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Synthesis of Trifluoromethyl-allenes by Gold-Catalyzed Rearrangement of Propargyl Benzyl Ethers

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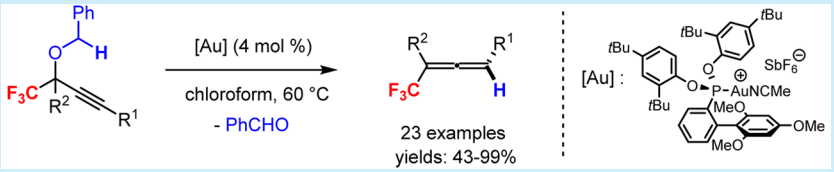
Supporting Information

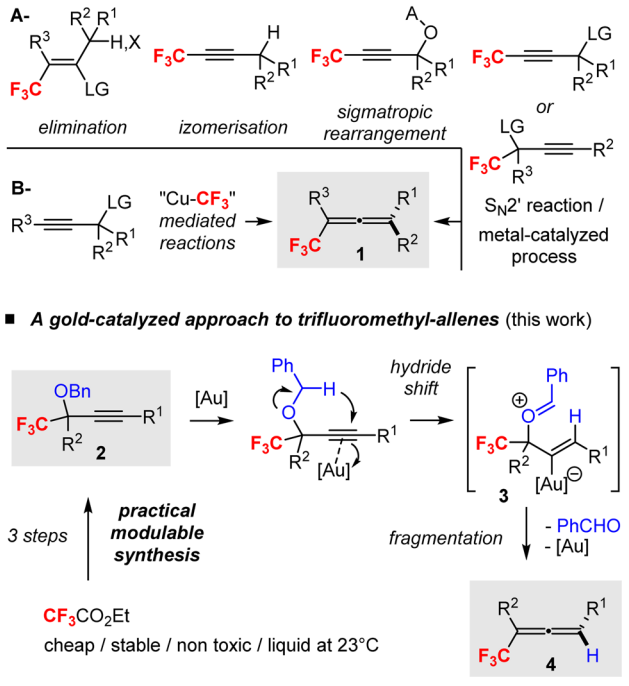


ABSTRACT: A new method for the synthesis of trifluoromethyl-allenes from easily accessible α-trifluoromethyl-propargyl benzyl ether derivatives following a gold-catalyzed intramolecular hydride transfer has been developed. Various di- and trisubstituted trifluoromethyl-allenes were obtained in good to excellent yields.

CF_3-containing building blocks are privileged structural motifs in medicinal chemistry and agrochemistry.[1] As a consequence, substantial efforts have been made over the years by synthetic organic chemists in order to design and develop methods allowing efficient access to a variety of trifluoromethylated species.[2] Given the unique reactivity of allenes[3] and their ability to react in a wide range of transformations to build up valuable complex structures,[4] special attention has naturally been brought to trifluoromethyl-allenes and how to access them. The first syntheses of CF_3-allenes, which were reported several decades ago,[5] generally suffer from low efficiency and exhibit limited scope. Current efforts in the domain are focused on addressing these issues. From a general point of view, currently available synthetic routes to CF_3-allenes **1** can be classified into two main categories **A** and **B** (Scheme 1, top). CF_3-allenes can be prepared starting from alkynyl or alkenyl substrates already possessing a CF_3 moiety (category **A**) by elimination reactions,[6] isomerizations,[7] sigmatropic rearrangements,[8] S_N2' reactions,[9] and metal-catalyzed processes.[10,11] A more recently developed alternative access to CF_3-allenes relies on the use of a "Cu-CF_3" reagent to introduce the CF_3 moiety on an activated alkynyl substrate (category **B**).[12] Even if these different methods are complementary with each other and allow an overall access to a variety of functionalized CF_3-allenes, they are still suffering some limitations mainly in terms of product formation selectivity and substrate accessibility.

Taking into account that alkyne derivatives are privileged substrates for the synthesis of CF_3-allenes **1** (Scheme 1, top) and considering the remarkable ability of gold catalysts to convert alkynes into a range of valuable structural motifs,[13] we envisaged gold catalysis as a potential useful synthetic tool for the rapid, efficient, and selective synthesis of a range of diversely substituted CF_3-allenes.[14]

Scheme 1. Synthetic Approaches to Trifluoromethyl-allenes



Our strategy, which is presented in the bottom part of Scheme 1, relies on previous findings by us and others that gold catalysts could be used to convert propargyl benzyl ethers into

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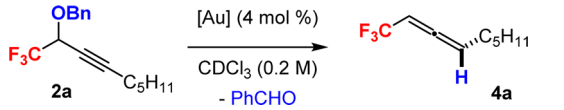
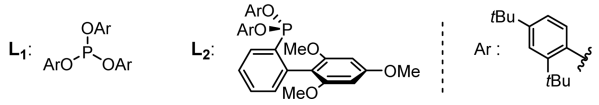
allenes.[15,16] We indeed conceived that an activation of alkyne substrate **2** by an electrophilic gold species might induce a 1,5-hydride shift that would lead to the formation of an oxocarbenium intermediate **3**. A subsequent elimination of benzaldehyde with concomitant regeneration of the gold catalyst would deliver CF_3-allene **4**. This approach, which could lead to the formation of up to trisubstituted CF_3-allenes, appeared to be particularly appealing since the required trifluoromethylated substrates **2** could be rapidly and conveniently obtained in a three-step sequence starting from the readily available and relatively cheap ethyl trifluoroacetate.

We started our investigations with model substrate **2a** and looked for catalytic conditions that could allow its conversion into CF_3-allene **4a**. The main results are compiled into Table 1.

Table 1. Optimization of the Catalytic System



entry	catalyst [Au]	temp (°C)	time (h)	yield **4a** (%)[a]
1	[(XPhos)Au(NCCH$_3$)]SbF$_6$ **5**	60	24	6
2	[**L$_1$**Au(NCPh)]SbF$_6$ **6**	60	1	76
3	[**L$_2$**Au(NCCH$_3$)]SbF$_6$ **7a**	60	1	77
4	[**L$_2$**Au(NCCH$_3$)]SbF$_6$ **7a**	23	1.5	40
5[b]	[**L$_2$**Au(NCCH$_3$)]SbF$_6$ **7a**	60	1	85
6	[**L$_2$**Au]NTf$_2$ **7b**	60	6	< 3

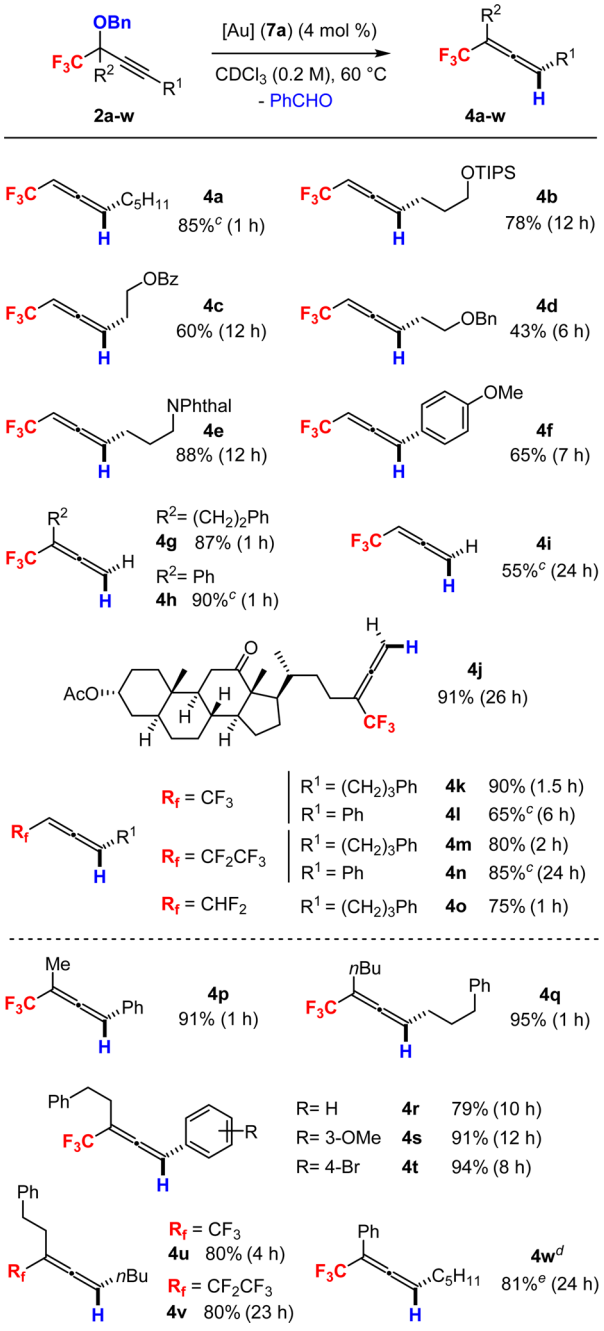


[a]**4a** is a volatile compound. The yield was assessed by ^{1}H NMR spectroscopy using 1,2-dichloroethane as an internal standard. [b]$CDCl_3$ was dried over 4 Å MS prior to usage.

The activity of **5**, a gold catalyst which proved its efficiency in hydride transfer reactions,[15,17] was first evaluated. Substrate **2a** was treated with 4 mol % of **5** in refluxing $CDCl_3$,[18] and the reaction was monitored by ^{1}H NMR spectroscopy (Table 1, entry 1). The formation of CF_3-allene **4a** could be observed, thus validating our approach, but the conversion of **2a** was very poor (<10%). In sharp contrast, a rapid conversion of **2a** (1 h) was observed when the more electrophilic phosphite and phosphonite based gold complexes **6**[19] and **7a**[20] were employed as the catalysts (entries 2 and 3). Under these conditions, CF_3-allene **4a** was obtained in 76% and 77% yield, respectively. While lowering the reaction temperature to 23 °C noticeably slowed down the conversion of **2a** (entry 4), a slight improvement in the yield was observed when $CDCl_3$ dried over 4 Å MS was employed as the solvent (entry 5).[21] Interestingly, gold complex **7b**, an analog of **7a** with a more coordinating NTf_2^- counteranion, was completely inefficient in catalyzing the desired transformation (entry 6).[22] Given the generally observed higher thermal stability of phosphonite gold complex **7a** when compared to **6**,[23] experimental conditions given in entry 5 (4 mol % of **7a** in dry chloroform at 60 °C) were retained to perform the scope of the reaction.

As seen in Scheme 2, the reaction proved to be widely applicable. A great variety of fluorinated substrates **2a–w** were converted into the corresponding di- or trisubstituted fluorinated allenes **4a–w** in yields ranging from 43% to 90%. The reaction was shown to tolerate various functional groups

Scheme 2. Substrate Scope: Gold-Catalyzed Formation of Trifluoromethyl-allenes[a]



[a]Reaction scale: 0.08–0.2 mmol. $CDCl_3$ was dried over 4 Å MS prior to usage.[18] [b]Isolated yields unless otherwise noted. [c]Volatile compound: yield determined by 1H NMR spectroscopy using 1,2-dichloroethane as an internal standard. [d]**6** (4 mol %) was used as the catalyst and the reaction was performed at 23 °C. [e]Isolated in mixture with indene **8w** (**2w**:**8w** = 5:1); see Scheme 3.

including silyl- and alkylethers (**4b** and **4d**), esters (**4c** and **4j**), ketone (**4j**), imide (**4e**), and aromatics (**4f** and **4s–t**). We were pleased to observe that the transformation was applicable to terminal alkyne substrates disubstituted at the propargylic position. In this case, the reaction proved to be particularly efficient as attested by the conversion of **2g–h** and **2j** into respectively 1,1-disubstituted CF_3-allenes **4g–h** and **4j** (87–91% yield). Notably, none of the previously described

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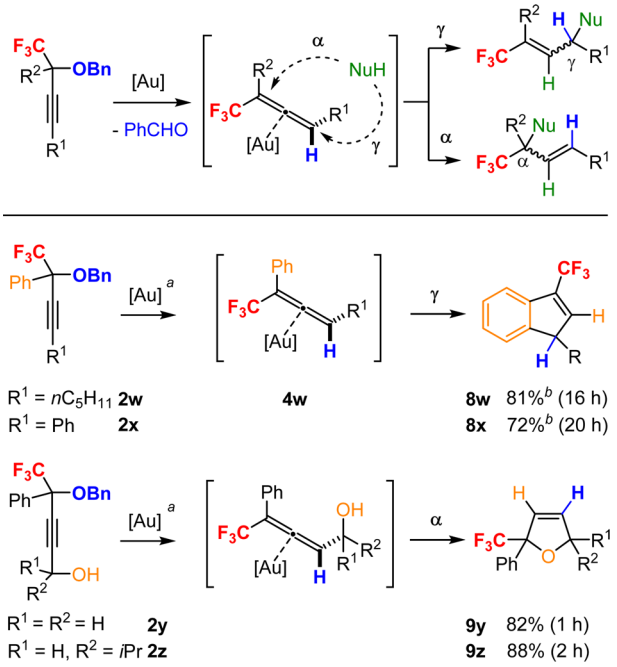
methods[6a,c,12h] allows the efficient and selective formation of alkyl-substituted CF_3-allenes such as **4g** and **4j**. The conversion of *epi*-cholestanol derivative **2j** into allene **4j** shows the functional group tolerance of the method and the possibility to apply it to structurally complex molecules. The formation of the simple CF_3-propadiene **4i** is particularly representative of the synthetic interest of the transformation. Indeed, the preparation of **4i** usually requires harsh experimental conditions or stoichiometric amounts of copper reagents.[5c,d,f] Finally, it is interesting to note that the method could be applied with the same efficiency to substrates possessing other fluorinated groups (**2m**, **2n**, and **2v**: CF_2CF_3; **2o**: CHF_2), thus expanding the synthetic potential of the process.

We then explored the possibility for further functionalizing the CF_3-allenes produced using this new method. By capitalizing on the possibility of gold catalysts to activate allenes toward their nucleophilic functionalization at position α or γ (see Scheme 3, top),[13] we envisaged to perform a one-pot

Scheme 3. Gold-Catalyzed Cascade Reactions Involving Trifluoromethyl-allenes Intermediates

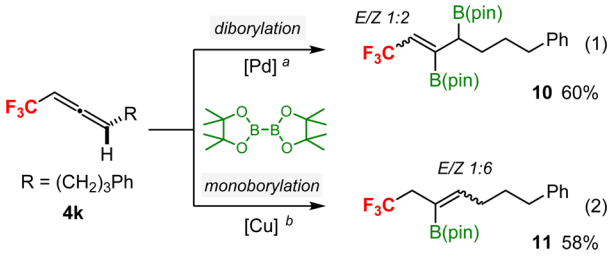


[a]Reaction conditions: **7a** (4 mol %), $CDCl_3$ (0.2 M),[18] 60 °C. [b]Yield determined by ^1H NMR spectroscopy using 1,2-dichloroethane as an internal standard.

sequence of gold-catalyzed allene formation/intramolecular nucleophilic addition. To validate this proposal, substrate **2w** possessing a potentially nucleophilic phenyl group at the propargylic position was subjected to the optimized catalytic conditions (Scheme 3).[24] We were pleased to observe the efficient formation of indene **8w** (81% yield) as the result of an intramolecular gold-catalyzed addition of the phenyl ring at the γ position of the intermediately produced allene **4w**. A similar result was obtained with substrate **2x**. With propargylic alcohol derivatives **2y** and **2z**, the nucleophilic addition of the hydroxyl functionality at the alternative α position of the allene moiety proceeded (Scheme 3).[9a,19,25] This led to the rapid and efficient formation of the synthetically valuable CF_3-dihydrofurans **9y** and **9z**.

The reactivity of disubstituted CF_3-allenes utilizing other transition metal catalysts was also rapidly explored. While previous studies have shown the ability of 1,1-disubtituted trifluoromethylated allenes to react under Ru, Pd, or Cu catalysis,[6c,12h] no example of metal-mediated transformations of 1−3-disubstituted CF_3-allenes has been reported so far. A Pd-catalyzed diborylation of CF_3-allene **4k** was first attempted (Scheme 4, eq 1).[26] We were pleased to observe that a

Scheme 4. Copper- and Palladium-Catalyzed Borylation of Trifluoromethyl-allenes



[a]Reaction conditions: **4k** (1 equiv), B_2pin_2 (1.4 equiv), $Pd(dba)_2$ (5 mol %), $P(NMe_2)_3$ (6 mol %), toluene (23 °C, 5 h). [b]Reaction conditions: **4k** (1 equiv), B_2pin_2 (1.4 equiv), IMesCuDBM (5 mol %), MeOH (6 equiv), THF (23 °C, 15 h).

regioselective reaction took place giving rise to the formation of the diborylated CF_3-alkene **10**. This one was isolated in 60% yield as a 1:2 mixture of *E*/*Z* isomers.[27] The Cu-catalyzed monoborylation of the same substrate proceeded with similar efficiency to afford the regioisomeric boroalkene **11** as a 1:6 mixture of *E*/*Z* isomers (Scheme 4, eq 2).[27,28] Notably, borylated compounds **10** and **11** represent a useful springboard for further (metal-catalyzed) functionalization.

In conclusion, an original access to polysubstituted trifluoromethyl-allenes starting from an inexpensive CF_3-source was developed. The new synthetic method was found to be easy to implement, efficient, selective, and applicable to a wide variety of functionalized substrates. The reaction scope highlighted the complementarity of the process with synthetic methods previously reported in the literature for accessing CF_3-allenes. Preliminary studies on the subsequent functionalization of these allenes by Au-, Pd-, or Cu-catalyzed reactions gave promising results. Further studies in this domain are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02636.

Experimental procedures and characterization of all new compounds including ^1H, ^{13}C, and ^{19}F NMR analysis (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Wang, J.; Sanchez-Rosello, M.; Acena, J. N.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(2) For selected recent reviews, see: (a) Barata-Vallejo, S.; Lantano, B.; Postigo, A. *Chem. - Eur. J.* **2014**, *20*, 16806. (b) Chu, L.; Qing, F.-L. *Acc. Chem. Res.* **2014**, *47*, 1513. (c) Alonso, C.; Martinez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847.

(3) (a) Ye, J.; Ma, S. *Acc. Chem. Res.* **2014**, *47*, 989. (b) For a series of reviews on the reactivity of allenes, see: *Chem. Soc. Rev.* **2014**, *43*, 2879.

(4) For a review on the use of allenes in synthesis, see: Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074.

(5) (a) Coe, P. L.; Milner, N. E. *J. Organomet. Chem.* **1974**, *70*, 147. (b) Hung, M.-H. *Tetrahedron Lett.* **1990**, *31*, 3703. (c) Burton, D. J.; Hartgraves, G. A.; Hsu, J. *Tetrahedron Lett.* **1990**, *31*, 3699. (d) Bouillon, J.-P.; Maliverney, C.; Merényi, R.; Viehe, H. G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2147. (e) Hu, C.-M.; Qing, F.-L.; Huang, W.-Y. *J. Org. Chem.* **1991**, *56*, 2801. (f) Duan, J.-X.; Chen, Q.-Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 725. (g) Werner, H.; Laubender, M.; Wiedemann, R.; Windmuller, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1237. (h) Werner, H.; Wiedemann, R.; Laubender, M.; Windmuller, B.; Steinert, P.; Gevert, O.; Wolf, J. *J. Am. Chem. Soc.* **2002**, *124*, 6966.

(6) (a) Han, H. Y.; Kim, M. S.; Son, J. B.; Jeong, I. H. *Tetrahedron Lett.* **2006**, *47*, 209. (b) Yamazaki, T.; Yamamoto, T.; Ichihara, R. *J. Org. Chem.* **2006**, *71*, 6251. (c) Sam, B.; Montgomery, T. P.; Krische, M. J. *Org. Lett.* **2013**, *15*, 3790.

(7) (a) Watanabe, Y.; Yamazaki, T. *J. Fluorine Chem.* **2010**, *131*, 646. (b) Yamazaki, T.; Watanabe, Y.; Yoshida, N.; Kawasaki-Takasuka, T. *Tetrahedron* **2012**, *68*, 6665. (c) Guissart, C.; Dolbois, A.; Tresse, C.; Saint-Auret, S.; Blanchard, N.; Evano, G. *Synlett* **2016**, DOI: 10.1055/s-0035-1562518.

(8) (a) Hanzawa, Y.; Kawagoe, K.- i.; Yamada, A.; Kobayashi, Y. *Tetrahedron Lett.* **1985**, *26*, 219. (b) Johnson, D.; Rodriguez, A.; Kennedy, G. D.; Krishnan, G. *J. Heterocycl. Chem.* **1994**, *31*, 871. (c) Li, P.; Liu, Z.-J.; Liu, J.-T. *Tetrahedron* **2010**, *66*, 9729.

(9) (a) Watanabe, Y.; Yamazaki, T. *Synlett* **2009**, *2009*, 3352. (b) Aikawa, K.; Hioki, Y.; Mikami, K. *Org. Lett.* **2010**, *12*, 5716.

(10) Pd-catalyzed reactions: (a) Sakamoto, T.; Takahashi, K.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 9467. (b) Shimizu, M.; Higashi, M.; Takeda, Y.; Jiang, G.; Murai, M.; Hiyama, T. *Synlett* **2007**, *2007*, 1163. (c) Shimizu, M.; Higashi, M.; Takeda, Y.; Murai, M.; Jiang, G.; Asai, Y.; Nakao, Y.; Shirakawa, E.; Hiyama, T. *Future Med. Chem.* **2009**, *1*, 921. (d) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, *29*, 1360.

(11) Ag-catalyzed reaction: Liu, J.; Liu, Z.; Wu, N.; Liao, P.; Bi, X. *Chem. - Eur. J.* **2014**, *20*, 2154.

(12) (a) Burton, D. J.; Hartgraves, G. A. *J. Fluorine Chem.* **2009**, *130*, 254. (b) Zhao, T. S. N.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 3966. (c) Jiang, X.; Qing, F.-L. *Beilstein J. Org. Chem.* **2013**, *9*, 2862. (d) Miyake, Y.; Ota, S.-I.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2013**, *49*, 7809. (e) Ji, Y.-L.; Kong, J.-J.; Lin, J.-H.; Xiao, J.-C.; Gu, Y.-C. *Org. Biomol. Chem.* **2014**, *12*, 2903. (f) Li, G.; Gagare, P. D.; Ramachandran, P. V. *Tetrahedron Lett.* **2014**, *55*, 5736. (g) Ambler, B. R.; Peddi, S.; Altman, R. A. *Synthesis* **2014**, *46*, 1938. (h) Ambler, B. R.; Peddi, S.; Altman, R. A. *Org. Lett.* **2015**, *17*, 2506. (i) Ji, Y.-L.; Luo, J.-J.; Lin, J.-H.; Xiao, J.-C.; Gu, Y.-C. *Org. Lett.* **2016**, *18*, 1000. See also refs 5b and 5d.

(13) For selected recent selected reviews on gold catalysis: (a) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902. (b) Wang, Y.-M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014**, *47*, 889. (c) Friend, C. M.; Hashmi, A. S. K. *Acc. Chem. Res.* **2014**, *47*, 729. (d) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (e) Jia, M.; Bandini, M. *ACS Catal.* **2015**, *5*, 1638. (f) Asiri, A. M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 4471.

(14) For selected contributions from our group in the field of gold catalysis, see: (a) Gronnier, C.; Boissonnat, G.; Gagosz, F. *Org. Lett.* **2013**, *15*, 4234. (b) Henrion, G.; Chavas, T. E. J.; Le Goff, X.; Gagosz, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 6277. (c) Prechter, A.; Henrion, G.; Faudot dit Bel, P.; Gagosz, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 4959.

(15) Bolte, B.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 7294.

(16) For selected gold-catalyzed reaction involving hydride transfers, see: (a) Vasu, D.; Das, A.; Liu, R.-S. *Chem. Commun.* **2010**, *46*, 4115. (b) Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2939. (c) Barluenga, J.; Sigüeiro, R.; Vicente, R.; Ballesteros, A.; Tomas, M.; Rodríguez, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 10377. (d) Wu, X.; Chen, S.-S.; Hu, Y.; Gong, L.-Z. *Org. Lett.* **2014**, *16*, 3820. For the formation of allenes, see: (e) Lo, V. K.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2008**, *10*, 517. See also: (f) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786. (g) Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213. (h) Tang, X.; Zhu, C.; Cao, T.; Kuang, J.; Lin, W.; Ni, S.; Zhang, J.; Ma, S. *Nat. Commun.* **2013**, *4*, 2450. (i) Jiang, G.-J.; Zheng, Q.-H.; Dou, M.; Zhuo, L.-G.; Meng, W.; Yu, Z.-X. *J. Org. Chem.* **2013**, *78*, 11783.

(17) Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543.

(18) Deuterated chloroform was used for convenience in order to monitor the course of the reactions and assess the crude yields of products. $CDCl_3$ can naturally be replaced by regular $CHCl_3$.

(19) Bolte, B.; Gagosz, F. *J. Am. Chem. Soc.* **2011**, *133*, 7696.

(20) For the synthesis and use of gold complex **7a**, see ref 14b.

(21) The presence of water in the solvent led to the formation of byproducts derived from an initial Au-catalyzed addition of H_2O on the alkyne moiety.

(22) It is assumed that the presence of the more coordinating NTf_2^- counteranion lowers the electrophilicity of the gold complex thus diminishing its ability to make possible the hydride transfer.

(23) Gold complex **6** degrades at 60 °C within a few hours. Complex **7a** exhibits higher stability (see ref 14b) and was therefore retained for studying the scope of the reaction assuming that longer reaction times might be necessary depending on the substrates.

(24) Marion, N.; Diez-Gonzales, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647.

(25) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537.

(26) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328.

(27) The reaction conditions were not optimized.

(28) Yuan, W.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 1867.

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Org. Lett. XXXX, XXX, XXX−XXX