A Au(I)-Catalyzed Alkoxylation-Induced Double Aldol Condensation Approach to 2,2'-Spirobi[indene] Derivatives

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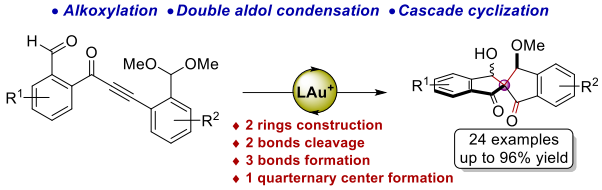
Supporting Information Placeholder

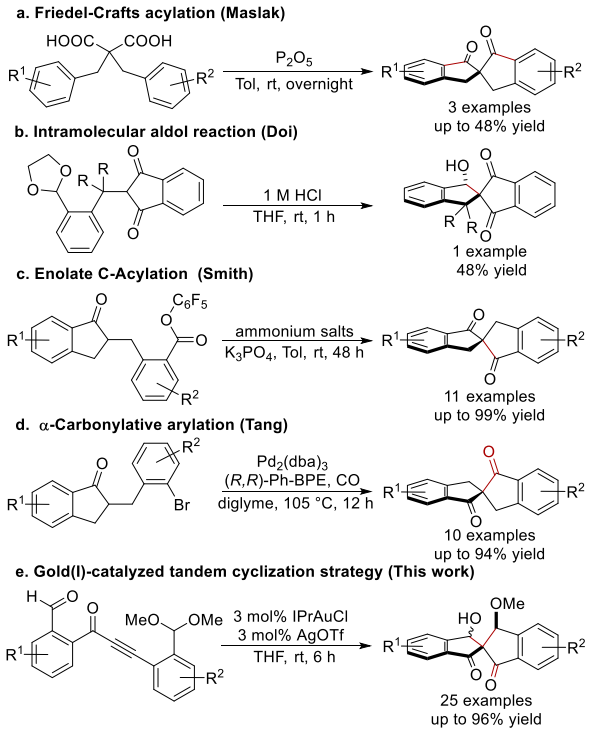


ABSTRACT: An efficient gold(I)-catalyzed intramolecular alkoxylation/double aldol condensation cascade cyclization strategy to synthesize 2,2'-spirobi[indene] derivatives has been developed. The scope of this strategy was examined by using a batch of synthetic alkynone substrates and a possible mechanism was proposed.

2,2'-Spirobi[indene] derivatives are the significant integral parts of several natural as well as unnatural products, which are versatile and valuable intermediates in synthetic chemistry.[1] Generally, design and synthesis of all-carbon spirocycles is a difficult task in organic chemistry because of the formation of highly rigid skeleton structure with a spiro-ring junction.[2] Due to the unique structure and reactivity pattern a great deal of attention has been paid to 2,2'-spirobi[indene], and a number of precedent studies on the construction of 2,2'-spirobi[indene] derivatives in different manners have been reported[3] as demonstrated in Scheme 1. For example, in 1999, Maslak and coworkers reported a Friedel-Crafts acylation strategy to spiroketones (Scheme 1, a).[3a] In 2016, Doi and coworkers described acid-catalyzed hydrolysis and intramolecular aldol reaction of 1,3-dioxolane to access spiromamakone A analogues (Scheme 1, b).[3e] In the same year, Smith and coworkers developed a counterion-directed intramolecular enolate enantioselective C-acylation method to synthesize spirobiindanones (Scheme 1, c).[3d] Recently, Tang and coworkers advanced a palladium-catalyzed enantioselective α-carbonylative arylation to construct chiral spirocyclic β,β'-diketones (Scheme 1, d).[3i] These strategies provided unique methods for the synthesis of 2,2'-spirobi[indene] derivatives, however, most of them constructed the spiro scaffold stepwise on the basis of a pre-installed indanone moiety via carbonyl chemistry. It is highly desirable to develop some straightforward and cascade strategies for synthesizing the core skeleton from relatively simple materials.

Recently, the development of homogeneous gold catalysis has been extraordinarily rapid, which is the most effective way to activate alkynes promoting the addition of a diverse host of nucleophiles. The novel reactivities and reaction modes of gold-catalyzed reactions have made them popular in many aspects, and a number of elegant pioneering works have been reported up to date,[4] including our previous efforts in this field.[5] Therefore, it is often a critical step in the synthesis of natural products, and is a powerful tool for tandem or domino reaction processes. Herein, we described our recent efforts on developing a gold(I)-catalyzed cascade cyclization strategy for the construction of 2,2'-spirobi[indene] derivatives bearing a quaternary carbon (Scheme 1, e).

Scheme 1. Reported Strategies and Our Cascade Cyclization Strategy to Synthesize 2,2'-Spirobi[indene] Derivatives



As our continuous interest in pursuing distinctive synthetic methodologies for constructing structurally diverse small molecules with privileged scaffolds via gold(I)-catalyzed cascade cyclizations, the unique structure of 2,2'-spirobi[indene] drew our attention. In our preceding work, we discovered that a gold(I)-catalyzed cycloisomerization via alkoxylation of

alkyne/nucleophilic addition furnished indanones, which could act as versatile intermediates to access structurally diverse skeletons (Figure 1). When there was nucleophilic substituent on the benzene ring (e.g. X=OH), a sequential intramolecular Michael addition reaction occurred to provide indenochromen-4-one derivatives (Figure 1, Path a).[5b] When there was no substituent (X=H), a sequential intermolecular condensation with *o*-phenylenediamine occurred to provide a series of benzo[*b*]indeno[1,2-*e*][1,4]diazepines (Figure 1, Path b).[5i] Inspired by the versatile reactivities of indanones, we hypothesized that if X were electrophilic carbonyl groups, such as ester, α,β-unsaturated ester, ketone and aldehyde, a sequential intramolecular nucleophilic addition might procced to give 2,2'-spirobi[indene] derivatives following the gold-catalyzed alkoxylation/aldol condensation (Figure 1, Path c).

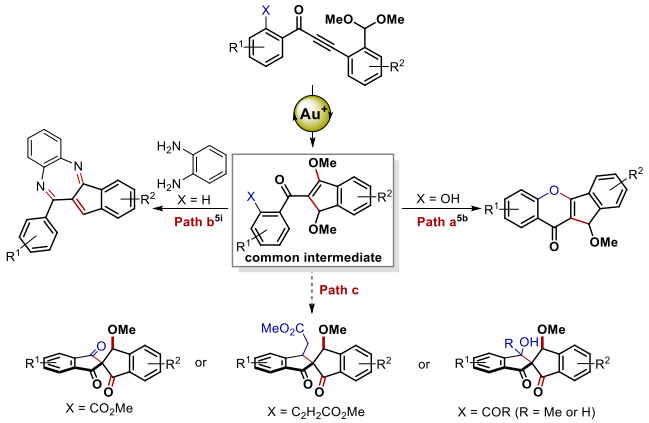
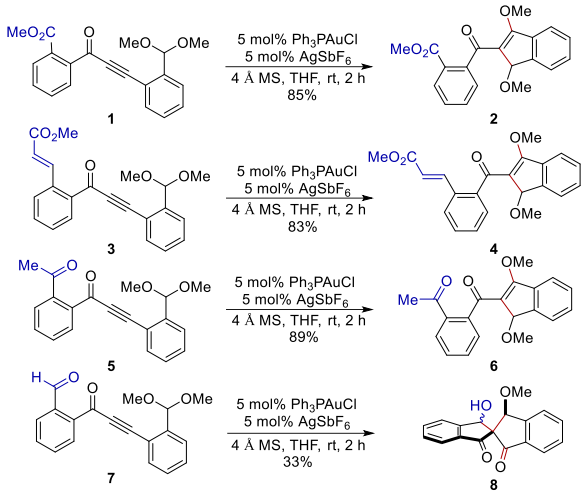


Figure 1. Previous Studies and This Design.

To test our design, the substrates **1**, **3**, **5** and **7** bearing different substitutions were prepared (see SI for the details) and subjected to the *in situ* prepared cationic gold(I) species as shown in Scheme 2.[6] It was found that when the substrates **1**, **3** and **5** with ester-/unsaturated ester-/keto- substitutions were treated with 5 mol% $Ph_3PAuCl/AgSbF_6$ in the presence of 4 Å MS in anhydrous tetrahydrofuran (THF), corresponding indanone derivatives **2**, **4** and **6** could be generated with excellent yields, however, the following intramolecular aldol condensation did not occur to deliver corresponding 2,2'-spirobi[indene] derivatives. To our delight, when the substrate **7** with aldehyde group was treated with the same condition, 2,2'-spirobi[indene] derivative **8** was generated in 33% yield (Scheme 2). These results suggested that the electronic nature of the carbonyl groups in the substrates had a great influence on the second cyclization.

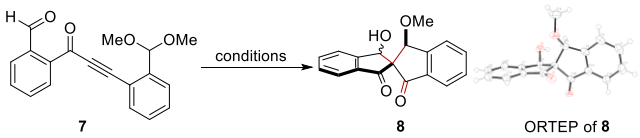
With our design verified, our research commenced with the optimization of the conditions such as catalysts, solvents and catalyst loadings using substrate **7**. Investigation on the ligands of the Au(I) catalyst showed that 5 mol% [1,3-bis(2,6-diisopropyl-phenyl)imidazol-2-ylidene] gold(I) chloride (IPrAuCl) combined with 5 mol% $AgSbF_6$ afforded the product **8** with the best yield (Table 1, entries 1–3). Examination of silver salts revealed that stirring the substrate **7** with the combination of 5 mol% IPrAuCl and 5 mol% silver trifluoromethanesulfonate (AgOTf) in anhydrous tetrahydrofuran (THF) at room temperature for 6 h gave the product **8** with a yield of 92% (Table 1, entries 4–5). As for other solvents such as dichloromethane (DCM), 1,2-dichloroethane (DCE), methanol and toluene were also screened and none of them was better than tetrahydrofuran (THF) (Table 1, entries 6–9). Decreasing the catalyst loading to 3 mol% illustrated no significant decrease in the yield, however increasing the loading to 10 mol% did not improve the yield,

Scheme 2. Attempts for the Synthesis of 2,2'-Spirobi[indene] Derivatives



therefore the optimal catalyst loading was determined as 3 mol% (Table 1, entries 10–11). The control experiment utilizing AgOTf alone could not catalyze this transformation, which showed that gold(I) catalyst should be the true reactive species (Table 1, entry 12). However, trifluoromethanesulfonic acid (TfOH) alone could catalyze this transformation with 37% yield,

Table 1. Condition Screening of the Synthesis of 2,2'-Spirobi[indene] Derivatives



entry	catalyst	additive	solvent	yield[a] (%)
1	Ph_3PAuCl	$AgSbF_6$	THF	46
2	IPrAuCl	$AgSbF_6$	THF	88
3	Johnphos(MeCN)$AuSbF_6$		THF	68
4	IPrAuCl	AgOTf	THF	92
5	IPrAuCl	$AgNTf_2$	THF	84
6	IPrAuCl	AgOTf	DCM	40
7	IPrAuCl	AgOTf	DCE	79
8	IPrAuCl	AgOTf	MeOH	35
9	IPrAuCl	AgOTf	Tol	80
10	IPrAuCl	AgOTf	THF	90[b]
11	IPrAuCl	AgOTf	THF	86[c]
12	AgOTf		THF	0
13	TfOH		THF	37
14	IPrAuCl	AgOTf	THF	68[d]

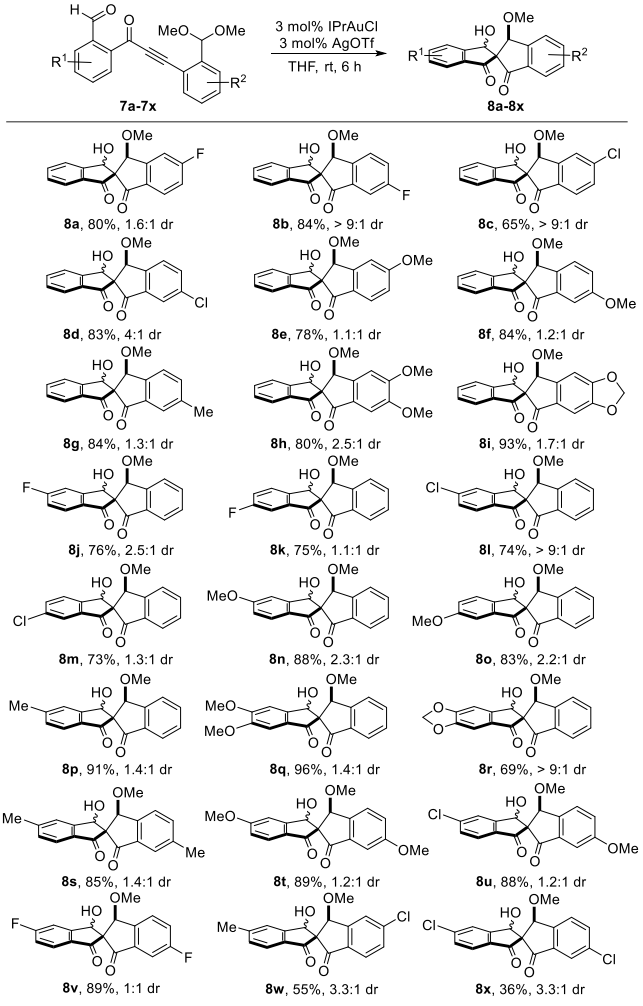
[a] Isolated yields and the ORTEP of **8** is shown with 50% probability ellipsoids. [b] 3 mol% IPrAuCl and 3 mol% AgOTf were used. [c] 10 mol% IPrAuCl and 10 mol% AgOTf were used. [d] 5 mol% 2,6-di-*tert*-butylpyridine was added. IPr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene].

and the control experiment by introducing 2,6-di-*tert*-butylpyridine as the proton scavenger in the IPrAuCl/AgOTf system showed significant decrease in the yield, which proved that trace amounts of acids have a certain effect on the reaction (Table 1, entries 13–14). Finally, the optimal reaction condition for

the cascade cyclization was determined as stirring the substrate at the catalysis of 3 mol% IPrAuCl/3 mol% AgOTf in anhydrous THF at room temperature for 6 h.

With the optimal conditions in hand, the scope of the cascade cyclization was examined using a variety of synthetic alkynone substrates **7a–7x**. It was observed that most of the synthetic substrates with both electron-donating and electron-withdrawing groups on the phenyl rings connected to the alkynyl could give satisfactory yields under the standard conditions (Scheme 3, **8a**–**8i**). The substrates with electron-donating groups on the benzaldehyde ring gave higher yields than those with electron-withdrawing groups (Scheme 3, **8j**–**8r**). When there were electron-donating groups (EDG), such as methyl and methoxy groups, on the dimethyl acetal phenyl ring, the substituents on the benzaldehyde ring had a minor influence on the yields, which were all above 85% (Scheme 3, **8s**–**8u**). The substrate with EDG substitution, like fluoro on both benzene rings gave satisfactory yield (Scheme 3, **8v**). However, the substrates bearing chloro substitution on the benzaldehyde ring provided poor yields, regardless of the substitutions on the dimethyl acetal phenyl ring, because those substrates were

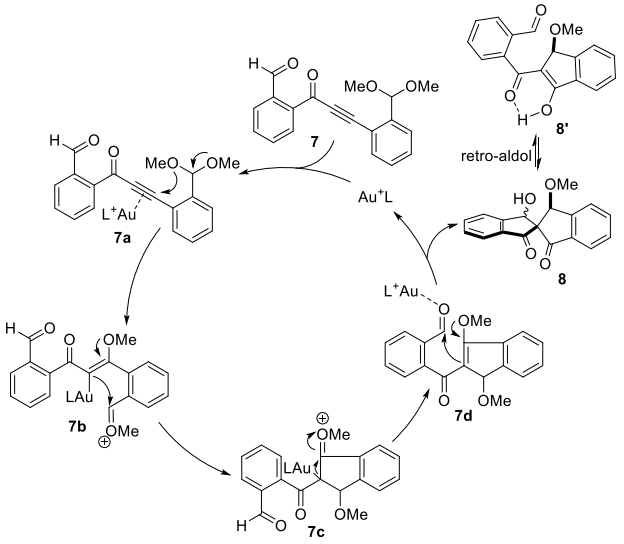
Scheme 3. Substrate Scope in the Au(I)-Catalyzed Cascade Cyclizations



to decomposing (Scheme 3, **8w**–**8x**). The diastereomeric ratios of the products were determined by ^{1}H NMR spectroscopy. The structures of the products were assigned based on ^{1}H NMR and unstable and prone ^{13}C NMR spectra, and further confirmed by single crystal X-ray diffraction (Table 1).

Based on precedent studies and our experimental results, a plausible mechanism was proposed for the gold(I)-catalyzed cascade cyclizations (Scheme 4).[3e,7] The reaction commences with the activation of triple bond by cationic gold(I) species, followed by the migration of methoxy group to afford vinylgold species **7b**. Then the oxonium in **7b** is attacked by vinyl ether through an intramolecular nucleophilic addition to afford intermediate **7c**. Finally, product **8** is obtained through an intramolecular nucleophilic addition of aldehyde group. It is difficult to isolate a single isomer in this cascade reaction owing to the existence of a retro-aldol process as shown in Scheme 4.

Scheme 4. The Proposed Mechanism



In summary, we have developed a gold(I)-catalyzed intramolecular alkoxylation-induced double aldol addition cascade cyclization strategy to yield 2,2'-spirobi[indene] derivatives. A number of precedent studies used to construct the spiro scaffold stepwise on the basis of a pre-installed indanone moiety via carbonyl chemistry. Our cascade strategy was complementary to those reported methods, featured with construction of two rings with a quaternary carbon junction through cleavage of two chemical bonds and formation of three new double bonds from readily prepared alkynones.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and compound characterization data, NMR spectra and X-ray analysis of the intermediates and target molecules (PDF)

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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