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Stereoselective Synthesis of Donor−Acceptor Substituted Cyclopropafuranones by Intramolecular Cyclopropanation of Vinylogous Carbonates: Divergent Synthesis of Tetrahydrofuran-3-one, Tetrahydropyran-3-one, and Lactones

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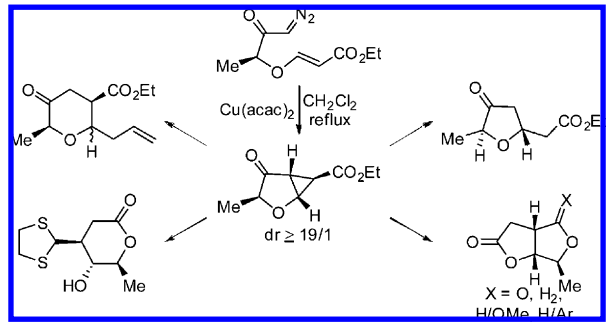
ABSTRACT



A new, highly stereoselective intramolecular cyclopropanation of vinylogous carbonate with carbenes using copper catalyst is described. Each of the cyclopropane bonds of these two acceptor substituted cyclopropafuranones can be cleaved with complete regiocontrol by judicious choice of reaction conditions, leading to a diverse array of frameworks such as tetrahydrofuran-3-one, tetrahydropyran-3-one, and lactones.

Heteroatom-substituted donor−acceptor cyclopropanes (DACs) are fast emerging as versatile building blocks in organic synthesis.[1] The oxygen-substituted DACs that are fused with furan/pyran ring have been found to be useful synthons in the synthesis of cyclic ethers and lactones. As a result of the push−pull effect of the donor and acceptor substituents, they show remarkably diverse reactivity with very high selectivity for cleavage of one of the cyclopropane bonds. This interesting reactivity of DACs has been exploited in the synthesis of a variety of natural products.[2] It has been shown that DACs can be used as 1,3-dipoles in cycloaddition reactions[3] and in ring-opening reactions with electrophiles and nucleophiles.[4] However, methods for the regioselective

(1) For recent reviews, see: (a) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.

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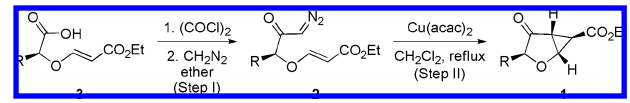
cleavage of all three bonds of a single DAC by simply changing the reaction conditions have until date been missing. One of the common methods for their synthesis is the intermolecular catalytic cyclopropanation of dihydrofuran/pyran derivatives with diazoesters.[5] However, the selectivity of such intermolecular cyclopropanation reaction is dependent on the pattern of substitution present in dihydrofuran/pyrans.[1] Herein, we describe a highly stereo- and regioselective synthesis of cyclopropafuranones **1** employing an intramolecular cyclopropanation of vinylogous carbonates using copper catalyst. We further demonstrate that these cyclopropafuranones are good precursors for a diverse array of structural motifs present in many natural products via regioselective cleavage of all three bonds of the cyclopropane moiety.

We envisioned that the cyclopropafuranone **1** with two different acceptors (CO and CO_2Et) could be manipulated chemoselectively, allowing for the regioselective cleavage of each of the cyclopropane bonds and thus leading to a diverse array of structural motifs. Vinylogous carbonates have been extensively used as excellent radical acceptors in the synthesis of cyclic ethers.[6] In continuation of our interest in studying the reactivity of vinylogous carbonates,[7a] particularly under nonradical conditions[7b] that still remain largely underdeveloped,[8] we decided to explore a new synthesis for the cyclopropafuranone **1** from the diazoketone **2** via a highly stereoselective intramolecular [2 + 1] cycloaddition of the vinylogous carbonate (Scheme 1).

Scheme 1



Preliminary studies examined the feasibility of the intramolecular cyclopropanation of the vinylogous carbonate on the diazoketone **2a** (R = Me) (Table 1). The requisite diazoketone **2a** was readily prepared in 79% yield by treatment of the acid **3a** with oxalyl chloride to furnish the corresponding acid chloride, followed by its reaction with an ethereal solution of diazomethane.[9] The thermal decomposition of the diazoketone **2a** in refluxing CH_2Cl_2 or cyclohexane was not successful (Table 1, entry 1). Even though reaction of diazoketone **2a** in the presence of a catalytic amount of $Cu(OTf)_2$ in CH_2Cl_2 at room temperature did not proceed at all, at reflux it gave cyclopropafuranone **1a** in 30% yield (Table 1, entry 2).[10] Anhydrous $CuSO_4$ was found to be a useful catalyst in refluxing (using two 100 W tungsten lamps) cyclohexane, giving rise to cyclopropafuranone **1a** in very good yield and diastereoselectivity. However, a huge excess of the catalyst was required as a result of the insolubility of catalyst in cyclohexane. Even though CuI and $AgNO_3$ did not provide the cyclopropanated product (Table 1, entries 3 and 8), CuI/Cu powder and $CuCl_2$ furnished the

Table 1. Optimization of the Intramolecular Cyclopropanation of Vinylogous Carbonate Using Diazoketone **2a** (R = Me)

entry	catalyst	equiv	solvent	temp (°C)	yield (%)[a,b]
1	none	0	C_6H_{12}	reflux	0
2	$Cu(OTf)_2$	0.1	CH_2Cl_2	reflux[c]	30
3	CuI/Cu (powder)	0.1	CH_2Cl_2	reflux[d]	68
4	anhyd $CuSO_4$	0.1	CH_2Cl_2	reflux[c]	0
5	anhyd $CuSO_4$	10	C_6H_{12}	reflux[e]	72
6	**$Cu(acac)_2$**	**0.1**	**CH_2Cl_2**	**reflux[c]**	**78**
7	$Rh_2(OAc)_4$	0.1	CH_2Cl_2	rt	74
8	$AgNO_3$	0.1	CH_2Cl_2	reflux	0
9	$CuCl_2$	0.1	CH_2Cl_2	reflux	34

[a] Isolated yield. [b] In all cases, dr was determined on the crude reaction mixtures by ^1H NMR and was found to be ≥19:1. [c] No reaction at rt. [d] No reaction with CuI alone. [e] Using two 100 W tungsten lamps.

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(9) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (c) Doyle, M. P. *Aldrichimica Acta* **1996**, *29*, 3.

(10) It is pertinent to mention that although Cu(II) salts are screened as catalyst precursors, the Cu(I) salts are the catalytically active species in these type of reactions; see: (a) Moser, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 1135. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

cyclopropanated product in moderate yields (Table 1, entries 3 and 9). $Cu(acac)_2$ (in refluxing CH_2Cl_2) was found to be an excellent catalyst for this intramolecular cyclopropanation, furnishing the cyclopropafuranone **1a** in very good yield with excellent diastereoselectivity (Table 1, entry 6).[11] Even though $Rh_2(OAc)_4$ too was found to work well (Table 1, entry 7), given the cost and the regioselectivity problems associated with it for some of the substrates (see Supporting Information), we decided to use $Cu(acac)_2$ as the catalyst of choice.

Table 2 outlines the scope of the intramolecular cyclopropanation reaction of vinylogous carbonates with $Cu(acac)_2$

Table 2. Scope of the Intramolecular Cyclopropanation of Vinylogous Carbonate (Scheme 1)

			yield (%)[a]			
entry	R		step I	step II	product	dr[b]
1	CH_3	**2a**	79	78	**1a**	≥19:1
2	H	**2b**	77	76	**1b**	≥19:1
3	CH_3CH_2	**2c**	70	80	**1c**	≥19:1
4	$CH_3(CH_2)_3$	**2d**	70	66	**1d**	≥19:1
5	$(CH_3)_2CHCH_2$	**2e**	78	70	**1e**	≥19:1
6	$PhCH_2$	**2f**	78	77	**1f**	≥19:1
7	Ph	**2g**	81	74	**1g**	≥19:1
8	$BnOCH_2$	**2h**	60	70	**1h**	≥19:1
9	$CH_3CH_2(CH_3)CH$	**2i**	69	74	**1i**	≥19:1
10	$CH_2{=}CH{-}CH_2$	**2j**	72	26[c]	**2i**	≥19:1

[a] Isolated yield. [b] Determined on the crude reaction mixtures by ^1H NMR. [c] Cyclopropanation of olefin was also observed (52%).

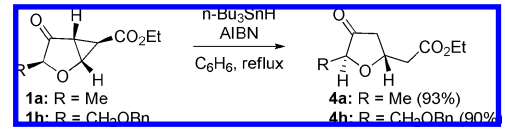
as the catalyst. This study demonstrated that vinylogous carbonates are good substrates for the intramolecular cyclopropanation with carbenes. The reaction proceeded smoothly in the presence of a variety of substitutions such as alkyl, aryl, or benzyloxy groups. It is interesting to note that cyclopropafuranones were obtained as the only detectable products in these cases, and competing side reactions such as C−H insertion (entries 4−7 and 9), cyclopropanation of phenyl group (entry 6), or 1,2-shift of the intermediate oxonium intermediate (entry 8) were not observed. Incidentally, in these cases, it was found that $Rh_2(OAc)_4$ gave a significant amount of these side products (see Supporting Information). Interestingly, when competitive reaction was set with a simple olefin present in the side chain, the cyclopropafuranone **1j** was found to be minor product (26%) and regioisomeric product obtained by intramolecular cyclopropanation of olefin was found to be the major product (52%) (entry 10). In all of the examples, the cyclopropanation of vinylogous carbonate moiety proceeded with very high diastereoselectivity. It is pertinent to mention here that the cyclopropafuranones **1a**, **1e**, **1f**, **1g**, and **1i** were prepared in enantiopure forms.

The stereochemistry of the substituents was assigned with the help of single crystal X-ray diffraction studies on the cyclopropafuranone derivative **1f**.[12] In other cases the stereochemistry assigned is by analogy to this example and on the basis of NOE experiments. The stereochemical outcome of these intramolecular cyclopropanation reactions are consistent with the transition state structures in which the cyclopropane ring prefers to be *syn* to hydrogen on the C-2 than the bulky alkyl substituent so as to avoid the steric interaction (see Supporting Information).

A systematic study was undertaken, to test the reactivity of the DACs synthesized with the emphasis on gaining access to reaction conditions such that regioselective cleavage of each bond of the cyclopropane ring can be achieved.

To begin with, the cyclopropafuranone **1a** was subjected to standard radical conditions using *n*-Bu_3SnH and AIBN in benzene under reflux.[13] The cyclopropane ring was cleaved in a highly regioselective manner, furnishing in quantitative yield the 3-furanone derivative **4a** (cf. scheme 2). The

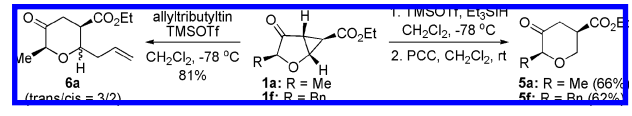
Scheme 2



reaction was found to work equally well when the side chain contained a benzyloxymethyl substituent (**1h**, R = CH_2OBn).

The reactivity of these two acceptor substituted DACs with Lewis acids was investigated next. The screening of several Lewis acids revealed that TMSOTf was able to open the cyclopropane bond of **1a** by preferentially complexing with the ketone leading to the formation of oxonium ion, which was trapped with hydride from triethylsilane. Initially formed ketone underwent further reduction, yielding diastereomeric mixture of the 3-hydroxytetrahydropyran, which was oxidized with PCC to the keto-ester **5a**. Repetition of the same reaction sequence with **1f** yielded the keto-ester **5f** in comparable yields (cf. Scheme 3).

Scheme 3



In another direction, the oxonium ion formed from the cyclopropafuranone **1a** on treatment with TMSOTf could be trapped by reaction with allyltributyltin furnishing ca. 3:2 (*trans/cis*) diastereomeric mixture of the trisubstituted tet-

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(12) CCDC 733601(**11a**), CCDC 733602 (**9a**), and CCDC 733603 (**1f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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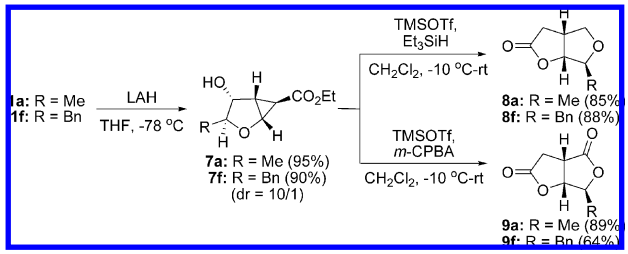
rahydropyran-3-one **6a**. This study demonstrated that cyclopropafuranones are versatile intermediates for the synthesis of THF and THP derivatives.

After demonstrating the regioselective cleavage of the two of the three cyclopropane bonds, we reasoned that if the carbonyl of the ester moiety complexes with the Lewis acid, it would lead to the cleavage of the third bond of the DA cyclopropane. Thus, chemoselective reduction of the ketones **1a/f** using lithium aluminum hydride furnished the corresponding alcohols **7a/f** in excellent yield and very good diastereoselectivity (Scheme 4). The alcohol **7a** was then

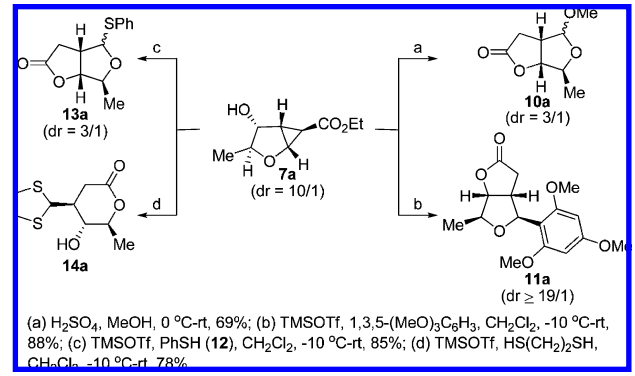
Scheme 4



subjected to treatment with TMSOTf and Et_3SiH. Interestingly, not only did it lead to the cleavage of the third bond of the DA cyclopropane but the free hydroxyl group underwent lactonization in a tandem fashion with the ester in situ, furnishing the furofuranone **8a**. In another direction, the intermediate oxonium formed from the alcohol **7a** in the presence of TMSOTf could be directly oxidized with *m*-CPBA with concomitant lactonization to furnish furofurandione **9a** in a single step from the alcohol **7a**.[12] The aryl group in **7f** was found to be unaffected under the reaction conditions employed and the products **8f** and **9f** were also formed in good yields. It is worthwhile mentioning that furofurandiones are part structures of a series of natural products such as xylobovide, canadensolide, and sporothriolide, and the developed method could be potentially applied to the synthesis of these natural products and analogues.[14,15]

This tandem cyclopropane ring-opening−lactonization sequence was found to be quite general, and a variety of nucleophiles could be used to trap the oxonium ion intermediate. Thus, reaction of the alcohol **7a** in methanol in the presence of a catalytic amount of sulfuric acid led to the formation of an epimeric mixture of the acetal **10a** (Scheme 5). Even a carbon nucleophile such as 1,3,5-trimethoxybenzene could be used to give the arylated furofuranone **11a** in 88% yield with excellent diastereoselectivity with aryl nucleophile trapping the oxonium ion from the less hindered convex face.[12] The oxonium ion intermediate trapping with sulfur nucleophiles was particularly interesting. Similar to MeOH, thiophenol (**12**) as the nucleophile led to the formation of the lactone **13a**. On the other hand, using ethanedithiol as the nucleophile furnished the δ-valerolactone derivative **14a** in 78% yield by tandem ring-opening−oxonium ion trapping with ethanedithiol, thioacetalization, and subsequent lactonization. This study unambiguously demonstrated the diverse and unique reactivity of these DACs.

Scheme 5



In conclusion, we have developed a highly regio- and diastereoselective synthesis of DACs employing intramolecular cyclopropanation of vinylogous carbonates with carbenes in the presence of $Cu(acac)_2$ as the catalyst. These two acceptor substituted DACs display hitherto unprecedented reactivity allowing for the regioselective cleavage of each of the cyclopropane bonds by appropriate choice of reagents leading to divergent synthesis of THF, THP, and lactone derivatives.

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Supporting Information Available: Characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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