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Gold-Catalyzed Asymmetric Transformation of Hydroxylated Propargylic Esters

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Abstract

By combining tandem asymmetric gold catalysis and subsequent stereoconvergent hydrolysis of enol ester in a one-pot process, hydroxylated propargylic esters are converted into chiral β-oxygenated ketones with mostly good enantiomeric ratios and in largely good to excellent yields. The product chiral center is formed via stereoselective cyclization of a hydroxylated allenyl ester intermediate, which is enabled by asymmetric gold-ligand cooperation.

Keywords

gold; catalysis; chiral; ligand; metal-ligand cooperation

Introduction

The introduction of metal-ligand cooperation[1] to homogeneous gold catalysis has yielded new strategies for the development of efficient and/or novel gold catalysis.[2] For example, we reported in 2017 that the 5-*exo*-trig cyclization of allenol is dramatically accelerated and highly enantioselective in the presence of a chiral binaphthyl-2-yldi(1-adamantyl)phosphine ligand featuring a 3'-amide function (i. e., **L1**).[3] This ligand remote amide group is essential and greatly facilitates the cyclization by playing the role of a general base in the transition state and intramolecularly shuttling proton during the reaction (Scheme 1A). In its absence, the cyclization is both comparatively sluggish, low-yielding due to competitive side reactions, and poorly enantioselective. To expand the synthetic utility of this strategy of chiral induction via rate acceleration in asymmetric gold catalysis,[4] we decided to couple it with an in-situ generation of the allene moiety via gold-catalyzed 3,3-rearrangement of propargylic ester.[5] As shown in Scheme 1B, this design enables the employment of readily accessible propargylic esters (**1**) as substrates. Upon gold-catalyzed *exo-trig* cyclization of the allenyl ester intermediate **2**, the resulting enol ester **3** is to be subjected to hydrolysis to deliver the chiral ketone **4** featuring a chiral *O*-heterocycle as the final product.[6] Since **2**

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Conflict of Interests

The authors declare no conflict of interest.

Supporting Information

The authors have cited additional references within the Supporting Information.[9–19]

would have a chiral axis, the challenge is whether our cooperative system renders efficient enantiocontrol during cyclization regardless of the axial chirality. An additional challenge is to find suitable hydrolytic conditions in the last step that afford the chiral ketone product with minimal racemization.

Results and Discussion

Reaction Optimization

We initiated our study by employing 9-hydroxy-1-phenylnon-3-yn-5-yl benzoate (**1a**) as the model substrate. The reaction optimization results are shown in Table 1. With (*S)*-**L1** as the ligand, the gold-catalyzed tandem 3,3-rearrangement and cyclization occurred smoothly, affording the tetrahydropyran enol benzoate **3a** with little control of the enol ester geometry (Z/E= 1.5 : 1, entry 1) but in nearly quantitative yield. All four stereoisomers of **3a** were separated by chiral HPLC. As expected, the geometric isomers of **3a** exhibited different enantiomeric ratios – 92 : 8 for the major isomer *Z*-**3a** and a better 97 : 3 for the minor *E*-**3a**. Subsequent hydrolysis of **3a** in the presence of NH_3 resulted in the formation of the desired tetrahydropyran ketone product **4a** in 80 % yield and with an enantiomeric ratio of 94 : 6 (see Table 2, entry 1). This result confirmed that the major enantiomer of *Z*-**3a** has the same configuration at its chiral center as that of *E*-**3a**, revealing that the chiral ligand instead of the allenyl ester axial chirality mostly dictates the cyclization stereochemistry. Changing the benzoyl group of **1a** to other acyl groups including acetyl, 4-methoxybenzoyl, and 4-nitrobenzoyl did not result in improvement in yield and/or enantioselectivity (see details in SI). Replacing the pyrrolidine-1-carbonyl moiety of (*S)*-**L1** with an *N,N*-dimethylcarbamoyl group in the case of (*S)*-**L2** led to marginal improvement in the enantiomeric ratio of *Z*-**3a** (93 : 7), but notable increase in the yield of the minor *E*-isomer, which exhibits identical excellent enantiomeric ratio (97 : 3), was realized (entry 2). (*S)*-**L3** with a bulkier *N,N*-diisopropylcarbamoyl moiety led to an appreciably lower yield, although the enantiomeric ratios of the geometric isomers are identical 95 : 5. The phosphonate ligand (*S)*-**L4** (entry 4) or the phosphine oxide ligand (*S)*-**L5** (entry 5) was not as effective in asymmetric induction. Additional solvents and chloride scavengers were examined with (*S)*-**L2** as the ligand. While toluene led to a lower enantiomeric ratio of the major *Z*-isomer (entry 6), no changes in enantiomeric ratios and geometric ratios were detected with DCE as the solvent, although the yield was slightly lower (entry 7). AgBARF.$(MeCN)_2$, $AgNTf_2$, and $AgBF_4$ all worked as well as NaBARF in activating the gold precatalyst (*S)*-**L2**AuCl (entries 8–10). Finally, JohnPhos is also capable of promoting the reaction, but the yield was moderate (entry 11).

With the optimal conditions (e. g., Table 1, entry 2) for the rearrangement and cyclization in hand, we set out to examine the hydrolysis conditions to convert **3a** to the desired tetrahydropyran ketone product **4a**. With **3a** generated under the optimized conditions having a calculated 95 : 5 configuration ratio at the stereogenic center, we initially tried the reaction in the presence of aqueous ammonia.[7] **4a** was formed in 80 % yield with slight diminishment of enantiomeric ratio (Table 2, entry 1). The reaction was sluggish and did not reach completion after 48 h. Doubling the reaction time resulted in complete hydrolysis, though with a further reduction in the enantiomeric ratio and with only a slight improvement in yield (entry 2). The erosion of product chirality is attributed to reversible

ring-opening elimination and ring-closing oxa-Michael addition, despite attempts to observe the hydroxylated enone intermediate not being successful. During our studies of the reaction scope, we discovered these hydrolysis conditions were insufficient in some cases, where the long reaction time led to increasing racemization. To this end, the use of $LiOH \cdot H_2O$[8] delivered the product expediently in half an hour (entry 3); although a small amount of **3a** remained, the yield was excellent, and no erosion of enantiomeric ratio was detected. Our attempts in driving the reaction to completion by increasing the reaction time to 1 h led to some chirality erosion and, moreover, a lower yield (entry 4).

Reaction Scope

The reaction scope is shown in Table 3. We first modified the methylene group γ to the HO group in **1a** (X= CH_2 in the generic structure **1**). An oxygen in the case of **4b** delivered the chiral 1,4-dioxane product in excellent yield and with a decent enantiomeric excess. A quaternary carbon center in the case of **4c** led to a lower enantioselectivity. An ethylene group resulted in the formation of the chiral oxepane **4d** with a 92 : 8 enantiomeric ratio and in 76% yield. In this case, $AgNTf_2$ was used as the chloride scavenger to achieve faster gold catalysis. Removal of the methylene group en route to a tetrahydrofuran ketone product resulted in an estimated 62 % ee at the newly established chiral center in the enol benzoate stage, but subsequent hydrolysis using either Method A or Method B led to complete racemization. Replacing the phenethyl group at the substrate alkyne terminus of **1a** with a phenyl group was largely inconsequential, and the chiral acylphenone **4e** was formed in 82 % yield and with a 92 : 8 enantiomeric ratio. We then proceeded to probe the substitution effects on the benzene ring of **4e**. A *para*- or *meta*-Me was allowed, and **4f** and **4g** was isolated in acceptable yields; however, extended hydrolysis using Method A led to erosion of e.r. With Method B, the hydrolysis went to completion in 45 min and delivered the final products with comparably lower e.r. On the other hand, the *ortho*-Me in the case of **4h** was much deleterious to stereochemical control, and the reaction exhibited poor enantioselectivity. We also probed the substituent electronic effects. An electron-withdrawing CF_3 group at the *para* or *meta* position was permitted, and **4i** or **4j** was isolated in a moderate yield and with a good enantiomeric excess. Other electron-withdrawing groups such as 4-nitro (**4k**), 4-acetyl (**4l**),4-fluoro (**4m**), and 4-bromo (**4n**) were also suitable for the chemistry, resulting in acceptable to good yields and with ≥10 : 1 enantiomeric ratios. However, the electron-donating MeO group in **4o** substantially lowered the product enantiomeric ratio. Finally, the use of a 3-benzyloxypropyl group in place of the phenethyl in **1a** was readily accommodated, and the reaction exhibited good yield and excellent e.r.

Conclusions

In this work, we have extended our asymmetric gold-ligand cooperation approach to hydroxylated propargylic benzoates. Despite the existence of a chiral center in racemic substrates, the tandem gold catalysis – 3,3-sigmatropic rearrangement and cyclization of hydroxylated allenyl benzoates – permits good levels of stereochemical induction in the presence of a chiral bifunctional binaphthylphosphine ligand. This chemistry allows one-pot conversion of readily available hydroxylated propargylic esters into ketones featuring a

chiral *O*-heterocycle in mostly good yields and with moderate to excellent enantiomeric ratios.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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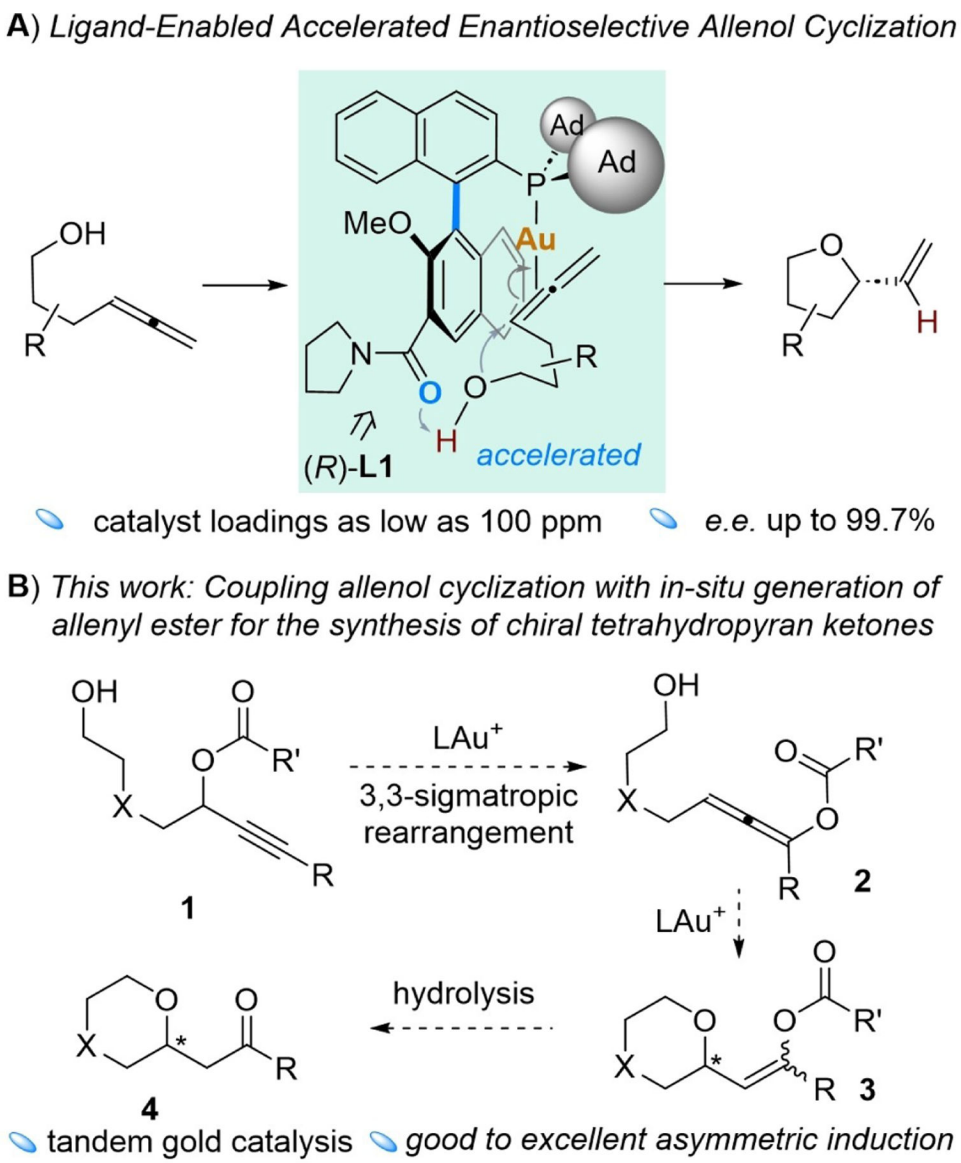
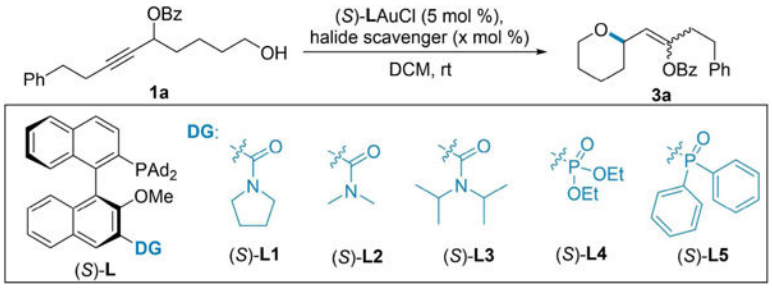


Scheme 1.

Gold-catalyzed asymmetric allenol cyclization achieved via metal-ligand cooperation: a previous study and this work.

Table 1.

Conditions optimization.



Entry	Ligand	HS (x mol %)[a]	Yield (%)	*Z*-3 a/*E*-3 a	er of *Z*-3 a; er of *E*-3 a
1	(*S*)-**L1**	NaBARF (10)	98	1.5 : 1	92 : 8; 97 : 3
2	(*S*)-**L2**	NaBARF (10)	96	1.2 : 1	93 : 7; 97 : 3
3	(*S*)-**L3**	NaBARF (10)	92	1.8 : 1	95 : 5; 95 : 5
4	(*S*)-**L4**	NaBARF (10)	92	2.6 : 1	78 : 22; 90 : 10
5	(*S*)-**L5**	NaBARF (10)	89	2.1 : 1	88 : 12; 95 : 5
6[b]	(*S*)-**L2**	NaBARF (10)	95	1.4 : 1	91 : 9; 98 : 2
7[c]	(*S*)-**L2**	NaBARF (10)	93	1.2 : 1	93 : 7; 97 : 3
8	(*S*)-**L2**	AgBARF[d] (5)	96	1.2 : 1	93 : 7; 97 : 3
9	(*S*)-**L2**	$AgNTf_2$ (5)	97	1.4 : 1	93 : 7; 97 : 3
10	(*S*)-**L2**	$AgBF_4$ (5)	98	1.4 : 1	92 : 8; 97 : 3
11	JohnPhos	NaBARF (10)	51	1.9 : 1	–

[a] HS-Halide Scavenger.

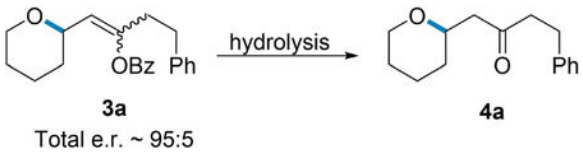
[b] Toluene as solvent.

[c] DCE as solvent.

[d] AgBARF: AgBARF· $(MeCN)_2$.

Table 2.

Examination of hydrolysis conditions.



3a

Total e.r. ~ 95:5

4a

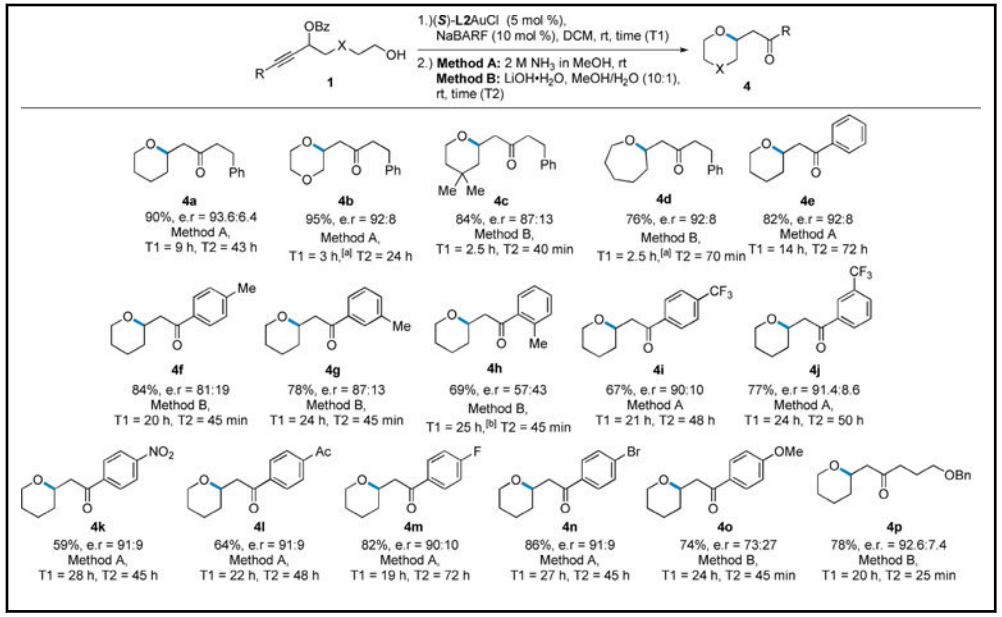
Entry	Reagent	Time (h)	Yield (%)	e.r.
1	2 M NH_3 in MeOH	48	80[a]	94 : 6
2	2 M NH_3 in MeOH	96	81	93 : 7
3	LiOH· H_2O[b]	0.5	93[a]	95 : 5
4	LiOH· H_2O[b]	1	79	94 : 6

[a] ~5 % **3a** remained.

[b] 0.1 M in MeOH/H_2O (10 : 1).

Table 3.

Reaction scope.



[a]Used $AgNTf_2$ (5 mol%).

[b]Heated to 50 °C.