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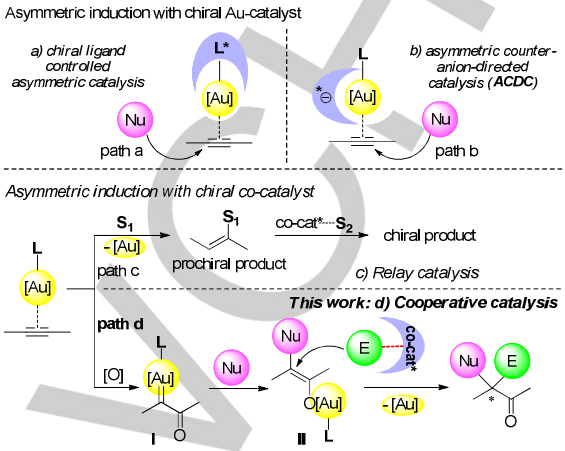
Enantioselective Oxidative Cyclization/Mannich Addition Enabled by Gold(I)/Chiral Phosphoric Acid Cooperative Catalysis

Hanlin Wei,[†] Ming Bao,[†] Kuiyong Dong,[†] Lihua Qiu,[†] Bing Wu,[†] Wenhao Hu,[*,‡] and Xinfang Xu[*,†,‡]

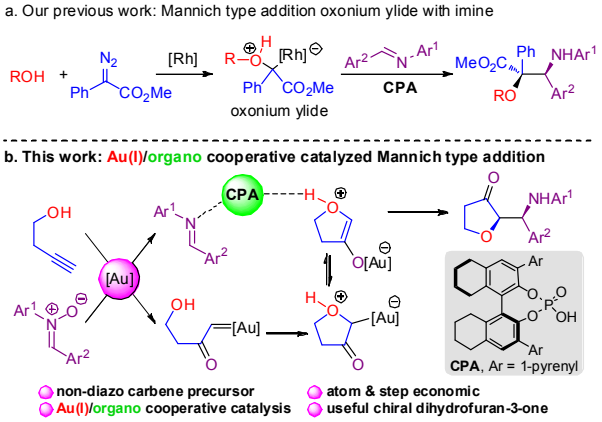
Abstract: *This work describes an enantioselective Mannich-type reaction of 3-butynol and nitrones to afford dihydrofuran-3-ones in good yields with excellent enantioselectivities. The reaction is initiated by gold-catalyzed alkyne oxidation, modification of the resulting gold carbene species with tethered hydroxyl group to form enolate species, and is terminated by an enantioselective Mannich-type addition with the assistance of chiral phosphoric acid (CPA) via hydrogen bonding. This novel pattern of alkyne transformation involving chemical bond cleavage, fragment modification and reassembly process provides an atom- and step-economic method, and is the first example of cooperative asymmetric catalysis in gold-catalyzed alkyne oxidations via an α-oxo gold carbene route.*

Gold-catalyzed oxidative cyclization of alkynes has found valuable applications in organic synthesis for the convenient construction of heterocyclic and carbocyclic frameworks.[1] One of the major breakthroughs of this approach would enable readily available and stable alkynes to replace α-diazo carbonyl compounds as α-oxo carbene precursors,[2] and intermediates possessing gold carbene character have been postulated and verified experimentally. These intermediate α-oxo carbenes can undergo a variety of synthetically challenging yet highly useful transformations such as Csp^3-H[3]/Csp^2-H[4] bond insertion, X-H insertion,[5] cyclopropanation,[6] ylide formation,[7] and others.[8] In recent decade, remarkable advances have been made in the development of enantioselective gold catalysis, but major challenges remain.[9] The main difficulties in developing efficient gold-catalyzed asymmetric transformations may be attributed to the linear coordination favored by Au(I),[10] which places the chiral ligand (L*) and the substrate on opposite side of the metal center, or far away from each other (Scheme 1a). The use of chiral counteranions to gold(I) catalysts has emerged as an effective asymmetric induction strategy,[11] and has shown versatile abilities in enantioselective functionalizations of alkynes (Scheme 1b).[12] The third successful method in asymmetric gold catalysis was reported by Gong, in which, a prochiral species was generated in the presence of achiral gold catalyst, followed by asymmetric transformations promoted by a chiral co-catalyst *via* relay catalysis (Scheme 1c).[13] Despite these significant achievements in catalytic asymmetric reactions of alkynes, the development of efficient asymmetric induction approach in gold-catalyzed oxidation of alkynes *via* an α-oxo gold carbene route is still limited, but highly desirable.



Scheme 1. Asymmetric induction models in gold catalysis.

Recently, the only two catalytic asymmetric cyclopropanation reactions of these in situ generated α-oxo gold carbene species were realized by L. Zhang[6a] and J. Zhang[6b] with chiral phophoramidite ligand and chiral P,N-bidentate ligand, respectively. Inspired by these significant achievements in asymmetric gold catalysis and our recent work on catalytic alkyne transformations,[14] we have been intrigued by the possibility of inducing the chirality in gold-catalyzed alkyne oxidation *via* cooperative catalysis. This approach could selectively activate the electrophile, and followed by an enantioselective interception of the prochiral intermediate, for example, gold enolate **II** (Scheme 1d),[15] enable asymmetric induction approach. Cooperative catalysis has been demonstrated as a powerful method in asymmetric multi-component reactions through the trapping of reactive ylide or zwitterionic intermediates with various electrophiles (Scheme 2a).[16],[17] However, analogous asymmetric transformation with alkynes as a non-diazo carbene precursor has not been reported.[18] Herein, we report a successful implementation of the design and development of a practical solution with achiral gold(I)/chiral phosphoric acid (CPA) cooperative catalysis to enable a highly enantioselective Mannich-type addition of an in



Scheme 2. Asymmetric Mannich-type addition of ylide/enolate.

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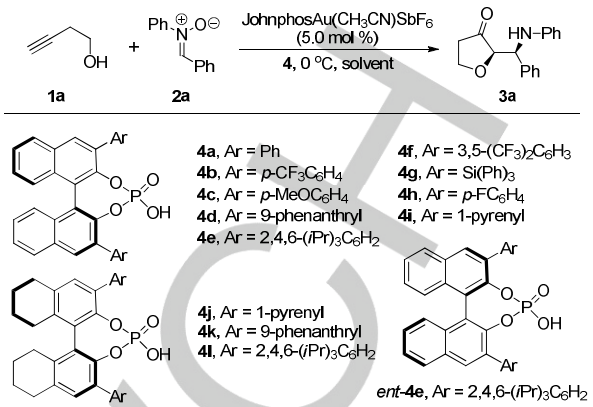
situ generated gold enolate intermediate with imine to form chiral dihydrofuran-3-ones (Scheme 2b). In this context, we envisioned that this method would allow replacement of β-hydroxyl diazoketone, which is challenging to prepare, with stable, cheap, and readily available homopropargylic alcohol; and the use of leaving fragment imine as electrophile would be highly appealing,[19] thereby establishing a succinct, safe, atom- and step-economic route to this class of heterocycles. Notably, the chiral dihydrofuran-3-ones are privileged heterocyclic motifs, that frequently occur in the structures of a plethora of biologically active molecules.[20] In addition, they can also serve as valuable building blocks for the synthesis of complex molecules.[21]

Table 1 shows the results of optimization of the asymmetric Mannich-type addition of 3-butynol **1a** and nitrone **2a** with JohnphosAu(CH_3CN)SbF_6 and chiral phosphoric acid **4** (CPA) at 0 °C. In a typical operation, **1a** was added to the reaction mixture over 2 h. Control experiment in the absence of the chiral phosphoric acid provided the racemic product **3a** in 59% yield (entry 1). Initial tests with various chiral phosphoric acids **4** in DCE (dichloroethane) led to the formation of product **3a** in >60% yields with most cases around 80% *ee* (entries 2-16). Lowering the CPA loading to 5.0 mol% was possible without decreasing product yield, and only resulted in a slight reduction of *ee* from 84% to 82% (entries 6 vs 12). Notably, when the reaction was catalyzed by CPA **4e**'s enantiomer, *ent*-**4e**, comparable reactivity was observed, and formation of the enantiomeric product **3a** occurred in 83% ee (entries 12 vs 17). Further screening of reaction conditions (see Table S1), gold(I) complexes (see Table S2), and chiral phosphoric acids **4** (CPA), including chiral spiro phosphoric acids (see Table S3),[23] did not improve the results. The best results were obtained in DCE with **4j** as co-catalyst at 0 °C to form **3a** as single *syn*-diastereoisomer in 67% isolated yield with 91% ee (entry 14) after evaluation of various solvents (entries 18-21). The absolute configuration of this product was confirmed by single-crystal X-ray diffraction analysis of its bromo-derivative **3b**.[22]

Under the optimized conditions, a wide variety of nitrones with 3-butynol **1a** were examined, and the results are summarized in Table 2. Notably, all the tested substrates gave the Mannich-type addition products **3** as single *syn*-diastereoisomers in good yields with excellent *ee*. Nitrones **2b**-**2h** bearing bromo, chloro, methyl, methoxyl, trifluoromethyl, cyano groups at the aniline moiety produced the expected products **3b**-**3h** in high yields with 90%-94% *ee*. The reaction proceeded smoothly irrespective of the electronic character (**3i**, **3r** and **3s**) and steric effect (**3j**-**3m**) of nitrones derived from substituted benzaldehydes, and in some cases, slightly modified conditions with 10 mol% of **4e** was used to ensure the high enantioselectivity (see note b). Moreover, piperonyl, thienyl, furyl, and styryl nitrones were all applicable substrates to deliver **3n**-**3q** and **3t** in 60%-82% yields with >90% ee. The *N*-methyl nitrone remained intact under these conditions (see Figure S3). The *gem*-dimethyl 3-butynol produced **3u** in 50% yield with 84% *ee*. The 2-ethynylphenol (**1c**) was also compatible under these conditions according to the ^{1}H NMR of the crude reaction mixture (see Figure S1). However, this product decomposed to give the α,β-unsaturated ketone in 63% yield after the column chromatography on silica gel *via* retro-aza-Michael addition. Other homologues, 4-phenyl-3-butynol or 3-butynoic acid didn't

Table 1: Condition optimization.[a]



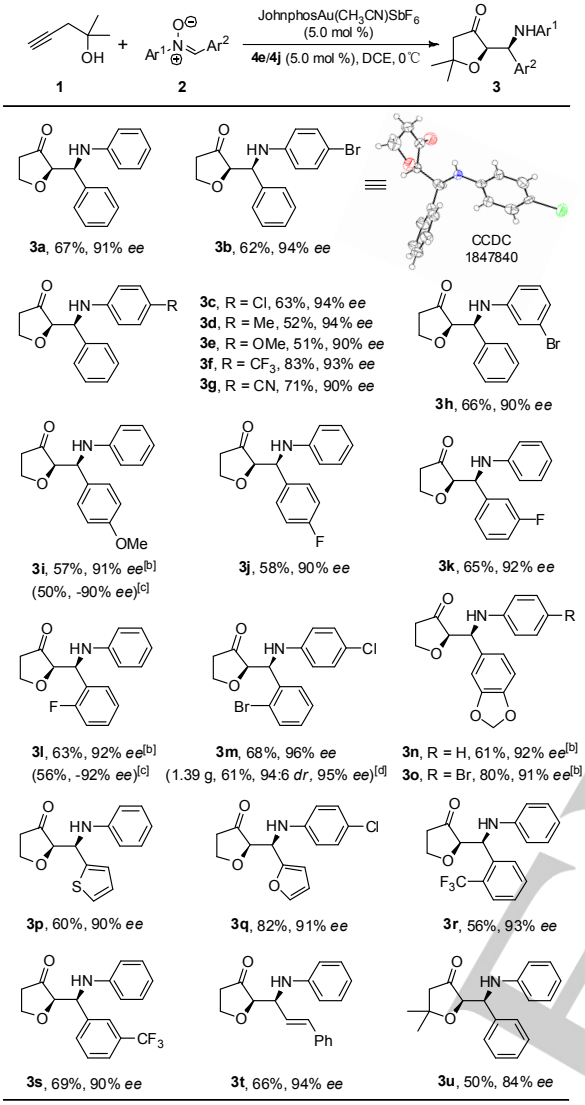
Entry	**4** (x mol %)	Solvent	Yield [%][b]	*dr*[c]	*ee* [%][e]
1	-	DCE	59	71:29	0
2	**4a** (10)	DCE	61	92:8	51
3	**4b** (10)	DCE	71	84:16	42(17)
4	**4c** (10)	DCE	63	89:11	71(20)
5	**4d** (10)	DCE	63	>95:5	81
6	**4e** (10)	DCE	61	>95:5	84
7	**4f** (10)	DCE	64	90:10	11(5)
10	**4g** (10)	DCE	61	>95:5	4
11	**4h** (10)	DCE	65	>95:5	78
12	**4e** (5)	DCE	63	>95:5	82
13	**4i** (5)	DCE	63	>95:5	81
14	**4j (5)**	**DCE**	**67**	**>95:5**	**91**
15	**4k** (5)	DCE	63	91:9	87
16	**4l** (5)	DCE	62	>95:5	72
17	*ent*-**4e** (5)	DCE	61	>95:5	-83
18	**4j** (5)	DCM	62	>95:5	88
19	**4j** (5)	$CHCl_3$	43	>95:5	74
20	**4j** (5)	TBME	25	89:11	78(6)
21	**4j** (5)	$PhCF_3$	46	94:6	78(8)

[a] Unless otherwise noted, the reaction was carried out on a 0.2 mmol scale: **1a** (0.3 mmol) in 1.0 mL solvent was added to a solution of JohnphosAu(CH_3CN)SbF_6 (5.0 mol %), chiral phosphoric acid (CPA) **4**, **2a** (0.2 mmol) in the same solvent (1.0 mL) under an argon atmosphere at 0 °C for 2 h, and the reaction continued for an additional 10 h under these conditions. [b] Isolated yields of **3a**. [c] The *dr* ratios were determined by ^{1}H NMR analysis of crude reaction mixture. [d] The *ee* values were determined by chiral HPLC analysis.

give the oxidative product with nitrone (see Figure S2). It's worth mentioning that, when the reaction was catalyzed by catalyst's enantiomer, *ent*-**4e**, similar reactivity was observed, and formation of the enantiomeric products demonstrated access to both stereoisomers with high *ee* (**3i** and **3l**, see note c). In addition, the reaction performed well on a gram scale to give the desired product in 61% yield with 94:6 *dr* and 95% *ee* (**3m**, see note d).

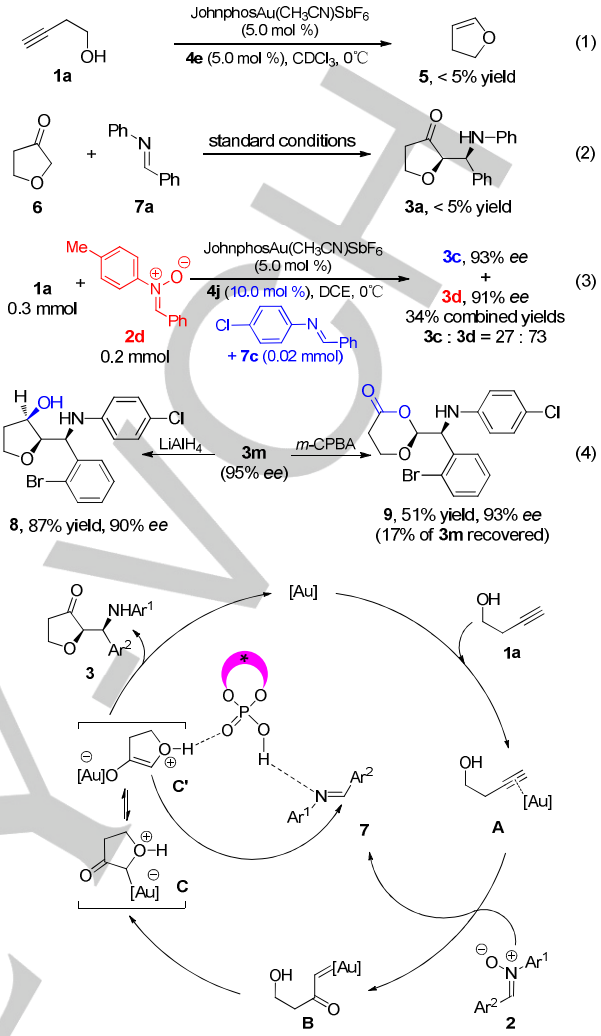
To understand the reaction pathway for this new process, several control experiments were initially performed. Reaction of **1a** with gold catalyst and CPA **4e** in the absence of nitrone in $CDCl_3$ gave no evidence of cycloisomerization to form 2,3-dihydrofuran **5** (eq 1, see Figure S4 for details), which is consistent with Liu's results,[18] and [3+2]-cycloaddition of **5** with nitrone **2** couldn't occur in this reaction.[24] To rule out the possibility that product **3** resulted from a stepwise reaction of an intramolecular O-H insertion and then a Mannich-type addition, an additional control experiment of premade O-H insertion product **6** with imine **7a** was conducted under standard conditions, but no **3a** was observed and most of the reactants

Table 2: Substrate scope.[a]



[a] Reaction conditions: **1** (0.3 mmol) in DCE (1.0 mL) was added to a solution of JohnphosAu(CH_3CN)SbF_6 (5.0 mol %), chiral phosphoric acid (CPA) **4j** (5.0 mol %), and **2** (0.2 mmol) in DCE (1.0 mL) under argon atmosphere at 0 °C in 2 h, and the reaction continued for an additional 10 h under these conditions. The yields are given in isolated yields. [b] The reactions were catalyzed with **4e** (10 mol %) instead of **4j**. [c] The reactions were catalyzed with *ent*-**4e** (10 mol %) instead of **4j**. [d] The reaction was carried out on a 6.0 mmol scale with 2.0 mol % gold catalyst (the minor diastereoisomer in 56% *ee*).

remain intact (eq 2, see Figure S5 for details). These results suggested a concerted reaction pathway, which is in agreement with previous studies in ylide intermediate trapping processes with electrophilic imines.[17],[25] To further confirm that the N-O bond cleavage of nitrone produces free imine species, external imine **7c** (1.0 equiv.) was introduced to the reaction of **1a** with **2d** under standard conditions. However, the reaction was inhibited dramatically in the presence of stoichiometric amount of imine, and no proton NMR signal of product **3c** was observed. To our delight, when the crossover experiment was conducted in the presence of 10 mol% imine **7c** and 10 mol% CPA **4j**, two products **3c** and **3d** were isolated in 34% combined yields with **3c**:**3d** = 27:73, in 93% and 91% *ee*, respectively (eq 3, see Figure S6-S8 for details). These results support the formation of



Scheme 3. Proposed reaction mechanism.

a free imine fragment and the Brønsted acid catalyzed reassembling process.

A reaction mechanism is proposed in Scheme 3 based on the aforementioned results and previous studies.[16]-[18] Initially, gold-catalyzed alkyne oxidation in the presence of nitrone **2** forms the gold carbene intermediate **B** *via* **A**, followed by intramolecular attack with the tethered hydroxyl group to give a proposed Au-associated oxonium ylide **C** or its enolate form **C'**. Then, reassembly with imine fragment **7** with the assistance of chiral phosphoric acid through hydrogen bonding produces the Mannich addition product **3** and regenerates the gold catalyst. The observed exceptionally high stereoselectivity of this reaction is attributed to the hydrogen bonding of chiral phosphoric acid (CPA) with two reactive species in the Mannich-type addition step, which served as a chiral proton-transfer shuttle.[23]

To demonstrate the synthetic utility of the current method, further transformations of product **3m** (95% ee) were conducted (eq 4). The reduction product **8** and oxidation product **9** were obtained in 87% (90% ee) and 51% (93% ee) yields, respectively.

In summary, we report a gold(I)/chiral phosphoric acid (CPA) cooperative catalyzed Mannich-type reaction of 3-butynol and

nitrones to afford dihydrofuran-3-one derivatives in good yields with excellent diastereoselectivities and enantioselectivities. This novel pattern of alkyne transformation involving chemical bond cleavage, fragment modification and reassembly process provides an atom- and step-economic method with stable, inexpensive, and readily available materials. In comparison with disclosed asymmetric gold catalysis approaches, this work presents the first example of catalytic asymmetric trapping of a gold enolate in alkyne oxidations *via* an α-oxo gold carbene route, and could inspire more discoveries in gold-catalyzed asymmetric alkyne transformations.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cooperative catalysis • gold catalysis • carbene • alkyne oxidation • enantioselective Mannich-type addition

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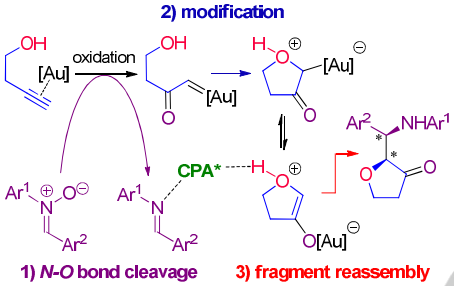
COMMUNICATION

A novel gold(I)/chiral phosphoric acid (CPA) cooperative catalyzed Mannich-type reaction has been disclosed, which presents the first example of asymmetric trapping of a gold enolate in alkyne oxidations *via* an α-oxo gold carbene route. This innovative pattern of alkyne transformation involving chemical bond cleavage, fragment modification and reassembly process provides an atom- and step-economic method with stable, inexpensive, and readily available materials.



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