

Copper-Catalyzed Oxy-Alkenylation of Homoallylic Alcohols to Generate Functional *syn*-1,3-Diol Derivatives**

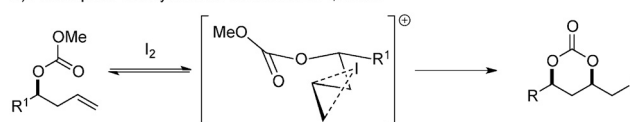
Dean Holt and Matthew J. Gaunt*

Abstract: A novel method for the synthesis of a wide range of functionalized 1,3-diol derivatives is reported. Employing a copper-catalyzed oxy-alkenylation strategy, a range of readily available, substituted homoallylic alcohol derivatives and alkenyl(aryl) iodonium salts combine to form *syn*-1,3-carbonates in excellent yield and with high selectivity. Furthermore, the products formed are amenable to an iterative reaction sequence, thus affording highly complex polyketide-like fragments.

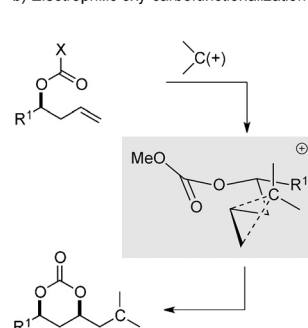
The 1,3-diol is an important structural feature commonly found in biologically active natural products and pharmaceutical agents.^[1] The diversity of polyketide natural products, in particular, has inspired the development of many strategies geared towards the synthesis of *syn* or *anti* isomers of the 1,3-diol functionality.^[2] Benchmarked by the aldol-directed reduction transformation,^[3] the stereocontrolled synthesis of the 1,3-diol motif can now be achieved by numerous methodologies which encompass a variety of possible bond disconnections around the two hydroxy groups. Notable among these seminal contributions are the anion relay addition of lithiated dithianes to epoxides^[4] and the addition of allyl nucleophiles to aldehydes,^[5] both of which require further manipulations to form the 1,3-diol function, and the tethered oxy-Michael additions to enoates.^[6] Recently, catalytic processes have emerged as powerful tactics to generate 1,3-oxygenation patterns from simple starting materials: Krische's tandem redox allylation of alcohols,^[7] Leighton's tandem silylformylation of homoallylic alcohol derivatives,^[8] and Yamamoto's tandem super-silyl Mukaiyama aldol-type coupling of aldehydes^[9] can all be used to rapidly generate complex 1,3-diol systems and have found widespread use in complex natural product synthesis. The unquestionable efficacy and utility of these transformations underlines the importance of the continual development of new strategies for the catalytic, stereocontrolled synthesis of 1,3-diol derivatives.^[10]

We were attracted to a classical, but underutilized method for 1,3-diol synthesis, that is, an electrophilic iodolactonization-type process which constructs a 1,3-cyclic carbonate from a homoallylic carbonate (Scheme 1 a).^[11] In this reaction, the

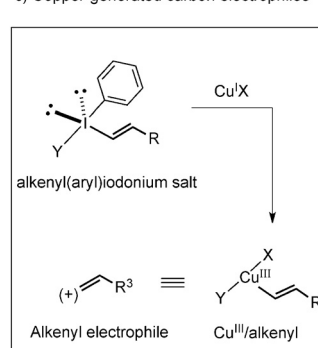
a) Electrophilic iodocyclization as a route to 1,3-diols



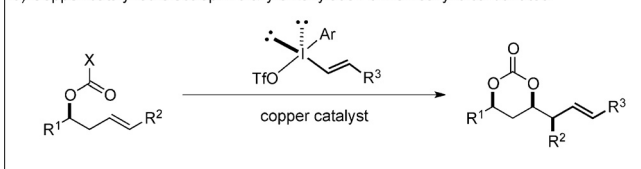
b) Electrophilic oxy-carbofunctionalization



c) Copper-generated carbon electrophiles



d) Copper-catalyzed electrophilic oxy-alkenylation of homoallylic carbonates



Scheme 1. Hypothesis of copper-catalyzed oxyalkenylation of to 1,3-*syn* diol derivatives. Tf = trifluoromethanesulfonyl.

iodine electrophile activates the alkene to form an iodonium species which is intercepted through intramolecular attack by the carbonyl oxygen atom of the pendant carbonate, thus resulting in concomitant formation of carbon–oxygen and carbon–iodine bonds. In a subsequent step, the carbon–iodine bond can be used to alkylate carbon nucleophiles, thus forming complex 1,3-diol fragments which are common in polyketide natural products. Inspired by this simple tactic, we questioned whether we could design a catalytic transformation which linked a related carbon–oxygen bond-forming event to a carbon–carbon bond formation to forge complex 1,3-diols directly from homoallylic alcohol derivatives by an electrophilic oxy-carbofunctionalization process (Scheme 1 b).^[12] Furthermore, if the electrophile component was an alkenyl derivative then the products of the transformation

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would, themselves, contain a homoallylic carbonate motif suitable for further elaboration.

Over the last seven years, our group has pioneered the use of diaryliodonium reagents in combination with copper salts as a catalytically generated source of aromatic electrophile equivalent.^[13] Proceeding via the intermediacy of a putative copper(III)/aryl species, this highly electrophilic organometallic reagent has been shown to undergo reaction with a variety of latent carbon nucleophiles, thus leading to the development of a range of previously unknown transformations. In the context of an electrophilic oxy-carbofunctionalization strategy towards synthetically versatile 1,3-diols, we reasoned that the action of a copper catalyst on an alkenyl(aryl)iodonium salt would generate a copper(III)/alkenyl species (Scheme 1c).^[14] This reactive intermediate would engage the alkene, thus polarizing the carbon–carbon double bond and promoting attack of the pendant carbonyl motif in such a way to form a carbon–oxygen bond and a new copper(III)–carbon bond. Reductive elimination from the high oxidation state copper(III) species would transfer the alkenyl group leading to a cyclic carbonate product, which was predicted to be the *syn* diastereoisomer in line with the related iodine-mediated reaction.

Herein, we report the successful realization of such a copper-catalyzed oxy-alkenylation strategy and show that a range of readily available, substituted homoallylic alcohol derivatives and alkenyl(aryl)iodonium salts can be combined to form *syn*-1,3-carbonates in excellent yield and with high selectivity (Scheme 1d). Moreover, a simple iteration of the process affords highly complex polyketide-like fragments which could be used to expedite the synthesis of natural products.

At the outset of our studies, we selected the simple mixed carbonate **1a** to assess the oxy-alkenylation strategy (Table 1). Based on our hypothesis, we first assessed simple

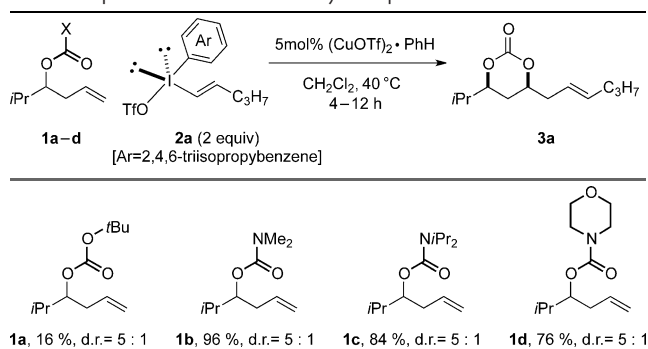
found that the use of the corresponding carbamate-derivative **1b** afforded excellent yield of the desired product with similar selectivity. Interestingly, close monitoring of the reaction revealed that **3a** was not formed in the crude reaction mixture until a hydrolytic work up was applied to form the cyclic carbonate. We found that the dimethylcarbamate gave superior yields to those of other amine derivatives, and that no variation of the solvent or the reaction temperature improved the selectivity. Therefore, optimal reaction conditions were concluded to involve treatment of **1b** with 2 equivalents of **2a** and 5 mol% of (Cu^IOTf)₂·PhH as the catalyst in a solution of dichloromethane at 40 °C for 4 hours, and resulted in the isolation of **3a** in 96% yield as a 5:1 mixture of *syn* and *anti* diastereoisomers.

We next assessed the scope of the new copper-catalyzed oxy-alkenylation reaction of homoallylic carbamates (Table 2). We were pleased to observe that the process works well on a range of substrates, thus providing access to a diverse array of functionalized *syn* carbonates. Substrates bearing simple alkyl substituents proved to be high yielding for the 1,3-carbonates **3b–d**. Interestingly, the diastereoselectivity observed across these products was relatively unaffected by the changing steric demands of the substrate, and marginal improvement was observed by increasing substituent size from methyl to isopropyl to *tert*-butyl (d.r. = 4:1 for **3c** to 6:1 for **3d**). A selection of synthetically versatile functional groups were compatible with the reaction and formed products in comparable yields and, in many cases, higher diastereoselectivity: homoallyl (**3e**), phenyl (**3f**), chloromethyl (**3g**), and protected hydroxy motifs (**3h** and **3i**) all proceeded well to provide useful cyclic carbonate products with selectivities between 5.5 and 10:1. Homoallylic carbonates with substituents displaying additional stereogenic centers reacted smoothly, again in good yield and diastereoselectivity, to form the stereotriads **3j** and **3k** commonly found in polyketide natural products.

In addition to the primary homoallylic carbamates that worked well to form the corresponding products, we were pleased to find that substituents on the internal position of the carbon–carbon bond worked well to form functionalized cyclic carbonates containing a quaternary carbon atom (**3m** and **3n**; Table 2). The reaction could also be deployed on allylic carbamates to form either the five-membered ring (**3o**) or six-membered (**3p**) cyclic carbonates, depending on the nature of the alkene substituent. The transferred alkenyl group can also be varied without significantly affecting the yield or diastereoselectivity (**3q–s**).

Having established that terminal alkenes were excellent reaction partners in the copper-catalyzed oxy-alkenylation, we next investigated whether 1,2-disubstituted carbon–carbon double bonds could also function as part of this process. Methyl substituents appended to the alkene were of particular interest because the product of the transformation would form vicinal stereocenters reminiscent of propionate motifs commonly found in polyketide natural products. We were pleased to find that the *Z*-alkene (*Z*)-**4** formed the *anti*-isomer **5a** with very good selectivity and in high yield (Scheme 2). Importantly, the *E*-alkene (*E*)-**4**, under similar reaction conditions, formed the corresponding *syn*-product

Table 1: Optimization of the carbonyl component of the substrate.^[a]



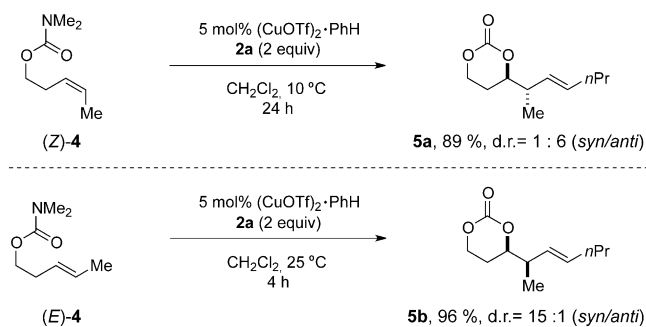
[a] Major diastereoisomer confirmed as *syn* by one-dimensional NOESY.

copper salts as catalysts with the pentenyl(triisopropylbenzene)iodonium triflate **2a** (readily available in our laboratories; see the Supporting Information for full details of optimization). We found that the desired reaction was best catalyzed by the copper(I) salt (Cu^IOTf)₂·PhH, thus affording the cyclic carbonate **3a** with good diastereoselectivity (d.r.), albeit in low yield. However, under the same reaction conditions, we

Table 2: Substrate scope for the oxy-alkenylation reaction.

1a–p	2a–d (2 equiv) (Ar=2,4,6-triisopropylbenzene)	5 mol% (CuOTf) ₂ ·PhH CH ₂ Cl ₂ , 40 °C 1–12 h ^[a]	3b–s
3b , 96 % ^[b]			3c , 96 %, d.r. = 4:1
			3e , 92 %, d.r. = 5.5:1
			3g , 75 % (d.r. = 7:1)
			3i , 85 %, d.r. = 6:1
			3k , 71 % (d.r. = 8:1) ^[c]
			3m , 96 %
			3o , 96 %
			3q , 95 %, d.r. = 5:1
			3s , 85 %, d.r. = 5:1

[a] See the Supporting Information for further details of temperature and time taken. [b] Yields of **3f**, **3g**, **3h**, **3k**, **3n**, and **3o** are quoted for the isolated product. All others yields are of quoted for an isolated mixture of diastereomers. The d.r. values are those observed for the crude reaction mixture by ¹H NMR spectroscopy. [c] Required 2 equivalents of K₂CO₃. [d] Confirmed as *syn* by one-dimensional NOESY. TBDPS = *tert*-butyldiphenylsilyl.


Scheme 2. Application of nonterminal alkenes (*E*)-**4** and (*Z*)-**4** to the copper-catalyzed oxy-alkenylation.

5b, in both excellent yield and selectivity. The selectivity here is comparable to that observed for the related iodine-mediated reactions on similar substrates. These selectivities were observed with a range of alkenyl(aryl)iodonium salts (Table 3). We were particularly pleased to observe the

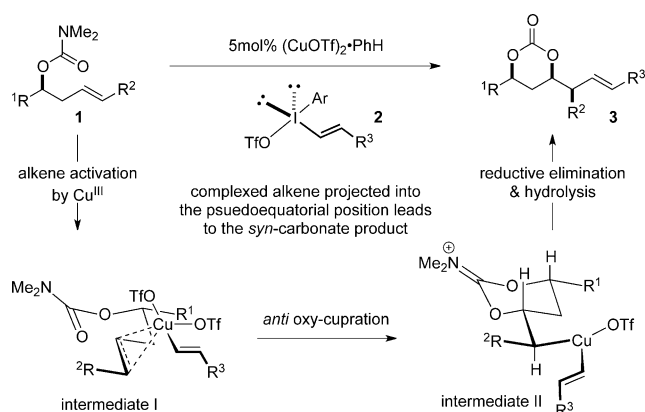
Table 3: Salt scope of the reaction.^[a]

(<i>E</i>)- 4	2a-i (2 equiv)	5b-j
5b , 96 %, d.r. = 15:1	5c , 96 %, d.r. = 15:1	5d , 96 %, d.r. = 15:1
5e , 78 %, d.r. = 15:1	5f , 62 %, d.r. = 10:1	5g , 81 %, d.r. = 15:1
5h , 89 %, d.r. = 10:1	5i , 41 %, d.r. = 10:1	5j , 68 %, d.r. = 10:1

[a] Yields are quoted for and isolated mixture of diastereomers. The d.r. values are those observed from the crude reaction mixture by ¹H NMR spectroscopy.

successful transfer of the propenyl motif (**5c**), acrylate moiety (**5i**), and notably, the ethenyl group (**5j**). Each reaction proceeded in good yield and excellent selectivity to deliver highly versatile products.

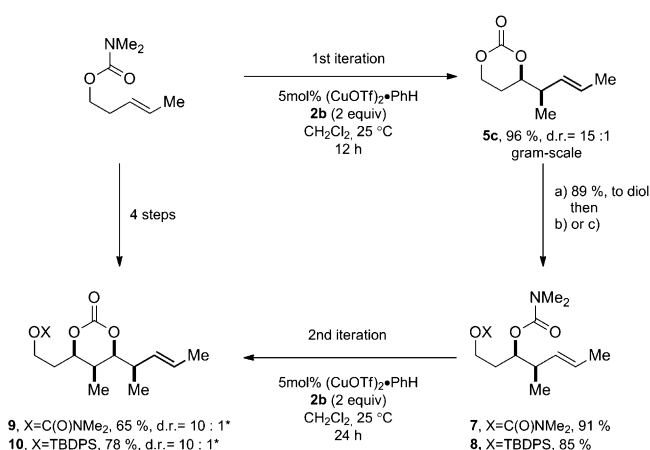
Based on the observations in Scheme 2, we propose that the reaction proceeds by a pathway related to the iodine-mediated cyclization of homoallylic carbonates.^[14] No formation of the product was observed either in the absence of copper at elevated temperatures, or with a variety of Lewis acid catalysts.^[15] Therefore, we propose that the copper-catalyzed oxy-alkenylation proceeds through a copper(III)/alkenyl species functioning as an electrophile which com-



Scheme 3. Proposed mechanism for the formation of *syn*- and *anti*-diastereoisomers in the reaction.

plexes the alkene (intermediate I), thus activating the carbon–carbon double bond towards an *anti* attack by the pendant carbonyl group via a chairlike intermediate (intermediate II) to form the *syn*-carbonate product (Scheme 3). The minor diastereoisomer could arise from attack on to the copper-complexed alkene in a pseudoaxial orientation to form the *anti*-carbonate product. A pathway involving delivery of the copper(III) species by complexation with the carbonyl is not consistent with the observed selectivity for the oxy-alkenylation.

The products of the copper-catalyzed oxyalkenylation reaction display a functional pattern which may be amenable to an iterative cycle of the process. To test this (Scheme 4), the carbonate **5c** was synthesized on gram-scale and cleaved to the corresponding 1,3-diol **6**, which could be readily transformed into the carbamate derivative **7**, or the differentially protected carbamate **8**, both of which were substrates for the oxy-alkenylation. We were delighted to observe that the



Scheme 4. Application of the 1,3-diol-carbonate product in an iterative reaction sequence. a) K_2CO_3 , MeOH, 89%. b) 1. 1,1-carbonyl diimidazole (3 equiv), MeCN, RT; 2. HNMe_2 (4 equiv), 91% **7**. c) 1. NET_3 , DMAP, TBDPSCl; 2. 1,1-carbonyl diimidazole (1.5 equiv), MeCN, RT; 3. HNMe_2 (2 equiv) to give **8**, 85%. [*] All-*syn* diastereoisomer: sum of all diastereoisomers. Yields are quoted for the diastereomer shown; the diastereomer was isolated as a pure compound. DMAP = 4-(*N,N*-dimethylamino)pyridine.

second iteration of the copper-catalyzed reaction proceeded smoothly to form the propionate stereotetrad **9** and **10** in good yield and selectivity. This short reaction sequence highlights the ability to rapidly access complex polypropionate fragments from readily accessible homoallylic alcohol starting materials using this strategy.

In summary, we have developed a new copper-catalyzed oxy-alkenylation of homoallylic carbamates. The transformation is tolerant to a wide range of functional groups and provides ready access to a broad range of 1,3-carbonate products in very high yields and good selectivity. The cyclic carbonate products can be further manipulated into 1,3-diol derivatives which are amenable to further iterations of the reaction. Ongoing research is focused on elaborating on these studies by applying the methodology in natural product synthesis.

Keywords: copper · diols · homogeneous catalysis · hypervalent compounds · synthetic methods

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- [15] None of the product **3a** was observed for reactions in the absence of copper at either 40 °C, 70 °C, or 110 °C, or with a range of Lewis acids [(Bi(OTf)₃, Sc(OTf)₃, Zn(OTf)₂ or BF₃·(OEt₂)].

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