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Gold(I)-catalyzed cycloisomerization of alcohol or amine tethered-vinylidenecyclopropanes providing access to morpholine, piperazine or oxazepane derivatives: a carbene *versus* non-carbene process†

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A gold(I)-catalyzed intramolecular cyclization of alcohol or amine tethered-vinylidenecyclopropanes *via* a carbene or non-carbene process was developed to afford functionalized morpholines, piperazines and oxazepanes in good yields with a broad scope and excellent functional group tolerance under mild conditions. The steric bulkiness or chain length can modulate the reaction pathway. Substrates with a less sterically hindered group located at the allene moiety afford morpholines or piperazines containing an alkylidenecyclopropane *via* the non-carbene process, while sterically bulky ones give morpholines or piperazines containing a cyclobutene unit through the carbene process. Moreover, extending the carbon chain length of vinylidenecyclopropane enables the formation of seven-membered oxazepane *via* the carbene process. The synthetic utility of this protocol was also highlighted by its gram-scale synthesis and various transformations of the cyclization products.

Morpholine, piperazine and oxazepane derivatives have gained extensive attention due to their positive physicochemical, metabolic and biological properties.[1] They are biologically active nitrogen-containing heterocycles involved in a variety of natural products and pharmaceuticals, such as the antibiotic drug finafloxacin,[2] antianginal drug trimetazidine,[3] antidepressant agents reboxetine[4] and befuraline,[5] dopamine D_4 receptor ligands,[6] noradrenaline reuptake inhibitors[7] and so on (Fig. 1). Although numerous methodologies have been established for the synthesis of these useful scaffolds,[8] the construction of functionalized morpholine, piperazine or oxazepane derivatives still remains challenging.

Recently, gold(I)-catalyzed nucleophilic additions to C–C multiple bonds as a popular research branch of gold chemistry have made significant progress.[9] Over the past two decades, considerable advancements have been made in gold(I)-catalyzed addition of X–H (X = O, N, C) bonds to unsaturated carbon–carbon bonds of olefins,[10] alkynes[11] and allenes.[12] For instance, Widenhoefer *et al.*[10a] reported the first example of gold(I)-catalyzed intramolecular hydroamination of unactivated alkenes, efficiently affording various tetrahydropyrrole and hexahydropiperidine skeletons (Scheme 1a). Later, Yamamoto *et al.*[12a] reported the gold(I)-catalyzed intermolecular hydroamination between allenes and morpholine. The appropriate steric environment around gold catalysts plays a pivotal role in carrying out such aliphatic hydroamination. In addition,

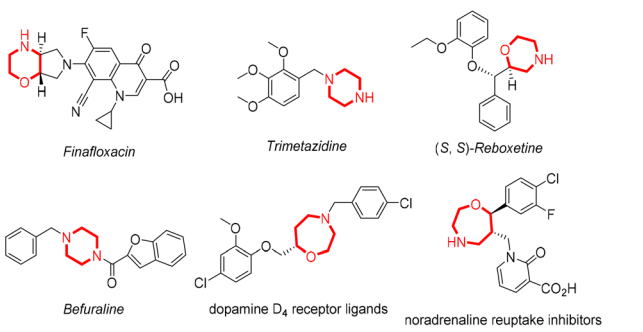

Fig. 1 Selected biologically active compounds containing morpholine, piperazine and 1,4-oxazepane skeletons.

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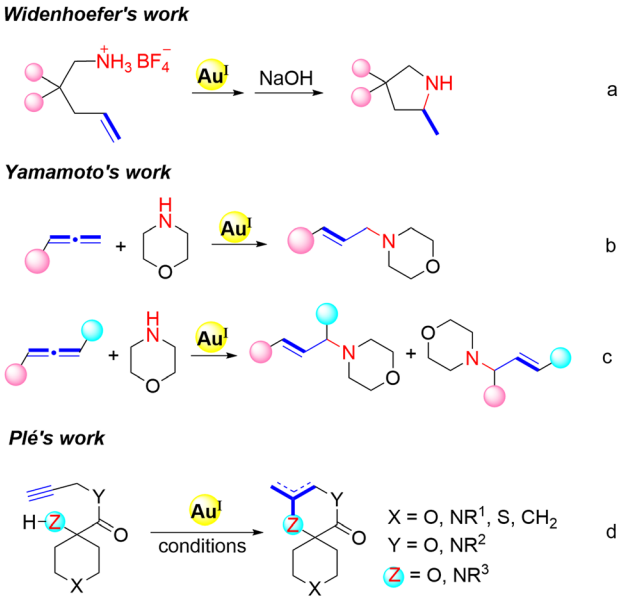
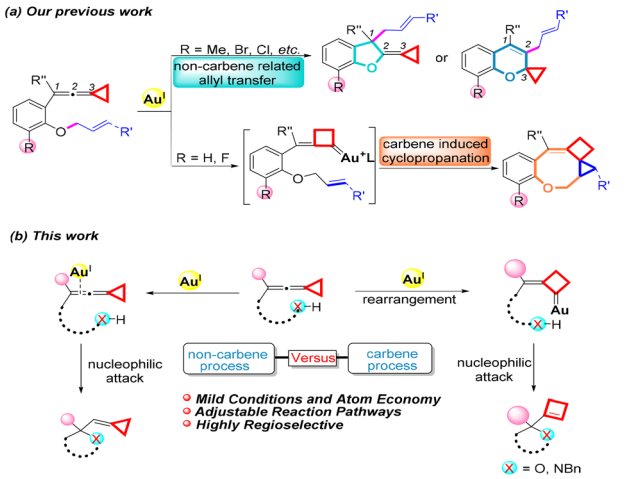


Scheme 1 Previous examples of gold(I)-catalyzed nucleophilic additions to C–C multiple bonds.



Scheme 2 Our previous work of gold(I)-catalyzed cycloisomerization of vinylidenecyclopropane-enes *via* a carbene or non-carbene process and this work.

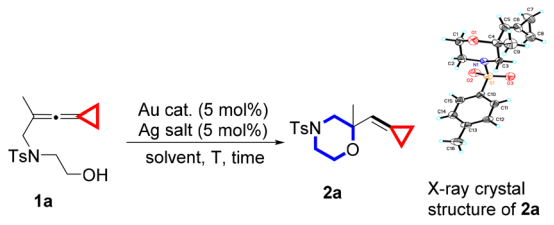
different from monosubstituted allenes (Scheme 1b), 1,3-disubstituted allenes usually gave a regioisomeric mixture and its ratio also depends on the steric effects (Scheme 1c). Moreover, an analogous cyclization reaction of alkynes has also been developed by Plé's group recently,[11a] giving N- and O-spirocycles in good to excellent yields (Scheme 1d).

In the meantime, it should be mentioned that catalytic transformations involving gold carbenes as key intermediates are also considered as some of the most important aspects of homogeneous gold catalysis.[13] To enrich the chemistry of gold carbene, a gold(I)-catalyzed cycloisomerization or allyl transfer of vinylidenecyclopropane-ene derivatives *via* controllable carbene or non-carbene processes has been explored in our laboratory,[14] providing a new synthetic route for the construction of O-bearing heterocyclic scaffolds containing a fused tricyclic system and fused five- and six-membered ring systems. Substituents adjacent to the oxygen atom on the aryl groups could switch the reaction mode (Scheme 2a).

Therefore, vinylidenecyclopropanes (VDCPs) can be realized as excellent candidates for gold(I)-catalyzed cycloisomerization due to their multiple reaction sites.[14,15] During our ongoing efforts on gold-catalyzed cycloisomerization of VDCPs, we subsequently designed and synthesized a series of VDCPs tethered with an alcohol or amine moiety to explore their reaction outcomes in gold(I)-catalyzed intramolecular cyclization (Scheme 2b, this work). Interestingly, we found that the cyclization could proceed through a carbene or a non-carbene process as well depending on the substrate's steric effect or the connected carbon chain length, affording various morpholine, piperazine or oxazepane derivatives in good yields under mild conditions. Herein, we wish to report the details in this context.

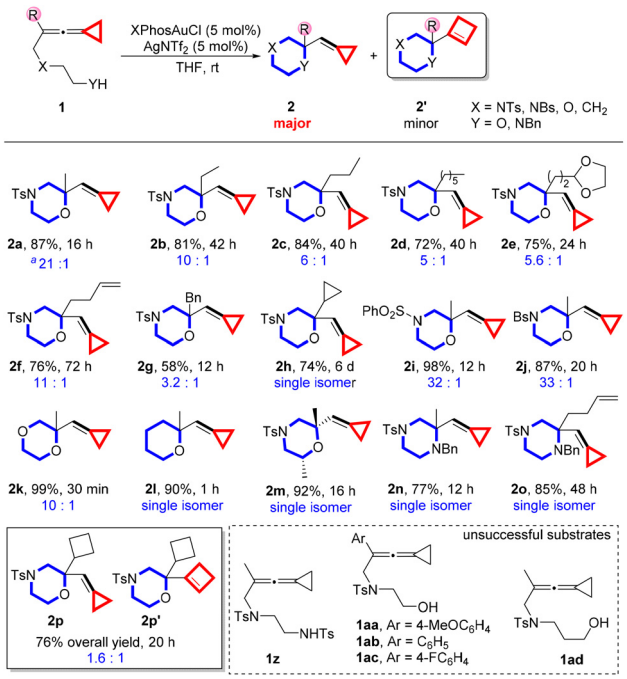
At the beginning of our investigation, VDCP **1a** was selected as the model substrate to optimize the reaction conditions of this gold(I)-catalyzed intramolecular cyclization. As shown in Table 1, a series of gold catalysts have been screened using $AgNTf_2$ as a silver salt additive and a pre-prepared JohnPhosAu(MeCN)SbF_6 complex upon heating in chlorobenzene at 90 °C (Table 1, entries 1–8), and it was found that the product **2a** was obtained in poor to moderate yields with complete consumption of substrate **1a**, and XphosAuCl was identified as the best gold(I) catalyst in this reaction, affording **2a** in 43% yield. Lowering the reaction temperature to 50 °C gave **2a** in 60% yield (Table 1, entry 9) and then, we found that by carrying out the reaction at room temperature and prolonging the reaction time, the yield of **2a** could be improved to 76% (Table 1, entry 10). The examination of the solvent effect with various commonly used solvents revealed that THF was the best solvent, giving **2a** in 95% NMR yield along with 87% isolated yield (Table 1, entries 11–16). During the screening of solvents, it is surmised that the use of acetonitrile as the solvent resulted in essentially complete recovery of the starting material without observing the formation of the product presumably due to its coordination with the monovalent gold(I) catalyst (Table 1, entry 12). Notably, compared to the *in situ* generation of the cationic gold catalyst, using cationic gold catalyst $XPhosAuNTf_2$ slightly reduced the yield of **2a** (Table 1, entry 17). Furthermore, the effect of silver salts on the reaction outcome was explored, identifying that $AgNTf_2$ led to a better result than other silver additives such as $AgBF_4$, AgOTf, and $AgSbF_6$ (Table 1, entries 18–20). No conversion was observed under the same conditions when the silver salt additive was replaced with NaBArF (Table 1, entry 21). As a consequence, alkylidenecyclopropane functionalized morpholine derivative **2a** was obtained in 87% isolated yield with excellent regioselectivity using 5 mol% XPhosAuCl as the catalyst and 5 mol% $AgNTf_2$ as the silver salt additive in THF at room temperature under an ambient atmosphere, which serve as the

Table 1 Optimization of the reaction conditions for the synthesis of **2a**



Entry[a]	Catalyst	Time (h)	Solvent	Temp. (°C)	Yield[b] (%)
1	IPrAuCl, $AgNTf_2$	12	PhCl	90	Trace
2	$(4\text{-}CF_3Ph)_3PAuCl$, $AgNT_2$	12	PhCl	90	Trace
3	$^iPr_3PAuCl$, $AgNTf_2$	12	PhCl	90	Trace
4	JohnPhosAuCl, $AgNTf_2$	12	PhCl	90	11
5	PPh_3AuCl, $AgNTf_2$	12	PhCl	90	35
6	$^tBu_3PAuCl$, $AgNTf_2$	12	PhCl	90	12
7	JohnPhosAu(MeCN)SbF_6	12	PhCl	90	38
8	XphosAuCl, $AgNTf_2$	12	PhCl	90	43
9	XphosAuCl, $AgNTf_2$	12	PhCl	50	60
10	XphosAuCl, $AgNTf_2$	16	PhCl	rt	76
11	XphosAuCl, $AgNTf_2$	16	1,4-Dioxane	rt	54
12	XphosAuCl, $AgNTf_2$	16	CH_3CN	rt	Trace
13	XphosAuCl, $AgNTf_2$	16	DCE	rt	40
14	XphosAuCl, $AgNTf_2$	16	THF	rt	95 (87)[c]
15	XphosAuCl, $AgNTf_2$	16	DCM	rt	46
16	XphosAuCl, $AgNTf_2$	16	Toluene	rt	68
17	$XphosAuNTf_2$	16	THF	rt	82
18	XphosAuCl, $AgBF_4$	16	THF	rt	50
19	XphosAuCl, AgOTf	16	THF	rt	83
20	XphosAuCl, $AgSbF_6$	16	THF	rt	86
21	XphosAuCl, NaBArF	16	THF	rt	Trace

[a] The reaction scale is 0.1 mmol of **1a** in untreated solvent (0.04 M). [b] Yield was determined from ^{1}H NMR spectroscopic data using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield.



Scheme 3 Substrate scope for the non-carbene process. Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol), XPhosAuCl (5 mol%) and $AgNTf_2$ (5 mol%) in THF (4.0 mL) at rt. Isolated yields. [a] Inseparable structural isomers of **2** and **2′** were formed and the ratio was determined on the basis of ^{1}H NMR spectroscopic data.

optimal conditions for the production of **2a**. The control experiments illustrated that silver salts such as $AgNTf_2$, Brønsted acid $HNTf_2$, and XPhosAuCl did not catalyze the reaction at all, indicating that this cyclization is indeed catalyzed by the gold(I) complex (see S8 in the ESI†). The crystal structure of **2a** was unequivocally determined by X-ray diffraction as shown in Table 1, and the ORTEP drawing and its CIF data are presented in the ESI.†

Next, we synthesized a variety of alcohol or amine tethered vinylidenecyclopropanes with different R groups located at allene moieties to explore the generality of this cyclization under the optimal conditions and the results are shown in Scheme 3. For alcohol tethered VDCPs **1b–1g**, in which the R group was a linear alkyl substituent, an alkyl chain with a terminal protected aldehyde group, a homoallyl group or a benzyl group, the reaction was tolerated, affording the corresponding products **2b–2g** in 58–87% yields along with a trace amount of inseparable cyclized compound **2′** derived from a gold–carbene induced cyclization. Remarkably, in the case of VDCP **1h** bearing a cyclopropane at the allene moiety, the desired product **2h** was formed in 74% yield as a single isomer perhaps due to the less steric hindrance of the cyclopropyl ring. Besides *N*-Ts protected VCDPs, *N*-phenylsulfonyl protected substrate **1i** and *N*-Bs protected substrate **1j** also performed very well, affording the desired products **2i** and **2j** in 98% and 87% yields, respectively. Substrates **1k** and **1l** connected by an oxygen atom or a carbon atom were also compatible, giving the corresponding products **2k** and **2l** in good yields ranging from 90% to 99% under the standard conditions. We were delighted to find that by replacing primary alcohol with a secondary alcohol, the substrate **1m** delivered the desired product **2m** in 92% yield as a single diastereoisomer and its stereochemical configuration was determined by ^{1}H NMR NOESY spectroscopic analysis. Moreover, amine tethered vinylidenecyclopropanes **1n** and **1o** gave the desired functionalized piperazines **2n** and **2o** as single isomers in 77% and 85% yields, respectively, illustrating that this reaction has excellent functional group tolerance. Interestingly, the use of VDCP **1p** as the substrate, which had a cyclobutane at the allene moiety, resulted in an inseparable mixture of **2p** and **2p′**, which contains a cyclobutene moiety, in an 8 : 5 ratio as determined by ^{1}H NMR analysis presumably due to its steric effect. Notably, when replacing the benzylamine unit with a tosylated amine group such as VDCP **1z**, no corresponding product could be obtained, perhaps due to its weaker nucleophilicity. In addition, aryl-substituted VDCPs **1aa–1ac** were not suitable substrates for this gold-catalyzed transformation, presumably because the aryl substituents on the allene moiety make them difficult to polarize by cationic gold species in our reaction system. Substrate **1ad** also failed to give the corresponding products under the standard conditions.

In order to gain a better understanding of the reaction processes, several sterically bulky R groups were introduced into the substrates, and we found that all of them could give the cyclobutene containing cyclized products **2q′–2t′** as major products in 56–86% yields (Scheme 4). The crystal structure of **2q′** was unambiguously determined by X-ray diffraction. The ORTEP drawing is given in Scheme 4 and its CIF data are also summarized in the ESI.† Particularly, different from VDCP **1p**, cyclobutyl containing amine tethered vinylidenecyclopropane **1v** furnished the desired product **2v′** as a sole product in 63% yield *via* a gold carbene process, indicating that the tethered nucleophile could also significantly affect the reaction pathway. To our surprise, further investigations revealed that our reaction system enables the formation of seven-membered 1,4-oxazepanes **2w′–2y′** in 67–88% yields as a sole product through a gold carbene process, indicating that the connected alkyl chain length of the substrate can modulate the reaction process.

In order to elucidate the impact of substrate steric bulkiness on the selectivity of reaction pathways, substrates **1a** and **1q** were selected to investigate the energy differences of several gold-VDCP intermediates since the *A*-value[16] of the methyl group is 1.8 kcal mol^{-1} and that of the isopropyl group is above 3.3 kcal mol^{-1}.[16d] The relative free energies of several key intermediates are shown in Fig. 2 (for details, see S135 in the ESI†). For substrate **1a**, the gold catalyst activates the allene double-bond away from the cyclopropyl unit, which is favored by 0.96 kcal mol^{-1}, suggesting that the non-carbene process is a dominant process for groups with less steric hindrance. For substrate **1q**, the gold species activates the allene double-bond connected to the cyclopropyl unit, which is favored by 0.86 kcal mol^{-1}, suggesting that the carbene process becomes a dominant process for groups with more steric hindrance. These results are in good agreement with our experimental findings (Schemes 3 and 4).

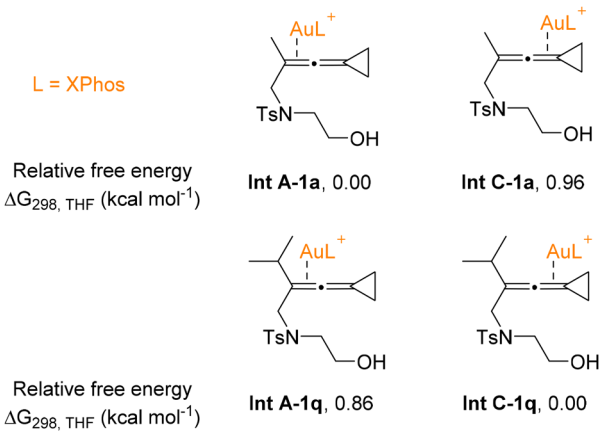
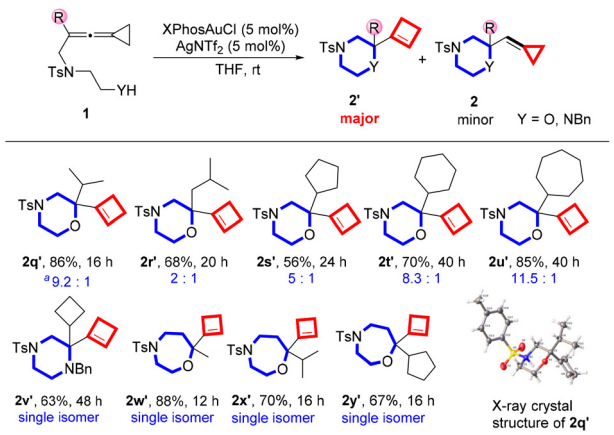
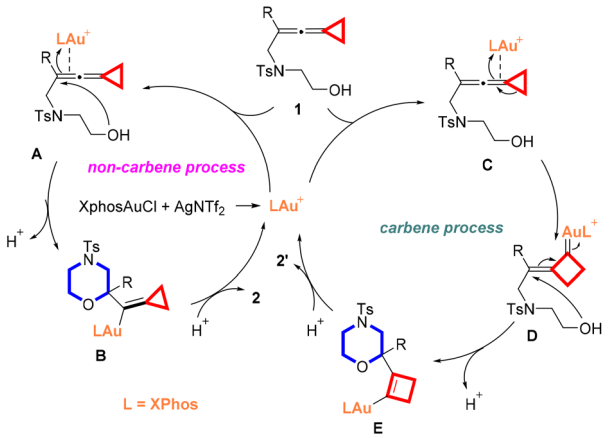


Fig. 2 The relative free energies of key intermediates.



Scheme 4 Substrate scope for the carbene process. Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol), XPhosAuCl (5 mol%) and $AgNTf_2$ (5 mol%) in THF (4.0 mL) at rt. Isolated yields. [a] Inseparable structural isomers of **2′** and **2** were formed and the ratios were determined on the basis of ^{1}H NMR spectroscopic data.

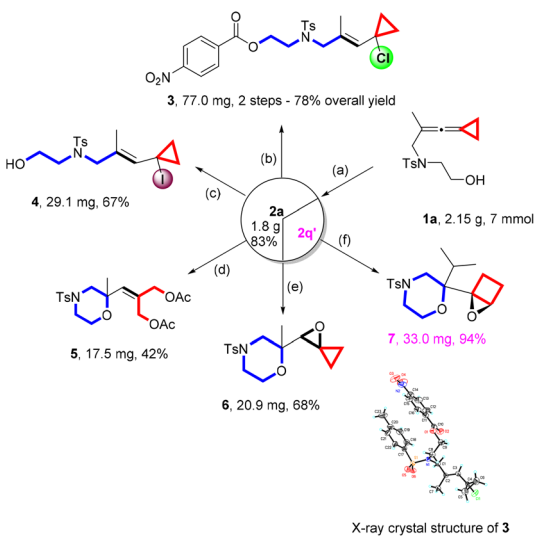
On the basis of the previous literature[12e,14,17] and our above results, a plausible mechanism for the present cyclization reaction is depicted in Scheme 5. Under the conditions of gold(I) catalysis, substrate **1** can undergo two different reaction pathways (carbene and non-carbene processes) depending on the steric hindrance of the R groups or the connected alkyl chain length. As for the non-carbene process, the π-activation of the double bond in the allene moiety with the *in situ* generated gold(I) complex takes place to furnish intermediate **A**, which triggers a 6-*exo*-*trig* cyclization through intramolecular nucleophilic addition by the hydroxyl group onto the electrophilic carbon center to afford the alkenyl gold intermediate **B**. The protodeauration of intermediate **B** produces the corresponding morpholine derivative **2** along with the regeneration of the Au (I) catalytic species for the catalytic cycle. In this pathway, the sterically less hindered R groups in substrate **1** may result in a lower transition state energy barrier of 6-*exo* cyclization, giving the products **2** as the major ones. However, the carbene and non-carbene pathways are competing cyclization processes in these reactions. Sterically more bulky groups at substrate **1**'s allene moiety may delay the direct 6-*exo* cyclization since the transition energy barrier is quite high and the carbene process



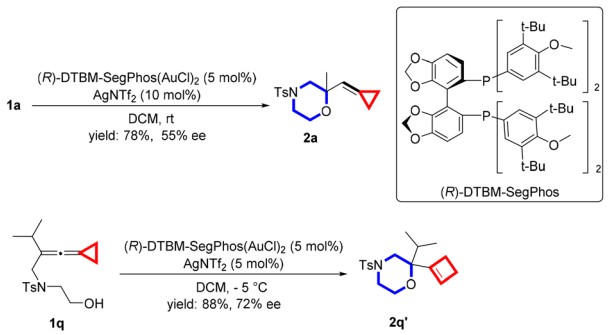
Scheme 5 Proposed reaction mechanisms.

becomes the main cyclization process, affording products **2′** as the major ones. The same reason can be applied for the prolonged alkyl chain since the direct cyclization will become a slow process and the carbene process will dominate the reaction pathway. Thus, coordination of the gold(I) complex with vinylidenecyclopropane **1** bearing a sterically bulky group gives intermediate **C**, which initiates a ring expansion to afford the gold carbenoid intermediate **D**. The intramolecular nucleophilic attack of the hydroxyl group onto the electrophilic carbon center in intermediate **D** and release of a proton furnish intermediate **E**, which undergoes protodeauration to produce the cyclized product **2′** and regenerates the gold catalyst. More comprehensive investigations on the mechanistic manipulation of carbene and non-carbene processes and the related density functional theory (DFT) calculations will be published in due course.

To illustrate the synthetic utility of the obtained product, a gram-scale reaction of **1a**, with 2.15 g (7.0 mmol), was performed and the reaction proceeded smoothly, delivering 1.8 g of **2a** in 83% yield (Scheme 6). Then, a variety of transformations of **2a** were conducted under different conditions (Scheme 6). Initially, treatment of **2a** with HCl aqueous solution (4.0 M in dioxane) gave a chlorine-substituted vinylcyclopropane tethered alcohol, which could be further transformed to compound **3** in 78% overall yield in the presence of *p*-nitrobenzoyl chloride, and its structure has been clarified by X-ray diffraction as shown in Scheme 6. Its CIF data are also presented in the ESI.† Next, iodine-substituted vinylcyclopropane tethered alcohol **4** was formed in 67% yield upon treating **2a** with 1.0 equiv. of $BF_3{\cdot}Et_2O$ and 1.5 equiv. of Bu_4NI in DCM at



Scheme 6 Gram-scale synthesis and transformations of the obtained products **2a** and **2q′**. All of the transformations were carried out using 0.1 mmol of **2a** or **2q′**. (a) XPhosAuCl (5 mol%), $AgNTf_2$ (5 mol%), THF, rt. (b) (1) HCl (4 M in dioxane), 80 °C; (2) DMAP (0.2 equiv.), DIPEA (3.0 equiv.), *p*-nitrobenzoyl chloride (2.5 equiv.), DCM, 0 °C. (c) Bu_4NI (1.5 equiv.), $BF_3{\cdot}Et_2O$ (1.0 equiv.), DCM, rt. (d) $Pd(OAc)_2$ (0.1 equiv.), Bu_4NI (1.0 equiv.), $PhI(OAc)_2$ (3.0 equiv.), CH_3CN, 60 °C. (e) *m*-CPBA (1.2 equiv.), DCM, rt. (f) *m*-CPBA (1.2 equiv.), DCM, rt.



Scheme 7 Asymmetric versions of the two processes for the production of **2a** and **2q′**.

room temperature. Considering that product **2a** contained an alkylidenecyclopropane subunit, treatment of **2a** with $Pd(OAc)_2$ and $PhI(OAc)_2$ afforded the corresponding diacetoxylated product **5** in 42% yield through a palladium-catalyzed ring-opening reaction according to our previous work.[18] Furthermore, epoxidation of **2a** and **2q′** with *m*-CPBA in DCM successfully gave the desired epoxide **6** in 68% yield as a 3 : 1 diastereomeric mixture and the epoxide **7** in 94% yield as a single diastereomer (Scheme 6).

Asymmetric variants of VDCPs **1a** and **1q** were also reacted with the chiral gold catalyst (*R*)-DTBM-SegPhosAuCl combined with $AgNTf_2$ in DCM at room temperature (for details, see S8 in the ESI†). As shown in Scheme 7, we found that treatment of **1a** with 5 mol% (*R*)-DTBM-SegPhosAuCl and 10 mol% $AgNTf_2$ afforded **2a** in 78% yield along with 55% ee value. For substrate **1q**, adding 5 mol% (*R*)-DTBM-SegPhosAuCl and 5 mol% $AgNTf_2$ gave the desired product **2q′** in 88% yield along with 72% ee value.

In conclusion, we have developed an efficient and novel synthetic protocol for the construction of morpholine, piperazine and oxazepane derivatives bearing an alkylidenecyclopropane or a cyclobutene moiety in good yields under mild conditions through a gold(I)-catalyzed intramolecular cycloisomerization of alcohol and amine tethered vinylidenecyclopropanes *via* a carbene or non-carbene process with a broad substrate scope. The steric bulkiness of the substituent at the allene moiety of vinylidenecyclopropanes and the chain length played key roles in the reaction pathway. In general, sterically bulky substituents and the prolonged alkyl chain prefer the gold(I)-catalyzed cyclization *via* a carbene process. In addition, a variety of transformations of the obtained product **2** have been performed to demonstrate their synthetic utility. Further investigations on the mechanistic paradigm of this gold(I)-catalyzed cyclization and the preparation of biologically active heterocycles are underway in our laboratory.

Author contributions

Shi, M. and Tavakol, H. directed the project and revised the manuscript. Wei, J. S., Shamsaddinimotlagh, S. and Yang, S.

wrote the manuscript and carried out the reactions. Wei, Y. checked the spectroscopic data and revised the manuscript.

Conflicts of interest

There are no conflicts of interest to declare.

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