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Gold(I)-catalysed [3+3] cycloaddition of propargyl acetals and nitrones

Sigvart Evjen, Anne Fiksdahl *

Department of Chemistry, Norwegian University of Science and Technology, Høgskoleringen 5, NO-7491 Trondheim, Norway

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ABSTRACT

In our series of investigations to expand the understanding of the gold(I) catalysis chemistry of propargyl acetals, a gold(I) catalysed [3+3] cycloaddition reaction of propargyl acetals with nitrones has been studied. A series of 5-methoxy-3,6-dihydro-2*H*-1,2-oxazine products with two stereogenic centres were obtained in a *cis*-stereoselective manner. The formal [3+3] cycloaddition reaction is supposed to go through O-nucleophilic attack of the nitrone on the *C*1 position of the gold complex generated from propargyl acetal followed by a final ring closure. An alternative C3 oxidation by nitrone affords aldehyde products and represents a competing pathway. The chemoselectivity of the cycloaddition reaction is discussed in order to demonstrate the potential and limitations of the reaction.

1. Introduction

Gold-catalysed reactions of propargyl esters are widely reported in the literature.[1a] The gold catalysed activation process of propargyl esters has shown to be a versatile strategy towards the generation of vinyl/enol gold carbene complexes.[1b–q] The propargyl ester–gold approach represents an important supplement to the conventional vinyl-metal carbenoids, generated in situ by metal-catalysed diazo decomposition, for the preparation of effective vinyl-carbene 1,3-dipolar reactants. The propargyl ester method has been applied in gold catalysed cyclopropanation reactions[2,9] (Scheme 1a) as well as in [2+2],[3a,b] [3+2],[4a–d] [4+2],[5] [4+3][6a–d] and [3+3][7] cycloaddition reactions.

However, studies on gold(I)-catalysed reactions of the corresponding propargyl acetals are scarce, with the exception of recent work published by groups of Toste and Zhang.[8] The Fiksdahl group has carried out a number of studies on chemoselective gold(I) catalysed cycloaddition reactions of propargyl acetals (**1**, Scheme 1b–e).[9–13] These substrates undergo gold-catalysed triple-bond activation and alkoxy migrations-fragmentation processes to afford the particularly reactive enol ether carbenoid/allylic gold(I) intermediates (**2′**/**2″**). It has been demonstrated that gold(I) activated propargyl substrates exist in rapid equilibrium with these gold species, allowing different novel cyclization pathways to take place and irreversibly lead to different stable products. The activating effect provided by the C2-vinylalkoxy group in the MeO-vinyl-gold carbenoid (**2′**/**2″**) facilitates subsequent reactions and explains the high reactivity and ability of propargyl acetals to undergo cycloadditions. By trapping the intermediates with different C–C, C–N multiple bond reactants, a great variety of complex cyclic products were readily prepared by novel [2+3], [2+5] and combined tandem cycloaddition reactions (Scheme 1b–e).[9–13]

To expand the knowledge of the highly reactive propargyl acetals, we wanted to investigate the potential of less common substrates, such as the nitrone 1,3-dipoles, to undergo chemoselective gold catalysed cycloaddition reactions.

1,3-Dipolar compounds are versatile and powerful synthetic tools to form five-membered rings by [2+3] cycloadditions with dipolarophiles. However, reports on corresponding [3+3] cycloaddition for the preparation of six-membered heterocyclic compounds have been limited. Nevertheless, during the recent few years, in particular, transition metal catalysed [3+3] cycloadditions have been developed. Such processes may typically involve active vinyl-metallocarbene intermediates or donor-acceptor cyclopropenes, generated by Rh-catalysis from vinyldiazoacetates. Thus, [3+3] cycloadditions of nitrones with TBSO-vinyl-rhodium-carbenes, generated from enoldiazoacetates, have been reported.[14a–e] These cycloadditions are facilitated by the stabilizing effect provided by the TBSO vinylic group.

A number of additional 1,3-dipolar compounds have been applied and azomethine imines,[14a,15a–d] azomethine ylides,[16a–e] and azides[17] have also been utilised as [3+3] cycloaddition reactants for

* Corresponding author. E-mail address: anne.fiksdahl@chem.ntnu.no (A. Fiksdahl).

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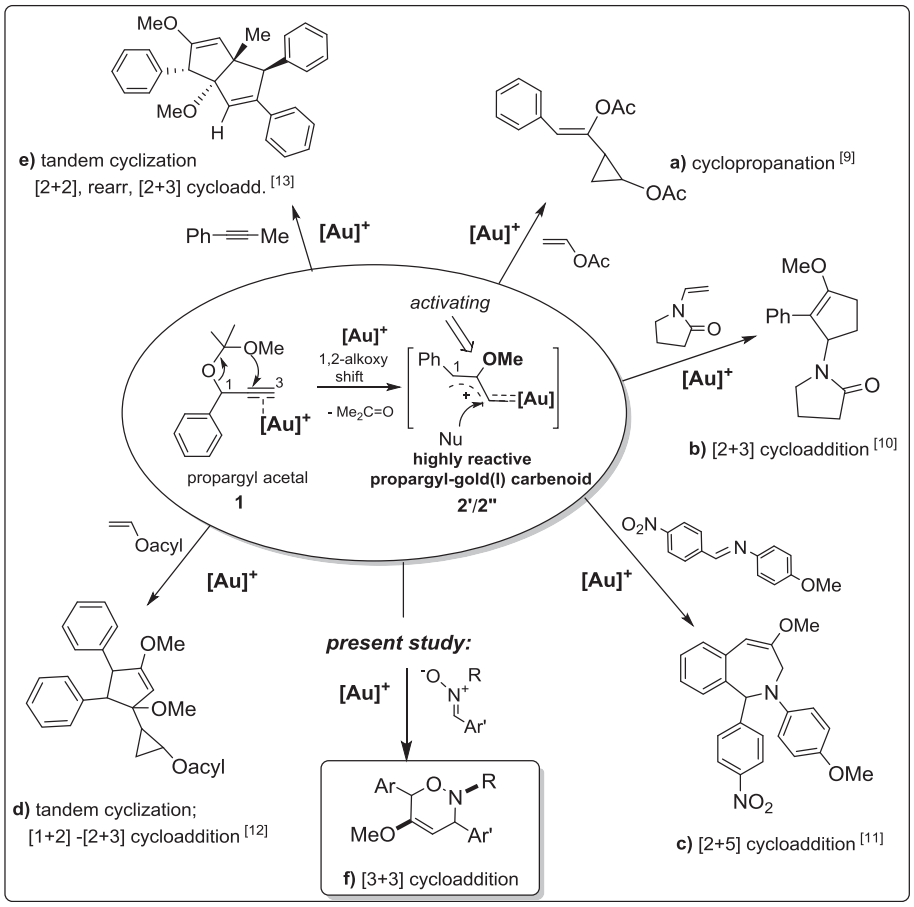


Scheme 1. Cycloaddition reactions of propargyl substrates.[9–13]

the construction of a range of six-membered heterocyclic structures. New strategies for Cu catalysed [3+3] cycloadditions of azomethine imines and azomethine ylides have recently been developed,[15c,d,16c] while other reactions are likewise promoted by $TiCl_4$,[17] Yb[18] or DABCO[15c] catalysis.

In general, many different cycloaddition reactions are initiated by gold activation of alkynes.[19] In a very few cases, [3+3] cycloadditions are involved. Furo-[1,2]oxazines have been prepared from alkynyl-alkenones and nitrones by gold-catalysed step-wise double cyclization, including [3+3] 1,3-dipolar cycloaddition.[20a] The reactions were also successfully carried out in diastereo- and enantioselective manners.[20b] The formation of diazabicycles (pyrazolo[1,2-*a*]pyridazines) from propargyl esters and azomethine imines demonstrated a gold(III) catalysed [3+3] cycloaddition reaction including an vinyl-gold-carbenoid.[7] Recently, a gold(I) catalysed [3+3] cycloaddition reaction of one 4-carboxylate propargyl acetal and *N*-phenyl-*N*-benzylidene-nitrones have briefly been reported to afford a 3,6-dihydro-2*H*-1,2-oxazine.[8c] 1,2-Oxazines derivatives are reported as good mglur1 antagonists[21] and show antibacterial activity. Dihydro-1,2-oxazines are often prepared utilizing [4+2] cycloaddition strategies. Both the combination of nitroso heterodienophiles with diene[22,23] and nitrosoalkene heterodiene with alkene are successful hetero-Diels–Alder approaches[24] as well as some organocatalytic transformations.[25] Reductive ring opening of 1,2-oxazines have been used in the synthesis of amino sugar mimetics.[26]

We herein report a study of gold(I) catalysed cycloaddition of different terminal propargyl acetals and a number of nitrones to give rise to polysubstituted and highly functionalised 3,6-dihydro-2*H*-1,2-oxazine products through a formal uncommon [3+3] cycloaddition process (Scheme 1f).

2. Results and discussion

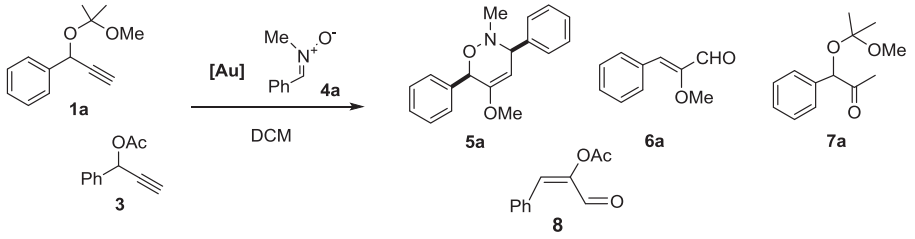
2.1. Studies on reaction conditions

Introductory studies on the gold(I) catalysed [3+3] cycloaddition reactions between propargyl acetal **1a** and nitrone **4a** in dichloromethane gave full conversion in 30 min at room temperature in the presence of 5 mol % of gold(I) catalyst **I**, [Au{P(*t*-Bu)$_2$(*o*-biphenyl)CH$_3$CN}]-SbF$_6$ (Table 1, entry 1), with the [3+3] cycloaddition product, 3,6-dihydro-2*H*-1,2-oxazine **5a**, being formed. However, under the initial condition, 3 equiv of nitrone **4a** were used and only minor amounts (8%) of product **5a** was isolated. Two other products, aldehyde **6a** and ketone **7a**, were also identified, the ratio of products **5a**:**6a**:**7a** was 10:10:80, as shown by ^{1}H NMR analysis of the un-purified reaction mixture.

The formation of aldehyde **6a** is supposed to take place by nitrone oxidation of the propargyl terminal carbon (Scheme 2 below), while the major ketone product **7a** is formally formed by direct hydration of the propargyl acetal **1a** alkyne moiety.

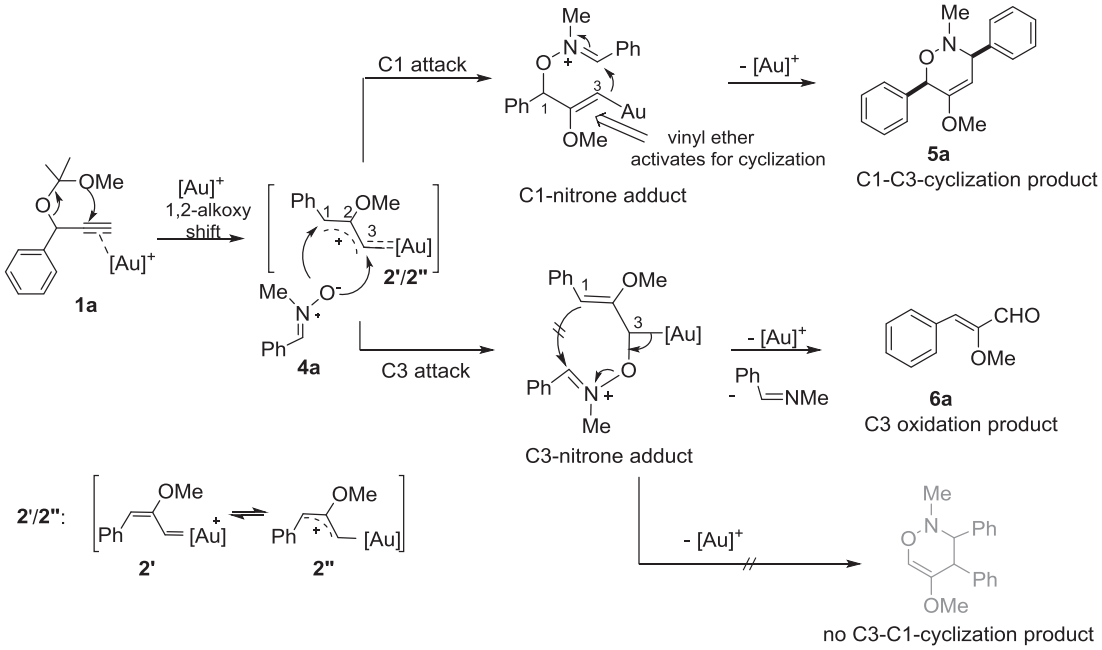
Performing the reaction under drying conditions, in the presence of molecular sieves (entry 1, footnote c), did not change the outcome of the reaction. Aqueous reaction conditions (10% H_2O in DCM, entry 2) significantly reduced the reactivity (8%

Table 1
Optimization studies of gold(I)-catalysed [3+3] cycloaddition reactions[a]



Entry	Gold-catalyst	Reactants	Time (h)	Conversion (%)	Products; distribution in crude mixture [%][b]		
					5a	**6a**	**7a**
1	**I**	**1a**+**4a** (3 equiv)[c]	0.5	99	10 (8[d])	10 (10[d])	80(40[d])
2	**I**	**1a**+**4a** (3 equiv)[e]	24	8	14	13	73
3	**I**	**1a**[f]	24	0	—	—	—
4	**I**	**1a**+**4a**[c]	0.5	99	46 (32[d])	42 (35[d])	12 (8[d])
5	**I**	**1a**+**4a**[g]	0.25	99	45	44	11
6	**I**	**1a**+**4a**[e]	24	6	50	41	9
7	**I**	**1a**+**4a**[h]	24	28	11	13	4
8	—[i]	**1a**+**4a**	24	0	—	—	—
9	$Ph_3PAu(I)Cl$	**1a**+**4a**	24	24	15	9	—
10	$Ph_3PAu(III)Cl_3$		24	<5	—	<5	—
11	$PicAu(III)Cl_2$		24	37	15	22	—
12	**I**	**3**+**4a**	24	<5	—	<5; prod. **8**	—
13	$Ph_3PAu(I)Cl$		24	<5	—	<5; prod. **8**	—
14	$Ph_3PAu(III)Cl_3$		24	7	—	7; prod. **8**	—
15	$PicAu(III)Cl_2$		24	25	—	25; prod. **8**	—

[a] The general reactions were performed with **2a**/**3a** (1 equiv) and **4a** (1 equiv) in DCM (approx. *c*=150 mM) together with 5 mol % catalyst (**I**: [Au{P(*t*-Bu)$_2$(*o*-biphenyl)CH_3CN}]SbF_6). The reactions were stirred at room temp before being quenched with NEt_3.
[b] Based on ^1H NMR.
[c] Identical results were also obtained when mol. sieve was added to the reaction mixture.
[d] Isolated yields.
[e] 10% H_2O/DCM was used as solvent.
[f] No nitrone **4a** was added.
[g] The reaction was carried out in DCE at 50 °C.
[h] The reaction was carried out in acetonitrile.
[i] No catalyst was added.



Scheme 2. Reaction mechanism for gold(I) catalysed [3+3] cycloaddition[8c] of propargyl acetals **1a** and nitrone **4a** and competing reaction pathways.

conversion in 24 h), but the relative amount of the products (**5a**, **6a**, and **7a**) was practically not affected, indicating that the formation of all three products, including the dominating hydration of acetal **1a** was nitrone-generated. Hence, no reaction took place in the absence of nitrone **4a** (entry 3). Applying only 1 equiv of nitrone **4a**, readily gave full conversion and successfully reduced the amount of ketone **7a** (12%, entry 4). The oxazine **5a** and aldehyde **6a** products were obtained in >40%, also at higher

temperature (DCE, 50 °C, 15 min, entry 5), while only partly conversion (28%) of reactants was observed in acetonitrile, even after 24 h (entry 7). Aqueous reaction conditions (10% H_2O in DCM) likewise reduced the reactivity (6% conversion in 24 h, entry 6, see also entry 2), and no reaction took place in the absence of the gold catalyst (entry 8).

A further solvent screening was not performed, as our previous studies showed DCM as the best solvent in related reactions.[10–12] The gold (I) catalyst **I** was applied according to optimum conditions formerly developed for gold catalysed propargyl acetal cycloadditions.[10–12] Other catalytic systems were briefly tested to observe possible new effects of other catalysts, however, both the triphenylphosphane-based gold(I) and gold(III) catalysts, as well as PicAu(III)Cl_2 slowed down the reaction (5–37% conversion in 24 h, entries 9–11). None of the reaction conditions or gold catalysts enabled [3+3] cycloaddition of the alternative propargyl acetate **3** with nitrone **4a**, and only low conversion into aldehyde **8** was observed (5–25% in 24 h, entries 12–15). The significantly lower reactivity of propargyl esters is in accordance with our previous observations.[9–13]

2.2. Reaction mechanism

The gold activated propargyl acetal **1a** may undergo a 1,2-alkoxy shift to generate the key gold(I) species alkoxyvinyl gold carbenoid species **2′** and the stabilized allyl cation **2″** (Schemes 1 and 2). All our previous gold(I) catalysed regioselective cycloadditions[9–13] of propargyl acetals, and also corresponding gold(III) catalysed [3+3] cycloaddition of propargyl esters with azomethine imines,[7] take place with initial nucleophilic attack at the *C*3-position (Scheme 2). In contrast, according to a proposed mechanism[8c] for the reaction of propargyl acetal **1a** and nitrone **4a**, the gold catalyst activates the vinyl carbene for nucleophilic attack of the nitrone at the *C*1-position to form a C1-nitrone adduct. The final ring closure in the [3+3] cycloaddition is facilitated by activation provided by the methoxy group. A final de-auration allows regeneration of the catalyst and affords the 1,2-oxazine product **5a**.

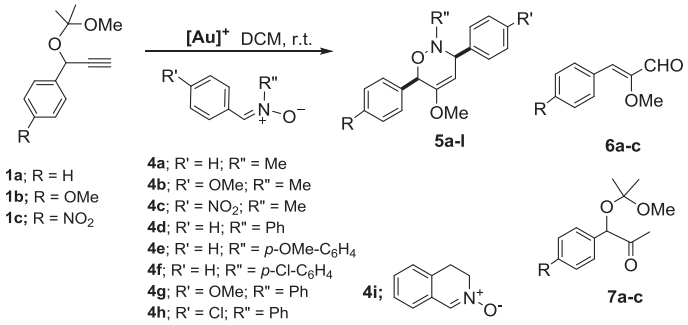
The formation of the aldehyde product **6a** represents a competing reaction pathway via an alternative nitrone attack at the *C*3 position. The resulting C3-nitrone adduct forms the aldehyde **6a** by oxidation through N–O bond cleavage and ring closure does not take place. The benzaldimine leaving group may hydrolyse into benzaldehyde during work-up. A similar C3 oxidation reaction has been developed[27] for the Au(I) catalysed nitrone oxidation of non-terminal propargylic esters with the 8-methylquinoline *N*-oxide, giving rise to α-carboxy-α,β-unsaturated ketones. This C3 propargylic esteroxidation regioselectivity is ascribed to inductive polarization by the electron-withdrawing ester moiety.

2.3. Reactivity

The novel [3+3] cycloaddition reaction was further studied by modifying the substrates. The results from the reactions after full conversion of propargyl acetals **1a–c** and nitrones **4a–i** in the presence of Au[P(*t*-Bu)$_2$(*o*-biphenyl)CH_3CN]SbF_6 in DCM are presented in Table 2. Modifying the electronic properties of the propargyl acetals and nitrone reactants proved to affect the reactivity and the outcome of the reactions.

The reactivity of the *N*-Me-nitrones **4b**,**c** (entries 2–3) and the propargyl acetals **1b**,**c** (entries 4–5) increased/decreased with the respective electron releasing and electron withdrawing group (ERG/EWG) character of the *para*-substituent (OMe/NO_2) on the phenyl moiety. The electron-deficient nitrone **4c** (*p*-NO_2, entry 3) slowed down the reaction (24 h), but the same product distribution was obtained as above (entry 1). However, the activated electron-rich nitrone **4b** (*p*-OMe) mainly afforded the C3 oxidation aldehyde **6a** product (47%, entry 2). An activating ERG *para*-substituent (OMe) on the propargyl acetal **1b** afforded a product mixture (**5d**, **6b**, **7b;** 1:1:1; entry 4), while an EWG *para*-substituent (NO_2) did not allow full conversion on the propargyl acetal **1c** at all (24 h, entry 5).

Table 2
Gold(I)-catalysed [3+3] cycloaddition of propargyl acetals **1a–c** and nitrones **4a–i**[a]



Entry	Substrates	Reaction time (full conv.)	Prod. (% isolated yield)		
			5	**6**	**7**
1	**1a**+**4a**	2 h	**5a** (32)	(35)	(8)
2	**1a**+**4b**	30 min	**5b** (<1)	**6a** (47)	**7a** (15)
3	**1a**+**4c**	24 h	**5c** (36)	**6a** (36)	**7a** (6)
4	**1b**+**4a**	30 min	**5d** (20)[b]	**6b** (21)	**7b** (20)[b]
5	**1c**+**4a**	24 h (25% conv.)	**5e**(<1)	**6c** (<1)	**7c** (19)[c]
6	**1a**+**4d**	30 min	**5f** (11)[c]	**6a** (41)	—[e]
7	**1a**+**4e**	10 min	**5g** (<1)	**6a** (49)	—[e]
8	**1a**+**4f**	25 min	**5h** (54/63[d])	**6a** (17)	—[e]
9	**1a**+**4g**	15 min	**5i** (6)	**6a** (54)	—[e]
10	**1a**+**4h**	30 min	**5j** (23)	**6a** (29)	—[e]
11	**1a**+**4i**	2 h	—	**6a**(<1)[f]	

[a] The general reactions were performed with **1** (1 equiv) and **4** (1 equiv) in DCM (approx. *c*=250 mM) together with 5 mol % catalyst **I** ([Au{P(*t*-Bu)$_2$(*o*-biphenyl)CH_3CN}]SbF_6). The reactions were stirred at rt before being quenched with NEt_3.
[b] Approximate yields based on ^{1}H NMR analysis of product mixture.
[c] Unstable product.
[d] Total yield of **5g** formed in the reaction, as shown by ^{1}H NMR of the crude product mixture.
[e] Minor amounts observed by ^{1}H NMR were not isolated.
[f] Only trace amount was identified, due to challenging chromatographic separation of complex product mixture.

The reactivity of the *N*-aryl-nitrones **4d–h** (entries 6–10) was also influenced by the electronic character of the *N*-aryl groups, as the *p*-chlorophenylnitrones **4f** and **4h** readily produces the oxazine products **5h** and **5i** (entries 8, 10). The *N*-*p*-chlorophenylnitrone **4f** was most effective and selective, affording more than 60% total yield in 25 min and 54% after complex chromatographic purification of target oxazine product **5h** (entry 8). The ERG aryl-*N*-phenylnitrones **4d**, **4e** and **4g** were highly reactive, but afforded mainly aldehyde **6a** (40–50%, entries 6, 7, 9). The cyclic nitrone **4i** and acetal **1a** gave a full conversion, but the target oxazine product could not be observed in the obtained complex product mixture (entry 11).

Previously, one deactivated non-terminal 3-carboxylate-propargyl acetal was briefly reported to undergo chemoselective [3+3] cycloaddition to give related 1,2-oxazine products.[8c] However, a prerequisite for the reaction, in the presence of $Ph_3PAuOTf$ and additional molecular sieve, was that both nitrone substituents had to be aromatic, as the 12 h reaction only was successful for aryl-*N*-phenylnitrones **4d** and **4g**. No reaction took place with *N*-Me-nitrone **4b**. In contrast, our present results show that terminal propargyl acetals **1** undergo [3+3] cycloaddition with both *N*-Me-nitrones and diaryl nitrones in the presence of the active gold catalyst ([Au{P(*t*-Bu)$_2$(*o*-biphenyl)CH_3CN}]SbF_6).

In all successful reactions, complete *cis*-diastereoselectivity was obtained. The configuration of *cis*-1,2-oxazine **5a** was determined based on NOESY NMR experiment, indication proximity of methine protons H3 and H6. The result is in accordance with previously proposed stereochemistry.[8c] No other diastereomers were observed.

3. Conclusions

We have studied a gold(I) catalysed [3+3] cycloaddition reaction for the stereoselective formation of *cis*-1,2-oxazine derivatives. 3,6-Dihydro-2*H*-1,2-oxazine products **5** were readily prepared in moderate yields (23–54% isolated) from highly reactive phenylpropargyl acetals **1** and nitrones **4** in the presence of a gold(I) catalyst. The reaction is supposed to follow an uncommon [3+3] cycloaddition pathway via a controlled nitrone O-attack at the gold carbene *C*1 position.

The outcome of the reaction is strongly dependant of the catalyst activity and the electronic nature of the reactants, as the [3+3] cycloaddition method is quite sensitive to catalyst and (de)activating groups in both substrates. We have demonstrated that the main challenge to successfully produce 3,6-dihydro-2*H*-1,2-oxazines **5** by the gold-nitrone cycloaddition method is the appropriate choice of suitable propargyl substrates and gold catalysts to precisely tune the reactivity towards regioselective O-nitrone attack at the gold-carbene-*C*1 position and subsequent ring closure.[8c] The most activated and electron-rich substrates tended to follow the competing reaction pathway by gold catalysed nitrone attack at the *C*3 position and subsequent oxidation[27] to mainly afford the aldehyde product **6**.

The results contribute to a better understanding of the chemistry of propargyl acetals in the presence of gold(I), which have been shown to undergo a diversity of cycloaddition reactions with different reactants.[9–13]

4. Experimental

4.1. General

All reactions were performed under nitrogen atmosphere. Commercial grade reagents were used as received. Dry solvents were collected from a solvent purification system. All reactions were monitored by GLC and thin-layer chromatography (TLC) using silica gel 60 F254 (0.25 mm thickness). Flash chromatography was carried out using silica gel 60 (0.040–0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded using a 400 or 600 MHz spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants (J) are reported in Hertz (Hz). The attributions of the chemical shifts were determined by means of COSY, HMQC, HMBC and NOESY experiments. Melting points (mp) were determined using a Stuart apparatus and are uncorrected. Accurate mass determination was performed on a 'Synapt G2-S' Q-TOF instrument from Waters. Samples were ionized with the use of ASAP probe, no chromatography separation was used before the mass analysis. IR spectra were obtained using a Smart Endurance reflection cell.

Propargyl acetals **1a**–**c**[8b] and nitrones **4a**–**i**[28] were generated as previously described. ^{1}H and ^{13}C NMR shifts were consistent with those in the literature.

4.2. General procedure for gold-catalysed reactions

The relevant propargyl acetal **1a**–**c** (1 equiv) and nitrone (1 equiv) were dissolved in dichloromethane (c=250 mM) and Au[P(*t*-Bu)$_2$(*o*-biphenyl)]SbF$_6$ (5 mol %) was added. The reaction was stirred for the given duration and the solvent was removed in vacuo. Products **5**, **6** and **7** were isolated by flash chromatography using an appropriate eluent system.

4.3. 5-Methoxy-2-methyl-3,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine (5a), 2-methoxy-3-phenylacrylaldehyde (6a) and 1-((2-methoxypropan-2-yl)oxy)-1-phenylpropan-2-one (7a)

Compounds **5a**, **6a** and **7a** were prepared according to the General procedure using propargyl acetal **1a** (54 mg, 0.26 mmol) and nitrone **4a** (36 mg, 0.26 mmol). Flash chromatography (*n*-pentane/EtOAc 100:1) and re-purification by a second flash column (*n*-pentane/EtOAc 20:1) afforded **5a**, **6a** and **7a** as colourless liquids.

5a: (25 mg, 32%) R_f=0.35 (*n*-pentane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55–7.57 (m, 2H, Ar), 7.27–7.39 (m, 8H, Ar), 5.18 (s, 1H, CH–O), 4.88 (s, 1H, CH=C), 4.25 (s, 1H, CH–N), 3.56 (s, 3H, O–CH_3), 2.37 (s, 3H, N–CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 154.2, 139.9, 139.6, 128.6, 128.8, 128.5, 128.1, 127.9, 98.1, 78.6, 69.1, 54.8, 43.0; IR (thin film, cm^{-1}) 2961, 1670, 1213, 714, 695; HRMS (ASAP) calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$ 282.1494, obsd 282.1496.

6a: (34 mg, 35%) R_f=0.60 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.37 (s, 1H, CH=O), 7.80–7.82 (m, 2H, Ar), 7.40–7.41 (m, 3H, Ar), 6.55 (s, 1H, CH=C), 3.97 (s, 3H, O–CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 189.5, 154.1, 135.0, 133.3, 130.2, 130.0, 128.7, 58.8; IR (thin film, cm^{-1}) 2940, 1683, 1455, 1359, 1150, 1032, 692; HRMS (ASAP) calcd for $C_{10}H_{11}O_2$ $[M+H]^+$ 163.0759, obsd 163.0758. ^{1}H and ^{13}C NMR shifts of **6a** were consistent with those in the literature.[29]

7a: (5 mg, 8%) R_f=0.19 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44–7.46 (m, 2H, Ar), 7.35–7.37 (m, 2H, Ar), 7.31–7.33 (m, 1H, Ar), 5.14 (s, 1H, C*H*–O), 3.09 (s, 3H, O–CH_3), 2.10 (s, 3H, CO–CH_3), 1.40 (s, 3H, C–CH_3), 1.32 (s, 3H, C–CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 207.6, 137.7, 128.6, 128.0, 126.7, 101.7, 79.0, 42.9, 25.1, 24.8.

4.4. 5-Methoxy-2-methyl-3-(4-nitrophenyl)-6-phenyl-3,6-dihydro-2*H*-1,2-oxazine (5c)

Compound **5c** was prepared according to the General procedure using propargyl acetal **1a** (118 mg, 0.58 mmol) and nitrone **4c** (110 mg, 0.61 mmol). Flash chromatography (*n*-pentane/EtOAc 5:1) afforded **5c** as a yellow oil (68 mg, 36%) R_f=0.13 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18–8.20 (m, 2H, Ar), 7.51–7.56 (m, 4H, Ar), 7.36–7.43 (m, 3H, Ar), 5.22 (s, 1H, CH–O), 4.81 (s, 1H, CH=C), 4.38 (s, 1H, CH–N), 3.58 (s, 3H, O–CH_3), 2.38 (s, 3H, N–CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 155.1, 148.6, 147.6, 138.9, 129.5, 128.5, 128.2, 124.3, 123.8, 96.6, 78.6, 58.2, 55.9, 43.1; IR (thin film, cm^{-1}) 2966, 1662, 1517, 1345, 1210, 1070, 838, 727, 696; HRMS (ASAP) calcd for $C_{18}H_{19}N_2O_4$ $[M+H]^+$ 327.1345, obsd 327.1346.

4.5. 5-Methoxy-6-(4-methoxyphenyl)-2-methyl-3-phenyl-3,6-dihydro-2*H*-1,2-oxazine (5d)

Compound **5d** was prepared according to the General procedure using propargyl acetal **1b** (102 mg, 0.44 mmol) and nitrone **4a** (59 mg, 0.44 mmol). Attempted purification by flash chromatography (*n*-pentane/EtOAc 10:1) afforded **5d** in an oily yellow mixture with **6b** and **7b**. Products **5d** and **7b** were characterized in this mixture.

5d: (32 mg, 23%) R_f=0.13 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50–7.52 (m, 2H, Ar), 7.36–7.40 (m, 5H, Ar), 6.95–6.97 (m, 2H, Ar) or 6.89–6.91 (m, 2H, Ar), 5.16 (s, 1H, CH–O), 4.90 (s, 1H, CH=C), 4.28 (s, 1H, CH–N), 3.85 (s, 3H, O–CH_3),

3.58 (s, 3H, O–CH_3), 2.38 (s, 3H, N–CH_3); HRMS (ASAP) calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$ 312.1600, obsd 312.1600.

7b: (23 mg, 21%) R_f=0.13 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36–7.40 (m, 2H, Ar), 6.95–6.97 (m, 2H, Ar) or 6.89–6.91 (m, 2H, Ar), 5.12 (s, 1H, CH–O), 3.82 (s, 3H, O–CH_3), 3.11 (s, 3H, O–CH_3), 2.11 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

4.6. 2-Methoxy-3-(4-methoxyphenyl)acrylaldehyde (6b)

Compound **6b** was obtained by subsequent flash chromatography (*n*-pentane/DCM 3:1) of the mixture of **5d**, **6b** and **7b** above, giving **6b** as colourless oil (19 mg, 22%) R_f=0.13 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.31 (s, 1H, CH=O), 7.78–7.80 (m, 2H, Ar), 6.93–6.94 (m, 2H, Ar), 6.52 (s, 1H, CH=C), 3.94 (s, 3H, O–CH_3), 3.87 (s, 3H, O–CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 181.3, 161.1, 152.9, 134.6, 132.2, 126.1, 114.2, 58.7, 55.4; IR (thin film, cm^{-1}) 1681, 1601, 1510, 1256, 1176, 1154, 1032. ^{1}H and ^{13}C NMR shifts of **6b** were consistent with those in the literature.[28]

4.7. 5-Methoxy-2,3,6-triphenyl-3,6-dihydro-2*H*-1,2-oxazine (5f)

Compound **5f** was prepared according to the General procedure using propargyl acetal **1a** (207 mg, 1.01 mmol) and nitrone **4d** (203 mg, 1.03 mmol). Flash chromatography (*n*-pentane/EtOAc 100:1) followed by a second flash column (*n*-pentane/DCM/EtOAc 100:2:1) gave **5f** as a colourless liquid (38 mg, 11%) R_f=0.46 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.52–7.54 (m, 2H, Ar), 7.24–7.37 (m, 5H, Ar), 7.22–7.23 (m, 2H, Ar), 7.19–7.20 (m, 1H, Ar), 7.11–7.14 (m, 2H Ar), 6.93–6.94 (m, 2H, Ar), 6.85–6.87 (m, 1H, Ar), 5.46 (s, 1H, CH–O), 5.27 (d, 1H, *J*=3.5 Hz, CH–N), 5.13 (d, 1H, *J*=4.3 Hz, CH=C), 3.58 (s, 3H, O–CH_3). ^{13}C NMR (600 MHz, $CDCl_3$) δ (ppm) 154.5, 148.1, 140.0, 137.0, 129.0, 128.5, 128.4, 128.3, 128.2, 128.1, 127.3, 122.3, 118.0, 96.7, 79.5, 63.4, 54.9; IR (thin film, cm^{-1}) 2925, 1599, 1492, 1453, 1225, 1174, 1054, 753, 696; HRMS (ASAP) calcd for $C_{23}H_{22}NO_2$ $[M+H]^+$ 344.1651, obsd 344.1647.

4.8. 2-(4-Chlorophenyl)-5-methoxy-3,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine (5h)

Compound **5h** was prepared according to the General procedure using propargyl acetal **1a** (116 mg, 0.57 mmol) and nitrone **4f** (133 mg, 0.58 mmol). Flash chromatography (*n*-pentane/EtOAc 100:1) gave **5h** as a colourless wax (116 mg, 54%) R_f=0.54 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.51–7.52 (m, 2H, Ar), 7.41–7.43 (m, 2H, Ar), 7.38–7.40 (m, 1H, Ar), 7.35–7.37 (m, 2H, Ar), 7.24–7.26 (m, 2H, Ar), 7.21–7.22 (m, 1H, Ar), 7.06–7.07 (m, 2H, Ar), 6.83–6.85 (m, 2H, Ar), 5.45 (s, 1H, CH–O), 5.20 (d, 1H, *J*=3.4 Hz, CH–N), 5.11 (d, 1H, *J*=4.3, CH=C), 3.57 (s, 3H, O–CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ (ppm) 154.4, 146.7, 139.6, 136.8, 129.0 (2 diff. C, as shown by HMBC), 128.6, 128.4, 128.3, 128,22, 128,17, 127.5, 119.3, 96.7, 79.8, 63.8, 54.9; IR (thin film, cm^{-1}) 1670, 1488, 1453, 1225, 1174, 1058, 828, 760, 731, 698; HRMS (ASAP) calcd for $C_{23}H_{21}NO_2{}^{35}Cl$ $[M+H]^+$ 378.1261, obsd 378.1255.

4.9. 5-Methoxy-3-(4-methoxyphenyl)-2,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine (5i)

Compound **5i** was prepared according to the General procedure using propargyl acetal **1a** (100 mg, 0.49 mmol) and nitrone **4g** (113 mg, 0.50 mmol). Flash chromatography gave **5i** as a colourless oil containing anisaldehyde (11 mg, 6%) R_f=0.29 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.53–7.54 (m, 2H, Ar), 7.40–7.41 (m, 2H, Ar), 7.38–7.39 (m, 1H, Ar), 7.29–7.30 (m, 2H, Ar), 7.12–7.13 (m, 2H, Ar), 6.93–6.94 (m, 2H, Ar), 6.86–6.87 (m, 1H, Ar), 6.76–6.77 (m, 2H, Ar), 5.46 (s, 1H, CH–O), 5.22 (d, 1H, *J*=6.4, CH–N), 5.12 (d, 1H, *J*=4.3, CH=C), 3.75 (s, 3H, O–CH_3), 3.58 (s, 3H, O–CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ (ppm) 158.8, 154.5, 148.2, 137.0, 131.9, 129.3, 129.0, 128.5, 128.3, 128.2, 122.3, 118.0, 113.4, 97.0, 79.7, 63.2, 55.1, 54.9; IR (thin film, cm^{-1}) 1601, 1512, 1454, 1251, 1161, 1024, 832, 744, 697. HRMS (ASAP) calcd for $C_{24}H_{24}NO_3$ $[M+H]^+$ 374.1756, obsd 374.1754.

4.10. 3-(4-Chlorophenyl)-5-methoxy-2,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine (5j)

Compound **5j** was prepared according to the General procedure using propargyl acetal **1a** (98 mg, 0.48 mmol) and nitrone **4h** (115 mg, 0.50 mmol). Flash chromatography (*n*-pentane/EtOAc 100:1) gave **5j** as a colourless wax (42 mg, 23%) R_f=0.56 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.49–7.50 (m, 2H, Ar), 7.40–7.41 (m, 2H, Ar), 7.39–7.40 (m, 1H, Ar), 7.31–7.32 (m, 2H, Ar), 7.19–7.20 (m, 2H, Ar), 7.13–7.15 (m, 2H, Ar), 6.92–6.93 (m, 2H, Ar), 6.88–6.90 (m, 1H, Ar), 5.46 (s, 1H, CH–O), 5.25 (d, 1H, *J*=4.0, CH–N), 5.10 (d, 1H, *J*=4.5, CH=C), 3.58 (s, 3H, O–CH_3). ^{13}C NMR (600 MHz, $CDCl_3$) δ (ppm) 155.1, 148.0, 138.6, 136.8, 133.2, 130.0, 129.0, 128.7, 128.5, 128.4, 128.3, 122.6, 117.9, 96.3, 79.7, 62.9, 55.1; IR (thin film, cm^{-1}) 1686, 1598, 1492, 1454, 1210, 1148, 1091, 1025, 1013, 833, 760, 745, 698; HRMS (ASAP) calcd for $C_{23}H_{21}NO_2Cl$ $[M+H]^+$ 378.1261, obsd 378.1254.

4.11. 1-((2-Methoxypropan-2-yl)oxy)-1-(4-nitrophenyl) propan-2-one (7c)

Compound **7c** was prepared according to the General procedure using propargyl acetal **1c** (130 mg, 0.52 mmol) and nitrone **4a** (71 mg, 0.53 mmol). Flash chromatography (*n*-pentane/EtOAc 5:1) gave **7c** as a yellow oil (26 mg, 19%) R_f=0.16 (*n*-pentane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21–8.23 (m, 2H, Ar), 7.65–7.67 (m, 2H, Ar), 5.23 (s, 1H, CH–O), 3.09 (s, 3H, O–CH_3), 2.15 (s, 3H, CO–CH_3), 1.44 (s, 3H, C–CH_3), 1.33 (s, 3H, C–CH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 206.8, 147.8, 145.0, 127.2, 123.8, 102.2, 78.3, 49.4, 25.1, 24.7.

4.12. 3-Oxo-1-phenylprop-1-en-2-yl acetate (8)

Compound **8** was prepared according to the General procedure using propargyl ester **3** (46 mg, 0.26 mmol) and nitrone **4a** (38 mg, 28 mmol) with $PicAuCl_2$ (5 mol %) as catalyst. Flash chromatography (*n*-pentane/EtOAc 20:1) gave **8** as a colourless oil (12 mg, 25%). ^{1}H and ^{13}C NMR shifts of **8** were consistent with those in the literature.[30]

Supplementary data

Supplementary data (spectroscopic data; ^{1}H and ^{13}C NMR) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.04.058.

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