Organic LETTERS

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Gold-Catalyzed Benzannulation of 5-Hydroxy-3-oxoalk-6-ynoate Esters to *o*-Phenolic Esters

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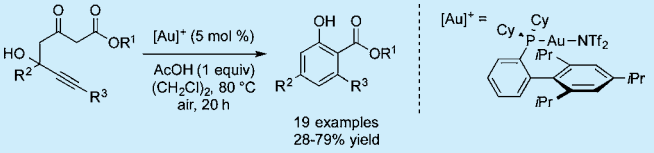
Supporting Information

ABSTRACT: A synthetic method to prepare *o*-phenolic esters efficiently by gold(I)-catalyzed benzannulation of 5-hydroxy-3-oxoalk-6-ynoate esters under mild conditions that did not require the exclusion of air or moisture is described.



The phenolic ester structural motif, in particular the *ortho*-substituted family member, is found in a myriad of bioactive natural products and pharmocologically interesting compounds (Figure 1).[1] The carbolic acid derivative is also a potentially useful building block in organic synthesis and drug discovery programs. As a consequence, the development of efficient synthetic methods to prepare the aromatic carbocycle with selective control of substitution patterns by using readily accessible substrates continues to be actively pursued.[2]

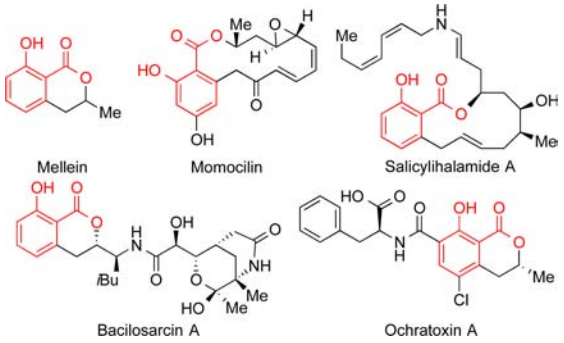
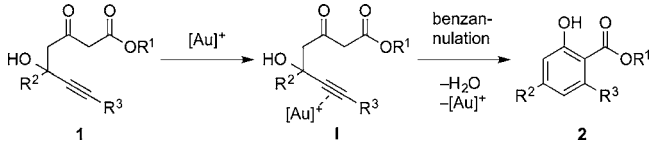


Figure 1. Examples of bioactive natural products containing the *o*-phenolic ester motif.

Over the past decade, gold-catalyzed alkyne cycloisomerizations have become one of the most efficient and atom-economical synthetic methods to increase molecular complexity and diversity.[3−13] An illustrative example of this is the immense number of elegant approaches to various synthetically useful arenes from gold-catalyzed benzannulation of the corresponding substituted alkyne.[4−6,14] While this has included many impressive works for phenol synthesis,[6] the analogous gold-catalyzed alkyne benzannulations leading to *ortho*-substituted phenolic esters have so far remained unrealized. In this context and as part of our ongoing efforts in the field of gold catalysis,[7] we became interested in exploring the potential Au(I)-catalyzed cyclization chemistry of propargylic alcohol tethered *β*-ketoesters **1** (Scheme 1).[8] We reasoned that the putative Au(I)-activated species **I** that would form in situ might be prone to undergo hydroalkylation involving nucleophilic addition of the *β*-ketoester unit to the C≡C bond in the intermediate.[9,10] Protodeauration followed by dehydrative aromatization would then be expected to provide the *o*-phenolic ester derivative **2**. Herein, we disclose the details of this benzannulation chemistry that delivers an expedient synthetic route to 2-hydroxybenzoate esters in moderate to excellent yields under conditions that did not require the exclusion of air or moisture.

Scheme 1. Au(I)-Catalyzed Cyclization of Alkynyl Tethered *β*-Ketoesters to *o*-Phenolic Esters

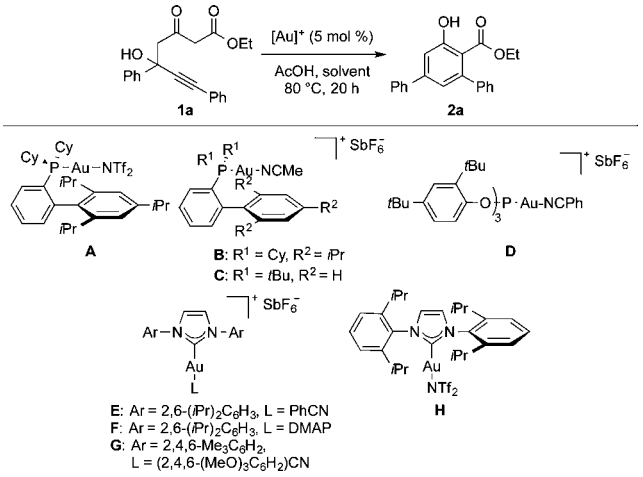


We began our investigations by examining the gold(I)-catalyzed cycloisomerizations of **1a** to establish the reaction conditions (Table 1). This study initially revealed that treating the model substrate with 5 mol % of Au(I) phosphine catalyst **A** in toluene at 80 °C for 20 h gave **2a** in 57% yield (entry 1). The structure of the aromatic carbocycle was confirmed by X-ray crystal structure analysis.[15] Lower product yields of 16−52% yield were obtained on replacing **A** with the gold(I) phosphine complexes **B** and **C**, gold(I) phosphite complex **D**, and NHC-gold(I) (NHC = *N*-heterocyclic carbene) complexes **E**−**H** as the catalyst (entries 2−8). A similar outcome was observed on changing the solvent from toluene to CH_2Cl_2, MeCN, or THF, with **2a** furnished in 30−45% yield (entries 15−17). On the other hand, either no reaction or a mixture of

Received: January 22, 2014
Published: February 11, 2014

   dx.doi.org/10.1021/ol5002363 | *Org. Lett.* 2014, 16, 1248−1251

Table 1. Optimization of the Reaction Conditions[a]



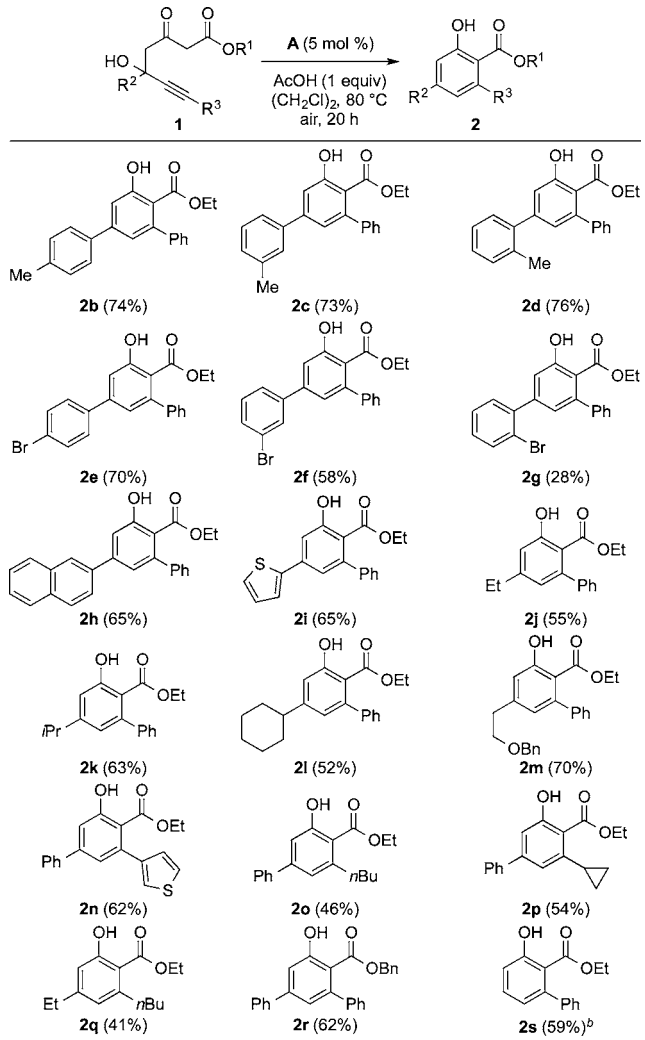
entry	catalyst	solvent	AcOH (equiv)	yield (%)[b]
1	**A**	PhMe		57
2	**B**	PhMe		52
3	**C**	PhMe		32
4	**D**	PhMe		19
5	**E**	PhMe		40
6	**F**	PhMe		16
7	**G**	PhMe		46
8	**H**	PhMe		29
9	AuCl	PhMe		*c*
10	$AgSbF_6$	PhMe		*d*
11	$AgNTf_2$	PhMe		*d*
12	TfOH	PhMe		*d*
13	*p*TSA	PhMe		*d*
14	TFA	PhMe		*d*
15[e]	**A**	CH_2Cl_2		45
16[e]	**A**	MeCN		44
17[e]	**A**	THF		30
18	**A**	$(CH_2Cl)_2$		60
19	**A**	$(CH_2Cl)_2$	0.1	67
20	**A**	$(CH_2Cl)_2$	0.5	74
21	**A**	$(CH_2Cl)_2$	1.0	82
22[f]	**A**	$(CH_2Cl)_2$	1.0	13
23[g]	**A**	$(CH_2Cl)_2$	1.0	79
24[h]	**A**	$(CH_2Cl)_2$	1.0	70
25		$(CH_2Cl)_2$	1.0	*d*

[a]All reactions were conducted at the 0.2 mmol scale with 5 mol % of catalyst at 80 °C for 20 h. [b]Isolated yield. [c]No reaction based on TLC or ^{1}H NMR analysis of the crude mixture. [d]Unknown side products obtained based on ^{1}H NMR analysis of the crude mixture. [e]Reaction performed at reflux. [f]Reaction performed in an open round-bottom flask at room temperature. [g]Reaction performed in an open round-bottom flask with a condenser. [h]Reaction performed in the presence of 10 mol % of di-*tert*-butyl pyridine in place of AcOH.

unidentifiable decomposition products was found in control experiments with toluene as the solvent and AuCl, $AgSbF_6$, $AgNTf_2$, TfOH, *p*TSA, or TFA instead of **A** was employed as the catalyst (entries 9−14). Our studies subsequently showed a comparable product yield of 60% was afforded on repeating the Au(I) phosphine complex **A**-catalyzed reaction in $(CH_2Cl)_2$ at 80 °C for 20 h (entry 18). Under these latter conditions, the introduction of 0.1 equiv of AcOH was found to lead to an increase in product yield from 60% to 67% (entry 19). The yield of **2a** was further increased from 67% to 74% to 82% on increasing the amount of AcOH from 0.1 to 0.5 to 1 equiv, respectively (entries 20 and 21). The analogous reactions of **1a** and 1 equiv of AcOH catalyzed by **A** contained in an open round-bottom flask at room temperature and 80 °C afforded, respective, product yields of 13% and 79% (entries 22 and 23). Further control experiments with 10 mol % of di-*tert*-butyl pyridine in place of the Brønsted acid or only 1 equiv of AcOH provided **2a** in 70% yield and a mixture of unidentifiable decomposition products, respectively (entries 24 and 25). On the basis of the above results, the procedure described in entry 23 was deemed to provide the optimum reaction conditions.

Scheme 2 summarizes our efforts to define the scope of the present procedure by examining the reactions of a variety of 5-hydro-3-oxoalk-6-ynoate esters. These experiments showed that with the Au(I) complex **A** as the catalyst, the reaction conditions were found to be broad, and a variety of substituted *o*-phenolic esters were afforded in moderate to excellent yields. Starting esters in which the carbinol carbon center bore a phenyl moiety with an electron-donating (**1b**−**1d**) or electron-

Scheme 2. Benzannulation of 5-Hydroxy-3-oxoalk-6-ynoate Esters 1b−s Catalyzed by A[a]



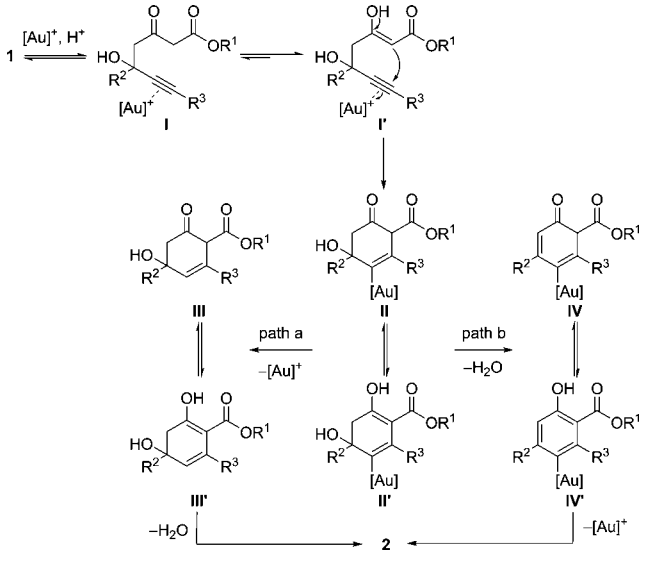
[a]All reactions were conducted at the 0.2 mmol scale with 5 mol % of **A** and 1 equiv of AcOH in 1,2-dichloroethane in an open round-bottom flask with a condenser at 80 °C for 20 h. Values in parentheses denote isolated product yields. [b]Reaction time = 50 min.

dx.doi.org/10.1021/ol5002363 | *Org. Lett.* 2014, 16, 1248−1251

withdrawing (**1e** and **1f**) group at the *para*-, *meta*-, or *ortho*-position were shown to proceed well and give the corresponding products **2b**−**2f** in 58−76% yield. Likewise, substrates containing a 2-naphthalenyl (**1h**), 2-thienyl (**1i**), alkyl (**1j** and **1k**), cyclohexyl (**1l**), or benzyl ethyl ether (**1m**) group at the same position were found to be well tolerated, providing the corresponding *o*-phenolic esters **2h**−**2m** in yields of 52−70%. The presence of a 3-thiophenyl (**1n**), *n*Bu (**1o**), or cyclopropyl (**1p**) substituent on the propargylic carbon center was found to have little influence on the course of the reaction with **2n**−**2p** obtained in 46−62% yield. Reactions of substrates with a pendant Et and *n*Bu moiety on the respective carbinol and propargylic carbon centers or a benzyl instead of an ethyl ester group or a secondary alcohol, as in **1q**−**1s**, were observed to work well. Under the standard conditions, these Au(I)-catalyzed reactions gave the corresponding *o*-carbolic acid derivatives **2q**−**2s** in 41−62% yield. In our hands, the only exception was the cyclization of **1g** containing a *o*-BrC_6H_4 substituent at the carbinol carbon center, which was found to give **2g** in a low yield of 28%. On the other hand, no other cycloisomerization products arising from possible 5-*exo*-dig cyclization of the substrate were detected by TLC and ^1H NMR analysis of the crude reaction mixtures.

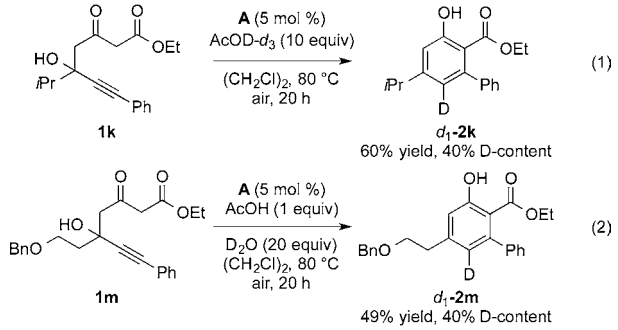
A tentative mechanism for the present Au(I)-catalyzed *o*-phenolic ester transformation is illustrated in Scheme 3. This

Scheme 3. Proposed Mechanism for Au(I)-Catalyzed Benzannulation of Alkynyl Tethered *β*-Ketoesters



could involve activation of the propargylic alcohol by coordination of the Group 11 metal catalyst to the C≡C bond in the substrate. This leads to the resulting Au(I)-coordinated species **I** and its tautomer **I′**, with the equilibrium presumably sitting in favor of the latter due to the acidic conditions, becoming prone to undergoing the hydroalkylation process. Involving *anti* addition of the enol form of the 1,3-dicarbonyl compound moiety to the alkyne bond of the adduct, this gives the vinyl gold intermediate **II** and its enolic isomer **II′**.[11−13] Subsequent protodeauration of this putative organogold species followed by dehydrative aromatization of the ensuing cyclohexenone species **III** and its 1,3-diene isomer **III′** might then result in the regeneration of the metal catalyst and provide the phenolic product (Scheme 3, path a). Alternatively, dehydrative aromatization may occur first to give the vinyl gold complex **IV** and its phenolic product **IV′**, which upon protodeauration would provide **2** (Scheme 3, path b). In addition to contributing to the keto−enol tautomerization process, our earlier studies described in Table 1, entries 24 and 25 showing the role of AcOH confined to promoting protodeauration and regeneration of the gold(I) catalyst suggests the latter of these deauration processes to be more likely.[13] Indeed, this was further supported by repeating the Au(I)-catalyzed cyclizations of **1k** with AcOD-d_3 and **1m** with D_2O under the respective conditions described in eqs 1 and 2 in Scheme 4. These control experiments led to d_1-**2k** and d_1-**2m**

Scheme 4. Control Experiments with 1k and 1m Catalyzed by A



being formed in 60% and 49% yield, respectively, and in both cases with 40% deuterium incorporation at the *para*-position of the *o*-phenolic ester. A gold(I)-catalyzed hydroalkylation step would also be consistent with the contrasting reactivities observed for the cyclizations of **1d** and **1g** depicted in Scheme 2. It may be anticipated that such a pathway might become less efficient as steric interactions between the incoming gold(I) complex and the aryl substituent at the carbinol carbon center significantly increase on going from *o*-MeC_6H_4 in **1d** to *o*-BrC_6H_4 in **1g**.

In summary, we have described an efficient Au(I)-catalyzed synthetic method for the construction of *o*-phenolic esters from 5-hydroxy-3-oxoalk-6-ynone esters. Achieved under conditions that did not require the exclusion of air or moisture, the reaction was shown to be applicable to a diverse set of propargylic alcohol tethered *β*-ketoesters. Efforts exploring the scope and synthetic applications of this approach to the carbolic acid derivative are in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experiment procedures, characterization data and ^1H and ^{13}C NMR spectra for all starting materials and products, and CIF file of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/ol5002363 | *Org. Lett.* 2014, 16, 1248−1251

■ ACKNOWLEDGMENTS

This work was supported by a College of Science Start-Up Grant from Nanyang Technological University and a Tier 2 Grant (MOE2013-T2-1-060) from the Ministry of Education of Singapore. A Yousef Jameel Scholarship (to W.T.T.) is gratefully acknowledged, and we thank Dr. Yongxin Li of this Division for the X-ray crystallographic data reported in this work.

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(15) CCDC 967743 (**2a**) contains the supplementary crystallographic data for this Article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.