Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

# Au(I)-catalyzed cycloaddition pathways of non-terminal propargyl substrates

Huey-San Melanie Siah, Helgi Freyr Jónsson & Anne Fiksdahl

**To cite this article:** Huey-San Melanie Siah, Helgi Freyr Jónsson & Anne Fiksdahl (2020): Au(I)-catalyzed cycloaddition pathways of non-terminal propargyl substrates, Synthetic Communications, DOI: 10.1080/00397911.2020.1731550

**To link to this article:** https://doi.org/10.1080/00397911.2020.1731550

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2020.1731550



# Au(I)-catalyzed cycloaddition pathways of non-terminal propargyl substrates

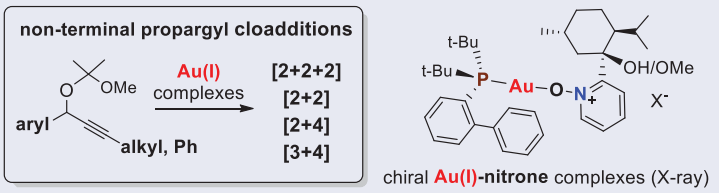
Huey-San Melanie Siah, Helgi Freyr Jónsson, and Anne Fiksdahl

Department of Chemistry, Norwegian University of Science and Technology, Hoegskoleveien, Trondheim, Norway

**ABSTRACT**

Novel chiral menthol-based pyridyl nitrone ligands were synthesized and Au(I) coordination of the ligands gave chiral Au(I)–nitrone complexes. $^{1}$H NMR studies of the gold(I) coordination experiments with nitrone ligands afforded a convenient method for monitoring complex formation. The catalytic effect of Au(I)–nitrone complexes, shown to tune catalytic systems to produce uncommon products, was evaluated in [2 + 2 + 2] cyclotrimerization and [2 + 4] cyclodimerization reactions of non-terminal propargyl acetals. Alternative gold(I)-catalyzed [2 + 2], [2 + 4] and [3 + 4] cycloaddition reaction pathways of non-terminal propargyl acetals with imine substrates gave a diverse range of *N*-heterocyclic products. The present screening study demonstrates the potential and the versatility of non-terminal propargyl acetals in gold(I)-catalyzed cycloaddition reactions.

**GRAPHICAL ABSTRACT**




**ARTICLE HISTORY**
Received 30 January 2020

**KEYWORDS**
Azetidine; benzazepine; cyclo-trimerization/-dimerization; gold(I)-nitrone complexes; non-terminal propargyl acetals; piperidine

## Introduction

The intensive development of gold chemistry the last decade has mainly focused on the discovery and understanding of new gold(I)-catalyzed reactions as well as the construction of new gold(I)-ligated complexes. We have contributed to the development of gold catalysis in organic synthesis in recent years by the development of a number of cycloaddition reactions based on the highly reactive terminal propargyl acetal substrates and a series of reactants, including nitrones.[1–10]

We have previously studied the interesting dual aspect of nitrones in gold-catalyzed reactions, both as substrate in gold(I)-catalyzed [3 + 3] cycloaddition with propargyl acetals,[5] but also as catalytic additives in gold(I)-catalyzed reactions, tuning the

CONTACT Anne Fiksdahl anne.fiksdahl@ntnu.no Department of Chemistry, Norwegian University of Science and Technology, Hoegskoleveien, Trondheim, 7491, Norway.

Supplemental data for this article can be accessed on the publisher's website.

catalytic system to produce uncommon products. We have shown that gold(I)-nitrone complexes, either generated *in situ* or isolated prior to reaction, may catalyze unusual transformations, such as regio- and chemo-selective [2 + 2 + 2] cyclotrimerization of non-terminal 1,3-diaryl propargyl acetals **1** (Scheme 1).[8,10] The cyclohexylidene trimeric products **2a–c** (up to 74% yield) were obtained as a mixture of three stereoisomers. Hydrolysis allowed isolation of 46% of the main *trans,trans,cis*-diastereomer.

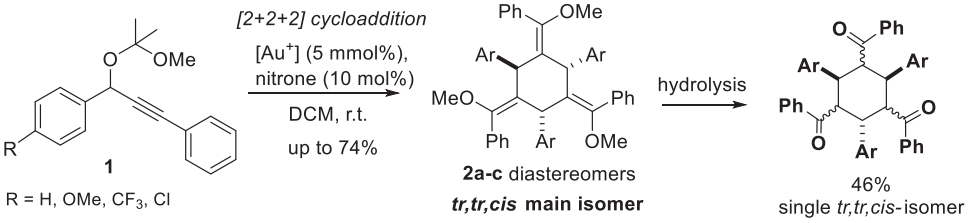
The cyclotrimerization approach demonstrates the ability of nitrones to tune the catalytic activity of Au(I) complexes and that unusual transformations may take place in the presence of Au(I)–nitrone complexes, which represent an interesting group of Au(I) _catalysts with specific properties. Chiral nitrones have been used as Lewis bases to induce enantioselectivity in organic reactions[11,12] and would have the potential to act as chiral ligands and thereby afford enantioselective gold-catalyzed reactions.

Our previous results show that non-terminal propargyl substrates have ability to undergo uncommon cycloaddition reactions. Therefore, we have further studied the potential cycloaddition pathways which may take place with non-terminal propargyl acetals in the presence of either new prepared chiral Au(I)–nitrone complexes or conventional Au(I) catalysts.

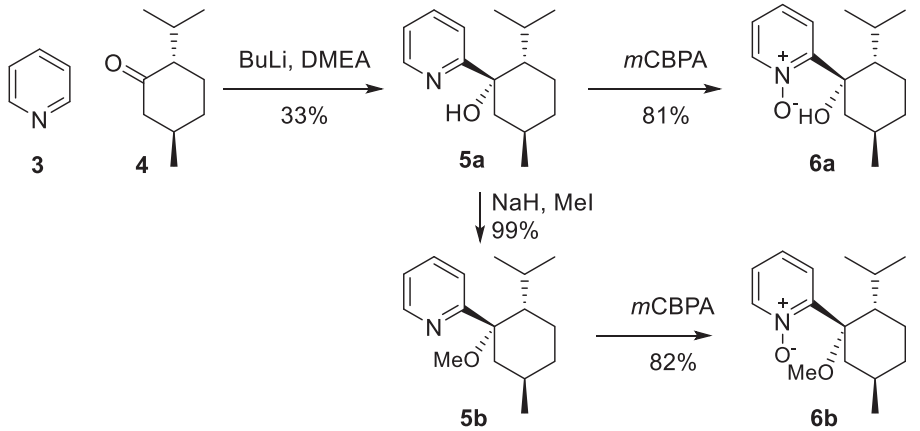
## Results and discussion

### Synthesis of chiral nitrone ligands and Au(I)–nitrone complexes

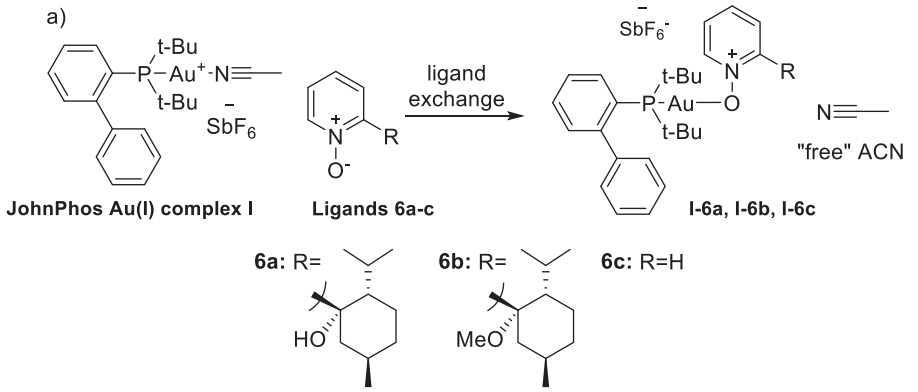
The chiral nitrone ligands **6a** and **6b** were synthesized via 2-pyridyl-menthol intermediate **5a**, which was formed (33%, Scheme 2) by enantioselective addition of lithiated



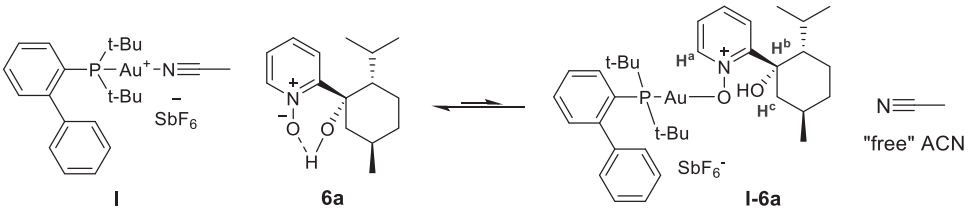

**Scheme 1.** Gold(I)-nitrone-catalyzed [2 + 2+2] cyclotrimerization of diarylpropargyl acetal **1**.




**Scheme 2.** Synthesis of chiral nitrone ligands **6a** and **6b.**




**Scheme 3.** *In situ* generation of Au(I)–nitrone complexes (**I–6a,b,c**) by ligand exchange of JohnPhosAu(I)(ACN)$SbF_6$ complex **I** with nitrones **6a–c**.




**Scheme 4.** Coordination of nitrone **6a** with JohnPhosAu(ACN)$SbF_6$ **I**, shown as an equilibrium between [complex **I** + **6a**] and [complex **I–6a** + "free" ACN].

pyridine to (-)-menthone **4**.[9] The methyl-ether **5b** was obtained in quantitative yields by methylation of alcohol **5a**. Oxidation of pyridyl-menthol derivatives **5a** and **5b** gave the chiral nitrone ligands **6a** and **6b** in high yields (81–82%).

Prior to use in reactions, Au(I)–nitrone complexes **I–6a**, **I–6b** and **I–6c** were generated *in situ* by acetonitrile ligand exchange of the JohnPhos Au(I)–ACN complex **I** with the chiral pyridyl-nitrone ligands **6a** and **6b** as well as the non-substituted pyridine *N*-oxide **6c** (Scheme 3; 1:2 ratio of complex **I**:nitrone **6**).

## $^1$H NMR coordination studies

$^1$H NMR analysis of gold(I) coordination experiments with nitrone ligands (Fig. 1), afforded a convenient method for monitoring Au(I) coordination (Scheme 4). The coordination abilities of pyridine-nitrones **6a** and **6b** to JohnPhosAu(I)$SbF_6$ complex **I** to give chiral nitrone complexes **I–6a** and **I–6b** were clearly ascertained by comparing the changes in $^1$H NMR shifts going from pure nitrone (**6a** or **6b**) and gold(I) complex **I**, respectively (Fig. 1a,b,d), to 1:1 mixtures of the relevant nitrone (**6a** or **6b**) and Au(I) complex **I** (Fig. 1c,e).

Formation of gold complex **I–6b** by coordination of nitrone ligand **6b** with Au(I) complex **I** is clearly visible by $^1$H NMR (Fig. 1d,e). All pyridine protons of nitrone **6b** are deshielded, but the most significant increases in chemical shifts ($\Delta\delta^1H_{coord} = \delta^1H_{complex} - \delta^1H_{ligand}$) were observed for the pyr-$H^a$ proton signal ($\Delta\delta^1H_{coord}$ 0.11 ppm). The opposite effect was seen for menthyl protons ROCC$H^b$ and ROCC$H^c{}_2$, which were strongly shielded

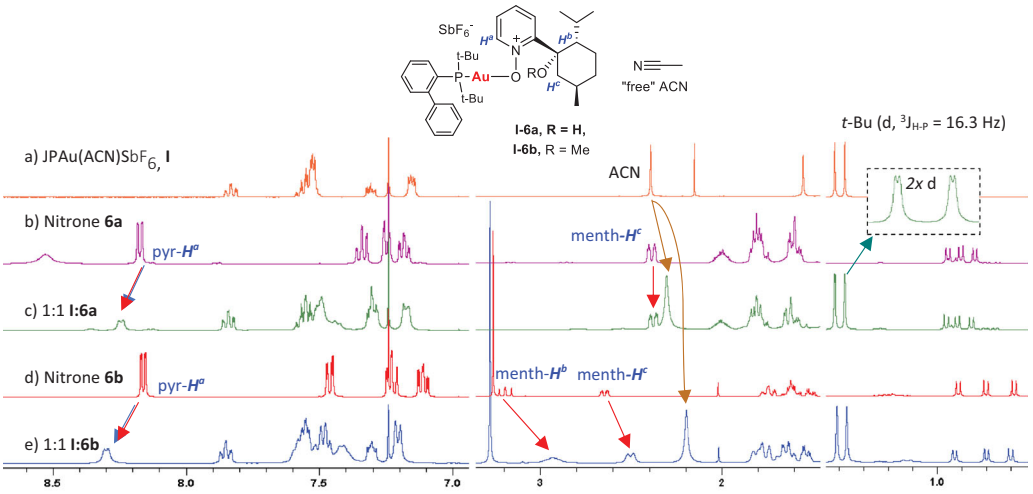


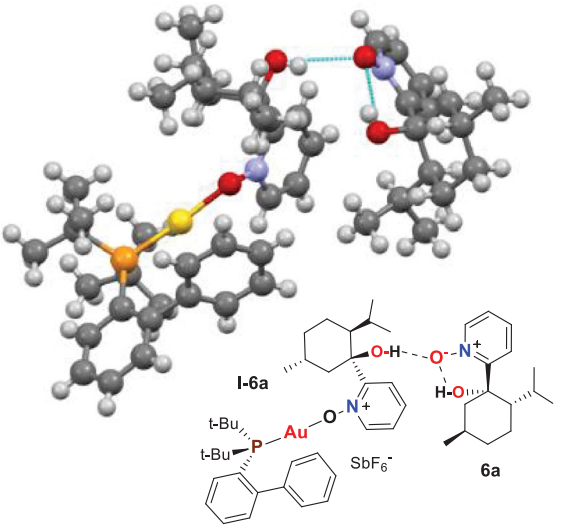

**Figure 1.** $^{1}$H NMR study of nitrones **6a** and **6b** coordination with JohnPhosAu(ACN)SbF$_6$ **I** (1:1 in $CDCl_3$).

($\Delta\delta^{1}H_{coord}$ −0.29 ppm and −0.17 ppm, respectively). The up-field shift of the ligated ACN signal of Au(I)-complex **I** (from 2.39 ppm to 2.20 ppm; $\Delta\delta^{1}H_{coord}$ −0.19 ppm, Fig. 1a,e) is a characteristic proof of ACN de-coordination and ligand exchange to give non-ligated "free" acetonitrile.[13] Also the aromatic protons of the phosphane ligand experienced minor deshielding effects.

Similar changes were observed for the **I:6a** mixture, indicating coordination of nitrone **6a**, as well. However, a weaker observed effect on the Au(I)–ACN signal (Fig. 1a,c), may indicate less efficient displacement of the ACN ligand and, hence, that nitrone **6a** is less strongly coordinated to the Au(I) than nitrone **6b**. A minor change of the *t*-Bu doublet ($^{3}J_{H-P}$ = 16.3 Hz), which appears as two doublets in the **I:6a** mixture, indicates that diastereotopic *t*-Bu groups are formed by coordination of the chiral ligand (Fig. 1b, expanded). Thus, the chiral nitrone **6a** may have a greater steric effect on the phosphane ligand than nitrone **6b** when coordinated to the Au(I) center.

Generally, the nitrone (**6a** and **6b**) signals in the 1:1 mixtures are broader, indicating a dynamic ligand exchange (Scheme 4). Several observations confirm that nitrone **6b** is more strongly bonded to the Au center than nitrone **6a**, as the menthol proton signals are more strongly shielded and the ligated ACN peak is more affected for mixture **I:6b** compared to mixture **I:6a**. Intramolecular H-bonding in the non-methylated nitrone **6a** unit (Scheme 4), shown in the crystal structure for **I**–**6a** (X-ray, Fig. 2), provides one explanation for the weaker coordination of ligand **6a**, compared to ligand **6b**, as H-bonding is not possible in the methylated nitrone **6b**

The Au(I) complexation of chiral nitrones **6a** and **6b** appears to be weaker compared to previously reported gold-nitrone complexes[10] which gave sharp $^{1}$H NMR peaks for 1:1 mixtures of complex **I** and nitrones. The bulkiness of the chiral nitrones **6a** and **6b** may affect the ability to undergo coordination to gold(I). To get better understanding of the dynamics of the Au(I)–nitrone coordination and the equilibrium between coordinated and uncoordinated states (Scheme 4), further $^{1}$H NMR studies of complex **I** and nitrone **6a** were carried out with increasing amounts of nitrone (ratio **I:6a** 1:1, 1:2, 1:5 and 1:10, Fig. 2 and Table 1).




| Complex | O-Au | Au-P | N-O | O-Au-P angle |
|---|---|---|---|---|
| **I-6a** | 2.064 | 2.225 | 1.349 | 176.9 |
| **I-6c**[10] | 2.074 | 2.230 | 1.349 | 177.4 |
| | | | | |
| **I-6d**[10] | 2.096 | 2.243 | 1.340 | 174.9 |

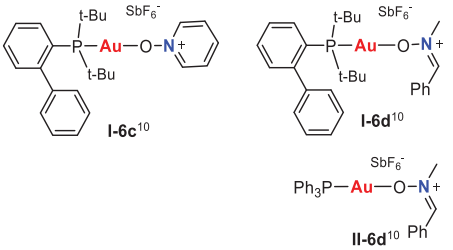



**Figure 2.** [1]H NMR coordination study of nitrone **6a** with Au(I) complex **I** with different **I:6a** ratios.

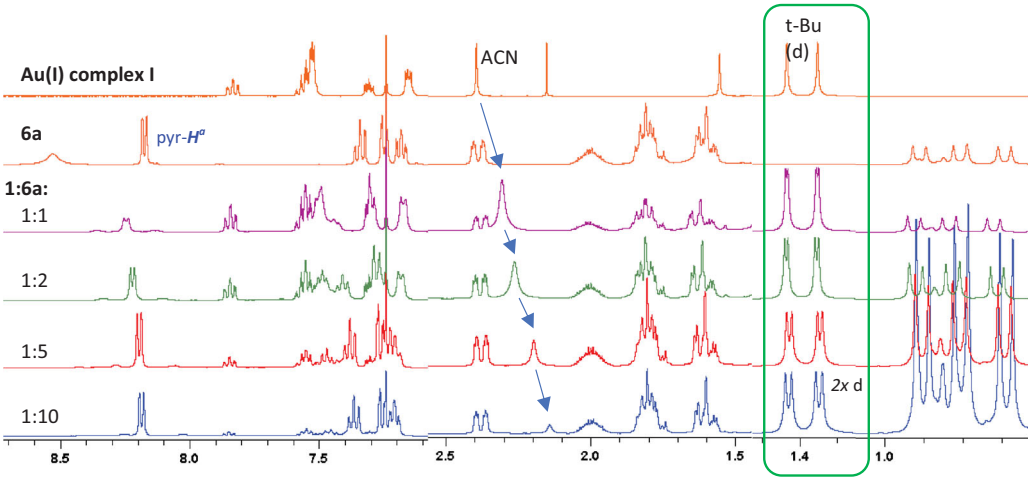



**Figure 3.** Crystal structure (X-ray) of Au(I)–nitrone complex **I–6a**. Selected bond lengths (Å) and angles (°) in gold(I)-nitrone complexes **I–6a**, **I–6c** and **I–6d** are given.

**Table 1.** Changes in [1]H NMR peak shifts, $\Delta\delta^1H_{coord}$[a] (ppm), of mixtures with decreasing **I:6a** ratio.

| | | | **I:6a** ratio: | | | |
|---|---|---|---|---|---|---|
| | | | $\Delta\delta^1H_{coord}$[a] | | | |
| Entry | Signal observed | $\delta$ (ppm) | 1:1 | 1:2 | 1:5 | 1:10 |
| 1 | **6a**: $H^a$ | 8.17 | 0.07 | 0.05 | 0.04 | 0.01 |
| 2 | **I**; ACN | 2.39 | 0.08 | 0.13 | 0.19 | 0.25 ($\delta$ 2.14) |
| 3 | **I**: *t*-Bu (d) | 1.40 | 0 | 0 | −0.01 | −0.01 |
| 4 | **I–6a** (2× d) | 1.40 | 0.003[b] | 0.005[b] | 0.007[b] | 0.009[b] |

[a] $\Delta\delta^1H_{coord} = \delta^1H_{complex} - \delta^1H_{ligand}$.
[b] $\Delta\delta^1H_{diastereomer} = \delta^1H_{isomer\,1} - \delta^1H_{isomer\,2}$.

A minor deshielding effect on the pyr-$H^a$ proton was initially observed by a 1:1 ratio (Table 1, entry 1). By increasing to excess amount of ligand **6a**, the presence of only one pyr-$H^a$ doublet indicates a dynamic process, and not two distinct nitrone states. $^1$H NMR of the mixtures showed that the ACN methyl signal was strongly affected by increased amount of nitrone **6a**, almost reaching the expected value of 2.10 ppm[14] for "free" acetonitrile at 1:10 (**I:6a**) ratio (Table 1, entry 2). In contrast to ligand **6b** (Fig. 1a,e), ligand exchange of nitrone **6a** with the ACN is less favored, as excess of nitrone appears necessary to promote full coordination to the gold center. By excess amount of ligand **6a**, the phosphane *tert*-butyl doublet splits into two doublets with increased difference in chemical shift ($\Delta\delta_{diastereomer}$ up to 0.009 ppm), demonstrating a significant diastereotopic effect by Au(I)–nitrone **2a** coordination (Table 1, entry 4), as also seen to a lesser extent above (Fig. 1c).

Similar $^1$H NMR coordination studies of nitrones **6a** and **6b** with the Au(I)-phosphane complex $Ph_3PAuSbF_6$ showed possible Au(I) coordination, in addition to decomposition of the phosphane or nitrone ligand. Coordination of $Me_3PAuSbF_6$ failed. The previously isolated $Ph_3PAu$(I)–nitrone complex **II–6d**[10] (Fig. 2) was obtained in much lower yields (38%) than the corresponding JohnPhos-Au(I)–nitrone complex **I–6d** (74%), indicating lower coordination ability of the less electron-rich $PPh_3$ ligand to give stable gold(I)-nitrone complexes.

## Crystal structures (X-ray)

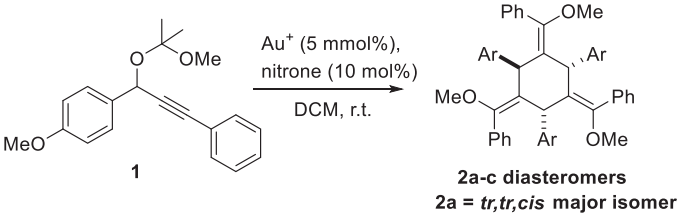
Crystalline complex **I–6a** was successfully obtained and the crystal structure was confirmed by X-ray analysis (Fig. 3), which showed the expected nearly linear nitrone-O-Au(I)-P coordination mode (176.9°). The deviation from linearity is less than for previously characterised[10] complex **I–6d**, and slightly more than observed for pyridine-*N*-oxide complex **I–6c**, likely due to steric effects. The shorter O-Au bond length (2.064 Å) of chiral complex **I–6a** than for **I–6c** and benzaldimine nitrone **I–6d**, indicates that nitrone ligand **6a** is more strongly bonded to the Au(I) center. This may be due to an electron donating effect of the menthol unit. The short N–O bond length of complex **I–6a** (1.349 Å) was similar to complex **I–6c**, indicating a N–O double bond character. The Au–P bond length (2.225 Å) in complex **I–6a** was comparable to that for complex **I–6c**, but shorter than for complex **I–6d**, likely due to the size of nitrone.

An uncoordinated nitrone **6a** unit, also visible in the crystal structure (Fig. 3, right), enables Au(I)–nitrone coordination by hindering intramolecular hydrogen-bonding of ligand **6a**, as the O-atom of the "free" nitrone unit forms an intermolecular H-bond to the OH group of the ligated nitrone **6a**. The intramolecular H-bond within the uncoordinated nitrone also supports the theory that nitrone **6a** has a poorer coordination ability to the Au center than MeO–nitrone **6b** because of competing internal H-bonds.

## Cycloaddition reactions of non-terminal propargyl acetals

The catalytic properties of the gold-nitrone complexes **I–6a, I–6b** and **I–6c** were evaluated in gold-catalyzed [2 + 2 + 2] cyclotrimerization[8] and [2 + 4] cyclodimerisation of novel propargyl acetal **10** (Tables 2–4).

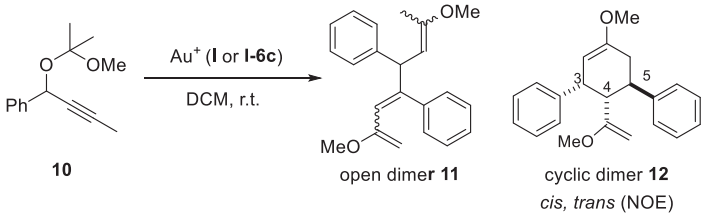
**Table 2.** Gold(I)-catalyzed [2 + 2 + 2] cyclotrimerisation of propargyl acetal **1** to trimer **2**.




| Entry | Au(I) complex[a] | Time | Yield[8] | **2a**[b]**:2b:2c** |
|---|---|---|---|---|
| 1 | **I** | 2–24 h | –[8] | – |
| 2 | **I–6a** | 18 h | 40% | 55:25:20 |
| 3 | **I–6b** | 18 h | 73% | 45:35:20 |
| 4 | **I–6c**[10] | 18 h | 66% | 45:25:30 |
| 5 | **I–6c**[c][8] | 2 h | 74% | n.r.[d] |

[a]Complex product mixture.
[b]**2a** = *trans,trans,cis*; main product.
[c](JohnPhosAuCl)$AgNTf_2$)–**6c**[8].
[d]n.r.: ratio not reported.

**Table 3.** Gold(I)-catalyzed dimerization of propargl acetal **10**.




| Au(I) complex | Time | Yield |
|---|---|---|
| **I** | 2 h | **11**, 25%[a] |
| **I–6c** | 24 h | **12**, 30%[a] |

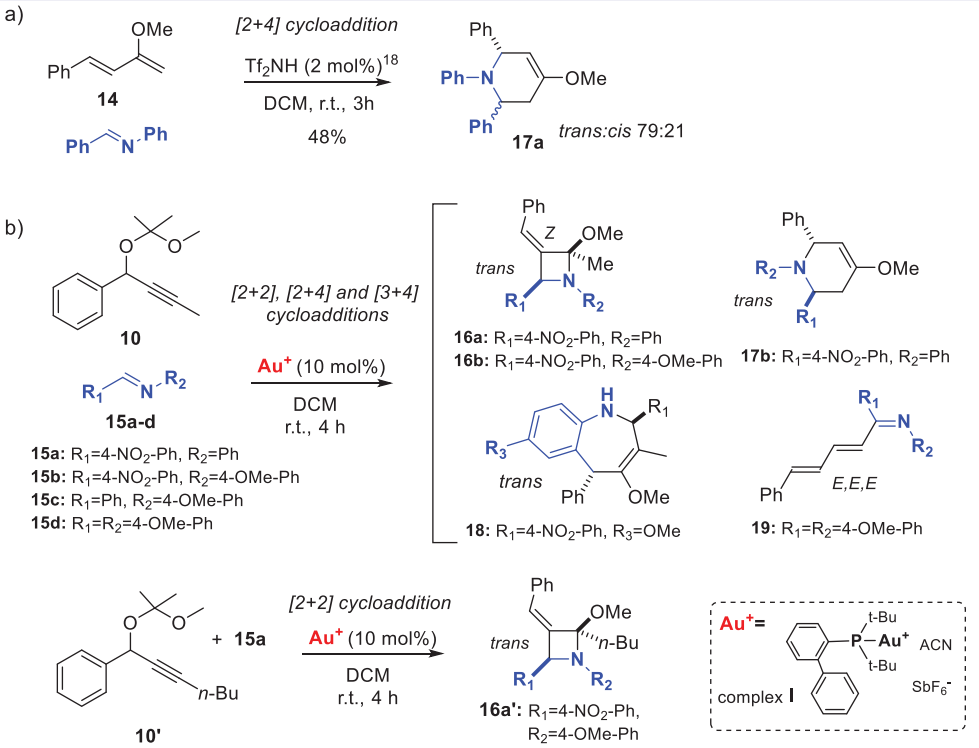
[a]Unstable.

## *Catalytic effect of gold-nitrone complexes*

*[2 + 2 + 2] Cyclotrimerisation.* The catalytic ability of complexes **I–6a, I–6b** and **I–6c** were tested in the gold(I)-nitronecatalysed [2 + 2 + 2] cyclotrimerization reaction of 1,3-diarylpropargyl acetals (**1**), which we have reported[10] to give cyclohexylidene products **2**. The presence of catalytic amounts of different nitrones was previously shown to be essential for successful selective cyclotrimerization, as Au(I) complex **I** gave no product **2** and complex product mixtures from diarylpropargyl acetal **1** in the absence of nitrone (Table 2, entry 1). A relevant hypothesis is that Au catalyst **I** is too active to afford selective trimerization, and that the reduced Au-catalyst activity by nitrone-Au coordination allows controlled chemoselective trimerization to take place.

The trimer **2** was obtained in moderate to good yields (40–73%) as mixtures of three diastereomers (**2a-c**, Table 2, entries 2–4). Complex **I–6b** gave highest yield (73%, entry 3), similar to the best yields reported[8] for this reaction (74%, entry 5, nitrone **6c**, counterion $NTf_2$). Complex **I–6a** gave lower yield (40%, entry 2), possibly because nitrone **6a** is more poorly coordinated to gold(I) than nitrone **6b**, as discussed above. The

**Table 4.** Cycloaddition reactions of (a) diene **14** with phenylbenzaldimine[18] and (b) aryl-alkyl-propargyl acetals **10** and **10′** with imines **15a–d**.

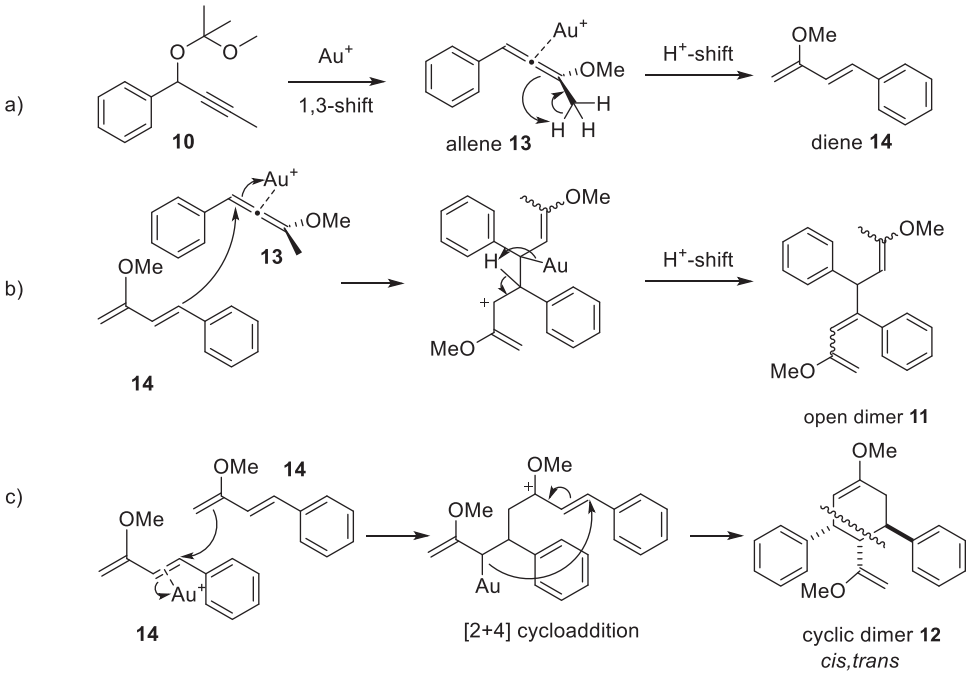



| | | | Yield | | | |
|---|---|---|---|---|---|---|
| Entry | Acetal | Imine | **16** | **17b** | **18** | **19** |
| 1 | **10** | **15a** | **16a**, 33% | 21% | – | – |
| 2 | **10** | **15b** | **16b**, 30% | – | 18% | – |
| 3 | **10** | **15c** | – | – | – | 29% |
| 4 | **10** | **15d** | Full conv. of **10**, no prod. isolated | | | |
| 5 | **10′** | **15a** | **16a′** <15% | – | – | |

success of the cyclotrimerisation reaction demands careful tuning of catalytic activity of the gold complex, and a stronger deactivation of the gold center than that provided by nitrone **6a** appears to be necessary.

Some differences in the diastereoisomeric product distribution (**2a–c**) were observed. Complex **I**–**6a** gave highest stereoselectivity toward the main *trans,trans,cis*-diastereomer (55%, entry 2), while nitrone complex **I**–**6b** was slightly more selective toward isomer **2b** than nitrone complex **I**–**6c** (35% vs 25%). The different isomer ratios could be attributed to a combination of factors, such as the bulk of the nitrones, as well as the strength of nitrone coordination to the gold center. Chiral HPLC separation of the three pairs of enantiomers in the product mixture for determination of possible % ee, was unsuccessful in our hands.

*[2 + 4] Cyclodimerisation.* As previous studies on non-terminal propargyl substrates only included phenyl-substituted propargyl acetals, such as diarylpropargyl substrate **1**[10] above, the reactivity of methyl-aryl-propargyl acetal **10** was explored. Catalytic amounts of both complexes **I** and **I**–**6c** gave full conversion of acetal **10**, however, to




**Scheme 5.** Proposed pathways for (a) gold-catalyzed generation of allene **13** and diene **14** intermediates from propargyl acetal **10**; (b) dimerization of diene **14** with allene **13** to give open dimer **11** and (c) dimerization of two units of diene **14** to give cyclic dimer **12**.

different products; proposed to be the open and the cyclic dimeric products **11** (25%) and **12** (30%), respectively (Table 3). Both products were rather unstable.

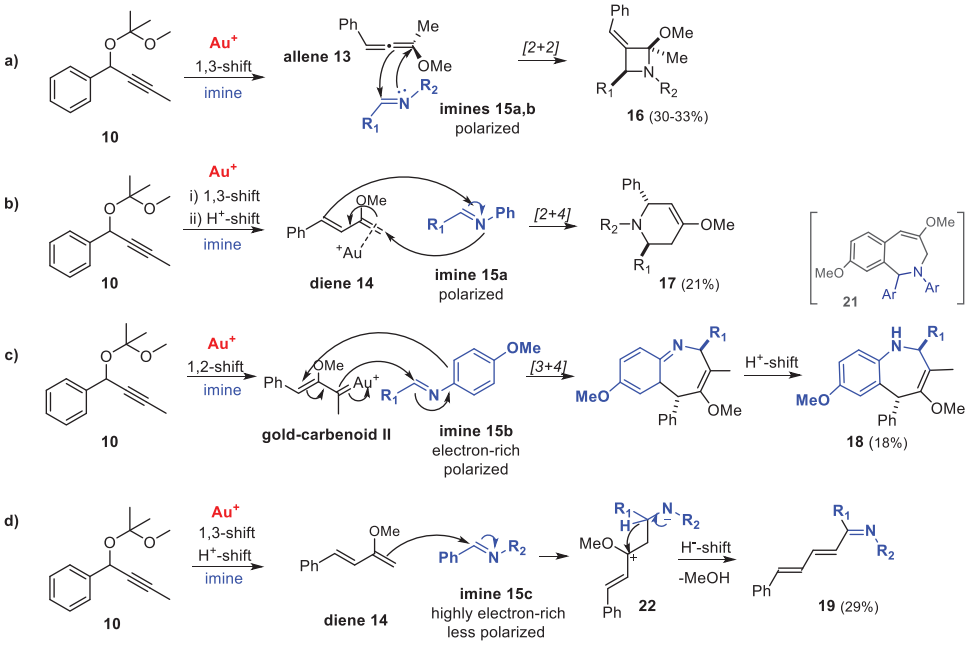
The different dimerization reaction pathway of methyl-aryl-propargyl acetal **10** from the trimerization taking place with diaryl-propargyl substrate **1**, may be explained by the proposed pathways for the formation of the octatriene **11** and *cis,trans*-cyclohexene **12** dimer products (Scheme 5). The trimerization of diaryl substrate **1** is proposed to proceed through [2 + 2 + 2] cycloaddition of allenic intermediates after gold-catalyzed 1,3-alkoxy rearrangement.[10] In accordance with literature,[8] the propargyl acetal **10** undergoes a gold-catalyzed 1,3-methoxy shift to give allenic intermediate **13**. However, unlike the mechanism for diaryl-propargyl acetals, the methyl-substituted allene **13** may undergo proton shift and isomerization to give diene **14** (Scheme 5a). Such gold catalyzed transformations are reported[15,16] to be faster for electron-rich than electron-deficient allenes.[17] Diene **14**, formed by isomerization of allene **13** may subsequently undergo two alternative dimerization pathways; either with allene **13** or with a second unit of diene **14** to give the open and the cyclic dimers **11** and **12**, respectively (Scheme 5b,c). NMR analysis of cyclohexene dimer **12** showed NOE correlations, such as between benzylic H3 and allylic H4 protons, which were used to establish the relative *cis-trans* stereochemistry of the diphenyl-vinyl-trisubstituted cyclohexene **12**.

In contrast to Au(I) complex **I**, producing the open dimer **11**, the results indicate that nitrone complex **I–6c** may have higher catalytic capacity for allene-to-diene

isomerization (Scheme 5a), which enables dimerization of two units of diene **14** to give cyclic dimer **12** by a Diels-Alder-like [2 + 4] cycloaddition.

## Cycloaddition studies of *in situ* generated intermediates from non-terminal propargyl acetals

Since alkyl-arylpropargyl acetal **10** seemed to generate allene **13** or diene **14** intermediates in the presence of Au(I) complexes, a series of possible Diels-Alder reactions were tested with substrate **10** and dienophiles. The reactions with alkene, alkyne, nitrile and carbonyl compounds failed to incorporate the dienophiles, and only dimers such as **11** and **12** (21–53%) were formed. However, as diene **14** is known to undergo hetero-Diels-Alder reactions with imines (48% yield of piperidine product **17a**, Table 4),[18] the ability of gold(I) to catalyze possible cycloaddition reactions of imines with *in situ* generated allene **13** or diene **14** from alkyl-arylpropargyl acetal **10**, was more promising. In fact, propargyl acetal **10** and aldimines **15a–d** did undergo several cycloaddition reactions in the presence of Au(I) complex **I** with *in situ* generated intermediates **13** or **14** (Table 4). The polarized nitro-phenyl imines (**15a** and **15 b**) mainly afforded the novel *E,trans*-benzylidene-diarylazetidine **16** (30–33%, entries 1 and 2), explained by the proposed [2 + 2] cycloaddition of imine and allene **13** (Scheme 6a). The more sterically hindered *n*-butyl-propargyl acetal **10′** gave similar product **16a′** in lower yield (<15%, entry 5). An analogous [2 + 2] cycloaddition is reported by the Fiksdahl group for dimerization of a diaryl propargyl ester to give a di-benzylidene-cyclobutyl product.[8] Azetidines, such as products **16**, are relatively stable; useful as biological scaffolds, reactive intermediates and chiral ligands.[19,20] They can be synthesized by several routes, commonly by intramolecular ring-closing, ring expansion or ring contraction, and a few




**Scheme 6.** Proposed mechanisms for formation of products **16–19**.

intermolecular methods are known.[19–21] Further chemical transformations of the azetidine moiety are useful in organic synthesis.[20] A few copper-catalyzed [2 + 2] cycloadditions between allenes and imines are reported to give azetidines.[20,22] The presently reported gold(I)-catalyzed [2 + 2] cycloaddition of propargyl acetal **10** and imines **15a,b** via *in situ* generated allene **13** represents a novel synthetic pathway to azetidines.

The reaction of polarized imine **15a** with diene **14** also generated the [2 + 4] cycloaddition by-product **17b** (21%, Table 4, entry 1 and Scheme 6b), while the more polarized and electron-rich **15 b** followed an unusual competing [3 + 4] cycloaddition, involving the e-rich MeO-phenyl unit to give the benzazepine-type by-product **18** via an uncommon gold-carbenoid **II** (18%, Table 4, entry 2 and Scheme 6c). This product is similar to the [2 + 5] cycloaddition product **21** formed with imine and terminal aryl-propargyl acetals, reported in earlier studies,[3] but the mechanism is different. The *trans* stereochemistry of heterocyclic products **16–18** was established from NMR NOE correlations between the respective substituents on the ring. The *Z*-configuration of **16** was based on NOE correlations between the relevant benzylidene protons and the $R_1$-aryl and Me/MeO groups.

Reaction with the less polarized and more electron-rich methoxy-phenyl imine **15c** followed a different reaction pathway than the cycloaddition seen for the polarized imine **15a** (Scheme 6b). The main product was a fully conjugated *E,E,E*-pentadien-1-imine **19** (29%, Table 4, entry 3), which may be formed by diene **14** attack on imine **15c**, followed by hydride shift and methanol elimination (Scheme 6d). The *E,E,E*-configuration of product **19** was assigned based on $^1$H NMR coupling constants and NOE correlations. Reaction with very electron-rich aldimine **15d** gave no products, indicating that the polarization of the imine bond is important to enable nucleophilic attack on the imine.

## Conclusions

Two novel chiral menthol-based pyridyl nitrones **6a** and **6b** were synthesized. Au(I)–nitrone complexes (**I–6a** and **I–6b**) were prepared by coordination of ligands **6a** and **6b** to JohnPhosAu(ACN)$SbF_6$ complex **I**. $^1$H NMR coordination studies indicated that the new nitrones coordinated poorer to Au(I) than previously studied nitrones, probably due to the bulk of the chiral menthol-based substituent, as well as the competing intramolecular hydrogen-bonds in non-methylated ligand **6a**.

The catalytic effect of Au(I)–nitrones **6a** and **6b** was evaluated in [2 + 2 + 2] cyclotrimerization and [2 + 4] cyclodimerization reactions. Complex **I–6b** gave highest yield (73%, entry 3), similar to the best yields reported previously (74%, nitrone **6c** with counterion $NTf_2$).[8] The obtained diastereoisomeric ratio of the Au(I)–nitrone catalyzed cyclotrimerization products **2** from diaryl-propargyl substrate **1**, was different than in previous studies,[8] indicating that the nitrones have a special effect in this particular reaction. Chiral HPLC analysis of trimeric products **2a–c** failed to give enantioseparation. Methyl-aryl-propargyl acetal **10** followed a different dimerization reaction pathway, based on *in situ* generated allene **13** and diene **14** intermediates, compared to the trimerization of diaryl-propargyl substrate **1**. The Au(I) nitrone complex **I–6c** afforded the

cyclic dimer **12** by a Diels-Alder-like [2 + 4] cycloaddition from methyl-aryl-propargyl **10**, in contrast to Au(I) complex **I**, producing the open dimer **11**.

Alternative pathways of non-terminal methyl-aryl propargyl acetal **10** were explored by testing the ability to undergo possible gold(I)-catalyzed cycloaddition reactions with different imines. Specific [2 + 2], [2 + 4] and [3 + 4] cycloaddition reactions of imines **15a–d** with *in situ* generated allene **13** and diene **14** intermediates from acetal **10** gave a diverse range of *N*-heterocyclic products **16–19** (18–30%). Mechanistic discussions of the selective reaction pathways are presented.

The present screening study demonstrates the potential and the versatility of non-terminal propargyl acetals in gold(I) catalyzed cycloaddition reactions. Further optimization of reaction conditions, substrate variation and gold catalyst tuning may give improved yields and more efficient synthetic methods for preparation of selective cycloaddition products.

## Experimental

### *(1S,2S,5R)-2-Isopropyl-5-methyl-1-(pyridin-2-yl)cyclohexanol (5a)*

Butyllithium (2.0 M in cyclohexane, 2.9 mL, 5.8 mmol) under inert atmosphere was cooled to 0 °C and 2-(dimethylamino)ethanol (0.29 mL, 2.9 mmol) in dry heptane (2 mL) was added slowly. The mixture was stirred at the same temperature for 15 min. The mixture was then cooled to −78 °C and pyridine (0.12 mL, 1.5 mmol) in dry heptane (2 mL) was added. The mixture became bright orange over 30 mins, then (2S,5R)−2-isopropyl-5-methylcyclohexanone (0.50 mL, 2.9 mmol) in dry THF (5 mL) was added slowly. The mixture was stirred at this temperature for 1 h. The reaction was quenched with sat. aq. $NH_4Cl$ (25 mL) and extracted with DCM (3 × 25 mL), dried with brine and $Na_2SO_4$, filtered and evaporated *in vacuo*. Flash chromatography (1:1 DCM:pentane) gave the desired product as a colorless oil (114.6 mg, 33%). $^1H$ and $^{13}C$ NMR data were in accordance with published literature.[9]

### *2-((1S,2S,5R)-2-Isopropyl-1-methoxy-5-methylcyclohexyl)pyridine (5 b)*

Compound **5a** (114.6 mg, 0.491 mmol) in dry THF (3 mL) was added dropwise to a suspension of NaH (93.8 mg, 3.91 mmol) in dry THF (12 mL). The mixture was stirred at r.t. for 30 mins then MeI (0.30 ml, 4.8 mmol) was added and the solution was stirred at r.t. for 3 h. The reaction was quenched carefully dropwise with sat. aq. $NH_4Cl$ (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried with sat. aq. NaCl (20 mL), dried over $Na_2SO_4$, filtered and evaporated *in vacuo*. Flash chromatography (1:30 EtOAc:pentane) gave **5b** as a colorless oil (119.6 mg, 99%). $[\alpha]20\ D = -51.1°$ (*c* 1.01, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.61 (ddd, 1H, $J = 4.8/1.7/0.9$ Hz, $NCH_{Ar}$), 7.65 (td, 1H, $J = 7.8/1.8$ Hz, $CH_{Ar}$), 7.45 (dt, 1H, $J = 7.9/1.0$ Hz, $CH_{Ar}$), 7.12 (ddd, 1H, $J = 7.4/4.8/1.2$ Hz, $CH_{Ar}$), 3.22 (s, 3 H, $OCH_3$), 2.03–1.94 (m, 2 H, $CH_3OCCH_2$), 1.85–1.82 (m, 1H, $CH_3OCCH_2CHCH_2$), 1.73–1.63 (m, 2 H, $CH_3CH$ and $CH_3OCCHCH_2$), 1.56–1.49 (m, 2 H, $(CH_3)_2CHCH$ and $CH_3OCCHCH_2$), 1.29 (sepd, 1H, $J = 6.9/1.5$ Hz, $(CH_3)_2CH$), 1.11 (qd, 1H, $J = 12.6/3.4$ Hz, $CH_3OCCH_2CHCH_2$), 0.96 (d, 3 H, $J = 6.5$ Hz, $CH_3$), 0.87 (d, 3 H, $J = 6.7$ Hz, $(CH_3)_2$), 0.58 (d, 3 H, $J = 6.9$ Hz,

$(CH_3)_2$); 13C NMR (100 MHz, $CDCl_3$): $\delta$ ppm 164.0, 149.4, 135.3, 121.5, 121.2, 84.8, 51.7, 50.3, 39.9, 35.2, 28.0, 26.5, 23.6, 22.4, 21.2, 18.2; HRMS (ASAP) calcd for $C_{16}H_{26}NO$ $[M+H]^+$ 248.2014, found 248.2012.

### 2-((1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methylcyclohexyl)pyridine 1-oxide (6a)

Compound **5a** (95.0 mg, 0.41 mmol) was dissolved in dry DCM (2 mL) under inert atmosphere at 0 °C. 3-chlorobenzoperoxoic acid (210.3 mg, 0.938 mmol) was added. The reaction mixture was stirred at 0 °C for 5 min then the ice bath was removed and the reaction was allowed to come to r.t. overnight (17.5 h). The reaction mixture was diluted with DCM (10 mL) and washed with aq. KOH (6 N, 3 × 5 mL) and the organic layer was dried over $Na_2SO_4$, filtered and the solvent evaporated *in vacuo*. Flash chromatography (1:1 EtOAc:pentane) gave **6a** as a colorless oil (82.0 mg, 81%). $[\alpha]20\ D = -79.4^\circ$ (*c* 1.01, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ ppm 8.58 (br s, 1H, OH), 8.20 (dd, 1H, $J$ = 6.5/0.8 Hz, $CH_{Ar}$), 7.38 (td, 1H, $J$ = 7.8/1.3 Hz, $CH_{Ar}$), 7.28 (dd, 1H, $J$ = 8.2/1.8 Hz, $CH_{Ar}$), 7.21 (td, 1H, $J$ = 6.9/2.0 Hz, 1H, $CH_{Ar}$), 2.43–2.39 (m, 1H, $CH_2COH$), 2.09–1.96 (m, 1H, CHCOH), 1.87–1.77 (m, 3 H, $CH_2CHCOH$ and $CH_2CH_2CHCOH$ and $CH(CH_3)_2$), 1.66–1.59 (m, 2 H, $CHCH(CH_3)_2$ and $CH_2CH_2CHCOH$), 0.98 (d, 3 H, $J$ = 6.7 Hz, $CH(CH_3)_2$), 0.93 (d, 3 H, $J$ = 7.0 Hz, $CH(CH_3)_2$), 0.87 (d, 3 H, $J$ = 6.7 Hz, $CHCH_3$); 13C NMR (100 MHz, $CDCl_3$): $\delta$ ppm 155.1 ($C_{Ar}$), 141.3 ($CH_{Ar}$), 127.8 ($CH_{Ar}$), 123.7 ($CH_{Ar}$), 123.6 ($CH_{Ar}$), 79.6 (COH), 47.8 ($CHCH(CH_3)_2$), 46.6 ($CH_2COH$), 35.0 ($CH_2CHCOH$), 27.8 ($CH(CH_3)_2$), 27.2 ($CHCH_3$), 23.8 ($CH(CH_3)_2$), 22.0 ($CHCH_3$), 21.1 ($CH_2CH_2CHCOH$), 18.7 ($CH(CH_3)_2$); HRMS (ASAP) calcd for $C_{15}H_{24}NO_2$ $[M+H]^+$ 250.1807, found 250.1809.

### General procedure for gold(I)-catalyzed reaction of propargyl acetal 10 and imines 15a-d

JohnPhosAu(ACN)$SbF_6$ (4.5 µmol) was dissolved in DCM (0.5 mL) and a mixture of acetal **10** (46 µmol) and the appropriate imine (0.138 mmol) in DCM (1 mL) was added. The reaction mixture was stirred at r.t. for 4 h, then the reaction was quenched with $NEt_3$ and solvent removed *in vacuo*. Product isolation and purification was done by silica chromatography (EtOAc:pentane).

**Supporting information:** Additional Supporting information with Full experimental detail, $^1$H and 13 C NMR spectra, may be found online in the Supplementary material.

## References

[1] Sperger, C. A.; Tungen, J. E.; Fiksdahl, A. Gold(I)-Catalyzed Reactions of Propargyl Esters with Vinyl Derivatives. *Eur. J. Org. Chem.* **2011**, *2011*, 3719–3722. DOI: 10.1002/ejoc.201100291.

[2] Iqbal, N.; Sperger, C. A.; Fiksdahl, A. Gold(I)-Catalysed Alkene Cycloaddition Reactions of Propargyl Acetals. *Eur. J. Org. Chem.* **2013**, *2013*, 907–914. DOI: 10.1002/ejoc.201201328.

[3] Iqbal, N.; Fiksdahl, A. Gold(I)-Catalyzed Benz[c]Azepin-4-ol Synthesis by Intermolecular [5 + 2] Cycloaddition. *J. Org. Chem.* **2013**, *78*, 7885–7895. DOI: 10.1021/jo401075n.

[4] Siah, H.-S. M.; Kaur, M.; Iqbal, N.; Fiksdahl, A. Gold(I)-Catalysed Tandem Cyclisation of Propargyl Acetals and Vinyl Esters. *Eur. J. Org. Chem.* **2014**, *2014*, 1727–1740. DOI: 10.1002/ejoc.201301674.
[5] Evjen, S.; Fiksdahl, A. Gold(I)-Catalysed [3 + 3] Cycloaddition of Propargyl Acetals and Nitrones. *Tetrahedron* **2016**, *72*, 3270–3276. DOI: 10.1016/j.tet.2016.04.058.
[6] Evjen, S.; Fiksdahl, A. Gold(I)-Catalysed Azepine Synthesis from Propargyl Acetals and Aryl Azides. *Eur. J. Org. Chem.* **2016**, *2016*, 2858–2863. DOI: 10.1002/ejoc.201600319.
[7] Siah, H.-S. M.; Hogsnes, M. C.; Iqbal, N.; Fiksdahl, A. Gold(I)-Catalysed Tandem Cyclization of Propargyl Acetals and Alkynes. *Tetrahedron* **2016**, *72*, 1058–1068. DOI: 10.1016/j.tet.2015.12.080.
[8] Jónsson, H. F.; Evjen, S.; Fiksdahl, A. Gold(I)-Catalyzed [2 + 2+2] Cyclotrimerization of 1,3-Diarylpropargyl Acetals. *Org. Lett.* **2017**, *19*, 2202–2205. DOI: 10.1021/acs.orglett.7b00411.
[9] Reiersølmoen, A. C.; Østrem, E.; Fiksdahl, A. Gold(III)-Catalysed Cis-to-Trans Cyclopropyl Isomerization. *Eur. J. Org. Chem.* **2018**, *2018*, 3317–3325. DOI: 10.1002/ejoc.201800419.
[10] Jónsson, H. F.; Fiksdahl, A. Studies on Gold–Nitrone Systems. *Dalton Trans.* **2019**, *48*, 142–149. DOI: 10.1039/C8DT04254C.
[11] Ulč, J.; Nečas, D.; Koukal, P.; Havlíček, V.; Tošner, Z.; Hybelbauerová, S.; Kotora, M. Chiral Unsymmetrically Substituted Bipyridine N,N′-Dioxides as Catalysts for the Allylation of Aldehydes. *Eur. J. Org. Chem.* **2018**, *2018*, 5109–5116. DOI: 10.1002/ejoc.201800485.
[12] Reep, C.; Morgante, P.; Peverati, R.; Takenaka, N. Axial-Chiral Biisoquinoline N,N′-Dioxides Bearing Polar Aromatic C–H Bonds as Catalysts in Sakurai-Hosomi-Denmark Allylation. *Org. Lett.* **2018**, *20*, 5757–5761. DOI: 10.1021/acs.orglett.8b02457.
[13] Siah, H.-S. M.; Fiksdahl, A. Dual-Gold(I)-Generated Trifluoromethylation of Terminal Alkynes with Togni's Reagent. *J. Fluorine Chem.* **2017**, *197*, 24–33. DOI: 10.1016/j.jfluchem.2017.01.004.
[14] Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010**, *29*, 2176–2179. DOI: 10.1021/om100106e.
[15] Brown, T. J.; Robertson, B. D.; Widenhoefer, R. A. Synthesis and X-Ray Crystal Structure of a Cationic Gold (I) $\pi$-(1,3-Diene) Complex Generated via Isomerization of a Gold $\pi$-Allene Complex. *J. Organomet. Chem.* **2014**, *758*, 25–28. DOI: 10.1016/j.jorganchem.2014.01.030.
[16] Jones, A. C. Gold $\pi$-Complexes as Model Intermediates in Gold Catalysis. In *Homogeneous Gold Catalysis*; Slaughter, L. M., Ed. Springer International Publishing: Cham, 2015; pp 133–165.
[17] Li, H.; Harris, R. J.; Nakafuku, K.; Widenhoefer, R. A. Kinetics and Mechanism of Allene Racemization Catalyzed by a Gold N-Heterocyclic Carbene Complex. *Organometallics* **2016**, *35*, 2242–2248. DOI: 10.1021/acs.organomet.6b00307.
[18] Takasu, K.; Shindoh, N.; Tokuyama, H.; Ihara, M. Catalytic Imino Diels-Alder Reaction by Triflic Imide and Its Application to One-Pot Synthesis from Three Components. *Tetrahedron* **2006**, *62*, 11900–11907. DOI: 10.1016/j.tet.2006.09.092.
[19] Mehra, V.; Lumb, I.; Anand, A.; Kumar, V. Recent Advances in Synthetic Facets of Immensely Reactive Azetidines. *RSC Adv.* **2017**, *7*, 45763–45783. DOI: 10.1039/C7RA08884A.
[20] Takizawa, S.; Arteaga, F. A.; Yoshida, Y.; Suzuki, M.; Sasai, H. Organocatalyzed Formal [2 + 2] Cycloaddition of Ketimines with Allenoates: Facile Access to Azetidines with a Chiral Tetrasubstituted Carbon Stereogenic Center. *Org. Lett.* **2013**, *15*, 4142–4145. DOI: 10.1021/ol401817q.

[21] Łysek, R.; Furman, B.; Kałuża, Z.; Frelek, J.; Suwińska, K.; Urbańczyk-Lipkowska, Z.; Chmielewski, M. [2 + 2] Cycloaddition of Chlorosulfonyl Isocyanate to Allenyl-Sugar Ethers. *Tetrahedron: Asymmetry* **2000**, *11*, 3131–3150. DOI: 10.1016/S0957-4166(00)00260-3.

[22] Akiyama, T.; Daidouji, K.; Fuchibe, K. Cu(I)-Catalyzed Enantioselective [2 + 2] Cycloaddition of 1-Methoxyallenylsilane with α-Imino Ester: Chiral Synthesis of α,β-Unsaturated Acylsilanes. *Org. Lett.* **2003**, *5*, 3691–3693. DOI: 10.1021/ol0353621.