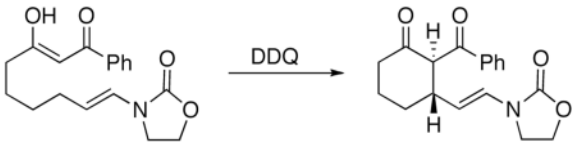
Published in final edited form as:
Org Lett. 2009 July 16; 11(14): 3152–3155. doi:10.1021/ol901188q.

Cyclization Reactions through DDQ-Mediated Vinyl Oxazolidinone Oxidation

Lei Liu and **Paul E. Floreancig***
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Abstract



Vinyl oxazolidinones react with DDQ to form α,β-unsaturated acyliminium ions in a new method for forming electrophiles under oxidative conditions. Appended nucleophiles undergo 1,4-addition reactions with these intermediates to form cyclic vinyl oxazolidinones with good levels of diastereocontrol, highlighting a new approach to utilizing oxidative carbon–hydrogen bond functionalization to increase molecular complexity.

Converting carbon–hydrogen bonds to functional groups through oxidative transformations provides excellent opportunities for increasing molecular complexity from readily accessible substrates,[1] and efforts toward expanding the scope of these processes are well warranted. We recently reported[2] that benzylic and allylic ethers are oxidized by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to form oxocarbenium ion intermediates that react with appended nucleophiles in an efficient cyclization process. The oxidative cation formation appears to proceed (Scheme 1) through a sequence of radical cation formation followed by hydrogen atom abstraction. Based on this hypothesis we proposed an alternative entry to unsaturated carbocations that proceeds from vinyl ethers or amides. This approach benefits from improved access to radical cation intermediates because of the lower oxidation potentials of heteroatom-substituted alkenes relative to allylic ethers.[3]

Vinyl oxazolidinones have recently become an increasingly well-studied structural family.[4] These compounds are easily prepared from oxazolidinones through direct condensation reactions with aldehydes,[5] cross coupling reactions,[6] and metal mediated additions across alkynes.[7] Vinyl oxazolidinones are electron rich alkenes and react readily with electron deficient reagents such as oxidants,[8] dihalides,[9] metallocarbenes,[4,10] and dicarbonyl compounds.[11] The facile access and electron wealth of these compounds suggested that they would be excellent precursors to α,β-unsaturated acyliminium ions upon oxidative carbon–hydrogen bond activation.[12] In this manuscript we demonstrate that vinyl oxazolidinones react readily with DDQ to form electrophiles that undergo 1,4-addition reactions with appended nucleophiles to form cyclohexane structures. The reactions proceed with good levels of diastereocontrol when tertiary carbons are formed. 1,3-Diketones can be used directly as nucleophiles in this process, obviating the need to preform the nucleophile.

florean@pitt.edu.

Supporting Information Available Schemes for substrate preparations, cyclization protocols, and complete characterization data for all substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

We chose to utilize the hydroxyl group as a nucleophile in initial studies (Scheme 2). Branching was alsoincorporated at the allylic position of the vinyl oxazolidinone to prevent product oxidation. Exposing **1** to DDQ in 1,2-dichloroethane (DCE) resulted in the formation of tetrahydropyran **3** in 98% yield after 20 min. This process proceeded through the formation of α,β-unsaturated acyliminium ion **2** followed by an intramolecular 1,4-addition reaction. Secondary alcohol **4** cyclized to form tetrahydropyran **5** at −30 °C in 85% yield with modest diastereocontrol as expected based on the steric similarity between methyl and vinyl groups. Diastereocontrol was somewhat higher when this reaction was conducted in toluene rather than dichloroethane.

Our initial studies in applying this approach for carbon–carbon bond formation focused on the use of enol acetate nucleophiles. These easily handled and readily accessible moities are excellent latent enolates in reactions that proceed through oxidatively-generated carbocations.[13] We postulated that the ketones that arise from these reactions would suppress overoxidation by destabilizing carbocations that could form the reaction between cyclization products and DDQ. While exposing substrate **6** to DDQ resulted in substantial amounts of overoxidation, adding $LiClO_4$ (15 mol%) to the reaction led to the formation of cyclohexanone **7** in 76% yield in 1 h (Scheme 3). Quaternary carbons can also be prepared through carbon–carbon bond formation, as illustrated by the conversion of **8** to **9**. This reaction proceeded to completion within 1 h to provide the desired product in 74% yield. In contrast allylic oxazolidinone **10**, which lacks heteroatom substitution on the alkene, was inert under the reaction conditions, thereby demonstrating the kinetic benefit of utilizing substrates with electron rich alkenes in these reactions.

We prepared several substrates to explore the scope of the process, the capacity to effect diastereoselective cyclization reactions, and the potential for expanding the scope of nucleophiles and product ring sizes in the reaction. The results of this study are shown in Table 1.

In general the reactions proceeded with good efficiency and diastereoselectivity. Notably, these are the first examples that we have observed in which carbocyclic structures have been prepared diastereoselectively through oxidative carbocation formation. The major products from substrates that contain alkyl branches (entries 1, 2, and 4) are consistent with chair-like transition states in which the alkyl groups and the α,β-unsaturated acyliminium ions occupy pseudoequatorial orientations. Interestingly the stereochemical outcome of the cyclization of methyl ether **15** (entry 3) is opposite from the cyclization of **13**. This suggests that the stereochemical outcomes of these reactions are controlled by kinetics rather than thermodynamics. Cycloheptanones can be formed through this method (entry 5), though this reaction proceeds less efficiently than reactions that produce lower homologs. Substrate **19**, however, contains no conformational control elements that could preorganize it for cyclization. Incorporating such constraints in the design of a cyclization substrate should improve cyclization efficiency. Silylallenes, which have proven to be excellent surrogates for propargylic anions[14] in oxidative cyclization reactions,[13a,b] are effective nucleophiles in the synthesis of alkynylcyclohexanes (entry 6). These substrates show low levels of diastereocontrol, as expected based on the minimal gauche and transannular interactions between the linear allene and the forming ring. Entries 7 and 8 show the results of our efforts at using β-dicarbonyl compounds as nucleophiles. The use of these nucleophiles is advantageous because no additional steps are required for the preparation of a latent nucleophile, and the cyclization products contain a high degree of substitution. The resulting process is an example of a cross-dehydrogenative coupling reaction[15] in which carbon–carbon bond formation occurs through a formal loss of H_2. We observed that the enol content of the substrate played a critical role in the success of these reactions. β-Diketones exist largely in the enol form in non-polar solvents, as illustrated in compound **23**, and are suitable nucleophiles

for the cyclization reaction. β-Keto esters, however, exist largely in the dicarbonyl form and are not effective nucleophiles.

The stereochemical outcome of the cyclization of ether substrate **15** illustrates the role that electrostatic effects can play in conformational equilibria (Scheme 4). The lone pairs on the oxygen of the equatorial methoxy group are separated from the electrophilic site by a greater distance in conformation **27** than the lone pairs of the axial methoxy group and the electrophilic site in conformation **28**. Since an axially-oriented methoxy group is only minimally disfavored relative to an equatorially-oriented methoxy group through steric effects, this electrostatic stabilization is sufficient to promote cyclization through conformation **28**. As a comparison we calculated (AM1) the distance between the oxygens of the methoxy groups and the corresponding carbons of axial- and equatorial-3-methoxy cyclohexanone (O → C_5). The axial oxygen is 2.92 Å from C_5 while the distance from the equatorial oxygen is 3.75 Å. Similar explanations have been proposed to describe the conformational preferences of cyclic alkoxy-substituted oxocarbenium ions.[16]

Vinyl oxazolidinones can serve as substrates for a number of transformations, providing significant flexibility to the types of structures that can ultimately be prepared through this sequence. Representative examples of these transformations are shown in Scheme 5. Ozonolytic cleavage of oxazolidinone **7** followed by reduction with Me_2S provides a 96% yield of aldehyde **29**. Exposing **7** to aqueous HCl results in vinyl oxazolidinone hydrolysis and subsequent aldol reaction to form the known[17] bridged bicycle **30** in an 81% yield. The ketone can be reduced by $NaBH_4$ to provide the alcohol as a 5:1 mixture of diastereomers in 93% yield. No reduction of the oxazolidinone was observed under these conditions. Acidic hydrolysis of the vinyl oxazolidinone followed by alcohol silylation yielded known[18] aldehyde **31**.

We have shown that vinyl oxazolidinones are excellent substrates for DDQ-mediated oxidative α,β-unsaturated acyliminium ion formation. The importance of alkene electron density is apparent through the significantly higher reactivity of vinyl oxazolidinones relative to allyl oxazolidinones. Cyclization through carbon–oxygen or carbon–carbon bond formation was demonstrated. Successful carbon–carbon bond formation was observed with enol acetate, silylallene, and β-diketone nucleophiles, with β-diketones being partularly attractive because they can be used without modification in cross-dehydrogenative coupling reactions. Diastereocontrol in the cyclizations is good to excellent when a chiral center is present in the substrate. The vinyl oxazolidinone groups in the reaction products can engage in a wide range of reactions to broaden the scope of products that are available through this method.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

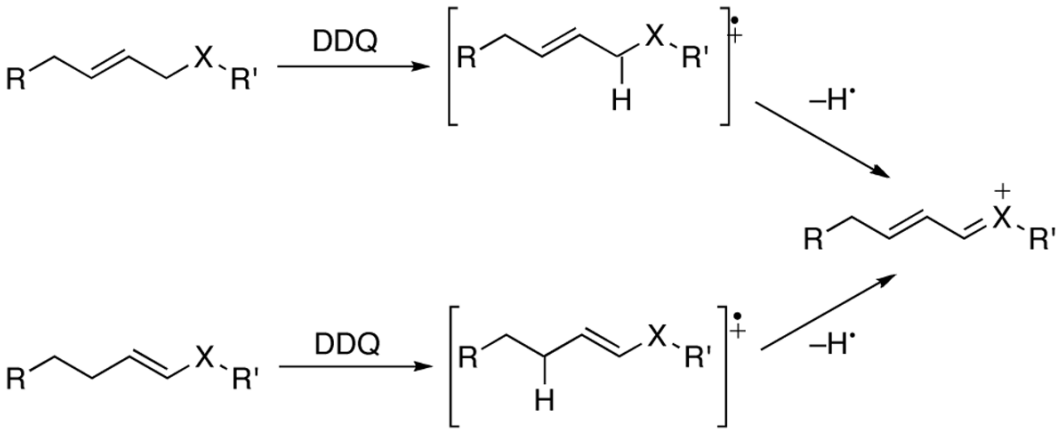
We thank the National Institutes of Health (GM062924) and the National Science Foundation (CHE—139851) for generous support of this work.

References

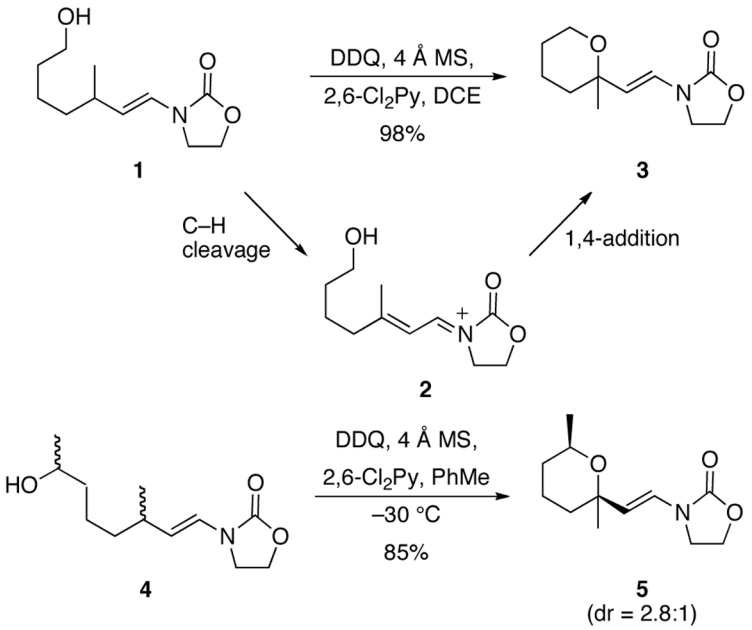
1. For representative examples, see: (a)Mukaiyama T, Hayashi Y, Hashimoto Y. Chem Lett 1986:1627. (b)Hayashi Y, Mukaiyama T. Chem Lett 1987:1811.(c)Murahashi SI, Komiya N, Terai H, Nakae T. J Am Chem Soc 2003;125:15312. [PubMed: 14664574](d)Ying BP, Trogden BG, Kohlman DT, Liang SX, Xu YC. Org Lett 2004;6:1523. [PubMed: 15128226](e)Zhang Y, Li CJ. J Am Chem Soc 2006;128:4242. [PubMed: 16568995](f)Catino AJ, Nichols JM, Nettles BJ, Doyle MP. J Am Chem

Soc 2006;128:5648. [PubMed: 16637627](g)Chen MS, White MC. Science 2007;318:783. [PubMed: 17975062](h)Niu M, Yin Z, Fu H, Jiang Y, Zhao Y. J Org Chem 2008;73:3961. [PubMed: 18407687] (i)Cheng D, Bao W. Adv Synth Catal 2008;350:1263.(j)Zhao L, Li CJ. Angew Chem, Int Ed 2008;47:7075.(k)Lin S, Song CX, Cai GX, Wang WH, Shi ZJ. J Am Chem Soc 2008;130:12901. [PubMed: 18778061]

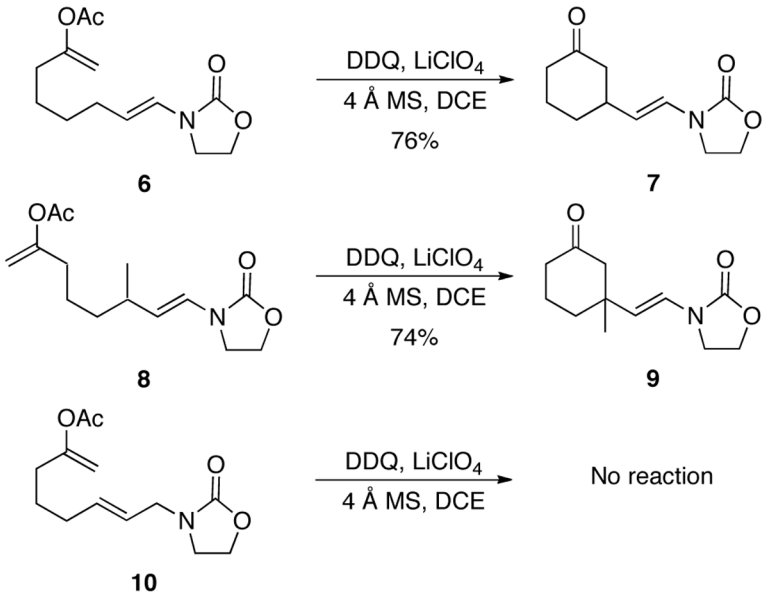
2. (a) Tu W, Liu L, Floreancig PE. Angew Chem, Int Ed 2008;47:4184. (b) Tu W, Floreancig PE. Angew Chem, Int Ed 2009;48:4567.
3. Rathore R, Kochi JK. Tetrahedron Lett 1994;35:8577.
4. Carbery DR. Org Biomol Chem 2008;6:3455. [PubMed: 19082143]
5. Song Z, Lu T, Hsung RP, Al-Rashid ZF, Ko C, Tang Y. Angew Chem, Int Ed 2007;46:4069.
6. (a) Jiang L, Job GE, Klapars A, Buchwald SL. Org Lett 2003;5:3667. [PubMed: 14507200] (b) Pan X, Cai Q, Ma D. Org Lett 2004;6:1809. [PubMed: 15151420] (c) Brice JL, Meerdink JE, Stahl SS. Org Lett 2004;6:1845. [PubMed: 15151429] (d) Bolshan Y, Batey RA. Angew Chem, Int Ed 2008;47:2109.
7. Goossen LJ, Rauhaus JE, Deng G. Angew Chem, Int Ed 2005;44:4042.
8. (a) Xiong H, Hsung RP, Shen L, Hahn JM. Tetrahedron Lett 2002;43:4449. (b) Adam W, Bosio SG, Wolff BT. Org Lett 2003;5:819. [PubMed: 12633080] (c) Sivaguru J, Saito H, Poon T, Omonuwa T, Franz R, Jockusch S, Hooper C, Inoue Y, Adam W, Turro NJ. Org Lett 2005;7:2089. [PubMed: 15901141] (d) Aciro C, Davies SG, Garner AC, Ishii Y, Key M-S, Ling KB, Prasad RS, Roberts PM, Rodriguez-Solla H, O'Leary-Steele C, Russel AJ, Sanganee HJ, Savory ED, Smith AD, Thomson JE. Tetrahedron 2008;64:9320.
9. Ko C, Hsung RP, Al-Rashid ZF, Feltenberger JB, Lu T, Yang JH, Wei Y, Zificsak CA. Org Lett 2007;9:4459. [PubMed: 17910461]
10. Lu T, Song Z, Hsung RP. Org Lett 2008;10:541. [PubMed: 18205371]
11. Gohier F, Bouhadjera K, Faye D, Gaulon C, Maisonneuve V, Dujardin G, Dhal R. Org Lett 2007;9:211. [PubMed: 17217267]
12. For related examples, see: (a)Magnus P, Lacour J. J Am Chem Soc 1992;114:767.(b)Evans PA, Longmire JM, Modi DP. Tetrahedron Lett 1995;36:3985.(c)Magnus P, Lacour J, Evans PA, Rigollier P, Tobler H. J Am Chem Soc 1998;120:12486.
13. (a)Seiders JR II, Wang L, Floreancig PE. J Am Chem Soc 2003;125:2406. [PubMed: 12603124](b) Wang L, Seiders JR II, Floreancig PE. J Am Chem Soc 2004;126:12596. [PubMed: 15453792](c) Jung HH, Seiders JR II, Floreancig PE. Angew Chem, Int Ed 2007;46:8464.. For the initial report of using enol acetates as latent ketone enolates, see: (d)Mukaiyama T, Izawa T, Saigo K. Chem Lett 1974:323.
14. Masse CE, Panek JS. Chem Rev 1995;95:1293.
15. Li CJ. Acc Chem Res 2009;42:335. [PubMed: 19220064]
16. (a) Woods RJ, Andrews CW, Bowen JP. J Am Chem Soc 1992;114:859. (b) Miljkovic M, Yeagley D, Deslongchamps P, Dory YL. J Org Chem 1997;62:7597. (c) Dudley TJ, Smoliakova IP, Hoffmann MR. J Org Chem 1999;64:1247. (d) Ayala L, Lucero CG, Romero JAC, Tabacco SA, Woerpel KA. J Am Chem Soc 2003;125:15521. [PubMed: 14664599]
17. Tzvetkov NT, Schmoldt P, Neumann B, Stammler HG, Mattay J. Tetrahedron: Asymmetry 2006;17:993.
18. Ren L, Crudden CM. J Org Chem 2002;67:1746. [PubMed: 11895387]



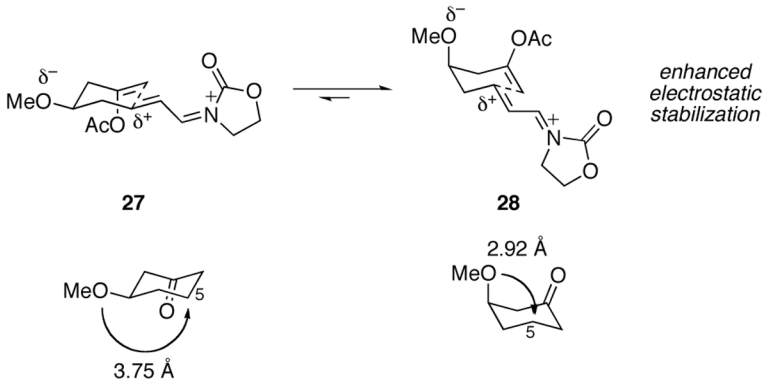
Scheme 1.
Alternate oxidative pathways to stabilized carbocations.



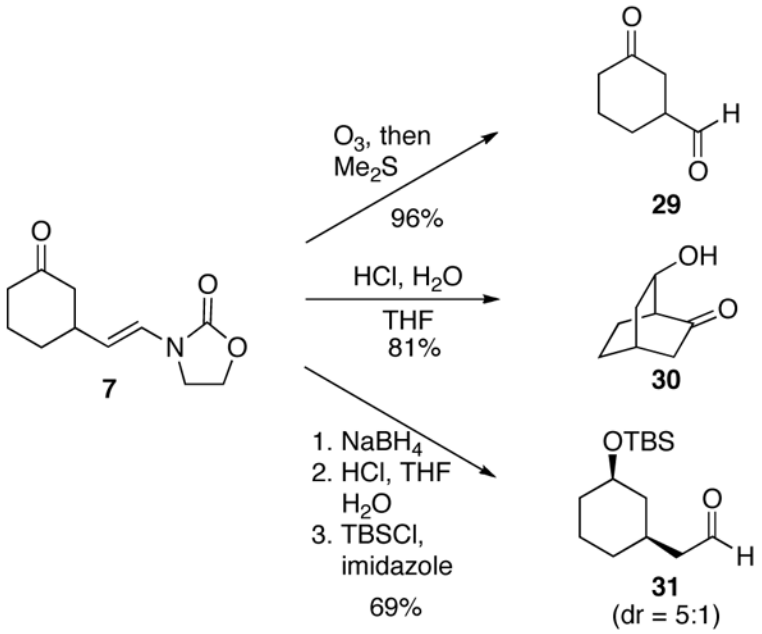
Scheme 2.
Allylic carbon–hydrogen bond activation from vinyl oxazolidinones.



Scheme 3.
Carbon–carbon bond formation.

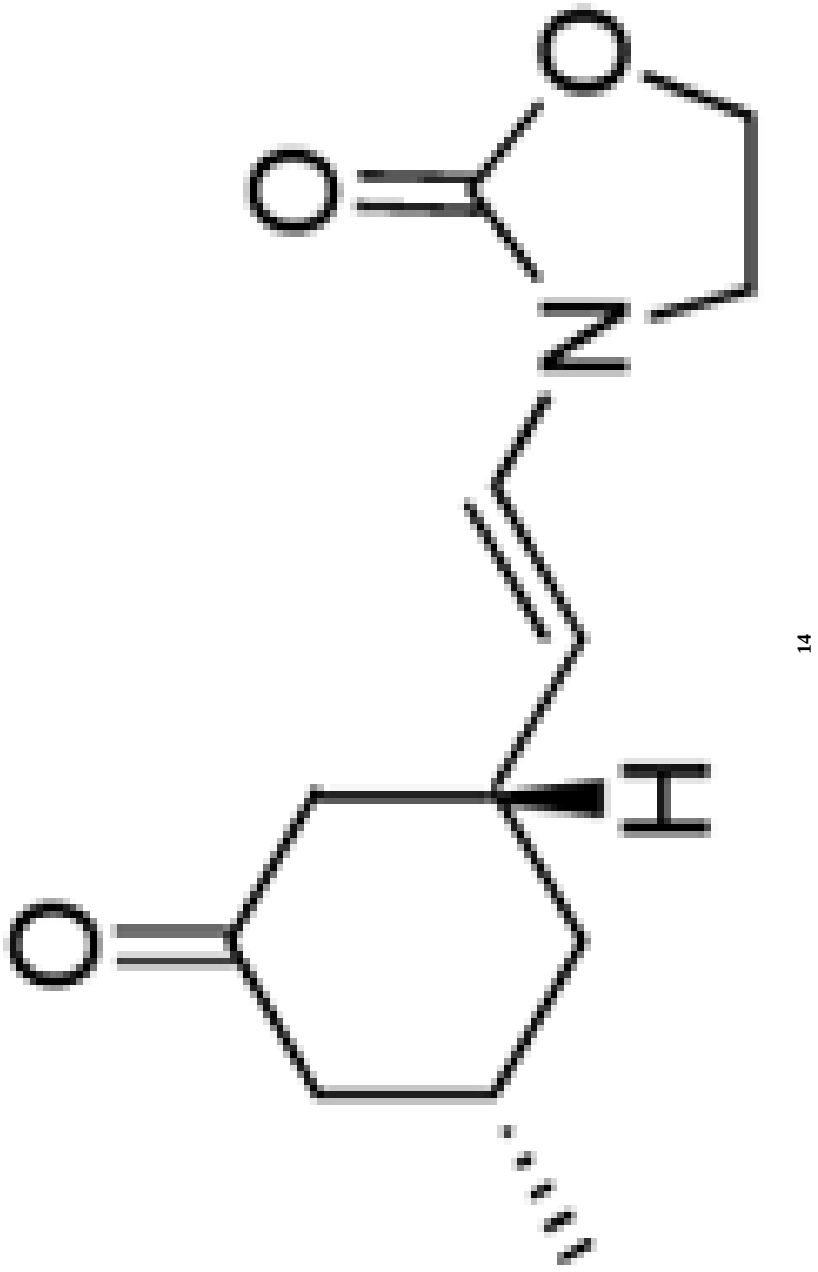


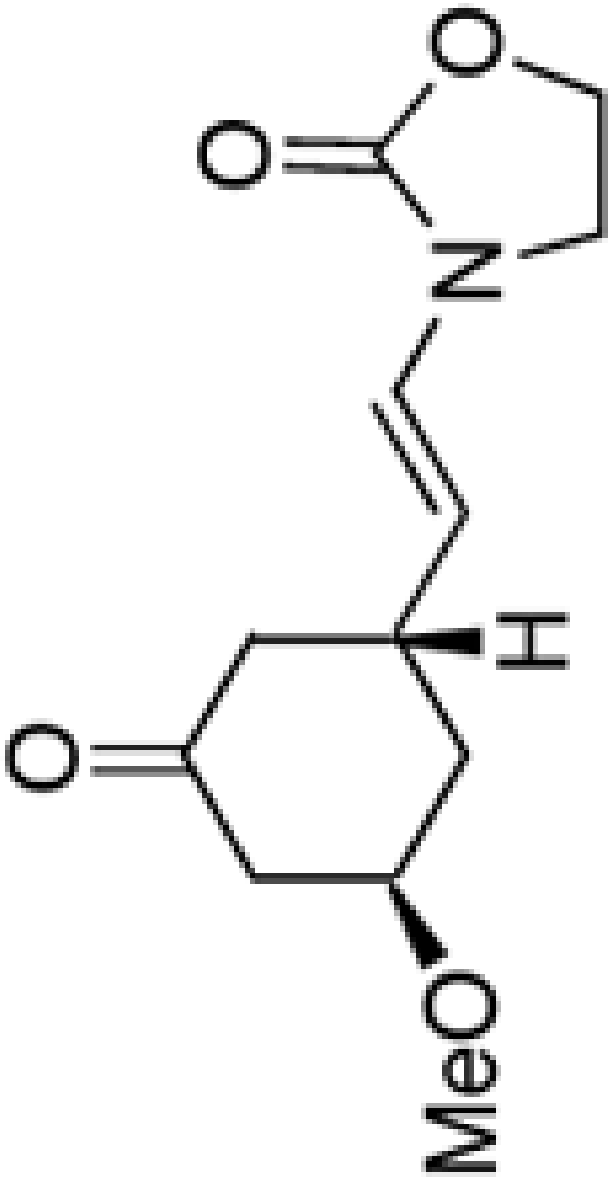
Scheme 4.
Conformational control through electrostatic effects.

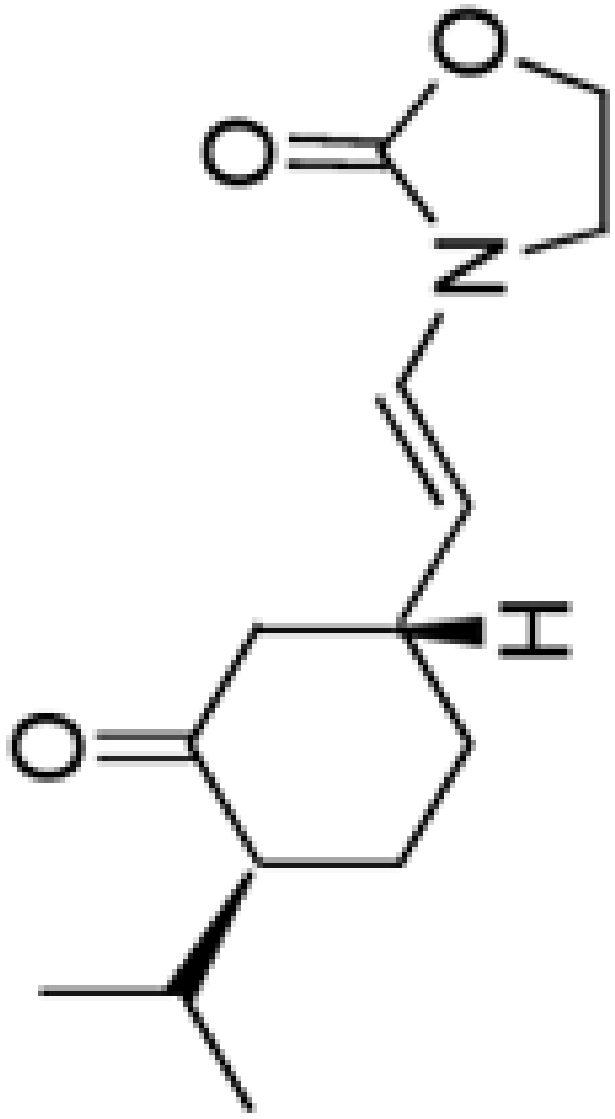


Scheme 5.
Vinyl oxazolidinone functionalization.

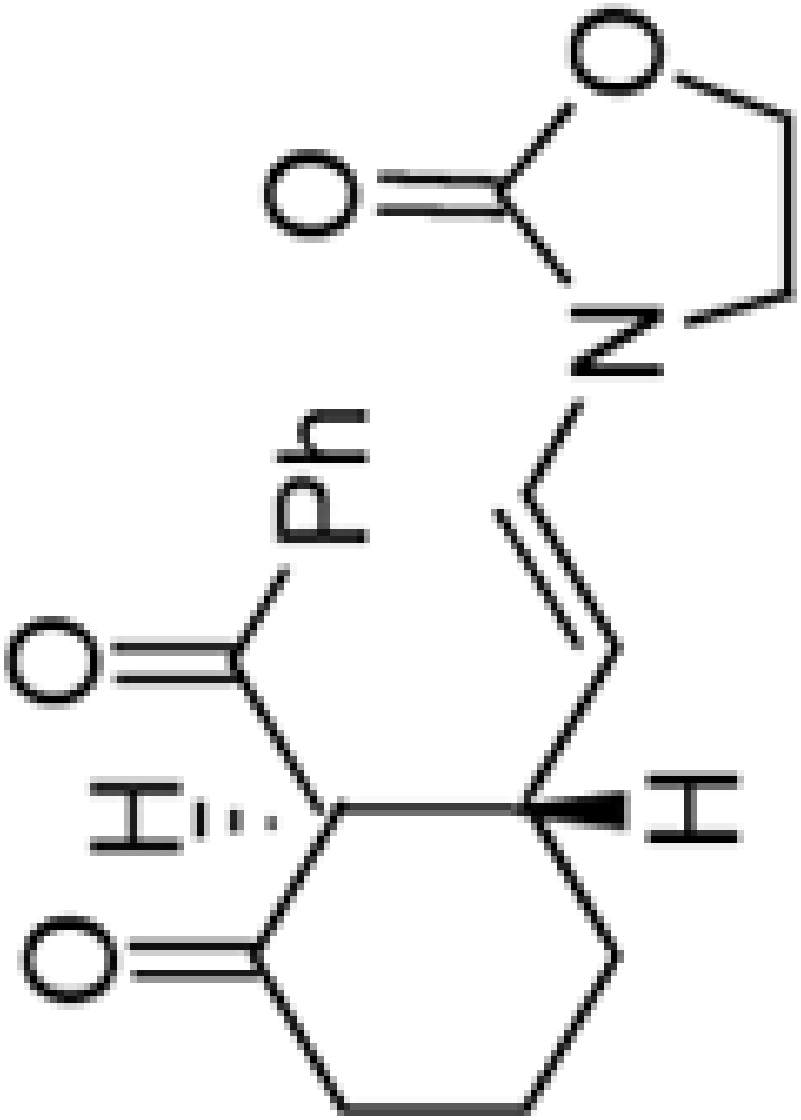
product	temp (°C)	yield (%)[b]	dr
12	−15	78	7.3:1

product	temp (°C)	yield (%)[b]	dr
 **14**	rt	69[c]	1:0

product	temp (°C)	yield (%)[b]	dr
 16	0	61[d]	1:0

product	temp (°C)	yield (%)[b]	dr
 18	−10	79	9:1

product	temp (°C)	yield (%)[b]	dr
20	0	30	-
22	0	63	1:1

product	temp (°C)	yield (%)[b]	dr
	−15	75	1:0

24

product	temp (°C)	yield (%)[b]	dr
26	0	-	-

ethane at the appropriate temperature. See Supporting