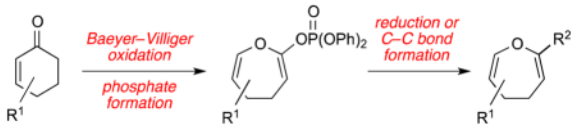
Published in final edited form as:
Org Lett. 2013 April 19; 15(8): 1994–1997. doi:10.1021/ol4006689.

A General Synthetic Approach to Functionalized Dihydrooxepines

K. C. Nicolaou[*], **Ruocheng Yu**, **Lei Shi**, **Quan Cai**[†], **Min Lu**, and **Philipp Heretsch**
Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and the Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

Abstract



A three-step sequence to access functionalized 4,5-dihydrooxepines from cyclohexenones has been developed. This approach features a regioselective Baeyer–Villiger oxidation and subsequent functionalization via the corresponding enol phosphate intermediate.

4,5-Dihydrooxepines are featured as structural motifs within various natural products, ranging from sesquiterpenes, such as miscandenin[1] and endiadric acid derivative beilshmiedin, [2] to polyketides, such as conioxepinol A[3] (Figure 1). This framework is also found in some of the most interesting members of the epidithiodiketopiperazine family as represented by aranotin [4] (Figure 1). Consequently, a number of approaches have been developed to access this structural motif. These include acid-catalyzed cyclization, [5] Rh-catalyzed cycloisomerization, [6] ring-closing metathesis, [7] [4+2] cycloaddition/epoxidation/retro [4+2] cycloaddition, [8] Cope rearrangement, [9] fragmentation, [10] and Criegee rearrangement.[11]

Despite this progress, the synthesis of related natural products in which the dihydrooxepine unit is highly functionalized remains challenging, in part because the scope and generality of existing methods are rather limited. Post-functionalization of pre-formed dihydrooxepines is also difficult due to the sensitive nature of these structural moieties. Therefore, a general approach through which substrates with a diverse array of substitution patterns can be reliably transformed into functionalized dihydrooxepines is highly desirable.

As part of our continuing efforts toward the total synthesis of members of the dihydrooxepine epidithiodiketopiperazine family,[8a,12] we opted to develop a method to synthesize 4,5-dihydrooxepines from cyclohexenones. Such a strategy would benefit from the ready availability of functionalized cyclohexenones, thus allowing access to a broad range of dihydrooxepine structures. We reasoned that ring expansion of the cyclohexenone could be achieved through a regioselective Baeyer–Villiger oxidation. Further

kcn@scripps.edu.
[†]Visiting Scientist from Chongqing University, China

Supporting Information Available: Experimental procedures, characterization and spectroscopic data for new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

functionalization of the resulting enol lactone through either reduction or C–C bond formation would give rise directly to the bis-enol ether moiety found in 4,5-dihydrooxepines (Figure 2).[13]

Our experimentation began with the Baeyer–Villiger oxidation of enone **1a** (Table 1). Thus, reaction of **1a** with *m*CPBA gave the desired enol lactone as a single regioisomer, albeit in low conversion (Table 1, entry 1). Attempts to use stronger oxidants such as CF_3CO_3H led to partial decomposition of the product (entry 2). We then reasoned that substrate activation by a suitable Lewis acid would improve conversion under milder reaction conditions that would avoid product decomposition. Indeed, the combination of $SnCl_4$ and bis(trimethylsilyl)peroxide (BTSP), in the presense of *trans*-1,2-diaminocyclohexane (ligand A), generated the desired product **2a** in 83% yield (entry 3).[14] The use of this ligand proved to be critical as it successfully tempered the Lewis acidity of $SnCl_4$. Neither $SnCl_4$ itself nor its combination with other ligands tested, such as *trans*-1,2-di(tosylamino)cyclohexane (ligand B), led to comparable yields (entries 4–6). The presence of dry molecular sieves was essential for the success of this reaction, as in its absence, only trace amounts of the product was observed (entry 7).

Conversion of the Baeyer–Villiger product **2a** to the corresponding enol phosphate **3a** went smoothly under our previously developed conditions (Scheme 1).[15] The phosphate group was chosen over the more common triflate group because the former is well-known to be more stable than the latter.[15]

Pd-catalyzed reduction of the diphenyl phosphate **3a** proved to be unsuccessful when using either Ph_2SiH_2 or nBu$_3$SnH as the reducing agent. After extensive screening, Et_3Al turned out to be the optimal reducing agent, giving the desired 4,5-dihydrooxepine **4a** in 81% yield (Scheme 1). However, when applying the same reduction conditions to phosphate **3b** (Table 2), we obtained an inseparable mixture of the desired product **4b** and the ethylated product **5b** in ca. 3:2 ratio (Table 2, entry 1). This result reflects the competition between β-hydride elimination and reductive elimination of the ethylated intermediate (see Table 2). [16] Attempts to optimize the reduction of **3b** by changing the solvent (entry 2) or using the diethyl phosphate **3b′** (entry 3) gave a mixture of **4b** and **5b**, albeit in different ratios (see Table 2). We then turned to some other reducing agents and found that $LiBH_4$ proved to be the best, giving exclusively the benzodihydrooxepine **4b** in good yield [entries 4 (66% yield) and 5 (67% yield)].

With the developed optimized conditions in hand, we then proceeded to assess the generality and scope of this three-step procedure to functionalized dihydrooxepines. As shown in Table 3, a variety of substrates with diverse substitution patterns and functional groups could be reliably transformed into the corresponding 4,5-dihydrooxepines. Cyclohexenones with either a methyl group on the olefinic bond (entries 3 and 5) or gem-dimethyl groups on the 4-position (entry 4) are good substrates for these transformation, although the latter exhibits lower reactivity in the first and third steps as compared to the others. Functional groups such as an isolated olefinic bond, an electron-rich arene, a TBS-protected secondary alcohol, or a ketal group are all tolerated in these procedures (entries 5–8). Most notably, the current method is also applicable to relatively complex structures, including the protected Wieland-Miescher ketone **1h** and the cholesterol derivative **1i** (entries 8 and 9, respectively). Thus, application of the present method to these substrates allows rapid access to the relatively complex dihydrooxepines **4h** and **4i**, respectively.

In addition to the above Pd-catalyzed reduction, the enol phosphate intermediate also provides a platform for a series of C–C bond forming reactions, thereby allowing further functionalization of the dihydrooxepine system. Thus, as demonstrated in Scheme 2, **3b**

could be successfully engaged in Ni-catalyzed Negishi (conditions a) and Kumada couplings (conditions b), leading to the corresponding alkyl-substituted products **5b** and **6b**, respectively, without competition from the β-hydride elimination pathway. Introduction of phenyl (conditions c), 3-thienyl (conditions d) and alkylnyl (conditions f) substituents can also be achieved in high yields using $PdCl_2$(dppf) as the catalyst (products **7b**, **8b** and **10b**, respectively). The same catalyst is also effective in converting the phosphate into an ester group (conditions e), albeit in moderate yield (product **9b**).

In summary, we have developed a three-step approach for the synthesis of functionalized dihydrooxepines from readily available cyclohexenones. This sequence features a regioselective Baeyer–Villiger oxidation, subsequent enol phosphate formation and Pd-catalyzed functionalization. The large variety of available cyclohexenones provides the basis for the generality of this approach, while the mildness of reaction conditions ensures their reliable transformation to functionalized dihydrooxepines with minimal loss due to facile decomposition. The current method holds considerable promise for application to the synthesis of bioactive natural products and their analogs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support for this work was provided by the National Science Foundation (grant CHE-1243661) and the National Institutes of Health, USA (grant AI 055475).

References

1. Herz W, Subramaniam PS, Santhanam PS, Aota K, Hall AL. J Org Chem. 1970; 35:1453. [PubMed: 5440337]
2. Chouna JR, Nkeng-Efouet PA, Lenta BN, Wensi JD, Kimbu SF, Sewald N. Phytochemistry Lett. 2010; 3:13.
3. Wang Y, Zheng Z, Liu S, Zhang H, Li E, Guo L, Che Y. J Nat Prod. 2010; 73:920. [PubMed: 20405881]
4. Nagarajan R, Huckstep LL, Lively DH, Delong DC, Marsh MM, Neuss N. J Am Chem Soc. 1968; 90:2980.
5. (a) Peng J, Clive DLJ. J Org Chem. 2009; 74:513. [PubMed: 19067592] (b) Peng J, Clive DLJ. Org Lett. 2007; 9:2939. [PubMed: 17580890]
6. Codelli JA, Puchlopek ALA, Reisman SE. J Am Chem Soc. 2012; 134:1930. [PubMed: 22023250]
7. (a) Gross U, Nieger M, Bräse S. Chem Eur J. 2010; 16:11624. [PubMed: 20809554] (b) Fustero S, Sánchez-Roselló M, Jiménez D, Sanz-Cervera JF, del Pozo C, Aceña JL. J Org Chem. 2006; 71:2706. [PubMed: 16555824]
8. (a) Nicolaou KC, Lu M, Totokotsopoulos S, Heretsch P, Giguère D, Sun YP, Sarlah D, Nguyen TH, Wolf IC, Smee DF, Day CW, Bopp S, Winzeler EA. J Am Chem Soc. 2012; 134:17320. [PubMed: 22978674] (b) Marx JN, Ajlouni A. Nat Prod Commun. 2010; 5:5. [PubMed: 20184009]
9. (a) Xu X, Hu WH, Zavalij PY, Doyle MP. Angew Chem Int Ed. 2011; 50:11152.(b) Shimizu M, Fujimoto T, Liu X, Takeda Y, Hiyama T. Heterocycles. 2008; 76:329.(c) Shimizu M, Fujimoto T, Liu X, Hiyama T. Chem Lett. 2004; 33:438.(d) Chou WN, White JB, Smith WB. J Am Chem Soc. 1992; 114:4658.(e) Clark DL, Chou WN, White JB. J Org Chem. 1990; 55:3975.(f) Aitken RA, Cadogan JIG, Gosney I, Hamill BJ, McLaughlin LM. J Chem Soc, Chem Commun. 1982:1164.
10. Leyhane AJ, Snapper ML. Org Lett. 2006; 8:5183. [PubMed: 17078673]
11. (a) Goodman RM, Kishi Y. J Org Chem. 1994; 59:5125.(b) Lu T, Vargas D, Fischer NH. Phytochemistry. 1993; 34:737.

12. (a) Nicolaou KC, Giguère D, Totokotsopoulos S, Sun Y. Angew Chem, Int Ed. 2012; 51:728.(b) Nicolaou KC, Totokotsopoulos S, Giguère D, Sun Y. J Am Chem Soc. 2011; 133:8150. [PubMed: 21548595]
13. In their elegant synthesis of acetylaranotin, Tokuyama et al. prepared the 4,5-dihydrooxepine structural motif of the molecule from a lactone via the corresponding enol triflate; see: Fujiwara H, Korugi T, Okaya S, Okano K, Tokuyama H. Angew Chem, Int Ed. 2012; 51:13062.
14. Götlich R, Yamakoshi K, Sasai H, Shibasaki M. Synlett. 1997:971.
15. Nicolaou KC, Shi GQ, Gunzner JL, Gärtner P, Yang Z. J Am Chem Soc. 1997; 119:5467.
16. Sato M, Takai K, Oshima K, Nozaki H. Tetrahedron Lett. 1981; 22:1609.

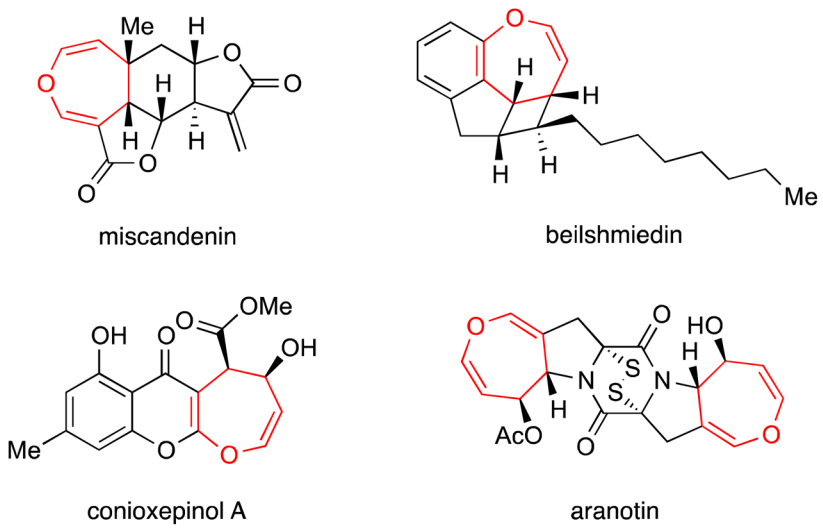


Figure 1.
Selected natural products containing the 4,5-dihydrooxepine structural motif.

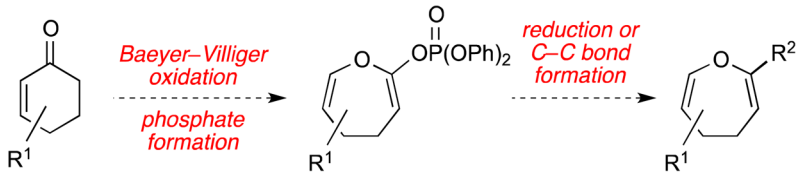
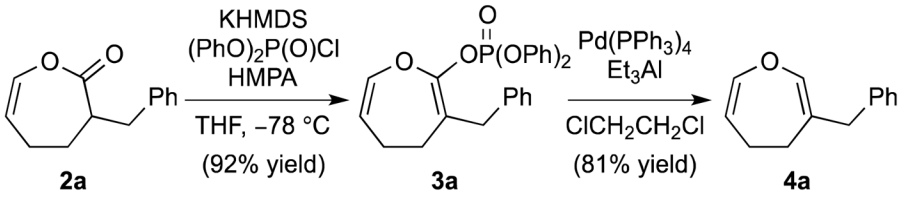
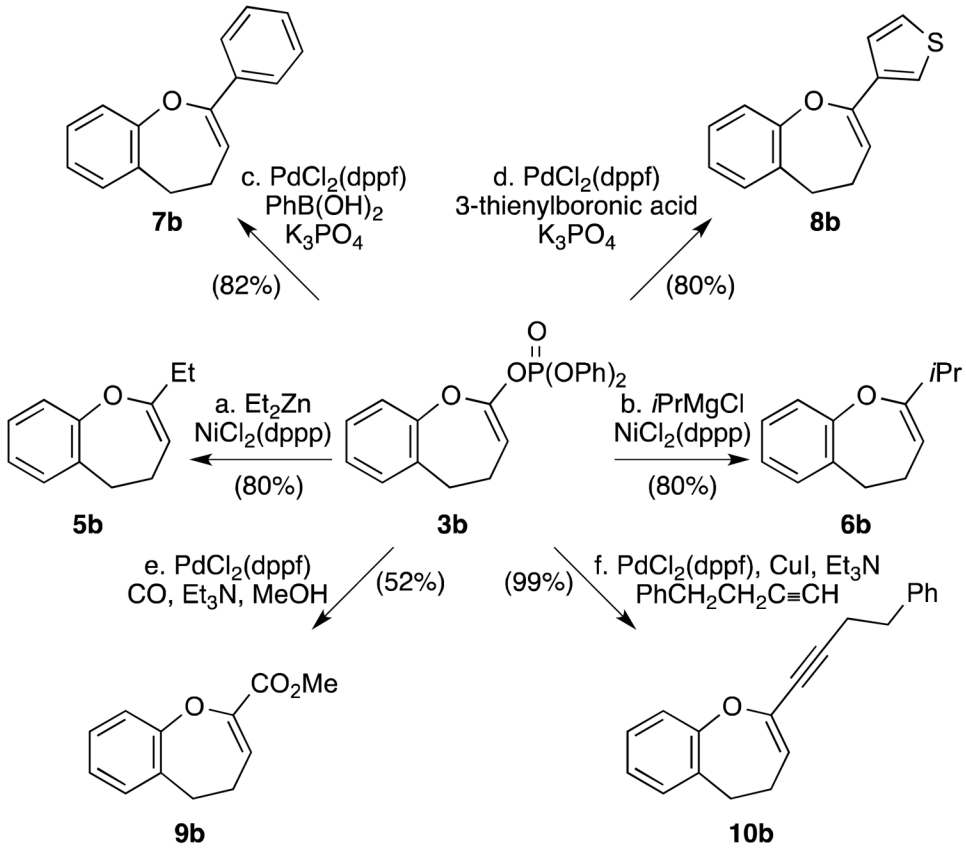


Figure 2.
Proposed synthesis of functionalized 4,5-dihydrooxepines from the corresponding cyclohexenones.



Scheme 1.
Enol Phosphate Formation and Pd-Catalyzed Reduction to 4,5-Dihydrooxepine

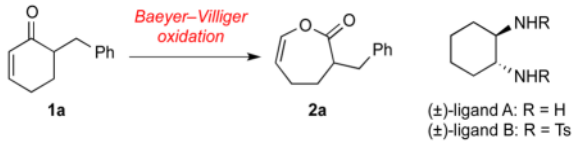


Scheme 2.

Functionalization of the 4,5-Dihydrooxepine Structural Motif via the Corresponding Enol Phosphate

Table 1

Study of the Baeyer–Villiger Oxidation of Enones[a]



1a 2a (±)-ligand A: R = H (±)-ligand B: R = Ts

entry	conditions	yield (%)[b]
1[c]	*m*CPBA, CH_2Cl_2	15
2[c]	UHP, TFAA, CH_2Cl_2	decomp.
3[c]	**BTSP, $SnCl_4$, ligand A, 4 Å MS, CH_2Cl_2**	**83**
4[d]	BTSP, $SnCl_4$, 4 Å MS, CH_2Cl_2	trace
5[d]	BTSP, $SnCl_4$, ligand B, 4 Å MS, CH_2Cl_2	22
6[d]	BTSP, $SnCl_4$, pyridine, 4 Å MS, CH_2Cl_2	32
7[d]	BTSP, $SnCl_4$, ligand A, CH_2Cl_2	trace

[a] Reactions were carried out on 0.25 mmol scale.

[b] ^{1}H NMR yield.

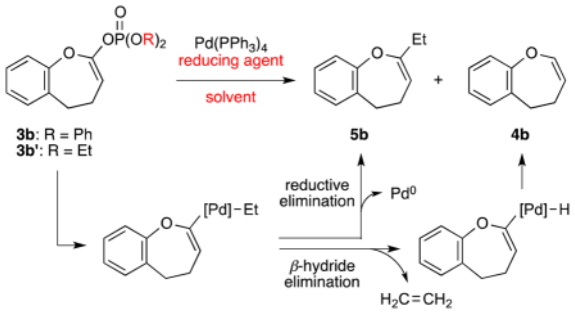
[c] Reactions were carried out at 0.1 M concentration with 0.5 equiv of $SnCl_4$, 0.5 equiv of ligand A, 3.0 equiv of BTSP and 50 mg 4 Å MS at 25 °C.

[d] Reactions were carried out under the identical conditions in entry 3 with changes indicated in the table.

*m*CPBA = *meta*-chloroperoxybenzoic acid, UHP = urea hydrogen peroxide, TFAA = trifluoroacetic anhydride, BTSP = bis(trimethylsilyl)peroxide.

Table 2

Optimization of Enol Phosphate Reduction[a]



entry	R	reducing agent	solvent	yield (%)[b] (4b+5b)	4b:5b[c]
1	Ph	Et_3Al	$ClCH_2CH_2Cl$	58	60:40
2	Ph	Et_3Al	CH_2Cl_2	62	37:63
3	Et	Et_3Al	$ClCH_2CH_2Cl$	70	90:10
4	Et	$LiBH_4$	THF	66	**4b** only
5	Ph	$LiBH_4$	THF	67	**4b** only

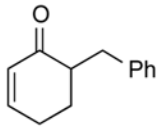
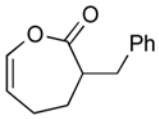
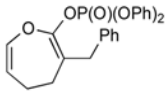
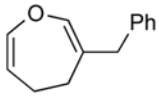
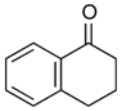
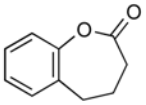
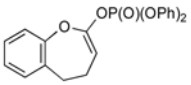
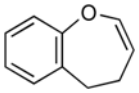
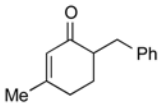
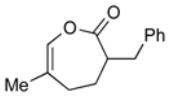
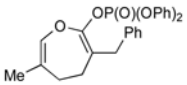
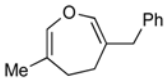
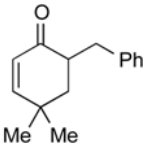
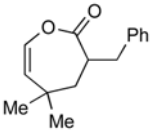
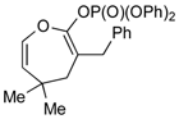
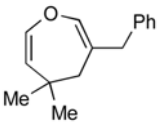
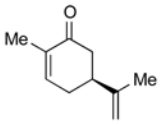
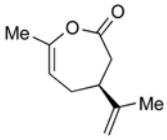
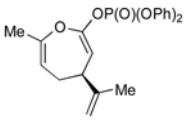
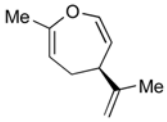
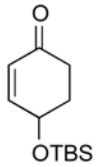
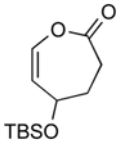
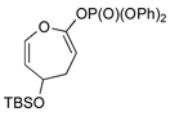
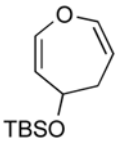
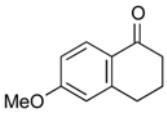
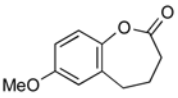
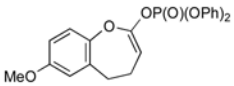
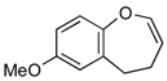
[a]Reactions were run on 0.1 mmol scale at 0.05 M concentration with 0.2 equiv of $Pd(PPh_3)_4$ and 2.5 equiv of Et_3Al at 25 °C or 10 equiv of $LiBH_4$ at 0 °C.

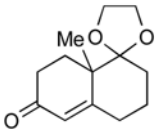
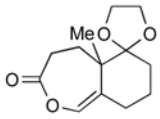
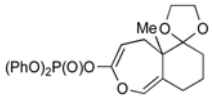
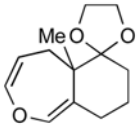
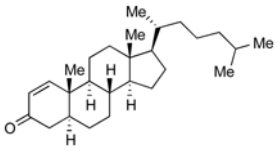
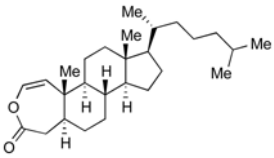
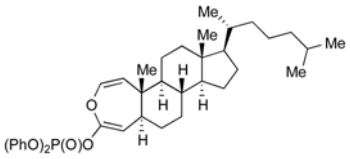
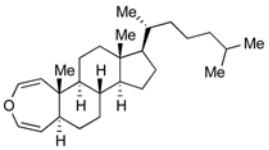
[b]^{1}H NMR yield.

[c]Ratios determined by ^{1}H NMR spectroscopic analysis.

Table 3

Scope and Generality of the 4,5-Dihydrooxepine-Forming Sequence[a]

entry	substrate	lactone (% yield)[b]	enol phosphate (% yield)[b]	4,5-dihydrooxepine (% yield)[b]
1	 **1a**	 **2a** (83)	 **3a** (92)	 **4a** (81)[c]
2	 **1b**	 **2b** (70)	 **3b** (93)	 **4b** (67)[d,e]
3	 **1c**	 **2c** (72)	 **3c** (89)	 **4c** (90)[c]
4	 **1d**	 **2d** (70)	 **3d** (55)	 **4d** (81)[c]
5	 **1e**	 **2e** (74)[e]	 **3e** (84)	 **4e** (61)[d,e]
6	 **1f**	 **2f** [34 (46 brsm)][f]	 **3f** (75)	 **4f** (64)[d,e]
7	 **1g**	 **2g** (79)	 **3g** (83)	 **4g** (86)[d]

entry	substrate	lactone (% yield)[b]	enol phosphate (% yield)[b]	4,5-dihydrooxepine (% yield)[b]
8	 **1h**	 **2h** (54)	 **3h** (90)	 **4h** (71)[d]
9	 **1i**	 **2i** (99)	 **3i** (57)	 **4i** (82)[d]

[a] Lactone formation: reactions were carried out on 1.0 mmol scale at 0.1 M concentration in CH_2Cl_2 with 0.5 equiv of $SnCl_4$, 0.5 equiv of ligand A, 3.0 equiv of BTSP and 200 mg 4 Å MS at 25 °C; enol phosphate formation: reactions were carried out on 0.5 mmol scale at 0.1 M concentration in THF with 2.0 equiv of KHMDS, 2.0 equiv of $(PhO)_2P(O)Cl$, 3.0 equiv of HMPA at −78 °C; dihydrooxepine formation (method A): reactions were carried out on 0.2 mmol scale at 0.05 M concentration in $ClCH_2CH_2Cl$ with 0.2 equiv of $Pd(PPh_3)_4$ and 2.5 equiv of Et_3Al; dihydrooxepine formation (method B): reactions were carried out on 0.2 mmol scale at 0.05 M concentration in THF with 0.2 equiv of $Pd(PPh_3)_4$ and 10 equiv of $LiBH_4$ at 0 °C.

[b] Isolated yield unless otherwise noted.

[c] Using method A.

[d] Using method B.

[e] Due to the volatility of the product, the yield refers to ^1H NMR yield.

[f] Anhydrous K_2CO_3 (200 mg) was added.

brsm = based on recovered starting material.