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Catalytic Ring Expansion of Vinyl Oxetanes: Asymmetric Synthesis of Dihydropyrans Using Chiral Counterion Catalysis**

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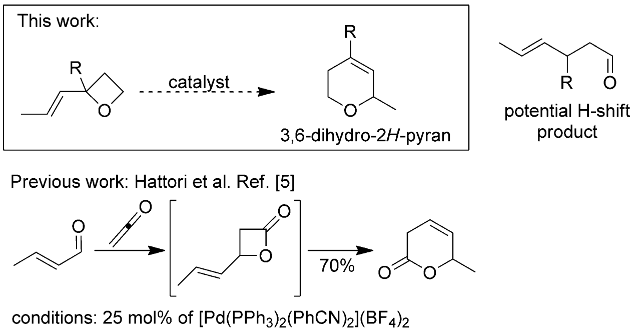
As a part of our program aimed at developing new ring-expansion reactions from strained heterocyclic precursors[1] we are exploring vinyl oxetanes as potential candidates. We were particularly eager to learn if our success with the ring expansion of vinyl oxiranes to 2,5-dihydrofurans using [Cu(hfacac)$_2$] could be translated into an equivalent transformation for vinyl oxetanes (Scheme 1). Given the allylic nature of the system and the favorable release of strain energy, vinyl oxetanes seemed like perfect ring-expansion candidates. Furthermore, we predicted that a broader range of catalysts would be competent for this new ring-expansion reaction because the competing 1,2-hydride shift pathway we needed to overcome for the vinyl oxirane ring expansion is less likely to occur for the vinyl oxetanes.

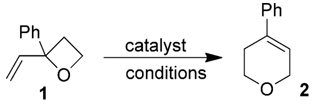


Scheme 1. Proposed catalytic ring expansion of vinyl oxetanes.

In general, vinyl oxetanes have received limited attention, where the few published studies have focused on nucleophilic ring openings[2] of vinyl oxetanes and insertions of heteroatoms[3] into the oxetane.[4] There is only one report in the literature of a related lactonic vinyl oxetane ring expansion (Scheme 1). In 2000, when trying to expand the scope of their cationic-palladium-mediated β-lactone synthesis to include conjugated aldehydes Hattori et al. realized that in many cases δ-lactones were formed.[5] The scope and yield of their cascade reaction, which was developed using classic palladium chemistry and relies on a superior leaving group to that in our ether ring expansion, was reasonable but limited to a few enals; enones were found to be poor substrates.

We selected vinyl oxetane **1** as our model substrate. It is readily accessible by a nucleophilic addition to a commercially available β-chloro carbonyl precursor[6] and it has a phenyl group that we postulated would aid oxetane bond breaking and stabilization of a cationic intermediate. When **1** was subjected to the standard catalytic [Cu(hfacac)$_2$] conditions we used for the vinyl oxiranes,[1a] ring expansion to 3,6-dihydro-2*H*-pyran **2** did indeed occur after prolonged heating at 150 °C, albeit in poor yield (Table 1, entry 1). The detrimental hydride shift pathway is presumably a far less likely competing path for vinyl oxetanes than vinyl oxiranes, therefore we decided to evaluate other stable readily available catalysts. Metal(II) triflates were the most effective catalysts and dichloromethane the best solvent. Copper(II) triflate (Table 1, entries 5–7) proved to be a remarkably well-suited catalyst for the ring expansion, thus affording the desired product (**2**) both rapidly and quantitatively using only 1 mol% of catalyst at −78 °C. These results prompted us to

Table 1: Catalyst screening for vinyl oxetane ring expansion.



Entry	Catalyst	mol%	Solvent	*T* [°C]	*t* [h]	% Conv.
1	[Cu(hfacac)$_2$]	5	toluene	150	5	15
2	Cu(OAc)$_2$	5	THF	RT	10	0
3	Cu(TFA)$_2$	5	THF	RT	10	0
4	CuI	5	THF	RT	10	0
5	Cu(OTf)$_2$	5	THF	RT	2.5	99
6	Cu(OTf)$_2$	5	CH_2Cl_2	RT	0.05	99
7	Cu(OTf)$_2$	1	CH_2Cl_2	−78	0.5	99
8	[Pd(hfacac)$_2$]	5	THF	RT	10	15
9	[PdCl$_2$(CH$_3$CN)$_2$]	5	THF	RT	10	56
10	[Ni(hfacac)$_2$]	5	THF	RT	10	0
11	[Zn(hfacac)$_2$]	5	THF	RT	10	0
12	Mg(OTf)$_2$	1	CH_2Cl_2	−78	0.5	0
13	Ni(OTf)$_2$	1	CH_2Cl_2	−78	0.5	15
14	Zn(OTf)$_2$	1	CH_2Cl_2	−78	0.5	35
15	Bi(OTf)$_2$	1	CH_2Cl_2	−78	0.5	88
16	TfOH	1	CH_2Cl_2	−78	0.5	99
17	*p*-TsOH	10	CH_2Cl_2	−78	5	63
18	TFA	10	CH_2Cl_2	−78	5	17
19	AcOH	10	CH_2Cl_2	−78	5	0
20	(EtO)$_2$P=O(OH)	10	CH_2Cl_2	−78	72	67

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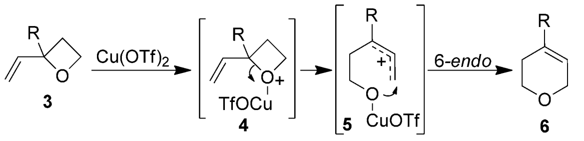
also evaluate Bronsted acids as catalysts (Table 1, entries 16–20). Within this series triflic acid (Table 1, entry 16) is an outstanding catalyst. Thus, we investigated to see if the catalytic activity of the metal triflates was due to the presence of trace amounts of triflic acid. When **1** was treated with $Cu(OTf)_2$ in the presence of an excess amount of 2,6-di-butyl pyridine the reaction proceeded with good conversion even though triflic acid catalysis was completely inhibited. This result suggests that the metal triflates are indeed operating as Lewis acid catalysts.

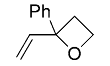
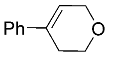
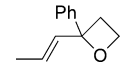
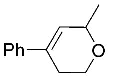
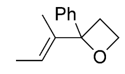
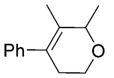
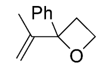
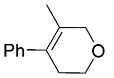
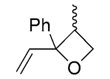
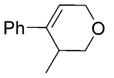
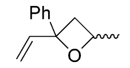
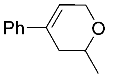
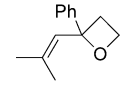
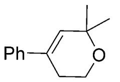
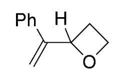
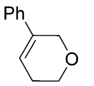
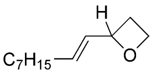
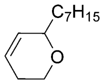
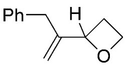
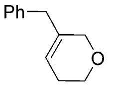
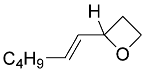
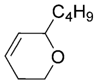
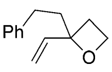
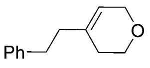
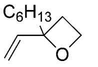
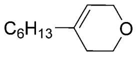
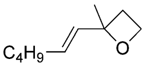
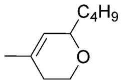
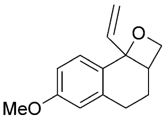
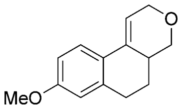
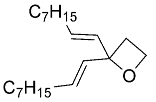
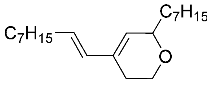
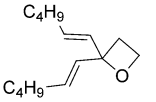
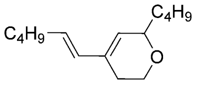
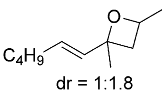
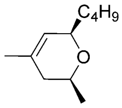
Encouraged by the mild catalytic reaction conditions detailed above, we set out to evaluate the scope of this new catalytic ring-expansion reaction. The results are presented in Table 2. The substrates shown were treated with 1 mol% of $Cu(OTf)_2$ in dichloromethane at −78 °C. As is evident from these seventeen examples, the ring expansion proceeds rapidly in uniformly excellent yields regardless of whether there is a cation-stabilizing group at the oxetane allylic carbon (phenyl or vinyl; Table 2, entries 1–7 and 15–17) or not (alkyl or H; Table 2, entries 8–14 and 18). All of the vinyl oxetane substitution patterns we have tried to date seem to be accommodated in this mild new catalytic ring-expansion reaction.

The fact that both Lewis and Bronsted acids are capable of catalyzing the ring expansion of vinyl oxetanes (**3**; Scheme 2) strongly suggests that the reaction proceeds through an allylic cation (**5**), which is then captured in a 6-*endo* fashion (**6**) by the oxygen atom. This mechanistic hypothesis and the fact that Bronsted acids are also competent catalysts (Table 1, entries 16–20) presented to us an opportunity to explore the use of chiral counterions.[7] Highly strained substrates are perfect for such studies as all the atoms in the precursor are present in the product. Thus there is no formation of byproducts that could hinder the chiral counterion pair.[8] We wondered if chiral catalysts could be used for the desymmetrization of divinyl oxetanes (Scheme 3). For this desymmetrization to succeed, the metal or the Bronsted acid counterion would have to be closely associated with either the oxygen atom or the allyl cation during the cyclization.



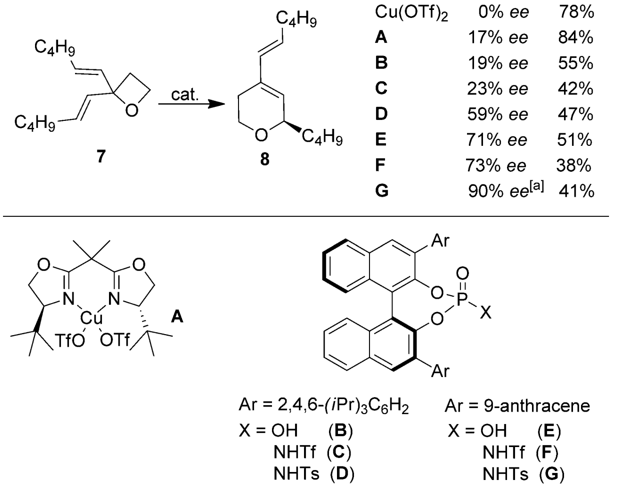
Scheme 2. Mechanistic hypothesis.

Table 2: $Cu(OTf)_2$ catalyzed vinyl oxetane ring expansion.

Entry	Substrate	Product	Yield [%]
1			95
2			91
3			89
4			93
5			87
6			92
7			98
8			91
9			93
10			90
11			83
12			96
13			78
14			93
15			96
16			86
17			78
18	 dr = 1:1.8		92

Reaction conditions: 1 mol% of $Cu(OTf)_2$, CH_2Cl_2, −78 °C, 30 min. Yields shown are of the isolated products.

Pleasingly, such desymmetrizations are indeed possible. We first evaluated a chiral variant of our copper catalyst (Scheme 3). Evans-type copper catalyst **A**[9] catalyzed the ring expansion of divinyl oxetane **7** to form **8** as fast and efficiently as $Cu(OTf)_2$, but the enantioselectivity observed was poor. Although this result was a gratifying proof of principle, we were convinced that the less-reactive Bronsted acids that we had shown in Table 1 to be competent catalysts, had a better chance of producing highly enantioenriched products. Many interesting chiral organic acids have been used for various catalytic tasks in recent years.[10] We concluded that chiral phosphoric acids might be well suited for this challenging desymmetrization.[11] Therefore we synthesized and evaluated



$Cu(OTf)_2$	0% *ee*	78%
A	17% *ee*	84%
B	19% *ee*	55%
C	23% *ee*	42%
D	59% *ee*	47%
E	71% *ee*	51%
F	73% *ee*	38%
G	90% *ee*[a]	41%

Scheme 3. Catalytic asymmetric desymmetrization. Reaction conditions: 5 mol% of $Cu(OTf)_2$ and **A** in CH_2Cl_2, −78 °C, 30 min, while 10 mol% of **B**–**G** in toluene, RT for 100 h. [a] 10 °C.

chiral phosphoric acids **B**–**G**.[12] Phosphoric acid (**B**) was the least successful catalyst. Triflamides (**C**) and sulfonamides (**D**) were identified as lead candidates. Changing the bulky *ortho* substituent on the binol core from 2,4,6-triisopropylphenyl to 9-anthracene further improved the selectivity, thus providing 3,6-dihydro-2*H*-pyran **8** with *ee* values as high as 90%.[13] By using a reliable asymmetric synthetic approach[14] we have unambiguously determined that when the *S* enantiomers of **B**–**G** are used the absolute stereochemistry of the major enantiomer of **8** is of the *R* configuration (as shown).[15] Although longer reaction times and higher reaction temperatures are needed when these chiral Bronsted acids are used to catalyze the vinyl oxetane ring expansion,[16] the *ee* values are superior and very encouraging for this challenging system.[17]

In summary, we have developed the first catalytic ring-expansion reaction of vinyl oxetanes. The reaction conditions are mild, the substrate scope is very broad, and yields are uniformly excellent. Furthermore, we have demonstrated that a symmetric divinyl oxetane can be desymmetrized to form highly enantioenriched 3,6-dihydro-2*H*-pyran products. Current efforts are focused on exploring the full potential[18] of this chiral counterion catalysis approach and extending it to other ring-expansion classes.[19]

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Keywords: homogeneous catalysis · chiral counterions · copper · ring expansion · vinyl oxetanes

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[6] a) K. Lucas, P. Weyerstahl, H. Marschall, F. Nerdel, *Chem. Ber.* **1971**, *104*, 3607–3616; b) B. Mudryk, T. Cohen, *J. Am. Chem. Soc.* **1993**, *115*, 3855–3865. Alternatively, we have found that appropriately substituted 1,3-diols can also serve as excellent oxetane precursors.

[7] For recent examples of chiral counterion, see: a) J. Lacour, V. Hebbe-Viton, *Chem. Soc. Rev.* **2003**, *32*, 373–382; b) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499; c) S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336–11337; d) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027–7030; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903–6906; e) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199; f) G. L. Hamilton, T. Kanai, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 14984–14986; g) X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 1135–1138; *Angew. Chem. Int. Ed.* **2008**, *47*, 1119–1122; h) G. Jiang, R. Halder, Y. Fang, B. List, *Angew. Chem.* **2011**, *123*, 9926–9929; *Angew. Chem. Int. Ed.* **2011**, *50*, 9752–9755.

[8] We were encouraged by a recent report from the Rueping research group that demonstrated that such dienyl cations (in his case, aryl and vinyl) could be converted into highly enantioenriched products: M. Rueping, U. Uria, M.-Y Lin, L. Atodiersei, *J. Am. Chem. Soc.* **2011**, *133*, 3732–3735. In this example, water needs first to be extruded to form the carbocation, which is then captured by a phenol group in a 6-*endo* fashion. Interestingly, our preliminary studies show that the divinyl 1,3-diol precursor that is used to synthesize oxetane **7** does not form **8** even after exposure to chiral phosphoric acids for days.

[9] a) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726–728; b) E. J. Corey, N. Imai, H.-Y. Zhang, *J. Am. Chem. Soc.* **1991**, *113*, 728–729.

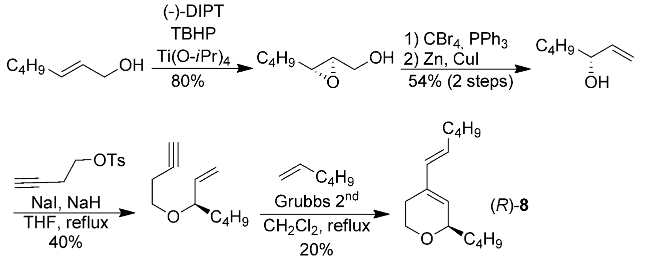
[10] A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.

[11] a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; b) M. Rueping, B. J. Nachtsheim, W. Leawsuwan, I. Atodiresei, *Angew. Chem.* **2011**, *123*, 6838–6853; *Angew. Chem. Int. Ed.* **2011**, *50*, 6706–6720.

[12] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592–1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; b) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626–9627.

[13] Because of Rueping's recent success (Ref. [8]) in using chiral phosphoric acids containing partially reduced binol backbones we also synthesized those variants of **E**, **F**, and **G** following his procedure: M. Rueping, B. J. Nachtsheim, R. M. Koenigs, W. Leawsuwan, *Chem. Eur. J.* **2010**, *16*, 13116–13126. These catalysts afforded **8** with *ee* values that were similar but not superior to those obtained when using **G**.

[14] (*R*)-**8** was synthesized from an allylic alcohol using the Sharpless asymmetric epoxidation in combination with ene-yne cross-metathesis as the key steps.



[15] This stereochemical outcome seems to be in agreement with a recently proposed model by Rueping and co-workers, see Ref. [8].

[16] For the current collection of Bronsted acids we have studied, yields are still generally lower than for the copper-catalyzed approach. We have not been able to characterize other products the pentadienyl cation forms when Bronsted acid catalysts are used.

[17] Our survey of literature referring to the chiral Bronsted acid catalysis suggests that this might be the first example of an ether-ring-expansion reaction.

[18] Following recommendations by the reviewers, I am pleased to report that the incredible chiral counterion results obtained for oxetane **7** translate to other substrates. For example, unoptimized ring expansions of oxetanes of entries 14 and 16 (Table 2) with chiral phosphoric acid **G** afforded the resulting dihydropyran products in 75% *ee* (68% yield) and 87% *ee* (53% yield), respectively.

[19] Interestingly, in a preliminary study we have learned that the 1,1-divinyl oxirane homologues of divinyl oxetane 7 do indeed form the desired pentadienyl cation but do not cyclize to form a chiral 2,5-dihydrofuran product and instead follow a facile Nazarov cyclization pathway.