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Gold/Brønsted Acid Relay Catalysis for Enantioselective Construction of Spirocyclic Diketones

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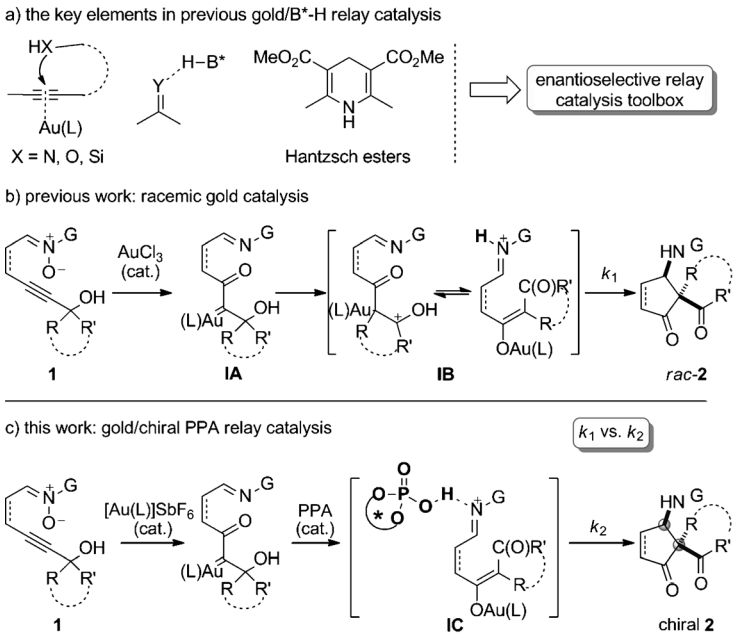
Enantiopure spirocycles[1] represent a structural motif present in natural products and biologically active compounds such as fusarisetin A, a potent cancer migration inhibitor,[2] and acutumine, an alkaloid with antiamnesic and selective T-cell cytotoxicity.[3] Furthermore, their rigid structures make them a privileged platform for the development of chiral ligands.[4] The ability to enantioselectively construct such important spirocyclic molecules in a rapid and efficient manner still represents a major challenge in modern organic synthesis.[5] Moreover, catalytic enantioselective synthesis of adjacent quaternary and tertiary chiral centers still remains scarce by existing methodologies.[1,6]

Gold catalysis has witnessed tremendous activity in recent years, which allows readily available substrates to be converted into diverse carbocyclic or heterocyclic scaffolds with a significant increase in molecular complexity.[7] Although inherently apt for asymmetric synthesis, current methods are mostly based on the principle of a chiral phosphine or carbene ligand on the metal center.[8] In this context, the successful variant of asymmetric gold catalysis applied to the cascade or domino reaction has been largely unexplored, which may result from the fact that enantioselectivity control in three or more mechanistically distinct reactions in a consecutive process by one simple gold complex is an extremely difficult task.[9] Very recently, gold/Brønsted acid relay catalysis is emerging as an alternative approach for the creation of new enantioselective transformations (Scheme 1a).[10–11] Despite being straightforward, the reported reactions have encountered several restrictions: 1) the reaction type disclosed so far is relatively onefold, in which the gold catalyst is commonly responsible for the alkyne hydrofunctionalization (hydroamination, hydroxylation, and hydrosiloxylation), 2) in most cases, stoichiometric Hantzsch esters for the asymmetric transfer hydrogenation are required, and 3) the intramolecular cascade version has not been achieved. Thus the attempted application of this gold/Brønsted acid relay catalysis strategy to other more various transformations, especially to those cascade reactions, is highly encouraged.



Scheme 1. Gold/chiral Brønsted acid catalyzed consecutive transformations.

Based on the importance of the spirocyclic scaffold, we focused our attention on the efficient redox-pinacol-Mannich cascade reaction developed by Shin and co-workers (Scheme 1b).[12] Undoubtedly, ability to control the reaction enantioselectivity is extremely attractive.[13] If successful, this would permit facile access to spirocyclic diketones with contiguous chiral centers, which is still an urgent need for enantioselective construction of quaternary stereocenters by using gold catalysts.[8,14] Specifically, it would provide a redox-, atom-, and step-economic approach to enantiopure spirocycles by starting from readily available nitrone compounds.

Our exploratory studies began with the first strategy, that is, using chiral-ligand-derived gold complexes to attempt the enenatioselective synthesis (Figure 1). Unfortunately, extremely poor levels of enantioinduction (up to 4% *ee*; *ee* = enantiomeric excess) and low to moderate diastereoselectivity were obtained when using those privileged chiral ligands in asymmetric gold catalysis, such as 1,1′-binaphthalene-2,2′-

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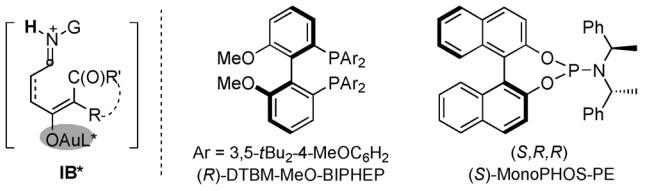


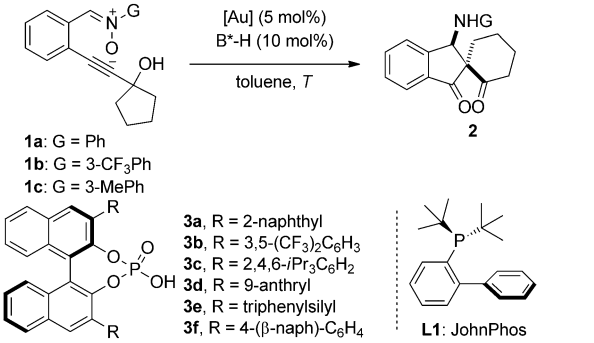
Figure 1. Chiral ligands for gold(I)-catalyzed reactions.

diylbis[bis(3,5-dimethylphenyl)phosphine] ((*S*)-xylylBINAP), (*R*)-DTBM-MeO-BIPHEP, and (*S*)-MonoPHOS-PE.[8,15] The failure is probably due to the linear coordination geometry of gold(I), which results in the long distance between the chiral ligand (L*) and the reaction site generating the stereocenters (Figure 1, **IB***).

Careful analysis of the possible mechanism reveals that an imine intermediate **IB** might be generated in situ (Scheme 1b). With the knowledge that chiral 1,1′-bi-2,2′-naphthol (BINOL) phosphoric acids (PPAs) have become recognized as excellent chiral Brønsted acid catalysts to activate imine substrates for enantioselective addition,[16] we then turned our attention to the gold/chiral Brønsted acid relay catalysis strategy,[10–11] that is, chiral PPAs activate the imine intermediates (shown as **IC**) which accelerate direct Mannich reactions in an enantioselective fashion. The key point to warrant in our above hypothesis is the difference between the reaction rates for Mannich addition of **IC** (k_2) promoted by chiral PPAs and the background reaction of **IB** (k_1) catalyzed by an achiral gold complex leading to the racemic form (Scheme 1).

With this hypothesis in mind, the asymmetric redox-pinacol-Mannich cascade reaction of compound **1** in the presence of various gold complexes and chiral BINOL phosphoric acids was investigated as depicted in Table 1. Consistent with our expectations, this combination of gold complex with BINOL-derived Brønsted acids indeed furnished promising results. Moreover, the addition of 5 or 4 Å molecular sieves (MS) resulted in an improvement of *ee* (see the Supporting Information). Although the reason is yet to be clear, it is likely that a trace amount of water may compete with PPA in binding with the imine moiety. Gratifyingly, under the simple metal salt of $AuCl_3$, the reaction of **1a** proceeded cleanly with excellent diastereoselectivity (diastereomeric ratio (d.r.) > 20:1). It was found that PPA **3b** with the electron-withdrawing aryl groups and the sterically hindered aryl-substituted catalyst **3c** gave moderate enantioselectivity (55–67 % *ee*; Table 1, entries 2,3). Reaction-temperature screening showed that −30 °C was a promising temperature and lowering the reaction to −60 °C would not bring further benefit (entries 3–5). Further investigations of the solvent effect suggested that the nonpolar toluene was the best solvent for this transformation (see the Supporting Information). As for the achiral gold complexes, the role of the ligand and the counteranion was also examined (entries 6–13). To our delight, the electron-rich and bulky JohnPhos derived cationic gold(I) complexes with either SbF_6^- or Tf_2N^- as the counteranion provided higher enantioselectivity (83 % *ee*), albeit the reactions required 40 h to be complete (entries 4, 12–13). The lower catalytic activity observed for [Au(L1)(Me)] (reacting with PPA to give a PPA-derived gold complex),[11a] [Au(L1)]OTf, and [Au(L1)]BF_4 can be rationalized in terms of the stronger coordinating counteranions (entries 9–11). An excellent *ee* was obtained in the case with **1b** as the substrate and **3d** as the relay catalyst (91 % *ee*, entry 14). Finally, a further enhanced result (92 % *ee*) could be achieved by using trifluorotoluene as the solvent with longer reaction time (entries 15 vs. 16). Similarly, with phosphoric acids **3e–f** as the relay catalysts, no higher enantiomeric excesses were observed (entries 17–18). Interestingly, replacing the *N*-3-CF_3-phenyl (**1b**) with *N*-3-Me-phenyl (**1c**) led to a decrease in the enantioselectivity (entries 19 vs. 16). All these results suggest that the electron-withdrawing, sterically demanding CF_3 substituent is beneficial to both the reactivity and enantioselectivity of the reaction. It is notable that trifluoromethylated arenes are essential structural motifs in a great number of pharmaceuticals, agrochemicals, and organic materials; the introduction of trifluoromethyl (CF_3) into pharmaceuticals can substan-

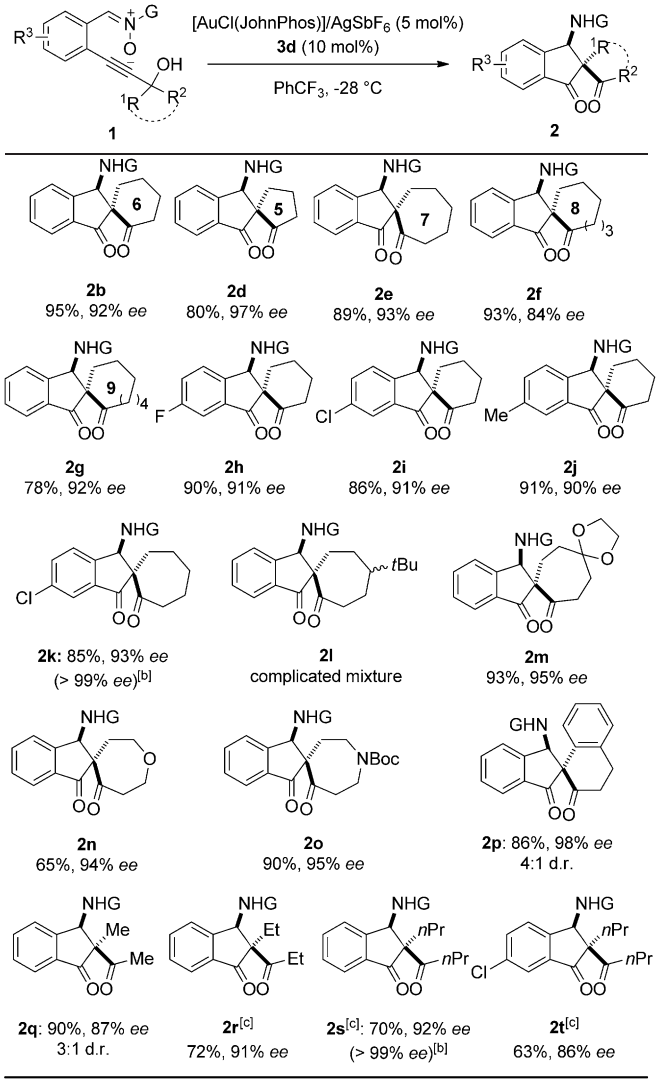
Table 1. Screening of reaction conditions.[a]



Entry	1	[Au][b]	B*−H	*T* [°C]	*t* [h]	*ee* [%][c]
1	**1a**	$AuCl_3$	**3a**	0	4	35
2	**1a**	$AuCl_3$	**3b**	−30	6	55
3	**1a**	$AuCl_3$	**3c**	0	2	67
4	**1a**	$AuCl_3$	**3c**	−30	2	77
5	**1a**	$AuCl_3$	**3c**	−60	30	72
6	**1a**	[$AuCl_2$(Pic)][d]	**3c**	−20	12	59
7	**1a**	[Au(IPr)]OTf	**3c**	−20	24	35
8	**1a**	[$Au(PPh_3)$]OTf	**3c**	−20	60	52
9[e]	**1a**	[Au(L1)(Me)]	**3c**	−30	72	n.d.
10[e]	**1a**	[Au(L1)]OTf	**3c**	−20	96	n.d.
11[e]	**1a**	[Au(L1)]BF_4	**3c**	−20	96	n.d.
12	**1a**	[Au(L1)]SbF_6	**3c**	−30	40	83
13	**1a**	[Au(L1)]NTf_2	**3c**	−30	40	83
14	**1b**	[Au(L1)]SbF_6	**3d**	−30	2	91
15[f]	**1b**	[Au(L1)]SbF_6	**3d**	−30	2	91
16[f,g]	**1b**	[Au(L1)]SbF_6	**3d**	−28	4	92
17[f,g]	**1b**	[Au(L1)]SbF_6	**3e**	−28	20	80
18[f,g]	**1b**	[Au(L1)]SbF_6	**3f**	−28	20	60
19[f,g]	**1c**	[Au(L1)]SbF_6	**3d**	−28	24	78

[a] Reactions were run on a 0.1 mmol scale in 2.0 mL of toluene, 5 Å molecular sieves (50 mg) were added. Unless specified otherwise, conversions were > 99 %. [b] Au^I catalysts were generated in situ from the [AuCl(L)] and AgX salts. [c] Determined by chiral HPLC analysis. [d] Pic = 2-picolinate. [e] The conversion was < 10 %. [f] 4 Å molecular sieves (50 mg) were used. [g] $PhCF_3$ as the solvent.

Table 2. Scope of substrates for relay-catalyzed cascade transformation.[a]



[a] All reactions were preformed with [AuCl(JohnPhos)]/$AgSbF_6$ (5 mol%) and **3d** (10 mol%) in $PhCF_3$ at −28 °C for 2–72 h. Yields are of materials isolated by silica gel chromatography. G = 3-CF_3Ph (Boc = *tert*-butoxycarbonyl). [b] *ee* following a single recrystallization. [c] A minor amount of isomers relative to **2r**, **2s**, and **2t** are given in the Supporting Information.

tially alter their properties, such as metabolic stability, lipophilicity, and ability to penetrate the blood/brain barrier.[17]

The scope of substrates for this relay-catalyzed cascade transformation was then studied under the optimized conditions (Table 2). In most cases, the reactions proceeded smoothly to give the desired products **2** in good to high yields (up to 95%) with up to >99% *ee*. The chiral spirocyclic diketones including five- to nine-membered ring structures (**2b–g**) could be well constructed. It is noteworthy that substrates **1m–o** containing heteroatoms within their cyclic skeletons are also compatible, providing excellent stereochemical outcomes (94–95% *ee*) and moderate to high yields. However, the result was frustrated by using **1l** as the substrate, giving a complicated mixture, which indicated that the chiral PPA may not be involved in the stereoselective pinacol rearrangement step. To our delight, this enantioselective cascade process can be applicable to acyclic *gem*-dialkyl substrates, leading to compounds **2q–t** with high enantioselectivity. Generally, both electron-withdrawing and -donating substituents at the C4-position of the aromatic core (**1h–k**, **1t**) were suitable for this asymmetric relay catalytic reaction (**2h–k**, **2t**). Furthermore, the enantiopurity of **2k** and **2s** increased to >99% *ee* after a single recrystallization.

During the investigation of the asymmetric cascade of *N*-benzyl-type substrate **1**, we found that the corresponding products **2** underwent racemization at room temperature. For instance, the enantiomerically enriched **2u** (94% *ee*) in isopropanol was periodically analyzed by HPLC analysis by using a chiral stationary phase. Continued analysis of the solution showed that the *ee* of **2u** was decreasing as shown in Figure 2. This phenomenon implies that the Mannich addition is a reversible process in this redox-pinacol-Mannich cascade reaction. Thus, a suitable N-substituent is also critical to the successful development of this asymmetric cascade.

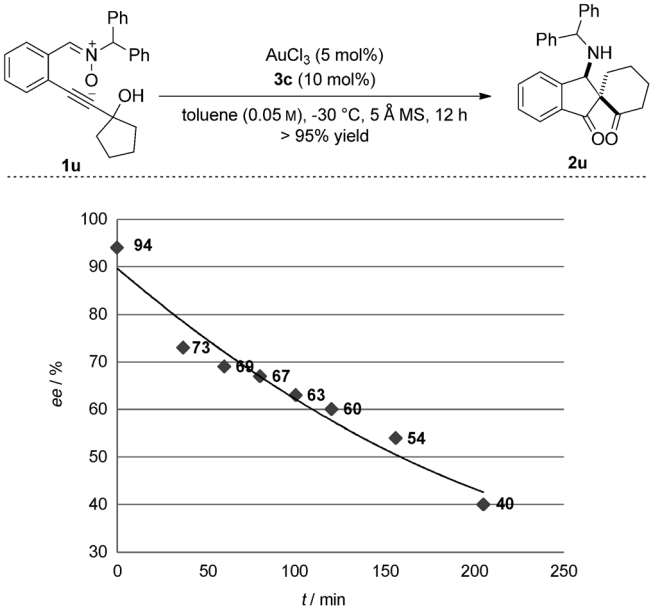
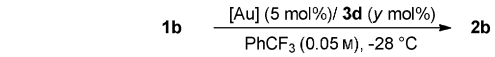


Figure 2. Racemization of **2u**.

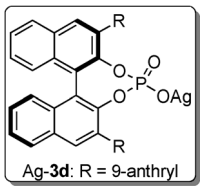
Finally, given the possibility of an exchange of the metal counteranion with chiral PPA, which could lead to the formation of a gold(I) complex cation-chiral counteranion ion pair to catalyze this reaction.[18] We conducted control experiments exploiting pure chiral gold phosphorate, derived from [AuCl(L1)] and chiral silver phosphorate Ag-**3d** as the catalyst (Table 3). The reaction with chiral gold phosphorate was incomplete, with a lower enantioselectivity in comparison with the optimized conditions. These outcomes indicate that 1) the anion of chiral phosphate has a higher coordinating character than [SbF_6^-], resulting in a much decreased catalytic performance of the relative gold complex, 2) the chiral gold phosphorate, even if it was formed, has little in-

Table 3. Control experiments.



[Au]	*y* [mol%]	*t* [h]	conv. [%]	*ee* [%]
[AuCl(L1)]/$AgSbF_6$	–	21	99	0
[AuCl(L1)]/$AgSbF_6$	10	4	99	92
[AuCl(L1)]/Ag-**3d**[a]	–	52	30	68

[a]



Ag-**3d**: R = 9-anthryl

fluence on the enantioselective Mannich addition, and 3) the PPA serves as the real catalyst for the enantiodetermining step (Scheme 1, $k_2 > k_1$).

In summary, we have successfully developed a gold/chiral Brønsted acid as a relay catalysis system for the efficient highly enantioselective redox-pinacol-Mannich cascade. Chiral β-amino spirocyclic and quaternary diketone derivatives were obtained in moderate to excellent yields with up to >99% *ee*. Critical to the successful development of this asymmetric transformation is the reaction for Mannich addition promoted by chiral Brønsted acid superior to the background reaction catalyzed by gold complexes. The reversible Mannich step in some substrates makes it very difficult to obtain high enantioselectivity and the rapid isolation operation is crucial to address this issue. The CF_3 groups on the structure of the solvent and substrate also bring benefit to improve enantioselectivity and slow down the racemization process. Further studies of the detailed mechanism and synthetic applications are under investigation.

Experimental Section

General: In a sealed dry glass tube, [AuCl(JohnPhos)] (0.005 mmol, 5 mmol%) and $AgSbF_6$ (0.005 mmol, 5 mmol%) under an argon atmosphere were taken up in trifluorotoluene (0.01 M based on substrate) and stirred at RT for 13 min. In another sealed dry glass tube, a solution of chiral PPA **3d** (0.01 mmol), nitrone-tethered tertiary propargyl alcohol **1** (0.1 mmol), and 4 Å molecular sieves (50 mg) in trifluorotoluene (1.5 mL) under an argon atmosphere was cooled to −28 °C for 15 min. The gold catalyst solution (0.5 mL) was quickly transferred to the substrate solution and the reaction was kept with stirring at −28 °C for 2–72 h. The resulting mixture was quenched with three drops of Et_3N (ca. 150 μL), diluted with AcOEt, and filtered through a pad of Celite. The filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography on Et_3N deactivated silica (hexanes/AcOEt 20:1 to hexanes/AcOEt 4:1) to yield the corresponding product **2**.

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Keywords: asymmetric catalysis · gold · quaternary center · relay catalysis · spirocycles

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