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Synergistic Gold(I)/Trimethylsilyl Catalysis: Efficient Alkynylation of N,O-Acetals and Related Pro-Electrophiles

Malina Michalska,[a] Olivier Songis,[a] Catherine Taillier,[a] Sean P. Bew,[b] and Vincent Dalla[a,*]

[a] URCOM, EA 3221, FR 3038, Faculté des Sciences et Techniques de l'Université du Havre, 25 rue Philippe Lebon, BP 540, F-76058 Le Havre, France
Fax: (+33)-2-3274-4391; phone: (+33)-2-3274-4401; e-mail: vincent.dalla@univ-lehavre.fr
[b] School of Chemistry, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, U.K.

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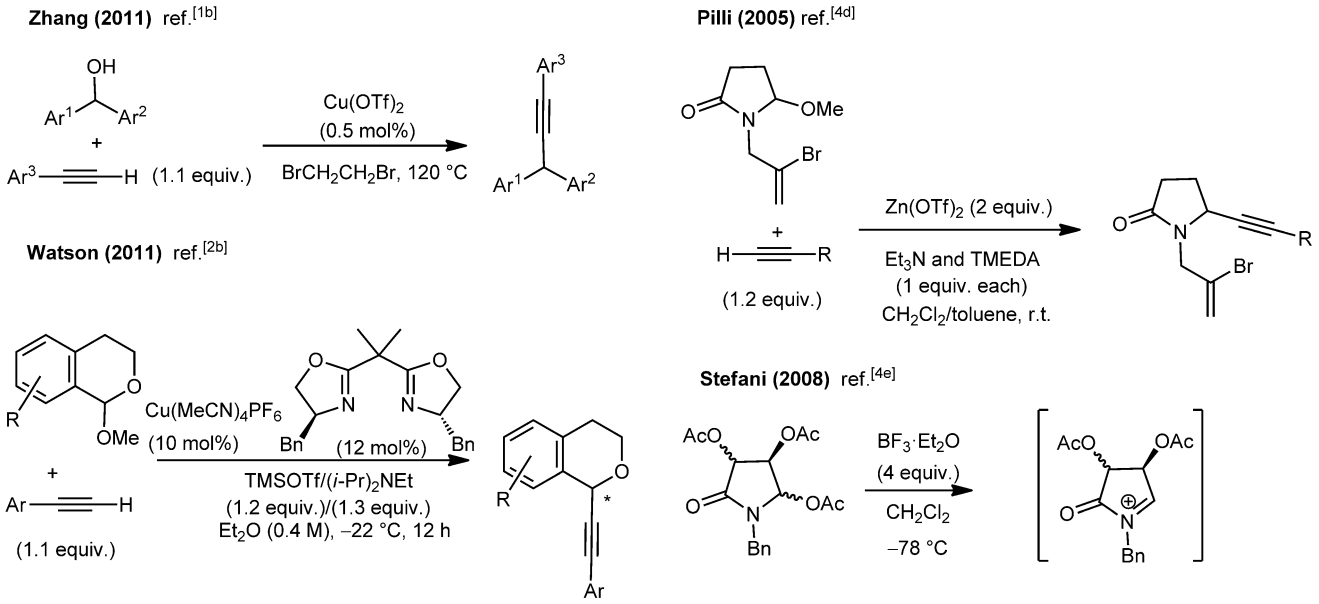
Abstract: We report a unique mechanism-guided reaction that enhances and expands the chemical space that readily generated gold(I) acetylides currently operate in. Our strategy exploits the propensity of gold(I) carbophilic catalysts with specific counteranions (LAuX – X = triflate or triflimidate) to efficiently activate and desilylate trimethylsilylalkynes, thereby mediating the *in situ* formation of equal and catalytic quantities of a silyl Lewis acid (TMSX) of tunable strength and a nucleophilic gold(I) acetylide. This unprecedented manifold opens avenues for developing synergistic silyl-gold(I)-catalyzed alkynylation strategies of diverse pro-electrophiles which were heretofore unattainable, the proof of concept being principally exemplified herein with the first catalytic alkynylation of N,O-acetals. The reaction proceeds at low catalyst loading, employs mild reaction conditions, is easily scalable, and affords propargylic lactam products in good to excellent yields. Furthermore, it is fully amenable to a diverse array of structure and function substrates, and also expands to other pro-electrophiles beyond N,O-acetals. Control experiments have been carried out that strongly support our dual reaction mechanism proposal which, furthermore, itself outlines an inextricable link between the strength of the ancillary silyl Lewis acid (TMSOTf *versus* $TMSNTf_2$) and the coordinating ability of the gold counter anion employed. This underlying feature of our system underscores its significant potential and flexibility, which indeed manifests with the demonstration that by carefully selecting the gold counter ion, it is possible to manipulate the strength of the ancillary silyl Lewis acid so that it can be tailored to the ionizing ability of a particular pro-electrophile.

Keywords: *N*-acyliminium ions; alkynylation; gold acetylide; supersilyl Lewis acid; synergistic catalysis

Introduction

Despite the widespread exploitation and application of the alkyne functional group the catalytic alkynylation of highly electrophilic cationic intermediates, for example, carbenium, *N*-acyliminium and oxonium ions, is surprisingly a methodology that has thus far received only scant attention from the organic synthesis community. This is quite revealing given the high synthetic 'value' associated with functionalized propargylic motifs. Thus only a handful of catalytic systems has been disclosed for the alkynylation of (highly) π-activated alcohols and their derivatives; see, for example, the recent report by Zhang et al. on the synthesis of arylated alkynes (Scheme 1).[1] Furthermore, as far as the authors are aware, there are only two reports dedicated to the catalytic alkynylation of acetals.[2]

The first by Watson et al. is an asymmetric protocol, however it requires an excess quantity of both trimethylsilyl trifluoromethanesulfonate (TMSOTf) and diisopropylethylamine (Scheme 1),[2b] while the second contribution is a gold-catalyzed alkynylation using terminal alkynes which, however, operates under harsh reaction conditions.[2a] In the context of our ongoing research interests in catalytic *N*-acyliminium ion chemistry,[3] we noted that the catalytic alkynylation of N,O-acetals is a synthesis methodology that has significant potential but has not yet been developed.[4] Thus, while the α-amidoalkylation of N,O-acetals with traditional nucleophiles such as allylsilanes, enol silanes, active methylene compounds, π-ar-

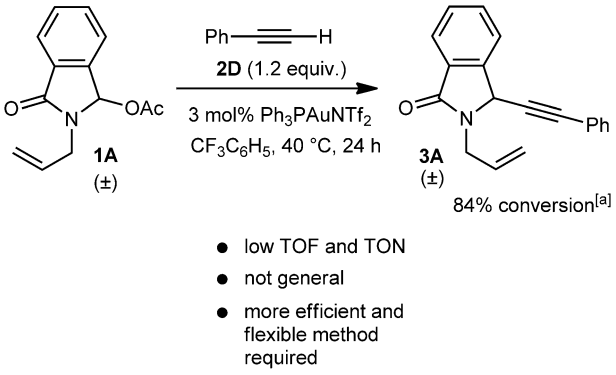


Scheme 1. Current state-of-the-art for catalytic alkynylation of carbenium and oxonium ions.

omatics, has been widely documented,[3,5] the related alkynylation reaction has not.[4] Thus, although a limited number of examples has been reported these often require pre-formed metal alkynylides to be used, in conjunction with harsh reaction conditions and, at best, *stoichiometric* quantities of Lewis acid mediators, for example, $BF_3{\cdot}OEt_2$, and TMSOTf. Of the different methods published on the alkynylation of N,O-acetals the most appealing was that by Pilli et al. (Scheme 2) who coupled terminal alkynes to N,O-acetals using 2 equivalents of $Zn(OTf)_2$.[4d]

Our preliminary attempts at developing an efficient catalytic alkynylation of N,O-acetals using *terminal* alkynes (Scheme 3) were disappointing. In summary, although the reaction would proceed using gold(I) catalysts we were unable to achieve sufficiently high catalytic turnovers that the starting material, for example **1A**, was transformed into the desired product (**3A**) in less than 24 h (Scheme 3).[6] For this reason we sought to design an alternative strategy with a view to developing a more efficient and, importantly, faster reaction process desirably amenable to structure and function diverse alkynes.

Scheme 2. Current state-of-the-art for the C-alkynylation of *N*-acyliminium ions.

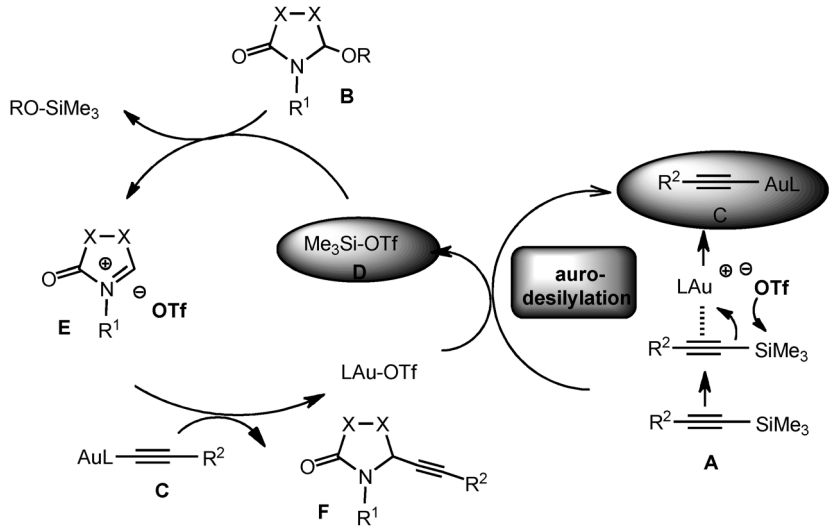


Scheme 3. Preliminary efforts towards generating a procedure for the direct catalytic alkynylation of N,O-acetals.

Design Plan

Inspired by previous reports of silylium catalysis[7] including our own contribution,[3a,b,d,e] we anticipated restoring the high catalytic activity desired in our alkynylative α-amidoalkylation by developing an unprecedented *catalytic gold/silyl synergistic approach*, which is also expected to have the potential to be a general alkynylative methodology beyond the *N*-acyliminium ion coupling targeted here. A generic overview of the reaction as we envisaged it is outlined in Scheme 4.

At the outset the reaction is initiated *via* the rapid complexation of the carbon-carbon triple bond of a trialkylsilylalkyne[8] with a cationic gold(I) salt. Subsequently an aurodesilylation event takes place which, importantly, generates both a nucleophilic gold(I) acetylide **C**[9,10] and a trimethylsilyl Lewis (super)acid **D**.[7] This process is reminiscent of the well-known protodesilylation of silicon-based nucleophiles by



Scheme 4. Design plan of our gold/silyl synergistic activation mode dedicated to the catalytic alkynylation of N,O-acetals.

Brønsted superacids.[7b,c] Critically, generating both intermediates **C** and **D** sets the reaction up well for the initiation of the subsequent, and important, dual catalysis process that follows. Here **D** 'activates' the N,O-acetal **B**, generating a transient and highly reactive *N*-acyliminium intermediate **E**, which is, when formed, immediately trapped by σ-gold(I) complex **C**. This C–C bond forming step releases the desired alkynylation product **F**, and regenerates the original gold(I) triflate catalyst which feeds back into the reaction cycle affording substrate turnover.

Key to success in this strategy is the judicious choice of gold counter anion. The counter anion must indeed exhibit a subtle balance, being sufficiently silaphilic to promptly mediate aurodesilylation,[11] and also weakly coordinating thus enhancing its ability to produce a suitable silicon-based Lewis acid which facilitates and mediates the rapid ionization of the N,O-acetal group generating the *N*-acyliminium species, i.e., **B**→**E** (Scheme 4). With these general considerations in mind, gold(I) triflate/triflimidate [LAuOTf/NTf_2] catalysts were assumed to hold the right balance of desirable chemical attributes to facilitate the efficient alkynylation of N,O-acetals.[3a–e,7,12] The formation of the 'super' silyl transfer reagent trimethylsilyl trifluoromethanesulfonate (TMSOTf) or trimethylsilyl bis(trifluoromethanesulfonyl)imide ($TMSNTf_2$), arising through a net trimethylsilyl transfer from the "protected" trimethylsilylalkyne, i.e., **A** to the triflate (or triflimidate) counter anion of the gold(I) salt, provides us with a highly convenient and efficient method of generating *in situ* and 'at source' catalytic quantities of the important naked Lewis acid. The presence then *of the trimethylsilyl group on the alkyne starting material is fundamentally important and cannot be considered as a 'superfluous' group*.

Bearing in mind the mechanistic considerations outlined in Scheme 4 we consider our approach of *in situ* generation of the catalytic agent to be superior to 'external' addition, we would for example anticipate catalyst synthesis at source or where required to be significantly more efficient, direct and atom-economic than the alternative reaction employing terminal alkynes and stochiometric quantities of Lewis acid (*vide supra*). We also anticipate our conceptually new mechanistic approach will have significant utility for the alkynylation of other structurally and functionally diverse electrophiles including cationic precursors and sp^2 functionalities.

Beside its doubtless synthetic utility as a novel alkynylative methodology, this mechanism-guided design strategy also manifests a conceptual interest since it can be regarded as an unprecedented approach where the incorporation of a single pre-catalyst (LAuX) mediates the initiation and *in situ* generation of two key catalytic species, namely a σ-gold acetylide and a 'super' silyl transfer reagent (TMSX), which when synergistically combined with the electrophilic reaction partner promote the efficient formation of high-value entities based on **F** (Scheme 4). When compared to 'traditional' synergistic catalysis, which systematically promote reactions with the aid of *two separate* catalysts (Figure 1A),[13] our *in situ* approach to synergistic catalysis (Figure 1B) is arguably of significant synthetic value from an academic, economic, time and atom-efficiency point of view. In addition, our approach has particular value if the catalytic species and/or catalyst(s) to be generated are not trivial to prepare and handle; as is the case here with σ-gold(I) acetylides and the formation of extremely water-sensitive and highly reactive Lewis acids TMSOTf and $TMSNTf_2$.

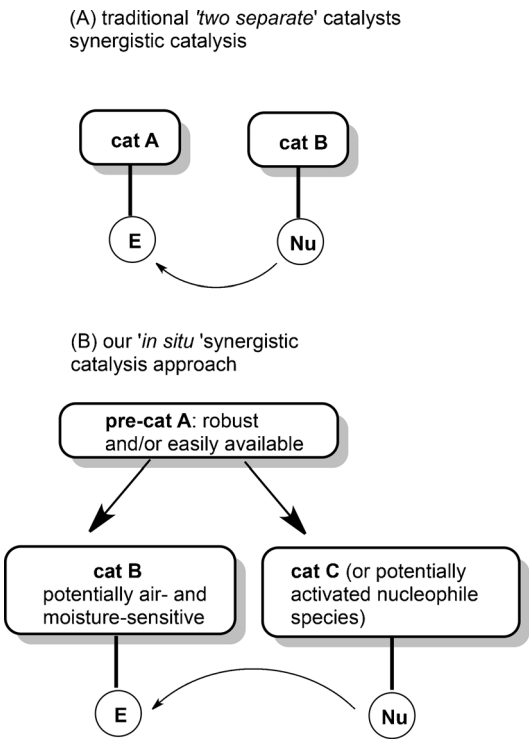


Figure 1. Conventional use of 'two separate catalysts' (**A**) *versus* our unprecedented *'in situ'* synergistic catalysis activation protocol (**B**).

Herein we report what we believe to be the first prototype of this exciting synergistic catalysis concept. Preliminary results are exemplified principally *via* the catalytic alkynylation of cyclic N,O-acetals but also with O,O-acetals, and the construction of the multicyclic 5,11a-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*]azepin-3(2*H*)-one ring system.

Results and Discussion

Alkynylation of N,O-Acetals: Optimization Study

In the first instance it was important to perform a feasibility study that aimed to explore the possibility of alkynylating the readily generated (±)-2-allyl-3-oxo-isoindolin-1-yl acetate **1A** with trialkylsilylphenylacetylene derivatives **2A–2C** (Table 1). Gratifyingly, after an extensive set of screening experiments had been performed the results from this study strongly supported our working hypothesis outlined in Scheme 4.[14] Examples of the most important and representative results from this preliminary study are depicted in Table 1.

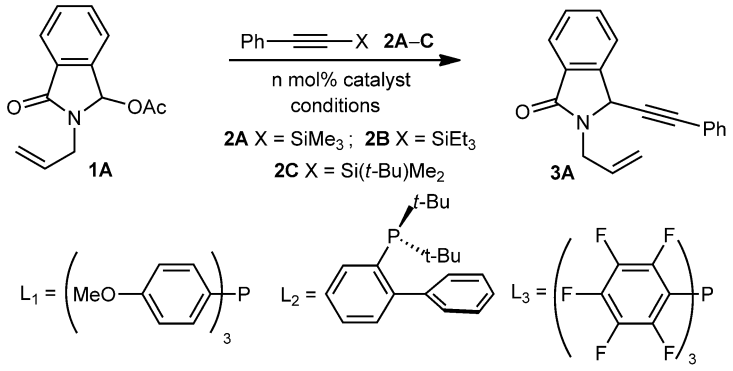
The following observations were particularly supportive of our mechanistic hypothesis: (i) As anticipated, the coupling of **1A** with trimethylsilylphenylacetylene **2A** outperformed the direct variant using terminal alkyne **2D** (Table 1, entry 3 *versus* Scheme 3).

(ii) Soft and rather carbophilic in nature, gold(I) salts[15] stabilized with a ligand were superior to other potential catalysts such as AuOTf, $Au(OTf)_3$, AgOTf, CuI, $Cu(OTf)_2$,[1b] I_2,[1f] and Tf_2NH.[14] In addition, a net *decrease* in the reaction conversion rate was observed as the steric bulk of the trialkylsilyl motif was *increased* (see entry 3 *versus* entries 1 and 2, Table 1).

(iii) As anticipated from our mechanistic postulate, a strong counter anion effect was observed (entry 3 *versus* entries 4–10). In particular and as anticipated (*vide supra*) Ph_3PAuX ($X = Cl^-$, I^-, TsO^- BF_4^- and SbF_6^-) were at best moderately effective in promoting the reaction.[12] Both $Ph_3PAuOTf$ and its triflimidate analogue were expected to generate Me_3SiOTf and Me_3SiNTf_2, respectively, with the latter anticipated to surpass the former in its ability to activate the N,O-acetal.[3b,c,7b,16] The fact that both *in situ* generated Gagosz pre-catalyst $Ph_3PAuNTf_2$ and its silver-free commercially available analogue exhibited *lower* activities than $Ph_3PAuOTf$ (compare entry 3 with entries 9 and 10) reflects the higher nucleophilicity/silaphilicity of the triflate anion over its triflimidate analogue.[7b,16] This strongly suggests that the rate-determining step in our mechanistic proposal is the formation of the silyl Lewis acid catalyst **D** (*via* aurodesilylation, i.e., **A** to **C**) rather than generation of the *N*-acyliminium ion (Scheme 4).[17,18] This, combined with the low conversions that were observed when more electrophilic gold catalysts such as $(C_6F_5)_3PAuOTf$ or AuOTf and $Au(OTf)_3$ (entries 17–19) were employed, strongly support our dual synergistic gold/silyl catalysis concept rather than an oxophilic gold-catalyzed N,O-acetal activation pathway.[3f,19]

(iv) Commensurate with our analysis, the reaction efficiency was significantly enhanced in apolar solvents,[14] this can be ascribed to a maximization of the electrophilic properties associated with the cationic gold(I) and the nucleophilic properties of the triflate and triflimidate anions. Minimization of side effects caused by silver might also be ascribed.[20] The solvent effect was optimized when α,α,α-trifluorotoluene was employed (compare entries 3 and 11), furthermore slightly warming the reaction to 40 °C established a highly effective set of reaction conditions that allowed complete and efficient alkynylation to take place in only 15 min, employing a slight excess (1.2 equivalents) of **2A** together with a low 3 mol% loading of the gold(I) pre-catalyst $Ph_3PAuOTf$ (entry 12). The simplicity and mildness of our reaction conditions are particularly noteworthy, and markedly contrast with the harsh reaction conditions,[1c–e] or the high catalyst loading (*viz.* 10 mol%)[1f,g] applied in association with extremely easily ionizable substrates

Table 1. Optimization of the gold(I)-catalyzed amidoalkylation of phenylacetylene derivatives **2A–C** with model N,O-acetal **1A**.[a]



Entry	2	Equiv. Nu	Catalyst (n mol%)	Solvent	Time	Conversion [%][b]
1[c]	**2B**	1.2	$Ph_3PAuOTf$ (3)[d]	$CF_3C_6H_5$	3 d	nr
2[c]	**2C**	1.2	$Ph_3PAuOTf$ (3)[d]	$CF_3C_6H_5$	5 h 40 min	16
3	**2A**	1.5	$Ph_3PAuOTf$ (7)[d]	toluene	45 min	100
4	**2A**	1.2	Ph_3PAuCl (7)	toluene	3 d	nr
5	**2A**	1.2	Ph_3PAuI (7)[d]	toluene	5 h 40 min	16
6	**2A**	1.2	$Ph_3PAuOTs$ (7)[d]	toluene	24 h	nr
7	**2A**	1.2	Ph_3PAuBF_4 (7)[d]	toluene	30 h	nr
8	**2A**	1.2	$Ph_3PAuSbF_6$ (7)[d]	toluene	4 h	73
9	**2A**	1.2	$Ph_3PAuNTf_2$ (7)[d]	toluene	4 h	100
10	**2A**	1.2	$Ph_3PAuNTf_2$ (7)[e]	toluene	1.5 h	100
11	**2A**	1.2	$Ph_3PAuOTf$ (7)[d]	$CF_3C_6H_5$	15 min	100
12[c]	**2A**	1.2	$Ph_3PAuOTf$ (3)[d]	$CF_3C_6H_5$	15 min	100[f]
13	**2A**	1.5	$Ph_3PAuOTf$ (3)[d]	toluene	30 min	44
14	**2A**	1.5	L_1AuOTf (3)[d]	toluene	30 min	100
15	**2A**	1.5	IPrAuOTf (3)[d]	toluene	30 min	100
16[c]	**2A**	1.5	L_2AuOTf (7)[d]	toluene	30 h	43
17	**2A**	1.5	L_3AuOTf (7)[d]	toluene	22 h	40
18	**2A**	1.5	AuOTf (7)[d]	toluene	20 h	32
19	**2A**	1.5	$Au(OTf)_3$ (7)[d]	toluene	20 h	[g]
19	**2A**	1.5	$Au(OTf)_3$ (7)[d]	toluene	20 h	[g]

[a] Unless otherwise indicated, the reactions were carried out at room temperature.
[b] Yields have been estimated *via* ^{1}H NMR.
[c] The reaction was carried out at 40 °C.
[d] Prepared by premixing commercially available gold(I) chloride with an equimolar amount of the silver salt.
[e] Commercially available Gagosz (silver-free) catalyst was employed.
[f] The isolated yield was 90%.
[g] A complex mixture was obtained.

employed in the related catalytic alkynylation of π-activated alcohols with alkynylsilanes.

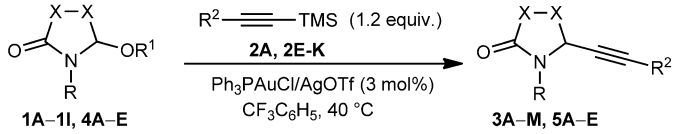
(v) Consistent with our mechanistic hypothesis, analysis of the preliminary 'model' reaction results[18] using gold(I) triflates bound to an electron-rich phosphine [*p*-MeO-$(C_6H_4)_3$P] or a σ-donor IPr ligand[21] indicated that these ligands generated a superior catalyst complex to that afforded with Ph_3P (entries 13–15), while sterically bulky triarylphosphines led to a significant rate retardation (entry 16). Owing to increased atom economy and lower cost considerations, triphenylphosphine was preferentially employed for continuation of this work.[22]

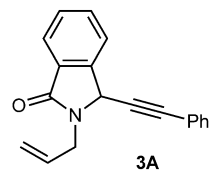
Finally, it is worth noting that in our alkynylation reaction turnover is virtually unaffected by the formation of the alkynylated product, this demonstrates the poor propensity of bulky product **3A** to reversibly bind to the Au(I) center thus competing with the less hindered and more productive trimethylsilylalkyne **2A**.

Reaction Scope

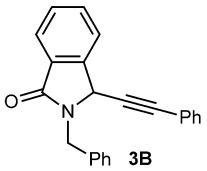
Having established and optimized the best combination of reaction partners, solvent, gold(I) salt catalyst

Table 2. Scope of the gold(I)-catalyzed amidoalkylation of trimethylsilylacetylene derivatives **2A** and **2E–K** with N,O-acetals **1A–I** and **4A–E**.

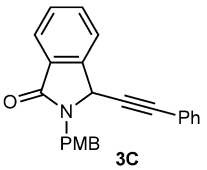




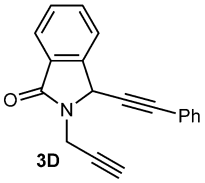
97% yield (15 min)



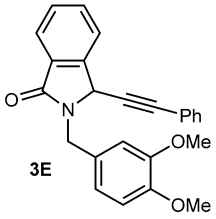
97% yield (1.5 h)[a]



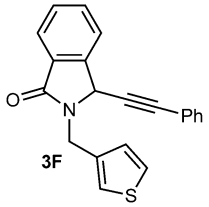
95% yield (45 min)



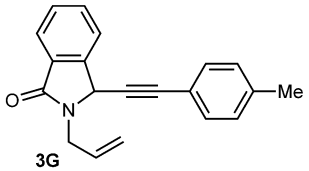
76% yield (3 h)[b]



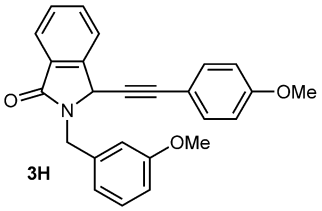
69% yield (2 h)



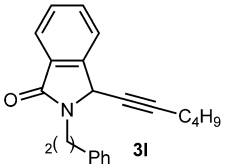
82% yield (15 h)



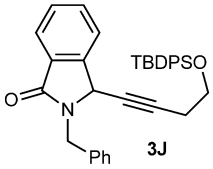
99% yield (5 h)



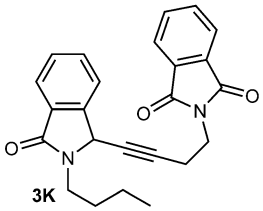
78% yield (4 h)



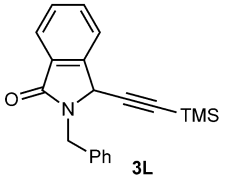
69% yield (5 h)



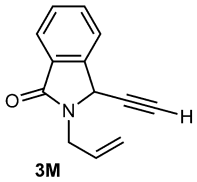
75% yield (5 h)



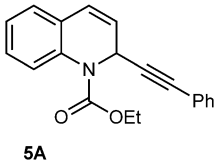
74% yield (20 h)



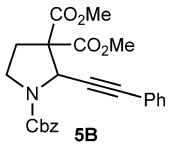
73% yield (3 h)[c]



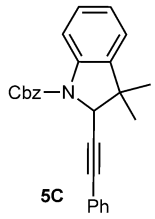
69% yield (2 h15 min)[d]



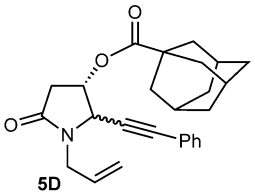
90% yield (24 h)[e]



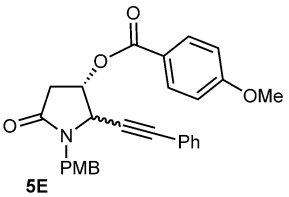
88% yield (16 h)[f]



70% yield (2 h 45 min)



100% yield (3 h 45 min)[b]
trans/cis = 52:48



94% yield (2 h)[b]
trans/cis = 58:42

[a] The reaction was carried out on a 500-mg scale with 1 mol% of $Ph_3PAuOTf$.
[b] 1.5 equiv. of the alkyne.
[c] 5 mol% of the catalyst with 2 equiv. of the alkyne.
[d] 7 mol% of the catalyst with 2 equiv. of the alkyne.
[e] 5 mol% of the catalyst.
[f] 10 mol% of $Ph_3PAuNTf_2$ with 2 equiv. of the alkyne.

and reaction time for a 'model' reaction system (see Table 1), we sought to further delineate and explore the reaction scope. With this in mind Table 2 outlines a representative selection of results that aim to demonstrate the broad applicability and generality of this innovative synergistic gold/silyl catalyzed alkynylation reaction. A series of isoindolic acetoxylactame **1A–I** bearing various structureally and functionally diverse *N*-substituents was evaluated using trimethylsilylphenylacetylene **2A** (all the structures of the starting materials and substrates used throughout this study are given in the Supporting Information).

We were delighted to observe formation of the desired alkynylated adducts **3B–F** (Table 2) in consis-

tently fast reaction times (45 min to 3 h) as well as very good (76%) to excellent (97%) yields.[23] Furthermore this study also verified and substantiated the catalytic alkynylation reaction to be fully amenable and highly effective when scaled-up, a fact that further exemplifies the potential value of our synergistic catalytic synthesis methodology. By way of an example, in an excellent 97% yielding reaction, 550 mg of **3B** were isolated from 500 mg of the parent α-acetoxylactam **1B** using *only 1 mol% of the $Ph_3PAuOTf$ pre-catalyst* in 90 min.

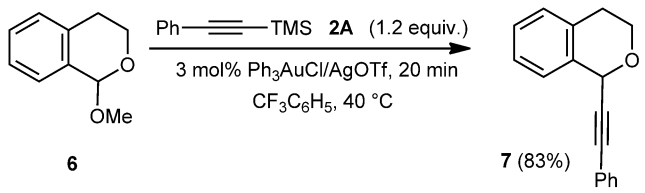
We have established that trimethylsilylalkynes containing diversely substituted aryl groups are viable substrates in the alkynylation reaction. Thus electron-rich *para*-tolylethynyltrimethylsilane **2E** and trimethylsilyl-*p*-methoxyphenylacetylene **2F** afforded **3G** and **3H** in excellent 99% and 78% yields, respectively, they did however require an extended reaction time relative to the electronically neutral phenyl ring of **2A**. It seemed that introducing a donor aryl group within the nucleophilic component had, as expected, reduced the electrophilicity of the silicon center within the gold π-alkyne complex. Thus the anticipated rate reduction associated with the aurodesilylation event manifests itself as an observable reduction in the reaction kinetics affording **3G** and **3H**.[24]

Perhaps most importantly, this methodology can be extended to non-aryltrimethylsilylalkynes, thus incorporating **2G**–**K**[25] afforded the corresponding propargylic amides, **3I**–**M** in good 69%–75% yields. Furthermore, the successful application of trimethylsilylalkynes **2H** and **2J** appended with the acid- (OTBDPS) and base-sensitive (TMS) functional groups, respectively, is particularly noteworthy. Both reactions afforded **3J** and **3l** in good 75% and 73% yields, respectively. More specifically the incorporation of bis(trimethylsilyl)alkyne **2J** within our gold-catalyzed N,O-alkynylation reaction is noteworthy for the fact that the second trimethylsilyl group was retained in the product **3l**. The stability of the alkynyl appended trimethylsilyl group to the reaction conditions employed further demonstrates the exceptional mildness of our synergistic catalysis methodology.[26] Moreover with this trimethylsilyl group in place, the possibility of undertaking a *second* C_{sp}–Si activation further exemplifies the significant potential that our new methodology has in the synthesis arena. Use of trimethylsilylacetylene **2K** afforded exclusively and as anticipated terminal alkyne **3M** in a good yield. This result lends credence to our proposed mechanism (Scheme 4) and, more specifically, also indicates a quite unusual and selective mode of C_{sp}–Si activation for trimethylsilylacetylene.[27,28] This result is further substantiated by the successful inclusion of *N*-propargylated α-acetoxylactam **1D** that afforded adduct **3D**. That **3D** and **3M** are both generated in good yields confirms that our reaction protocol is fully tolerant of terminal alkynes in either of the reaction partners.

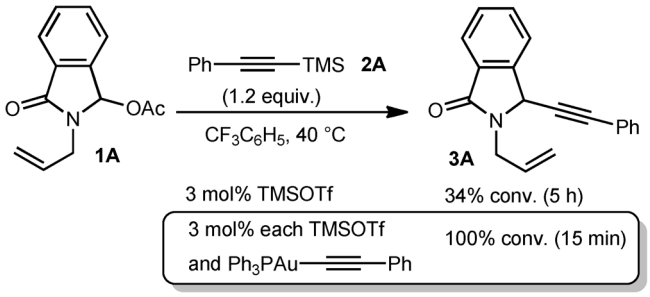
Further analysis of the substrates that underwent reaction and in particular those affording **3F**, **3H**, **3J**, **3K**, and **5A–E** allows us to conclude that the incorporation of Lewis basic sites in either of the two starting materials is tolerated. Thus although the reaction seems relatively insensitive to the presence of these Lewis bases in general the reaction rates were slower, however the overall yields were comparable to those without Lewis basic sites. An additional and important feature of this methodology lies in the fact that the propargylic lactam products bearing various *N*-arylmethyl and *N*-heteroaryl methyl groups (**3B**, **C**, **3E**, **F**, **3H–J** and **3l**) have the potential to undergo an intramolecular hydroarylation,[29] to our delight, however we found no evidence for this and the desired products were all isolated in good to excellent yields.

Further demonstrating the general applicability of our synergistic gold/silyl-catalyzed alkynylation reaction, we sought to investigate the coupling of *non-isoindolic* N,O-acetals, i.e., **4A**–**E**. Commercially available 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) **4A** was alkynylated using trimethylsilylphenylacetylene **2A**, the desired propargylic *N*-carbamate adduct **5A** was afforded in an excellent 90% yield, although the reaction rate was significantly slower in comparison to the isoindolic series. In spite of the adjacent steric bulk associated with the *N*-Cbz group and *gem*-dimethyl subunit that are close to its reactive center, the α-acetoxylactam-derived oxindole **4C** reacted smoothly and efficiently affording, again, the desired product **5C** in a good yield. Exploring the potential of the synergistic catalysis alkynylation methodology in asymmetric synthesis, we were delighted that two α-acetoxylactams derived from (*S*)-malic acid,[4e] afforded the expected adducts **5D** and **5E** in quantitative and excellent 94% yields, respectively. Unfortunately, although these reactions were extremely efficient there was little diastereocontrol, even in the presence of a *para*-methoxybenzyl or bulky adamantyl ester groups, poor *trans-/cis*-diastereocontrol was observed (see Table 2).

Triphenylphosphine gold(I) triflate ($Ph_3PAuOTf$) consistently displayed greater reactivity than $Ph_3PAuNTf_2$ in the alkynylation of highly reactive N,O-acetals such as α-acetoxylactams, this was attributed to the fast formation of a gold(I) acetylide intermediate (see Scheme 4). In contrast, we considered the possibility that this situation could be reversed when a *less* reactive *N*-acyliminium ion precursor was engaged in the reaction and would, in fact, require a stronger silyl Lewis acid activator to be employed.[10b,17] Testing for this assumption we were immediately rewarded with the alkynylation of the challenging N,O-acetal carbamate **4B** that is equipped with two neighbouring and deactivating ester groups.[3e]



Scheme 5. Synthesis of **7** *via* the dual synergistic gold(I)/silyl alkynylation of *O*-methoxy acetal **6**.



Scheme 6. Mechanistic 'model' experiment that supports our dual synergistic gold(I)/silyl catalysis hypothesis.

Exposure of **4B** to our standard alkynylation protocol in the presence of $Ph_3PAuOTf$ resulted in poor conversion, possibly due to the inability of *in situ* generated TMSOTf to efficiently generate, under such mild reaction conditions, the required *N*-acyliminium ion.

However, switching to $Ph_3PAuNTf_2$ as an *in situ* source of $TMSNTf_2$ we were delighted that a *significant rate enhancement* was observed when 10 mol% of the Gagosz pre-catalyst was employed and **5B** was afforded in an excellent 88% yield.

Expanding the Substrate Scope of the Alkynylation Reaction: Evaluating Alternative Pro-Electrophiles

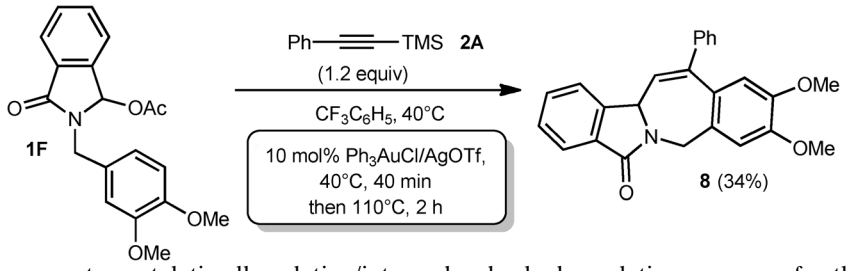
Our gold-initiated synergistic silyl/gold catalysis alkynylation concept could, in principle, be extended to the inclusion of a wide variety of alternative electrophilic substrates related to the reported α-amidoalkylation reaction. As a preliminary research effort towards probing this goal we were delighted to observe that the isochroman *O*-methoxy acetal **6**[2b] was fully compliant and engaged successfully in the catalytic alkynylation methodology. Thus, the desired 1-alkynylisochroman **7** (Scheme 5) was afforded from **6** in a similar reaction time and yield as observed for the previously generated α-amidoalkylation adducts (see Table 1 and Table 2).

Mechanistic Considerations

Confident that our reaction protocol was robust, we opted to initiate a preliminary study aimed at gaining an insight into the reaction mechanism. Attempting the model reaction outlined in Table 1 using trimethylsilylacetylene **2A** with 3 mol% trimethylsilyl triflate as an 'externally added' Lewis acid catalyst resulted, as anticipated, in a slow conversion rate to the alkynylated product **3A** (34% conversion after 5 h reaction time), this suggests that trimethylsilylalkynes are probably insufficiently nucleophilic to efficiently mediate this catalytic alkynylation process (Scheme 6). However, repeating the reaction in the presence of 3 mol% of both trimethylsilyl triflate and the easily prepared σ-gold(I) alkynylide $Ph_3PAuC{\equiv}CPh$,[30] it was our aim to mimic within the reaction medium the *key* catalytic components considered to undertake critical roles *viz*. **C** and **D** and which we assumed were generated in the mechanism outlined in Scheme 4. To our delight, and as anticipated, we restored the high reactivity exhibited in our optimized synergistic reaction procedure (see Table 1, entry 12). Substrate **1A** was transformed in a *clean, efficient and quantitative process into alkynylated product **3A** in only 15 min*. This result strongly corroborates our working mechanistic hypothesis (Scheme 4) that the critical formation of two synergistic gold(I)/silyl species is required for the efficient alkynylation of N,O-acetals.

Synthetic Utility of the Alkynylation Products: Efficient Multicyclic Ring Synthesis

A preliminary study was undertaken to explore the potential of our methodology for the synthesis of multicyclic ring systems *via* a two-step, one-pot alkynylation/hydroarylation sequence of reactions. Gratifyingly using $Ph_3PAuOTf$ (10 mol%) the intended cascade alkynylation/hydroarylation reaction sequence was observed with the desired tetracyclic compound **8** generated in an acceptable, unoptimized 34% yield (Scheme 7). Otherwise, examination of an array of ordinary hydroarylation gold(I) catalysts was investigated for the cyclization of pre-isolated product **3E** in α,α,α-trifluorotoluene, in a view of possibly improving the one-pot alkynylation/hydroarylation sequence by a *two-gold catalysts* approach.[3f] Unfortunately, the cyclization was invariably complicated by several side reactions and the desired compound **8** could not be isolated in yields greater than 55%, which did not encourage us to pursue with the two reactions sequence. Future efforts within our laboratory will be dedicated at improving the efficiency of this sequence by testing additional substrates and gold catalysts or applying recent methodological[31] and technological advances.[32]



Scheme 7. Two-stage, one-step catalytic alkynylation/intramolecular hydroarylation sequence for the synthesis of multicyclic **8**.

Conclusions

In summary, we have developed the first catalytic alkynylation of N,O-acetals. The reaction employs readily synthesised trimethylsilylalkynes as nucleophilic partners and, typically, low pre-catalyst loadings, i.e., 1–5 mol% of LAuOTf. The reaction operates under mild reaction conditions, exhibits high chemical efficiency and diverse applicability. This reaction has been engineered *via* a design mechanism which proceeds *via* an unprecedented synergistic silyl–gold(I) catalysis approach which is initiated from a single readily available gold(I) pre-catalyst. Furthermore, our protocol has the practical advantage of generating *in situ* the air and moisture-sensitive super silyl transfer reagents, i.e., TMSOTf/$TMSNTf_2$, which act as critical components within the catalytic cycle that we have proposed and consolidated by means of control experiments. To the best of our knowledge, this is the first report of a synergistic catalytic system that proceeds *via* the simultaneous *in situ* synthesis of both *key* catalytic components. We have briefly demonstrated the potential flexibility and applicability of this protocol with its extension to pro-electrophilic substrates related to N,O-acetals such as acetals (Scheme 5), and their transformation into new multicyclic and heterocyclic ring systems (Scheme 7). Perhaps more importantly, we have also shown that with the careful selection of the gold counter ion, it is possible to manipulate the strength of the ancillary silyl Lewis acid so that it complements the inherent reactivity, *viz.* the ionizing ability, of a particular pro-electrophilic substrate. We are currently exploring the *in situ* approach for synergistic catalysis in other substrate studies, which we anticipate will open up new directions in gold chemistry and stimulate the discovery of new reactions in the synthesis arena.[33,34]

Experimental Section

Representative Procedure for the Gold(I)-Catalyzed Alkynylation of N,O-Acetals with TMS Alkynes

To a solution of $Ph_3PAuOTf$ (0.01–0.1 equiv.) *in situ* formed by mixing Ph_3PAuCl and AgOTf (1/1 mixture) in α,α,α-trifluorotoluene ([substrate] = 0.48 mol/L) in a round-bottom flask with a Teflon stirring bar, was added a solution of the nucleophile (1.2–2 equiv.) and the acetoxy- or alkoxylactam (1 equiv.) [substrate] = 0.8 mol/L)]. The reaction mixture was then stirred at 40 °C in an oil bath. At the end of the reaction (^1H NMR or TLC monitoring), the reaction mixture was directly purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate) to afford the corresponding alkynylated products.

Further experimental details of the experimental procedures, optimization studies, characterization along with copies of ^1H and ^{13}C NMR spectra of all new isolated compounds are available in the Supporting Information.

Acknowledgements

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[18] The neutral triphenylphosphine group likely contributes to form a weak $[Au]^+$/triflate ion-pair which is easier to dissociate. The tighter ion-pairing resulting from the use of more electrophilic gold salts with no ligand or electron-poor triarylphosphines, probably re-

duces silaphilicity of the triflate anion and then retards the overall reaction rate.
[19] The use of 2,6-di-*tert*-butylpyridine inhibited the reaction in the case of an *in situ* generated $Ph_3PAuOTf$. Furthermore while the reaction catalyzed by IPrAuOTf was significantly retarded it did almost reach completion but only after a 24h reaction time. These results are amazing and remain unclear at this stage, as they fully contradict the mechanism proposal that we have consolidated (see Scheme 7) – more work will be required to clarify this point.
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[22] The superiority of IPrAuOTf over $Ph_3PAuOTf$ as a catalyst was not general for all substrates throughout the reaction scope partly depicted in Table 2.
[23] The reaction times presented in Table 2 are for reactions exceeding 2–3 h, are unoptimized and are more than likely less than indicated.
[24] The alkynylation of silylacetylenes with an electron-deficient aryl group was not studied for the following reason: their direct C–H coupling was evaluated under the optimal reaction conditions, and around 90% conversions were reached with *p*-NO_2- and *p*-CF_3-phenylacetylene. This enhancement of the conversion reflected our assumption that the location of an electron-withdrawing substituent on the nucleophile may increase the acidity of the terminal alkynyl proton and therefore accelerate its deprotonation thus facilitating gold(I) acetylide formation. Unfortunately, the alkynylation products appeared to be particularly sensitive and partial decomposition was observed during chromatography purification on silica gel.
[25] The nature of the R^2 substituents within TMS-alkynes **2E–H** is seen in the accordant propargylic lactams **3G–M** depicted in Table 2.
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[28] a) For selected examples of chemoselective gold-catalyzed C_{sp}–H activation of TMS-acetylene in the presence of an amine component, please see: refs.[10h–j]; b) For a quite rare example of chemoselective C_{sp}–$SiMe_3$ activation of TMS-acetylene, see ref.[1f]
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[30] For the preparation of LAu alkynylide using a lithium base and LAuCl, see: a) H. Werner, H. Otto, T. Ngo-Khac, C. Burschka, *J. Organomet. Chem.* **1984**, *262*, 123; b) O. Schuster, H. Schmidbaur, *Organometallics* **2005**, *24*, 2289.
[31] A. Guérinot, W. Fang, M. Sircoglou, C. Bour, S. Bezzenine-Lafollée, V. Gandon, *Angew. Chem. Int. Ed.* **2013**, *52*, 5848.
[32] For the acceleration of a hydroarylation using microwave irradiation, see: a) X.-Y. Liu, P. Ding, J.-S. Huang, C.-M. Che, *Org. Lett.* **2007**, *9*, 2645; b) S. Pascual, C. Bour, P. de Mendoza, A. M. Echavarren, *Beilstein J. Org. Chem.* **2011**, *7*, 1520.
[33] During the preparation of this manuscript, we became aware of an excellent paper by Gonzáles and co-workers who describe the bis-alkynylation of aryl aldehydes with TMS-alkynes catalyzed by gold triflimidate salts. The mechanistic investigations described by these authors fully support our own synergistic gold/silyl activation mode. B. Rubial, A. Ballesteros, J. M. González, *Adv. Synth. Catal.* **2013**, *355*, 3337–3343.
[34] Our work is fully independent from that of the previous reference, and had been initially submitted elsewhere for publication on July 5th, 2013.