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Silver Effect in Regiodivergent Gold-Catalyzed Hydroaminations

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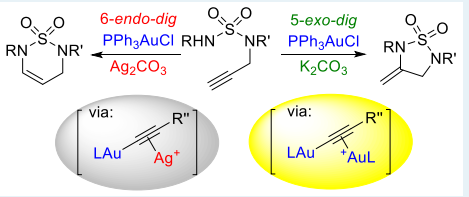
Supporting Information

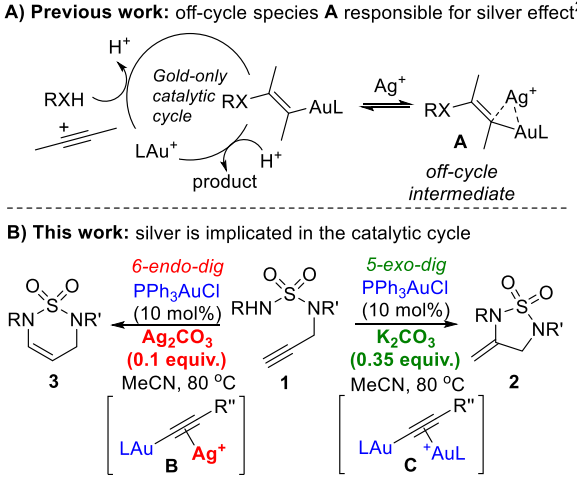
ABSTRACT: We report a silver-induced switching of regioselectivity in gold-catalyzed reactions, and we provide mechanistic evidence to suggest a true "silver effect": that is, one that is implicated in the catalytic process itself, via σ-gold π-silver acetylides. These results are of significance because they clearly show that the use of silver as halide abstractors in gold-catalyzed reactions may result in "silver effects" when terminal alkyne substrates are involved.



KEYWORDS: *gold, silver, silver-effect, hydroamination, regiodivergent, gold acetylide, digold*

Homogenous gold catalysis is widely used in synthesis for the activation of π-bonds toward nucleophilic attack.[1] Within this context, silver salts (AgX) are commonly used to convert LAuCl to the active cationic complex LAuX via halogen abstraction.[1,2] However, there have long been suspicions that silver is not totally innocent in many of these gold-catalyzed reactions, so much so that the term "silver effect" has been coined and its existence debated.[3] In particular, Zhdanko and Maier have recently carried out detailed studies to explain and classify many of the "silver effects" previously observed in the literature, with the conclusion that none were *true* silver effects.[2] In contrast, formation of argento vinyl gold species **A**[4] has recently been shown to be responsible for observed silver effects in gold-catalyzed hydrofunctionalization of alkynes,[2] but **A** affects the fraction of available in-cycle organogold intermediates rather than the mechanism of the catalytic process itself (Scheme 1A). A true "silver effect" within gold-catalysis (i.e., one that affects the catalytic cycle) has so far not been discovered.[2]

Scheme 1. Silver Effect



While investigating the gold-catalyzed hydroamination[5,6] of terminal alkynyl sulfamides[7] **1**,[8] we serendipitously discovered that the presence of silver causes a dramatic change in regioselectivity from 5-*exo-dig* to 6-*endo-dig* (**2** vs **3**, Scheme 1B). We herein provide evidence to suggest that this switching of selectivity is an example of the elusive true "silver effect" and propose that the mechanism for the formation of **3** involves a σ,π-mixed silver−gold acetylide **B**, whereas **2** involves the σ,π-digold acetylide **C** (Scheme 1B).

Our investigations commenced with the screening of catalysts, silver, and bases to form **2a** or **3a** (Table 1, see Supporting Information for full optimization studies). In the presence of PPh_3AuNTf_2, no reaction occurred (entry 1). However, a mixture of PPh_3AuCl and $AgSbF_6$ produces the 6-*endo-dig* product **3a**, albeit with undesired **4** as the main product (entry 2). This encouraged us to test other silver salts in combination with PPh_3AuCl (entries 3−5). The use of $AgNTf_2$ led to undesired sulfamide **4** as the only product (entry 3) and AgOTf furnished **3a** as the major product but still with an appreciable amount of **4** (entry 4). Pleasingly, further screening (see Supporting Information) revealed that the combination of Ag_2CO_3 and PPh_3AuCl catalyzes the formation of **3a** with high efficiency and total regiocontrol (entry 5). Lowering the catalyst loading is detrimental to the reaction, yielding mainly **4** (entries 6 and 7). In stark contrast, control reactions using only either Ag_2CO_3 or PPh_3AuCl resulted in no reaction (entries 8 and 9). Therefore, the combination of PPh_3AuCl and Ag_2CO_3 is necessary for successful formation of **3a**.

The intriguing role of the Ag_2CO_3 prompted us to study other bases in the reaction. The addition of Et_3N resulted in no reaction (entry 10). While replacing Ag_2CO_3 with K_2CO_3 (0.1 equiv) provided a complex mixture of products (entry 11), increasing the amount of base is beneficial for the formation of 5-*exo-dig* cyclization product **2a**, which is the regioisomer of **3a**

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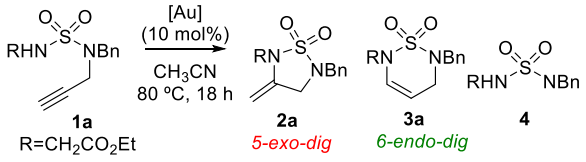
Table 1. Screening of the Catalyst



entry	[Au]	additive	ratio **2a:3a:4**[a]	conv. (%)[a]
1	PPh_3AuNTf_2	-	n.d.	0
2	PPh_3AuCl	$AgSbF_6$[b]	0:25:75	100
3	PPh_3AuCl	$AgNTf_2$[b]	0:0:100	43
4	PPh_3AuCl	AgOTf[b]	0:75:25	70
5	**PPh_3AuCl**	**Ag_2CO_3**[b]	**0:100:0**	**100**
6	PPh_3AuCl[c]	Ag_2CO_3[c]	0:22:78	65
7	PPh_3AuCl	Ag_2CO_3[c]	0:0:100	100
8	-	Ag_2CO_3[b]	n.d.	0
9	PPh_3AuCl	-	n.d.	0
10	PPh_3AuCl	Et_3N[d]	n.d.	0
11	PPh_3AuCl	K_2CO_3[b]	n.d.[e]	100
12	PPh_3AuCl	K_2CO_3[f]	100:0:0	65
13	**PPh_3AuCl**	**K_2CO_3**[g]	**100:0:0**	**100**
14	PPh_3AuCl	Na_2CO_3[g]	100:0:0	100
15	PPh_3AuCl	Cs_2CO_3[g]	100:0:0	23

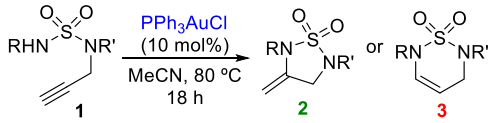
[a]Determined by ^{1}H NMR analysis. n.d. = not determined. [b]10 mol %. [c]5 mol %. [d]1 equiv. [e]Complex mixture. [f]20 mol %. [g]35 mol %.

(entries 12−13). Gratifyingly, the use of 0.35 equiv. K_2CO_3 enabled the formation of **2a** with total regiocontrol and full conversion (entry 13). Other alkaline carbonates (Na_2CO_3 and Cs_2CO_3)[9] also provide **2a** exclusively (entries 14−15). Therefore, the evidence so far seems to point toward the silver counterion in Ag_2CO_3 being responsible for switching the regioselectivity from 5-*exo* (**2a**, entries 13−15) to 6-*endo* (**3a**, entries 4−5).[10]

Before attempting to investigate the role of silver in this dramatic switch of regioselectivity, we decided to first study the scope of both the 5-*exo-dig* as well as 6-*endo-dig* reactions (Table 2). Using K_2CO_3 as base (method A) allowed the reaction to proceed smoothly with alkyl derivatives (R′ = alkyl), providing the 5-*exo* product **2** with excellent regioselectivity (>20:1 **2**:**3**) and good yields (86−88%, entries 1−4). The steric size of the substituent R′ does not affect the yield or regioselectivity, although in the case of R′ = ^{t}Bu, method A has to be modified to 60 °C (entry 4) in order to avoid isomerization of the *exo*-alkene in **2d** to the corresponding *endo*-alkene isomer. When K_2CO_3 is replaced with Ag_2CO_3 (method B) for these R′ = alkyl substrates, all the 6-*endo* products **3a**−**3c** were obtained with decent to good yields (58−84%) and excellent regioselectivity (>20:1 **3**:**2**), except for **1d** (R′ = ^{t}Bu), which afforded a complex mixture. Steric hindrance on R′ is therefore tolerated for the 5-*exo* reaction, but not the 6-*endo* (entry 4).

When aromatic *N*-derivatives are employed (R = Ar), method A required a further optimization of temperature in order to obtain the best regioselectivity for **2** (entries 5−7, Table 2). Such an approach was successful for **1e** and **1f** (>20:1 **2**:**3** at 25 and 60 °C respectively), but in the case of **1g** the regioselectivity could only be improved to 2.6:1 (**2g**:**3g**). In contrast, all R = Ar derivatives **1e**−**1g** successfully yielded the 6-*endo-dig* isomers **3e**−**g** with good yields (74−82%) and excellent regiocontrol (>20:1 **3**:**2**, entries 5−7).

Table 2. Scope of the Reaction



Method A: K_2CO_3 (0.35 equiv.) favors **2**
Method B: Ag_2CO_3 (0.1 equiv.) favors **3**

entry	substrate	method A (green) **2**:**3**, yield (%)[a]	method B (red) **3**:**2**, yield (%)[a]
1	R = CH_2CO_2Et R′= CH_2Ph **1a**	>20:1,[b] 86% **2a**	>20:1,[c] 84% **3a**
2	R = CH_2CO_2Et R′ = ^{n}Bu **1b**	>20:1, 86% **2b**	>20:1, 58% **3b**
3	R = CH_2CO_2Et R′ = ^{i}Pr **1c**	>20:1, 88% **2c**	>20:1, 74% **3c**
4	R = CH_2CO_2Et R′ = ^{t}Bu **1d**	>20:1,[d] 88% **2d**	complex mixture
5	R = Ph R′ = Bn **1e**	>20:1,[e] 86% **2e**	>20:1,[f] 74% **3e**
6	R = *p*-MeO-C_6H_4 R′ = Bn **1f**	>20:1,[b] 90% **2f**	>20:1, 78% **3f**
7	R = *p*−Cl-C_6H_4 R′ = Bn **1g**	2.6:1,[g] (100%)[h]	>20:1, 82% **3g**
8	R = Bn R′ = Bn **1h**	>20:1,[d,f] 94% **2h**	>20:1,[f] 64% **3h**
9	R = ^{n}Bu R′ = Bn **1i**	>20:1,[i] 86% **2i**	>20:1,[f] 84% **3i**
10	R = ^{i}Pr R′ = Bn **1j**	>20:1,[i,e] (14%)[h] **2j**	traces
11	R = Me R′ = Bn **1k**	4.7:1,[j] 82% **2k**	>20:1, 11% **3k**
12	R = CH_2CH_2OMe R′ = Bn **1l**	>20:1,[i] 72% **2l**	>20:1, 78% **3l**

[a]Isolated yields unless otherwise stated. [b]8 h. [c]5 h. [d]60 °C. [e]25 °C, 4 d. [f]7 h. [g]**2g** decomposes upon column chromatography. [h]Conversion by ^{1}H NMR analysis. [i][Au] = 15 mol %. [j]2 d.

Entries 8−12 demonstrate that the 5-*exo* products **2h**−**i** and **2k**−**l** can be effectively and selectively formed using method A when R = alkyl. However, the reaction is sensitive to steric hindrance on the nucleophilic *N*, with a secondary alkyl on **1j** causing a drop in conversion to 14% (entry 10). The formation of **3h**−**l** using method B is also affected by steric size on R. While **3h**−**i** and **3l** are formed smoothly (entries 8−9 and 12), **1j**, where R = ^{i}Pr, is reluctant to undergo hydroamination presumably due to sterics as in the case above (entry 10). Surprisingly, the methyl substituted **1k** also produces a low conversion and yield of 11% (entry 11).

The results in Table 2 demonstrate that the switching between 5-*exo-dig* and 6-*endo-dig* using methods A and B, respectively, is a general phenomenon for terminal alkynyl sulfamides, regardless of the identity of substituents R or R′ on **1**.

The terminal alkyne on **1**, however, was found to be crucial for the switching of regioselectivity between **2** and **3** to be effective. This is clearly demonstrated using internal alkyne **1m**, where both methods A and B resulted in exactly the same 10:90 **2m**:**3m** ratio, albeit with a lower conversion using K_2CO_3 compared to Ag_2CO_3 (60% vs 100%, Scheme 2). This difference in reactivity could be attributed to the lower efficiency of K vs Ag as chlorine scavenger in the formation of the cationic gold complex.[13]

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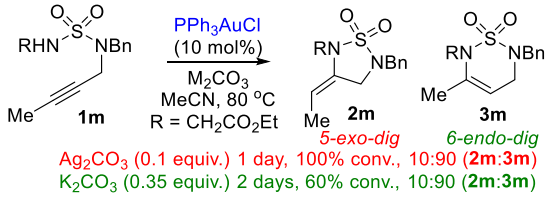
Scheme 2. Reaction of Internal Alkyne 1m with Both Catalytic Systems



This unexpected result prompted us to undertake a mechanistic study in order to gain insight into the reason for regiodivergence. The formation of **3m** as the major isomer, even under optimal conditions for **2** (method A), led us initially to hypothesize that a gold acetylide could be an intermediate in the formation of the 5-*exo-dig* products **2a**–**l**, which is activated via *σ*,*π*-digold complex (**C′**, Scheme 3A),[11] while formation of the 6-*endo-dig* regioisomer **3a**–**l** might be promoted by classical *π*-activation-only of the alkyne (**D**, Scheme 3A).

In order to investigate our initial hypothesis, deuterated **D-1h** was submitted to methods A and B (Scheme 3B). The complete loss of the D-label in **2h** is consistent with the in situ generation of a gold acetylide, as expected. However, the unexpected loss of D in the presence of Ag_2CO_3 would suggest the presence of a gold acetylide in the formation of **3h** as well, thereby ruling out our initial hypothesis of *π*-activation only for the formation of **3**. We therefore revised our hypothesis to suggest that the formation of both **2** and **3** proceeds via a gold acetylide complex **E** (see later, Scheme 3C). Only when formation of the gold acetylide is not possible (e.g., **1m**) does competitive *π*-activation-only (**D**) occur, thereby explaining the identical ratio of **2m**:**3m** under both conditions (Scheme 2).

In order to ascertain how much silver is required for regioselectivity switching, the influence of the Ag:Au ratio was investigated (Table 3). Regioselectivity is not affected when silver is doubled (entry 2). In contrast, when the Ag:Au ratio is lower than 2:1, the formation of **2a** starts to be competitive (entry 3). Finally, when 1:1 Ag:Au is employed, only 5-*exo* isomer **2a** is formed (entry 4). Thus, under our optimal conditions, the silver needs to be in excess of the gold catalyst for the switching of regioselectivity to take effect. It should be noted, however, that for other commonly used and more cationic silver sources such as $AgSbF_6$ and AgOTf, the **3a**:**2a** ratio is >20:1 even when the Ag:Au ratio is 1:1 (entries 2 and 4, Table 1). Therefore, the silver need not always be in excess of gold for the silver effect to take place.

With the evidence shown in Scheme 3B and Table 3 in mind, a mechanistic proposal was postulated (Scheme 3C). The proposed catalytic cycle begins with the *π*-coordination of the cationic gold complex[9,12] to the alkyne (**D**).[13] This coordination increases the acidity of the terminal alkyne proton, thus boosting the formation of the gold acetylide **E** in the presence of the carbonate base.[111] An alternative possibility involving a silver acetylide en route to **3** was ruled out, since control experiments with silver acetylide favors the formation of **2** instead of **3** (see Supporting Information).

E can then either be activated via the *σ*–*π*-digold complex[11] **C′** in the presence of an excess of LAu^+ or the *σ*-gold *π*-silver activated alkyne[14] **B′** when Ag^+ is available. Next, cyclization and protodemetalation promoted by bicarbonate produces **2** and **3** from **C′** and **B′**, respectively, while regenerating the gold catalyst and carbonate base.

To support our hypothesis, we attempted to synthesize the gold acetylide **E** from **1h**. While attempts to isolate the L=

Scheme 3. Possible Activation Modes, D-Labeling Studies and Mechanistic Proposal

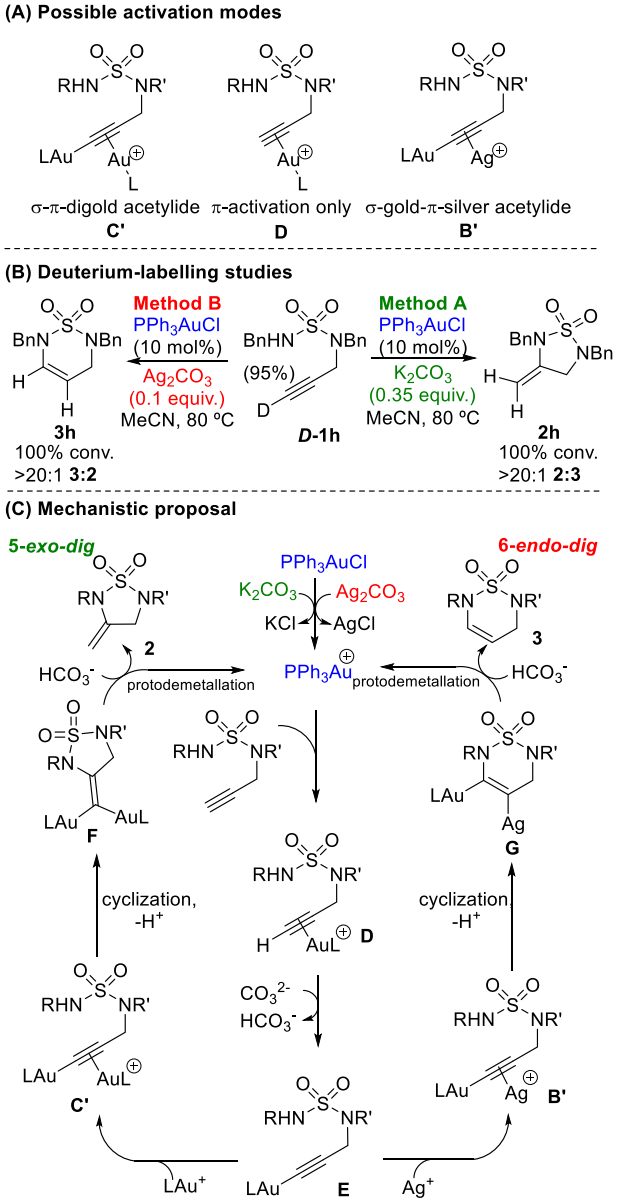
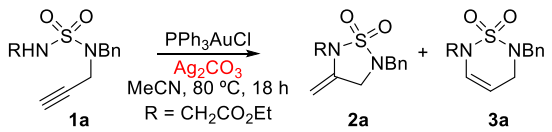


Table 3. Influence of Ag:Au Ratio on Regioselectivity



entry	Ag_2CO_3 (mol %)	PPh_3AuCl (mol %)	Ag:Au	3a:2a[a]
1	10	10	2:1	>20:1
2	20	10	4:1	>20:1[b]
3	10	15	1.5:1	1.25:1
4	10	20	1:1	1:>20

[a]Determined by ^1H NMR analysis. [b]Decomposition of starting material observed.

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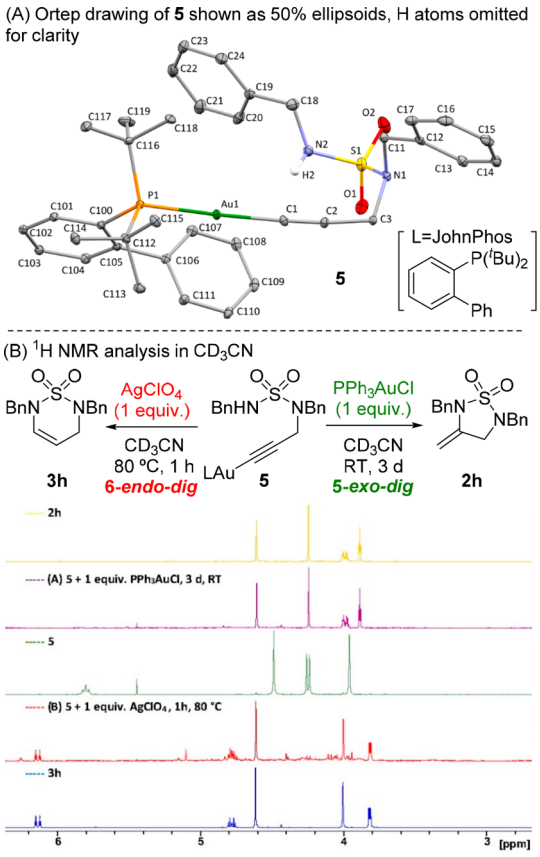
PPh_3 complex failed due to stability issues, reaction of **1h** with JohnPhosAuCl pleasingly provides the stable gold acetylide **5**, confirmed by single crystal X-ray diffraction (Scheme 4A).

Scheme 4. Structure and ^{1}H NMR Analysis of 5



To our delight, and as predicted, the exposure of **5** to PPh_3AuCl induced the clean formation of the 5-*exo-dig* isomer **2h**, whereas exposure of **5** to Ag^+ provides the 6-*endo-dig* product **3h** as the major product (Scheme 4B).[15] Although we are not yet able to ascertain *why* different intermediates produce different regioisomers, these results are nevertheless fully consistent with the proposed mechanism shown in Scheme 4 and lend support toward the activation via **C′** and **B′** respectively. Furthermore, coordination of gold or silver to gold acetylides (forming **C** and **B**, respectively) has been reported to be more favorable than to the parent terminal alkyne (forming **D**),[14] which may explain why **D** only operates when the formation of gold acetylide is not possible (e.g., Scheme 2).

In conclusion, the presence of silver can induce a dramatic switch in regioselectivity in gold-catalyzed hydroamination of terminal alkynyl sulfamides, and mechanistic studies suggest that the regiodivergence results from either σ–π-digold acetylides **C′** in the absence of silver to produce **2**, or σ-gold π-silver acetylides **B′** in the presence of silver to produce **3**. These results are of significance because it clearly shows that utilizing silver salts in gold-catalyzed reactions with terminal alkynes may result in "silver effects".

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b00249.

Full optimization studies, experimental procedures, NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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