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Regiodivergent Hydration–Cyclization of Diynones under Gold Catalysis

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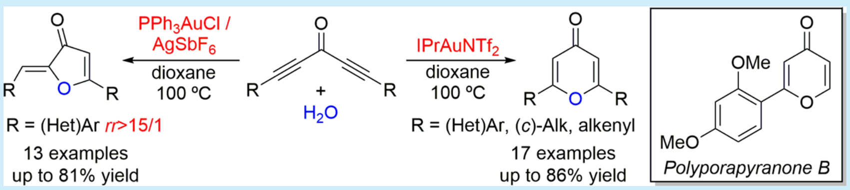

ABSTRACT: Skipped diynones, efficiently prepared from biomass-derived ethyl lactate, undergo a tandem hydration–oxacyclization reaction under gold(I) catalysis. Reaction conditions have been developed for a switchable process that allows selective access to 4-pyrones or 3(2*H*)-furanones from the same starting diynones. Further application of this methodology in the total synthesis of polyporapyranone B was demonstrated.

Because of the availability and renewability of biomass-derived chemicals, the development of useful synthetic organic procedures that employ eco-friendly and sustainable feedstocks represents a major challenge in current chemistry.[1] For example, ethyl lactate (EL) has demonstrated great potential as a green solvent and building block for the preparation of value-added products.[2] In this field, we have recently reported the synthesis of symmetric 1,4-diyn-3-ones **2** by the oxidative cleavage of the corresponding 1,2-diols **1** using EL as a carbonyl source (Scheme 1, eq 1).[3] These skipped diynones **2** are interesting functionalized molecules that possess a wide variety of synthetic applications.[4]

On the other hand, oxygenated heterocycles, such as γ-pyrones and 3(2*H*)-furanones, are interesting compounds as well as intermediates for the preparation of other products with relevant biological activities. The 4-pyrone ring occurs in many therapeutic agents and bioactive molecules.[5] In the same way, several natural products that possess antibiotic and antitumoral properties present the 3(2*H*)-furanone core as a key structure.[6] Thus, the synthesis of these heterocyclic frameworks has attracted considerable attention in recent years, and so many γ-pyrone and 3(2*H*)-furanone derivatives and their synthetic methods have been disclosed in the literature, traditionally related with condensation cyclization reactions of carbonyl compounds typically involving multistep sequences or limited scope.[7] More recently, different strategies based on transition-metal-catalyzed cyclizations have been reported.[8] However, one of the simplest and most atom-economical approaches involves the hydration/cyclization of diynones or the cyclization of acetylenic β-diketones. The first one has been developed by different authors toward the synthesis of 4-pyrones using Brønsted acids, such as triflic[9] acid or *p*-toluenesulfonic acid,[10] as catalysts (Scheme 1, eq 2). Nevertheless, this useful reaction suffers from moderate yields when the substituent of the alkyne is an alkyl group or a hydrogen atom, and no examples have been reported with alkenyl groups as substituents. Using 4-pentyn-1,3-diones as starting materials, which are synthesized from ynals and silyl enol ethers in two steps, their cyclization provides mixtures of 3(2*H*)-furanones, via 5-*exo*, and γ-pyrones, via 6-*endo*. The latter alternative is the most favorable pathway with an additional influence of the alkyne substituent (Scheme 1, eq 3).[11] Both approaches face a critical challenge: the regiocontrol of the cyclization: 5-*exo* vs 6-*endo*. This regiochemistry affair in cyclization reactions is relatively general allowing, in an ideal situation, the access of two different scaffolds from the same starting material.[12]

Taking advantage of our efficient procedure for accessing diynones **2**,[3] as well as from our experience in gold chemistry,[13] we planned to tackle their selective transformation in the corresponding 4-pyrones **3** and 3(2*H*)-furanones **4** by an hydration–cyclization sequence catalyzed by gold complexes (Scheme 1, eq 5). However, a 1,3-transposition of skipped diynones **2** to the corresponding conjugated isomers **5** has been reported by Gevorgyan et al., thus adding an additional competitive pathway to our initial proposal (Scheme 1, eq 4).[14] Also in this field, the hydration of ynones to 1,3-diketones has been reported.[15] Herein, we report the gold(I)-

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Scheme 1. Previous Work and Proposed Hydration−Cyclization of Skipped Diynones

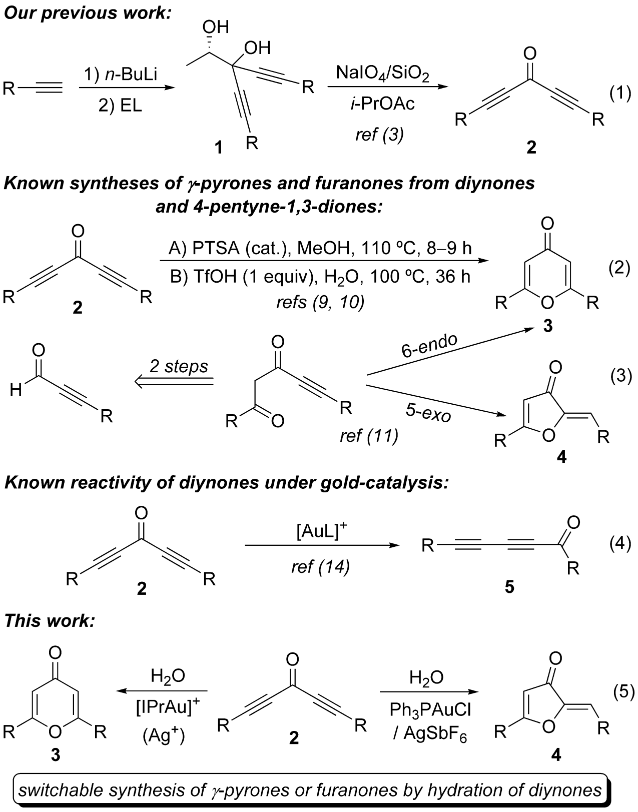
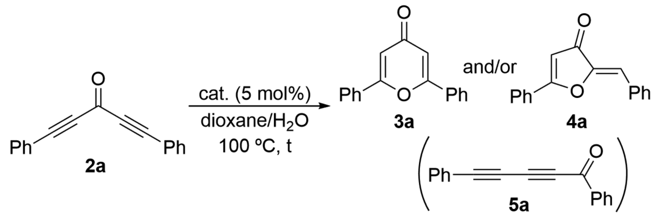


Table 1. Optimization of the Reaction Conditions for the Hydration−Cyclization of 2a[a]



ent.	catalyst	time (h)	products (yield, %)[b]	3a/4a
1[c]	$Ph_3PAuNTf_2$	3	**3a** (11) + **4a** (64) + **5a** (7)	1/5.8
2	$Ph_3PAuCl/AgOTf$	5	**3a** (7) + **4a** (71) + **5a** (5)	1/9.6
3	$Ph_3PAuCl/AgNTf_2$	5	**3a** (8) + **4a** (65) + **5a** (7)	1/8.4
4	$Ph_3PAuCl/AgSbF_6$	5	**3a** (4) + **4a** (78)	1/19
5[d]	$Ph_3PAuCl/AgSbF_6$	6	**3a** (8) + **4a** (53) + **5a** (10)	1/6.6
6	$(t\text{-Bu})_3PAuCl/AgSbF_6$	5	**3a** (11) + **4a** (69)	1/6.3
7	$(C_6F_5)_3PAuCl/AgSbF_6$	5	**3a** (30) + **4a** (52)	1/1.7
8[e]	$AgSbF_6$	8	**3a** (12) + **4a** (18)	1/1.5
9	$SPhosAuNTf_2$	3	**3a** (56) + **4a** (29)	1.9/1
10	$JohnPhosAu(MeCN)SbF_6$	5	**3a** (60) + **4a** (25)	2.4/1
11[f]	$XPhosAuNTf_2$	3	**3a** (67) + **4a** (11)	6/1
12[f]	$IPrAuNTf_2$	1	**3a** (73) + **4a** (8)	9/1
13	$IPrAuCl/AgNTf_2$	5	**3a** (58) + **4a** (26)	2.2/1

[a]Reaction conditions: H_2O (1 mL) was added to the catalyst (5 mol %) in dioxane (1 mL) and submerged into an oil bath at 100 °C, then **2a** (0.2 mmol) in dioxane (1 mL) was added and the mixture stirred at 100 °C for the specified time. [b]Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c]At rt for 24 h, only **5a** was obtained with 50% conversion. [d]H_2O (0.1 mL instead 1 mL). [e]31% conversion. [f]At rt for 16 h the major compound was **5a** (∼50%).

catalyzed pathway-switchable tandem hydration-oxacyclization to 4-pyranones and 3(2*H*)-furanones from skipped diynones.[16]

We selected symmetric diynone **2a** as a model substrate for attempting the proposed hydration−cyclization reaction. After having assayed a variety of Lewis acids, we found that only gold(I) complexes[17] possess significant activity for the planned sequence using dioxane as solvent.[18] Gagosz's catalyst,[19] $Ph_3PAuNTf_2$, led to a ca. 1/6 mixture of the oxacyclic products **3a** and **4a**, along with the rearranged conjugated diynone **5a**, which was the only compound at rt (Table 1, entry 1). The effect of the presence of silver was then tested (entries 2−4),[20] observing a positive effect on the regioselectivity of the process in favor of **4a**. Moreover, the counterion of the gold complex also had a significant effect on the **3a**/**4a** ratio, resulting that SbF_6^- provided an almost complete selectivity toward **4a** (entry 4). Not unexpectedly, decreasing the amount of water led to the competitive formation of conjugated diynone **5a** (entry 5). Other phosphines were tested, although lower regioselectivities were observed (entries 6 and 7). Silver salts, on their own, did not provide satisfactory results (entry 8). Interestingly, a switch to bulkier phosphine ligands caused a change in the regioselectivity of the cyclization leading to the major formation of **3a** (entries 9−11). Looking for an even more successful switch of the regioselectivity, we gratifyingly found that the use of $IPrAuNTf_2$, bearing a bulky NHC ligand, gave rise to **3a** with a higher regioselectivity in a shorter reaction time (entry 12). In this case, the presence of silver led to a significant decrease in the regioselectivity (entry 13).

With the optimal reaction conditions in hand for both regiodivergent cyclizations, we investigated the scope of the gold-catalyzed formation of 4-pyrones **3**. Table 2 shows the results obtained in the hydration−cyclization of a selection of diynones **2**, which provides a variety of 4-pyrones **3** in high yields. Diynones bearing aryl substituents with either electron-donating groups or electron-withdrawing groups (entries 2−5) led to the corresponding 4-pyrones **3b**−**e** with even higher regioselectivity compared with model **2a** (entry 1). A heteroaromatic group is also suitable, although a slightly lower regioselectivity was observed (entry 6). Changing to (cyclo)alkyl-substituted diynones **2h**−**j**, the corresponding pyrones **3h**−**j** were also efficiently obtained with an almost complete selectivity (entries 7−9). Interestingly, alkenyl substituents were also well-tolerated, allowing access to 4-pyrones **3k**,**l** with excellent regioselectivity (entries 10 and 11). It is worthy to note that **3k** could not be prepared by any of the reported Brønsted acid catalyzed methods.[21] Finally, we also expand successfully the scope of this reaction to diynones **2m**,**n** bearing additional functional groups on the alkyne substituent (entries 12 and 13).

Having evaluated the synthesis of 4-pyrones **3** from diynones **2**, we decided to explore the scope of the process to gain access to the isomeric 3(2*H*)-furanones **4** (Table 3). By using the catalytic conditions established in the optimization study (Table 1, entry 4), a variety of furanones **4a**−**g** possessing (hetero)aromatic groups were synthesized in high yields (entries 1−7). In contrast to (hetero)aryl-substituted diynones **2a**−**g**, the presence of linear aliphatic or cyclopropyl-substituted alkynes greatly influences the regioselectivity of

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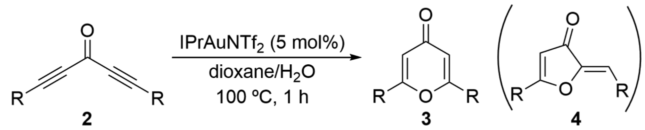
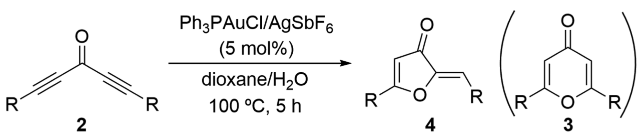
Table 2. Synthesis of 4-Pyrones 3[a]



entry	diynone	R	3/4[b]	product	yield[c] (%)
1	**2a**	Ph	9/1	**3a**	73 (78)[d]
2	**2b**	*p*-Tol	10/1	**3b**	81
3	**2c**	4-MeOC$_6$H$_4$	12/1	**3c**	83
4	**2d**	3-MeOC$_6$H$_4$	>20/1	**3d**	78
5[e]	**2e**	4-FC$_6$H$_4$	10/1	**3e**	79
6	**2f**	3-Th[f]	5/1	**3f**	70
7	**2h**	*n*-Bu	>20/1	**3h**	81
8	**2i**	*c*-C$_3$H$_5$	>20/1	**3i**	80
9	**2j**	(CH$_2$)$_2$Ph	>20/1	**3j**	86
10	**2k**	*c*-C$_6$H$_9$[g]	>20/1	**3k**	67
11	**2l**	C(CH$_3$)=CH$_2$	>20/1	**3l**	74
12	**2m**	CH$_2$O(4-MeOC$_6$H$_4$)	>20/1	**3m**	65
13	**2n**	CH$_2$O[3,5-(MeO)$_2$C$_6$H$_3$]	>20/1	**3n**	70

[a]Reaction conditions: **2** (0.5 mmol), IPrAuNTf$_2$ (5 mol %), H$_2$O (1 mL) in dioxane (2 mL) at 100 °C for 1 h. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Isolated yield after column chromatography. [d]Reaction carried out at 4 mmol scale. [e]10 mol % of catalyst was used. [f]3-Thienyl. [g]Cyclohexen-1-yl.

Table 3. Synthesis of 3(2*H*)-Furanones 4[a]



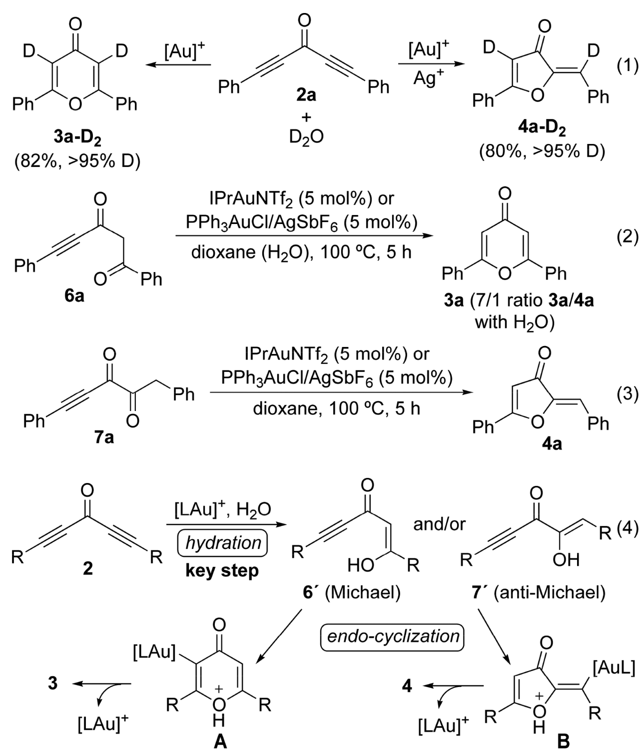
entry	diynone	R	4/3[b]	product	yield[c] (%)
1	**2a**	Ph	18/1	**4a**	80 (79)[d]
2	**2b**	*p*-Tol	11/1	**4b**	77
3	**2c**	4-MeOC$_6$H$_4$	>20/1	**4c**	81
4	**2d**	3-MeOC$_6$H$_4$	>20/1	**4d**	79
5[e]	**2e**	4-FC$_6$H$_4$	10/1	**4e**	70
6	**2f**	3-Th[f]	18/1	**4f**	79
7	**2g**	2-Th[g]	18/1	**4g**	74
8[h]	**2h**	*n*-Bu	1/1.5	**4h**	35
9[h]	**2i**	*c*-C$_3$H$_5$	1/2.5	**4i**	26

[a]Reaction conditions: **2** (0.5 mmol), Ph$_3$PAuCl/AgSbF$_6$ (5 mol %), H$_2$O (1 mL) in dioxane (2 mL) at 100 °C for 5 h. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Isolated yield after column chromatography. [d]Reaction carried out at 4 mmol scale. [e]10 mol % of catalyst was used. [f]3-Thienyl. [g]2-Thienyl. [h]Reaction time: 8 h.

the process.[22] Diynones **2h,i** gave rise to mixtures of **3** and **4**, with ratios in favor of the products **3**, though the furanones **4h,i** could even be isolated in low to moderate yields (entries 8 and 9).

To gain some insight into the plausible mechanism, some control experiments were carried out. Using D$_2$O instead of H$_2$O, dideuterated **3a-D$_2$** and **4a-D$_2$** were obtained under the respective standard conditions with almost complete deuterium incorporation (Scheme 2, eq 1). We prepared known alkynyl-1,3-diketone **6a**[23] and submitted it to both of the gold-catalyzed oxacyclization conditions in the presence and in the absence of water. Surprisingly, **3a** was selectively generated with the two gold catalytic systems, with a slight influence of the presence of water on the regioselectivity (Scheme 2, eq 2).[24] Next, alkynyl-1,2-diketone **7a**[25] was treated under two different gold-catalyzed conditions leading exclusively to

Scheme 2. Mechanistic Investigation and Proposal



furanone **4a** (Scheme 2, eq 3). So, both diketones **6** and **7**, or their tautomers **6′** and **7′**, seem to be plausible intermediates. Next, the role of the catalyst was evaluated. Xu, Hammond, and co-workers[26] have pointed that Ph$_3$PAuOTf complex is unstable, causing disproportionation into Au(0), Au(III), and OPPh$_3$, being accelerated at higher temperatures. Based on these findings, it is conceivable that under the described reaction conditions, this process could take place, affording Au(0) clusters or nanoparticles that may be responsible for the differential reactivity leading to the formation of furanones **4**, whereas more stable catalysts[27] such

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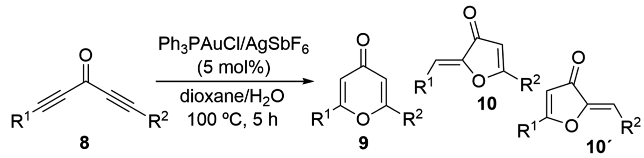
Table 4. Oxacyclization of Unsymmetrical Diynones 8



entry	8	R^1	R^2	products[a]	9/10 + 10′[b]	10/10′[b]
1	**8a**	Ph	*n*-Bu	**9a** (35) + **10a** (42)	1/1.25	1/0
2[c]	**8a**	Ph	*n*-Bu	**9a** (82)	>20/1	
3	**8b**	Ph	*c*-C_3H_5	**9b** (37) + **10b** (35)	1/1.1	14/1
4	**8c**	Ph	4-$MeOC_6H_4$	**10c** (71)	1/20	3/1
5	**8d**	4-FC_6H_4	4-$MeOC_6H_4$	**9d** (8) + **10d** (72)	1/10	4/1
6	**8e**	Ph	H	**9e** (74)	>20/1	
7[c]	**8e**	Ph	H	**9e** (76)	>20/1	

[a]The isolated yield for each compound after column chromatography is shown in parentheses. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Carried out with $IPrAuNTf_2$ for 1 h (**8a**) and 5 h (**8e**).

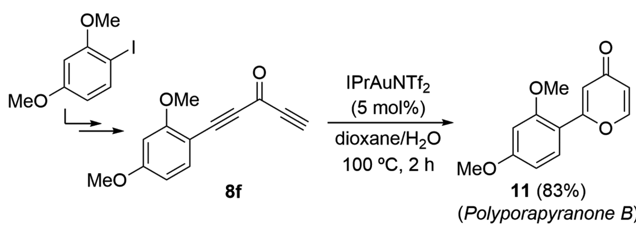
as $IPrAu^+$ favor the formation of pyrones **3**. When $Ph_3PAuCl/AgSbF_6$ was heated at 100 °C in dioxane/water mixtures, considerable amounts of $OPPh_3$ were observed from the crude by ^{31}P NMR analysis, which could suggest the formation of Au(0) species.[18] Additionally, the higher stabilization of the gold complex provided by the NTf_2^- counteranion[26] over SbF_6^- also explains the lower ratio **3**/**4** observed (Table 1, entries 3 vs 4).

Thus, our mechanistic proposal involves a key initial gold(I)-catalyzed hydration of ynone moiety that would lead to **6′** or **7′** depending on the Michael or anti-Michael addition pathway (Scheme 2, eq 4). Then an intramolecular oxacylization would take place, giving rise to six- or five-membered *O*-heterocycles **A** and **B**, depending on the diketone intermediate. Lastly, protodeauration affords the final compounds **3** and **4** recovering the catalytic species. Thus, our results indicate that the regiocontrol of the process is determined by the initial hydration reaction instead of by a more intuitive 6-*endo* vs 5-*exo* oxacyclization from a common intermediate **6′**.

At this point, starting skipped diynones **8** bearing two different alkyne units were also evaluated under the conditions favoring the furanone formation (Table 4).[28] Initially, diynones **8a**,**b** possessing an aryl- and a (cyclo)alkyl-substituted alkyne were used, giving rise to ~1/1 mixtures of the corresponding pyrones **9** and furanones **10** (entries 1 and 3). In both cases, the furanone derivative obtained possesses a benzylidene moiety. These results seem to indicate that the initial hydration takes place over the two alkynes in a similar extension, but in a Michael mode on the alkyl-substituted alkyne and in an anti-Michael way onto the aryl-substituted one. Upon employing unsymmetrical diynones **8c**,**d**, bearing two different aryl-substituted alkyne moieties, the furanone formation was, not unexpectedly, favored (entries 4 and 5). In these cases, although two regioisomeric furanones (**10** and **10′**) can be formed, the one derived from an initial anti-Michael hydration of the more electron-poor alkyne moiety is favored. Finally, an unsymmetrical diynone **8e** bearing a terminal alkyne was studied. With this substrate both catalytic conditions led to the same result, the selective formation of 4-pyrone **9e** (entries 6 and 7), thus suggesting a favored initial Michael addition of water onto the terminal alkyne.

Additionally, the first total synthesis of polyporapyranone B (**11**) employing the reaction reported herein as the key step was undertaken (Scheme 3). Rukachaisirikul and co-workers isolated this pyrone derivative from two seagrass-derived fungi

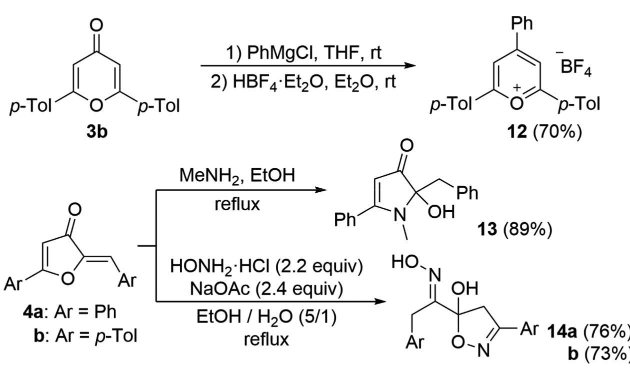
Scheme 3. Synthesis of Polyporapyranone B



Polyporales, and it is a rare example of naturally occurring 2-substituted *γ*-pyrones.[29] Our synthetic route involves the preparation of asymmetric diynone **8f**, which was accessed from commercially available 2,4-dimethoxyiodobenzene in an overall, though nonoptimized, 40% yield, through standard reactions: (a) Sonogashira coupling with propargylic alcohol; (b) oxidation; (c) addition of ethynylmagnesium bromide, and (d) oxidation.[18] The key gold-catalyzed oxacyclization of **8f** proceeds efficiently under our established conditions leading to *γ*-pyrone **11** in high yield (Scheme 3).

Finally, products **3** or **4** can be readily prepared on gram scale,[18] enabling further transformations as shown in Scheme 4. First, treatment of pyrone **3b** with a Grignard reagent and subsequent addition of HBF_4 led to the pyrylium salt **12**. This type of compound has been demonstrated as a useful organic

Scheme 4. Synthetic Applications of Selected 4-Pyranone 3b and Furanones 4a,b



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photoredox catalyst.[30] Meanwhile, furanones such as **4a,b** react with *N*-nucleophilic reagents leading to functionalized *N*-heterocycles such as 5-hydroxy-2-pyrrolin-4-one **13**[31] and 4,5-dihydroisoxazoles **14**[32] (Scheme 4).

In summary, we have established complementary conditions for selectively accessing 4-pyrones and 3(2*H*)-furanones from a common skipped diynone precursor, which in turn is synthesized from biomass-derived ethyl lactate. Achieving a fine-tuning of the gold ligands, the silver salt and counteranion effects is decisive in developing this strategy for the divergent synthesis of oxacyclic compounds. The initial hydration reaction can take place in a Michael or anti-Michael manner depending on the catalytic system used. This hydration has been revealed as the key step that determines the final reaction outcome. The intermediate diketones evolve through an *endo*-oxacyclization reaction affording the *O*-heterocyclic derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02892.

Full experimental procedures, characterization data, and copies of NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **1b**, **1d**, **1e**, **2b**, **2d**, **2e**, **3a**, **3a-d2**, **3b−f**, **3h−n**, **4a**, **4a-d2**, **4b−i**, **6a**, **7a**, **8a−f**, **9a**, **9b**, **9e**, **10a−d**, **11−13**, **14a**, **14b**, **IIf**, **IIIf**, **IVa−f** (ZIP)

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Notes

The authors declare no competing financial interest.

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