Synthetic Methods

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Stereoselective Ring Expansion of Vinyl Oxiranes: Mechanistic Insights and Natural Product Total Synthesis**

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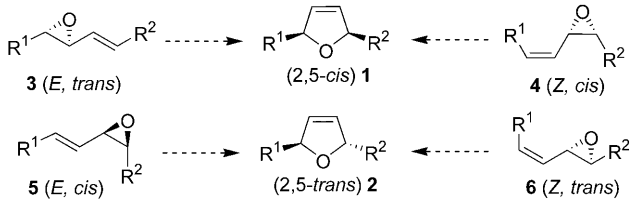
The central part of our research program is the development of broadly applicable atom-efficient synthetic methods to generate structural complexity. We recently reported a new copper-catalyzed ring expansion of vinyl oxiranes using commercially available, structurally simple, and air-stable copper(II) catalysts.[1] These studies demonstrated the success of this reaction for a broad range of substrates. Missing from these early studies were experiments focused on assessing the stereoselective potential of the ring expansion. The studies presented herein are aimed at addressing this point to learn if the oxirane C–O bond, which is broken during the ring expansion, could be stereoselectively transferred to the olefin terminus. Moreover, an added benefit to the proposed studies would be critical mechanistic insights that could shed additional light on the exact mechanism of this unique catalytic ring-expansion reaction. If vinyl oxiranes can indeed be stereoselectively ring expanded using copper catalysts then the practical benefits of this new reaction would be significantly expanded. Also this transformation would rival existing methods[2] to stereoselectively access 2,5-dihydrofurans in terms of efficiency and scope.

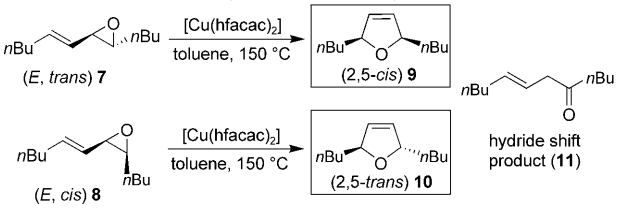
Our studies have focused on disubstituted vinyl oxirane substrates (Scheme 1), which depending on their stereochemistry and olefin geometry could serve as precursors for accessing either a 2,5-*cis*- or a 2,5-*trans*-substituted 2,5-dihydrofuran product. In the case of a stereoselective ring expansion, vinyl oxiranes **3** and **4** would be expected to afford the *cis* product **1.** whereas **5** and **6** should afford the *trans* product **2**. When these substrates are ranked with respect to steric crowding during formation of the new C–O bond, vinyl oxiranes **3** and **5** emerge as more suitable precursors for accessing the 2,5-*cis*- and 2,5-*trans*-dihydrofuran products, respectively.



Scheme 1. Stereoselective vinyl oxirane ring expansions.

Therefore we synthesized vinyl oxiranes **7** and **8**,[3] which differ only in the oxirane stereochemistry (*trans*- or *cis*-substituted oxiranes). Ring expansion of these two substrates afforded the symmetrically substituted *cis*- and *trans*-dihydrofurans **9** and **10** (Table 1). Under the standard reaction conditions used in our previous paper (Table 1, entries 2 and 6) we were able to obtain both dihydrofurans in good diastereomeric purity but with low chemical yield because of the formation of the by-product **11**. Reaction optimization revealed that the success of the reaction relied most strongly on the reaction temperature and appropriate catalyst loading. After thorough optimization we were delighted to learn that the dihydrofuran products **9** and **10** could be obtained with high levels of stereoselectivity and good chemical yield (Table 1, entries 4 and 8). In general, we observe that both a lower catalyst loading and slow addition of the catalyst improves the yield (chemoselectivity) of the product. These results establish for the first time that vinyl oxiranes can be stereoselectively ring expanded to 2,5-dihydrofurans.[4]

Table 1: Stereoselective synthesis of dihydrofurans **9** and **10**.



Entry	Substr.	Cat. [mol%]	*t* [h]	Chemosel. (**9**+**10**)/**11**	Stereosel. **9**/**10**	Yield [%][a]
1	**7**	10	15	1:1	10:1	45
2	**7**	5	1	3:1	11:1	69
3	**7**	1	6	3:1	>20:1	75 (70)
4	**7**	5[b]	8	11:1	15:1	86 (79)
5	**8**	10	1	1:7	1:10	11
6	**8**	5	2	2:1	1:12	62
7	**8**	1	15	1:1	1:8	44
8[c]	**8**	5	3	2.5:1	1:18	68 (66)

[a] Estimated by NMR analysis (yield of isolated product). [b] Added by syringe pump (1.25 mol% h^{-1} for 4 h). [c] 0.13 M in benzene. hfacac = hexafluoroacetylacetonate.

These results are even more profound when one considers the stability of reactants and products. DFT calculations[5] (B3LYP/6-311 + G(d,p)) on **7**–**11** revealed that the vinyl

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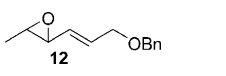
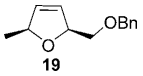
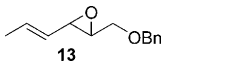
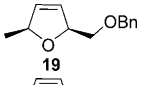
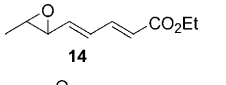
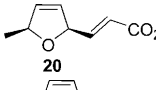
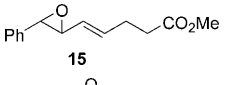
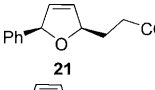
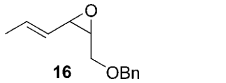
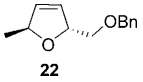
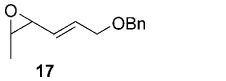
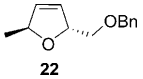
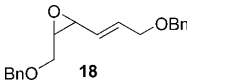
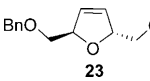
oxiranes **7** and **8** are very similar in energy. Closer examination reveals that oxirane **7** (0.0 kcal mol^{-1}) forms the less stable *cis* product **9** (−13.7 kcal mol^{-1}), whereas oxirane **8** (1.1 kcal mol^{-1}) affords the preferred *trans* product **10** (−13.9 kcal mol^{-1}). Both dihydrofuran products **9** and **10** are less stable than the by-product **11** (−27.1 kcal mol^{-1}) formed in the reaction. These energy relationships strongly discredit a mechanism involving a carbocation intermediate.

We have expanded our studies to include the seven additional examples[6] presented in Table 2. Our results are in agreement with what we learned from the ring expansion of vinyl oxiranes **7** and **8**, wherein high selectivity was achieved by lowering the catalyst loading. As expected, *cis*-2,5-dihydrofuran products (**19**–**21**) were stereoselectively obtained from (*trans*,*E*)-vinyl oxirane precursors (**12**–**15**), and *trans*-2,5-dihydrofuran products (**22**–**23**) were accessed by ring expanding (*cis*,*E*)-vinyl oxirane substrates (**16**–**18**). Both the yields (isolated) and stereoselectivies are excellent for all substrates. Functional groups such as ethers, esters, enoates, and aryl groups are well-tolerated. These new stereoselective results allow strategic design of routes to either *cis*- or *trans*-2,5-dihydrofuran targets by employing the appropriate vinyl oxirane precursor.

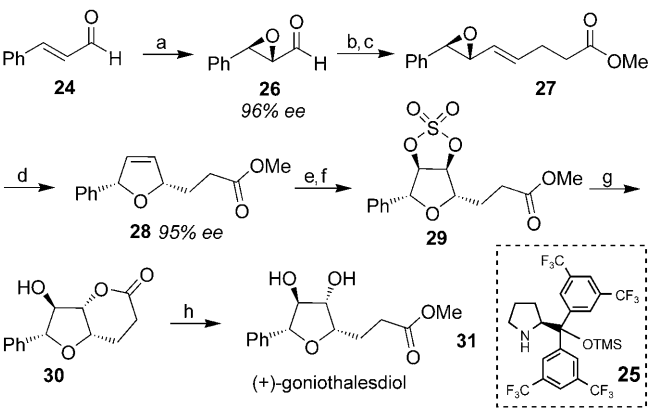
As part of our program to use synthetic chemistry to efficiently access natural products, the anticancer agent (+)-goniothalesdiol[7] (Scheme 2) was chosen as a target for assessing the value of the new stereoselective copper-catalyzed ring-expansion protocol and to showcase it using an enantiopure oxirane substrate. (+)-Goniothalesdiol, a densely decorated tetrahydrofuran-based structure, seemed like a perfect target for this task. Towards that end, cinnamaldehyde (**24**) was converted into chiral epoxy aldehyde **26** using Jorgensen's asymmetric organocatalytic epoxidation protocol.[8] Treatment of **26** with vinyl magnesium bromide and subsequent Johnson–Claisen rearrangement[9] of the resulting allylic alcohol efficiently formed vinyl oxirane **27** as a single olefin isomer. The copper-catalyzed rearrangement of this chiral oxirane afforded *cis*-2,5-dihydrofuran **28** in 70% yield and excellent enantiopurity after separation from the *trans* diastereomer. Substrate-controlled epoxidation of the olefin was expected to give an epoxide that could be opened in an intramolecular fashion to lactone **30**.[10] Surprisingly, epoxidation proved troublesome affording only the furan. This situation was solved by constructing a cyclic sulfate instead of an epoxide. Gao and Sharpless have shown that these reactive synthons can be obtained from vicinal hydroxy groups.[11] Dihydroxylation of **28** selectively afforded 4-*epi*-goniothalesdiol in high yield. Upon treatment of this diol with thionyl chloride and ruthenium tetroxide, the cyclic sulfate **29** was obtained. This activated diol was efficiently opened in an intramolecular fashion to lactone **30** by the carboxylate group.[12] Opening of the lactone with Amberlyst-15 in methanol afforded goniothalesdiol in only eight steps from cinnamaldehyde. This short asymmetric synthesis of (+)-goniothalesdiol is a testament to the value of our new stereoselective ring-expansion protocol.

Detailed kinetic studies of vinyl oxirane **7** revealed a sigmoidal curve for the formation of dihydrofuran product **9**, which is in perfect agreement with our vinyl aziridine trace.[1c] When similar kinetic analyses for *cis*-vinyl oxirane substrate **8** are performed, the same general observations are made with the added insight that formation and disappearance of small amounts of *trans*-vinyl oxirane **7** can also be observed in the kinetic trace. This suggests that the active catalyst accommodates oxirane isomerization while suppressing the other-

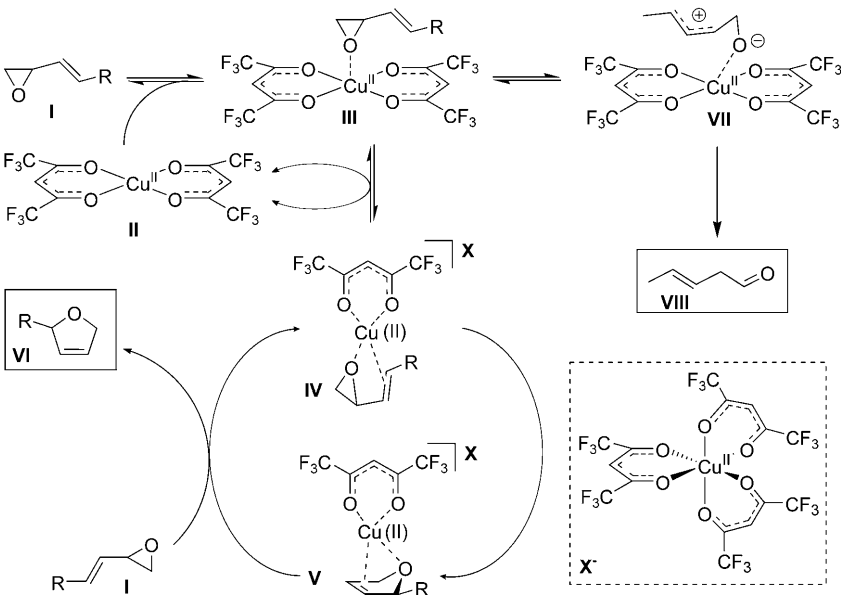
Table 2: Stereoselective ring expansion of vinyl oxiranes. Reaction conditions: 5 mol% [Cu(hfacac)$_2$] in toluene at 150°C.

Starting material	Product (*rac*)	Yield [%]	*cis*/*trans*
 **12**	 **19**	94[a,b]	>20:1
 **13**	 **19**	88[a,b]	13:1
 **14**	 **20**	84[a,c]	8:1
 **15**	 **21**	70[a,d]	8:1
 **16**	 **22**	92[e,f]	1:6
 **17**	 **22**	96[f,g]	1:8
 **18**	 **23**	93[f]	1:7

[a] Yield of diastereomerically pure material upon isolation. [b] Added by syringe pump (0.6 mol% h^{-1} for 8 h). [c] 2 mol% added by syringe pump (0.11 mol% h^{-1} for 17 h). [d] Added by syringe pump (2.5 mol% h^{-1} for 2 h). [e] 100°C. [f] Yield of both diastereomers upon isolation. [g] Benzene.



Scheme 2. Asymmetric total synthesis of (+)-goniothalesdiol. Reagents and conditions: a) H_2O_2, **25**, 80%; b) CH_2=$CHMgBr$, 47%; c) $CH_3C(OMe)_3$, cat. propionic acid, 83%; d) 1 mol% [Cu(hfacac)$_2$], toluene, 150°C, 70%; e) cat. OsO_4, NMO, acetone, H_2O, 99%; f) $SOCl_2$, Et_3N then $NaIO_4$, $RuCl_3{\cdot}3H_2O$, CH_3CN, H_2O, 88%; g) 15% H_2SO_4, THF, 65°C, 87%; h) Amberlyst-15, MeOH, 99%. NMO = *N*-methylmorpholine-*N*-oxide, TMS = trimethylsilyl.



Scheme 3. Proposed catalytic cycle.

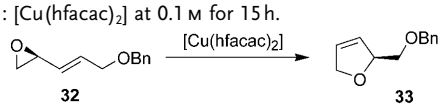
wise detrimental hydride-shift pathway (also observed for **16**–**18**). Based on our data, the catalytic cycle shown in Scheme 3 is proposed.

The kinetic data seems to suggest that after an induction period a more active catalyst is formed, which then proceeds to stereoselectively ring-expand vinyl oxiranes. We envision that [Cu(hfacac)$_2$] (**II**) reversibly coordinates to the oxirane **I** lone pair of electrons thereby forming substrate–catalyst complex **III**, which upon reacting with another [Cu(hfacac)$_2$] (**II**), is transformed into chelated substrate-bound cationic copper(II) complex **IV**, wherein [Cu(hfacac)$_3$]$^-$ serves as the non-nucleophilic counterion (**X**$^-$).[13] This cationic catalyst acts as the optimal Lewis acid which holds the substrate together in such a way that the chirality of C–O bond is transferred without scrambling to the olefin terminus and thereby form the dihydrofuran-bound copper complex **V**. This complex is a weaker chelate than **IV**, which prompts coordination to another vinyl oxirane (**I**) and concomitant release of the product **VI** thereby reforming **IV** and completing the first round of the catalytic cycle. Furthermore, we propose that the competing hydride-shift product (**VIII**) is formed from copper complex **VII**, wherein the C–O oxirane bond has already been broken. An equilibrium arrow is placed between catalyst–substrate complexes **III** and **VII** based on the kinetic data obtained for vinyl oxirane **8** as discussed above.[14]

Challenging the reaction additionally, we decided to evaluate if chiral monosubstituted vinyl oxirane substrates such as **32**[15] could be ring expanded into dihydrofuran **33**[16] without any stereochemical scrambling.[17] As is evident from entries 1–5 in Table 3, the [Cu(hfacac)$_2$] catalyst loading impacts the stereoselectivity of the reaction, with 0.5 mol% being optimal.[18] We decided to evaluate how changing the solvent would impact the stereoselectivity. When the standard toluene (Table 3, entry 4) conditions are compared to that used in Table 3, entries 6–9, it was determined that hexafluorobenzene negatively impacts stereoselectivity, *n*-pentane almost completely erodes it, and benzene and fluorobenzene are on par with toluene. The ring expansion can be done at several different temperatures with very comparable stereochemical outcomes (Table 3, entries 10–12). When this data is analyzed and put together (Table 3, entries 5, 8, and 11), the result was excellent, affording dihydrofuran product **33** in 92% *ee* (Table 3, entry 13).

In summary, we have demonstrated that this new copper-catalyzed vinyl oxirane ring expansion can be performed stereoselectively, therein providing access to *cis* or *trans* products simply by starting with the matching oxirane precursor. Similarly we have demonstrated that chiral 2-substituted dihydrofuran products of high optical purity can also be obtained. We propose that the active catalyst for the ring expansion is an in situ generated cationic copper(II) catalyst. These results were utilized to accomplish the shortest asymmetric synthesis of the natural product goniothalesdiol, highlighting the powerful retrosynthetic option this new catalytic synthetic method offers.

Table 3: Stereoselective ring expansion of vinyl oxirane **32**. Reaction conditions: [Cu(hfacac)$_2$] at 0.1 M for 15 h.



Entry	Cat. [mol%]	*T* [°C]	Solvent	*ee* [%][a]
1	10	150	toluene	61
2	5	150	toluene	63
3	2.5	150	toluene	72
4	1	150	toluene	73
5	0.5	150	toluene	77[b]
6	1	125	*n*-pentane	20
7	1	150	benzene	77
8	1	150	fluorobenzene	78
9	1	150	hexafluorobenzene	56
10	1	125	toluene	78
11	1	175	toluene	81
12	1	200	toluene	79
13	0.5	175	fluorobenzene	92[c,d]

[a] The *ee* value for **33** was determined by chiral HPLC analysis. [b] 45 h. [c9 24 h. [d] 60% yield of isolated product. Bn = benzyl.

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[5] Details regarding calculations can be found in the Supporting Information.

[6] See the Supporting Information for the synthesis of epoxides **12**–**18**.

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[12] This cyclization could also be performed using bases such as KOH and NaOH, but yields of **30** were significantly lower. Lactone **30** has previously been prepared and completes the formal syntheses of (+)-altholactone (P. Somfai, *Tetrahedron* **1994**, *50*, 11315 – 11320) and (−)-etharvensin (A. Bermejo, M. A. Blazquez, A. Serrano, M. Carmen Zafra-Polo, D. Cortes, *J. Nat. Prod.* **1997**, *60*, 1338 – 1340).

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[14] Cu^{I} mechanistic proposals do not seem to match our data. [Cu(hfacac)(BTMSA)] (BTMSA = bis(trimethylsilyl)acetylene) is the only Cu^{I} catalyst that we have shown to ring-expand vinyl oxiranes, which results from the fact that it disproportionates under the reaction conditions to the active catalyst, [Cu(hfacac)$_2$], and Cu^{0}. This fact is commonly exploited in the field of chemical vapor deposition (CVD), wherein fluorinated acetylacetonate copper catalysts are routinely employed: J. Rickerby, J. H. G. Steinke, *Chem. Rev.* **2002**, *102*, 1525 – 1549. Neither spectroscopic data or in situ reduction experiments of [Cu(hfacac)$_2$] using classic reducing agents such as cobaltocene, hydrazine, or AIBN support a Cu^{I} mechanism.

[15] For a synthesis of this chiral vinyl oxirane, see: J. A. Marshall, J. D. Trometer, *Tetrahedron Lett.* **1987**, *28*, 4985 – 4988.

[16] Both enantiomers of dihydrofuran **33** are known: a) S. Aragones, S. Bravo, Y. Diaz, M. A. Matheu, S. Castillon, *Tetrahedron: Asymmetry* **2003**, *14*, 1847 – 1856; b) J. Cleophax, S. D. Gero, *Tetrahedron Lett.* **1966**, *7*, 5505 – 5510.

[17] The product **33** does not epimerize under the reaction conditions.

[18] This increase in enantioselectivity with a decrease in catalyst loading, although rare, is not without precedence for metal-catalyzed reactions; a) I. J. S. Fairlamb, G. C. Lloyd-Jones, *Chem. Commun.* **2000**, 2447 – 2448; b) D. A. Evans, K. R. Fandrick, H.-J Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942 – 8943; c) D. A. Evans, K. R. Fandrick, . H.-J. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029 – 10041.

