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Cationic Gold Catalyzes ω-Bromination of Terminal Alkynes and Subsequent Hydroaddition Reactions

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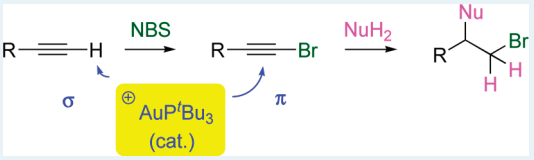
Supporting Information

ABSTRACT: Orthogonal σ,π-bisfunctionalization of terminal alkynes can be achieved with a cationic gold complex in catalytic amounts. First, the terminal C−H bond is transformed to the corresponding bromoalkyne which is then activated toward nucleophilic attack. This reactivity correlates with the structural nature of isolated gold-alkyne complexes.



KEYWORDS: gold catalysis, aurophilic interactions, terminal alkynes, σ,π-bisfunctionalization, bromoalkynes

1. INTRODUCTION

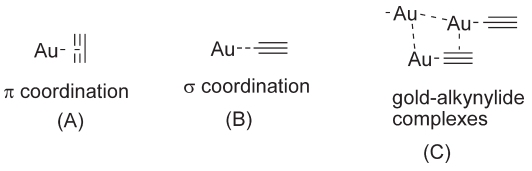
Homogeneous and heterogeneous catalysis by gold has gained much attention in the past years,[1−7] and new reactions are systematically unveiled.[8−11] In particular, activation of alkynes by gold compounds and nanoparticles has opened unexpected reaction pathways.[12−14] Mechanistically, it is accepted that, in general, gold acts as a Lewis acid on the triple bond through π-coordination (Scheme 1, A)[15] while, for some reactions of terminal alkynes, a gold alkynylide intermediate is postulated (B). Curiously, the structure of isolated gold-alkynylides compounds does not fit only one of these two simple models but a combination of them: the gold atom presents η^1,η^2-hapticity to the alkyne, together with aurophilic interactions (C).[16−18]

The potential role of gold as bifunctional σ,π-activator of terminal alkynes has been little explored in catalysis. Of course, neat alkyne-gold complexes are not formed under catalytic conditions, and the structure of the gold intermediate in the reaction differs significantly from that of the corresponding isolated complex. However, an orthogonal σ,π-bisfunctionalization might be expected if significant amounts of the Au-alkyne η^1,η^2-complex are formed under reaction conditions.[19] Here, some results in this regard are presented.

2. RESULTS AND DISCUSSION

During the metal-catalyzed bromination of phenylacetylene **1a** with *N*-bromosuccinimide (NBS) **2a**, we found that the cationic gold(I) complex $AuP^tBu_3NTf_2$ is able to activate the terminal C−H bond of **1a** to give the corresponding 1-bromophenylacetylene **3a** in high yield (Table 1, entries 1 and 16).[20] Other Au species (entries 3−10 and 24) and Ag (entries 11−15), Cu (entry 19), Hg (entry 20),[21] and Pt (entry 21) salts gave no product. Only $AgNO_3$ (entry 18), the catalyst of choice

Scheme 1. Coordination of Gold to Alkynes



for this transformation,[22−27] and Hg and Pt triflimides (entries 22−23) were able to catalyze the reaction in moderate yields.

As it can be seen in Table 1, the solvent also influences the product formation. A comparison between $AuP^tBu_3NTf_2$ and $AgNO_3$ in different solvents (see Supporting Information, Table S1) shows that the former is highly active in DCM, CH_3CN, ethers, and water while, in contrast, the catalytic activity of $AgNO_3$ correlates with the solubility of NBS (acetone ≫ DCM > *n*-hexane). This solvent-dependence suggests a distinct mechanism for gold and silver as catalysts and reflects the insolubility of the silver alkynylide intermediate (see below). In fact, $AuP^tBu_3NTf_2$ and $AgNO_3$ catalyze independently the formation of **3a** when put together in the reaction medium at low catalytic amounts (see footnote in Supporting Information, Table S1).

At this point, the question is how a highly cationic gold complex such as $AuP^tBu_3NTf_2$ activates so efficiently the terminal σ-CH bond of the alkyne.[28−30] In principle, a η^2-(π)-coordination of gold to the alkyne should be expected, but according to the structure of gold coordination polymers[16] (structure C in Scheme 1) and recently isolated cationic gold-alkyne complexes,[31] a possible η^1,η^2-hapticity under the reaction conditions could occur. To check this hypothesis, the corresponding

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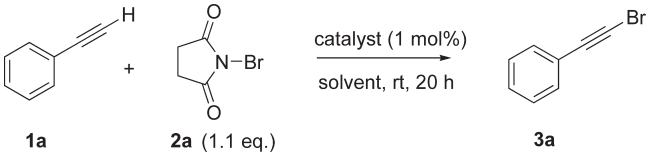
Table 1. Formation of 1-Bromophenylacetylene 3a in the Presence of Different Catalysts



1a **2a** (1.1 eq.) **3a**

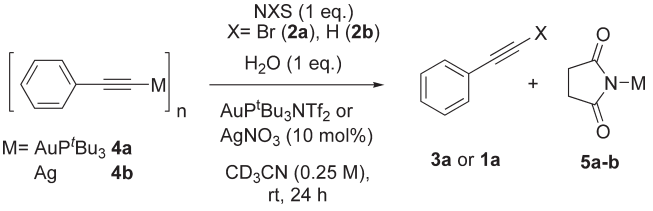
run	catalyst	solvent	conversion (%)[a]
1	**AuP^{t}Bu$_3$NTf$_2$**	**1,4-dioxane**	**91**
2	none		0
3	$AuCl_3$		0
4	$HAuCl_4 \cdot 3H_2O$		0
5	$AuNTf_2$		<5[b,c]
6	$Au(NTf_2)_3$		0[b]
7	$AuPPh_3NTf_2$		<5[c]
8	$AuPPh_3Cl$		0[c]
9	$AuSPhosNTf_2$		0[c]
10	AuDavePhos		<5[c]
11	$AgNO_3$		0[c]
12	AgOTf		0[c]
13	$AgPF_6$		0[c]
14	$AgBF_4$		0[c]
15	$AgNTF_2$		<5
16	**AuP^{t}Bu$_3$NTf$_2$**	**DCM**	**100**
17	none		0
18	$AgNO_3$		61
19	CuCl		0
20	$HgCl_2$		<5
21	$PtCl_2$		0
22	$Hg(NTf_2)_2$		35[b]
23	$Pt(NTF_2)_2$		47[b]
24	Au-CeO_2		<5[d]

[a] GC yield. Selectivity to **3a** typically accounts for >80%, the rest mainly corresponding to oligomeric compounds. [b] Formed in situ from the corresponding chloride and silver triflimide by stirring at room temperature (rt) for 10 min. [c] Bromination of the solvent was found. [d] 83 mg of 2.8 wt % Au on CeO_2 (5 mol %).

metal coordination polymers $[M\text{-}C{\equiv}CPh]_n$ (M = AuP^{t}Bu$_3$ **4a**,[32] Ag[33,34] **4b**) were prepared and tested in the reaction (Table 2). These polymers could be in monomeric form to some extent under the reaction conditions.

Bromodemetalation of the complexes **4a**−**b** readily occurs[35,36] (entries 1−2), even in the presence of water (entries 3−4), and the corresponding metal-imide species **5a**−**b** are formed concomitantly. While **5a** is soluble and can be isolated in quantitative yield, **5b** is quite insoluble and precipitates in the reaction medium. In contrast, protodemetalation of **4a**−**b** with water does not occur although a catalyst is present (entries 5−8). Significantly, protodeauration[36−38] of **4a** can be induced with *N*-succinimide **2b** as proton source (entries 9−10), and the presence of AuP^{t}Bu$_3$NTf$_2$ slightly accelerates this substitution. The above observations suggest that the combination of π- and σ-Au-alkyne interactions might be beneficial for the formation of the new C−H(Br) bond. Protodeargentation with **2b** does not occur for silver (entries 11−12). Although the coordination polymer **4a** is fully soluble in CD_3CN and **4b** is not, characterization of **4a** reveals a

Table 2. Metal Coordination Polymers as Substrates for the Reaction



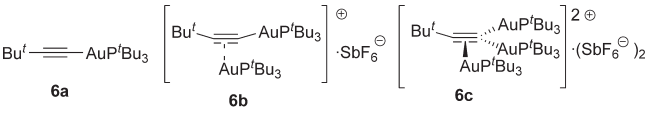
M= AuP^{t}Bu$_3$ **4a**
Ag **4b**

3a or **1a** **5a-b**

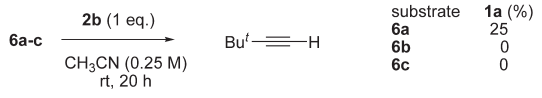
run	metal polymer	NXS	H_2O	catalyst	product (%)[a]
1	**4a**	**2a**			**3a** (100)
2	**4b**	**2a**			**3a** (100)
3	**4a**	**2a**	yes		**3a** (100)
4	**4b**	**2a**	yes		**3a** (100)
5	**4a**		yes		**1a** (<5)
6	**4b**		yes		**1a** (<5)
7	**4a**		yes	AuP^{t}Bu$_3$NTf$_2$	**1a** (<5)
8	**4b**		yes	$AgNO_3$	**1a** (<5)
9	**4a**	**2b**			**1a** (15)
10	**4a**	**2b**		AuP^{t}Bu$_3$NTf$_2$	**1a** (25)
11	**4b**	**2b**			**1a** (<5)
12	**4b**	**2b**		$AgNO_3$	**1a** (<5)

[a] NMR yield.

Scheme 2. Organogold η^1,η^2-Au(I) Acetylide Complexes as Substrates



6a **6b** **6c**



substrate	**1a** (%)
6a	25
6b	0
6c	0

symmetric network similar to that of **4b** (see Scheme 1, C),[39] as assessed by IR (one single C≡C band peaking at υ = 2114 cm^{-1}) and NMR spectroscopy (single P and ^{t}Bu signals in ^{31}P- and ^{1}H NMR, respectively). However, the silver alkynylide **4b** presents a more elongated C≡C bond (υ = 2055 cm^{-1})[34] which reflects a stronger metal-alkyne π-network that could, in part, explain the lack of reactivity and the insolubility issues observed.

To further check the influence of Au-π-coordination on the reaction, the well-defined σ- and π-Au(I) acetylide complexes **6a**−**c** were prepared[31] and tested as substrates for the protodeauration with succinimide **2b** (Scheme 2).

It was found that stoichiometric amounts of π-coordinating cationic $[AuP^tBu_3]^+$ species completely inhibited the reaction. This result contrasts to the better yield found when AuP^{t}Bu$_3$NTf$_2$ was used in catalytic amounts on **4a** (Table 2, entry 10). Nevertheless, the results above indicate that the σ-acetylide complex is the key intermediate of the reaction. Furthermore, $[P^tBu_3Au{-}C{\equiv}CPh]_n$ **4a** and Au-*N*-succimide **5a** are both competent as catalysts when treated with $HNTf_2$ (Scheme 3). According to the microscopic reversibility principle, both species should be considered as reaction intermediates.

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The possible formation of **4a** under catalyzed conditions was studied by isotopic experiments. Since *N*-succinimide **2b** is active for the protodemetalation of **4a** (Table 2, entry 9), the *H/D*-exchange between deuterated phenylacetylene **1a** (d^1) and succimide **2b** must occur if **4a** is formed under catalyzed conditions (Table 3).[28] Indeed, $AuP^tBu_3NTf_2$ is active as catalyst for the *H/D*-exchange (entry 1). Other metallic species of Au, Ag, and Cu gave poorer results (entries 2−7) but, in contrast, $AgNO_3$ is an extremely active catalyst, giving **1a** in optimum yield (entry 8, 50% is the maximum yield under equilibrium conditions). Taking in account the lack of reactivity of $[Ag{-}C{\equiv}CPh]_n$ **4b** (Table 2, entries 11−12), silver phenylacetylides should be ruled out as intermediates in this reaction.

With these results in hand, a possible reaction pathways for the $AuP^tBu_3NTf_2$-catalyzed σ-bromination of terminal alkynes is proposed (Scheme 4). Deprotonation of the C−H bond would occur after gold π-coordination leading to $[Au{-}C{\equiv}CPh]_n$-type species.[21,40] This intermediate would brominate fast at the terminal position and the gold catalyst would be regenerated after protonation of **5a**. For *N*-succinimide **2b**, an alternative gold-catalyzed hydroimidation of the alkyne might take place through π-attack of the amine, protodeauration, and 1,2-elimination of **2b**. Anyway, this second proposal features some inconsistencies: (a) to date, no gold-catalyzed intermolecular hydroimidations of alkynes have been reported[41,42] and (b) α-imidosubstituted styrenes (those intermediates formed with **2a**[43] and **2b**-type[44,45] imides) are stable compounds.

Kinetic experiments support the first pathway. The deprotonation of the alkyne is the rate-limiting step since kinetic isotopic effect (KIE) is observed (**2a**, k_H/k_D = 2.3, Figure 1A). The use of NIS[46−49] **2c** instead of NBS **2a** (Figure 1B) improves the initial reaction rate (k_{NIS}/k_{NBS} = 1.9); however, the reaction rate decreases fast with time because of catalyst poisoning by traces of iodine (Figure 1C). Finally, a radical mechanism must be rejected since reported unfavorable conditions for radical brominations with NBS[50] **2a**, such as darkness, inert atmosphere, and anhydrous medium, did not decrease the reaction rate ($k_{\text{"radical"}}/k_{non}$ = 0.7, Figure 1D).

A third reaction pathway (not shown) would involve the oxidative addition of NBS to Au(I), the resulting Au(III)-Br species being responsible for the catalysis after alkyne coordination and reductive elimination. Although this reactivity is possible when selectfluor is used in related reactions,[35,51,52] NBS is not such a good oxidizing agent.[53−55]

The scope of the reaction was examined, and both aryl and alkyl alkynes are brominated when $AuP^tBu_3NTf_2$ is used as catalyst (Table 4). Halo and nitro groups are compatible under the reaction conditions, and the electronic density on the ring exerts some influence on the activity (entries 1−5).

Ortho-substitution (steric hindrance) is permitted but more catalyst must be used (entry 6). The catalytic activity is typically higher in DCM than in CH_3CN, but selectivity issues are better controlled with the latter (entry 7). For alkyl alkynes, yields are good or moderate, and other functional groups are also tolerated (entries 7−10).

At this point, cascade reactions, in which the gold catalyst would act first as σ- and then as π-activator, were considered. Intensification of chemical processes by consecutive reactions is an important trend in sustainable chemistry and, since $AuP^tBu_3NTf_2$ is a good π-activator of alkynes toward hydroaddition reactions[56−61] and gold-catalyzed hydroadditions to haloalkynes have been reported,[62−64] a possible further functionalization of the in situ formed bromoalkyne **3a** was explored (Scheme 5).

The cascade process indeed works, and bromoderivatives **7a**−**d** were obtained in good yields. Suitable nucleophiles include alcohols, thiols, and amines. In particular, the latter resembles those intermediates in the synthesis of drugs such as

Scheme 3. Organogold Compounds as Catalysts

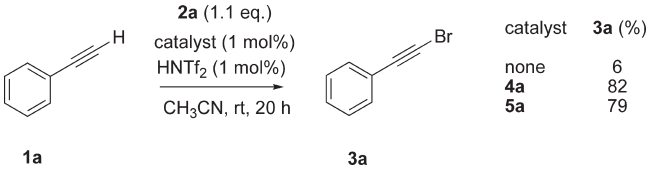
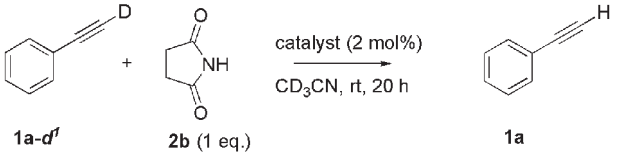


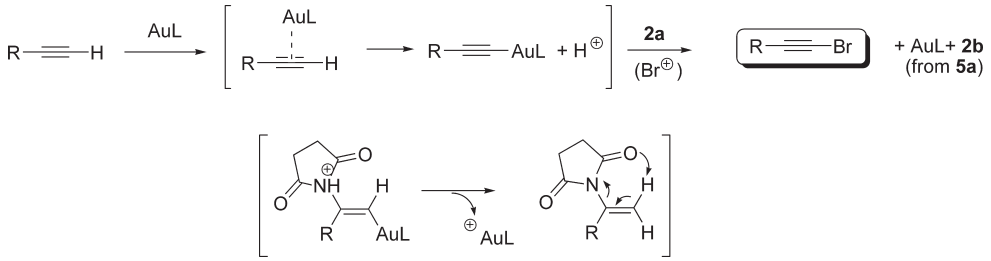
Table 3. *H*-Exchange between 1a-d^1 and 2b



run	catalyst	1a (%)[a]
1	**$AuP^tBu_3NTf_2$**	**31**
2	AuP^tBu_3Cl	0
3	$AgNTf_2$	0
4	AuCl	13
5	$AuNTf_2$	13[b]
6	CuCl	<5
7	$CuNTf_2$	0[b]
8	**AgNO3**	**50**

[a] NMR yield. [b] Formed in situ from the corresponding chloride and silver triflimide.

Scheme 4. Possible Reaction Pathways[a]



[a] L = P^tBu_3.

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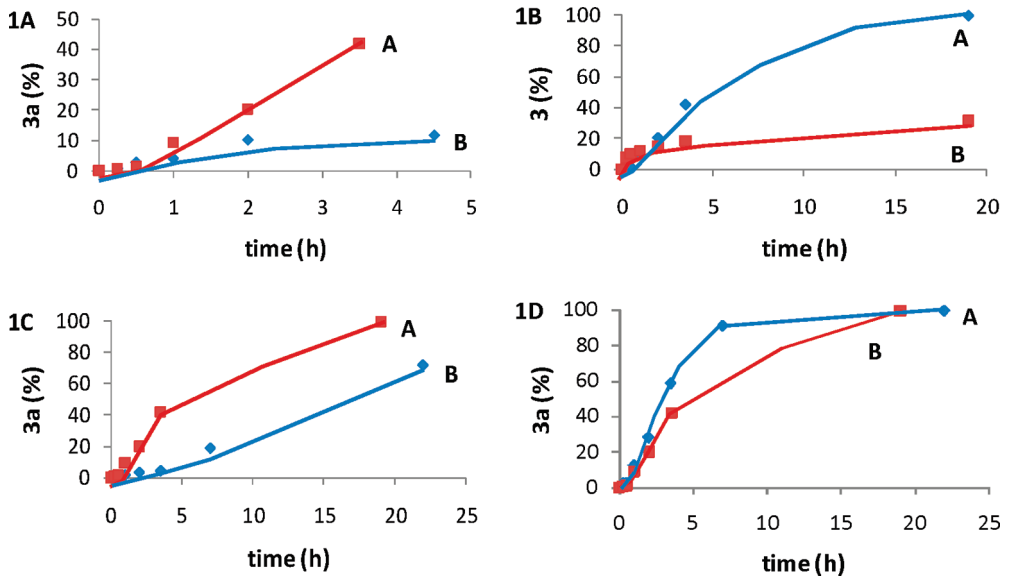
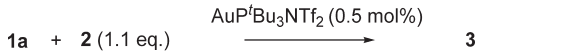


Figure 1. Plot-time yields for the formation of 1-haloalkynes when (1A) **1a** (A) or **1a-*d*[1]** were used as substrates; (1B) NBS **2a** (A) or NIS **2c** (B) were used as substrates; (1C) no additive (A) or I_2 (B, 2 mol %) was added; (1D) the reaction was performed with anhydrous and deareated DCM, under darkness, and nitrogen atmosphere (A), or under typical conditions (B).

Table 4. Scope of the Reaction

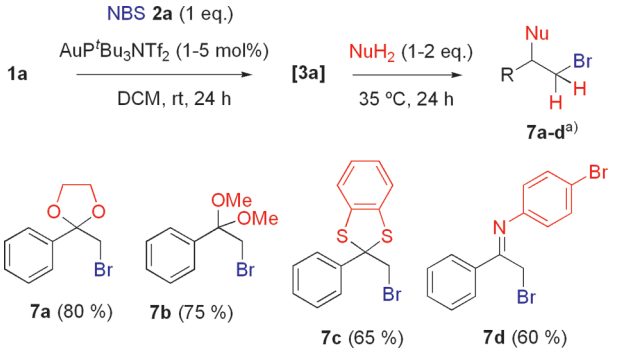


Run	R		Catalyst amount/time/solvent	Product yield (%)[a]
1		X= H **1a**	1 mol%, 24 h, DCM	**3a**, 83[b]
2		X= Cl **1b**	2 mol%, 48 h, DCM	**3b**, 84
3		X=NO_2 **1c**	2 mol%, 72 h, DCM	**3c**, 95
4		X= Br **1d**	5 mol%, 24 h, DCM	**3d**, 95[c]
5		X= Me **1e**	2 mol%, 24 h, DCM	**3e**, 74[c]
6	 **1f**		10 mol%, 24 h, CH_3CN	**3f**, 52
7	$C_{12}H_{25}$- **1g**		5 mol%, 24 h, CH_3CN	**3g**, 83[d]
8	^{t}Bu- **1h**		5 mol%, 24 h, CH_3CN	**3h**, 80[e]
9	$Cl(CH_2)_3$- **1i**		5 mol%, 24 h, DCM	**3i**, 64[c]
10	$HO(CH_2)_9$- **1j**		5 mol%, 24 h, DCM	**3j**, 40[c]

[a] Isolated yield. [b] *N*-bromophtalimide is also suitable as brominating agent (CH_3CN, same conditions, 81% GC yield). [c] GC yield. [d] 100% selectivity, rest is unreacted material. [e] NMR yield.

Zolpidem (insomnia treatment) or Alpidem (anxyolitic).[65,66] Significant protodehalogenation of the product was found in some cases (**7c**−**d**), which could come from Au insertion into the new C−Br bond.

Scheme 5. AuP^{t}Bu$_3$NTf$_2$-Catalyzed Cascade Reactions



[a] GC yields.

3. CONCLUSIONS

AuP^{t}Bu$_3$NTf$_2$ acts as catalyst for the formation of 1-bromoalkynes from terminal alkynes and NBS. Subsequently, gold(I)-catalyzed hydroaddition reactions are feasible in one-pot. The mechanism of the bromination points to the formation of a terminal σ−Au-C≡C-R bond after π-coordination of the cationic gold(I) center to the alkyne. The catalyst of choice for this transformation, $AgNO_3$, seems to follow a distinct reaction pathway. Since the latter presents some solvent limitations and is not competent for π-additions on the triple bond below 100 °C,[67] the gold(I)-catalyzed system reported here is unique in terms of reactivity and mildness. Considering that bromoalkynes[68] and bromoketals[69] are gaining importance in organic synthesis in the past years, together with the appearance of plant-metabolism products containing C-halogen bonds,[70] the methodology here presented could be of interest to both catalytic and synthetic chemists.

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4. EXPERIMENTAL SECTION

Reaction Procedure for the Synthesis of 1-Bromophenylacetylene 3a (Table 4, entry 1). $AuP^tBu_3NTf_2$ (13.6 mg, 0.02 mmol) and NBS **2a** (355.6 mg, 2 mmol) were placed in a vial equipped with a magnetic stirrer. DCM (2 mL) and phenylacetylene **1a** (220 μL, 2 mmol) were added, the vial was closed with a septum cap, and the resulting mixture was stirred for 24 h at room temperature. Then, an aliquot was taken for GC analysis, and *n*-hexane (20 mL) was added to the reaction mixture. The resulting suspension was stirred for 15 min, filtered and concentrated under vacuum to give **3a** (330 mg, >90% purity, 83% yield). Column chromatography of the reaction mixture lead to the analytically pure compound, but significant weight loss was observed, probably by decomposition of the product on column. R_f (*n*-hexane): 0.56. MS (*m*/*z*, relative intensity): 182 (100), 180 (100), 101 (48), 75 (26). IR (υ, cm^{-1}): 2369−2320 (several peaks), 2200, 1697, 1221, 1176. ^1H NMR (δ, ppm): 7.37 (aromatic C*H*, 2H, mult), 7.26−7.23 (aromatic C*H*, 3H, mult). ^{13}C NMR (δ, ppm): 132.0 (aromatic, 2CH), 128.7 (aromatic, CH), 128.3 (aromatic, 2CH), 122.7 (aromatic, C), 80.0 (alkyne, C), 49.7 (alkyne, C−Br).

Cascade Reaction (7a, Scheme 5). $AuP^tBu_3NTf_2$ (34 mg, 0.05 mmol) and NBS **2a** (177.8 mg, 1 mmol) were placed in a vial equipped with a magnetic stirrer. DCM (1 mL) and phenylacetylene **1a** (110 μL, 1 mmol) were added, the vial was closed with a septum cap, and the resulting mixture was stirred for 8 h at room temperature. Then, ethylene glycol (55.5 μL, 1 mmol) was added, and the vial stirred in a preheated oil bath at 35 °C for 24 h. The mixture was analyzed by GC and GC-MS.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, additional table, and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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