ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: P. de Andrade Horn, M. J. E. Collins, C. C. Gudeman, A. Fresh and M. Dai, *Chem. Commun.*, 2024, DOI: 10.1039/D4CC03255A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/D4CC03255A

Journal Name

COMMUNICATION

Divergent Synthesis of δ-Valerolactones and Furanones via Palladium or Copper-Catalyzed α-Hydroxycyclopropanol Ring Opening Cyclizations

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Pedro de Andrade Horn,[a,d] Michael J. E. Collins,[b,d] Cyrus C. Gudeman,[b] Alexandra A. Fresh,[a] and Mingji Dai*[b,c]

Cyclopropanols are versatile starting materials which can undergo various ring opening reactions due to their intrisic ring strain. Herein, we report two transition metal-catalyzed α-hydroxycyclopropanol ring opening cyclizations to divergently transform the same α-hydroxycyclopropanol substrate into two different products of enhanced value. One is a palladium-catalyzed α-hydroxycyclopropanol ring opening carbonylative lactonization to synthesize δ-valerolactones. The other one is a copper-catalyzed α-hydroxycyclopropanol ring opening cyclization to access furanones.

Cyclopropanols have been widely utilized in organic synthesis because of their unique and versatile reactivity profiles.[1-3] Due to the intrinsic ring strain of the cyclopropane and the reactivity of the hydroxy functional group, cyclopropanols can undergo various ring opening reactions. In general, a one-electron cyclopropanol ring opening pathway would generate a β-keto radical and a two-electron cyclopropanol ring opening pathway would give a homoenolate. If a transition metal is involved in the ring opening process, a metal homoenolate would be produced.[4] The resulting β-keto radical and (metal) homoenolate can then engage in different downstream reactivity profiles to give various products.[5-7] We have been developing transition metal-catalyzed cyclopropanol ring opening reactions to facilitate chemical synthesis of biologically active natural products and pharmaceutically important compounds.[8-11] In 2016 and 2020, we reported palladium-catalyzed hydroxycyclopropanol ring opening carbonylative lactonizations to synthesize either oxaspirolatones (Figure 1A, **1**→**2**→**3**)[12] or fused bicyclic lactones (Figure 1B, **4**→**5**→**6**)[13] and have applied these enabling carbonylation chemistry to synthesize a collection of natural products.[14-16] While we were developing the fused bicyclic lactone synthesis, we discovered

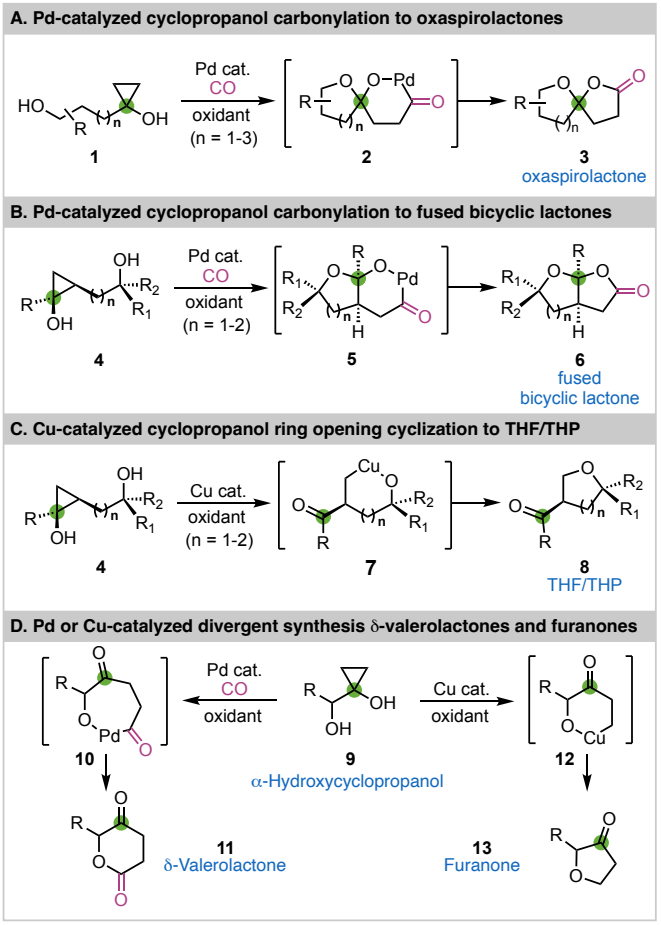


Figure 1. Our previous development in Pd and Cu-catalyzed cyclopropanol ring opening (carbonylative) cyclization and this work.

[a] Department of Chemistry, Purdue University, West Lafayette, IN 47907, USA.
[b] Department of Chemistry, Emory University, Atlanta, GA 30322, USA. Email: mingji.dai@emory.edu. Tel: 001-404-727-4299.
[c] Department of Pharmacology and Chemical Biology, Emory University, Atlanta, GA 30022, USA
[d] Contributed equally

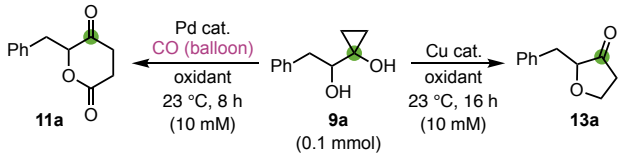
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online DOI: 10.1039/D4CC03955A

that the same cyclopropanol starting material **4** can undergo a copper-catalyzed cyclopropanol ring opening cyclization to give THF/THP-containing product **8** presumably via intermediate **7** (Figure 1C).[17] We then wondered if α-hydroxycyclopropanol **9** can undergo similar divergent pathways to synthesize δ-valerolactone **11** via the palladium-catalyzed ring opening carbonylative lactonization process and furanone **13** via the copper-catalyzed ring opening cyclization process (Figure 1D). To realize these transformations, a few challenges need to be addressed. First, the 1,2-diol moiety of **9** can chelate on the transition metal and may deactivate the catalyst. Second, such α-hydroxycyclopropanol is prone to Pinnacol rearrangement to partially release the ring strain and produce a cyclobutanone.[18] Third, the lactonization process would generate a six-membered lactone, which has not been reported from a cyclopropanol ring opening carbonylation process. Fourth, once the Pd or Cu homoenolate is generated, β-hydride elimination, dimerization, and over oxidation are always competing pathways which need to be suppressed. Despite these challenges, the proposed divergent synthesis of δ-valerolactone **11** and furanone **13** from α-hydroxycyclopropanol **9** would further expand cyclopropanol chemistry and offer alternative methods to prepare the target structures, which are frequently found in biologically active molecules, especially natural products.[19-23] Herein, we report the details of our exploration which led to divergent approaches to either δ-valerolactone **11** or furanone **13** from the same α-hydroxycyclopropanol **9** via a Pd-catalyzed ring opening carbonylative lactonization or a Cu-catalyzed ring opening cyclization, respectively.

We started our investigation with cyclopropanol **9a**, which was prepared via a modified Kulinkovich reaction (see the Supporting Information)[24] and used as a model compound for optimization of the reaction conditions (Table 1). When it was treated with $Pd(OAc)_2$ (10 mol%) and DDQ (2.0 equiv) in benzene at room temperature (the conditions we developed for the bicyclic lactone synthesis),[13] desired product **11a** was only produced in 13% yield (entry 1). Changing the palladium catalyst from $Pd(OAc)_2$ to $Pd(PPh_3)_4$ (entry 2), $Pd(TFA)_2$ (entry 3), and $Pd(PPh_3)_2Cl_2$ (entry 4) only slightly affected the reaction yield (11-19%). Switching the solvent from benzene to THF increased the yield more significantly (entry 5 and 6). When the combination of $Pd(OAc)_2$ and THF was used, the yield of the desired product **11a** increased to 55% yield (entry 6). When the amount of DDQ was reduced from 2.0 equivalents to 1.2 equivalents, **11a** was isolated in 59% yield (entry 7). THF was also found to be superior to MTBE (methyl *tert*-butyl ether), 1,4-dioxane, and DMSO (entries 8-10). Interestingly, when $Cu(OTf)_2$ (2.0 equiv) was used as oxidant, instead of **11a**, furanone **13a** was obtained in 73% yield (entry 11), which encouraged us to further develop a general cyclopropanol ring opening cyclization to synthesize furanones.

We then started to further optimize the furanone synthesis conditions and learned that palladium catalyst is not necessary. With 10 mol% of $Cu(OTf)_2$ as catalyst and DDQ (1.0 equiv) as oxidant, **13a** was obtained in 74% yield (entry 12). While $CuCl_2$ (entry 13), $CuBr_2$ (entry 14), $CuSO_4$ (entry 15), and CuTC (copper thiophene-2-carboxylate, entry 16) are less effective than $Cu(OTf)_2$, the more economical $Cu(OAc)_2$ (entry 17) is superior to $Cu(OTf)_2$ and **13a** was produced in 93% isolated yield. Further reducing the catalyst loading to 5 mol% (entry 18) and 1.0 mol% (entry 19) resulted in lower yields (84% and 58%, respectively). Other oxidants including TFBQ (tetrafluoro-1,4-benzoquinone, entry 20), Chloranil (entry 21), 2,5-DCBQ (2,5-dichloro-1,4-benzoquinone, entry 22) and 2,6-DCBQ (2,6-dichloro-1,4-benzoquinone, entry 23) gave reduced yield. In addition, if DDQ or its byproduct complicates the reaction or purification, the reaction can be conducted with a stoichiometric amount of $Cu(OAc)_2$ to produce **13a** in 79% yield (entry 24). Given the similar price of DDQ and $Cu(OAc)_2$, the stoichiometric condition doesn't significantly affect the overall cost. In addition, no product was obtained without the copper catalyst (entry 25).[25]



entry	conditions for **9a** to **11a**	yield[a] (**11a**)
1	$Pd(OAc)_2$ (10 mol%), DDQ (2.0 eq), PhH	13%[b]
2	$Pd(PPh_3)_4$ (10 mol%), DDQ (2.0 eq), PhH	18%
3	$Pd(TFA)_2$ (10 mol%), DDQ (2.0 eq), PhH	11%
4	$Pd(PPh_3)_2Cl_2$ (10 mol%), DDQ (2.0 eq), PhH	19%
5	$Pd(PPh_3)_2Cl_2$ (10 mol%), DDQ (2.0 eq), THF	28%
6	$Pd(OAc)_2$ (10 mol%), DDQ (2.0 eq), THF	55%
7	$Pd(OAc)_2$ (10 mol%), DDQ (1.2 eq), THF	59%[b]
8	$Pd(OAc)_2$ (10 mol%), DDQ (1.2 eq), MTBE	25%
9	$Pd(OAc)_2$ (10 mol%), DDQ (1.2 eq), 1,4-dioxane	35%
10	$Pd(OAc)_2$ (10 mol%), DDQ (2.0 eq), DMSO	0%
11	$Pd(OAc)_2$ (10 mol%), $Cu(OTf)_2$ (2.0 eq), PhH	70% (**13a**)
entry	conditions for **9a** to **13a**	yield[a] (**13a**)
12	$Cu(OTf)_2$ (10 mol%), DDQ (1.0 eq), THF	74%
13	$CuCl_2$ (10 mol%), DDQ (1.0 eq), THF	66%
14	$CuBr_2$ (10 mol%), DDQ (1.0 eq), THF	49%
15	$CuSO_4$ (10 mol%), DDQ (1.0 eq), THF	0%
16	CuTC (10 mol%), DDQ (1.0 eq), THF	82%
17	$Cu(OAc)_2$ (10 mol%), DDQ (1.0 eq), THF	93%[b]
18	$Cu(OAc)_2$ (5.0 mol%), DDQ (1.0 eq), THF	84%
19	$Cu(OAc)_2$ (1.0 mol%), DDQ (1.0 eq), THF	58%
20	$Cu(OAc)_2$ (10 mol%), TFBQ (1.0 eq), THF	74%
21	$Cu(OAc)_2$ (10 mol%), Chloranil (1.0 eq), THF	69%
22	$Cu(OAc)_2$ (10 mol%), 2,5-DCBQ (1.0 eq), THF	37%
23	$Cu(OAc)_2$ (10 mol%), 2,6-DCBQ (1.0 eq), THF	19%
24	$Cu(OAc)_2$ (1.0 eq), THF	79%
25	DDQ (1.0 eq), THF	0%

[a]NMR yield; [b]isolated yield

Table 1. Optimization of Reaction Conditions

With both the δ-valerolactone and furanone synthesis conditions established, we started to probe the substrate scope

View Article Online
DOI: 10.1039/D4CC03255A

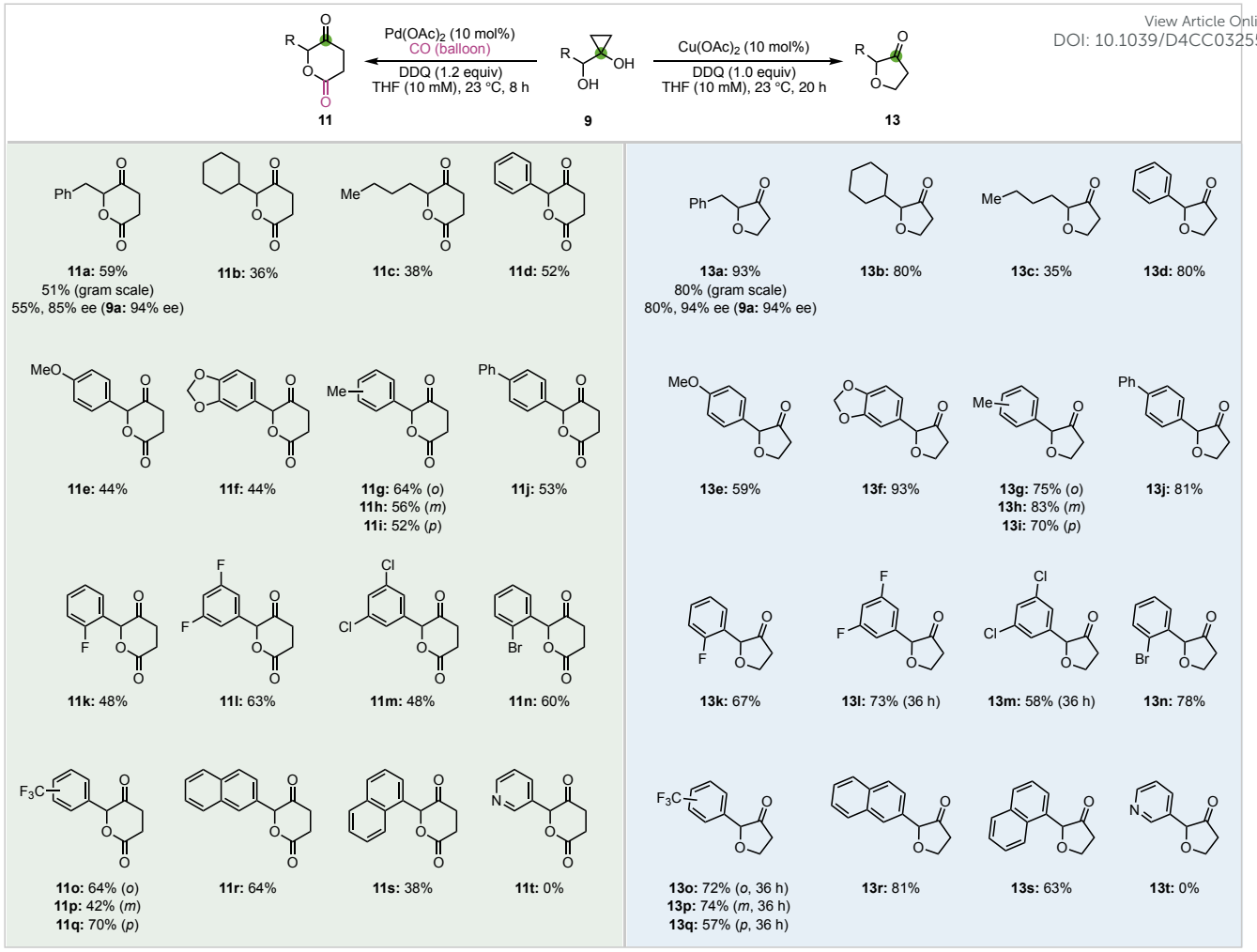


Figure 2. Substrate Scope.

of both transformations (Figure 2). Twenty different α-hydroxycyclopropanols were prepared and subjected to the optimized reaction conditions. In general, the Cu-catalyzed furanone synthesis tends to give higher yield than the corresponding Pd-catalyzed δ-valerolactone synthesis. Both transformations can be conducted on gram scale with only a slight drop of the reaction yields. Alkyl (**11/13a-c** and aryl groups (**11/13d-s**) are tolerated. The electronic properties of the aryl groups doesn't influence the reaction yield significantly. Halides such as fluoride, chloride, and bromide are not affected under both reaction conditions. The tolerance of chloride and bromide offers opportunity for cross coupling reactions to further functionalize the corresponding products. While both 1- or 2-naphthyl group containing substrates are effective, no desired products (**11t**) were obtained for substrate **9t** with a 3-pyridyl under both reaction conditions. Finally, we prepared enantio-enriched starting material **9a** (94% ee) from L-phenylalanine and evaluated if both reaction conditions would erode the stereochemistry at the α-position of the newly formed ketone. When **9a** (94% ee) was subjected to the carbonylation conditions, product **11a** was obtained in 55% yield and 85% *ee*. When **9a** (94% ee) was subjected to the furanone synthesis conditions, product **13a** was obtained in 80% yield and 94% *ee*. These results indicate the mildness of the reaction conditions and the potential application of these two methods to prepare enantio-enriched δ-valerolactones and furanones.

In summary, two novel cyclopropanol ring opening cyclization reactions were developed to divergently transform the same α-hydroxycyclopropanol substrate to either a δ-valerolactone or a furanone. The δ-valerolactone synthesis was catalyzed by $Pd(OAc)_2$ under carbon monoxide atmosphere and the furanone synthesis was catalyzed by $Cu(OAc)_2$. DDQ was used as external oxidant in both reactions. An array of δ-valerolactones and furanones were prepared. The reactions can be scaled up to gram scale and no stereochemistry erosion was observed at the α-position of the newly formed ketone. Overall, these two cyclopropanol ring opening cyclization reactions provide mild alternatives to synthesize δ-valerolactones and furanones, which are frequently found in biologically active molecules.

View Article Online
DOI: 10.1039/D4CC03255A

This work was financially supported by NSF 2349014.

Data Availability Statement

The Supplementary Information includes the experimental procedures, compound characterization data, and NMR spectra. Electronic Supplementary Information (ESI) is included in the submission and will be available to the readers via the Chemical Communication online publication system.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 X. Cai, W. Liang, M. Dai, *Tetrahedron,* 2019, **75**, 193–208.
2 O. G. Kulinkovich, *Chem. Rev.*, 2003, **103**, 2597–2632.
3 D. H. Gibson, C. H. DePuy, *Chem. Rev.*, 1974, **74**, 605–623.
4 A. Nikolaev, A. Orellana, *Synthesis*, 2016, **48**, 1741–1768.
5 T. R. McDonald, L. R. Mills, M. S. West, S. A. L. Rousseaux, *Chem. Rev.* 2021, **121**, 3–79.
6 L. R. Mills, S. A. L. Rousseaux, *Eur. J. Org. Chem.*, 2019, 8–26.
7 H. Yan, G. S. Smith, F.-e. Chen, *Green Syn. Catal.* 2022, **3**, 219–226.
8 Y. Li, Z. Ye, T. M. Bellman, T. Chi, M. Dai, *Org. Lett.*, 2015, **17**, 2186–2189.
9 Z. Ye, M. Dai, *Org. Lett.*, 2015, **17**, 2190–2193.
10 Z. Ye, K. E. Gettys, X. Shen, M. Dai, *Org. Lett.*, 2015, **17**, 6074–6077.
11 Z. Ye, X. Cai, J. Li, M. Dai, *ACS. Catal.*, 2018, **8**, 5907–5197.
12 D. C. Davis, K. L. Walker, C. Hu, R. N. Zare, R. M. Waymouth, M. Dai, *J. Am. Chem. Soc.*, 2016, **138**, 10693–10699.
13 X. Cai, W. Liang, M. Liu, X. Li, M. Dai, *J. Am. Chem. Soc.*, 2020, **142**, 13677–13682.
14 K. Ma, X. Yin, M. Dai, *Angew. Chem. Int. Ed.*, 2018, **57**, 15209–15212.
15 X. Yin, K. Ma, Y. Dong, M. Dai, *Org. Lett.*, 2020, **22**, 5001–5004.
16 H. S. Sims, P. de Andrade Horn, R. Isshiki, M. Lim, Y. Xu, R. H. Grubbs, M. Dai, *Angew. Chem. Int. Ed.*, 2022, **61**, e202115633.
17 W. Liang, X. Cai, M. Dai, *Chem. Sci.*, 2021, **12**, 1311–1316.
18 M. M. Hussain, H. Li, N. Hussain, M. Ureña, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.*, 2009, **131**, 6516–6524.
19 V. K. Omanakuttan, J. John, H. Hopf, *Eur. J. Org. Chem.* 2021, 163–201.
20 A. Husain, S. A. Khan, F. Iram, M. A. Iqbal, M. Asif. *Eur. J. Med. Chem.* 2019, **171**, 66–92.
21 R. Liu, S. Yang, Z. Chen, X. Kong, H. Ding, X. Fang, *Org. Lett.* 2020, **22**, 6948–6953.
22 Y. Matsuda, T. Iwabuchi, T. Wakimoto, T. Awakawa, I. Abe, *J. Am. Chem. Soc.*, 2015, **137**, 3393–3401.
23 M. Dangalov, A. Fernández-Figueiras, M. A. Ravutsov, E. Vakarelska, M. K. Marinova, N. R. Candeias, S. P. Simeonov, *ACS Catal.* 2023, **13**, 1916–1925.
24 J. S. Kingsbury, E. J. Corey, *J. Am. Chem. Soc.*, 2005, **127**, 13813–13815.
25 Note: with $Cu(OTf)_2$ (2.0 equiv) in toluene at room temperature, **9a** underwent a Pinnacol rearrangement to give the corresponding cyclobutanone in 80% yield. The cyclobutanone is a known compound: T. Nordvik, U. H. Brinker *J. Org. Chem.* 2003, **68**, 9394–9399.

View Article Online
DOI: 10.1039/D4CC03255A

The Supplementary Information includes the experimental procedures, compound characterization data, and NMR spectra. Electronic Supplementary Information (ESI) is included in the submission and will be available to the readers via the Chemical Communication online publication system.