Stereoselective Gold(I)-Catalyzed Intermolecular Hydroalkoxlation of Alkynes

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Supporting Information

ABSTRACT: We report the use of cationic gold complexes [Au(NHC)(CH3CN)][BF4] and [{Au(NHC)}2(μ−OH)][BF4] (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 = 2188 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 conditions² 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 Th¹³ 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 heterocycles¹⁶ 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,c These reports have established that internal alkynes are more challenging substrates in hydroalkoxylation reactions compared to their terminal congeners. Although monoaddition 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)(CH3CN)][BF4] and [{Au(NHC)}2(μ−OH)][BF4] (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 chemoselectivity 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)][BF4] (1a) in toluene at 80 °C (Table 1, entry 1; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene). After 18 h, 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,d,²⁰ and stereoselectivity of 98% (Z)-4a. To the best of our knowledge, hydroalkoxylation reactions have not been reported previously.

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Table 1. Catalyst Screening with NHC-Gold(I) Complexes

| entry | catalyst | t (h) | conversion (%) |
|-------|----------|-------|----------------|
| 1d    | [Au(IPr)][(μ-CH2)] [BF4] 1a (1) | 18 | >99 (9/1) |
| 2d    | [Au(IPr)(NTf2)] (2) | 18 | 7 |
| 3     | [Au(IPr)][(μ-CH2)] [BF4] 1a (1) | 1 | >99 |
| 4     | [Au(IPr)][(μ-CH2)] [BF4] 1b (0.3) | 0.5 | 51 (32/1) |
| 5     | [Au(SIPr)][(μ-CH2)] [BF4] 1b (0.3) | 0.5 | 63 (31/1) |
| 6     | [Au(IPr)][(μ-CH2)] [BF4] 1c (0.3) | 0.5 | 86 (17/1) |
| 7     | [Au(IPr)(CH3CN)][BF4] 1d (0.6) | 0.5 | 51 (2/1) |
| 8     | [Au(IPr)(CH3CN)][BF4] 1e (0.6) | 0.5 | 74 (1/1) |
| 9     | [Au(SIPr)][(μ-CH2)] [BF4] 1b (0.3) | 2 | >99 (9/1) |
| 10    | [Au(IPr)][(μ-CH2)] [BF4] 1c (0.3) | 2 | >99 (8/1) |

*a*SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene. Reaction conditions: 2a (0.50 mmol), 1a (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 1 M PhCH3.

with secondary benzylic alcohols.\(^{18\text{c}}\) 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)-(NTf2)]\(^{21}\), 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, 4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene ([IPrCl]([Au(IPrCl)]2(μ-CH2))[BF4] (1c)) enhanced the reactivity but reduced the chemoselectivity. The use of solvate monogold complexes [Au(NHC)(CH3CN)][BF4] (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)][(μ-CH2)] [BF4] (1b) or [[Au(IPr)][(μ-CH2)] [BF4] (1c) at 80 °C under solvent-free conditions. Indeed, after carrying out these hydroalkoxylation reactions for 2 h (Table 1, entries 9–10), the desired vinyl ether 4a was formed with high chemoselectivity and stereo-selectivity, 96% and 95% (Z)-4a, respectively.

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 chemoselectivity 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 stereo-selectivities.

The reactivity of various symmetrical and unsymmetrical internal alkynes 2b–j was evaluated next (Scheme 3). Despite the need for longer reaction times, 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 NO2 or MeO substituents were present, (alkynes 2b,c, vinyl ethers 4m,n), whereas 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.

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 stereo-selectivity toward the (E)-vinyl ether, along with alcohol condensation...
Table 2. Addition of Aliphatic Alcohols to Diphenylacetylene 2a^ab

| 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)       |

Reaction conditions: 2a (0.5 mmol), 3a (0.55 mmol, 1 equiv), neat, in air. bYield of isolated product. cDetermined by 1H NMR spectroscopy.

Table 3. Addition of MeOH to DMAD 2f

| entry | catalyst (mol %) | t (h) | conversionb (%) (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)              |

Reaction conditions: 2f (0.5 mmol), MeOH (0.5 mmol, 1 equiv), neat, in air. bConversion with respect to 2f. cDetermined by 1H NMR spectroscopy.
observed the formation of (Z)-6e after 2 h (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. 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).

Scheme 4. Proposed Isomerization of (Z)-Vinyl Ethers to (E)-Vinyl Ethers

Alternatively, a thermal process or rotation around the C–C bond of the vinylgold intermediate could be envisioned. This latter route would be particularly fast for vinyl ethers from DMAD because of its ability to be involved in keto–enol tautomerization.

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 and 3) involving 1-phenylethanol (3a), isomerization of vinyl ether (Z)-4a was found to be slow (Table 4, entries 1, 2). Appreciable isomerization was only observed in the presence of 1-phenylethanol (3a) and monogold catalyst 1e (Table 4, entry 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 the process does not involve or require the addition of a second molecule of alcohol.

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$_3$OD to catalytic conditions (Scheme 5).

Scheme 5. Reaction of (Z)-6d with CD$_3$OD

Apart from the previously observed Z/E isomerization, no formation of acetal or incorporation of CD$_3$O was observed. The reverse experiment, the reaction of d$_6$-6d with MeOH, gave an analogous result. The incorporation of small amounts of deuterium in the vinylic position suggests the formation of an alkyldgold species (as in Scheme 4) that is subsequently deuterodeaurated under these conditions.

In conclusion, we have demonstrated that both [Au(NHC)-(CH$_3$CN)]$\mu$[BF$_4$]$_2$ and [Au(NHC)$_2$($\mu$–OH)]$\mu$[BF$_4$]$_2$ 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 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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### Table 4. Isomerization Reactions of Pure (Z)-4a and (Z)-6d

| 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)-6d| none      | 1c (0.3)         | 1    | 93/7   |
| 5     | (Z)-6d| none      | 1e (0.3)         | 1    | 80/20  |
| 6     | (Z)-6d| none      | 1e (0.6)         | 1    | 80/20  |

$^a$Reaction conditions: neat, in air. $^b$Determined by $^1$H NMR spectroscopy.

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The authors declare no competing financial interest.
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