Stereoselective Gold(I)-Catalyzed Intermolecular Hydroalkoxylation of Alkynes

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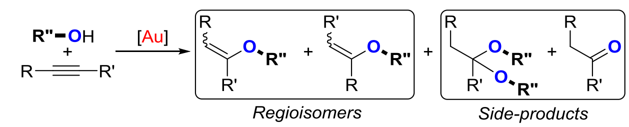
ABSTRACT: We report the use of cationic gold complexes [Au(NHC)(CH_3CN)][BF_4] and [{Au(NHC)}$_2$(μ-OH)][BF_4] (NHC = N-heterocyclic carbene) as highly active catalysts in the solvent-free hydroalkoxylation of internal alkynes using primary and secondary alcohols. Using this simple protocol, a broad range of (Z)-vinyl ethers were obtained in excellent yields and high stereoselectivities. The methodology allows for the use of catalyst loadings as low as 200 ppm for the addition of primary alcohols to internal alkynes (TON = 35 000, TOF = 2 188 h^{-1}).

KEYWORDS: gold, hydroalkoxylation, alkynes, vinyl ethers, solvent-free

The development of synthetic methods for the formation of C-O bonds is of great interest in synthetic organic chemistry. A very effective approach is the addition of alcohol O-H bonds across unsaturated C-C bonds in inter- or intramolecular fashion to provide ethers.[1] To avoid the use of harsh reaction conditions[2] and/or the need for strong bases,[3] these hydroalkoxylation reactions are usually performed employing metal-catalyzed conditions. Numerous procedures have been developed that make use of complexes of Cu,[4] Zn,[5] Hg,[6] Ru,[7] Rh,[8] Ir,[9] Pd,[10] Pt,[11] Au,[12] or Th[13] as catalysts. These catalytic procedures are desirable over substitution reactions (that would form the same products) because the method avoids the generation of stoichiometric amounts of waste.[14]

The rapid growth of the field of homogeneous gold catalysis has resulted in the development of a vast number of gold-catalyzed organic transformations, most of which rely on the ability of cationic gold complexes to activate unsaturated C-C bonds.[15] While gold-catalyzed intramolecular hydroalkoxylation reactions have been successfully employed in the synthesis of various heterocycles[16] and natural products,[17] reports on the more challenging intermolecular hydroalkoxylation reactions remain scarce.[18] Teles and co-workers were the first to report intermolecular hydroalkoxylation of terminal alkynes.[18a] The groups of Corma and Sahoo later achieved the addition of secondary and tertiary alcohols as well as phenols to internal alkynes.[18b, 18c] These reports have established that internal alkynes are more challenging substrates in hydroalkoxylation reactions compared to their terminal congeners. While mono-addition to alkynes had already been demonstrated to be difficult, other challenges remain in terms of chemoselectivity, stereoselectivity, regioselectivity and substrate scope (Scheme 1).

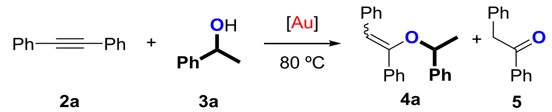
Scheme 1. Common side-products formed in hydroalkoxylation reactions.



Cationic gold complexes [Au(NHC)(CH_3CN)][BF_4] and [{Au(NHC)}$_2$(μ-OH)][BF_4] (NHC = N-heterocyclic carbene) have been demonstrated to be highly active catalysts in various silver- and acid-free gold-catalyzed transformations.[19] Herein, we showcase their efficiency to achieve good chemo- and stereoselectivity in hydroalkoxylation reactions of internal alkynes.

We first examined the addition of 1-phenylethanol (**3a**) to diphenylacetylene (**2a**), catalyzed by 1 mol% [{Au(IPr)}$_2$(μ-OH)][BF_4] (**1a**) in toluene at 80 °C (Table 1, entry 1). After 18 hours, full conversion was observed (as monitored by GC) with high chemoselectivity, 90% of the desired vinyl ether **4a** and only 10% of its corresponding hydrolysis product **5**,[18c, 18d, 20] and stereoselectivity of 98% (*Z*)-**4a**. To the best of our knowledge, hydroalkoxylation reactions have not been reported previously with secondary benzylic alcohols.[18c] Moreover, we were delighted to see that the corresponding acetal, resulting from the addition of two molecules of **3a** to **2a,** was not detected. Interestingly, the use of Gagosz-type monogold [Au(IPr)(NTf_2)],[21] resulted in poor reactivity (Table 1, entry 2). Gratifyingly, better chemoselectivity and faster reactions were obtained under solvent-free conditions (Table 1, entry 3). Other NHC ligands were then tested using lower catalyst loading (0.3 mol%, Table 1, entries 4-6). Catalysts **1a** and **1b** bearing IPr and SIPr ligands gave very similar chemoselectivities. The catalyst bearing the least electron-donating NHC ligand, IPr^{Cl}, [{Au(IPr^{Cl})}$_2$(μ-OH)][BF_4] (**1c**) enhanced the reactivity but reduced the chemoselectivity. The use of solvate monogold complexes [Au(NHC)(CH_3CN)][BF_4] **1d** and **1e** as catalysts led to a large decrease in chemoselectivity (Table 1, entries 7-8). We concluded that the hydroalkoxylation reaction could be performed most effectively using 0.3 mol% of [{Au(SIPr)}$_2$(μ-OH)][BF_4] (**1b**) or [{Au(IPr^{Cl})}$_2$(μ-OH)][BF_4] (**1c**) at 80 °C under solvent-free conditions. Indeed, after carrying out these hydroalkoxylation reactions for 2 hours (Table 1, entries 9-10), the desired vinyl ether **4a** was formed with high chemoselectivity and stereoselectivity, 96% and 95% (*Z*)-**4a**, respectively.

Table 1. Catalyst screening with NHC-gold(I) complexes.[a]



entry	catalyst (loading in mol%)	t (h)	conversion (%)[b] (4a/5)[c]
1[d]	[{Au(IPr)}$_2$(μ-OH)][BF$_4$] **1a** (1)	18	>99 (9/1)
2[d]	[Au(IPr)(NTf$_2$)] (2)	18	7
3	[{Au(IPr)}$_2$(μ-OH)][BF$_4$] **1a** (1)	1	>99
4	[{Au(IPr)}$_2$(μ-OH)][BF$_4$] **1a** (0.3)	0.5	51 (32/1)
5	[{Au(SIPr)}$_2$(μ-OH)][BF$_4$] **1b** (0.3)	0.5	63 (31/1)
6	[{Au(IPr^{Cl})}$_2$(μ-OH)][BF$_4$] **1c** (0.3)	0.5	86 (17/1)
7	[Au(IPr)(CH$_3$CN)][BF$_4$] **1d** (0.6)	0.5	51 (2/1)
8	[Au(IPr^{Cl})(CH$_3$CN)][BF$_4$] **1e** (0.6)	0.5	74 (1/1)
9	[{Au(SIPr)}$_2$(μ-OH)][BF$_4$] **1b** (0.3)	2	>99 (9/1)
10	[{Au(IPr^{Cl})}$_2$(μ-OH)][BF$_4$] **1c** (0.3)	2	>99 (8/1)

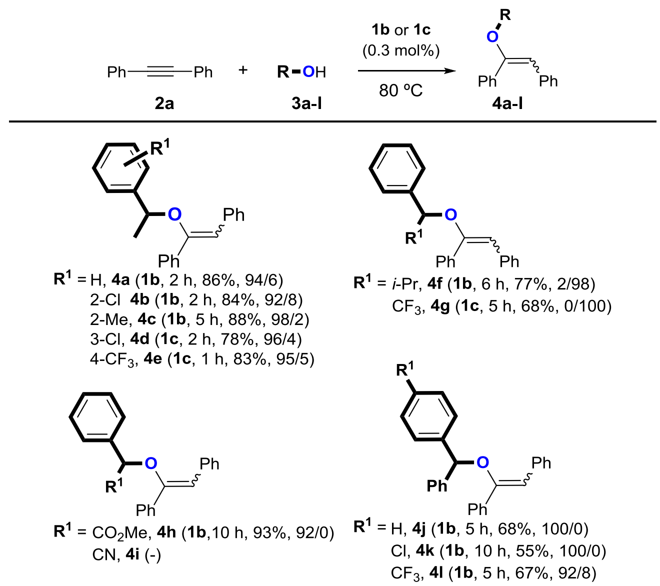
[a]Reaction conditions: **2a** (0.50 mmol), **3a** (0.55 mmol, 1.1 equiv.), neat, 80 °C, in air. [b]Determined by GC analysis, with respect to **2a**. [c]Determined by ^{1}H NMR spectroscopy. [d]Reaction in 1M PhCH$_3$.

We evaluated the performance of both **1b** and **1c** in the hydroalkoxylation reactions of diphenylacetylene (**2a**) with various secondary benzylic alcohols **3a-l** (Scheme 2). Substituents at the *ortho*, *meta* and *para* positions of the aryl group of 1-phenylethanol derivatives were tolerated and the corresponding vinyl ethers **4a-e** were obtained in good yields. Interestingly, the electronic properties of the aryl group of the alcohol did not affect the stereoselectivity of the reaction and the (*Z*)-isomer was obtained predominantly in all cases. Importantly, the hydroalkoxylation reaction of (*S*)-1-phenylethanol was found to produce one enantiomer of the vinyl ether with **1b** or **1c** as catalysts.

Changing the methyl moiety at the α'-position of the alcohol (**3f-i**) required longer reaction times for the transformation to reach completion. Interestingly, substitution of this methyl group with an isopropyl (**3f**) or trifluoromethyl (**3g**) group led to a reversal in selectivity and gave instead (*E*)-vinyl ethers **4f** and **4g** as main products. We hypothesized that this change in selectivity was linked to the electronic nature of the substituent in the α'-position. The addition of methyl mandelate **3h** to **2a**, however, resulted again in the predominant formation of (*Z*)-vinyl ether **4h**. Mandelonitrile **3i** did not undergo the reaction, most likely because of competitive coordination of the catalyst to the triple bond of the nitrile moiety. We also tested benzhydrol (**3j**) and derivatives **3k-l** under these reaction conditions. Longer reaction times were required to reach completion in these instances, as these possess increased steric bulk. Nonetheless, the corresponding (*Z*)-vinyl ethers **4j-l** were obtained in modest yields with excellent stereoselectivities.

The reactivity of various symmetrical and unsymmetrical internal alkynes 2b-j was evaluated next (Scheme 3). Despite the need for longer reaction times,[22] the hydroalkoxylation reactions of unsymmetrical diaryl-substituted alkynes **2b-f** proceeded well. The corresponding vinyl ethers **4m-p** were isolated in good yields as mixtures of regioisomers with high stereoselectivity favoring the (*Z*)-isomer. A preferential addition to the less electron-rich center was observed when NO$_2$ or MeO substituents were present, (alkynes **2b-c**, vinyl ethers **4m-n**), while a 1:1 mixture of regioisomers was obtained with 1-chloro-4-(phenylethynyl)benzene (alkyne **2d**, vinyl ether **4o**) that lacks such a substituent. With both MeO and Cl substituents at the para positions of the phenyl rings (alkyne **2e**, vinyl ether **4p**), the preference of addition to the less electron-rich center was restored.

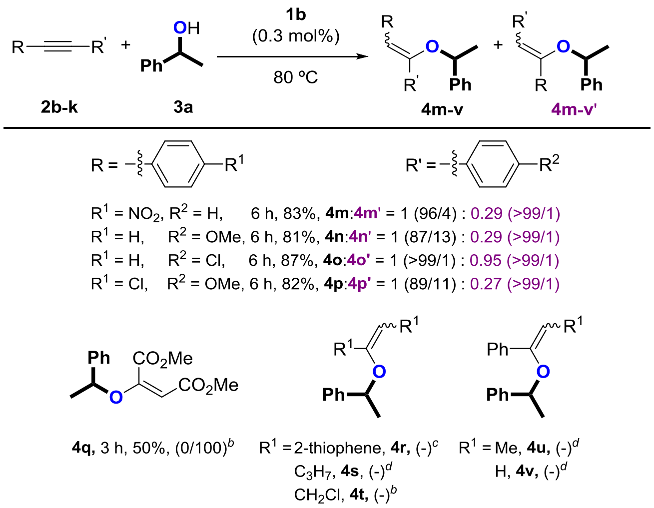
Scheme 2. Hydroalkoxylation of alkynes using various secondary benzylic alcohols.[a]



[a]Reaction conditions: **2a** (0.50 mmol), **3a–o** (0.55 mmol, 1.1 equiv.), **1b** or **1c** (0.3 mol%), neat, 80 °C, in air. The catalyst giving the best result, reaction time, yield of isolated product and Z/E ratio of product are given in parentheses. The results for the other catalyst are given in the ESI.

Next, hydroalkoxylation with symmetrical alkynes was evaluated. The reaction of strongly activated dimethylacetylene dicarboxylate (DMAD, **2f**) with **3a** afforded a 1:1 mixture of the desired vinyl ether **4q**, with complete stereoselectivity towards the (*E*)-vinyl ether, along with alcohol condensation side-product (oxybis(ethane-1,1-diyl))dibenzene.[23] In agreement with the report of Teles and co-workers, the hydroalkoxylation reactions of 1,4-bis(2-thiophene)butyne **2g**, 4-octyne **2h** and 1,4-dichlorobutyne **2i** to form vinyl ethers **4r-t** were unsuccessful under these reaction conditions.[18a] Replacing one phenyl group of diphenylacetylene **2a** with a methyl (**2j**) hampered the hydroalkoxylation reaction and led to the formation of a complex mixture of products instead of the vinyl ether **4u**. The hydroalkoxylation reaction of phenylacetylene **2k** led to the formation of a complex mixture of products. Digold hydroxide catalysts [{Au(NHC)}$_2$(μ-OH)][BF$_4$] are known to be able to dissociate into a Lewis acidic [Au(NHC)][BF$_4$] and a Brønsted basic [Au(NHC)(OH)] components.[24] Competitive deprotonation of the acetylenic proton of phenylacetylene by the latter might explain the incompatibility with this substrate.[25] Attempts to form vinyl ether **4v** by using non-Brønsted basic catalysts **1d** or **1e**, however, were unsuccessful and ketone **5** and (oxybis(ethane-1,1-diyl))dibenzene formed as the sole products.

Scheme 3. Substrate scope for the hydroalkoxylation of alkynes using various symmetrical/unsymmetrical alkynes.[a]



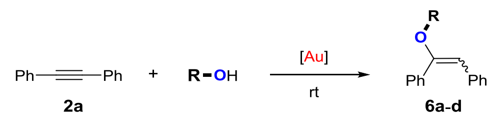
[a]Reaction conditions: **2b**-**2k** (0.50 mmol), **3a** (0.55 mmol, 1.1 equiv.), **1b** (0.3 mol%), neat, 80 °C, in air. Reaction time and yield are given. *Z*/*E* ratios are given in parentheses. [b]Alcohol condensation side-product (oxybis(ethane-1,1-diyl))dibenzene was observed as the major product. [c]**5** was observed as the major product. [d]A complex mixture formed.

To assess the efficiency of catalyst **1b**, once the reaction between alkyne **2a** and alcohol **3a** was complete, iterative additions of both substrates (0.5 and 0.55 mmol, respectively) were performed. As a result, 2.5 mmol of **2a** was converted to **4a** over 12 hours affording a high turnover number (TON) of 840 and a modest turn over frequency (TOF) of 70 h^{-1}. In addition, the performance of the new digold hydroxide catalyst (**1c**) was evaluated by conducting the hydroalkoxylation reaction between **2a** (5.0 mmol) and **3a** (5.5 mmol) on a gram scale using 0.3 mol% **1c**. This reaction afforded vinyl ether **4a** in excellent yield (1.4 g, 94%) without loss of stereoselectivity (*Z*/*E* = 98/2).

Previous studies examining gold-catalyzed hydroalkoxylation reactions have used aliphatic alcohols such as MeOH, *i*-PrOH, *n*-BuOH and BnOH as model substrates.[18a, 18c] Their addition to diphenylacetylene (**2a**) proceeded smoothly at room temperature using **1c** as catalyst and the corresponding vinyl ethers were obtained in excellent yields and selectivities (Table 2). As reported previously, the reactivity increases from *i*-PrOH to MeOH by one order of magnitude (Table 2, entries1 and 4).[18a] These results constitute a significant improvement compared to previous catalyst systems with regards to reaction conditions, catalyst loading and chemo- and stereoselectivity.[18c]

We compared the performance of monogold catalyst **1e** to digold hydroxide catalyst **1c** for the addition of MeOH to diphenylacetylene (**2a**). We found that **1e** was more active in the addition of MeOH than digold hydroxide **1c**, but the selectivity towards the (*Z*)-vinyl ether decreased to 85% (Table 2, entry 5). We found that monogold catalyst **1e** was much more active than digold **1c** when the catalyst loading was drastically decreased (Table 2, entries 6-7). Indeed, while the formation of vinyl ether **6d** stopped after 50% conversion using 250 ppm of digold **1c**, this product could be isolated in quantitative yield and complete stereoselectivity *after 16 h using only 200 ppm of monogold catalyst **1e***. This catalyst loading enables a very high *TON of 35 000 and a TOF of 2 188 h^{-1}*.

Table 2. Addition of aliphatic alcohols to diphenylacetylene 2a.[a]



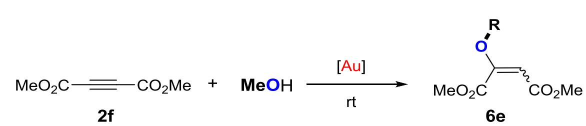
entry	R-OH	catalyst (mol%)	t (h)	product	yield (%)[b] (*Z*/*E*)[c]
1	*i*-PrOH	**1c** (0.3)	12	**6a**	>99 (100/0)
2	*n*-BuOH	**1c** (0.1)	4	**6b**	96 (100/0)
3	BnOH	**1c** (0.3)	3	**6c**	98 (100/0)
4	MeOH	**1c** (0.3)	2	**6d**	98 (100/0)
5	MeOH	**1e** (0.6)	1	**6d**	96 (85/15)
6	MeOH	**1c** (0.025)	28	**6d**	50 (100/0)
7	MeOH	**1e** (0.020)	16	**6d**	>99 (100/0)

[a]Reaction conditions: **2a** (0.5 mmol), **3** (0.5 mmol, 1 equiv.), neat, in air. [b]Yield of isolated product. [c]Determined by ^{1}H NMR spectroscopy.

We continued to examine the difference between catalysts **1c** and **1e** at different loadings in the hydroalkoxylation reaction of MeOH and DMAD (**2f**) (Table 3). This transformation proceeded rapidly at room temperature and reached completion after 3 hours using either catalysts (Table 3, entries 1-2). Interestingly, the corresponding (*E*)-vinyl ether **6e** was obtained selectively. At reduced catalyst loadings, however, we observed the formation of (*Z*)-**6e** after 2 hours (*Z*/*E* = 15/85 at 55% conversion for digold catalyst **1c** and *Z*/*E* = 33/67 at 24% conversion for monogold catalyst **1e**), which was then predominantly converted to (*E*)-**6e** after prolonged reaction time (Table 3, entries 3-4). These results suggest that the hydroalkoxylation reaction and the subsequent isomerization are competitive processes.

Corma and co-workers have proposed a mechanism to account for the conversion of (*Z*)-vinyl ethers into (*E*)-vinyl ethers.[18c] This mechanism involves a *trans*-addition of a second molecule of alcohol to the (*Z*)-vinyl ether and subsequent *cis*-elimination to form the (*E*)-vinyl ether (Scheme 4). Alternatively, a thermal process or rotation around the C-C bond of the vinylgold intermediate could be envisioned.[26] This latter route would be particularly fast for vinyl ethers from DMAD because of its ability to be involved in keto-enol tautomerization.

Table 3. Addition of MeOH to DMAD 2f.[a]

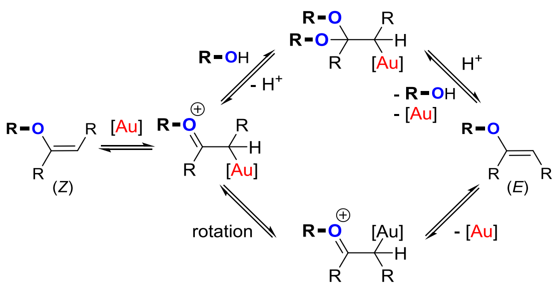


entry	catalyst (mol%)	t (h)	conversion [b] (%)(*Z*/*E*)[c]
1	**1c** (0.3)	3	>99 (4/96)
2	**1e** (0.6)	3	>99 (4/96)
3	**1c** (500 ppm)	6	87 (7/93)

4	**1e** (0.1)	6	34 (26/74)

[a]Reaction conditions: **2f** (0.5 mmol), MeOH (0.5 mmol, 1 equiv.), neat, in air. [b]Conversion with respect to **2f**. [c]Determined by ^{1}H NMR spectroscopy.

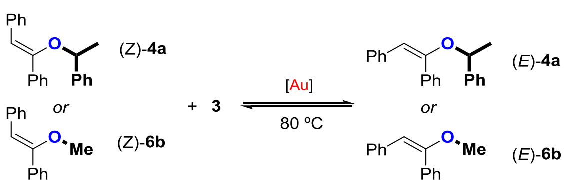
Scheme 4. Proposed isomerization of (Z)-vinyl ethers to (E)-vinyl ethers.[18c]



To shed light on the isomerization process, the direct isomerization reactions of pure vinyl ethers (*Z*)-**4a** and (*Z*)-**6d** catalyzed by digold catalyst **1c** and monogold catalyst **1e** were surveyed (Table 4). As expected from the high stereoselectivity obtained in reactions (Schemes 2-3) involving 1-phenylethanol (**3a**), isomerization of vinyl ether (*Z*)-**4a** was found to be slow (Table 4, entry 1).

Appreciable isomerization was only observed in the presence of 1-phenylethanol (**3a**) and monogold catalyst **1e** (Table 4, entries 2-3). We found that isomerization of (Z)-**6d** occurred spontaneously at 80 °C and was accelerated when catalytic amounts of either the mono- or digold hydroxide catalyst was added (Table 4, entries 4-6). No appreciable isomerization was observed at lower temperatures and the proposed acetal intermediates were never observed. These results suggest that the isomerization process from (Z)-vinyl ethers to (E)-vinyl ethers occurs spontaneously at elevated temperature and is accelerated by cationic gold species, but does not involve or require the addition of a second molecule of alcohol.

Table 4. Isomerization reactions of pure (Z)-4a and (Z)-6d.[a]

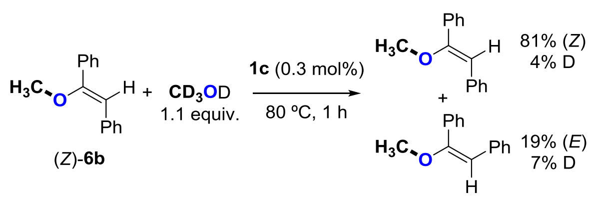


entry	ether	3 (equiv.)	Catalyst (mol%)	t (h)	*Z*/*E*[b]
1	(*Z*)-**4a**	**3a** (1.5)	none	24	100/0
2	(*Z*)-**4a**	**3a** (1.5)	**1c** (0.3)	24	96/4
3	(*Z*)-**4a**	**3a** (1.5)	**1e** (0.6)	24	89/11
4	(*Z*)-**6b**	none	none	1	93/7
5	(*Z*)-**6b**	none	**1c** (0.3)	1	80/20
6	(*Z*)-**6b**	none	**1e** (0.6)	1	80/20

[a]Reaction conditions: neat, in air. [b]Determined by ^{1}H NMR spectroscopy.

We further probed whether the vinyl ether products could be transformed into other vinyl ethers. To this end, we subjected vinyl-ether **6d** and CD_3OD to catalytic conditions (Scheme 5). Apart from the previously observed *Z*/*E* isomerisation, no formation of acetal or incorporation of CD_3 was observed. The reverse experiment, the reaction of d_4-**6d** with MeOH, gave an analogous result. The incorporation of small amounts of deuterium in the vinylic position suggests the formation of a alkylgold species (as in Scheme 4) that is subsequently deutero-deaurated under these conditions.

Scheme 5. Reaction of 6b with CD_3OD.[a]



[a]*Z*/*E* ratios are determined by ^{1}H NMR analysis, deuterium content was determined by ^{1}H NMR analysis and confirmed by ^{2}D NMR analysis.

In conclusion, we have demonstrated that both $[Au(NHC)(CH_3CN)][BF_4]$ and $[\{Au(NHC)\}_2(\mu\text{-}OH)][BF_4]$ complexes are highly effective catalysts for the stereoselective intermolecular hydroalkoxylation of alkynes. Their use under solvent-free conditions constitutes a practical, operationally simple and scalable strategy for the assembly of a range of new vinyl ethers in high yields. In particular $[Au(IPr^{Cl})(CH_3CN)][BF_4]$ (**1e**) has been shown to be highly active in the addition of aliphatic alcohols to internal alkynes. Experiments have also revealed that monogold and digold hydroxide catalysts display different behavior in the isomerization of the two stereoisomers of the vinyl ethers at different catalyst loadings. Further synthetic and mechanistic studies focusing on the catalytic uses of these complexes are ongoing in our laboratories.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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ASSOCIATED CONTENT

Supporting Information Available

Experimental procedures, optimization studies, mechanistic studies and characterization data. This information is available free of charge via the internet at http://pubs.acs.org.

ABBREVIATIONS

NHC, *N*-heterocyclic carbene;

IPr, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; SIpr, 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene; IPr^{Cl}, 4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)imid- azol-2-ylidene.

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Gold-NHC complexes have been shown as highly efficient catalysts in the hydroalkoxylation of unactivated internal alkynes. The methodology provides access to a broad range of vinyl ethers in high yields and stereoselectivity.