **2004**, 69, 3669. (c) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 2, 167.
- (9) (a) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, 386. (b) Kar, A.; Mangu, N.; Kaiser, H. M.; Tse, M. K. *J. Organomet. Chem.* **2009**, 694, 524.
- (10) Further studies can be found in the Supporting Information.
- (11) (a) Wegner, H. A.; Ahles, S.; Neuenburg, M. *Chem.–Eur. J.* **2008**, 14, 11310. (b) Cui, L.; Zhang, G.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2009**, 19, 3884. (c) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009**, 48, 3112.
- (12) Reaction of **4** with **2a** under the optimized conditions from Table 1 did not afford compound **3a**, ruling out a gold-catalyzed Sonogashira reaction mechanism; see: González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, 46, 1536.
- (13) A Au-catalyzed ethynylation of indoles and pyrroles appeared during the preparation of this manuscript; see: Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, 48, 9346.
- (14) Bruce, M. I.; Horn, E.; Matison, J. G.; Snow, M. R. *Aust. J. Chem.* **1984**, 37, 1163.
- (15) (a) Iglesias, A.; Muñoz, K. *Chem.–Eur. J.* **2009**, 48, 9346. (b) MuSchuster, O.; Liao, R.-Y.; Schier, A.; Schmidbaur, H. *Inorg. Chim. Acta* **2005**, 358, 1429.
- (16) If C_{sp}²–H activation would be involved, primary KIE should have been observed: Gretz, E.; Oliver, T. F.; Sen, A. *J. Am. Chem. Soc.* **1987**, 109, 8109.

JA909726H