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Silver-Catalyzed *tert*-Butyl 3-Oxopent-4-ynoate π-Cyclizations: Controlling the Ring Size—Hydroxypyrone or Pulvinone Formation—by Counterion and Additive Optimization

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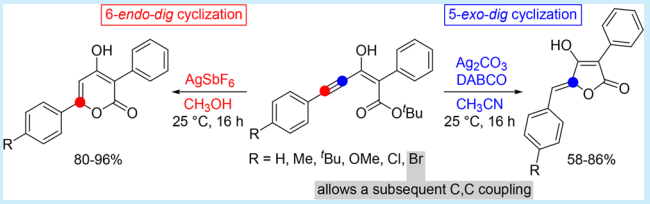
Supporting Information

ABSTRACT: *tert*-Butyl 2,5-diaryl-3-oxopent-4-ynoates, obtained from arylacetylenes and the acid chloride of *tert*-butyl 2-phenylmalonate, represent strongly enolized β-ketoesters. Their C≡C bonds were activated by Ag(I) salts so that de-*tert*-butylating π-cyclizations occurred. The latter followed a 6-*endo*-*dig* mode giving 3,6-diaryl-4-hydroxy-2-pyrones, or a 5-*exo*-*dig* mode giving (*Z*)-configured 2-aryl-4-(arylmethylidene)tetronic acids ("pulvinones"). Perfectly selective pyrone formations were induced by $AgSbF_6$ in methanol and equally selective pulvinone formations by Ag_2CO_3 and DABCO in acetonitrile.



Two-fold unsaturated 6-membered ring lactones ("2-pyrones") abound in nature.[1] In contrast, 3,6-diaryl-2-pyrones **1** (Figure 1) are rare and 3,6-diaryl-4-hydroxy-2-pyrones **2** (other than aryl-free 4-hydroxy-2-pyrones[2]) are even rarer, both in nature (e.g., ref 3) and synthesis (like the pesticide **3**[4]). 3-Aryl-5-(arylmethylidene)furan-2(5*H*)-ones **4** are 5-membered ring isomers of 3,6-diaryl-2-pyrones **1** and originate rather from synthesis[5] than from nature.[6] Similarly, 3-aryl-5-(arylmethylidene)-4-hydroxyfuran-2(5*H*)-ones **5**—or "pulvinones"—are 5-membered ring isomers of 3,6-diaryl-4-hydroxy-2-pyrones **2**. If (*Z*)-configured, they are well-known naturally[7]—e.g., aspulvinone E (**6**[7a])—and synthetically.[8] Some have evoked interest by their bioactivity.[9]

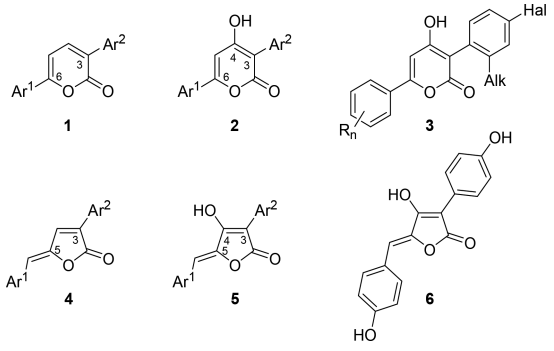


Figure 1. 3,6-Diaryl-2-pyrones (**1**), 3,6-diaryl-4-hydroxy-2-pyrones (**2**), type-**2** compounds **3** from a pesticide patent,[4] (*Z*)-2-aryl-5-(arylmethylidene)furan-2(5*H*)-ones (**4**), and pulvinones (**5**), to which aspulvinone E (**6**[7a]) belongs.

Unsaturated 6- and 5-membered ring lactones have been synthesized, inter alia, by acid-, base-, or metal-promoted π-cyclizatitions of pent-4-ynoic acids and their derivatives.[10] This includes synthesizing type-**1** pyrones[11] and type-**4** furanones. However, to the best of our knowledge, type-**2** hydroxypyrones have never been prepared in this manner and pulvinones **5** only once (**5a**: $Ar^1 = Ar^2 = Ph$[8e]). The present study fills this void by accessing, selectively, diarylhydroxypyrones **2** as well as pulvinones **5** by silver-induced π-cyclizations of enol-containing *tert*-butyl pent-2-en-4-ynoates **7** and/or their β-ketoester tautomers *keto*-**7** (Figure 2). This required conducting such cyclizations 6-*endo*-*dig*-selectively[12] (→ **2**) and 5-*exo*-*dig*-selectively[12] (→ **5**), respectively.

The preferred cyclization mode of pent-2-en-4-ynoic acids, their salts or their esters are affected by the nature of their C═O bond,[13] α,β-[14] or δ-substituent,[15] the attacking electrophile[16]

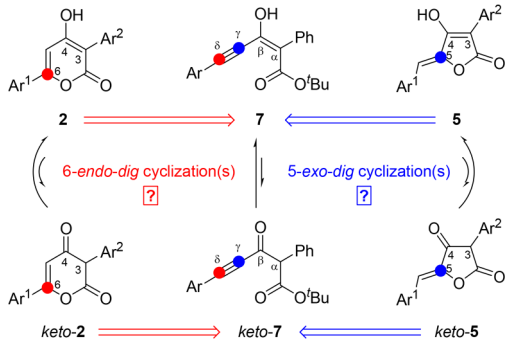


Figure 2. Considering 3,6-diaryl-4-hydroxy-2-pyrones (**2**) and pulvinones (**5**) or their respective β-ketolactone tautomers (keto-**2**, keto-**5**) as de-*tert*-butylated π-cyclization products of $C^{\gamma}\equiv C^{\delta}$-containing β-ketoesters *keto*-**7** or their enols **7**.

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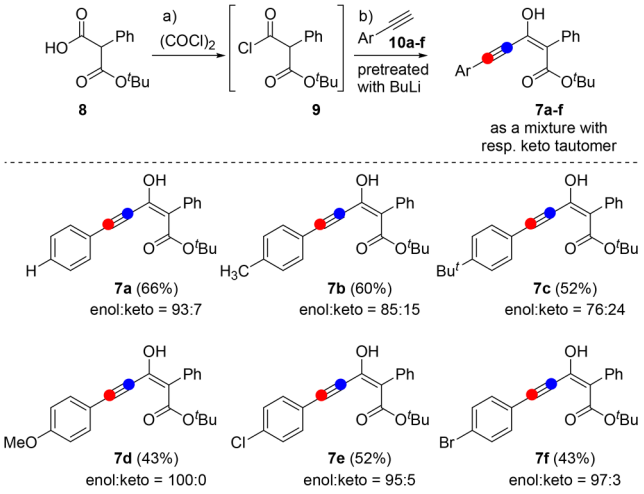
including its oxidation state, ligand, or counterion,[17] the solvent,[18] "additives",[19] and the temperature.[20] Therefore, the outcome of such cyclizations is difficult to predict.[21]

Choosing *tert*-butyl 5-arylpent-2-en-4-ynoates **7**—containing 0−24% of the tautomeric ketoester *keto*-**7**—as our substrates, we explored several accesses.[22] We settled on acylating an excess of the lithiated arylethynes **10** with the chloride **9** of mono-*tert*-butyl phenylmalonate (**8**; Scheme 1); **9** was obtained from **8** in

Scheme 1. Synthesis of the Pent-2-en-4-ynoates 7a−7f from the Arylacetylenes 10a−10f and the Chloride 9 of Mono-*tert*-butyl Phenylmalonate[a]



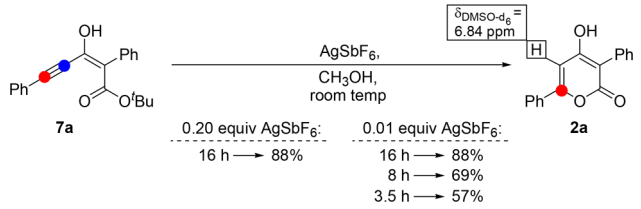
[a]Reaction conditions: (a) $(COCl)_2$ (1.0−1.7 equiv), DMF (cat.), CH_2Cl_2, room temperature, 30−90 min; evaporation of the volatiles at 10^{-2} mbar; (b) **10a−10f** (2.1−2.8 equiv), *n*-BuLi for **10a−10e** and MeLi for **10f** (2.1−2.6 equiv), THF, −78 °C for **10a−10c,10e**, 0 °C for **10f**, and −30 °C for **10d**, 15−120 min; addition of **9** in THF, 30−65 min.

situ. Alkyne lithiation in THF using *n*-BuLi or MeLi (for **10f**, lest Br/Li exchange interfered), acylation at −78 °C, quenching with saturated aqeuous NH_4Cl, extractive workup, and purification by flash-chromatography on silica gel[23] immediately thereafter (for minimizing decomposition) afforded 43%−66% yields of the *tert*-butyl 5-arylpent-2-en-4-ynoates **7a−7f**.

We treated *tert*-butyl 5-phenylpent-2-en-4-ynoate (**7a**) with six different Ag(I) salts in 10 different solvents and with AuCl or $AuCl_3$ in DMF. π-Cylizations always ensued, but mostly with little ring-size control. The hydroxypyrone **2a** resulted best from an $AgSbF_6$-induced cylization in CH_3OH. The pulvinone **5a** formed best in the presence of Ag_2CO_3 in CH_3CN. Ring-size control was due to both the counterion and the solvent. For instance, exposure of the ester **7a** to $AgSbF_6$ in CH_3OH—as mentioned—or in acetone gave the hydroxypyrone **2a** exclusively; **2a**/**5a** mixtures resulted in $(F_3C)_2CHOH$ or 1,3-dimethyl-2-imidazolidinone (~70:30) or CH_3CN or DMF (~30:70). Similarly, the ester **7a** and Ag_2CO_3 gave the pulvinone **5a** as the major product in CH_3CN—as mentioned—(**5a**:**2a** = 93:7) or DMF (85:15); **5a** was the minor product in 1,3-dimethyl-2-imidazolidin-2-one (49:51), acetone (42:58), CH_3OH (34:66), or $(F_3C)_2CHOH$ (20:80).

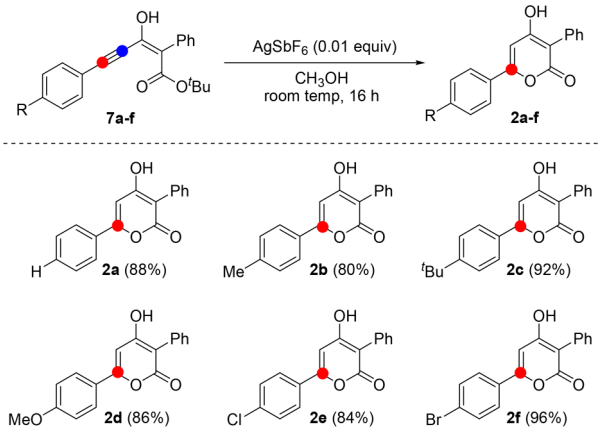
Regarding the conversion of our simplest *tert*-butyl 5-arylpent-2-en-4-ynoates **7a** into the hydroxypyrone **2a** in CH_3OH, we decreased the amount of $AgSbF_6$ from our screening (20 mol %) to as little as 1 mol % (Scheme 2). The yield was unaffected when the reaction time remained 16 h. It sunk when we worked up after 8 h or less.

Scheme 2. 6-*Endo-dig* Cyclizations of the *tert*-Butyl 5-Phenylpent-2-en-4-ynoate 7a, Giving the 3,6-Diphenyl-4-hydroxypyrone 2a: Effect of Catalyst Loading



Under the conditions of Scheme 2, the *tert*-butyl 5-arylpent-2-en-4-ynoates **7b−7f** cyclized to the corresponding hydroxypyrones **2b−2f** with the same perfect selectivity as **7a** (see Scheme 3). Only the hydroxypyrone **2c** was isolated by

Scheme 3. Optimized 6-*endo-dig* Cyclizations of the *tert*-Butyl 5-Arylpent-2-en-4-ynoates 7a−7f Giving the 3,6-Diaryl-4-hydroxypyrones 2a−2f



extractive workup and purification by flash chromatography on silica gel.[23] The hydroxypyrones **2a**, **2b**, and **2d−2f** were poorly soluble, so they precipitated while their formation was underway. We isolated them in yields of 80%−96% by centrifugation, removing the supernatant, and triturating the remaining solid successively with H_2O, ^{i}PrOH, and *n*-pentane or toluene.

As previously mentioned, *tert*-butyl 5-phenylpent-2-en-4-ynoate (**7a**) and Ag_2CO_3 in CH_3CN provided the highest proportion of pulvinone **5a** during our initial screening. Nevertheless, some hydroxypyrone **2a** formed as well. Its proportion in the product amounted to 2%−7%, as a result of somewhat scattering outcomes of seemingly identical experiments (Scheme 4, first row, "no additive"). Aggravatingly, this contaminant could not be removed from the desired pulvinone. This forced us to vary the reaction parameters until we attained a perfectly ring-size specific cyclization of our substrate. We noticed that diluting the substrate *without diluting the catalyst* decreased the proportion of the hydroxypyrone **2a**. This led us to speculate whether the basicity of the carbonate counterion favored the desired 5-*exo-dig* vs the undesired 6-*endo-dig* cyclization. As a consequence, we added 2 equiv of a base to the original Ag_2CO_3/CH_3CN system (Scheme 4). They were composed of amines, a diamine (DABCO), an amidine (DBU),

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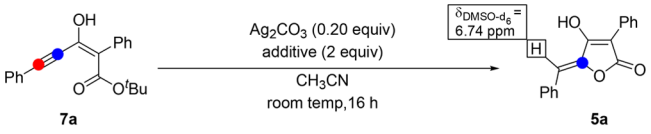
Scheme 4. 5-*Exo-dig* Cyclizations of the *tert*-Butyl 5-Phenylpent-2-en-4-ynoate 7a Giving Pulvinone (5a): Base Effects



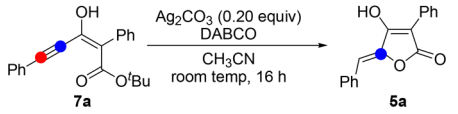
additive	yield	rel-% pulvinone	additive	yield	rel-% pulvinone
none	57-72%	98:2-93:7[a]	K_2CO_3	52%	100:0
DBU	28%	95:5	$HNEt_2$	63%	
TBD	45%	98:2	NEt_3	65%	
$^iPr_2NEt$	45-57%	99:1	DABCO	73%	

[a]The amount of pulvinone **5a** was dependent on the concentration of the reactants and the amount of Ag_2CO_3. Abbreviations: DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; and DABCO, 1,4-diazabicyclo[2.2.2]octane.

a guanidine (TBD), and K_2CO_3. Each base increased the pulvinone/hydroxypyrone ratio, with the order being DBU < TBD < $^iPr_2NEt$ (Scheme 4, left table) < K_2CO_3 or $HNEt_2$ or NEt_3 or DABCO (Scheme 4, right table). Also, each base, with the exception of DABCO, caused a silver mirror or black flakes (amorphous Ag?) to form during the 16 h of reaction time. Moreover, DABCO gave the highest yield. Accordingly, our further optimizations maintained the latter.

The more DABCO we applied to our substrate **7a**, the higher the yield of pulvinone **5a** (see Scheme 5). It seemed as if ≥2

Scheme 5. 5-*Exo-dig* Cyclizations of the *tert*-Butyl 5-Phenylpent-2-en-4-ynoate 7a Giving Pulvinone (5a): Effect of Varying Amounts of DABCO

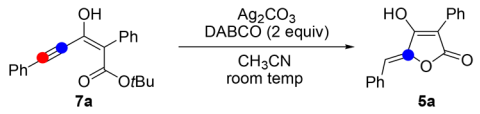


DABCO (equiv)	yield
0.1	63%
1.0	63%
2.0	73%
4.0	80%

equiv of DABCO precipitated this pulvinone from the reaction mixture as a solid. Finally, we found that the amount of Ag_2CO_3 could be reduced to 0.01 equiv without affecting the yield after 16 h of reaction time (Scheme 6). However, in the absence of Ag_2CO_3, 2 equiv of DABCO left the substrate **7a** unaltered under otherwise identical conditions throughout 6 $^3/_4$ h. This proves that DABCO alone cannot cyclize **7a** at all.

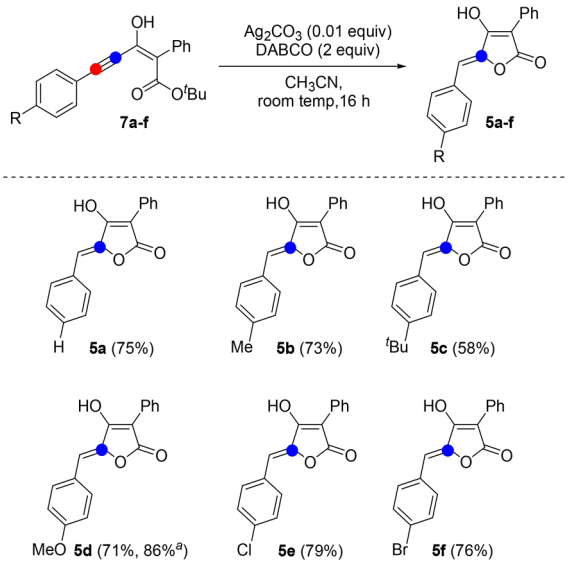
Under the conditions of Scheme 6, the *tert*-butyl 5-arylpent-2-en-4-ynoates **7b**–**7f** cyclized giving the corresponding pulvinones **5b**–**5f** (Scheme 7) with the same perfect selectivities with

Scheme 6. 5-*Exo-dig* Cyclizations of the *tert*-Butyl 5-Phenylpent-2-en-4-ynoate 7a Giving Pulvinone (5a): Effect of Catalyst Loading



Ag_2CO_3 (equiv)	time	yield	Ag_2CO_3 (equiv)	time	yield	Ag_2CO_3 (equiv)	time	yield
0.01	5 h	69%	0.05	5 h	69%	0.20	5 h	69%
	16 h	75%		16 h	69%		16 h	69%

Scheme 7. Optimized 5-*exo-dig* Cyclizations of the *tert*-Butyl 5-Arylpent-2-en-4-ynoates 7a–7f Giving the Pulvinones 5a–5f



[a]Obtained from ester **7d** by employing 4 equiv of DABCO.

which **7a** gave **5a**. After 16 h, the crude pulvinones **5a**–**5f** were first extracted from ether into saturated aqueous $NaHCO_3$ as an anion. The aqueous phases were acidified (HCl) so that the respective pulvinone **5a**–**5f** re-formed as a yellow precipitate. The latter was dissolved upon back-extraction with ether. Removal of the volatiles provided pure pulvinones (58%–86% yields).

The hydroxypyrone **2f** (Scheme 3) and the pulvinone **5f** (Scheme 7) contain a C–Br bond. It originated from (4-bromophenyl)acetylene and was introduced via *tert*-butyl 5-(4-bromophenyl)pent-2-en-4-ynoate (**7f**; see Scheme 1). The C–Br bonds were intended to allow late stage modifications of the two lactones by Pd-catalyzed C,C or C,Het coupling reactions. Their feasibility is illustrated in Scheme 8 by Sonogashira–Hagihara couplings with hept-1-yne. They were effected after protecting the OH group of the hydroxypyrone **2f** as methyl ether **11** and the OH group of the pulvinone **5f** as methyl ether **12**. These compounds and hept-1-yne coupled, affording the heptynylated pyrone ether **13** and the heptynylated pulvinone ether **14** in excellent yields. It is unclear whether the C≡C bond introduced in these couplings would have interfered with the π-cyclizations—which *established* the respective hydroxypyrone and pulvinone scaffolds—if they had already been present then. The modus procedendi of Scheme 8 avoids such incertitudes.

The pulvinone syntheses described here circumvent the nonadoptability of our π-cyclization route to aryl-(arylmethylidene)butenolides ("desoxypulvinones") **16**[5f] to yield the corresponding pulvinones, e.g., compound **5a** (see Scheme 9). This would have required the oxidation of the respective hydroxybutanolide intermediates **15**, e.g., compound **15a**, which we accessed by π-cyclizing the type-**17** substrate not with Ag_2CO_3 in dimethylformamide (DMF),[5f] but with $AgNO_3$ in 1,2-dimethoxyethane (DME).[24]

Sadamitsu et al. reached one pulvinone (**5a**) by an AgOTf-mediated π-cyclization of the ketopentynoate **19**, which was generated in situ from the ynone **18** and CO_2 (see Scheme 10).[8e] Their access looks generalizable, but is more demanding than

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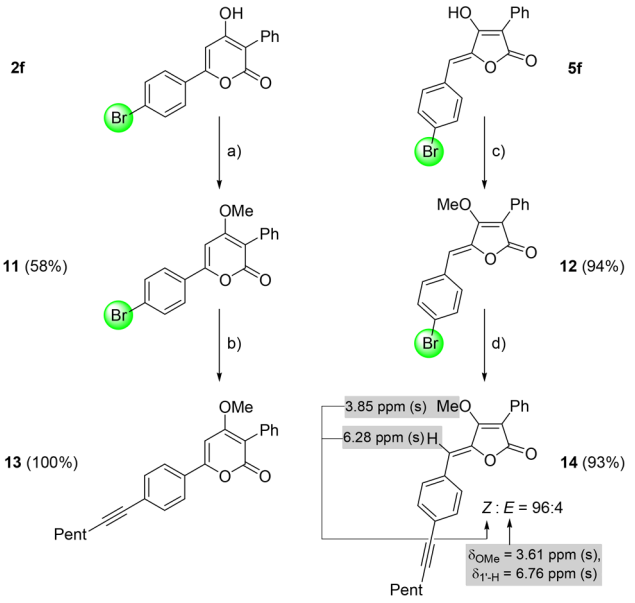
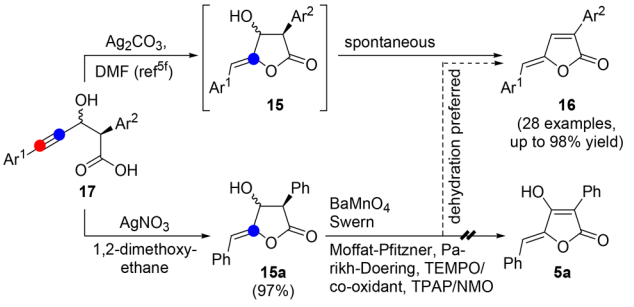
Scheme 8. Post-Cyclization Modifications of the Hydroxypyrone 2f and the Pulvinone 5f by a Sonogashira–Hagihara Couplings with Their C–Br Moieties[a]



[a]Reagents and conditions: (a) Me_2SO_4 (1.93 equiv), K_2CO_3 (1.60 equiv), acetone, reflux, 3.5 h; (b) hept-1-yne (2.14 equiv), $PdCl_2(PPh_3)_2$ (0.02 equiv), CuI (0.05 equiv), $^iPr_2NH$/THF (1:2), reflux, 4.5 h; (c) Me_2SO_4 (2.03 equiv), K_2CO_3 (1.69 equiv), acetone, reflux, 1.5 h; (d) hept-1-yne (2.14 equiv), $PdCl_2(PPh_3)_2$ (0.02 equiv), CuI (0.04 equiv), $^iPr_2NH$/THF (1:2), reflux, 3 h.

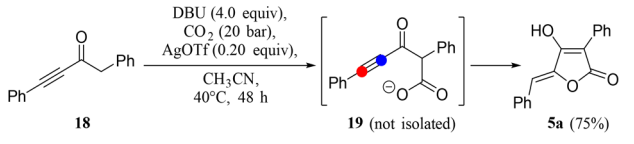
Scheme 9. A π-Cyclization Route to Aryl(arylmethylidene)butenolides 16[5f] **and Its Nontransferability to Reaching the Pulvinone 5a**



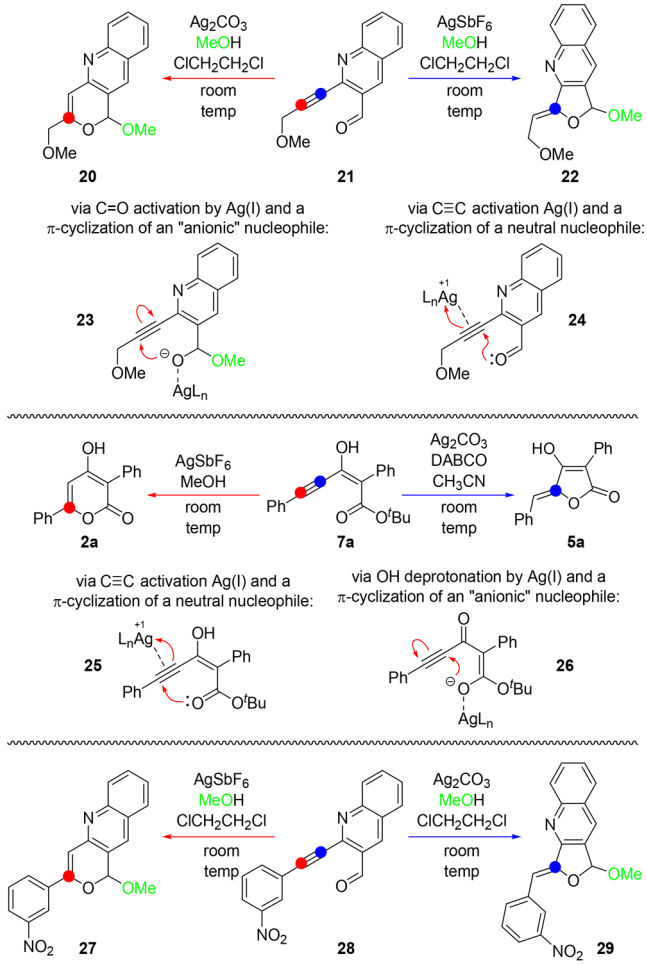
ours (CO_2 was pressurized at 20 bar) and more expensive (they used 20 times as much Ag(I) as we did).

It would be nice if there was a rationale for the ring-size selectivities that we observed. However, we cannot provide one. Ag(I) can act both as a π-electrophile toward C≡C motifs and as a σ-electrophile toward C═O motifs.[21c] Both properties were invoked by Belmont et al., independently, to explain why the (alkynylaryl)aldehyde **21** 6-*endo*-*dig*-cyclizes with Ag_2CO_3 (→ **20**) but 5-*exo*-*dig*-cyclizes with $AgSbF_6$ (→**22**; see Scheme 11, top):[21b] Ag_2CO_3 would act as a σ-Lewis acid and thereby induce

Scheme 10. Only π-Cyclization That Afforded a Pulvinone, Namely the Parent Compound 5a, before Our Study[8e]



Scheme 11. Juxtaposition of the Salt-Dependent π-Cyclizations of the Present Study (Center) and of Selected Substrates from ref 21b (at the Top and Bottom)



the formation of the hemiacetal "anion" **23**, which cyclizes 6-*endo*-*dig* selectively. $AgSbF_6$ would act as a π-Lewis acid and thus allow the resulting complex **24** to cyclize 5-*exo*-*dig* selectively. Unfortunately, these cyclization modes of their substrate (**21**) contrast with those of ours (**7a**; see Scheme 11, center). If the preceding reasoning[21b] was correct, $AgSbF_6$ should let the **7a**-based π-complex **25** cyclize, Ag_2CO_3/DABCO the **7a**-based σ-complex **26**. But why would the resulting rings be oppositely sized—6-membered (**2a**) vs 5-membered (**5a**)—than the rings formed via Belmont's π-complex **24** and σ-complex **23**, which are 5-membered (**22**) vs 6-membered (**20**)? Interestingly, the Ag(I)-catalyzed π-cyclizations of the (alkynylaryl)aldehyde **28** display the *identical* ring-size/salt correlations (→ **27**/**29**; see Scheme 11, bottom)[21b] as our π-cyclizations (see Scheme 11, center). Belmont et al. noticed the contrast to their **21**-cyclizations (see Scheme 11, top) but had no explanation.

In summary, we developed an access to 3,6-diaryl-4-hydroxypyrones **2** and pulvinones **5** from *tert*-butyl 2,5-diaryl-3-hydroxy-2-en-4-ynoates **7** as common precursors. The latter stemmed from acylating arylacetylenes **10** with the chloride **9** of *tert*-butyl phenylmalonate (**8**). These *tert*-butyl 2,5-diaryl-3-hydroxy-2-en-4-ynoates **7** underwent perfectly regioselective 6-

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endo-dig cyclizations when treated with $AgSbF_6$ in CH_3OH and equally regioselective 5-*exo-dig* cyclizations when treated with Ag_2CO_3 and DABCO in CH_3CN. Both cyclization modes were brought about by just 1 mol % of Ag salt.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03214.

Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra for pentynoic esters **7a−7f**, 3,6-diaryl-4-hydroxypyrones **2a−2f**, and pulvinones **5a−5f**, along with additional references to citations given as refs 10 and 15−17 (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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