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Construction of spirocarbocycles *via* goldcatalyzed intramolecular dearomatization of naphthols[†]

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A highly efficient, gold-catalyzed intramolecular dearomatization reaction of naphthols *via* 5-*endo-dig* cyclization is described. This facile and direct approach furnishes spirocarbocycles in excellent yields under mild conditions.

Spirocarbocycles have captured the close attention of organic chemists due to their unique structural characteristics, including fully substituted carbon centers. Moreover, spirocarbocycles often appear in diverse natural products and biologically active molecules (Fig. 1).¹ Given the distinctive properties of spirocarbocycles, especially the relatively congested quaternary carbon center, it has been a challenging task for chemists to develop a synthetically applicable methodology for a long time, until recent progress in organometallic catalysis.² However, highly efficient, mild and streamlined synthetic routes are still in great demand.

Meanwhile, gold catalysis has exhibited remarkable capacity for the construction of complex molecules since the new millennium.³ The potent soft Lewis acidity of cationic gold(1) complexes enables, upon coordination, efficient attack on alkynes and alkenes by various nucleophiles, thereby leading to the formation of functional products including spirocarbocycles. Despite remarkable progress, there are relatively few

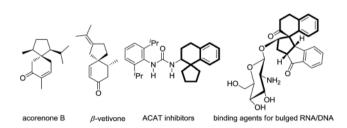
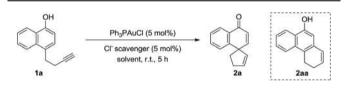


Fig. 1 Examples of natural products and biologically active compounds containing spirocarbocyclic backbones.

reports on the application of gold catalysis in dearomatization reactions.^{4,5} Particularly, dearomatization reactions of phenol and derivatives have been much under-developed despite potential direct access to highly functionalized spirocarbocycles.^{6,7} In this regard, Hamada and coworkers recently reported an elegant gold-catalyzed 5-*exo-dig* carbocyclization of phenols in the presence of methanesulfonic acid and 2,6-di-*tert*-butylpyridine.⁶ Interestingly, we found 5-*endo-dig* cyclization

Table 1 Optimization of reaction conditions^a



Entry	Cl ⁻ scavenger	Solvent	Conversion ^{b} (%)	$\operatorname{Yield}^{b}(\%)$
1	NaBARF	DCM	72	72
2	AgOTf	DCM	>95	<5
3 ^c	AgNTf ₂	DCM	>95	<5
4^d	$Cu(OTf)_2$	DCM	>95	<5
5	AgOMs	DCM	>95	>95 (96)
6	AgOMs	Toluene	42	42
7	AgOMs	THF	10	10
8	AgOMs	MeOH	<5	<5
9^e	AgOMs	DCM	<5	<5
10		DCM	<5	<5
11^{f}	_	DCM	<5	<5
12^g	_	DCM	>95	>95 (92)
13^h	AgOMs	DCM	>95	>95 (96)

^{*a*} Reaction conditions: **1a** (0.1 mmol), Ph₃PAuCl (5 mol%), Cl⁻ scavenger (5 mol%) in 1.0 mL solvent, r.t, 5 h. ^{*b*} Determined by ¹H NMR using CH₂Br₂ (0.1 mmol) as internal standard; isolated yield in parentheses. ^{*c*} **2aa** was isolated in 86% yield. ^{*d*} 2.5 mol% of Cu(OTf)₂ was added. ^{*e*} Reaction was performed without Ph₃PAuCl. ^{*f*} Reaction was performed with HOMs (5 mol%) instead of Ph₃PAuCl. ^{*g*} Reaction was performed open-flask.



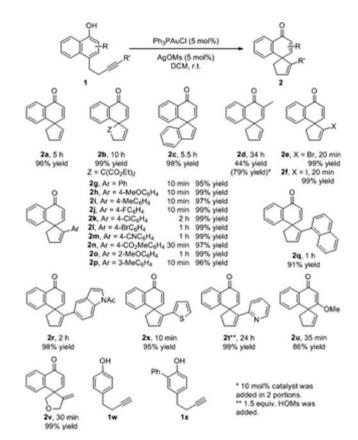


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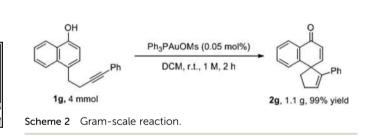
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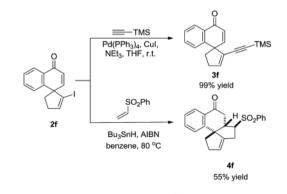
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Scheme 1 Substrate scope. Reaction conditions: 1 (0.2 mmol), Ph₃PAuCl (5 mol%), AgOMs (5 mol%) in 2.0 mL DCM, r.t.





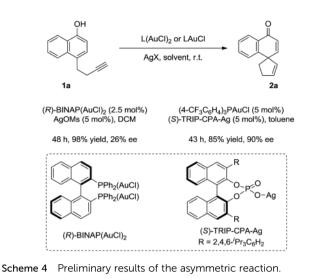
Scheme 3 Transformations of product 2f.

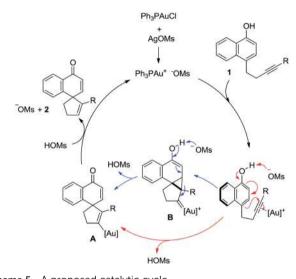
products could be selectively obtained *via* gold-catalyzed dearomatizations of naphthols under mild conditions. Herein, we report our findings.

We began our investigation by testing 1-naphthol derivative 1a with commercially available gold complex Ph₃PAuCl and various chloride scavengers. The results are summarized in Table 1. To our delight, in the presence of Ph₃PAuCl (5 mol%) and NaBARF (tetrakis[3,5-bis(trifluoromethyl)phenyl]boron sodium) (5 mol%), the gold-catalyzed dearomatization reaction of 1a (0.1 mmol) in DCM (1.0 mL) at room temperature proceeded smoothly to afford the desired spirocarbocyclic product 2a in 72% yield (100% yield based on conversion) in 5 h, albeit with incomplete conversion (entry 1, Table 1). However, other chloride scavengers such as AgOTf, AgNTf₂, and Cu(OTf)₂ (entries 2-4, Table 1) led to little desired product despite nearly complete substrate consumption. In the presence of AgNTf₂, the tricycle product 2aa was isolated in 86% yield. Interestingly, AgOMs was found to be the best chloride scavenger, and the reaction proceeded to completion in 5 h, affording 2a in excellent yield (>95% NMR yield, entry 5, Table 1). Next, solvent screening was carried out. Among the solvents evaluated, toluene and THF (entries 6 and 7, Table 1) led to slow reactions while no desired product 2a was detected in MeOH (entry 8, Table 1). As expected, Ph₃PAuCl, AgOMs, or HOMs alone could not catalyze this dearomative spirocylization (entries 9-11, Table 1), suggesting that the combination of Ph₃PAuCl and AgOMs is essential for this reaction. Ph₃PAuOMs is most likely the catalyst. Indeed, when Ph₃PAuOMs (entry 12, Table 1) was prepared in pure form and used as the catalyst, the reaction outcome was identical to that when the catalyst was prepared in situ (entry 5). Moreover, the reaction could be conducted openflask without erosion of the yield (entry 13, Table 1).

Under the above optimized reaction conditions, we then explored the substrate scope of this reaction. The results are summarized in Scheme 1. For substrates bearing terminal alkyne pendants, the dearomatization reactions all proceeded well, delivering the corresponding spirocarbocyclic products 2a, 2b and 2c in satisfactory yields (2a, 96% yield; 2b, 99%) yield; 2c, 98% yield). Despite the fact that the reaction of a substrate with a 2-methyl group on the naphthyl ring was sluggish (2d, 44% yield, 44% conversion after 34 h), the yield of 2d could be improved to 79% with the addition of 10 mol% catalyst in 2 portions. Next, various substrates bearing internal alkyne tethers were examined. Pleasingly, halogen-substituted alkynes did not interfere with the gold-catalyzed cyclization and the corresponding products (Br, 2e; I, 2f) could be obtained in nearly quantitative yields within 20 minutes. In addition, when phenyl-substituted alkyne substrate 1g was subjected to the reaction conditions, the reaction was completed even faster, delivering spirocarbocyclic product 2g in 95% yield in 10 min. Moreover, different electron-donating groups (2h, MeO; 2i, Me) or electron-withdrawing groups (2j, F; 2k, Cl; 2l, Br; 2m, CN; 2n, CO₂Me) on the para-position of the phenyl ring were compatible with this reaction, and the corresponding spirocarbocyclic products were formed in superb yields (97-99%). Likewise, a methyl or methoxyl group at either the ortho- or meta-position on the phenyl ring had little influence on the reaction, and the spirocarbocyclic products 20 and 2p were isolated in 99% and 96% yields, respectively. It is worth mentioning that substrates with other aromatic rings

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Scheme 5 A proposed catalytic cycle.

attached to the alkyne moiety also underwent the spirocyclization smoothly, affording spirocyclic products containing 1-naphthyl (2q), 5-indolyl (2r), or 2-thienyl (2s) motifs again in excellent yields (91–98%), and even pyridine-containing substrate 1t was converted into the corresponding spirocarbocyclic product 2t in 99% yield with an additional 1.5 equivalents of HOMs. Additionally, substrate 1u bearing a 3-OMe substituent was also compatible with this reaction, delivering 2u in 86% yield. When the linker was further extended, 5-*exo*-cyclization product 2v was observed in 99% yield. Simple phenolic substrates 1w and 1x were unreactive under the standard reaction conditions.

To test the practicality of this new methodology, a gram-scale reaction was conducted. As shown in Scheme 2, only 0.05 mol% of Ph₃PAuOMs was required to accomplish the dearomatization reaction to give spirocarbocyclic compound **2g** in 99% yield after 2 hours. This level of efficiency in gold catalysis has only been observed in limited reports.⁸

To illustrate the synthetic utility of this methodology, transformations of product **2f** were conducted. The vinyl iodine moiety readily underwent the Sonogashira coupling reaction with ethynyltrimethylsilane to afford enyne **3f** in 99% yield. In addition, **2f** smoothly participated in radical reactions.⁹ Treatment with phenyl vinyl sulfone in the presence of Bu₃SnH and AIBN afforded the polycyclic spiro-product **4f** with considerable molecular complexity in 55% yield (Scheme 3).

A preliminary attempt at the asymmetric reaction revealed that good enantioselectivity (90% ee) could be achieved in the presence of a catalytic amount of $(4-CF_3C_6H_4)_3PAuCl$ and chiral silver phosphate ((*S*)-TRIP-CPA-Ag),¹⁰ while moderate enantio-control (26% ee) was obtained by using (*R*)-BINAP(AuCl)₂ (Scheme 4).

A catalytic cycle is proposed in Scheme 5. The *in situ* generated cationic gold(I) complex coordinates with and activates the C-C triple bond in 1, and the subsequent 5-endo-dig cyclization is facilitated by the concomitant deprotonation by the counter anion MsO⁻, directly yielding the spirocyclic gold intermediate A. Alternatively, this cyclization might follow a typical 1,5-enyne cycloisomerization route to afford a cyclopropyl gold carbene intermediate B, which in turn would undergo MsO⁻-promoted deprotonative fragmentation to arrive at the same intermediate. Although with relatively basic MsO⁻ as the counter anion the direct route is more likely, the intermediacy of B in the step-wise route offers a straightforward rationale for the formation of 2aa, where in the presence of less basic NTf₂⁻ the fragmentation of the bold bond of the cyclopropane ring in **B** is preferred over the depicted deprotonative fragmentation. Protodemetallation of A by the in situ generated MsOH then delivers the desired spirocarbocyclic product 2 while regenerating the active gold catalyst (Scheme 5).

Conclusions

In conclusion, we have realized a highly efficient and straightforward construction of spirocarbocycles *via* the gold-catalyzed dearomatization reaction of naphthols under mild reaction conditions. The employment of commercially available catalysts and the compatibility with reaction scale-up and low catalyst loading point to the potential synthetic application of this methodology.

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