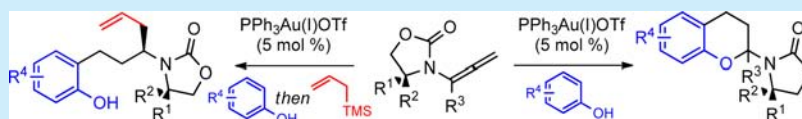


The Au(I) Catalyzed Activation of Allenamides and Their Subsequent Transformation into Chromanes: A Method for the Regiocontrolled Addition to the α - and γ -Positions of the Allene Unit

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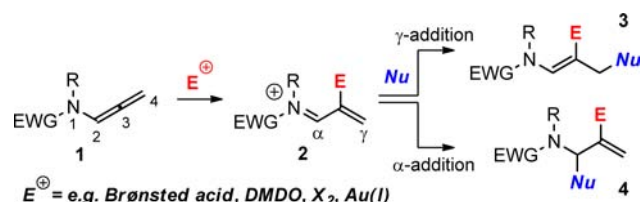
S Supporting Information



ABSTRACT: Au(I) activation of allenamides in the presence of phenols leads to the formation of chromanes in moderate to good yields. This catalytic process is dependent on the counterion which facilitates the activation of the *in situ* formed imine. Furthermore, this iminium can be intercepted by trimethylsilyl silane, via the Hosomi–Sakurai reaction, giving a formal procedure for the regioselective intermolecular addition of two carbon nucleophiles to an allenamide at the α - and γ -positions.

Allenamides (**1**) are a unique class of allenes that can undergo selective electrophilic activation leading to the subsequent addition of nucleophiles at either the α - or γ -positions of the allene unit (Scheme 1).¹ The electrophilic

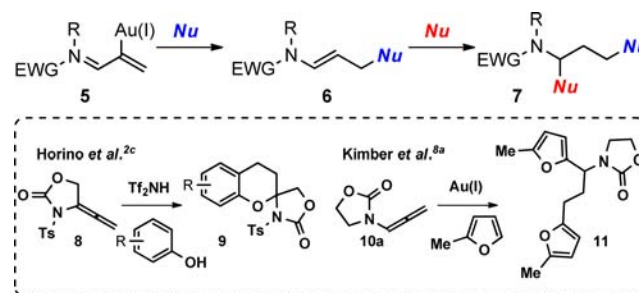
Scheme 1. Allenamide Reactivity with Electrophiles



activation of the allenamide can be achieved using a number of synthetic methods, including Brønsted acids,² halogenation via treatment with I₂ and NIS,³ oxidation (e.g., DMDO),⁴ or the use of metal catalysts,^{1a} with cationic Au(I) salts proving to be one of the most facile yet mild methods for their activation.^{1a} The reactivity that allenamides display in the presence of cationic Au(I) has led to this reaction manifold being successfully exploited in a number of powerful transformations. These include gold catalyzed [2 + 2]- and [4 + 2]-cyclizations,^{2h,5,6} intra- and intermolecular hydroaminations,⁷ hydroarylation⁸ and hydroalkoxylation transformations,^{3d,9} Nazarov type cyclizations,¹⁰ and cyclopropanations,¹¹ with all of these reactions presumably proceeding via an Au(I)-intermediate, such as **2**, which is in turn generated by the electrophilic activation of the allenamide at the 3-position by the Au(I) cation.

Within the context of intermolecular hydroarylation and hydroamination reactions we have shown that the Au(I)-catalyzed addition of the nucleophile to monosubstituted allenamides exclusively occurs at the γ -position (**6**) (Scheme 2).^{7b,8b} While this process gives *E*-enamides in high yields, and

Scheme 2. Au(I) Activation of Allenamides



under mild reaction conditions, it also opens up the prospect of adding further nucleophiles, chemoselectively, to the enamide unit (**7**).

To date the only reported addition to both the γ - and α -positions of an activated allenamide substrate is that of Horino and co-workers, who successfully demonstrated that allene sulfonamides of the type **8**¹² which are structurally related to allenamides but contain an additional electron-withdrawing group directly attached to the nitrogen, successfully undergo a formal [3 + 3]-cycloaddition with phenols to deliver chromanes (**9**).^{2c} The current authors also reported a related Au(I) catalyzed bis-hydroarylation of **10a**; however, this bis-hydroarylation (**11**) occurred with no measurable chemoselectivity and in modest overall yield.^{8b} As a consequence within this study we would like to report our findings on the Au(I)-catalyzed formal [3 + 3]-cycloaddition of phenols to allenamides containing only one electron-withdrawing group attached to the nitrogen, the role of the Au(I)-counterion in the process, and the first regiocontrolled intermolecular addition of two carbon nucleophiles to an allenamide at both the α - and γ -

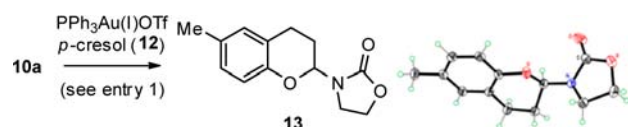
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positions. The synthetic advantages of using allenamides are (i) their ease of synthesis, (ii) their utility in diastereoselective reactions, and (iii) their flexibility in substitution and configuration;^{1a,b} however, this is tempered by their reported decomposition in the presence of Brønsted acids.^{8b}

We therefore began our study by investigating the addition of *p*-cresol to **10a** using the mild activation conditions we have previously reported (5 mol % $\text{PPh}_3\text{Au}(\text{I})\text{OTf}$).^{7b,8b,c} Consequently, stirring **10a** (1 equiv) with *p*-cresol (**12**, 2 equiv) at room temperature in CH_2Cl_2 gave the chromane **13** in a very respectable conversion of 91% and an isolated yield of 88% (Scheme 3). The identity of **13** was ascertained by a

Scheme 3. Chromane Formation



combination of ^1H , ^{13}C NMR and infrared spectroscopy; specifically the ^1H NMR showed a diagnostic doublet doublets at 5.68 ppm ($J = 3.2$ and 10.0 Hz) indicative of the C–H of the aminal. Additionally, **13** proved to be crystalline, and single crystal X-ray analysis was performed confirming its structure.¹³

We then optimized this process and in particular probed the nature of the Au(I)-counterion (Table 1). We were able to

Table 1. Optimization Conditions for the Formation of **13**^a

entry	catalyst	equiv	conversion ^b [%] ^c
1	$\text{PPh}_3\text{Au}(\text{I})\text{OTf}$	2.0	91 [88%] ^c
2	$\text{PPh}_3\text{Au}(\text{I})\text{OTf}$	1.5	89
3	$\text{PPh}_3\text{Au}(\text{I})\text{OTf}$	1.1	88 [86%] ^c
4	$\text{PPh}_3\text{Au}(\text{I})\text{BF}_4$	1.1	25
5	$\text{PPh}_3\text{Au}(\text{I})\text{PF}_6$	1.1	26
6	$\text{PPh}_3\text{Au}(\text{I})\text{NTf}_2$	1.1	82
7	$\text{PPh}_3\text{Au}(\text{I})\text{Cl}$	1.1	— ^d
8	$\text{Ag}(\text{I})\text{OTf}$	1.1	16
9	—	1.1	—
10	Tf_2NH	1.1	25 ^e

^aReactions run with 5.0 mol % of catalyst¹⁴ in CH_2Cl_2 at room temperature for 16h unless otherwise stated. ^bConversion was determined by ^1H NMR using trimethoxybenzene as an internal standard. ^cisolated yield in brackets. ^dNo consumption of starting material was seen after 16 h. ^eSignificant degradation of the allenamide **10a** was evident.

reduce the amount of *p*-cresol to 1.1 equiv with limited impact on the conversion or isolated yield (entries 2 and 3). The importance of the counterion in the formation of the chromane product was ascertained with the reaction being undertaken with $\text{PPh}_3\text{Au}(\text{I})$ and the counterions BF_4^- and PF_6^- , respectively, which both gave a moderate conversions to **13** of 25% and 26% (entries 4 and 5), and also with NTf_2^- which gave a conversion to **13** on parity with the OTf^- counterion example in entry 3 (entry 6). When the cyclization was undertaken with PPh_3AuCl , no conversion was recorded (entry 7); however, when AgOTf was used, this led to a 16% conversion to **13**, presumably by the generation of TfOH on exposure to phenol (entry 8). Next we undertook the cyclization in the absence of any catalysts which gave none of the desired product (entry 9), and the cyclization was also undertaken under the conditions of Horino and co-workers

(catalytic Tf_2NH)^{2c} which did deliver **13**, but in a modest conversion of 25% (entry 10). It must be noted that significant amounts of degradation products were observed for entry 10.

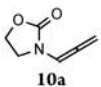
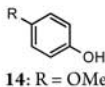
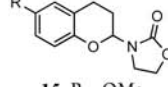
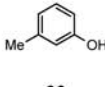
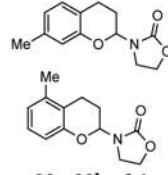
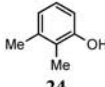
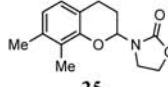
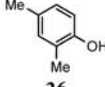
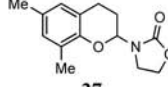
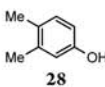
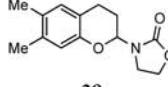
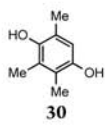
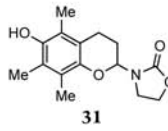
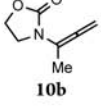
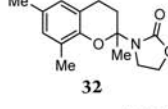
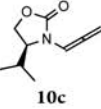
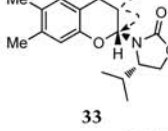
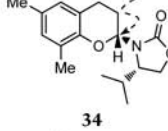
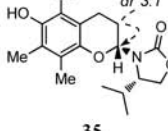
The results of this screen clearly show that the conditions in entry 3 are ideal for the formation of the chromane **13** from **10a**, and as a consequence the scope of this transformation was next investigated (Table 2). Various phenols reacted smoothly with the allenamide **10a** under the $\text{PPh}_3\text{Au}(\text{I})\text{OTf}$ conditions, with the exception of 4-nitrophenol (entry 4). When the reaction was undertaken with 4-bromophenol (**18**) at room temperature the desired chromane **19** was isolated in a modest yield of 28%, which paralleled the result obtained by Horino.^{2c} However, if the reaction was heated to 60°C in dichloroethane this could be increased to an acceptable 62% (entry 3). When *m*-cresol (**22**) was used, an inseparable 2:1 mixture of **23a** and **23b** was obtained in 78% yield, with the predominant product **23a** presumably being preferentially formed on steric grounds (entry 5). Pleasingly, 2,3,5-trimethylbenzene-1,4-diol (**30**) added cleanly to the activated allenamide under our Au(I) catalyzed conditions, providing chromane **31** in a good yield of 86% (entry 9), and as a consequence this gives a nice entry into the heterocyclic core of the tocopherols and tocotrienols.¹⁵ The 1,1-disubstituted allenamide **10b**, synthesized from **10a**,¹⁶ also participated in this transformation with **26**, providing chromane **32**, in a good yield of 73% (entry 10). To end this screen, we investigated the use of chiral allenamide **10c** to see if the stereogenic center within the oxazolidinone would have any diastereomeric control in the formation of the chromanes. Treatment of **10c** with **28** gave the chromane **33** in a good yield of 72% with a dr of 96:4, with the predominant diastereoisomer being confirmed by NOE (entry 11). Similarly, treatment of **10c** with **26** also gave a predominant diastereoisomer **34** in a good yield of 68% with a dr of 94:6 (entry 12). Surprisingly, treatment of **10c** with 2,3,5-trimethylbenzene-1,4-diol (**30**) did yield the desired chromane **35** in a good isolated yield of 74%, but with a modest dr of 3:1 (entry 13).

The mechanism of this formal [3 + 3]-addition of phenols to allenamides under Au(I) catalyzed conditions deserves discussion with respect to the counterion (Scheme 4).

The initial activation of the allenamide **1** under cationic Au(I) conditions presumably gives **5**. This then undergoes arylation with **16**, giving the Au(I) intermediate **36** and concomitant formation of TfOH , which further promotes the proto-deauration to give the arylated enamide intermediate **37**. The cyclization of **37** to **39** is supported by an iminium peak at 9 ppm in the crude products which may correspond to **38**. The observation within the NMR of the crude products of an iminium peak presents an opportunity to intercept this iminium with a suitable external nucleophile. Accordingly, using the Hosomi–Sakurai reaction¹⁷ of acetals as a foundation we elected to introduce an equivalent allyltrimethylsilane to the reaction upon conversion to the chromane (Scheme 5).

Initially, the reaction was left to stir at room temperature which gave **41** in a modest yield of 32%; however, this could be increased to a yield of 70% if the reaction mixture was heated to reflux overnight.¹⁸ This procedure was then used to give the allylated products **42** and **43**, both in satisfactory yields of 86%. Additionally, when the chiral allenamide **10c** was used in this transformation the allylated product **44** was obtained in a yield of 83%, and importantly with a dr of 4:1, implying that the presence of a stereogenic center at the C2 of the oxazolidinone

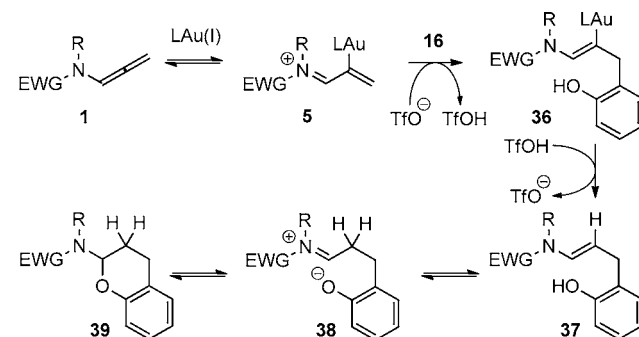
Table 2. Reaction Scope for the Au(I) Catalyzed Chromane Formation from Allenamides^a

entry	allenamide	nucleophile	product	yield [%] ^b
1		 14: R = OMe	 15: R = OMe	70
2	10a	16: R = H	17: R = H	63
3 ^c	10a	18: R = Br	19: R = Br	62
4	10a	20: R = NO ₂	-	-
5	10a		 23a: 23b = 2:1	78
6	10a			72
7	10a			89
8	10a			72
9	10a			86
10		26		73
11 ^d		28	 dr 96:4	72
12 ^d	10c	26	 dr 94:6	68
13 ^d	10c	30	 dr 3:1	74

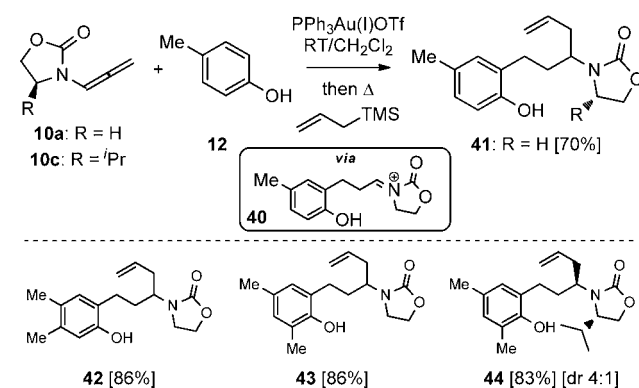
^aReactions run with 5.0 mol % of catalyst in CH₂Cl₂ at room temperature at 1 M unless otherwise stated. ^bIsolated yield. ^cReaction run at 60 °C in dichloroethane. ^dDr determined by ¹H NMR using the CH₃ signal of the isopropyl group.

ring results in diastereoselectivity in the allyl addition to the iminium.

Scheme 4. Proposed Mechanism



Scheme 5. Chemoselective Addition to Allenamides



In summary, we have shown that Au(I) catalysis is suitable for the formal [3 + 3]-addition of phenols to allenamides containing one electron-withdrawing group. While the Au(I) catalyzed hydroarylation proceeds as previously reported, the OTf⁻ counterion is key to the activation of the enamide, and the subsequent cyclization to the chromane. Additionally, we have demonstrated that the *in situ* formed chromane can be allylated via the iminium, therefore giving a formal procedure for the regioselective intermolecular addition of two carbon nucleophiles to an allenamide to the α- and γ-positions. The use of this Au(I) catalyzed approach for further functionalization of allenamides and in intermolecular processes will be reported on in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra and characterization for all new materials. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (13) Crystal data for **13**: C₁₃H₁₅NO₃, *M* = 233.26, triclinic, *P* $\bar{1}$, *a* = 10.7856(14) Å, *b* = 11.0756(15) Å, *c* = 12.1131(16) Å, α = 69.1857(19)°, β = 65.3217(18)°, γ = 63.0462(19)°, *V* = 1147.1(3) Å³, *Z* = 4, μ (Mo *K* α) = 0.096 mm⁻¹, 17 838 reflections measured, 7213 unique, *R*_{int} = 0.0216, *R*₁[*F*² > 2 σ (*F*²)] = 0.0409, *wR*₂ (all data) = 0.1175. Two similar molecules in the asymmetric unit. CCDC 1015343 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- (14) The catalysts PPh₃AuOTf, PPh₃AuBF₄, and PPh₃AuPF₆ were preformed from PPh₃AuCl and AgOTf, AgBF₄, and AgPF₆, respectively. Additionally, PPh₃AuNTf₂ was purchased from a commercial supplier.
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- (18) To support the formation of the iminium **40** during the Au(I) catalyzed arylation, the purified chromane **13** was treated with allyltrimethylsilane in the absence of Lewis acid, which failed to give **41**. Allylation was achieved with excess TiCl₄ giving **41** in an acceptable isolated yield of 68%.