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The Regio- and Stereospecific Intermolecular Dehydrative Alkoxylation of Allylic Alcohols Catalyzed by a Gold(I) *N*-Heterocyclic Carbene Complex

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Abstract

A 1:1 mixture of (IPr)AuCl [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] and AgClO₄ catalyzes the intermolecular dehydrative alkoxylation of primary and secondary allylic alcohols with aliphatic primary and secondary alcohols to form allylic ethers. These transformations are regio- and stereospecific with preferential addition of the alcohol nucleophile at the γ -position of the allylic alcohol *syn* to the departing hydroxyl group and with predominant formation of the *E* stereoisomer. The minor α -regioisomer is formed predominantly through a secondary reaction manifold involving regioselective γ -alkoxylation of the initially formed allylic ether rather than via the direct α -alkoxylation of the allylic alcohol.

Keywords

Alcohols; Allylic compd.; Allylation; Au; Stereoselective catalysis

Introduction

Alkyl allylic ethers are found in a number of naturally occurring and biologically active compounds and are versatile building blocks for further synthetic manipulation.^[1] As a result, considerable effort has been directed toward the development of efficient and selective methods for the synthesis of allylic ethers.^[2,3] The transition metal-catalyzed alkoxylation of allylic alcohol derivatives represents an attractive route to allylic ethers with the potential to form C–O bonds under mild conditions and with high levels of regio- and stereocontrol.^[3,4] Indeed, Pd⁰,^[5] Rh^{II},^[6] Ru,^[7] and Ir^I^[8] complexes catalyze the alkoxylation of allylic carboxylates, carbonates, and related substrates with metal alkoxides, silanoates, alcohols, and phenols, and a number of these transformations occur with high enantioselectivity.

With the goal of condensing synthetic sequences and minimizing byproduct formation, there has been an ongoing interest in the utilization of underivatized allylic alcohols as electrophiles for the transition metal-catalyzed allylation of heteroatom nucleophiles.^[9] Regarding the formation of carbon–oxygen bonds, Pd^{II},^[10] Au^I,^[11–16] and Ru^{II}^[17] complexes catalyze the intramolecular dehydrative alkoxylation of allylic alcohols with simple alcohol nucleophiles. Conversely, the intermolecular alkoxylation of underivatized allylic alcohols remains an unsolved challenge in homogeneous catalysis. The most notable

example of such a transformation is the iridium(I)-catalyzed, regio- and enantioselective alkoxylation of secondary allylic alcohols with aliphatic alcohols to form secondary alkyl allylic ethers.^[18-20] However, given the ready access to regio- and stereochemically pure allylic alcohols,^[21] an effective method for the regio- and stereospecific conversion of substituted allylic alcohols to allylic ethers would also be significant, particularly if these transformations occurred with concomitant 1,3-allylic transposition.^[22]

We have recently reported the intermolecular dehydrative amination of allylic alcohols with imidazolidin-2-ones catalyzed by a mixture of (**1**)AuCl [**1** = P(*t*-Bu)₂*o*-biphenyl] and AgSbF₆.^[23,24] The γ -regiospecificity and *syn*-stereospecificity displayed by this transformation distinguished it from extant methods for the amination of allylic alcohols. In this context, we considered that a similar catalyst system might also effect the regiospecific and stereospecific intermolecular dehydrative alkoxylation of allylic alcohols with alcohol nucleophiles. Indeed, here we report the γ -regioselective and *syn*-stereospecific intermolecular alkoxylation of underivatized allylic alcohols with primary and secondary aliphatic alcohols catalyzed by a gold *N*-heterocyclic carbene complex.^[20]

Results and Discussion

Development of the Protocol

An initial experiment directed toward the gold(I)-catalyzed intermolecular dehydrative alkoxylation of allylic alcohols was encouraging. Treatment of a 1:4 mixture of *trans*-2-buten-1-ol and 4-methylbenzyl alcohol with a catalytic 1:1 mixture of (**1**)AuCl and AgSbF₆ in dioxane at room temperature for 48 h led to 53% conversion to form a 96:4 mixture of the γ -addition product **2a** and the α -addition product **3a** (Scheme 1).^[25] Substitution of AgSbF₆ with AgClO₄ led to 98% conversion after 25 h at room temperature to generate a 92:8 mixture of **2a** and **3a** (Scheme 1).

Unfortunately, continued experimentation revealed the shortcomings of the (**1**)AuCl/AgClO₄ catalyst system. For example, reaction of a 1:4 mixture of *trans*-4-hexen-3-ol and 4-methylbenzyl alcohol catalyzed by a 1:1 mixture of (**1**)AuCl and AgClO₄ in dioxane at room temperature for 24 h led to 85% conversion to form a 64:36 mixture of the γ -addition product **4** and the α -addition product **5** (Table 1, entry 1). To improve upon this result, the gold-catalyzed reaction of 4-methylbenzyl alcohol and *trans*-4-hexen-3-ol was screened as a function of supporting ligand, silver salt, and solvent (Table 1). Among the supporting ligands tested, the *N*-heterocyclic carbene ligand IPr gave the best combination of conversion (99%) and selectivity (75:25) after 24 h at room temperature (Table 1, entries 2-4). Among the different solvents screened utilizing the (IPr)AuCl/AgClO₄ catalyst mixture, methylene chloride and chloroform showed reactivity and selectivity comparable to that realized in dioxane (Table 1, entries 5-9). Among the silver salts tested, AgOTf, AgOTs, and AgPF₆ proved less effective than AgClO₄ (Table 1, entries 10-14). However, two experiments utilizing AgOTs pointed to a potential relationship between conversion and regioselectivity. Specifically, whereas reaction of 4-methylbenzyl alcohol with *trans*-4-hexen-3-ol catalyzed by (IPr)AuCl/AgOTs for 24 h gave 47% conversion with 92% selectivity for **4**, reaction for 4 h led to only 10% conversion, but with >99% selectivity for **4** (Table 1, entries 12 and 13).

Origin of the α - and γ -regioisomers in gold-catalyzed allylic alkoxylation

The conversion dependent regioselectivity of the reaction of 4-methylbenzyl alcohol with *trans*-4-hexen-3-ol catalyzed by (IPr)AuCl/AgOTs suggested that α -substitution product **5** was formed through a secondary process involving gold-catalyzed alkoxylation of γ -substitution product **4**. Supporting this contention, Aponick has shown that allylic ethers are

competent electrophiles for the gold(I)-catalyzed intramolecular allylation of alcohols.^[12] To more thoroughly probe for the presence of primary and secondary reaction pathways in the gold-catalyzed formation of **4** and **5**, a CD₂Cl₂ solution consisting of a 1:4 mixture of *trans*-4-hexen-3-ol and 4-methylbenzyl alcohol and a catalytic 1:1 mixture of (IPr)AuCl and AgClO₄ was analyzed periodically by ¹H NMR spectroscopy at room temperature. In accord with our expectations, the corresponding concentration versus time plot revealed rapid formation of **4** early in the reaction superimposed on slower formation of **5**, which led to degradation of the **4**:**5** ratio with increasing conversion (Figure 1). For example, **4** constituted 97% of the product mixture at 50% conversion, 91% of the product mixture at 85% conversion, and 82% of the product mixture at 100% conversion. Following complete consumption of *trans*-4-hexen-3-ol, the isomerization of **4** to **5** was apparent to ultimately generate an equilibrium ~1:1 mixture of the two regioisomers (Figure 1).

Periodic analysis of the gold-catalyzed reaction of *trans*-2-buten-1-ol and 4-methylbenzyl alcohol also revealed the rapid formation of γ -alkoxylation product **2a** superimposed on the slower, secondary formation of α -alkoxylation product **3a** (**2a**:**3a** = 95:5 at 63% conversion; **2a**:**3a** = 92:8 at 85% conversion; Figure S9). One additional experiment further established the reactivity of alkyl allylic ethers toward gold-catalyzed alkoxylation. Specifically, treatment of a 1:4 mixture of allylic ether **7a** with catalytic 1:1 mixture of (IPr)AuCl and AgClO₄ at room temperature for 24 h led to 63% conversion to the corresponding allylic ether **7b** (Scheme 2). Taken together, these experiments established that the gold-catalyzed reaction of 4-methylbenzyl alcohol with either *trans*-2-buten-1-ol or *trans*-3-penten-2-ol occurs with high γ -selectivity (>95%) and that the minor α -regioisomers are formed predominantly via secondary reaction pathways involving gold-catalyzed γ -alkoxylation of the initially formed allylic ether (Scheme 3).

Scope of Dehydrative Alkoxylation

The procedure used for the preparatory-scale, gold-catalyzed dehydrative alkoxylation of allylic alcohols draws from our observations regarding the intermolecular alkoxylation of *trans*-2-buten-1-ol and *trans*-3-penten-2-ol. Preparative-scale reactions were typically run with a four-fold excess of the nucleophilic alcohol to enhance the reaction rate and minimize self condensation and utilized the (IPr)AuCl/AgClO₄ catalyst system in methylene chloride at room temperature.^[25] Reactions were run to 80-95% conversion to maximize the formation of the primary γ -addition product while minimizing the formation of the α -addition byproduct generated in the secondary reaction manifold. In all cases, the minor α -regioisomer was removed by a single column chromatographic separation to provide the regiochemically pure γ -addition product in good to excellent yield.

The scope of the gold-catalyzed intermolecular alkoxylation of allylic alcohols was evaluated as a function of both the allylic and nucleophile alcohol component (Table 2). Intermolecular alkoxylation of primary (*E*)-allylic alcohols that contained a single methyl, ethyl or *n*-propyl substituent at the γ -position with primary or secondary alcohol nucleophiles led to isolation of the corresponding secondary allylic ethers **2**, **6**, and **8** in 79-95% yield as single regioisomers (Table 2, entries 1-7). Similarly, both (*E*)-**9** and (*Z*)-**9** that possessed a more electron deficient γ -benzyloxymethyl substituent underwent gold-catalyzed alkoxylation with *n*-butanol with complete regioselectivity, albeit in modest yield (Table 2, entries 8 and 9). This pair of transformations revealed no significant impact of the C=C bond geometry on the rate or regioselectivity of allylic alkoxylation. Further establishing the γ -regiospecificity of gold(I)-catalyzed allylic alkoxylation, gold-catalyzed alkoxylation of 3-buten-2-ol with 4-methylbenzyl alcohol formed the primary allylic ether **3a** in 98% yield with 89% regioselectivity, from which regiochemically pure **3a** was isolated in 85% yield as an 84:16 mixture of *E/Z* isomers (Table 2, entry 10).

We likewise explored the gold-catalyzed dehydrative alkoxylation of secondary allylic alcohols substituted at the γ -position. In addition to the gold-catalyzed formation of **4** from reaction of *trans*-4-hexen-3-ol and 4-methylbenzyl alcohol (Table 2, entry 11), gold-catalyzed alkoxylation of the mono-benzyl protected *trans*-2-pentene-1,4-diol **11** with either *n*-butanol or methanol led to isolation of 1,2-diethers **12** as single regioisomers in >75% yield (Table 2, entries 12 and 13). The analogous reaction of *n*-butanol with the mono-benzyloxy protected *trans*-2-pentene-1,4-diol **13** formed allylic ether **14** with 94% regioselectivity, but with diminished yield (Table 2, entry 14). 1,2-Dioxygenated compounds such as **12** and **14** are potentially important synthetic building blocks.^[24] Both the symmetrically disposed allylic alcohol (*E*)-pent-3-en-2-ol and the tertiary allylic alcohol 2-methyl-3-penten-2-ol also underwent efficient gold-catalyzed dehydrative alkoxylation to form allylic ethers **7** and **15**, respectively (Table 2, entries 15-17).

1,3-Chirality transfer in gold-catalyzed dehydrative alkoxylation

Efficient 1,3-chirality transfer from chiral, non-racemic secondary allylic alcohols has been previously observed in the gold(I)-catalyzed inter-^[23] and intramolecular^[27] dehydrative amination and intramolecular dehydrative alkoxylation of allylic alcohols^[13,14] We therefore sought to evaluate the extent of 1,3-chirality transfer in the gold-catalyzed intermolecular dehydrative alkoxylation of allylic alcohols. These experiments were conducted so that sufficient quantities of both the γ - and α -regioisomeric allylic ethers were isolated so that the stereoselectivity of both the primary and secondary reaction pathways could be evaluated. In one experiment, gold(I)-catalyzed reaction of (*R,E*)-**11** (98% *ee*) with *n*-butanol (4 equiv) at 40 °C for 24 h led to isolation of two chromatographic fractions. The first fraction consisted of an 8:1 mixture of (*R,E*)-**12a** (97% *ee*) and (*S,Z*)-**12a** (87% *ee*) in 81% combined yield and the second fraction consisted of a 7.2:1 mixture of (*R,E*)-**16** (97% *ee*) and (*S,Z*)-**16** (87% *ee*) in 15% combined yield (Scheme 4).^[28] A second experiment involving the gold-catalyzed reaction of (*R,Z*)-**11** (98% *ee*) with *n*-butanol likewise led to isolation of two chromatographic fractions. The first fraction consisted of a >50:1 mixture of (*S,E*)-**12a** (95% *ee*) and (*R,Z*)-**12a** (85% *ee*) in 81% combined yield and the second fraction consisted of a 6.2:1 mixture of (*S,E*)-**16** (94% *ee*) and (*R,Z*)-**16** (85% *ee*) in 19% combined yield (Scheme 5).^[28]

Several conclusions can be drawn from the gold-catalyzed alkoxylation of enantiomerically enriched (*R,E*)-**11** and (*R,Z*)-**11**. Firstly, high levels of chirality transfer were observed in the primary reaction pathway (**11** $\rightarrow$ **12a**) for both (*R,E*)-**11** and (*R,Z*)-**11**, particularly in the pathways leading to major diastereomer (*E*)-**12a**, which occurred with 97% transfer of chirality; the pathways leading to the minor diastereomer (*Z*)-**12a** occurred with ~88% chirality transfer. Also worth noting is the high *E*-selectivity of the alkoxylation of (*R,Z*)-**11**, which was not revealed by the alkoxylation of primary allylic alcohol (*Z*)-**9** (Table 2, entry 9). Secondly, the stereochemical outcome of these primary alkoxylation pathways, specifically the conversion of (*R,E*)-**11** to (*R,E*)-**12a** and (*S,Z*)-**12a** and the conversion of (*R,Z*)-**11** to (*S,E*)-**12a** and (*R,Z*)-**12a**, establish the net *syn*-displacement of the hydroxyl group by *n*-butanol. Thirdly, high levels of chirality transfer were likewise observed in the secondary reaction pathways that convert the initially formed γ -allylic ethers (*R,E*)-**12a**/*(S,Z)*-**12a** and (*S,E*)-**12a**/*(R,Z)*-**12a** to the regioisomeric α -allylic ethers (*R,E*)-**16**/*(S,Z)*-**16** and (*S,E*)-**16**/*(R,Z)*-**16**, respectively (97% chirality transfer leading to (*E*)-**16**, ~88% chirality transfer leading to (*Z*)-**16**). Fourthly, this stereochemical outcome likewise establishes the net *syn*-displacement of the butoxy group of (*E*)-**12a** or (*Z*)-**12a** by *n*-butanol.^[29] Together these observations indicate that the mechanism and origin of stereocontrol in the secondary alkoxylation pathway is similar to that of the primary alkoxylation pathway.

Brønsted- and Lewis acid-catalyzed pathways for dehydrative alkoxylation

The *syn*-stereoselectivity observed for the gold(I)-catalyzed alkoxylation of both (*R,E*)-**11** and (*R,Z*)-**11** with *n*-butanol is characteristic of a concerted S_N2' substitution reaction^[30] involving the σ -activation of the hydroxyl group by gold(I) or Brønsted acid generated under reaction conditions. Importantly, Toste has demonstrated that bis(gold) phosphine complexes are sufficiently Lewis acidic to acidify the hydroxyl group of an alcohol.^[31] For this reason, we investigated the efficiency and regio- and stereoselectivity of Brønsted- and Lewis acid-catalyzed pathways for intermolecular alkoxylation of allylic alcohols. In one experiment, a 1:4 mixture of (*R,E*)-**11** (98% *ee*) and *n*-butanol was treated with a catalytic amount of triflic acid (5 mol %) in methylene chloride at 40 °C and analyzed periodically by GC. After 5 h, 30% of (*R,E*)-**11** was consumed to form a 40:60 mixture of regioisomeric allylic ethers **12a** and **16**, indicating that both regioisomers were formed directly from **11** (Scheme 6).^[32] After 24 h, the regioisomeric ratio had not changed significantly (**12a**:**16** = 36:64) and purification of the reaction mixture at this time led to isolation of two chromatographic fractions. One fraction consisted of a 5.8:1 mixture of (*E*)-**12a** (10% *ee*) and (*Z*)-**12a** (<5% *ee*) in 22% combined yield while the second fraction consisted of (*E*)-**16** (8% *ee*) in 40% yield (Scheme 6). In a second experiment, treatment of a 1:4 mixture of (*R,E*)-**11** and *n*-butanol with a catalytic amount of BF₃·OEt₂ (5 mol %) in methylene chloride at 40 °C for 24 h generated a ~30:70 mixture of **12a** and **16** (Scheme 7). Purification of the reaction mixture led to isolation of two chromatographic fractions. One fraction consisted of a >50:1 mixture of (*E*)-**12a** (14% *ee*) and (*Z*)-**12a** (5% *ee*) in 22% combined yield while the second fraction consisted of (*E*)-**16** (5% *ee*) in 26% yield (Scheme 7).

Although HOTf catalyzed the intermolecular dehydrative alkoxylation of (*R,E*)-**11** with *n*-butanol, this transformation occurred with neither the regioselectivity nor stereoselectivity displayed by the gold(I)-catalyzed alkoxylation of (*R,E*)-**11**. Also worth noting is that triflic acid failed to catalyze the intermolecular alkoxylation of *trans*-2-buten-1-ol with 4-methylbenzyl alcohol.^[32] Therefore, HOTf is neither a selective nor general catalyst for the intermolecular dehydrative alkoxylation of allylic alcohols. Furthermore, there is no indication that the acidity of a gold-complexed hydroxyl group approaches that of triflic acid.^[31] Taken together, we can confidently rule out a mechanism for gold-catalyzed intermolecular alkoxylation involving σ -activation of the hydroxyl group by Brønsted acid. Similarly, because gold(I) is a much weaker and less oxophilic Lewis acid than is BF₃·OEt₂, the sluggish dehydrative alkoxylation of (*R,E*)-**11** catalyzed by BF₃·OEt₂ argues strongly against a mechanism for gold-catalyzed dehydrative alkoxylation involving σ -activation of the hydroxyl group by gold(I).

Mechanism of dehydrative alkoxylation

In 2010 we proposed a mechanism to account for the γ -regiospecificity and *syn*-stereospecificity of the gold(I)-catalyzed intermolecular dehydrative amination of allylic alcohols,^[23] which was inspired by the computational analyses of Maseras.^[33] This mechanism invoked initial π -complexation of the C=C bond of the allylic alcohol to gold followed by outer-sphere, *anti*-addition of the nucleophile facilitated by an intramolecular N–H...O hydrogen bond, *anti*-elimination of water, and decomplexation of gold.^[23] Aponick later invoked an analogous mechanism to account for the gold(I)-catalyzed intramolecular dehydrative alkoxylation of allylic alcohols^[13] and provided further support for this mechanism through a combined experimental/computational study.^[14] Therefore, it appears likely that a similar π -activation mechanism is responsible for the gold(I)-catalyzed intermolecular dehydrative alkoxylation of allylic alcohols. Complexation of gold to either of the diastereotopic C=C π -faces of (*R,E*)-**11** or (*R,Z*)-**11** followed by outer-sphere, *anti*-addition of *n*-butanol facilitated by an O–H...O hydrogen bond would form the gold σ -alkyl

intermediates **I** (Scheme 8). Subsequent *anti*-elimination of water and displacement of gold would form allylic ethers **12a** with γ -regioselectivity and net *syn*-stereoselectivity (Scheme 8).

In addition to accounting for the regio- and stereospecificity of gold-catalyzed intermolecular alkoxylation of (*R,E*)-**11** and (*R,Z*)-**11**, the proposed mechanism provides a rationale for the predominant formation of the (*E*)-**12a** stereoisomers in these transformations (Scheme 8). For example, in the gold(I)-catalyzed alkoxylation of (*R,E*)-**11**, intermediate **Ia**, which leads to major product (*R,E*)-**12a**, possess a *trans,trans* arrangement of the benzyloxymethyl, gold phosphine, and methyl groups, whereas in intermediate **Ib**, which leads to minor product (*S,Z*)-**12a**, the methyl group and gold phosphine moiety are arranged in a less favorable *cis* orientation (Scheme 8). Likewise, in the gold(I)-catalyzed alkoxylation of (*R,Z*)-**11**, intermediate **Ic**, which leads to major product (*S,E*)-**12a**, possesses a *cis,trans* arrangement of the benzyloxymethyl, gold phosphine, and methyl groups, whereas intermediate **Id**, which leads to minor product (*R,Z*)-**12a**, possesses a *cis,cis* arrangement of these groups and what appears to be a particularly destabilizing 1,3-diaxial interaction that may help explain the high *E/Z* selectivity (>50:1) observed in this transformation (Scheme 8).

Conclusion

In summary, we have developed a gold(I)-catalyzed method for the intermolecular dehydrative alkoxylation of primary and secondary allylic alcohols with primary and secondary aliphatic alcohols to form allylic ethers in good yield under mild conditions. These transformations occur via regio- and stereospecific addition of the alcohol nucleophile to the γ -position of the allylic alcohol on the C=C π -face *syn* to the departing hydroxyl group. Analysis of concentration versus time plots for the gold(I)-catalyzed alkoxylation of *trans*-4-hexen-3-ol and stereochemical analysis of the gold-catalyzed alkoxylation of (*R,E*)-**11** and (*R,Z*)-**11** revealed that the minor α -substitution products are formed predominantly through secondary reaction pathways involving γ -regiospecific and *syn*-stereospecific alkoxylation of the allylic ethers formed in the primary reaction pathway.

Experimental Section

1-((Hex-3-en-2-yloxy)methyl)-4-methylbenzene (**4**)

A mixture of (IPr)AuCl (9.3 mg, 1.5×10^{-2} mmol) and AgClO₄ (3.1 mg, 1.5×10^{-2} mmol) in CH₂Cl₂ (0.3 mL) was stirred at room temperature for 5 min. To this was added a solution of 4-methylbenzyl alcohol (147 mg, 1.20 mmol) and *trans*-4-hexen-3-ol (36 μ L, 0.30 mmol) in CH₂Cl₂ (0.2 mL), and the resulting mixture was stirred at 23 °C for 4 h. Flash column chromatography of the crude reaction mixture (pentane–CH₂Cl₂ = 4:1 $\rightarrow$ 1:1) gave **4** (47 mg, 76%, *E/Z* = 9.1:1) as a colorless oil. The *E*-configuration of the major stereoisomer of **4** was established by the vicinal olefinic sp²–sp² coupling constant of $^3J_{HH} = 15.6$ Hz in the ¹H NMR spectrum. TLC (hexanes–CH₂Cl₂ = 1:1): *R*_f = 0.47. ¹H NMR: δ = 7.23 (d, *J* = 8 Hz, 2 H), 7.14 (d, *J* = 7.6 Hz, 2 H), [5.66 (td, *J* = 6, 15.6 Hz), 5.55 (td, *J* = 7.6, 10.8 Hz), 9.1:1, 1 H], 5.38 (tdd, *J* = 1.6, 8, 15.6 Hz, 1 H), 4.51 (d, *J* = 12 Hz, 1 H), [4.33 (d, *J* = 12 Hz), 4.31 (d, *J* = 11.6 Hz), 9.1:1, 1 H], 3.87 (qd, *J* = 6.4, 7 Hz, 1 H), 2.34 (s, 3 H), 2.08 (qd, *J* = 7.6, 6.2 Hz, 2 H), [1.26 (d, *J* = 6.8 Hz), 1.24 (d, *J* = 6.8 Hz), 9.1:1, 3 H], [1.02 (t, *J* = 7.6 Hz), 0.98 (t, *J* = 7.6 Hz), 9.1:1, 3 H]. ¹³C{¹H} NMR: δ = 136.9, 135.9, 134.7, 130.9, 129.0, 127.8, 75.5, 69.4, 25.2, 21.7, 21.1, 13.6. IR (neat, cm^{−1}): 2967, 2928, 2863, 1454, 1369, 1074, 969, 910, 799, 732, 475. HRMS calcd (found) for C₁₄H₁₉ [(MH–H₂O)⁺]: 187.1481 (187.1178).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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28. The absolute configurations of (*E*)-**12a**, (*Z*)-**12a**, (*E*)-**16**, and (*Z*)-**16** were determined by HPLC correlation with authentic samples obtained through independent synthesis. Experiment procedures for the independent synthesis of (*R,E*)-**12a**, (*R,Z*)-**12a**, (*R,E*)-**16**, and (*R,Z*)-**16** are described in the Supporting Information.
29. Note the stereoconvergence of the secondary reaction manifold. *Syn*-selective alkoxylation of both (*R,E*)-**12a** and (*S,Z*)-**12a** form a mixture of (*R,E*)-**16** and (*R,Z*)-**16**. Likewise, *syn*-selective alkoxylation of both (*S,E*)-**12a** and (*R,Z*)-**12a** form a mixture of (*S,E*)-**16** and (*R,Z*)-**16**.
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Figure 1. Concentration versus time plot for the reaction of a 1:4 mixture of *trans*-4-hexen-3-ol () with 4-methylbenzyl alcohol catalyzed by a 1:1 mixture of (IPr)AuCl and AgClO₄ (5 mol %) in CD₂Cl₂ at room temperature to form **4** (□) and **5** (Δ).

Scheme 1. Gold-catalyzed alkoxylation of *trans*-2-buten-1-ol with 4-methylbenzyl alcohol.

Scheme 2.

Gold-catalyzed alkoxylation of allylic ether **7a** with benzyl alcohol.

Scheme 3.

Minor regioisomer **5** is formed primarily via secondary γ -alkoxylation of **4** and not through direct α -alkoxylation of trans-3-penten-2-ol.

Scheme 4.

Stereochemical analysis of the gold-catalyzed reaction of (*R,E*)-**11** with *n*-butanol.

Scheme 5.

Stereochemical analysis of the gold-catalyzed reaction of $(R,Z)\text{-11}$ with n -butanol.

Scheme 6.

Regio- and stereochemical outcomes of the triflic acid catalyzed intermolecular alkoxylation of $(R,E)\text{-11}$.

Scheme 7.

Regio- and stereochemical outcomes of the $\text{BF}_3 \cdot \text{OEt}_2$ catalyzed intermolecular alkoxylation of (R,E) -**11**.

Scheme 8.

Proposed mechanism for the gold-catalyzed γ -regioselective and *syn*-stereoselective alkoxylation of (R,E) -11 and (R,Z) -11.

Table 1

Effect of ligand, counterion and reaction conditions on the gold(I)-catalyzed intermolecular allylic alkoxylation of *trans*-4-hexen-3-ol with 4-methylbenzyl alcohol.

Entry	L	Solvent	X ⁻	Time [h]	Conv'n/yield [%][a]	4:5[b]
1	1	dioxane	ClO ₄ ⁻	24	85 (81)	64:36 (67:33)
2	IPr	dioxane	ClO ₄ ⁻	24	99 (90)	75:25 (75:25)
3	PPh ₃	dioxane	ClO ₄ ⁻	24	100 (89)	55:45 (55:45)
4	P(<i>n</i> -Bu) ₃	dioxane	ClO ₄ ⁻	24	90	62:38
5	IPr	toluene	ClO ₄ ⁻	24	100	69:31
6	IPr	<i>m</i> -xylene	ClO ₄ ⁻	24	99	73:27
7	IPr	CH ₃ CN	ClO ₄ ⁻	24	<5	–
8	IPr	C ₂ H ₄ Cl ₂	ClO ₄ ⁻	24	99	71:29
9	IPr	CH ₂ Cl ₂	ClO ₄ ⁻	24	99	75:25
10	IPr	CHCl ₃	ClO ₄ ⁻	5	91	85:15
11	IPr	CHCl ₃	OTf ⁻	4	85	86:14
12	IPr	CHCl ₃	OTs ⁻	4	10	99:1
13	IPr	CHCl ₃	OTs ⁻	24	47	92:8
14	IPr	CHCl ₃	PF ₆ ⁻	4	76	79:21

^[a] Conversion determined by GC analysis of the crude reaction mixture; value in parenthesis refers to isolated yield of a mixture of **4** and **5**.

^[b] Isomer ratio determined by GC analysis of the crude reaction mixture at the indicated time; value in parenthesis refers to isomer ratio of the purified mixture as determined by GC analysis; for both **4** and **5**, *E:Z* $\approx$ 9:1.

Table 2

Intermolecular alkoxylation of allylic alcohols with alcohol nucleophiles (ROH, 4 equiv) catalyzed by a mixture of (IPr)AuCl (5 mol %) and AgClO₄ (5 mol %) in methylene chloride (0.6 M) at 23 °C.

Entry	R of ROH	Allylic alcohol	Allylic ether	Time [h]	Convsn/Yield [%] ^[a]	γ / δ ^[b]	E/Z ^[c]
1	CH ₂ -4-C ₆ H ₄ Me	R' = Me	2a	4	96 (76)	94:6	–
2	CH ₂ -Ph	R' = Me	2b	5	98 (95)	>99:1	–
3	CH ₂ -4-C ₆ H ₄ Me	R' = Et	6a	9	95 (83)	92:8	–
4	CH ₂ -Ph	R' = Et	6b	14	83 (81)	>99:1	–
5	CH ₂ CH ₂ Ph	R' = Et	6c	11	88 (87)	93:7	–
6 ^[d]	Cy	R' = Et	6d	21	87 (76)	90:10	–
7	CH ₂ -4-C ₆ H ₄ Me	R' = <i>n</i> -Pr	8	18	82 (79)	92:8	–
8 ^[e]	<i>n</i> -Bu			24	ND (52)	>99:1	–
		(<i>E</i>)- 9					
9 ^[e]	<i>n</i> -Bu			24	ND (57)	>99:1	–
		(<i>Z</i>)- 9					
10	CH ₂ -4-C ₆ H ₄ Me			12	98 (85)	89:11	84:16
		3a					

Entry	R of ROH	Allylic alcohol	Allylic ether	Time [h]	Conv ⁿ /Yield [%] ^[a]	γ / α ^[b]	E/Z ^[c]
11	CH ₂ -4-C ₆ H ₄ Me			4	82 (76)	92:8	90:10
12 ^[d]	<i>n</i> -Bu			24	ND (80)	84:16	89:11
13 ^[d]	Me			7	ND (77)	84:16	91:9
14 ^[f]	<i>n</i> -Bu			24	ND (53)	94:6	93:7
15	CH ₂ -4-C ₆ H ₄ Me			7	100 (96)	–	90:10
16	CH ₂ -Ph			14	100 (99)	–	91:9
17	CH ₂ -4-C ₆ H ₄ Me			1	100 (88)	>99:1	–

^[a] Conversion determined by GC analysis of the crude reaction mixture at the indicated time; ND = not determined. Value in parentheses refers to isolated yield of the γ -regioisomer in >95% regioisomeric and chemical purity.

^[b] γ / α Ratio determined by GC analysis of the crude reaction mixture at the indicated time point.

^[c] E/Z ratio determined by ¹H NMR analysis of the purified reaction mixture.

^[d] Reaction temperature = 40 °C.

^[e] Catalyst system = (1)AuCl (5 mol %) and AgClO₄ (5 mol %) in dioxane at 60 °C.

^[f] Reaction performed in neat *n*-BuOH (0.5 M) at 50 °C.