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Catalytic Dehydrative Lactonization of Allylic Alcohols

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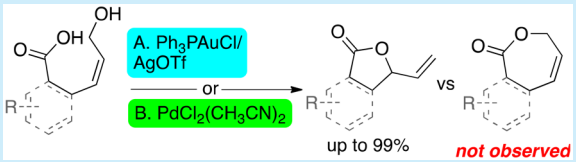
Supporting Information

ABSTRACT: A convenient strategy for the synthesis of phthalides and γ-butyrolactones is reported. The method utilizes readily prepared allylic alcohols in formal Au(I)- and Pd(II)-catalyzed S_N2' reactions. Using these catalysts, exclusive formation of the desired five-membered lactones is observed, completely avoiding the competing direct lactonization pathway that forms the undesired seven-membered ring with protic acids and alternative metal salts. This mild and operationally simple method notably tolerates exomethylene groups and should find use in both phthalide and terpene syntheses.



Phthalides are a prevalent class of natural products with a myriad of biological activities[1] that are important for lead compounds[2] and even find clinical use (e.g., noscapine,[3] **4** Figure 1). The family comprises nearly 200 compounds isolated from more than 100 plant sources.[4] The highly diverse structures are derived from the polyketide biosynthetic machinery and also may fall the under alkaloid classification when basic nitrogen atoms are present.[5] Structurally, these compounds are characterized by a benzo-fused γ-butyrolactone motif with substitution on the arene, as well as at the γ-position of the lactone. The γ-butyrolactone moiety is also found in a variety of terpene natural products,[6] as illustrated by parthenolide **6**,[7] and this widespread distribution among different natural product classes makes it an interesting target nucleus for developing new synthetic strategies.

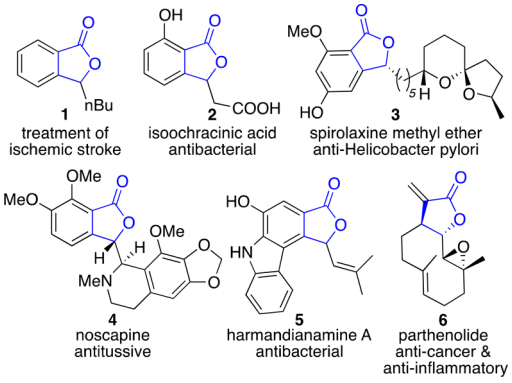
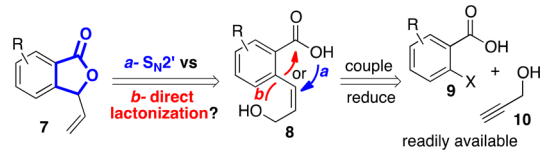


Figure 1. Representative phthalide natural products (**1**−**5**) and γ-butyrolactone terpene **6**.

Although many strategies have been reported,[8] in their comprehensive review,[8a] Mal and co-workers categorize phthalide syntheses into nine distinct groups, the principal of which is lactone formation, and the chemistries for this are quite diverse. It occurred to us that a direct strategy for the introduction of the lactone could be through an S_N2' reaction of a carboxylate onto a *cis*-allylic alcohol (path *a*, Scheme 1). This seemed particularly attractive because the requisite substrate **8** should be preparable from inexpensive and readily available benzoic acids **9** and propargylic starting materials, **10**, by Sonogashira coupling[9] followed by partial reduction of the ensuing alkyne.[10] If successful, the strategy would be direct and also introduce a vinyl group that could potentially enable further transformations and provide facile access to this important structural motif.

Scheme 1. Proposed Lactone Synthesis



A survey of the literature revealed little with regard to similar substrates, especially *cis*-olefins, which are readily prepared from alkynes, but may suffer direct formation of the seven-membered lactone and could pose a problem in the presence of Bronsted acids or oxophilic Lewis acid catalysts (path *b*, Scheme 1).[11] Kitamura reported an elegant Ru-catalyzed cyclization of a *trans*-allylic alcohol to prepare a phthalide,[12] and the majority of the substrates described were aliphatic *trans*-allylic alcohols, which worked best. Their reaction proceeds at 100 °C in DMA via a π-allyl intermediate formed by the action of a sophisticated bifunctional catalyst that features both soft Ru and hard Bronsted acid sites. The authors point out that with more traditional π-allylmetal systems the lactone likely reversibly opens, and this may be why there are not more reports utilizing π-allyl chemistry for phthalide synthesis.

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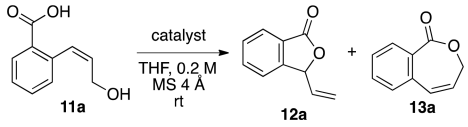
As part of a program aimed at developing dehydrative cyclization reactions, we have found that, while the possibility for both Bronsted acidity and traditional Lewis acidity exists, Au(I)-[13] and Pd(II)-catalysts[14] efficiently act as π-acids in our systems to effect formal S_N2' reactions.[15,16] As such, it seemed possible that these complexes could efficiently moderate the proposed transformation (path *a*, Scheme 1) and avoid the aforementioned issue; however, this would present a suitable stress-test for these catalyst systems as phthalide-forming substrates, in particular, are likely prone to direct lactonization. Herein, we report our studies in this area, which have resulted in an efficient strategy for the formation of γ-butyrolactones from benzoic acid derivatives and propargyl alcohols.

At the outset, benzoic acid **11a** was prepared and subjected to several sets of conditions to test the feasibility of this idea (Table 1). Initial attempts focused on employing simple metal salts that had previously been reported in dehydrative cyclization reactions of allylic alcohols to form ethers[17] and nitrogen heterocycles.[18] While using AuCl as a catalyst demonstrated a very low reactivity (entry 1), the use of the more strongly electrophilic $AuCl_3$[19] produced both the five- and seven-membered ring lactones **12a** and **13a** in 48% yield with an 83:17 ratio, respectively (entry 2). While these initial results demonstrated the viability of the idea, it was clear that both the selectivity and yield would need to be improved and other conditions were screened. Cossy's Fe-catalyzed conditions[20] completely reversed the chemoselectivity, favoring **13a** (entry 3), but a ligated Au(I) catalyst gave the desired γ-butyrolactone **12a** in quantitative yield with near perfect selectivity (entry 4). Use of $PdCl_2(CH_3CN)_2$ also yielded **12a** with similar results (entry 5), and both systems would be explored further. Control experiments with AgOTf and TfOH demonstrated that neither the silver salt nor the protic acid were catalyzing the γ-butyrolactone-forming reaction (entries 6 and 7), and other common protic acids were also demonstrated to form lactone **13a** (entries 8–10). These results further demonstrated that competitive formation of **13a** with protic acids and Lewis acidic metal-based catalysts could be problematic.[21]

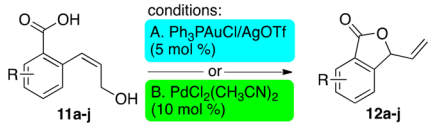
The scope of the reaction was then examined under both Au- and Pd-catalyzed conditions A and B, respectively (Table 2). Electron donating and electron withdrawing groups on the aromatic ring would be expected to impact the electronic character of both the carboxyl group and the allylic alcohol depending on the position. A variety of phthalides were produced in good to excellent yields with minimal exception. Under Au-catalysis, groups that donate to both the carboxylate and the

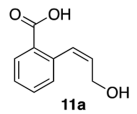
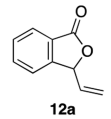
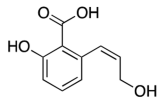
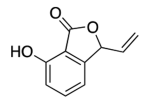
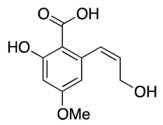
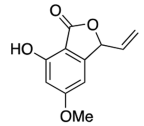
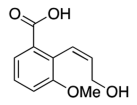
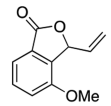
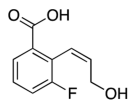
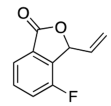
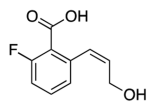
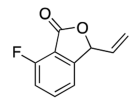
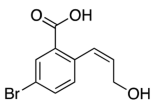
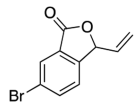
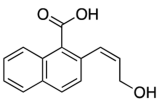
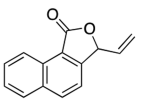
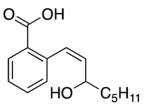
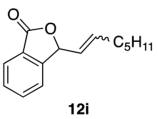
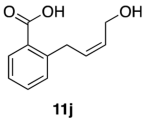
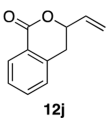
Table 1. Catalyst Screening



entry	catalyst (mol %)	time (h)	yield (%)	12/13
1	AuCl (10)	20	<5	n.d.
2	$AuCl_3$ (10)	20	48	83:17
3	$FeCl_3{\cdot}6H_2O$ (10)	20	88	15:85
4	$Ph_3PAuCl/AgOTf$ (5)	1	99	>99:1
5	$PdCl_2(CH_3CN)_2$ (10)	0.25	99	>99:1
6	AgOTf (10)	20	n.r.	
7	TfOH (10)	0.5	75	1:>99
8	HCl in ether (10)	5	56	1:>99
9	CSA (10)	5	94	1:>99
10	$TsOH{\cdot}H_2O$ (10)	5	94	1:>99

Table 2. Phthalide Substrate Scope



entry	conditions	substrate	time (h)	product	yield (%)
1	A	 **11a**	1	 **12a**	99
2	B		0.25		99
3	A	 **11b**	1	 **12b**	80
4	B		0.25		85
5	A	 **11c**	1	 **12c**	95
6	B		0.25		92
7	A	 **11d**	1	 **12d**	92
8	B		0.25		94
9	A	 **11e**	12	 **12e**	67
10	B		12		85
11[a]	A	 **11f**	12	 **12f**	n.r.
12[a]	B		0.5		95
13	A	 **11g**	1	 **12g**	80
14	B		0.5		90
15	A	 **11h**	0.25	 **12h**	87
16	B		0.16		94
17	A	 **11i**	6	 **12i**	n.r.
18	B		12		91%[b]
19	A	 **11j**	0.33	 **12j**	94%
20	B		6		90%

[a]EtOAc was used as solvent. Under the standard conditions A and B, no conversion and low conversion were observed, respectively, likely because **11f** displays poor THF solubility. [b]*trans*/*cis* = 3:1.

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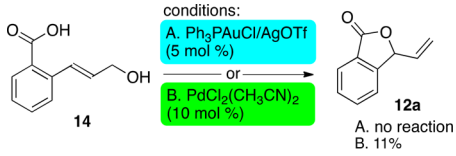
allylic alcohol functioned better in the reaction than those with electron-withdrawing groups in these positions (cf. **11b** vs **11c**, entries 3 and 5; and **11d** vs **11e**, entries 7 and 9). With Pd-catalysis, these electronic effects were less pronounced. As seen in Table 2, phthalide products with a variety of substituents were formed in excellent yields, mostly >90%. Furthermore, with Pd(II), substituents were tolerated at the allylic position (e.g., **12i**, formed in 91%). This difference may be due to the ability of the Pd-catalyst to access alternative reaction pathways as previously described and supported by computational studies.[22,23] Both Au- and Pd-catalysts also functioned to form the six-membered lactone **12j**, suggesting that the strategy may be utilized for targets other than phthalides.

The substrates described thus far contain a *cis*-olefin due to their convenient preparation from the propargylic intermediates that result from the Sonogashira coupling strategy. While it has been previously observed that, in related Au-catalyzed dehydrative cyclizations of allylic diols,[24] *cis*-allylic alcohols are more reactive than the corresponding *trans*-substrates, the *trans*-allylic alcohols still function quite well in those reactions. To test the relative reactivity of the olefins, the *trans*-substrate **14** was prepared and subjected to both sets of conditions (Scheme 2). Much to our surprise, no reaction was observed under the Au-catalysis conditions, and **12a** was isolated in only 11% under the Pd(II) conditions.

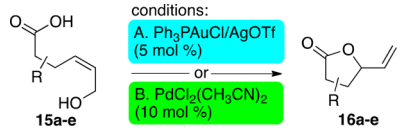
Scheme 2. Reactivity of *trans*-Olefin

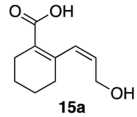
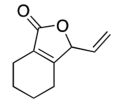
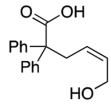
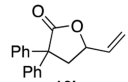
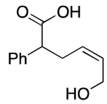
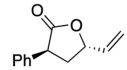
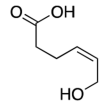
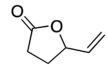
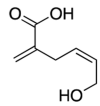
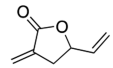


To expand the scope of the reaction, we also sought to deploy this strategy for the synthesis of aliphatic butenolides where it might find use in terpene syntheses.[25] As can be seen in Table 3, the reaction also functions quite well for these simple butenolides. The Pd(II) conditions were again more robust, and extremely rapid in some cases (e.g., entries 2 and 4), providing all the products in excellent yield. One of the most noteworthy reactions is that of **15e** to produce the highly electrophilic exomethylene containing lactone **16e** in 90% after a 30 min reaction time with the Pd-conditions. Interestingly, the differential reactivity with the two catalyst systems is most striking when the degree of substitution is reduced. Using the catalyst generated in situ from Ph_3PAuCl and AgOTf, the reaction appeared to be sensitive to entropic effects, as observed in entries 3, 5, and 7 where the yield drops from 95% for **16b** to no observable product for **16c**/**d**. In these cases, it is also possible that enolizable substrates are problematic; but regardless of the source of the issue with Au-catalysis, the Pd(II)-conditions were still quite efficient.

The reaction conditions described employ somewhat high catalyst loadings, and it would be desirable to reduce this for larger scale reactions. To study the feasibility of this, substrate **11a** was treated under the Pd(II)-conditions and the loading varied. As can be seen in Table 4, the reaction was nearly as rapid and high yielding with a 5 mol % loading, but this dropped off precipitously when 2 and 1 mol % $PdCl_2(CH_3CN)_2$ were employed (entries 2−4). It occurred to us that reduced catalyst concentration might be responsible for this sluggish reactivity. As can be seen in entry 5, when the concentration was increased, the product was again isolated in high yield. The reaction was also scaled up to 2 mmol at 2 mol % loading (entry 6) with no loss in yield.

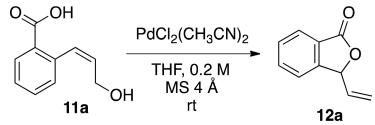
Table 3. γ-Butyrolactone Substrate Scope



entry	conditions	substrate	time (min)	product	yield (%)
1	A	 **15a**	30	 **16a**	97
2	B		1		98
3	A	 **15b**	10	 **16b**	95
4	B		1		99
5	A	 **15c**	n.r.[a]	 **16c**	-
6	B		60		93[b]
7	A	 **15d**	n.r.[a]	 **16d**	-
8	B		180		91
9	A	 **15e**	n.r.[a]	 **16e**	-
10	B		30		90

[a]No reaction was observed after 20 h. [b]The major diastereomer isolated (**16c**) was 3,5-*trans*, dr = 1.75:1.

Table 4. Catalyst Loading Studies



entry	catalyst loading (mol %)	time (h)	yield (%)
1	10	0.25	99
2	5	0.33	97
3	2	12	22
4	1	12	trace
5[a]	2	12	96
6[b]	2	12	95

[a]0.5 M in **11a** [b]2 mmol scale.

The products of the transformation described here contain an olefin that we initially hypothesized would be useful for further functionalization. Although a myriad of transformations are known for the conversion of alkenes into other synthetic handles, considering the substitution patterns in this family of natural products, it would be particularly important for phthalide synthesis if oxygenation could be introduced at the terminal position. To explore this, the simple natural products isoochracinic acid and isoochracinol[1a] were targeted. To this

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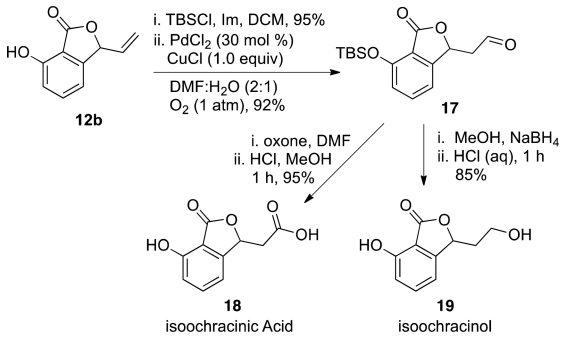
end, after protection of the phenol **12b** as its silyl ether, the olefin was readily oxidized under Wacker conditions known to produce the aldehyde instead of the more traditional methyl ketone product.[26] Further oxidation of **17** to the carboxylic acid or reduction to the alcohol and deprotection produced the natural products **18** and **19**, respectively (Scheme 3).

Scheme 3. Conversion to Isoochracinic Acid and Isoochracinol



In summary, we have described a direct route for the formation of butenolides. The reaction proceeds from readily available precursors and is enabled by Au(I) and Pd(II) catalysts that catalyze the transformation without the direct lactone formation observed with protic or oxophilic Lewis acids. It is also important to note that, although Au-catalysis has made a tremendous impact on the field, Pd(II)-based catalyst systems can function equally well and, in this case, proved to be more general than the Au(I)-catalysts employed. The method described is applicable to both phthalide and aliphatic butenolide synthesis and is predicted to find widespread use in synthetic schemes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01063.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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