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Versatile and Expeditious Synthesis of Aurones via Au^{I}-Catalyzed Cyclization

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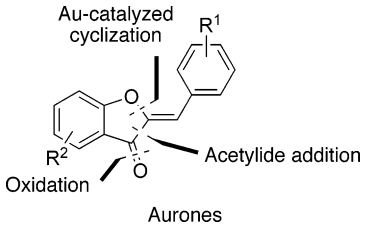
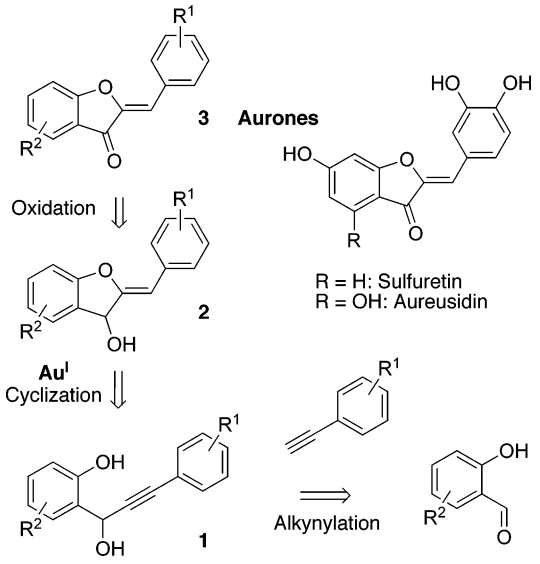


Aurones are conveniently formed in a three-step procedure including a gold^{I}-catalyzed cyclization of 2-(1-hydroxyprop-2-ynyl)phenols as a highly regio- and stereoselective key step. A wide diversity of derivatives can be obtained starting from substituted salicylaldehydes. Synthesis of natural 4,6,3′,4′-tetramethoxyaurone and structure revision of two natural products (dalmaisione D and 4′-chloroaurone) were achieved.

Flavonoids represent a large class of plant natural products, exhibiting multiple biological activities.[1] Among them, aurones,[2] i.e., (*Z*)-2-benzylidenebenzofuran-3(2*H*)-ones (Scheme 1), constitute a subclass contributing to the pigmentation of flowers and fruits,[3] especially to the bright golden yellow color of flowers.[4] Aurones also exhibit a strong and broad variety of biological activities.[2] For example, they have been described as antifungal agents,[5] as insect antifeedant agents,[6] as inhibitors of tyrosinase,[7] and as antioxidants.[8] Aureusidin, a common

SCHEME 1. General Retrosynthesis of Aurones and Structure of a Few Natural Aurones



aurone (Scheme 1), proved to be an inhibitor of iodothyronine−deiodinase, an enzyme involved in hormone synthesis and regulation.[9] Non-natural aurones have been found to bind to the nucleotide-binding domain of P-glycoprotein, which mediates resistance of cancer cells to chemotherapy,[2] inhibit cyclin-dependent kinases in connection with antiproliferative properties,[10] and act as anticancer agents.[11]

Numerous aurone syntheses were reported in the literature: the Wheeler aurone synthesis from chalcone dihalides,[12] oxidative cyclization of 2′-hydroxychalcones,[13] and ring closure of *o*-hydroxyaryl phenylethynyl ketones.[14] These methods give generally good stereoselectivity, but they usually cannot completely prevent the formation of flavones. The most popular preparation of aurones[6−11] was developed by Varma[15] and is based on the condensation of benzofuran-3(2*H*)-ones with benzaldehydes. However, this aldol-like coupling reaction gives sometimes low yields and requires the synthesis of benzofuran-3(2*H*)-ones from substituted 2-phenoxyacetic acids by an intramolecular Friedel−Craft reaction. Such a reaction is usually carried out under harsh conditions and yields are modest.

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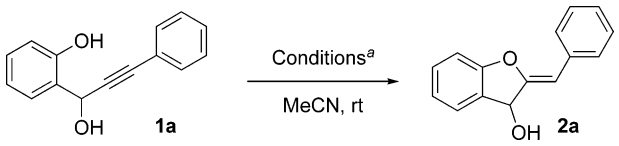
TABLE 1. Screening of Gold Catalysts for the Cyclization of 1a



entry	catalyst (mol %)	additive (mol %)	time (h)	yield[b] (%)
1	none	K_2CO_3 (10)	24	0
2	AuCl (10)	none	0.5	*c*
3	AuCl (10)	K_2CO_3 (10)	**2**	**78**
4	AuCl (10)	$NaHCO_3$ (10)	24	67
5	AuCl (10)	NEt_3 (10)	24	50
6	AuCl (10)	pyridine (10)	24	0
7	AuCl (10)	NaH (100)	24	42[d]
8	PPh_3AuCl (5)	none	24	0
9	PPh_3AuCl (5)	K_2CO_3 (10)	15	55
10	PPh_3AuCl (5)	$AgSbF_6$ (5)	15	*c*
11	$AuCl_3$ (10)	none	0.1	*c*
12	$AuCl_3$ (10)	K_2CO_3 (10)	24	22
13	AuCl (1)	K_2CO_3 (1)	**30**	**86**

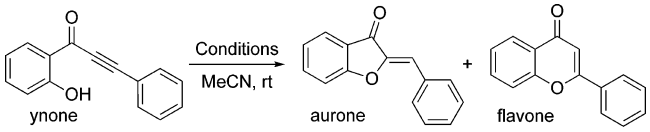
[a] Reactions run under argon, $c = 0.1$ mol/L. [b] Yields of **2a** were calculated by ^{1}H NMR relative to an internal standard (hexamethylbenzene). [c] Degradation products. [d] 14% of flavone and 35% of ynone[19] product were observed by ^{1}H NMR of the crude mixture.

The aurone biological properties and the lack of regioselective syntheses led us to develop an alternative route. We decided to take advantage of our experience in oxygenated heterocycles preparations,[16] and we wish to report here a simple three-step synthesis of aurones. Indeed, we reasoned that aurones **3** should be available through metal-catalyzed cyclization of substituted 1-(2-hydroxyphenyl)-3-phenylpropynols **1** followed by oxidation. The latter would be easily obtained by alkynylation of salicylaldehyde derivatives (Scheme 1).

Various 2-(1-hydroxy-3-arylprop-2-ynyl)phenols **1a**−**h** were easily produced by addition of 2 equiv of lithium arylacetylides,[17] substituted or not, at low temperature in THF to several substituted salicylaldehydes. The yields were routinely higher than 70%. In order to find more appropriate conditions for the cyclization reaction of such substrates and based on previous results,[16f,18] we applied various conditions and gold catalysts to the simplest aurone precursor **1a** (Table 1).

Potassium carbonate alone was not able to promote any cyclization, and the starting material **1a** was recovered even after prolonged contact time (entry 1). In sharp contrast, gold(I) chloride alone rapidly led to decomposition (entry 2). But premixing the base (10 mol %) and the starting material in acetonitrile before adding AuCl (10 mol %) gave the expected cyclization product **2a** in 78% yield as *a single 5-exo-dig regioisomer and Z stereoisomer* (entry 3). The regio- and stereochemistry were unambiguously established after comparison of the oxidation product **3a** to the known aurone.[20,21] Indeed, after a rapid screening of oxidation conditions of **2a**, MnO_2 appeared to be the most effective reagent and smoothly furnished aurone **3a** in 90% yield. To better understand the cyclization step, we then screened other bases associated with AuCl. Sodium hydrogenocarbonate or triethylamine were also efficient in the gold catalysis cyclization but gave lower yields and longer reaction times (entries 4 and 5). Pyridine was completely ineffective in this reaction, presumably due to its coordination with gold chloride (entry 6).[22] Preformed phenolate only afforded a modest yield of **2a** (entry 7). Other gold catalysts were also less effective than AuCl. Surprisingly, the more soluble triphenylphosphane gold chloride required longer reaction time than gold chloride itself and gave only a modest yield of the expected cyclized product (entry 9 vs 3). It is worth mentioning that with this catalyst also, the presence of potassium carbonate was required to get some transformation (entry 8). More electrophilic catalysts either derived from triphenylphosphane gold chloride treated with silver salt or gold(III) trichloride alone gave decomposition product (entries 10 and 11). Nevertheless, in the presence of potassium carbonate, gold trichloride gave the cyclization product but in very low yield (entry 12). Interestingly, with a low catalyst loading (1 mol %), the yield was slightly increased without any loss in regioselectivity, but the reaction time was, however, longer (entry 13 vs 3).

TABLE 2. Comparison with the Cyclization of an Analogue Ynone



entry	catalyst (mol %)	additive (mol %)	time (h)	aurone yield[a] (%)	flavone yield[a] (%)
1	none	K_2CO_3 (10)	1	25	65
2	AuCl (10)	none	24	traces	38
3	AuCl (10)	K_2CO_3 (10)	24	0	traces

[a] Yields of aurone and flavone were calculated by ^{1}H NMR relative to an internal standard (hexamethylbenzene).

Knowing that arylated ynones could be cyclized into a mixture of aurones and flavones,[14] we were curious at this point to compare our optimized conditions with these classical basic conditions. The corresponding ynones were thus easily prepared by MnO_2 oxidation of **1a**. This ynone was then submitted to the known basic conditions and to gold catalysts in various conditions (Table 2). The former led as expected to a mixture of aurone and flavone (entry 1). Surprisingly, AuCl alone gave almost exclusively the flavone, but in low yield (entry 2), and K_2CO_3/AuCl failed to promote any cyclization.[23] These results and the experiment with the preformed phenolate (Table 1, entry 7) clearly evidenced the key role of the base in the Au-catalyzed cyclization of 1-(2-hydroxyphenyl)-3-phenylpropynols.

The above results showed that aurones could be obtained in three steps from salicylaldehyde and phenylacetylene through

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(20) ^{13}C NMR allowed us to clearly distinguish between the aurone and flavone structures; the C3 carbonyl signal of aurone **3a** appeared at 184.8 ppm, while the one of the corresponding flavone was at 177.4 ppm.

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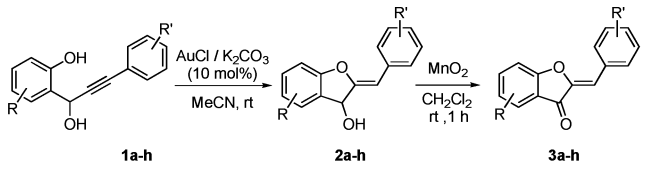
TABLE 3. Scope of the Au-Catalyzed Aurone Synthesis



1a-h 2a-h 3a-h

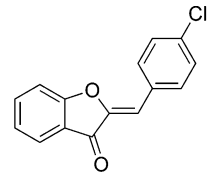
entry	addition yield (%)	cyclization yield (%)	aurone oxidation yield (%)
1	**1a**, 73	**2a**, 84[a]	**3a**, 90
2	**1b**, 94	**2b**, 86	**3b**, 99
3	**1c**, 85	**2c**, 79	**3c**, 77
4	**1d**, 87	**2d**, 70	**3d**, 88
5	**1e**, 71	**2e**, 65	**3e**, 83[b]
6	**1f**, 67	**2f**, 70	**3f**, 86[b]
7	**1g**, 68	**2g**, 69	**3g**, 87
8	**1h**, 21[c]	**2h**, 83[d]	**3h**[e], 64[f]

[a] Cyclization yield obtained with 1 mol % of catalysts. [b] Trace of *E*-aurone was observed (<5%). [c] The adduct is instable on silica gel. [d] Yield was determined by ^{1}H NMR on the crude mixture. [e] The natural product isomerized in solution.[24] [f] Yield of isolated *E*/*Z* products (ratio: 27/73), determined over the two steps.

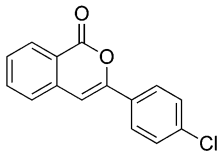
alkynylation, gold-catalyzed cyclization, and oxidation. We then explored the scope of this new synthesis of aurones by applying this sequence to variously substituted salicylaldehydes and alkynes (Table 3).

The yields of cyclic products **2a**−**h** were always good, remaining between 65 and 86%. In all cases, no trace of other regio- or stereoisomers was observed. The oxidation step gave generally aurones **3a**−**h** in high yields with sometimes trace of *E*-aurones (entries 5 and 6), probably due to aurone instability (entry 8).[24]

Some of the synthesized aurones in Table 3 need more detailed comments. Indeed, we focused on the synthesis of natural products to illustrate our strategy. We prepared (*Z*)-4′-chloroaurone **3e** since it was described as a natural product

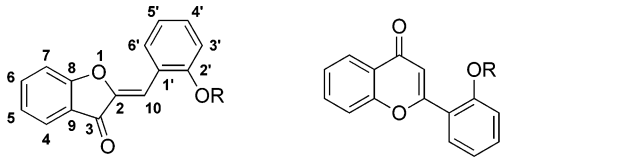


(*Z*)-4'-chloroaurone (**3e**)



Revised structure
3-(4'-chloroisocoumarin)

FIGURE 1. Structural revisions.

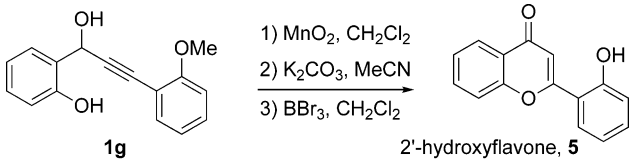


R = H : (*Z*)-2'-hydroxyaurone (**4**) R = H : 2'-hydroxyflavone (**5**)

R = Glc—(6)—Glc : Dalmaisione D R = Glc—(6)—Glc : Revised structure (**6**)

FIGURE 2. Structural revisions.

SCHEME 2. Synthesis of 5, Aglycon of Dalmaisione D



1g

2'-hydroxyflavone, **5**
17% over 3 steps

isolated from the marine brown alga *Spatoglossum variabile*.[25] However, spectroscopic data of the synthetic **3e** we obtained did not match with those reported. The vinylic proton resonated at 6.84 ppm as a singlet, while it was reported at 6.91 ppm. Comparison with related compounds led us think that the natural product was misassigned and that it should correspond to an isocoumarin. Indeed, Subbaraju[26] et al. published during our own attempts to elucidate this structure, a structural revision and reassigned it as the known 3-(4′-chloroisocoumarin) (Figure 1).

We also chose to prepare aurone **3g** since it is the *O*-methylated form of the aglycone of dalmaisione D, a natural product isolated from roots of *Polygala dalmaisiana*,[27] which is composed of a disaccharide (*β*-glucopyranosyl-(*β*-1→6)-glucopyranosyl) tethered to the (*Z*)-2′-hydroxyaurone **4** (Figure 2). But again, the spectral data reported for the compound obtained after acid hydrolysis of dalmaisione D did not match with the synthetic **4** we obtained after demethylation of **3g** with BBr_3.[23] Indeed, NMR shifts of carbonyl (C_3 = 177.1 ppm) and olefinic proton (H_{10} = 7.13 ppm) seem to correspond to the flavone isomer **5**. Unfortunately, reported NMR data of 2′-hydroxyflavone[28] were confusing, which forced us to synthesize **5** in three steps from phenol **1g** (Scheme 2). We were pleased to find that ^{1}H and ^{13}C NMR data of synthetic **5** were now consistent with the natural aglycon. These data led us to reassign the natural product dalmaisione D as compound **6** (Figure 2).[21]

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Finally, the synthesis of natural (*Z*)-4,6,3′,4′-tetramethoxyaurone[24] **3h** isolated from *Cyperus capitatus* highlights this new aurone access. It is noteworthy that although only one stereoisomer was formed during the cyclization step, a mixture of *E*/*Z* **3h** was obtained after oxidation due to equilibrium of the two isomers in the presence of light or on silica gel.[24]

In conclusion, we have reported *for the first time* an original route toward aurones. This three-step approach based on a gold-catalyzed cyclization led to an efficient and expeditious synthesis of aurones. Moreover, a single regioisomer and stereoisomer is produced in the cyclization step. We have accomplished the synthesis of the natural 4,6,3′,4′-tetramethoxyaurone and reassigned the structures of dalmaisione D and another natural product isolated from a marine brown alga.

Further work is now underway to understand the role of the base involved in the gold-catalyzed reaction, to expand the use of gold catalysts[29] in organic synthesis, and to broaden the scope of this reaction.

Experimental Section

General Procedure 1 for the Alkynylation. To an arylacetylene (2.2 mmol) in dry THF (5 mL) was slowly added *n*-BuLi (2.1 mmol, 1.6 M in THF) at −78 °C. The reaction mixture was heated up to −40 °C and then cooled down to −78 °C. A solution of the corresponding salicylaldehyde (1 mmol in 5 mL of THF) was dropwise added via cannula. The reaction mixture was stirred at −78 °C for 4 h and was then quenched with saturated NH_4Cl solution. Excess of THF was removed in vacuo, and the aqueous phase was extracted with Et_2O. Combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. Crude product was purified by flash chromatography.

2-(1-Hydroxy-3-phenylprop-2-ynyl)phenol (1a).[14b] Following the general procedure 1, salicylaldehyde (1.22 g, 10 mmol) and phenylacetylene (2.04 g, 22 mmol) gave **1a** (1.64 g, 73%) as a pale white solid: TLC R_f 0.4 (cyclohexane/EtOAc 30%); mp 88 °C; IR ($CHCl_3$) ν_{max} 2580, 3368, 3022, 2927, 2851, 2229, 1588, 1489, 1458, 1443, 1366, 1282, 1258, 1228, 1216, 1152, 1097, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.46 (m, 3 H), 7.35−7.24 (m, 5 H), 6.94 (m, 2 H), 5.91 (s, 1 H), 2.97 (br, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 155.2, 131.9, 131.8, 130.2, 130.2, 128.9, 128.4, 127.8, 124.6, 122.0, 120.3, 117.1, 88.1, 86.6, 64.3; MS (EI) *m*/*z* 223 (8, $M^{+\bullet}$ − H), 206 (100).

General Procedure 2 for the Au-Catalyzed Cyclization. To the alcohol (0.5 mmol, **1a**−**h**) in dry acetonitrile (2.5 mL) was added K_2CO_3 (0.05 mmol) at room temperature. The reaction mixture was stirred for 5 min, and AuCl (0.05 mmol) was then added in one portion. The reaction was monitored by TLC until complete conversion of starting material. Acetonitrile was removed in vacuo, and the residue was purified by flash chromatography.

(*Z*)-2-Benzylidene-2,3-dihydrobenzofuran-3-ol (2a). Following the general procedure 2, alcohol **1a** (116 mg, 0.5 mmol) gave **2a** (98 mg, 84%) as a white solid: TLC R_f 0.32 (cyclohexane/EtOAc 30%): mp 110−111 °C; IR (KBr) ν_{max} 3305, 1684, 1613, 1600, 1478, 1466, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 7.9 Hz, 2 H), 7.50 (d, J = 7.2 Hz, 1 H), 7.41−7.32 (m, 3 H), 7.27−7.22 (m, 1 H), 7.11−7.07 (m, 2 H), 6.01 (d, J = 1.5 Hz, 1 H), 5.77 (d, J = 7.5 Hz, 1 H), 2.20 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.7, 157.0, 134.5, 130.6, 128.7, 128.5, 126.9, 126.8, 125.6, 122.9, 110.7, 106.0, 72.5; MS (ESI) *m*/*z* 223 (100, $M^{+\bullet}$ − H); HR-MS 223.0380 ($C_{15}H_{12}O_2$ − H calcd 223.0354).

General Procedure 3 for the Oxidation. To the corresponding benzofuranol (0.2 mmol, **2a**−**h**) in dry CH_2Cl_2 (5 mL) was added MnO_2 (2 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature and was then filtered through a pad of Celite. The organic phase was evaporated, and the crude residue was purified by flash chromatography.

(*Z*)-Aurone (3a).[6] Following the general procedure 3, benzofuranol **2a** (100 mg, 0.45 mmol) gave **3a** (90 mg, 90%) as a yellow solid: TLC R_f 0.54 (Cyclohexane/EtOAc 30%); mp 99−100 °C; IR (KBr) ν_{max} 3030, 1714, 1652, 1594, 1472, 1462, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.0, 1.8 Hz, 2 H), 7.82 (ddd, J = 7.7, 1.6, 0.7 Hz, 1 H), 7.65 (t, J = 8.1 Hz, 1 H), 7.50−7.41 (m, 3 H), 7.34 (d, J = 8.3, 1.2 Hz, 1 H), 7.22 (td, J = 7.5, 1.6 Hz, 1 H), 6.91 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 184.8, 166.8, 146.9, 137.0, 132.3, 131.9, 129.9, 128.9, 124.7, 123.5, 121.7, 113.1, 113.0; MS (ESI) *m*/*z* 245 (100, $M^{+\bullet}$ + Na), 223 (28); HR-MS 245.0548 ($C_{15}H_{10}O_2$ + Na calcd 245.0573).

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Supporting Information Available: Spectral and characterization data of each compound **1a**−**h**, **2a**−**h**, **3a**−**h**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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