Gold Catalysis

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# Gold(I)-Catalyzed Addition of Silylacetylenes to Acylsilanes: Synthesis of Indanones by C–H Functionalization through a Gold(I) Carbenoid

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*Dedicated to Professor José Barluenga on the occasion of his 75th birthday*

***Abstract:*** *A gold(I)-catalyzed synthesis of indanones from trimethylsilylacetylenes and acylsilanes is presented. The reaction is initiated through a synergistic acylsilane activation–gold acetylide formation and involves consecutive alkyne σ-gold(I) addition, π-activation, and 1,2-migration of a silyl group. Studies performed on the reaction mechanism allowed to establish the nature of the silyl migrating group and invoke the participation of a gold(I) carbenoid intermediate. The reaction is completed by a gold(I) C–H functionalization step.*

During the last decade homogeneous gold catalysis has emerged as one of the most powerful tools in organic synthesis and a huge number of transformations of increasing molecular complexity have been achieved.[1] While processes involving π-carbophilic gold activation of alkynes have been extensively studied, σ-gold alkyne activation has received less attention.[2] Our group has recently reported a synergistic trimethylsilyl activation/double gold(I) catalytic alkynylation of aldehydes (Figure 1 a).[3] As a continuation of this work, we explored a special class of carbonyl groups: the acylsilanes, as they can act as aldehyde equivalents.[4]

As a working hypothesis, a synergistic acylsilane activation/gold acetylide addition could trigger a 1,2-silyl migration[5] possibly leading to a gold carbenoid intermediate. In this context, the search for alternative routes involving gold carbenoids as intermediates,[6] thus avoiding the use of hazardous and potentially explosive diazo compounds as precursors,[7] is highly pursued. General methodologies involve intramolecular procedures as 1,2-acyloxy migrations,[8] cycloisomerization of enynes,[9] ring cleavage of cyclopropenes,[10] retro-Buchner reactions,[11] and alkyne oxidations with sulfoxides[12] or *N*-oxide oxidants.[13] However, intermolecular procedures beyond the methodology involving intermolecular oxygen incorporation to alkynes by pyridine *N*-oxide derivatives are lacking.[13]

Here we present an efficient synthesis of indene derivatives as the result of an intermolecular formal [3+2] gold(I)-catalyzed cycloaddition between trimethylsilylacetylenes and acylsilanes (Figure 1 b).

First, we selected benzoylsilane **1** and trimethylsilylalkyne **2** as model compounds to test the activity of different gold(I) complexes. The reaction was performed at 70 °C in the presence of 5 mol % of the corresponding gold(I) catalyst, leading, after a period of 30 min, to the formation of indene derivatives **3** (Scheme 1).[14] As the result of these preliminary assays, we selected phosphite $P(ArO)_3$ as the appropriate ligand in terms of conversion and yield of indene **3**. As the counterion we selected bis(trifluoromethanesulfonyl)imidate on a routine basis, thus avoiding the use of silver salts to generate the corresponding gold catalyst.[15]

Due to the low stability of enol ether **3**[16] we decided to incorporate to the experimental procedure a quenching step

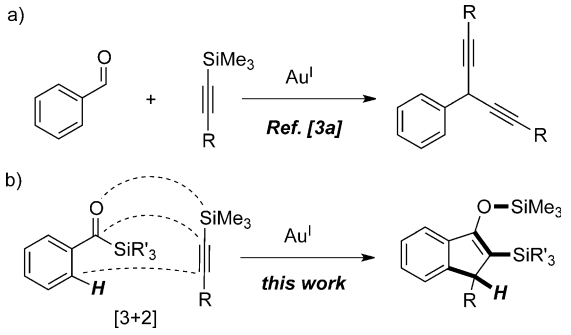
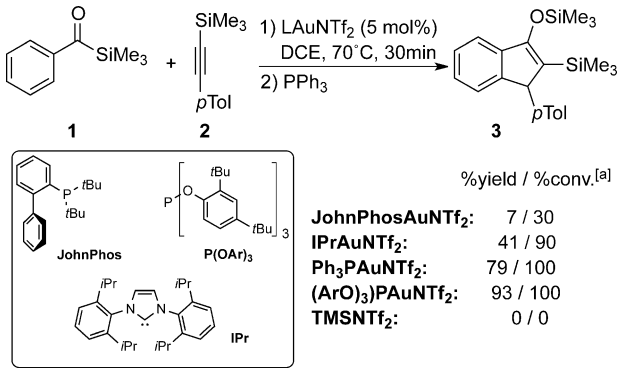



***Figure 1.*** Gold(I)-catalyzed addition of trimethylsilylalkynes to carbonyl derivatives.




***Scheme 1.*** Gold(I)-catalyzed formation of indene **3**.[a] Yields and conversions were determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard.

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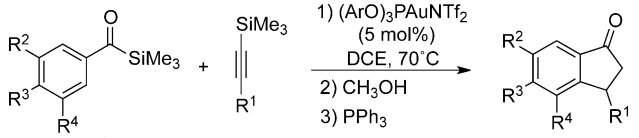
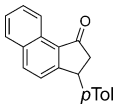
***Table 1:*** Gold(I)-catalyzed synthesis of indanones **6**.

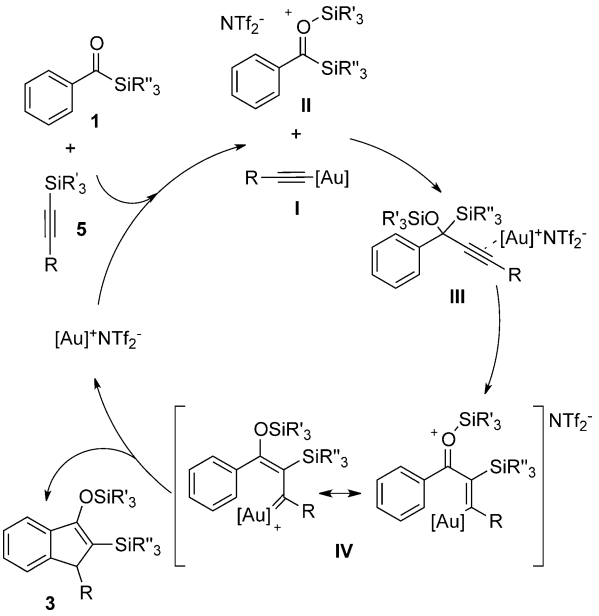



| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | *t* | **6** | Yield [%] |
|---|---|---|---|---|---|---|---|
| 1 | *p*Tol | H | H | H | 30 min | **6a** | 93 |
| 2 | Ph | H | H | H | 30 min | **6b** | 73 |
| 3 | $pMeOC_6H_4$ | H | H | H | 30 min | **6c** | 72[a] |
| 4 | $pBrC_6H_4$ | H | H | H | 30 min | **6d** | 80 |
| 5 | $pFC_6H_4$ | H | H | H | 30 min | **6e** | 88 |
| 6 | $pNO_2C_6H_4$ | H | H | H | 30 min | **6f** | 45[b] |
| 7 | $nC_8H_{18}$ | H | H | H | 30 min | **6g** | 77 |
| 8 | Bn | H | H | H | 30 min | **6h** | 82 |
| 9 | $cC_3H_5$ | H | H | H | 15 h | **6i** | 80[c] |
| 10 | *p*Tol | H | Me | H | 30 min | **6j** | 85 |
| 11 | *p*Tol | H | Br | H | 40 min | **6k** | 74 |
| 12 | *p*Tol | H | OMe | H | 25 min | **6l** | 84 |
| 13 | *p*Tol | H | OTBDMS | H | 30 min | **6m** | 74 |
| 14 | *p*Tol | H | $CO_2Me$ | H | 30 min | **6n** | 77 |
| 15 | *p*Tol | Me | H | H | 30 min | **6o** | 81[d] |
| 16 | *p*Tol | Cl | H | H | 30 min | **6p** | 75[e] |
| 17 | *p*Tol | Me | H | Me | 30 min | **6q** | 80 |
| 18 |  | | | | 16 h | **6r** | 61 |
| 19 |  | | | | 70 min | **6s** | 48 |

[a] Reaction performed at room temperature. [b] 55% Conversion. [c] Reaction performed at 60°C. [d] Mixture (ca. 5:1) with its isomer $R^2$ = H, $R^4$ = Me. [e] Mixture (ca. 3:1) with its isomer $R^2$ = H, $R^4$ = Cl. TBDMS = *tert*-butyldimethylsilyl.

with methanol in order to transform indene **3** into indanone **6** (Table 1). Next, we explored the scope of the reaction with respect to the nature of acylsilane **4** and trimethylsilylalkyne **5** (Table 1). The reaction proceeds satisfactorily with aromatic alkynes with electron-donating (entries 1 and 3) or electron-withdrawing groups (entries 4–6). Aliphatic alkynes can also be employed (entries 7–9). Similar results were obtained with respect to the acylsilane substitution pattern (entries 10–17), as the reaction tolerates the presence of different functional groups. Unfortunately, no reaction was observed with acylsilanes *ortho*-substituted on the aromatic ring, probably due to steric hindrance in the addition step. Finally, benzofused indanone **6r** or heteroaromatic fused cyclopentanone **6s** could also been obtained.

A mechanistic proposal for the formation of the silyl enol ether **3**—the precursor of indanone **6**—is outlined in Scheme 2. The catalytic cycle could be initiated by gold(I) activation of the alkyne to form the gold acetylide intermediate **I**.[17] Next, gold acetylide **I** can attack intermediate **II**, that was synergistically activated by the coordination of the oxophilic silyl moiety, to form the first carbon–carbon bond. After formation of **III**, this intermediate could evolve through a π-gold activation followed by 1,2-silyl migration[5] with

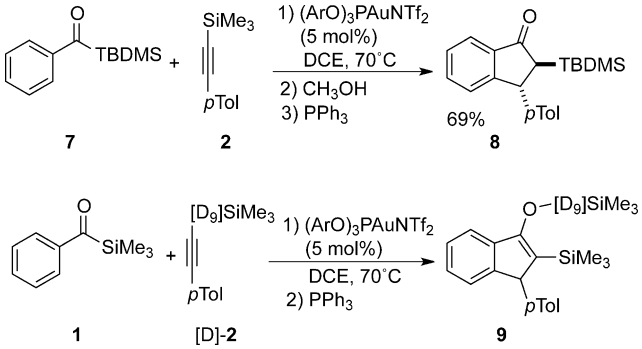



***Scheme 2.*** Mechanistic proposal. [Au] = $AuP(OAr)_3$.

formation of the gold carbenoid intermediate **IV**.[18,19] Finally, C–H functionalization of the aromatic ring would lead to indene **3**.

In order to provide experimental support, a number of experiments were designed to verify participation of the reported intermediates. First it was found that the reaction of acylsilane **1** with alkyne **2** is also catalyzed by an isolated catalytic amount (5 mol%) of the corresponding triphenylphosphine gold(I) acetylide in the presence of $TMSNTf_2$. This transformation supports the formation of intermediate **I**. Without $TMSNTf_2$ no reaction took place, highlighting the activation of the acylsilane by the trimethylsilyl group.[20]

Next, the nature of the silyl migrating group was identified through two independently performed experiments (Scheme 3). First, the use of acylsilane **7** with a TBDMS group leads to the formation of **8** with the silyl group at the C-2 position of the indanone. This result supports a mechanistic proposal involving a 1,2-silyl migration of the silyl group linked to the acyl moiety. Additionally, this outcome also represents an easy access to α-silylated indanones. In a similar, but more accurate experiment, we incorporated an isotopi-

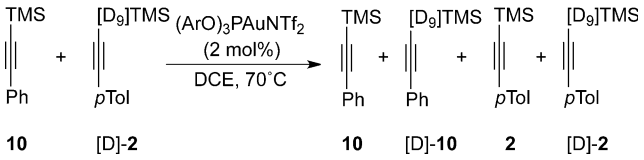



***Scheme 3.*** Investigations on 1,2-silyl migration.

cally labeled trimethylsilyl group to the alkyne and employed non-deuterated acylsilane **1**. When this reaction was performed under standard conditions, enol ether **9** was selectively obtained with no scrambling of the two silyl groups.

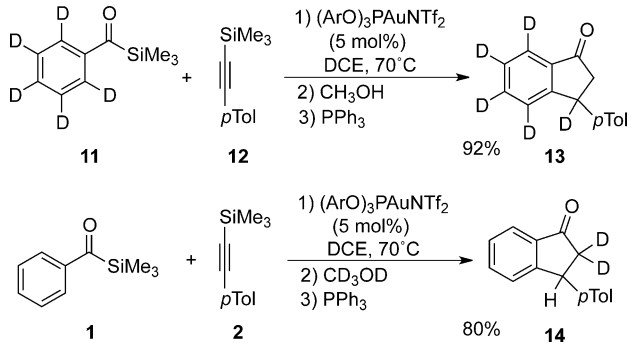
The absence of scrambling points to an intramolecular rearrangement without the leaving of the TMS group assisted by the triflimidate counterion present in solution. To further validate this hypothesis, the nature of the 1,2-silyl migration was investigated. Reaction between acetylenes **10** and [D]-**2** in the presence of 2 mol% of catalyst led to the formation of acetylenes **2** and [D]-**10**[21] indicating the participation of two different salts: $TMSNTf_2$ and TMS-[$D_9$]$NTf_2$ (Scheme 4). As the silyl group did not exchange during indene formation the conclusion follows that an "internal" silyl migration occurs. This observation rules out the formation of a new triflimidate




***Scheme 4.*** Crossover experiment.

salt and the participation of a mixture of deuterated and nondeuterated acetylenes.

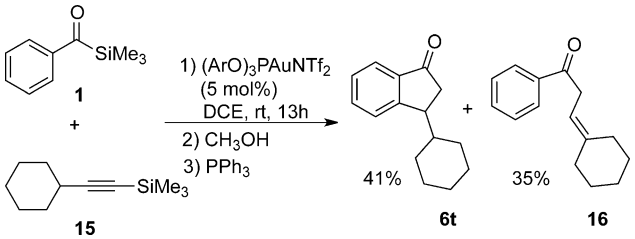
As additional support for the mechanistic proposal, the use of perdeuterated acylsilane **11** or deuterated methanol clarified the origin of the three new hydrogens of indanone **6** (Scheme 5). The hydrogen or deuterium in position C-3 stems from C–D gold(I) functionalization of the aromatic ring and the methylene group of C-2 emerges from the methanol addition. It should be noted that combination of perdeuterated starting materials and deuterated methanol could




***Scheme 5.*** Labeling experiments.

provide access to completely deuterated indanones, which are not easily available by other methodologies.

Finally, indirect evidence of carbenoid intermediate **IV** was found by reacting (cyclohexylethynyl)trimethylsilane **15** with acylsilane **1** (Scheme 6). In addition to indanone **6t** an almost equimolar amount of ketone **16** was obtained. β,γ-Unsaturated ketone **16** was identified as a protodemetalation




***Scheme 6.*** Indirect evidence for the carbenoid intermediate **IV**.

product formed through 1,2-hydrogen migration from the corresponding gold carbenoid intermediate **IV**. This evidence lets us to consider this a new methodology to access gold(I) carbenoids—compounds widely proposed as intermediates in gold-catalyzed organic transformations. However, for this particular reaction, taking into account the nature of the gold ligand and the final C–H functionalization step,[22] the cationic resonance form of intermediate **IV** should be considered as prevalent.[19]

In summary, acylsilanes have emerged as valuable substrates for addition reactions with gold acetylides. After the initial gold acetylide addition, a 1,2-silyl migration triggers the formation of a gold carbenoid intermediate, validating our initial hypothesis. The results describe a new intermolecular methodology to access these valuable reactive compounds. Moreover, the synthesis of indene derivatives presented here also involves consecutive alkyne σ-gold(I) formation and π-activation and a C–H functionalization step. Experimental studies of the reaction mechanism verified the mechanistic proposal.

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*Angew. Chem.* **2015**, *127*, 13882–13885

[1] Selected reviews: a) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403; b) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; *Angew. Chem.* **2007**, *119*, 3478–3519; c) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3321; d) S. P. Nolan, *Acc. Chem. Res.* **2010**, *44*, 91–100; e) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994–2009; f) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657–1712; g) M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2011**, *47*, 6536–6544; h) C. Obradors, A. M. Echavarren, *Chem. Commun.* **2014**, *50*, 16–28; i) R. Dorel, A. Echavarren, *Chem. Rev.* **2015**, DOI: 10.1021/cr500691k.

[2] a) C.-J. Li, *Acc. Chem. Res.* **2010**, *43*, 581–590; b) T. de Haro, C. Nevado, *Synthesis* **2011**, 2530–2539; c) J. C. Lima, L. Rodríguez, *Chem. Soc. Rev.* **2011**, *40*, 5442–5456.

  

[3] a) B. Rubial, A. Ballesteros, J. M. González, *Adv. Synth. Catal.* **2013**, *355*, 3337 – 3343; b) For an alkynylation of *N,O*-acetals, see: M. Michalska, O. Songis, C. Taillier, S. P. Bew, V. Dalla, *Adv. Synth. Catal.* **2014**, *356*, 2040 – 2050.
[4] For a recent review on acylsilanes: H.-J. Zhang, D. L. Priebbenow, C. Bolm, *Chem. Soc. Rev.* **2013**, *42*, 8540 – 8571.
[5] For platinum- and gold-induced 1,2-silyl migration, see: a) D. A. Rooke, E. M. Ferreira, *J. Am. Chem. Soc.* **2010**, *132*, 11926 – 11928; With other electrophiles, see: b) N. T. Barczak, D. A. Rooke, Z. A. Menard, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2013**, *52*, 7579 – 7582; *Angew. Chem.* **2013**, *125*, 7727 – 7730.
[6] a) Y. Wang, M. E. Muratore, A. M. Echavarren, *Chem. Eur. J.* **2015**, *21*, 7332 – 7339; b) D. Qian, J. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 677 – 698.
[7] For the seminal contribution, see: a) M. R. Fructos, T. R. Belderrain, P. de Fremont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo, P. J. Perez, *Angew. Chem. Int. Ed.* **2005**, *44*, 5284 – 5288; *Angew. Chem.* **2005**, *117*, 5418 – 5422; for recent work, see: b) G. Xu, C. Zhu, W. Gu, J. Li, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 883 – 887; *Angew. Chem.* **2015**, *127*, 897 – 901.
[8] a) M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002 – 18003; b) N. Marion, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2750; *Angew. Chem.* **2007**, *119*, 2806.
[9] a) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326 – 3350; b) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2014**, *47*, 902 – 912.
[10] a) F. Miege, C. Meyer, J. Cossy, *Beilstein J. Org. Chem.* **2011**, *7*, 717 – 734; b) A. Archambeau, F. Miege, C. Meyer, J. Cossy, *Acc. Chem. Res.* **2015**, *48*, 1021 – 1031.
[11] a) C. R. Solorio-Alvarado, Y.-H. Wang, A. M. Echavarren, *J. Am. Chem. Soc.* **2011**, *133*, 11952 – 11955; b) Y. Wang, P. R. McGonigal, B. Herle, M. Besora, A. M. Echavarren, *J. Am. Chem. Soc.* **2014**, *136*, 801 – 809.
[12] For two selected references, see: a) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 4160 – 4161; b) G. Li, L. Zhang, *Angew. Chem. Int. Ed.* **2007**, *46*, 5156 – 5159; *Angew. Chem.* **2007**, *119*, 5248 – 5251.
[13] For recent revisions, see: a) H.-S. Yeom, S. Shin, *Acc. Chem. Res.* **2014**, *47*, 966 – 977; b) L. Zhang, *Acc. Chem. Res.* **2014**, *47*, 877 – 888.
[14] At the end of the 30-min period, 20 mol % of triphenylphosphine was added to inactivate the catalyst.
[15] N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133 – 4136.
[16] Indene **3** could be isolated after filtration through a short pad of celite and high vacuum evaporation of the remaining alkyne.
[17] a) G. C. Fortman, A. Poater, J. W. Levell, S. Gaillard, A. M. Z. Slawin, I. D. W. Samuel, L. Cavallo, S. P. Nolan, *Dalton Trans.* **2010**, *39*, 10382 – 10390; b) T. N. Hooper, M. Green, C. A. Russell, *Chem. Commun.* **2010**, *46*, 2313 – 2315; c) P. Starkov, F. Rota, J. M. D'Oyley, T. D. Sheppard, *Adv. Synth. Catal.* **2012**, *354*, 3217 – 3224; d) Refs. [3a] and [3b].
[18] For a similar intermediate in the synthesis of indenes, see: N. Marion, S. Díez-González, P. de Fremont, A. R. Noble, S. P. Nolan, *Angew. Chem. Int. Ed.* **2006**, *45*, 3647 – 3650; *Angew. Chem.* **2006**, *118*, 3729 – 3732 and references therein for other metals.
[19] The gold(I) carbene carbocation nature of this type of complexes has been widely discussed: a) D. Benítez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard III, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482 – 486; b) A. Fürstner, L. Morency, *Angew. Chem. Int. Ed.* **2008**, *47*, 5030 – 5033; *Angew. Chem.* **2008**, *120*, 5108 – 5111; c) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2008**, *47*, 6754 – 6756; *Angew. Chem.* **2008**, *120*, 6856 – 6858; d) A. M. Echavarren, *Nat. Chem.* **2009**, *1*, 431 – 433; e) M. W. Hussong, F. Rominger, P. Kraemer, B. F. Straub, *Angew. Chem. Int. Ed.* **2014**, *53*, 9372 – 9375; *Angew. Chem.* **2014**, *126*, 9526 – 9529; f) G. Seidel, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, *53*, 4807 – 4811; *Angew. Chem.* **2014**, *126*, 4907 – 4911; g) Ref. [6a].
[20] This activation is very sensitive to the TMS-donating capability of the anion as no reaction was observed using TMSOTf instead of triflimidate or an in situ prepared gold acetylide triflate complex: A. Hasegawa, K. Ishihara, H. Yamamoto, *Angew. Chem. Int. Ed.* **2003**, *42*, 5731 – 5733; *Angew. Chem.* **2003**, *115*, 5909 – 5911.
[21] All four alkynes were obtained in an almost equimolar amount.
[22] For a single example of C–H functionalization on benzoylsilanes: P. Becker, D. L. Priebbenow, R. Pirwerdjan, C. Bolm, *Angew. Chem. Int. Ed.* **2014**, *53*, 269 – 271; *Angew. Chem.* **2014**, *126*, 273 – 275.

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