Homogeneous Catalysis

Gold(I)-Assisted α-Allylation of Enals and Enones with Alcohols

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Abstract: The intermolecular α-allylation of enals and enones occurs by the condensation of variously substituted allen-amides with allylic alcohols. Cooperative catalysis by [Au-(ItBu)NTf₂] and AgNTf₂ enables the synthesis of a range of densely functionalized α-allylated enals, enones, and acyl silanes in good yield under mild reaction conditions. DFT calculations support the role of an α-gold(I) enal/enone as the active nucleophilic species.

Gold-containing oxocarbenium derivatives **A** have been utilized extensively in homogeneous gold catalysis for the synthesis of new carbon–carbon and carbon–heteroatom bonds.[1] This family of activated [Au]−C(sp²) species is commonly accessible through initial gold-promoted [3,3] rearrangement of the corresponding propargylic carboxylates, followed by inter- as well as intramolecular electrophilic interception.[2] Alternatively, hydrolysis of the oxocarbenium adducts has been postulated to deliver the corresponding α-gold(I) enals/enones **B** during oxidative cross-coupling reactions (Scheme 1 a).[3]

Faza and López have investigated the mechanism of the [Auᴵ]-catalyzed oxidative cross-coupling in silico. Their study revealed the presence and role of α-gold(I) enone species in the [Auᴵ/Auᴵᴵᴵ]-based redox transformation.[4] In this context, we recently reported the spectroscopic identification of an analogous α-gold(I) enal adduct **B′** upon treatment of the complex [Au(P(2,4-tBu₂C₆H₃O)₃)(tfa)] (tfa = trifluoroacetate)[5] with the allenamide **C**[6] in wet CDCl₃ or CD₂Cl₂ (Scheme 1 b).[7]

To the best of our knowledge, this alternative approach to α-[Auᴵ] enals is unprecedented. On the basis of these recent findings, and in conjunction with our interest in the gold(I)-

and [H⁺]-assisted manipulation of allenamides,[5, 8] we envisioned the possibility of exploiting the intrinsic nucleophilic character of **B′**-type adducts to develop the first gold-mediated α-allylation of unsaturated carbonyl moieties.[9] Moreover, to validate the chemical sustainability of this method, we selected environmentally desirable allylic alcohols[10] as potential alkylating agents (Scheme 2). Allenamides have already been used in numerous elegant applica-
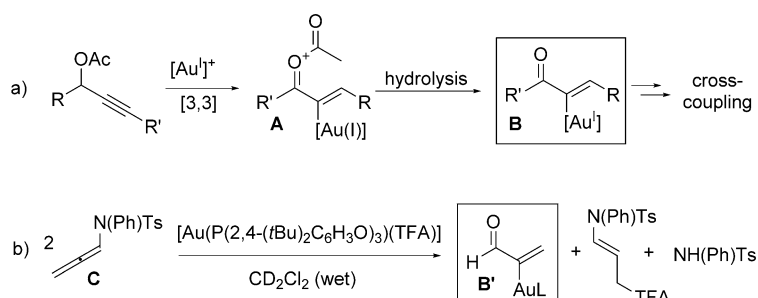
Scheme 1. a) Classical approach to the in situ generation of α-[Auᴵ]-substituted enals and enones. b) Our approach to the nucleophilic organogold intermediate (L = P(2,4-tBu₂C₆H₃O)₃). TFA = trifluoroacetate, Ts = *p*-toluenesulfonyl.
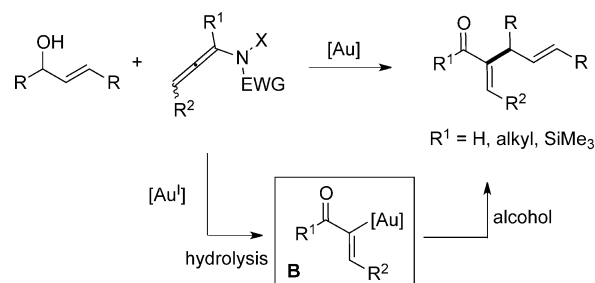
Scheme 2. Working hypothesis for the gold(I)-assisted α-allylation of α,β-unsaturated carbonyl compounds. EWG = electron-withdrawing group.
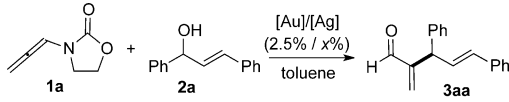
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    Supporting information for this article is available on the WWW
    under http://dx.doi.org/10.1002/anie.201507218.

tions in gold catalysis; however, most often the condensation of *nucleophilic* species with the metal-activated allenyl unit is the dominant chemical event in these transformations.[11] In contrast, the proposed methodology would involve the *electrophilic* trapping of the organogold intermediate derived from the hydrolysis of a gold–allenamide adduct.[12]

Allenamide **1a** and the secondary alcohol **2a** (model substrates) were initially subjected to various reaction conditions (Table 1). First attempts with [Au(P(2,4-tBu₂C₆H₃O)₃)(tfa)] (2.5 mol%) led to the formation of the desired product **3aa** in modest yield (28%) and also to the concomitant formation of by-products **II** and **III** in varying

Table 1: Optimization of the reaction conditions for the formal α-allylation of "acrylaldehyde".[a]

Entry	[Au]/[Ag] (x [mol%])	T [°C]/ t [h]	Yield of 3aa [%][b]	Yield of I/II/III [%][c]
1	[Au(P(OtBu₂Ph)₃)(tfa)]/–	110/4	28	–/40/50
2	[Au(PPh₃)Cl]/AgNTf₂ (2.5)	110/4	60	35/–/25
3	[Au(JohnPhos)Cl]/AgNTf₂ (2.5)	110/4	61	32/–/–
4	[Au(XPhos)(NTf₂)]/–	110/4	61	30/–/18
5	[Au(IPr)(NTf₂)]/–	110/4	70	53/–/–
6	[Au(ItBu)(NTf₂)]/–	110/2	84	44/–/–
7	[Au(IPr)Cl]/AgNTf₂[d]	110/4	96	36/–/–
8[e]	[Au(IPr)Cl]/AgNTf₂ (2.5)	110/4	68	55/–/–
9[f]	[Au(IPr)Cl]/AgNTf₂ (5)	110/4	89	41/–/–
10[g]	[Au(IPr)Cl]/AgNTf₂ (7.5)	110/4	97	35/–/–
11[h]	[Au(IPr)Cl]/AgNTf₂ (10)	110/4	35	40/–/–
12	[Au(IPr)(NTf₂)]/AgNTf₂ (5)	110/4	96	–/–/–
13	[Au(ItBu)Cl]/AgNTf₂ (7.5)	25/24	99	34/–/–
14[g]	[Au(ItBu)Cl]/AgNTf₂ (7.5)	110/4	94	37/–/–
15	[Au(IAd)Cl]/AgNTf₂ (7.5)	110/4	65	57/–/–
16	[Au(IPr*)Cl]/AgNTf₂ (7.5)	110/4	71	53/–/–
17	–/AgNTf₂ (7.5)	110/4	68	26/–/9
18	–	110/4	NR	–/–/–

[a] Reactions were carried out under anhydrous conditions (1a/2a/catalyst 1:1.5:0.025). [b] Yield of the isolated product after flash chromatography. [c] Yield after flash chromatography. The yields of I and III are given with respect to the initial amount of alcohol 2a. By-product II was always isolated as a 1:1 diastereomeric mixture. [d] An unweighed amount of AgNTf₂ was used. [e] [Au]/[Ag] 1:1. [f] [Au]/[Ag] 1:2. [g] [Au]/[Ag] 1:3. [h] [Au]/[Ag] 1:4. IAd = 1,3-di(adamantyl)imidazol-2-ylidene, ItBu = 1,3-di(tert-butyl)imidazol-2-ylidene, IPr = 1,3-di(isopropylphenyl)-imidazol-2-ylidene, IPr* = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazo-2-ylidene, NR = no reaction, Tf = trifluoromethanesulfonyl.

amounts (Table 1, entry 1). Among them, the condensation product derived from the oxazolidinone and 2a (compound II), was present in high enough amounts to be isolated. We were encouraged by these early results, and the presence of II supports our working hypothesis of the initial electrophilic activation of the allenyl group by the metal.
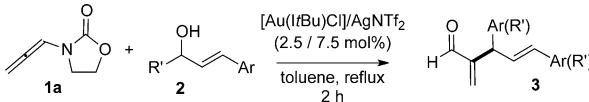
We reasoned that the isolation of II could be attributable to the use of a highly electrophilic gold species, and that more σ donating ligands could result in the formation of a more nucleophilic organogold(I) intermediate, thereby, hopefully, enabling 3aa to be obtained in higher yields. Gratifyingly, 3aa was obtained in higher yield by moving from phosphite- to phosphine-based gold catalysts. In this context, [Au(PPh₃)-(NTf₂)][13] and [Au(JohnPhos)(NTf₂)] formed in situ, and preformed [Au(XPhos)(NTf₂)], provided 3aa in comparable amounts (Table 1, entries 2–4).
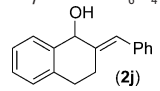
Next, the gold–N-heterocyclic-carbene (NHC) complexes [Au(IPr)(NTf₂)] and [Au(ItBu)(NTf₂)] were tested, with very promising results (Table 1, entries 5 and 6).[14] Intriguingly, when we carried out the reaction by in situ cation formation

(Au(IPr)Cl with AgNTf₂), a marked improvement in chemical yield was observed (96%; Table 1, entry 7). We reasoned that this improved performance might be due to the presence of excess AgNTf₂ with respect to the gold source and therefore carefully investigated the impact of the [Au]/[Ag] ratio on the reaction outcome (Table 1, entries 8–11). Optimal chemoselectivity was reached by the use of a 1:3 [Au]/[Ag] ratio (2.5:7.5 mol%), which provided a nearly quantitative amount of 3aa (97% yield; Table 1, entry 10). This optimization classifies the present gold catalysis as a "silver-assisted" transformation (see below).[15,16] A peculiarity distinguishing carbene-based from other phosphorus-based gold species is the complete suppression of the formation of by-product III, which was not detected in the crude product mixture. This outcome stresses the higher selectivity of NHC-based catalysts in promoting the cross-condensation over "homocoupling" processes. Notably, the use of AgNTf₂ alone led to the formation of a complex product mixture (Table 1, entry 17), and no reaction was observed in the absence of catalytic species (entry 18).

We then examined the scope of the reaction by conducting the cross-condensation of a range of allylic alcohols 2 with allenamide 1a (Table 2). A tolerance towards both electron-withdrawing and electron-donating substituents on the aryl moiety (at the ortho, meta, and para position) provided the

**Table 2:** Scope of the formal α-allylation of acrylaldehyde.[a]

Entry	R (1)	Ar/R' (2)	Yield [%] (3)[b]
1	H (1a)	Ar/R' = p-MeC₆H₄ (2b)	95 (3ab)/(71)
2	H (1a)	Ar/R' = o-MeC₆H₄ (2c)	94 (3ac)
3	H (1a)	Ar/R' = m-MeOC₆H₄ (2d)	55 (3ad)
4	H (1a)	Ar/R' = p-FC₆H₄ (2e)	94 (3ae)
5	H (1a)	Ar/R' = p-ClC₆H₄ (2f)	94 (3af)
6	H (1a)	Ar/R' = o-ClC₆H₄ (2g)	86 (3ag)/(trace)
7	H (1a)	Ar/R' = p-BrC₆H₄ (2h)	84 (3ah)/(52)
8	H (1a)	Ar/R' = o-BrC₆H₄ (2i)	84 (3ai)/(trace)
9	H (1a)	(2j)	88 (3aj)[c]
10	H (1a)	Ar = Ph/R' = p-ClC₆H₄ (2k)	45 (3ak)[d]

[a] Reactions were carried out under anhydrous conditions with 0.1 mmol of 1 (1a/2 1:2.5). [b] Yield of the isolated product after flash chromatography. Values in brackets are the yields observed with AgNTf₂ (7.5 mol%) as the catalyst. [c] Product 3aj was isolated as a 4:1 mixture of regioisomers; the major isomer featured an exocyclic C=C bond. [d] A 1:1 mixture of products was obtained.

corresponding α-allylated acrylaldehydes in good to excellent yield (55–95%; Table 2, entries 1–8).[17] Furthermore, the asymmetrically substituted allylic alcohols 2j and 2k were converted into the desired products 3aj and 3ak in moderate to good yield (45–88%) as mixtures of regioisomers (up to 4:1). These results point to a possible SN1-type mechanism of C–C bond formation (see below for a mechanistic discussion).[18]

The scope of the methodology was further assessed by applying the optimal reaction conditions to α-substituted allenamides **1b–f** (Table 3). Chemical manipulation at the C1 position of the starting allene would also allow direct access to α-allylated keto derivatives.[19] Gratifyingly, a range of α-allylated enones **4** were isolated in moderate to good yield (40–65%), regardless of the nature of the α substituent or the electronic properties of the allylic alcohol (Table 3, entries 1–9). The introduction of a substituent at the α carbon atom of the allenyl unit of **1** significantly enhanced the overall reactivity of the π system towards the allylation
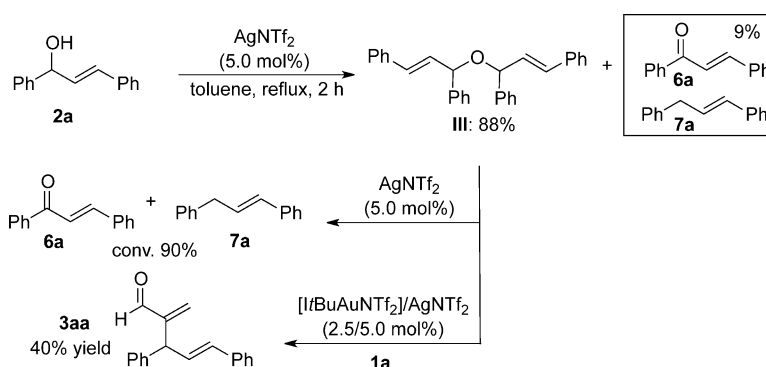
Scheme 3. Experiments in support of the proposed role of AgNTf₂ in the activation of **2a** and ether **III**.

Table 3: Formal α-allylation of enones and acyl silanes.[a]

Entry	R/R¹ (1)	Ar (2)	Yield [%] (4/5)[b]
1	Bn/H (**1b**)	C₆H₅ (**2a**)	52 (**4ba**)
2	Bn/H (**1b**)	p-MeC₆H₄ (**2b**)	57 (**4bb**)
3	Bn/H (**1b**)	p-FC₆H₄ (**2e**)	65 (**4be**)
4	Bn/H (**1b**)	p-ClC₆H₄ (**2f**)	48 (**4bf**)
5	Bn/H (**1b**)	p-BrC₆H₄ (**2h**)	50 (**4bh**)
6	p-FC₆H₄CH₂/H (**1c**)	C₆H₅ (**2a**)	63 (**4ca**)
7	p-FC₆H₄CH₂/H (**1c**)	p-MeC₆H₄ (**2b**)	40 (**4cb**)
8	p-FC₆H₄CH₂/H (**1c**)	p-FC₆H₄ (**2e**)	46 (**4ce**)
9	Me/H (**1d**)	C₆H₅ (**2a**)	50 (**4da**)
10[c]	H/Me (**1e**)	C₆H₅ (**2a**)	36 (**4ea**)
11[c]	SiMe₃/H (**1f**)	C₆H₅ (**2a**)	77 (**5a**)
12[c]	SiMe₃/H (**1f**)	p-ClC₆H₄ (**2b**)	70 (**5b**)
13[c]	SiMe₃/H (**1f**)	p-FC₆H₄ (**2e**)	57 (**5e**)

[a] Reactions were carried out with 0.1 mmol of **1** under nitrogen in dry toluene (**1**/**2** 1:1.5). [b] Yield after flash chromatography. [c] The reaction was carried out under reflux for 2 h. Bn=benzyl.

reaction, so that the temperature could be lowered and the reaction time shortened to just a few minutes![20]

Importantly, the method could also be extended to the α-allylation of α,β-unsaturated acyl silanes **5** (Table 3, entries 11–13), which are a well-known class of synthetically versatile building blocks. The products of these reactions were obtained in 57–77% yield (reflux, 2 h). Additionally, the γ,γ-disubstituted allenamide **1e** was treated with **2a** under the optimized conditions. The corresponding enal **4ea**, featuring a tetrasubstituted C=C double bond, was isolated in moderate yield (36%; Table 3, entry 10).

Mechanistically, this transformation poses several questions, for example: What is the role of the excess silver? What is the reaction profile of the C−C bond-forming event? What is the nature of the nucleophilic species? Insight into the C−C bond-forming step comes from the isolation of products **3aj** and **3ak** as mixtures of regioisomers (Table 2, entries 9 and 10). Accordingly, a Sₙ1-type mechanism involving stabilized allylic carbocations could be invoked.[21]

Experiments toward the elucidation of the role of AgNTf₂ were next carried out (Scheme 3). We had observed that AgNTf₂ alone (7.5 mol%) does promote the reaction, but with lower chemoselectivity (Table 1, entry 17). This trend was more evident when a selection of secondary allylic alcohols was treated under similar conditions for comparison (see Table 2, entries 1 and 6–8).[22] We reasoned that the presence of an excess amount of the Lewis acid could promote the activation of the allylic alcohol (i.e. formation of the allylic carbocation) and/or convert the ether **III** into a chemically active alkylating form. To test this hypothesis, **2a** was heated at reflux in the presence of a catalytic amount of AgNTf₂ in toluene for 2 h. The corresponding ether **III** was isolated in high yield (88%) along with the disproportionation products **6a** and **7a** in 9% combined yield.[23,24] Moreover, when **III** was used as the starting material in combination with water (1 equiv) and AgNTf₂, a mixture of **6a** and **7a** was obtained with high conversion (90%), and when **III** was used as the starting material in combination with **1a** (2 equiv) and [Au(I*t*Bu)(NTf₂)]/AgNTf₂, the desired product **3aa** was isolated in 40% yield. These experimental results support the key role of the silver salt in activating **2a** and "recycling" **III** towards nucleophilic trapping.[25,26]

We fully examined the reaction profile by DFT calculations (see the Supporting Information for an exhaustive discussion), which accounted for the initial formation of the postulated organogold intermediate of type **B** through hydrolysis[26] of the gold-activated allenyl unit, and its site-selective Sₙ1 addition to the allylic carbocation formed in situ (see Figures S1–S3 in the Supporting Information). Analogous calculations with AgNTf₂ as the catalytic agent led to significantly higher energy barriers (see the Supporting Information for more details).

Although the coexistence of a background reaction involving the spontaneous condensation of the unactivated allenamide **1a** with allylic cationic species cannot be completely excluded, this reaction pathway seems noncompetitive with the gold-assisted pathway in terms of chemoselectivity (see also Table 2, entries 1 and 6–8 for comparison with gold catalysis). Indeed, when a "naked" allylic carbocation generated in situ was directly treated with **1a**,[27] the corresponding enal **3aa** was obtained in only 40% yield along with a large amount of unknown by-products.

Finally, the further transformation of model allylated products **3** and **5** highlights their synthetic utility (Scheme 4). Acyl silane **5a** was conveniently converted into the corresponding α,β-unsaturated carboxylic acid **8a** in 99% yield by treatment with an aqueous mixture of H_2O_2 and NaOH
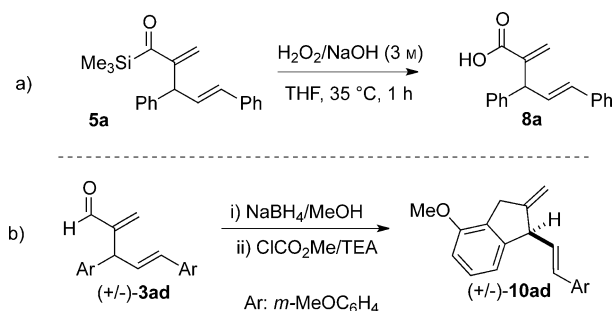
Scheme 4. Synthetic manipulation of the allylated compounds **3** and **5**: a) 99% yield; b) i) room temperature, 15 min, 77%; ii) CH_2Cl_2, room temperature, 4 h, 41%. TEA = triethylamine.

(Scheme 4a).[28] Additionally, aldehyde **3ad** was converted in two steps into the densely functionalized *exo*-methylene dihydroindene structure **10ad** (Scheme 4b).[29]

In conclusion, we have disclosed a gold(I)/silver(I)-cocatalyzed α-allylation of unsaturated carbonyl compounds with allylic alcohols that provides rapid access to substituted enals, enones, and acyl silanes. The cooperative action of gold and silver salts was elucidated by experimental as well as computational studies. The present methodology represents a valuable synthetic alternative to the well-known Baylis–Hillman reaction[30] for the α-functionalization of α,β-unsaturated carbonyl compounds, which has found sporadic application for allylic alkylation. We are currently developing an enantioselective variant of the present protocol.

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[17] Differently substituted allylic alcohols, such as cyclohexen-2-ol and (*E*)-pent-3-en-2-ol were also tested, but unfortunately they were found to be unreactive under the optimized conditions. Decomposition the allylic alcohol **2a** was observed, with the

formation of the corresponding compound of type **III** as the main side product.

[18] The allenamide **C** and the aryloxyallene **D** were also tested as allylating agents; however, **3aa** was isolated in lower yield: 52 and 33 % yield, respectively.
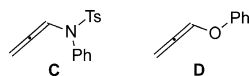
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[20] The temperature profile for the reaction of the α-alkylated allenamide **1b** was investigated (see the Supporting Information for details).

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[22] When AgNTf$_2$ (7.5 mol %) was tested with alcohol **2a** at room temperature for 24 h, **3a** was isolated in 70 % yield.

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[24] [Au(I*t*Bu)(NTf$_2$)] also enabled the formation of **III** (55 % yield, toluene, reflux), in agreement with the efficiency of silver-free catalytic systems.

[25] In the absence of AgNTf$_2$, only trace amounts of ether **III** were detected when **2a** was heated at reflux in toluene for 4 h.

[26] The water for the hydrolysis of the immonium intermediate could be derived from the silver-assisted dehydrative dimerization of **2a** to give **III**. The addition of activated molecular sieves seriously eroded the performance of the catalytic system (yield of **3a**: 41 %).

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