

Copper-Catalyzed Rearrangement of Vinyl Oxiranes

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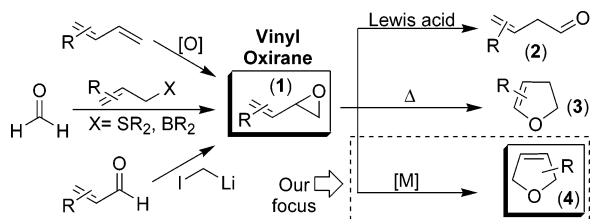
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Members of the furan family can be found in thousands of natural products, bulk commodity chemicals, and a number of pharmaceutical agents.¹ Despite a host of creative approaches, there is still a need for simple and scalable synthetic methods for making dihydro- and tetrahydrofurans.² We envisioned that a practical method to form 2,5-dihydrofurans would also serve as an excellent platform to access tetrahydrofurans. Here we report progress toward the development of catalytic conditions for the rearrangement of vinyl oxiranes to 2,5-dihydrofurans.

Vinyl oxiranes are versatile synthons that can be readily accessed by either oxidation of dienes or nucleophilic addition of activated allyl or methyl groups to aldehydes or ketones.³ Three types of vinyl oxirane (**1**) rearrangements are most relevant to our pursuit (Scheme 1). First, it is well documented that a number of different Lewis acids can be used to activate vinyl oxiranes and induce a hydride shift to form β,γ -unsaturated aldehydes (**2**).⁴ Second, it has been shown that, when vinyl oxiranes are heated above 300 °C, the oxirane ring opens to an oxonium ylide, which then rapidly rearranges to a 2,3-dihydrofuran (**3**).⁵ Third, studies on the ring expansion of vinyl oxiranes to a 2,5-dihydrofuran (**4**) have been performed almost exclusively by industry and have predominantly focused on butadiene monoxide. Despite decades of effort, suitable process conditions for this rearrangement have still not been identified,⁶ and the full scope of this transformation as a synthetic method for organic chemistry remains relatively unexplored.

Scheme 1. Vinyl Oxirane Rearrangements



Our objective was to conduct a full study of the rearrangement of vinyl oxiranes to 2,5-dihydrofurans using a catalyst without any additives. We hypothesized that an electrophilic metal catalyst capable of coordinating simultaneously to the olefin and the oxirane oxygen atom could facilitate the rearrangement by bringing the two ends into closer proximity. To make the method most practical, only simple and air-stable catalysts were considered, and specifically, electrophilic copper(II) catalysts substituted with non-nucleophilic ligands were selected. This choice is in part based on the great number of synthetically useful organic transformations that copper seems best suited to facilitate, many of which are believed to involve olefin coordination.⁷

Vinyl oxirane **5** was chosen as a test substrate for our initial studies. In addition to copper catalysts, a number of other metals were also surveyed, and these experiments led to the recovery of epoxide **5**, aldehyde formation (**7**), or decomposition of the starting

Table 1. Copper-Catalyzed Vinyl Oxirane Rearrangement^a

entry	catalyst ^b	mol %	time (h)	6:7 ^c
1	Cu powder	100	14	no rxn
2	Cu(OAc) ₂	10	14	no rxn
3	CuCl ₂	10	14	> 1:20
4	CuSO ₄ ·5H ₂ O	10	14	> 1:20
5	Cu(TFA) ₂	10	15	1:8
6	Cu(acac) ₂	5	17	5:1
7	Cu(tfacac) ₂	5	2	12:1
8	Cu(hfacac) ₂	5	0.25	13:1
9	Cu(hfacac) ₂	1	2	17:1
10	Cu(hfacac)(BTMSA)	5	4	15:1
11	Cu(dbm) ₂	5	24	4:1
12	Cu(ptfm) ₂	5	4	7:1
13	Cu(acyc) ₂	5	20	5:1
14	Cu(tfaccy) ₂	5	4	8:1
15	Cu(fod) ₂	5	2	11:1

^a Reactions are performed in a sealed tube in toluene at 150 °C with the specified catalyst loading. ^b See ref 9. ^c Based on molar ratios as determined from NMR integration.

material.⁸ In accordance with our hypothesis, a series of copper catalysts were examined (Table 1), and from these studies, the acetylacetonate ligand framework emerged as being superior to all other catalysts examined thus far. As a result, efforts focused primarily on Cu(acac)₂, Cu(tfacac)₂, and Cu(hfacac)₂.⁹ All of these catalysts successfully rearranged vinyl oxirane **5** to form only 2,5-dihydrofuran **6** and a mixture of aldehydes (**7**) (Table 1, entries 6–9). Product ratios varied according to the electronics of the ligand. The least electrophilic of these catalysts, Cu(acac)₂, was slow and exhibited only moderate product selectivity, while switching to Cu(tfacac)₂ led to significant improvement in both the reaction rate and product ratio. The rearrangement proceeded even more rapidly, while maintaining excellent selectivity, when the more electrophilic Cu(hfacac)₂ was used as the catalyst. Further improvements to selectivity were achieved through the use of a lower catalyst loading (entry 9). In a comparison of copper(II) and copper(I) catalysts (entries 8–10), copper(II) was significantly faster at obtaining similar product ratios.

In an effort to develop new catalysts for the rearrangement with more steric and electronic tuning opportunities, dibenzoylmethane and 2-acetylcyclohexanone were explored as acac surrogates. Each parent and fluorinated catalyst was successful in rearranging vinyl oxirane **5** to 2,5-dihydrofuran **6** (entries 11–14). Additionally, a more functionalized version of Cu(tfacac)₂ was shown to be equally successful in rearranging **5** (entry 15). In agreement with our earlier observations, the more electrophilic catalysts (entries 12 and 14) were both faster and more selective than the parent catalyst (entries 11 and 13).

Table 2. 2,5-Dihydrofuran Synthesis^a

entry	substrate	product	mol %	time (h)	DHF: Ald/Ket	yield
1			0.5	2	17:1	94%
2			0.5	2	5:1	59%
3			5 ^b	2	16:1	86%
4			1	20	3:1	60%
5			1	1	10:1	88%
6			5	48	>20:1	92%
7			5	0.25	>20:1	95%
8			0.5	2	13:1	93% ^c
9			5	2	>20:1	97%
10			5	24	10:1	91% ^c
11			5	4	>20:1	72%

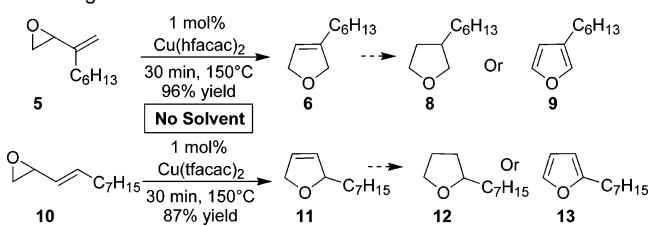
^a Reactions are performed in a sealed tube in toluene at 150 °C with Cu(hfacac)₂ at the specified loading. ^b Cu(tfacac)₂ is the catalyst. ^c Volatile compound; yield based on molar ratios from NMR integration.

The synthetic utility of this copper-catalyzed rearrangement was explored using a series of monosubstituted vinyl oxiranes (Table 2). Vinyl oxiranes substituted at the 2- or 3-position rearranged efficiently to form 3-substituted 2,5-dihydrofurans (entries 1, 2, and 5), while 1- and 4-substituted vinyl oxiranes (entries 3 and 4) rearranged to form 2-substituted 2,5-dihydrofurans. These results illustrate an important synthetic aspect of this rearrangement where each dihydrofuran product can originate from at least two regioisomeric vinyl oxiranes or even from their mixture.

Next, various disubstituted vinyl oxiranes were evaluated (Table 2, entries 6–11), and these studies revealed that 1,1-, 1,3-, 1,4-, and 2,3-substitutions on the vinyl oxiranes were well tolerated. The difference in the regioisomeric and sterically encumbered substrates of entries 6 and 7 is particularly interesting. The 1,1-disubstituted vinyl oxirane (entry 6) rearranged slowly to a 2,5-dihydrofuran, while the 4,4-disubstituted vinyl oxirane (entry 7) rapidly formed aldehyde. Within these studies, we have explored cyclic diene monoepoxides (Table 2, entries 10 and 11) and found that both cycloheptadiene (entry 10) and cyclooctadiene (entry 11) monoepoxides rearranged readily to their respective oxabicyclic products.

With a vision toward the development of a greener and more practical variant of the rearrangement, we have successfully rearranged oxiranes **5** and **10** in the absence of solvent while maintaining a high 2,5-dihydrofuran selectivity (Scheme 2). This may prove useful for the industrial production of 3-methyltetrahydrofuran¹⁰ and 2-methyltetrahydrofuran¹¹ via a highly atom economical route commencing from a mixture of the monoepoxides of isoprene and piperylene. Unlike current synthetic approaches, no unnecessary hydroxyl or carbonyl functionalities would need to be reduced, thus eliminating challenging separations of products from alcohol and/or water byproducts.

In summary, we have developed conditions for the use of copper(II) complexes to catalyze the rearrangement of vinyl oxiranes to 2,5-dihydrofurans. This method is attractive because it uses low catalyst loadings, has good tolerance of substitution patterns, and

Scheme 2. Neat Copper-Catalyzed Vinyl Oxirane Rearrangements¹²

can be done in the absence of solvent. Further studies on the scope, limitations, and mechanism of this rearrangement are currently underway.

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Supporting Information Available: Full experimental details and physical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) For control experiments and a complete list of catalyst systems explored, see Supporting Information.
- (9) acac = acetylacetonate, tfacac = trifluoroacetylacetonate, hfacac = hexafluoroacetylacetonate, BTMSA = bis(trimethylsilyl)acetylene, dbm = dibenzoylmethane, ptfm = 1,3-bis(4-fluoromethyl)phenyl]-1,3-propanedionate, accy = 2-acetylcyclohexanone, tfacy = 2-trifluoroacetylcyclohexanone, and fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate.
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