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Gold-Catalyzed Dearomative Spirocyclization of Aryl Alkynoate Esters

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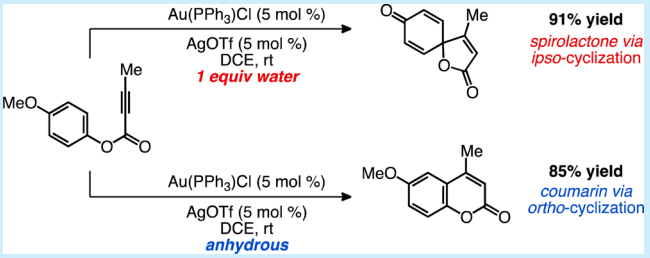
Supporting Information

ABSTRACT: Aryl alkynoate esters undergo gold-catalyzed spirocyclization under mild conditions, affording spirolactones in high yields. This approach obviates the need for stoichiometric halogenating reagents typically employed for alkyne activation in related transformations. Water was found to play a critical role in governing the product selectivity. Anhydrous conditions lead selectively to coumarin products, as has previously been observed for aryl alkynoate esters, while the addition of 1 equiv of water leads selectively to spirocycle formation.



Spirocycles are a common structural pattern found at the core of numerous natural products of varying complexity. Their prevalence in medicinally and pharmaceutically desirable compounds, as well as the synthetic challenges associated with the construction of the highly substituted centers that characterize this motif, have made spirocycles an attractive target for chemists.[1] One commonly exploited mechanistic approach among these synthetic methods is the dearomative spirocyclization of functionalized phenols and related alkoxyarenes. These reactions typically proceed by the electrophilic activation of a pendant functional group (alkyne in **1**, Figure 1) triggering a Friedel–Crafts-type nucleophilic attack of the arene leading to C–C bond formation with concomitant dearomatization and spirocycle formation (**1** to **2**, Figure 1).[2−4]

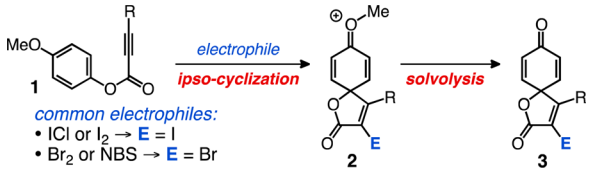
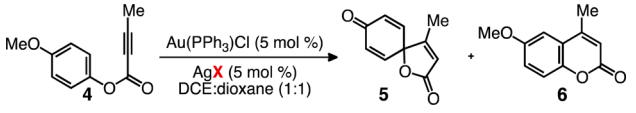


Figure 1. Electrophilic spirocyclization of aryl alkynoates.

Within this reaction paradigm, the halo-spirocyclization of alkynyl arenes has recently emerged as a robust method for the synthesis of halogenated spirocycles.[4] This approach utilizes electrophilic halogenating reagents as alkyne activators, under basic conditions. While this approach can deliver high yields of halo-spirocycles, the stoichiometric use of highly reactive halogenating reagents and bases exhibits low atom economy and has limited scope due to potential cross-reactivity of the requisite reagents with other functional groups. We envisioned the use of π-acidic metal complexes as alternatives to stoichiometric electrophiles, with the anticipation that such species might enable a catalytic method for the spirocyclization of aryl alkynoate esters.[5]

Our investigation began with the use of cationic gold complexes. Such electrophiles have been employed for the π-activation of alkynes,[6] particularly the hydroarylation of alkynyl arenes,[7] with aryl alkynoate esters leading to coumarins via *ortho*-cyclization (Table 1).[8] Ester **4** was subjected to 5 mol % of

Table 1. Selective Spirocycle Formation



entry	silver salt activator	spirocycle **5** yield (%)	coumarin **6** yield (%)
1	$AgSbF_6$	39	48
2	$AgBF_4$	53	19
3	AgOTf	93	

$Au(PPh_3)Cl$ and $AgSbF_6$ in a 1:1 mixture of dichloroethane and 1,4-dioxane. These conditions afforded a mixture of both the *ortho*-cyclized coumarin **6** and the *ipso*-cyclized spirocyclic lactone **5** in 48% and 39% yields, respectively. With this proof-of-concept result we evaluated alternative silver salts with the expectation that the counterion might impact the reactivity of the gold catalyst in its activated form. Although a mixture was still obtained, $AgBF_4$ switched the selectivity of the cyclization, favoring spirocyclization. Moreover, AgOTf led to complete spirocycle selectivity, affording **5** in 93% yield after 5 h.

Optimization studies initially focused on the reaction solvent, with the goal of eliminating the 1,4-dioxane (Table 2). We found that DCE alone not only led to selective spirocyclization in a

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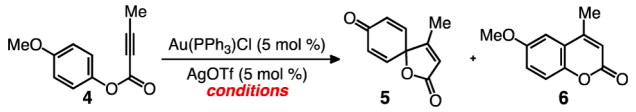
Table 2. Product Selectivity Dictated by Water



entry[a]	solvent (0.05M)	water (equiv)	time	% yield 5:6[b,c]
1	DCE/1,4-dioxane		5 h	93:0
2	DCE		20 min	91:0 (3)
3	DCE, anhydrous		6 h	6:85
4	DCE, anhydrous	1	30 min	91:0 (3)
5	1,4-dioxane	1	5 h	97:0
6	DCM	1	30 min	98:0 (trace)
7	DCM		6 h	15:61

[a]Reactions conducted at room temperature. [b]^{1}H NMR yields determined using 4-nitrobenzaldehyde as an external standard. [c]Percent yield of β-keto ester shown in parentheses.

comparable 91% yield but did so with a reduction in reaction time from 5 h to 20 min (entry 2). In an attempt to avoid potential deactivation of the catalyst by water or oxygen, we next ran our reaction with dry DCE, as opposed to our initial screen, which employed benchtop solvent. Under these anhydrous conditions the selectivity switched to favor the coumarin product, which formed in 85% yield after 6 h (entry 3). These results suggested the presence of water was critical for selective spirocycle formation. Similar water-controlled product selectivity has been observed in related transformations.[4a]

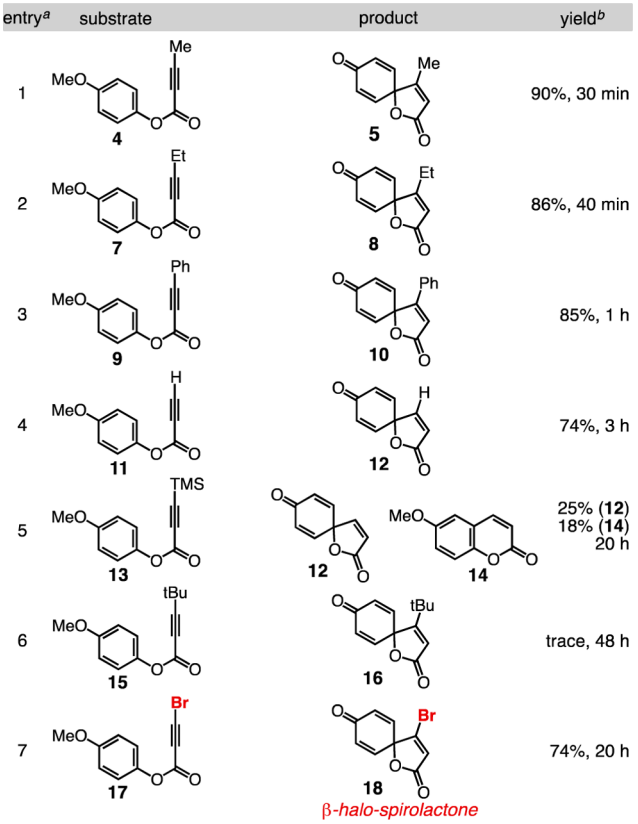
We were able to restore the spirocycle selectivity with the addition of 1 equiv of water to our anhydrous DCE (entry 4). These conditions gave the spirocycle in an identical 91% yield after 20 min. Presumably, the success of our initial experiments was the fortuitous result of using "wet" solvent. Moving forward, 1 equiv of water was added to all solutions prior to the addition of the substrate. Most of the solvents screened led to mixtures of spirocycle, coumarin, and β-keto ester arising from alkyne hydration. We found benchtop dichloromethane (DCM) at 0.05 M concentration of substrate with 1 equiv of water to be the ideal solvent conditions, yielding the spirocycle in 90% isolated yield.

We then turned our attention to the catalyst. Re-examination of the initial catalyst screen (Table 1) showed similar selectivities and yields (see the Supporting Information for complete screen). AgOTf-activated Au(P(p-CF_3Ph)$_3$)Cl and (dppm)$(AuCl)_2$ also furnished the spirocycle selectively in high yield, but with longer reaction times. Catalyst control experiments were conducted by subjecting ester **4** to Au(PPh_3)Cl and AgOTf independently. We found that Au(PPh_3)Cl failed to promote any reaction, while AgOTf afforded 6% of the spirocycle after 24 h. We also examined platinum salts ($PtCl_4$, PtI_4), which have been shown to be competent catalysts for alkyne hydroarylation.[8c,9] Surprisingly these salts failed to promote any reaction.

Our study of the substrate scope employed 5 mol % Au(PPh_3)Cl and AgOTf in DCM at 0.05 M with 1 equiv of water and began with an examination of the tolerance for substitution on the alkyne (Table 3). Ethylated substrate 7 performed comparably to the methyl-bearing substrate **4**, affording **8** in 86% yield. The substantially bulkier phenyl substituent was also similarly tolerated, affording the β-phenyl spirocycle **10** in 85%. Removing the substituent altogether in substrate **11** resulted in a 74% yield of the unsubstituted spirocycle **12**.

To further test the steric allowance at the β-carbon we prepared substrates **13** and **15**. Surprisingly, **13** afforded the desilylated product **12** in 25% yield along with 18% of the

Table 3. Substitution at the Alkynyl Position



[a]reactions conducted at room temperature in DCM (0.05 M) with 1 equiv of H_2O, 5 mol % of Au(PPh_3)Cl, and AgOTf; [b]Average yield of three trials.

desilylated coumarin **14**. Desilylation of TMS-alkynes has previously been observed during gold catalysis and here likely leads to the formation of substrate **11** in situ while sequestering the water needed for spirocycle formation to trimethylsilanol.[11] The more congested substrate **15**, however, failed to undergo any appreciable reaction, leading to a trace of spirocycle **16** by ^{1}H NMR along with 23% β-keto ester and 70% unreacted substrate.

The final substrate in this series was the β-bromo ester **17**. We expected the C−Br bond to be a potential pitfall, as oxidative addition might occur, although oxidative addition at gold remains rare.[10] However, this substrate delivered a 74% yield of the β-bromo spirocycle **18**. We view this result as a complement to the halogen-promoted methods, which yield α-halogenated spirocycles.[4b]

We next directed our investigation to the aromatic ring of the substrate (Table 4). The incorporation of methyl groups *meta* to the ester in substrates **19** and **21** had little impact on the reaction, yielding the methylated products **20** and **22** in 65% and 90% yield, respectively. Substrate **23** with both *ortho*-positions methylated led to trimethyl spirocycle **24** in quantitative yield, while the monomethylated substrate **25** also led exclusively to spirocyclization, affording **26** in 97% yield. The product selectivity exhibited in these two reactions suggests that the presence of an *ortho*-substituent, albeit a compact one, is not enough to preclude spirocyclization nor promote *ortho*-cyclization.

Elaborating on this substrate and endeavoring to explore possible electronic influences on the reaction, we prepared substrate **27** with an *o*-methoxy group, which spirocyclized to

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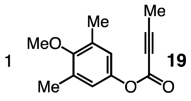
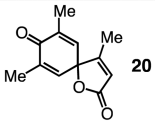
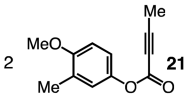
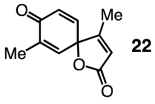
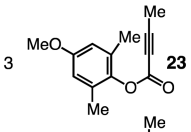
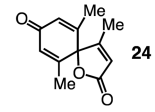
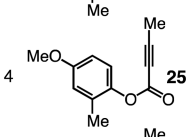
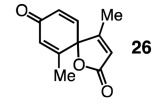
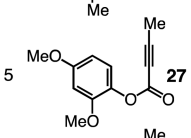
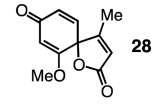
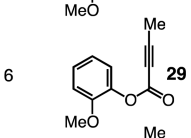
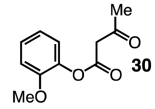
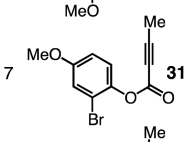
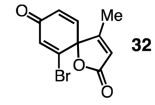
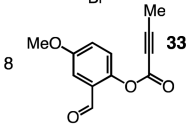
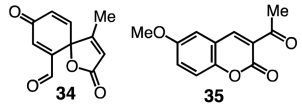
Table 4. Substitution on the Aromatic Ring

entry[a]	substrate	product	yield[b]
1	 **19**	 **20**	65%, 30 min
2	 **21**	 **22**	90%, 30 min
3	 **23**	 **24**	quant., 30 min
4	 **25**	 **26**	97%, 50 min
5	 **27**	 **28**	92%, 1 h
6	 **29**	 **30**	22%, 3 h
7	 **31**	 **32**	86%, 1 h
8	 **33**	 **34** **35**	23% (**34**) 24% (acetal) 25% (**35**) 2 h

[a]reactions conducted at room temperature in DCM (0.05 M) with 1 equiv of H_2O, 5 mol % of $Au(PPh_3)Cl$, and AgOTf. [b]Average yield of three trials.

afford **28** in 92% yield. The success of this substrate prompted us to investigate the potential spirocyclization of substrate **29** in order to see whether the *o*-methoxy group alone could activate the arene for nucleophilic attack. This substrate failed to undergo cyclization, leading to a complex mixture, with *β*-keto ester **30** as the only isolable product.

Investigations of electronic-withdrawing group influences were carried out using substrates **31** and **33**. Bromo arene **31** proved to be particularly reactive, affording bromo spirocycle **32** in 86% yield. The aldehyde-bearing substrate **33**, however, led to a mixture of products with the target spirocycle **34** being isolated in 23% yield along with the related dimethyl acetal in 24% yield. Interestingly, a new side product, coumarin **35**, was observed and isolated in 25% yield. This coumarin is distinct from those discussed above (**6** and **14**) as it does not arise from hydroarylation of the alkyne but rather through condensation of the aldehyde substituent with the *β*-keto ester following alkyne hydration.

The final class of substrates we explored was inspired by the recently discovered antifungal natural product perenniporide A (Figure 2).[12] The core benzo-fused spirocycle prompted us to investigate the spirocyclization of naphthyl alkynoate esters. Esters **36** and **38** were found to undergo spirocyclization to **37** and **39** in 89% and 77% yields, respectively. In a final investigation of alkynyl substitution, we synthesized the methyl

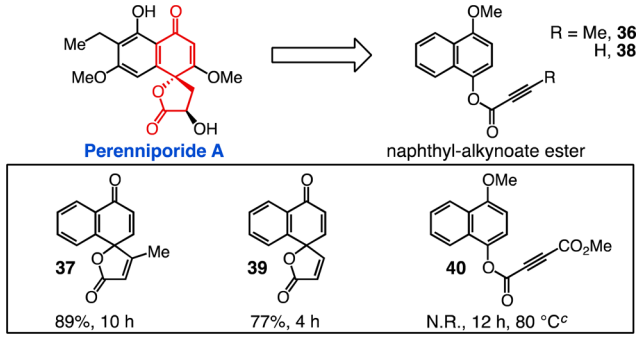


Figure 2. Naphthyl alkynoate esters: (a) reactions conducted at room temperature in DCM (0.05 M) with 1 equiv of H_2O, 5 mol % of $Au(PPh_3)Cl$, and AgOTf; (b) average yield of three trials; (c) no reaction (N.R.) was observed.

ester substituted substrate **40**. Unfortunately, even after stirring at 80 °C no reaction was observed. The additional ester likely decreased the Lewis basicity of the alkyne, thereby inhibiting its activation by the catalyst.

In regard to the mechanism of this transformation, we propose the initial step to be formation of an alkyne−gold *π*-acid complex (Figure 3, **I**). This alkyne activation induces a nucleophilic attack

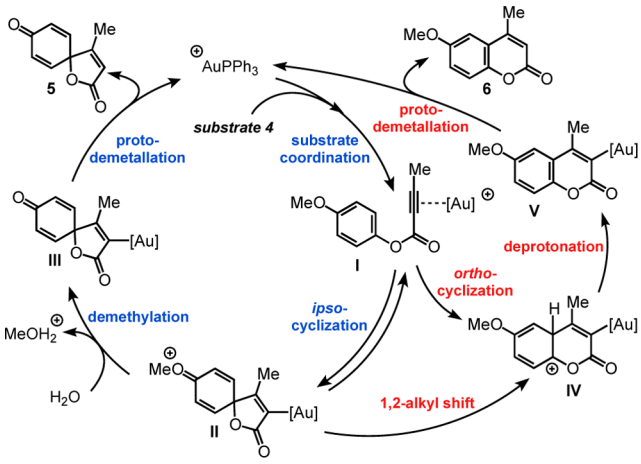


Figure 3. Proposed spirocyclization mechanism.

of the arene forging the new C−C bond. The resulting spirocyclic intermediate **II** then undergoes hydrolytic demethylation. Protodemetalation of **III** leads to spirocycle formation and catalyst regeneration. In the absence of water, however, demethylation is not possible. Alternatively, a 1,2-alkyl shift can occur, leading to bicyclic intermediate **IV**, which then undergoes rearomatization followed by protodemetalation to afford the coumarin product.

The dramatic differences we observed in the rates of formation of the spirocycle versus the coumarin suggest that this 1,2-alkyl shift is a slow process. While we cannot entirely rule out the possibility of a direct hydroarylation mechanism (*ortho*-cyclization), this would seem unlikely given the relative lack of electron density at the *ortho*-carbon. Moreover, gold-catalyzed hydroarylation of aryl alkynoate esters is typically rapid, suggesting that *ortho*-cyclization is not inherently slower than *ipso*-cyclization.[8c]

In summary, we have demonstrated that the dearomative spirocyclization of aryl alkynoate esters can be achieved by gold catalysis to afford a broad scope of spirocyclic lactones in good to

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excellent yields in short reaction times under mild conditions, requiring only water as a stoichiometric additive. The inclusion of water and the presence of a *p*-methoxy group in the substrate are crucial for the selective formation of the desired spirocyclic products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H and ^{13}C NMR, and HRMS data. 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.

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(5) Palladium-catalyzed spirocyclization of alkynyl arenes has been demonstrated; however, the mechanism relies on activation of propargyl and allylic carbonates rather than direct Lewis acid alkyne activation as we report herein. For examples, see: (a) Nemoto, T.; Ishige, Y.; Yoshida, M.; Kohno, Y.; Kanematsu, M.; Hamada, Y. *Org. Lett.* **2010**, *12*, 5020−5023. (b) Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4455−4458. (c) Nemoto, T.; Zhao, Z.; Yokosaka, T.; Suzuki, Y.; Wu, R.; Hamada, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 2217−2220.

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