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RESEARCH ARTICLE

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Asymmetric Allylation by Chiral Organocatalyst Promoted Formal Hetero-Ene Reactions of Alkylgold Intermediates

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Dedication ((optional))

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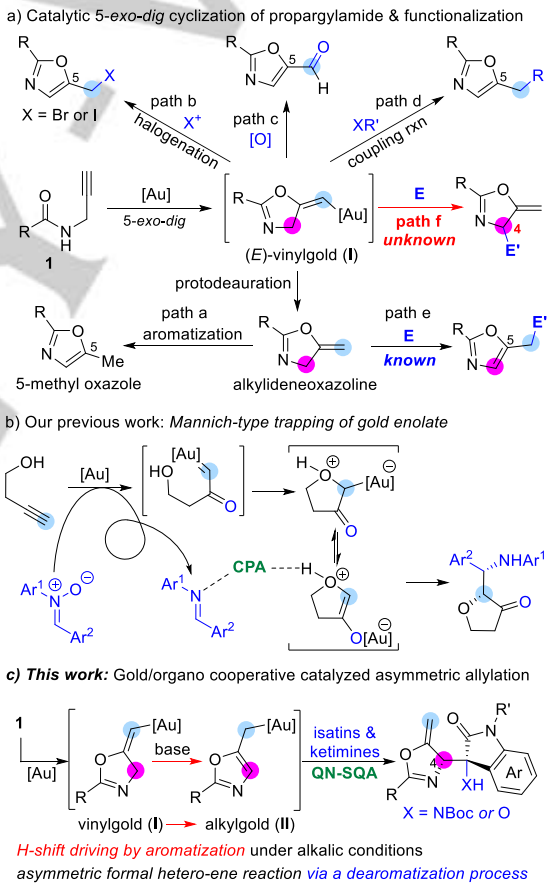
Abstract: An unprecedented catalytic asymmetric allylation of isatins and isatin-derived ketimines enabled by gold and chiral organocatalyst cooperative catalysis strategy is reported. This method offers expeditious access to chiral 2,5-disubsituted alkylideneoxazolines containing vicinal stereogenic centers, mainly in optically pure form and otherwise impossible to access. Mechanistic evidence revealing the alkylgold intermediate, especially its X-ray crystal structure, illuminates its unique stability and reactivity as an allylgold species. An asymmetric formal hetero-ene reaction of this gold intermediate involving a dearomatization process is enabled with assistance of quinine-derived squaramide catalyst. This novel discovery extends the synthetic application of gold-complex and versatility of gold catalysis.

Introduction

Oxazoles and their derivatives are regarded as privileged scaffolds in numerous natural and synthetic bioactive molecules that display versatile biological activities,[1] and highly efficient and practical methodologies have been developed for their construction.[2] Among these methods, the catalytic cyclization of *N*-propargylamides **1**, which are readily available materials, has been recognized as general and atom-economical.[3-11] The initial conversion, promoted by acid, was reported in 1962,[4] followed by the base catalyzed version *via* an allene intermediate in 1989.[5] In the recent two decades, significant progress has been made in this area with a variety of transition metal catalysts, including those of Au,[6] Ag,[7] Pd,[8] Cu,[9] Zn,[10] and others.[11] In these expanding studies, gold-catalyzed transformations have attracted the most attention in terms of the mechanism studies and synthetic applications (Scheme 1a).[6,12]

Gold complexes have proven to be one of the most effective catalysts for the activation of alkynes.[13] The most general reactivity pattern is the addition of carbon, oxygen, and nitrogen nucleophiles to alkyne-gold π-complexes, and vinylgold complexes are key intermediates in most of these transformations.[14] In this context, Hashmi *et al.* reported that the gold-catalyzed cyclization of terminal *N*-propargylamides *via* an *anti*-oxyauration process delivers alkylideneoxazoline through key (*E*)-vinylgold intermediates (Scheme 1a).[6,15] The vinyl-AuIPr and vinyl-Au(III) complexes have been isolated and characterized by X-ray crystallography analysis in subsequent



Scheme 1. Gold-catalyzed transformations of *N*-propargylamides.

studies independently by Hashmi, Shi, and Ahn.[12] One of the general reaction pathways of these vinylgold intermediates is protodeauration, followed by aromatization to form 5-methyl oxazoles (Scheme 1a, path a).[6] Recently, efforts have been made by various research groups to explore new reactivities of vinylgold complexes, including halogenation (path b),[16] oxidation (path c),[12b,12c,17] coupling (path d),[18] and others.[19] These advances have provided an expeditious entry to a range

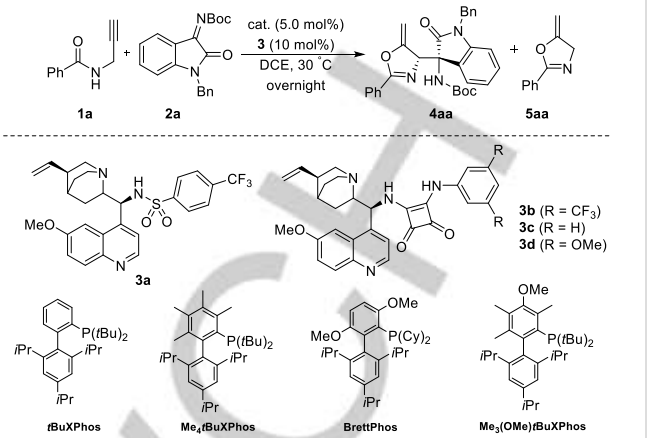
of available oxazoles containing various functional groups on the 5-position *via* different types of manipulations over the exocyclic C=C bond. However, challenges and limitations remain in this area: the asymmetric transformation of vinylgold intermediates has not been disclosed so far, although elegant enantioselective Alder-ene reaction[20] and allylic aromatization reaction of alkylideneoxazolines, which are demetallated derivatives of vinylgold species, have been reported by Feng,[21a-21c] Hashmi,[21d] and You[21e] with corresponding chiral metal complexes (Scheme 1a, path e). On the other hand, all of the oxazoles/oxazolines that were formed as the final products did not contain any functionality on the 4-position, which means that novel reactivity on this position has not been realized so far (Scheme 1a, path f).

Recently our group has reported an enantioselective Mannizch-type reaction of *in situ* generated gold enolate intermediate and imine with the assistance of chiral phosphoric acid **CPA** (Scheme 1b).[22,23] As a continuation of our research program on multicomponent reactions *via* trapping reactive ylide/zwitterionic intermediates,[24,25] we envisioned that novel interception transformation on the inert 4-position might be enabled through the alkylgold intermediate **II**, which could be generated *via* an aromatization drived *H*-shift process of vinylgold species **I** with the assistance of appropriate alkalic cocatalyst, instead of direct protodeauration. Herein, we report a gold/quinine-derived squaramide (**QN-SQA**) cooperative catalysis as an effective strategy to realize the asymmetric allylation of isatins and their ketimine derivatives *via* an asymmetric formal hetero-ene reaction of alkylgold intermediate **II**, which shows unique reactivity as an allylgold species (Scheme 1c).[21a-d,26] In catalytic allylations,[27,28] the reactions typically utilize activated allylic substrates that usually containing a leaving group,[29-33] thus generating stoichiometric quantities of waste material. This direct asymmetric allylation method, which is the first example of formal hetero-ene reaction of alkylgold intermediate that involves a dearomatization process, is an atom- and step-economic advance in this area.[34]

Results and Discussion

The readily accessible *N*-propargylamide **1a** and ketimine **2a** were used as model substrates in the presence of Me_4*t*BuXPhosAuNTf$_2$ in 1,2-dichloroethane (DCE) at 30 °C (Table 1). Initially, a variety of quinine derived organocatalysts were investigated in an effort to delay the protodeauration of vinylgold intermediate and facilitate the designed process *via* forming the alkylgold species (for the details of the discovery of this reaction, see Table S1 in SI). Commercially available quinine and its sulfamide derivative **3a** promoted the transformation smoothly, producing the allylation product **4aa** in moderate to good yields with 9% and 85% *ee*, respectively (entries 1 and 2). To improve the selectivity of the reaction, dual-functional quinine-derived squaramide catalysts **3b**-**3d** were examined (entries 3-5),[35] and these catalysts showed much higher reactivity and selectivity. The phenyl substituted catalyst **3c** gave the best results with 92% yield, >20:1 *dr* and >99% *ee* (entry 4). Control experiments in the absence of either the gold catalyst or the organocatalyst resulted in either no reaction or formation of **5aa** as the major product, respectively (entries 6 and 7). These results confirmed the importance of cooperative

Table 1: Condition Optimization.[a]



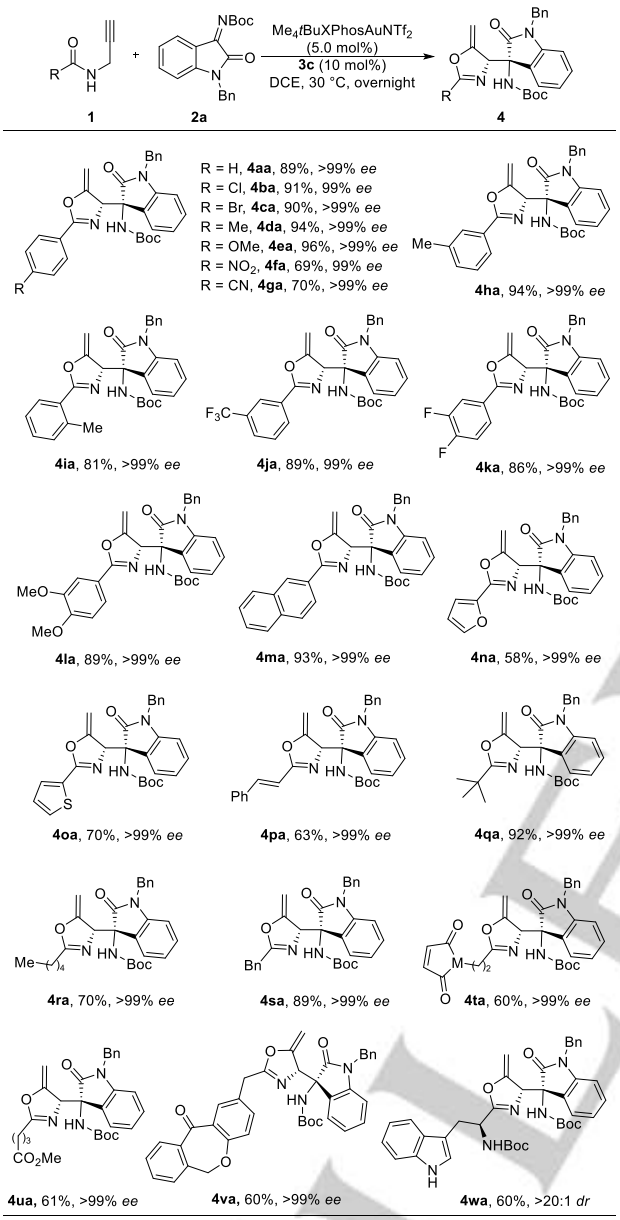
Entry	Cat. (5.0 mol %)/**3** (10 mol%)	Yield [%][b] **4aa/5aa**	*dr*[c]	*ee* [%][d]
1	Me_4*t*BuXPhosAuNTf$_2$/quinine	43/22	>20:1	9
2	Me_4*t*BuXPhosAuNTf$_2$/**3a**	61/27	>20:1	85
3	Me_4*t*BuXPhosAuNTf$_2$/**3b**	93/<5	2:1	98(49)
4	Me_4*t*BuXPhosAuNTf$_2$/**3c**	92/<5	>20:1	>99
5	Me_4*t*BuXPhosAuNTf$_2$/**3d**	86/13	>20:1	>98
6	(-)/**3c**	NR	-	-
7	Me_4*t*BuXPhosAuNTf$_2$/(-)	17/75	>20:1	-
8	PPh_3AuNTf$_2$/**3c**	19/56	>20:1	94
9	BrettPhosAuNTf$_2$/**3c**	27/67	>20:1	99
10	IPrAuCl + AgNTf$_2$/**3c**	7/92	>20:1	-
11	JohnphosAuNTf$_2$/**3c**	20/68	>20:1	93
12	*t*BuXPhosAuNTf$_2$/**3c**	32/60	>20:1	>98
13	Me_3(OMe)*t*BuXPhosAuNTf$_2$/**3c**	93/<5	>20:1	>99

[a] The reaction was carried out on a 0.1 mmol scale: to the solution of **2a** (33.6 mg, 0.1 mmol), catalyst (5.0 mol%) and additive in DCE (1.5 mL), was added **1a** (19.1 mg, 0.12 mmol) in DCE (0.5 mL) under argon atmosphere at 30 °C in 15 min, and the reaction was running overnight. [b] Determined by ^{1}H NMR of the crude reaction mixture with 1,3,5-trimethoxybenzene as internal reference. [c] The *dr* ratios were determined by ^{1}H NMR of the crude reaction mixture. [d] The *ee* values were determined by chiral HPLC analysis. NR = no reaction.

catalysis in enabling this unprecedented transformation. With the identified optimal organocatalyst **3c**, various gold catalysts were further screened (entries 8-13). All these catalysts showed high reactivity, and the only comparable excellent selectivity was obtained with Me_3(OMe)*t*BuXPhosAuNTf$_2$ (entry 13, 93% yield, >20:1 *dr*, and >99% *ee*). Considering the cost of the catalysts, Me_4*t*BuXPhosAuNTf$_2$ and **3c** were chosen as the optimal combination for the subsequent asymmetric allylation reaction (entry 4). The absolute configuration of this product was confirmed by single-crystal X-ray diffraction analysis of its chloro-derivative **4ah**,[36] and other products were tentatively assigned by analogy.

With the optimized conditions in hand, various *N*-propargylamides **1** were prepared to evaluate the reaction scope. The results are summarized in Table 2. Good substrate

Table 2: Scope of *N*-propargylamides.[a]

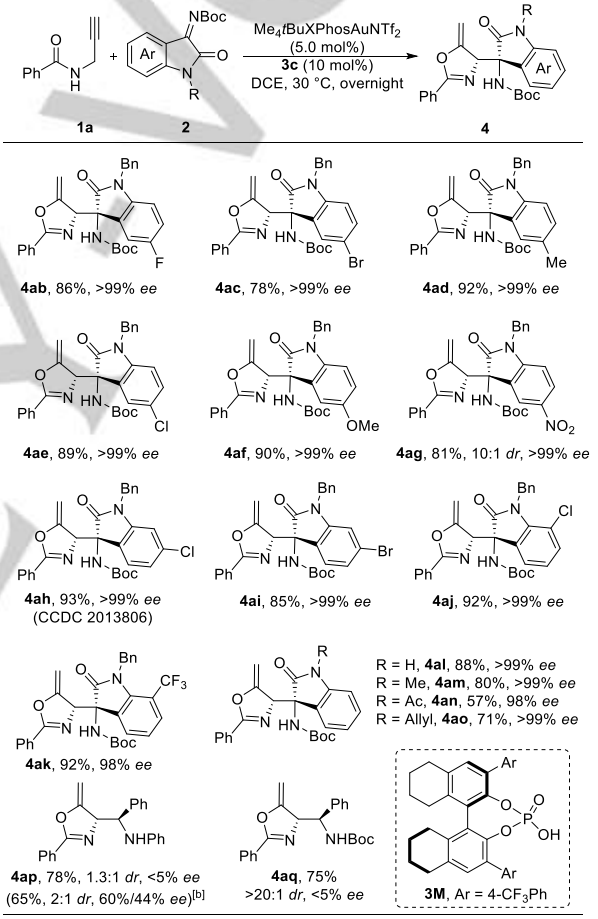


[a] Reaction conditions: **1** (0.24 mmol), **2a** (67.2 mg, 0.2 mmol), Me_4*t*BuXPhosAuNTf$_2$ (10.0 mg, 5.0 mol%), and organocatalyst **3c** (10.0 mg, 10 mol%) in DCE (4.0 mL) under argon atmosphere at 30 ℃ overnight, and the yields are given in isolated yields, all the *dr* values were >20:1.

compatibility was observed with this cooperative catalysis system, and only one diastereomer was observed in all of the tested propargylamides (>20:1 *dr*). Substrates with EDGs and EWGs on different position of aryl ring all furnished the allylation products in good to excellent yields with each as a single enantiomer (**4aa**-**4la**, >99% *ee*). Relatively low yields were observed in the cases of substrates with EWGs, which may due to the lower nucleophilicity of the carbonyl species that is detrimental for the intramolecular cyclization.[15] The 2-naphthyl and heteroaromatic substrates also worked well, delivering the optically pure **4ma**-**4oa** in 58%-93% yields. Aliphatic substituted propargyl amides, including styryl, *tert*-butyl, pentyl, benzyl, and alkyl tethered with amide and ester, all performed well, yielding the optically pure products in good to excellent yields (**4pa**-**4ua**). To further evaluate the generality of this method, bioactive molecules isoxepac and natural amino acid *L*-tryptophan derived amides were used, and the desired oxazolines **4va** and **4wa** were isolated in good yields with >99% *ee* and >20:1 *dr*, respectively.

The scope of the transformation with respect to ketimines bearing diverse substituents on the aryl ring was then examined (Table 3). The current method turned out to be highly efficient,

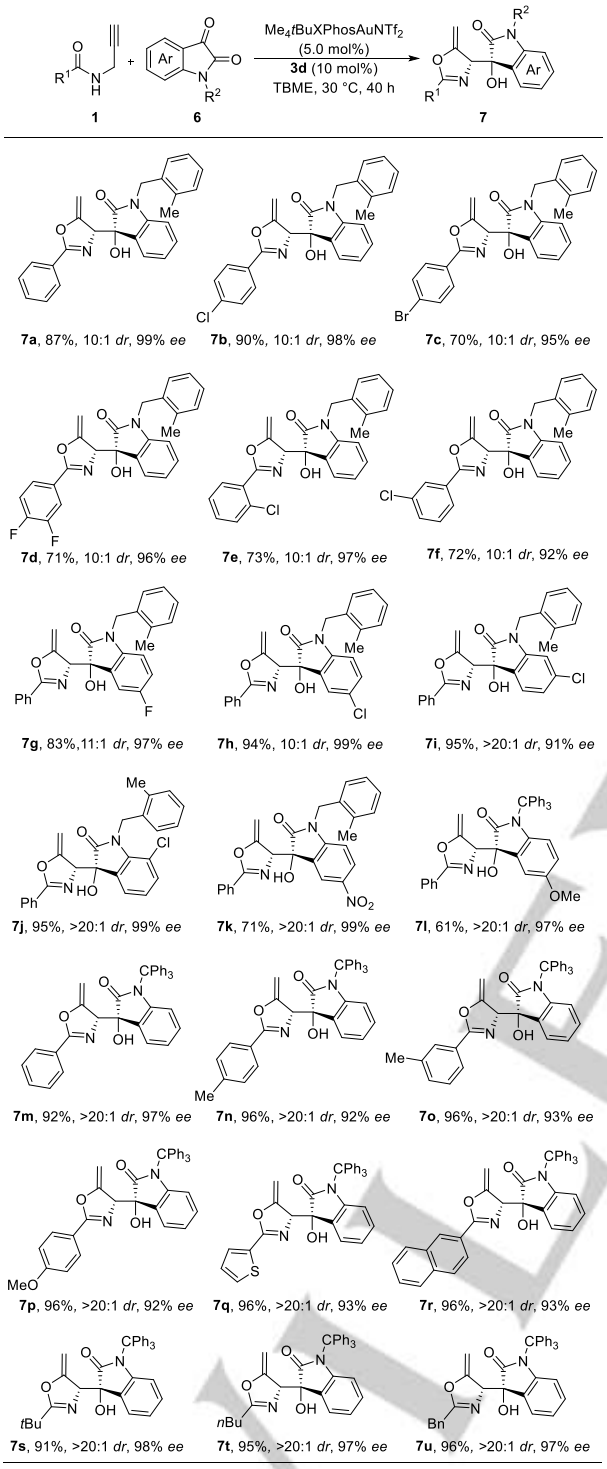
Table 3: Scope of ketimines.[a]



[a] Reaction conditions: **1a** (38.2 mg, 0.24 mmol), **2** (0.2 mmol), Me_4*t*BuXPhosAuNTf$_2$ (10.0 mg, 5.0 mol%), and organocatalyst **3c** (10.0 mg, 10 mol%) in DCE (4.0 mL) under argon atmosphere at 30 ℃ overnight. The yields are given in isolated yields. Unless otherwise noted, the *dr* values were >20:1. [b] The reaction was conducted in the presence of **3M** (10 mol%) instead of **3c**.

with all of the tested ketimines showing good to excellent reactivity and selectivity. Except for the nitro substituted ketimine, which formed the corresponding product **4ag** with a 10:1 *dr*, all other allylation products were generated with excellent stereoselectivity (**4ab**-**4af** and **4ah**-**4ak**, >20:1 *dr*, >98% *ee*). Notably, the *N*-unprotected ketimine was also compatible for this reaction, yielding **4al** in 88% yield with 99% *ee*. Ketimines with

Table 4: Scope of isatins.[a]

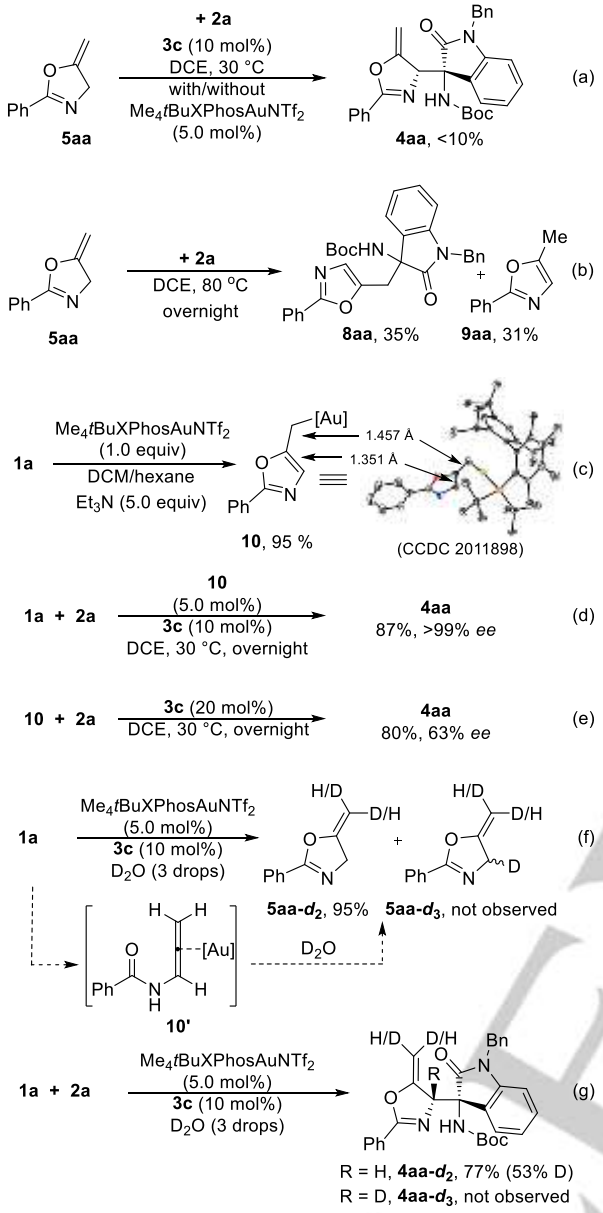


[a] Reaction conditions: **1** (0.24 mmol), isatins **6** (0.2 mmol), Me$_4$*t*BuXPhosAuNTf$_2$ (10.0 mg, 5.0 mol%), and organocatalyst **3d** (11.2 mg, 10 mol%) in TBME (4.0 mL) under argon atmosphere at 30 ℃ for 40 h, and the yields are given by isolated yields.

other protecting groups, including methyl, acetyl, and allyl, were all tolerated well and produced the desired products **4am**-**4ao** in 57%-80% yields with 98%-99% *ee*. Beyond the isatin-derived ketimines, non-cyclic imines also reacted smoothly to give the corresponding products **4ap** and **4aq** in high yields, however, there is no enantioselectivity in these cases. In the case with glyoxylate-derived ketimine, no allylation reaction occurred under current conditions. Further optimization for the reaction with diphenyl imine in the presence of various chiral phosphonic acids was conducted (Scheme S1 in SI for details), leading to **4ap** as a mixture of two diastereosiomers (total 65% yield with 2:1 *dr*) in up to 60% and 44% *ee*, respectively (Table 3 note b), which implied the potential for achieving highly asymmetric versions in this direction.

Encouraged by the above results, we directed our attention into the evaluation of asymmetric allylation of isatins. After optimization of conditions and substrate modification, the quinine-derived sulfamide catalyst **3d** in *tert*-butyl methyl ether (TBME) showed higher stereoselectivity in allylation of the carbonyl compound (see Table S2-S3 in SI for detail). The *N*-protection groups on isatins play a key role in the selectivity control, *o*-methylbenzyl and triphenylmethyl have been identified as optimal choices in terms of the reactivity and stereoselectivity (see Table S4 in SI for detail). As shown in Table 4, the organocatalyst **3d** promoted asymmetric allylation of isatins showed good substrate generality. Various electron-neutral, electron-rich, and election-deficient substitutions on the aryl rings of propargylamides and isatins were suitable for this reaction, producing the allylation products in good to high yields with >10:1 *dr* in 91%-99% *ee* (**7a**-**7p**). The 1-thienyl, 2-naphthyl, and various alkyl groups were also tolerated under optimal conditions, furnishing corresponding products **7q**-**7u** in >91% yields with >20:1 *dr* and 93%-98% *ee*. Substrates with internal alkynes, inducing *N*-(3-phenylpropargyl)benzamide and *N*-(but-2-ynyl)benzamide, did not work under current conditions with most of starting material recovered, which is consistent with previous reports.[12,37]

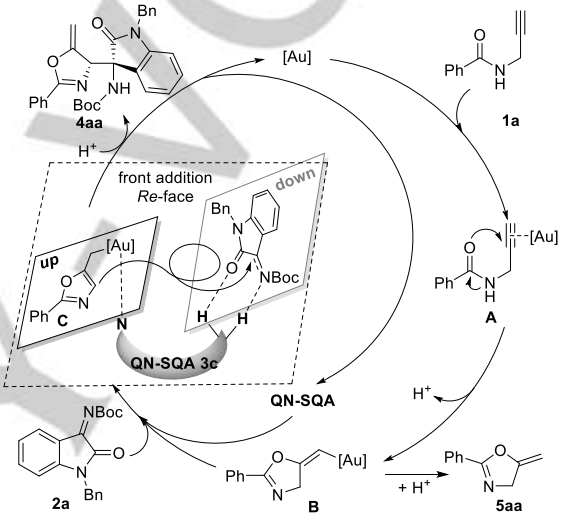
To gain insight into the reaction mechanism of this new process, several control experiments were performed. Model reactions in the absence of the gold catalyst (Table 1, entry 6) or the organocatalyst (Table 1, entry 7) revealed no reaction or formation of alkylideneoxazoline **5aa** as the major product, respectively. These results indicated that the gold catalyst responsible for the catalytic cyclization of *N*-propargylamide, while the organocatalyst is essential in enabling the allylation step. To explore whether this transformation went through a gold/organo cooperative[38] or relay[39] catalysis manner, alkylideneoxazoline **5aa** and **2a** were applied to the standard conditions with or without the gold catalyst, majority of the materials remained intact and no **4aa** was observed by the proton NMR spectrum of the reaction mixture (Scheme 2a, and see Figures S1 and S2 in SI for details). Moreover, when this reaction was conducted under thermal conditions, the ene reaction product **8aa** was isolated in 35% yield,[20,21] contaminated with aromatized oxazole **9aa** in 31% yield (Scheme 2b). These results ruled out the possibility of a stepwise catalytic relay *via* alkylideneoxazoline **5aa**. Further effort focused on exploration of the identity of the key intermediate that might be generated in situ *via* gold catalyzed cyclization. Equal amounts of *N*-propargylamide **1a** and the gold catalyst Me$_4$*t*BuXPhosAuNTf$_2$ were dissolved in a mixed solvent (DCM/hexane) in the presence of triethylamine, and the gold-complex **10** was formed and crystallized in 95% yield *via* slow volatilization of the solvent under an argon atmosphere. The structure of this complex was confirmed by X-ray crystallography (Scheme 2c, and see SI for detail).[36] The red bond length of intermediate **10** is 1.351 Å, which is shorter than the single bond



Scheme 2. Control experiments.

reported by Ahn (1.502 Å)[12c] and is closer to the data of C-C double bond. Based on these observations, an alkylgold structure **10** with allylgold reactivity, rather than the vinylgold species, is assigned in this reaction. The vinylgold species is the only intermediate that has been proposed and characterized in gold-catalyzed cyclization of *N*-propargylamides (Scheme 1a).[12] This is the first example of observation of alkylgold intermediate in this area, which has been characterized by X-ray crystal analysis.[40] Combined with **3c**, this gold-complex could catalyze the model reaction, producing the allylation product **4aa** with comparable high yield and excellent enantioselectivity (Scheme 2d, 87% yield and >99% *ee vs* model reaction 89% yield and >99% *ee*). Moreover, the quantitive reaction between **10** and **2a** in the presence of **3c** also smoothly led to **4aa** in 80% yield with 63% *ee*, and the low *ee* may due to the background reaction between the materials without the assistance of the organocatalyst **3c** (Scheme 2e). These results strongly suggested that the alkylgold **10** is the key reactive reaction intermediate in this reaction. To rule out the possibility that product **4aa** resulted from an allene species **10'**, control experiments under standard conditions in the presence of D_2O were conducted. No product with deuterium on the allylic position was detected either in the formation of **5aa** or in the model reaction (Scheme 2f and 2g).[5] These results not only confirmed that the formation of **5aa** *via* direct protodeauration of vinylgold species, but also indicated a one-way transformation from vinylgold to alkylgold *via H*-shift driving by aromatization, and the later could not lead to the alkylideneoxazoline **5aa** anymore under current conditions.[41]

Based on the above results and the reported literature,[6,12] a rationalized mechanism is proposed in Scheme 3. The reaction



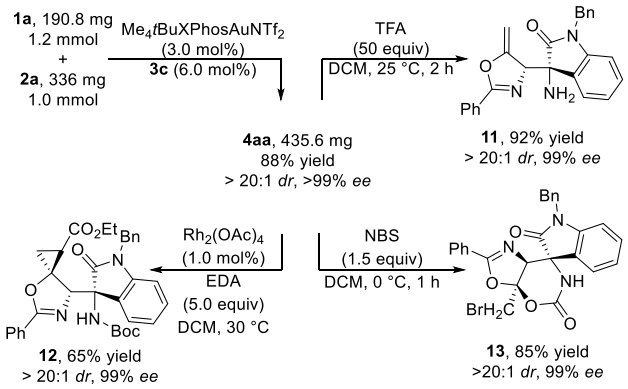
Scheme 3. Proposed reaction mechanism.

is initiated *via* the formation of a π-complex **A** with the gold catalyst and *N*-propargylamide **1a**. Then a 5-*endo-dig* cyclization of complex **A** *via anti*-oxyauration process delivers the key (*E*)-vinylgold intermediate **B**.[12] Protodeauration of **B** would lead to the alkylideneoxazoline **5aa**, followed by aromatization to form the 5-methyl oxazole **9aa**. In this reaction, *H*-shift driving by the aromatization is enabled with the assistance of alkalic co-catalyst, leading to the key alkylgold species **C**. The final asymmetric allylation process through a formal hetero-ene reaction is realized by the dual functional chiral organocatalyst, producing the product **4aa** and regenerating the catalysts. Although other types of SE2' addition of allylgold species with imine-like electrophiles have some precedent,[42] the current work is the first example of asymmetric catalytic version in this area.

According to the X-ray crystal structure of the catalyst, as well as the absolute configuration of the product,[36] a possible transition state is proposed (Scheme 3, in dashed box) to elucidate the source of stereoselectivity of this reaction. The squaramide hydrogens of the bifunctional catalyst activates the ketimine *via* double hydrogen bonding;[35] whereas, the *N*-atom on the quinoline part of the organocatalyst might interact with the gold catalyst.[43] And all these interactions enable the intermolecular reaction *via* a formal intramolecular model. The

nucleophilic addition occurs on the *Re*-face of ketimine, affording the (*R*, *S*)-enantiomer. In this case, the steric hinderance between the bulky gold catalyst and the approaching electrophile could be avoided since the gold species toward outside the aryl ring of the ketimine.

To show the synthetic utility of this cooperative catalysis strategy, the asymmetric allylation reaction of *N*-propargylamide **1a** with ketimine **2a** was expanded to a 1.0 mmol scale in a reduced catalyst loading, and **4aa** was isolated in 88% yield with



Scheme 4. Synthetic utility.

>20:1 *dr* and >99% *ee* (Scheme 4). The free amino derivative **11** and cyclopropane product **12** could be obtained *via* TFA mediated deprotection and Rh-catalyzed cyclopropanation reaction in 92% and 65% yields, respectively. Furthermore, **4aa**, which is a bicyclic framework containing an enocyclic enol ether motif, could be converted to the spiro structure in the presence of NBS, forming **13** in 85% yield. In all these tested transformations, the stereochemistry is well maintained and the products, **11**-**13**, are obtained in nearly optically pure form. The structure of **13** was confirmed by X-ray diffraction analysis.[36]

Conclusion

In summary, we have reported an unprecedented asymmetric allylation reaction of isatins and isatin-derived ketimines with *N*-propargylamides. This atom-economic transformation is enabled by gold/organo cooperative catalysis, which offers expeditious access to chiral 2,5-disubsituted alkylideneoxazolines mainly in an optically pure form. Mechanistic studies indicate that the alkylgold species, which has been characterized by X-ray crystallographic analysis for the first time, is the key intermediate and possesses allylgold reactivity. The asymmetric formal hetero-ene reaction of this intermediate is achieved with the assistance of a bifunctional quinine-derived squaramide catalyst. The novel reactivity disclosed here should in principle be transferable to many other asymmetric reactions involving analogous gold-complexes and could expand our present knowledge of gold catalyzed transformation.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric allylation• alkylgold • gold/organo cooperative catalysis • heter-ene reaction • *N*-propargylamide

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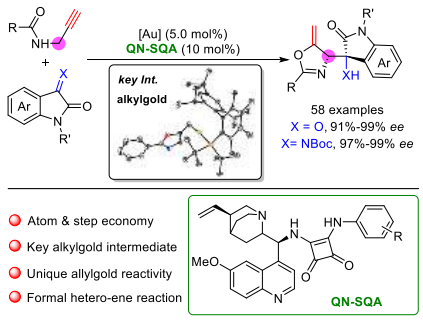
Entry for the Table of Contents



An asymmetric allylation reaction of isatins/ketimines with *N*-propargylamide is reported, which offers expeditious access to alkylideneoxazolines mainly in optically pure form. The key alkylgold intermediate, which possesses allylgold reactivity, has been confirmed by X-ray crystallographic analysis for the first time. The asymmetric formal hetero-ene reaction of this species involving a dearomatization process is enabled with the assistance of a quinine-derived squaramide catalyst.