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Gold(I)-Catalyzed Cyclization for the Synthesis of 8-Hydroxy-3-substituted Isocoumarins: Total Synthesis of Exserolide F

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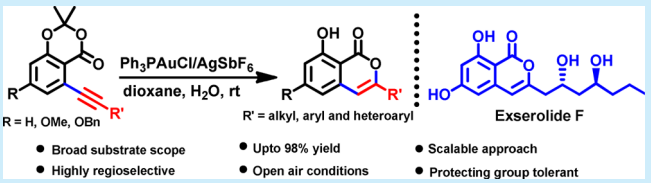
Supporting Information

ABSTRACT: A highly regioselective gold(I)-catalyzed 6-*endo-dig* cyclization of 2,2-dimethyl-5-(alkynyl)-4*H*-benzo[*d*]-[1,3]dioxin-4-ones for the synthesis of 8-hydroxy-3-substituted isocoumarins is described. Key features of the reaction include the broad substrate scope, scalability, and tolerance for protecting groups. The synthetic utility of this novel method is demonstrated by the first total synthesis of exserolide F, an isocoumarin-containing polyol natural product.



Isocoumarins (1*H*-2-benzopyran-1-ones) are naturally occurring lactones that exhibit a wide range of biological activities including anticancer, anti-HIV, antibacterial, antifungal, antiinflamatory, antiangiogenic, antioxidative, and antimicrobial activities.[1] As important structural motifs, 8-hydroxy-3-substituted isocoumarins are present in many natural products isolated from various organisms and studied with respect to their potential therapeutic applications (Figure 1).[2] The hydroxyl group at the 8-position is responsible for activities such as antifungal activity and inhibition of histamine release.[3]

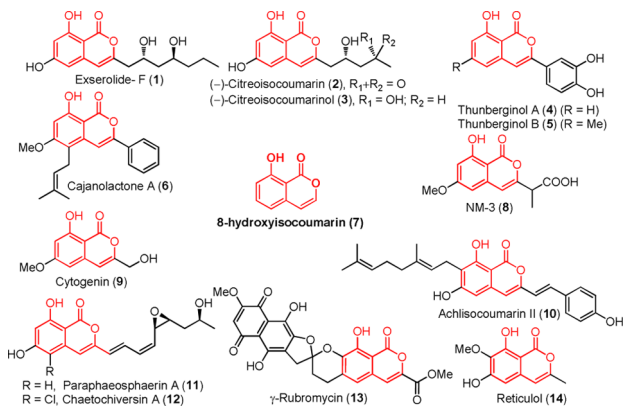


Figure 1. Representatives of naturally occurring and pharmacologically important 8-hydroxy-3-substituted isocoumarins.

Owing to the wide range of biological activities associated with these compounds, several methods were recorded for the synthesis of isocoumarins.[1a,b,4] Prior syntheses of substituted isocoumarins employed catalytic cyclization of *o*-alkynylbenzoic acid derivatives as a dominant approach.[1a,5] Cu(I)-catalyzed reaction of *o*-halobenzoic acids with 1,3-diketones is another approach for isocoumarin syntheses.[6] Transition-metal-catalyzed C−H activation and alkyne annulation directed by a carboxylate group has been developed for the synthesis of 3,4-disubstituted isocoumarins.[7] Recently, Aidhen et al. reported the synthesis of 8-hydroxy-3-arylisocoumarins using acyl anion chemistry.[8] However, the majority of these methods suffer from formation of isomeric mixtures of products and limited substrate scope. Thus, a simple, efficient, mild, scalable, regioselective preparation of 8-hydroxy-3-substitued isocoumarins is still highly desirable.

There has been significant progress in the development of gold-catalyzed transformations of *o*-alkynyl carboxylic acid derivatives.[9] Gold(III)-catalyzed cycloisomerization has been reported by Weghe et al.[9i] for the synthesis of alkylidene lactones. This method suffers from the formation of a mixture of isomers as well as low yields. In 2014, Blum and co-workers explored the dual catalytic synthesis of 3,4-disubstituted isocoumarins by gold and palladium.[9b] Alternatively, De Brabander's group also studied the cycloisomerization of *o*-alkynyl benzoic acid under various gold catalysts in the total synthesis of psymberin.[9d] In continuation of our research on gold-catalyzed transformations,[10] herein we report the synthesis of 8-hydroxy-3-substituted isocoumarins by the regioselective 6-*endo-dig* cyclization of 2,2-dimethyl-5-(alkynyl)-4*H*-benzo[*d*]-dioxin-4-ones.

We focused our initial attention on optimizing reaction conditions for the cyclization of **16a**, which in turn was synthesized by utilizing Sonogashira coupling[11] between aryl triflate (**15a**) and phenylacetylene as the test substrate using different gold catalysts (3 mol %), 1.5 equiv of water, and different solvents (Table 1).

The use of gold catalysts such as AuCl and $AuCl_3$ alone in DCE did not provide desired cyclic product (entries 1 and 2, Table 1). Interestingly, the combination of AuCl with a silver cocatalyst (AgOTf) gave the cyclized product **17a** in 40% yield (entry 3). The ^1H and ^{13}C NMR spectrum of the product revealed a single regioisomer. The other silver cocatalysts, such

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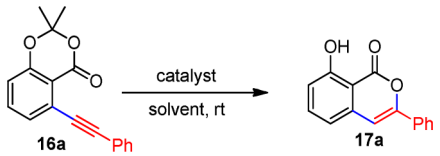
Table 1. Optimization of the Gold-Catalyzed Cyclization Reaction



entry[a]	catalyst(s)	solvent	time (h)	yield[b] (%)
1	AuCl	DCE	12	NR
2	$AuCl_3$	DCE	24	NR
3	AuCl/AgOTf	DCE	6	40
4	$AuCl_3$/AgOTf	DCE	12	20
5	$AuCl_3$/$AgSbF_6$	DCE	12	25
6	$AuCl_3$/$AgNTf_2$	DCE	12	15
7	$(Ph_3P)AuCl/AgBF_4$	DCE	6	55
8	$(Ph_3P)AuCl$/AgOTf	dioxane	6	82
9	$(Ph_3P)AuCl/AgBF_4$	dioxane	6	65
10	$(Ph_3P)AuCl/AgSbF_6$	CH_3CN	12	65
11	$(Ph_3P)AuCl/AgSbF_6$	DCE	12	90
12	$(Ph_3P)AuCl/AgSbF_6$	THF	12	85
13	**$(Ph_3P)AuCl/AgSbF_6$**	**dioxane**	**6**	**92**[c]
14	$AgSbF_6$	dioxane	6	31[d,e]
15	AgOTf	dioxane	6	22[d,e]
16	$(Ph_3P)AuCl$	dioxane	6	NR[e]

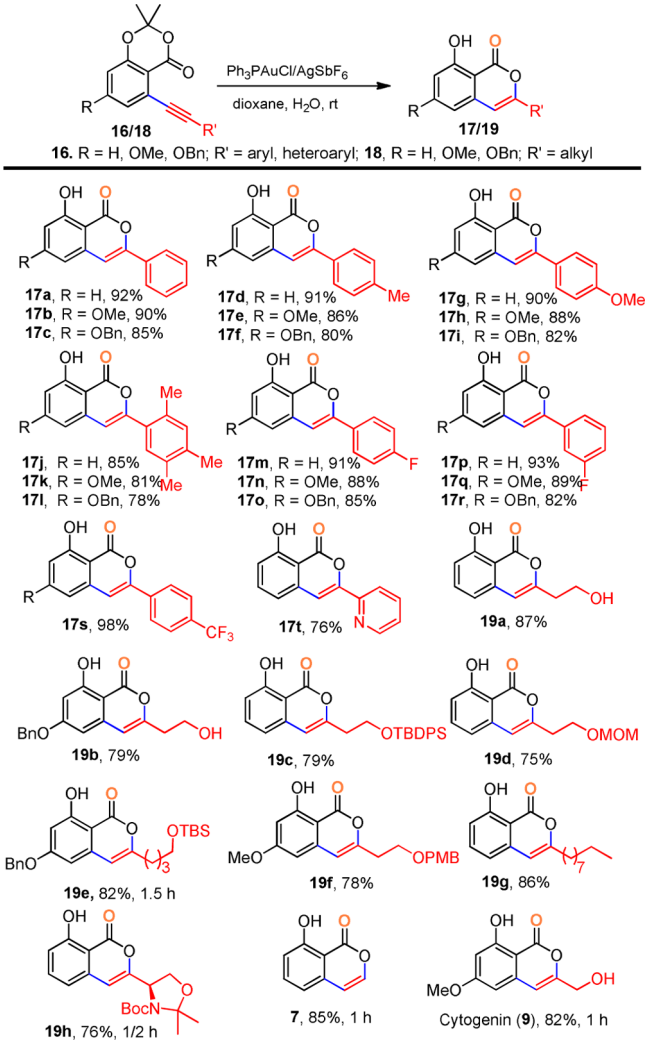
[a]The reactions were performed with **16a** (0.5 mmol), catalyst (3 mol %), and water (1.5 equiv) in solvent (1 mL) at room temperature under ambient atmosphere. [b]Yield of isolated product after column chromatography. [c]Used 1 mol % of gold and 2 mol % of silver catalysts. [d]Used 4 mol % of each catalyst. [e]The reaction was also continued for 48 h. NR = no reaction.

as $AgSbF_6$, $AgNTf_2$, and $AgBF_4$ (3 mol % of each), along with gold(I) catalyst led to an improved yield of the product (entries 5−7). Screening with different solvents (1,4-dioxane, acetonitrile, dichloroethane, THF) led to further improvement in the yield (entries 8−12). The best results were obtained with PPh_3AuCl in combination with $AgSbF_6$ in 1,4-dioxane as the solvent and allowed us to reduce the amount of gold and silver catalysts to 1 and 2 mol %, respectively (entry 13). Use of only $AgSbF_6$ or AgOTf in the reaction afforded **17a** in 31% and 22%, respectively, even after prolonged reaction time and more catalyst loading (entries 14 and 15). In addition, Au(I) catalyst, PPh_3AuCl, in the absence of silver cocatalyst did not afford any cyclic product (entry 16).

With the optimized conditions in hand, the scope and generality of the cyclization were then examined (Scheme 1).

In general, a wide variety of substrates containing aromatic as well as aliphatic groups at the alkyne terminus were subjected to cyclization to obtain the corresponding cyclic products in good to excellent yields. All reactions proceeded smoothly, and the method provided 8-hydroxy-3-substituted isocoumarins despite the electronic effects of the substituents. The methoxy and benzyloxy substituents on the substrates **16b** and **16c** had no influence, and the substrates were converted to the corresponding cyclic products **17b** and **17c**, respectively. The substrates containing electron-donating groups (EDG) on the aryl group of the terminal alkyne had no impact on the yield of the reaction (**16d**−**l**). The substitution of electron-withdrawing groups also had no adverse effect on the rate as well as yield of the reaction (**17m**−**s**). Encouraged by these results, the method was also successfully implemented on the substrates containing aliphatic groups at the alkyne terminus (**18a**−**h**) to obtain

Scheme 1. Substrate Scope of Gold(I)-Catalyzed Cyclization[a]



[a]The reactions were performed with **16** or **18** (0.5 mmol), Ph_3PAuCl (0.01 mmol), $AgSbF_6$ (0.02 mmol), and water (1.5 equiv) in dioxane (2.0 mL) at room temperature for 1 h unless until mentioned. Isolated yields.

corresponding cyclic products (**19a**−**h**) in good yields. It is worth mentioning that most of the protecting groups such as TBDPS, MOM, TBS, and PMB in the substrates **18c**, **18d**, **18e**, and **18f** were compatible with the reaction conditions and afforded corresponding products **19c**, **19d**, **19e**, and **19f**, respectively, in good yields.

The long-chain-substituted alkyne (**18g**) was also found to be a suitable substrate to furnish the desired product (**19g**) in 86% yield. The cyclization reaction also proceeded smoothly for the chiral substrate **18h**, without any racemization as well as with the retention of acetonide and Boc protections, to give the cyclic product **19h** in 76% yield. The simple 8-hydroxyisocoumarin (**7**) was obtained from the substrate having a TMS group at the alkyne terminus (**18i**) under optimized conditions with TMS-deprotected product in situ with 85% yield. Cytogenin (**9**), a natural product having significant biological activities like antitumor, immuno regulator, antibiotic, and also an active ingredient for the diabetic retinopathy[12] was synthesized following this protocol in 82% yield. Importantly, the

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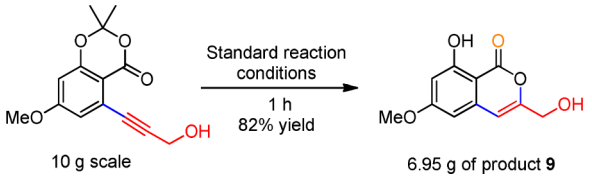
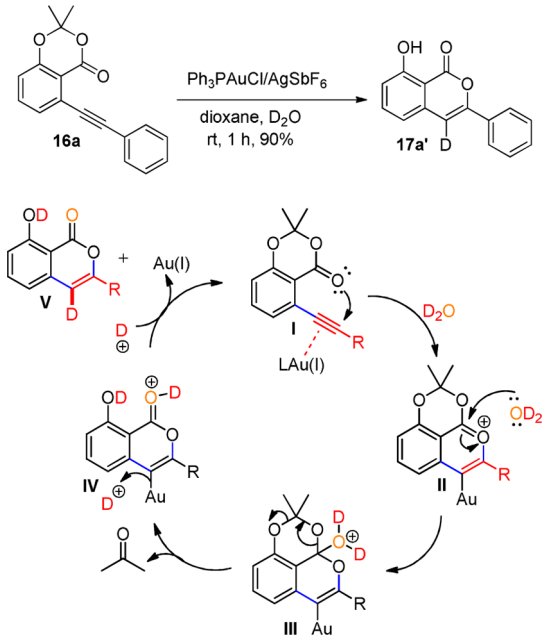
cyclization reaction is not limited to the small scale but also performed on a 10 g scale and provided **9** in excellent yield under the same standard conditions (Scheme 2).

Scheme 2. Gram-Scale Synthesis of 9



After successful demonstration of the gold-catalyzed cyclization, the mechanistic insights of the reaction were next examined. To probe the mechanism of this cyclization, the reaction was carried out under standard conditions with **16a** using 5 mmol of D_2O under inert atmosphere, which afforded **17a′** with deuterium incorporation at the olefinic position, which was confirmed by ^1H NMR and HRMS analysis. On the basis of the above results, a plausible mechanism was proposed for this cyclization (Scheme 3). The cyclization pathway

Scheme 3. Plausible Mechanism for the Gold(I)-Catalyzed Cyclization

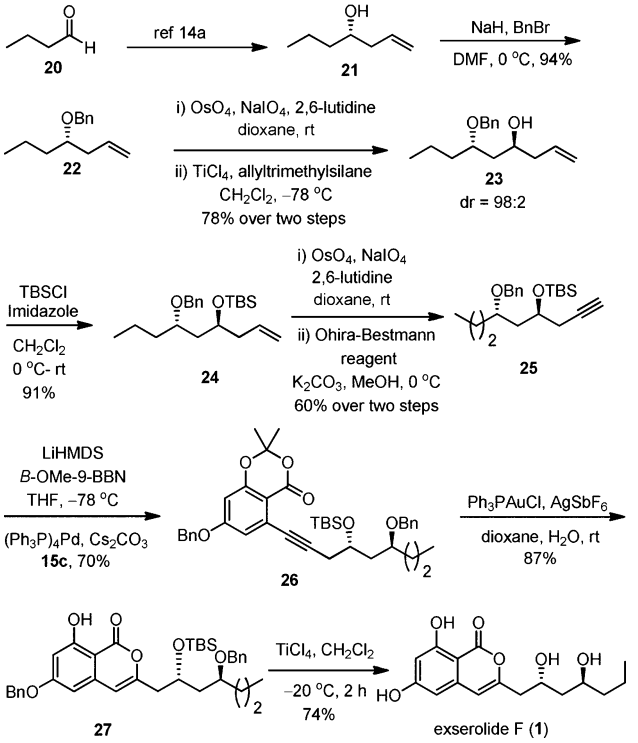


involves the coordination of Au(I) to the alkyne (**I**) followed by the *6-endo-dig* attack of carbonyl oxygen leading to the formation of vinylidene gold intermediate **II**. Then nucleophilic addition of water to the electrophilic gold intermediate results in **III**, which follows the subsequent elimination of acetone and protodeauration, gives the cyclized product (**V**).

To demonstrate the synthetic utility of the present method for the synthesis of biologically active natural products, we explored the synthesis of naturally occurring isocoumarin exserolide F (**1**). It was isolated from the solid cultures of plant endophytic fungus of *Exserohilum* sp. by Yin and co-workers in 2014 and shows significant antimicrobial activity.[13] The synthetic strategy involves the present gold-catalyzed cyclization and Suzuki coupling as the key steps.

The synthesis of **1** was initiated with a known secondary alcohol **21**[14a] obtained by Maruoka allylation[14b] of butyraldehyde **20** (Scheme 4). Benzyl protection of secondary alcohol **21**

Scheme 4. Total Synthesis of Exserolide F (1)



with benzyl bromide in the presence of NaH in DMF afforded **22** in 94% yield. To obtain the homoallylic alcohol **23** with the required stereochemistry, 1,3-induced chelation-controlled allylation was utilized. Accordingly, olefin **22** was oxidatively cleaved using Jin's one-pot protocol[15] under OsO_4, $NaIO_4$, and 2,6-lutidine at room temperature to afford the corresponding aldehyde, which was immediately treated with allyltrimethylsilane at −78 °C in the presence of $TiCl_4$[16] to furnish homoallylic alcohol **23** in 78% yield over two steps with 96% diastereoselectivity. The absolute configuration of the newly created stereogenic center was established by Mosher's modified method.[17] After the configuration of the hydroxyl group in compound **23** was assigned, it was protected as its silyl ether using TBSCl in the presence of imidazole in CH_2Cl_2. Oxidative cleavage of olefin **24** was carried out under Jin's[15] one-pot conditions followed by one-carbon homologation of aldehyde using Ohira−Bestmann reagent[18] gave alkyne **25** in 60% yield over two steps. The Suzuki coupling reaction[19] of alkyne **25** with aryl triflate **15c** provided the corresponding coupled product **26** in 70% yield. Having the coupled product **26** in hand, our gold-catalyzed cyclization reaction was carried out under optimized conditions (see Table 1, entry13) to obtain cyclic product **27** in 87% yield, which on global deprotection using excess $TiCl_4$[20] completed the total synthesis of exserolide F (**1**) in 74% yield (Scheme 4).

In summary, we have developed a highly efficient and regioselective gold(I)-catalyzed cyclization for the synthesis of 8-hydroxy-3-substituted isocoumarins in good to excellent yields. The described methodology is operationally simple, mild, and equally efficient for large-scale synthesis, showing a broad range of substrate scope and good protecting group

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tolerance. One of the applications of the present method was demonstrated in the first total synthesis of exserolide F. Further studies toward the asymmetric synthesis of 8-hydroxy-3,4-dihydroisocoumarins are in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00673.

Detailed experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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