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Intermolecular Oxonium Ylide Mediated Synthesis of Medium-Sized Oxacycles

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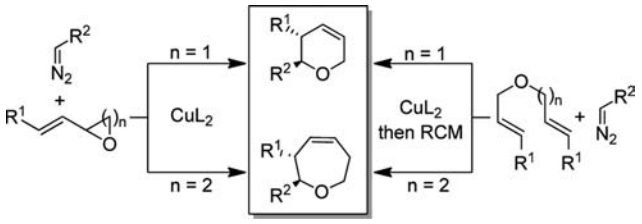
ABSTRACT



Detailed in this account are our efforts toward efficient oxacycle syntheses. Two complementary approaches are discussed, with both employing chemoselective allyl ether activation and rearrangement as the key step. Vinyl substituted oxiranes and oxetanes provide a single step access to dihydropyrans and tetrahydrooxepines. Oxiranes proved to be poor substrates, while oxetanes were slightly better. An alternative approach using substituted allyl ethers proved successful and addressed the limitations encountered in the ring expansions.

The formation and rearrangement of allyl ether oxonium ylides has been investigated over the past four decades by several research groups.[1] These types of oxonium ylides are usually generated by decomposing a diazo precursor to a reactive metallocarbenoid, which then reacts with the lone pairs of the allylic ether to form the requisite oxonium ylide. Depending on the substrate, this intermediate then undergoes either a [2,3]-rearrangement or a [1,2]-alkyl shift. The majority of these studies are intramolecular.[2] The more challenging intermolecular variant has received far less attention.[3] In these handful of studies, diastereoselectivity is moderate at best and competing cyclopropanation and carbenoid dimerizations pathways commonly interfere. Only a few intermolecular asymmetric allyl ether activation studies have been reported. These used rhodium catalysts and were limited by either low yield or poor enantioselectivity.[4]

It was our original intention to develop a method for the ring expansion of small vinylic oxacycles to larger oxacycles via an oxonium ylide mediated [2,3] sigmatropic ring expansion. Specifically, a vinyl-oxirane, oxetane, or tetrahydrofuran precursors would undergo the ring expansion to form dihydropyran, tetrahydrooxepine, or tetrahydrooxocine

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(1) (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919–939. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons, Inc.: New York, 1998.

(2) (a) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060–6062. (b) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062–6063. (c) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817–824. (d) Doyle, M. P.; Peterson, C. S. *Tetrahedron Lett.* **1997**, *38*, 5265–5268. (e) Clark, J. S.; Bate, A. L.; Grinter, T. *Chem. Commun.* **2001**, 459–460. (f) Marmsaeter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144–5145.

(3) (a) Kirmse, W.; Kapps, M. *Chem. Ber.* **1968**, *101*, 994–1003. (b) Ando, W.; Kondo, S.; Nakayama, K.; Ichibori, K.; Kohoda, H.; Yamato, H.; Imai, I.; Nakaido, S.; Migita., T. *J. Am. Chem. Soc.* **1972**, *94*, 3870–3876. (c) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917–1925. (d) Doyle, M. P.; Bagheri, V.; Harn, N. K. *Tetrahedron Lett.* **1988**, *29*, 5119–5122. (e) Doyle, M. P.; Hu, W. *J. Org. Chem.* **2000**, *65*, 8839–8847.

(4) (a) Pierson, N.; Fernandez-Garcia, C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705–4708. (b) Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A. *Tetrahedron Lett.* **1998**, *39*, 97–100. (c) Doyle, M. P.; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 7653–7654. (d) Hodgson, D. M.; Petroliagi, M. *Tetrahedron: Asymmetry* **2001**, *12*, 877–881. (e) Kitagaki, S.; Yanamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361–6364. (f) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594–4595.

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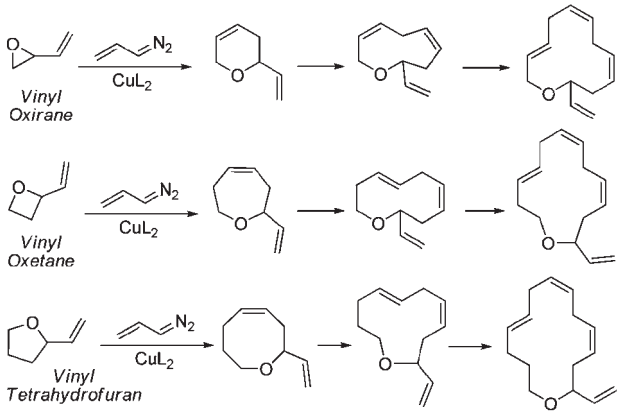
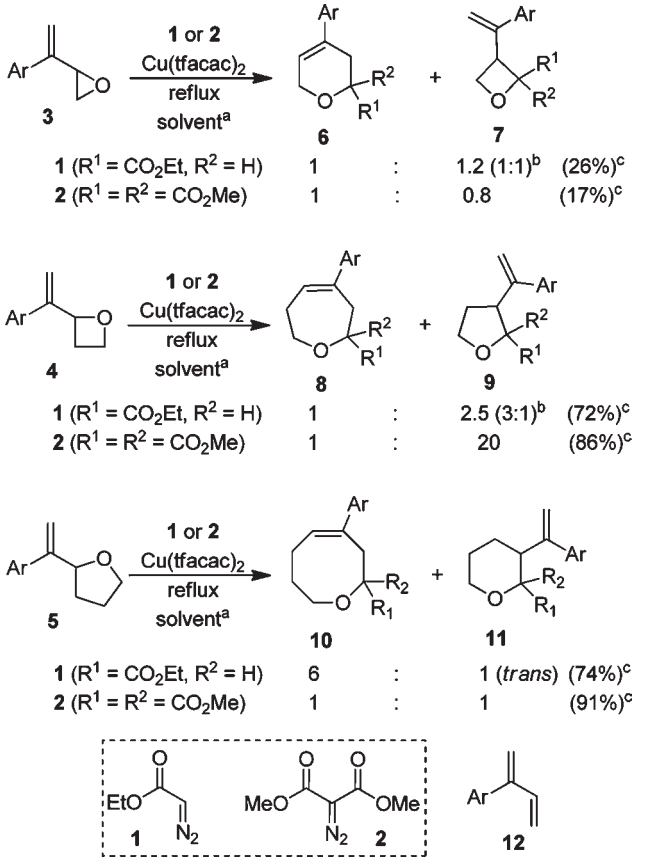
products respectively upon treatment with a metal carbenoid (Scheme 1). If a vinyl diazo compound was used, the resulting product would have an ethereal oxygen in an allylic relationship with the newly formed olefin, which would make it poised to undergo a second ring expansion. In the ideal scenario, by continuously adding vinyl carbenoids, these products could continue to ring expand three carbon atoms at a time. For a vinyl oxirane, the ring expansion sequence would proceed to a six, nine, and twelve membered ring (3→6→9→12) or beyond. Similarly, vinyl oxetane and 2-vinyl tetrahydrofuran substrates would initiate a 4→7→10→13 and 5→8→11→14 ring expansion sequence respectively.[5]

Scheme 1. Copper Mediated Iterative Ring Expansions



We began our investigations by studying 3-tolylvinyl oxirane (**3**, Scheme 2). We chose ethyl diazoacetate (**1**) and diazo malonate (**2**) as the carbenoid precursors and copper(II) trifluoroacetylacetonate as the catalyst. Intramolecular ylide examples suggested that copper catalysts would be well matched for this task.[2e,f] When **3** was subjected to conditions favoring oxonium ylide formation, three products were isolated (**6**, **7**, and **12**). The major product was that of the epoxide deoxygenation pathway (**12**).[6] Other products were determined to be that of a [1,2]-insertion (**7**) and a [2,3]-sigmatropic (**6**) rearrangement respectively. Screening of a variety of reaction variables, including temperature, solvent, catalyst, and diazo structures, did not offer improvements.[7] Despite the lack of success in ring expanding vinyl oxirane **3**, we were encouraged that all three products originated from the desired oxonium ylide intermediate. Furthermore, the vinyl-oxetane (**4**) and tetrahydrofuran (**5**) substrates would not be expected to have to battle the detrimental deoxygenation pathway. Gratifyingly, when **4** and **5** were subjected to the same reaction conditions the observed products were only that of the [1,2]-insertion (**9** and **11**) and the desired [2,3]-ring expansion (**8** and **10**). Although overall yields of ylide products were high the product distribution varied significantly depending on what combination of diazo compounds and substrates were used. For example when diazomalonate (**2**) was used, the [1,2]-insertion path predominated when it was reacted with oxetane **4**, while no ylide selectivity was observed for tetrahydrofuran **5**. In contrast, when ethyldiazoacetate (**1**) was employed as a carbene precursor, the desired [2,3]-ring expansion path was favored for vinyl-tetrahydrofuran **5** while it was not selective for oxetane **4**.

Scheme 2. Ring Expansion of Small Cyclic Ethers[a]



[a] 5 mol % catalyst, diazo compounds **1** (5 equiv) and **2** (1.2 equiv) were added via syringe pump over 12 h. Ar = 4-MePh for oxirane **3**, while Ar = Ph for oxetane **4** and tetrahydrofuran **5**: (a) CH_2Cl_2 was used as solvent for ethyl diazoacetate **1** while 1,2-dichloroethane was used for dimethyl diazomalonate **2**, (b) diastereomer ratio (*trans*:*cis*), (c) isolated yield of oxonium ylide products (**6**+**7**, **8**+**9**, and **10**+**11**),

While vinyl oxetane **4** and tetrahydrofuran **5** were shown to be good substrates for the ylide mediated ring expansion, vinyl oxirane **3** could not be rescued from the deoxygenation pathway. We wondered if these tetrahydropyran products (**13**, Scheme 3) could be accessed using an alternate copper carbenoid ylide/[2,3]-rearrangement approach. We hypothesized that symmetrical diallyl ethers (**14**) could be desymmetrized using copper carbenoids and

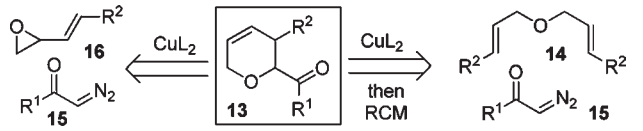
(5) Vedejs and co-workers have demonstrated success with an analogous reaction sequence for sulfur containing heterocycles. Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358–364.

(6) Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 215–254.

(7) There was a single prior precedence prior to our work. Kirmse and coworkers had shown for butadiene monoxide that 5,6-dihydro-2*H*-pyran could be accessed in 7% yield using copper iodide: (a) Kapps, M.; Kirmse, W. *Angew. Chem., Int. Ed.* **1969**, *8*, 75–75. Quinn and coworkers ran into similar challenges and nicely demonstrated that *trans*-divinyl epoxides are one class of substrates that can overcome this problem: (b) Quinn, K. J.; Biddkick, N. A.; DeChristopher, B. A. *Tetrahedron Lett.* **2006**, *47*, 7281–7283.

that the resulting products could be cyclized in the presence of ruthenium carbenes to **13** in the same pot. The structural simplicity of the starting materials, ease of synthesis, and the extension of this strategy to larger heterocycles and other useful motifs by using alternate etheral substituents was an attractive feature to this new approach.

Scheme 3. Revised Oxonium Ylide Retrosynthesis

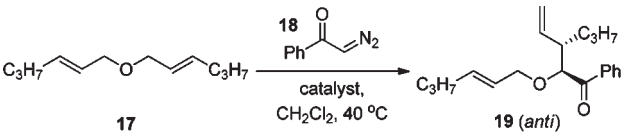


In the 1980s, Doyle and co-workers evaluated the activation and [2,3]-rearrangements of methyl allyl ethers using rhodium carbenoids.[3d] They demonstrated that the [2,3]-sigmatropic rearrangement occurred preferentially. Since the stereoselectivity did not change when other rhodium catalysts were used, they proposed a free oxonium ylide. A few years later, Doyle showed that chiral rhodium catalysts could indeed induce asymmetry for this reaction.[4c] This limited success came at the expense of worse chemoselectivity and yield. No signifcant advancement has been made since then, and copper has not been investigated for this specific allyl ether reaction challenge.

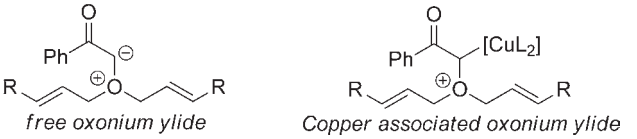
We were eager to learn if readily available and stable copper(II) catalysts could be used to chemoselectively form oxonium ylides using substituted allyl ethers (**14**). Diallyl ether **17** was subjected to a range of copper(II) catalysts in the presence of diazo acetophenone **18**[8] (Scheme 4). We were delighted to learn that the reactions are indeed oxonium ylide selective and that the competing [1,2]-insertion and cyclopropanation pathways are easily suppressed.[9] Our results suggest that $Cu(tfacac)_2$ and $Cu(FOD)_2$ are superior to all other catalysts tried with respect to both reaction efficiency and diastereoselectivity (entries 1−2), favoring *anti* isomer **19**. We were encouraged to learn that the six different copper(II) acetylacetonate based catalysts varied significantly with respect to both yields and stereoselectivity. These catalyst dependent fluctuations in diastereoselectivity[10] are strongly suggestive of a metal associated oxonium ylide being involved in the rearrangement part of the reaction, which bodes well for developments of an asymmetric variant of this reaction.

Our attention next turned to the ring closing metathesis of diene **19** and the process of optimizing this reaction for a one-pot operation. Cyclization to form dihydropyran **20** was quick and efficient (95%). The one-pot procedure simply involved a slight dilution of the reaction mixture following completion of the [2,3]-rearrangement, prior to

Scheme 4. Activation and Rearrangement of Diallyl Ether **17**



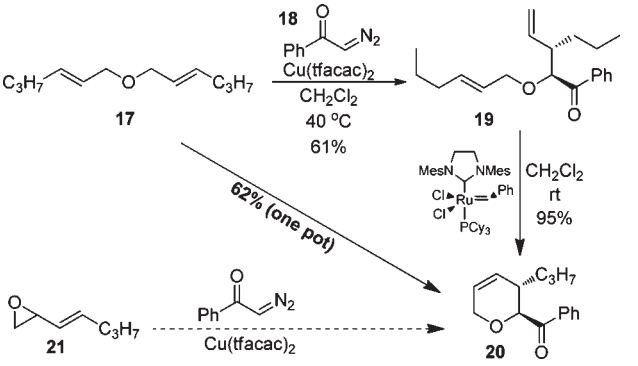
entry	catalyst[a]	yield[b]	*anti*:*syn*
1	**$Cu(FOD)_2$**	**74**	**11:1**
2	**$Cu(tfacac)_2$**	**61**	**14:1**
3	$Cu(hfacac)_2$	48	2:1
4	$Cu(acac)_2$	32	5:1
5	$Cu(dbm)_2$	28	4:1
6	$Cu(ptfm)_2$	21	3:1
7	$Rh_2(OAc)_4$	30	4:1
8	$Rh_2(esp)_2$	12	3:1
9	$Rh_2(S\text{-}DOSP)_4$	23	5:1



[a] 5 mol % catalyst and 5 equiv of **18** were added slowly via syringe pump over 12 h.[11] [b] Isolated yields.

addition of a Grubbs second generation catalyst.[12] Using this one-pot procedure, dihydropyran **20** was obtained in 62% yield (Scheme 5). This new one-pot synthetic approach represents a solution to the vinyl oxirane ring expansion problem (**21** → **20**) we encountered in Scheme 2.

Scheme 5. A New Two-Step Approach to Substituted Pyrans[a]



[a] 5 mol % $Cu(tfacac)_2$ and 5 equiv of **18** were added over 12 h.

Following the success in forming **20** we sought to expand this approach to unsymmetrical allyl ethers containing useful functional group handles. For this strategy to succeed

(8) We chose to use diazoacetophenone **18** for diallyl ether substrate **17** as we found the resulting products easier to separate and purify. Excess amount of **18** is needed to ensure full conversion of starting material.

(9) When the olefin terminus is not substituted, cyclopropanation becomes a competing pathway resulting in around 10−25% of cyclopropantated products.

(10) Treatment of the pure product (**19**) with an inferior catalyst such as $Cu(hfacac)_2$ does not result in any observable epimerization.

(11) Catalyst ligand abbreviations: dbm = dibenzoylmethane, ptfm = *p*-bis(trifluoromethyl) dibenzoylmethane, FOD = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,4-octanedienoate, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, *S*-DOSP = 1-[[4-alkyl-(C11-C13)phenyl]sulfonyl]-(2*S*)-pyrrolidinecarboxylate.

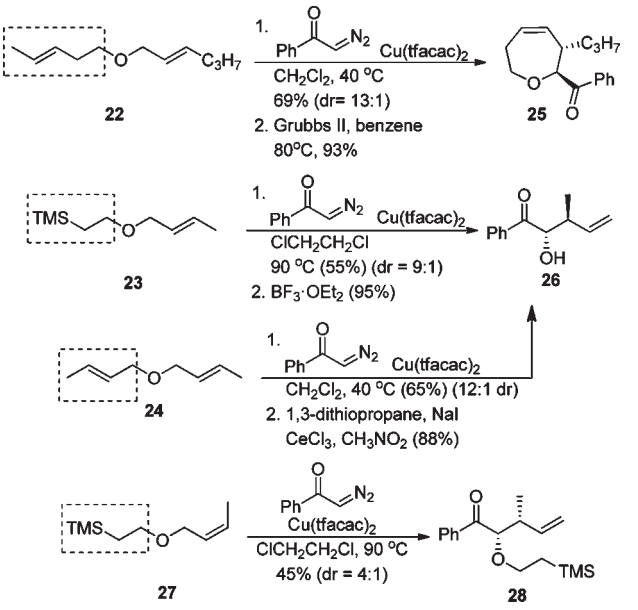
(12) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

the nonallylic group cannot contain a competing ylide functional group or crowd the etheral oxygen so as to preclude productive coordination with the copper carbenoid. Toward that end, we first studied the rearrangement of allyl ether **22** (Scheme 6). Combining the rearrangement of **22** with ring closing metathesis would serve as a complementary route to the vinyl oxetane ring expansion approach. Gratifyingly, **22** underwent the [2,3]-rearrangement in high yield and similar selectivity to the diallyl substrate.[13] Ring closing metathesis of the product afforded the desired tetrahydrooxepine substrate (**25**) in excellent yield.

Thinking about the products of this reaction more like protected aldol products than cyclization precursors, we wondered what protecting group would be a good match for this oxonium ylide mediated approach. We argued that groups like TMS-ethyl would be perfect protecting group candidates because of their small size, lack of competing heteroatoms or double bonds, and easy removal. Toward that end, allylic ether **23** was made from 2-(trimethylsilyl)-1-ethanol. Activation and rearrangement of this substrate (**23**) were efficient and highly selective. The protecting group was removed using $BF_3 \cdot OEt_2$, thus affording hydroxyketone **26**.[14] A testament to the flexibility of this approach, symmetrical allyl ether **24** can also be used to access **26** by using an alternate deprotection step.[15] Finally, by employing a *Z*-allyl ether substrate (**27**), *syn* products like **28** can be selectively formed.

In summary, we have reported a chemoselective intermolecular activation and [2,3]-rearrangement of cyclic and acyclic allyl ethers using commercially available copper(II) catalysts. The challenges encountered using the ring expansion approach we have shown can be solved by using acyclic allyl ether precursors and subjecting them to a one-pot approach involving ylide formation, rearrangement, and cyclization. The fact that a range of functionalized allyl ethers are compatible with this strategy means that this approach can be adapted by choosing the correct allyl capping group to suit a vast range of synthetic tasks.

Scheme 6. Beyond Allyl: Other Etheral Functional Groups[a]



[a] 5 mol % $Cu(tfacac)_2$ were used for all four substrates, and 5 equiv of **18** were added slowly via syringe pump over 12 h.

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

(13) No cyclopropanation products were isolated.

(14) Enders, D.; Backhaus, D.; Runsink, J. The minor (*syn*) diastereomer of **26** perfectly matches a product previously made by Enders. *Tetrahedron* **1996**, *52*, 1503–1528.

(15) Bartoli, G; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Marcantoni, E.; Procopio, A. *Synlett* **2001**, 1897–1900.