Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Pd-Catalyzed Asymmetric Allylic Cycloaddition of Vinyloxetanes with Formaldehyde

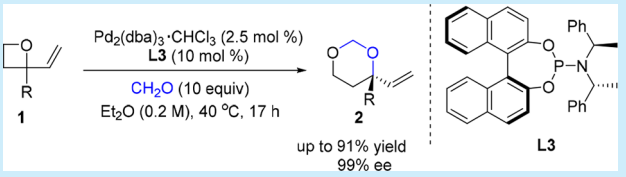
Hang Xu,[†] Sardaraz Khan,[†] Hongfang Li,[†,‡] Xue Wu,[‡] and Yong Jian Zhang*[,†]

[†]School of Chemistry and Chemical Engineering, and Shanghai Key Laboratory of Electrical Insulation and Thermal Aging, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, People's Republic of China

[‡]Key Laboratory for Organism Resources of the Changbai Mountain and Functional Molecules, Ministry of Education, and Department of Chemistry, College of Science, Yanbian University, 977 Gongyuan Road, Yanji, Jilin 133002, People's Republic of China

Supporting Information

ABSTRACT: An efficient method for the enantioselective construction of tertiary 1,3-diols via Pd-catalyzed asymmetric allylic cycloaddition of vinyloxetanes with an abundant feedstock, formaldehyde, is developed. Using the palladium complex generated in situ from $Pd_2(dba)_3{\cdot}CHCl_3$ and phosphoramidite **L3** as a catalyst under mild conditions, the process allows one to convert racemic 2-substituted 2-vinyloxetanes (**1**) to the corresponding 1,3-dioxanes (**2**) as methylene acetal protected tertiary 1,3-diols in high yields with good to excellent enantioselectivities.



Chiral tertiary 1,3-diols are prevalent motifs in a wide variety of medicinally relevant agents and natural products, such as phoslactomycin B deamino precursor,[1] convolutamydine E isolated from the Floridian marine bryozoan *Amathia convoluta*,[2] potential anticancer agent **a**,[3] and potent 11β-HSD1 inhibitor **b**[4] (Figure 1). The importance

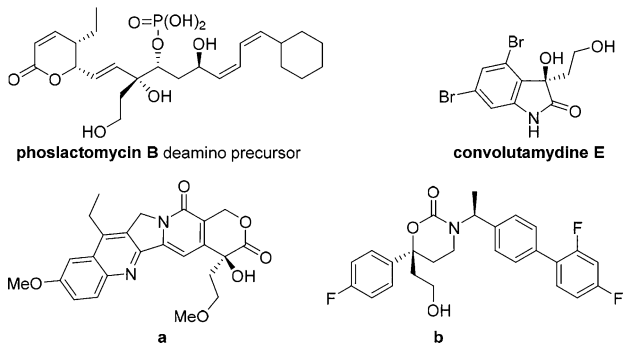


Figure 1. Representative medicinally relevant agents and natural products containing tertiary 1,3-diols.

of this particular framework has prompted chemists to develop efficient asymmetric catalytic methods for the synthesis of chiral tertiary alcohols bearing useful functionalities. Nevertheless, multistep transformations are generally required to access chiral tertiary 1,3-diols. Most common approaches to chiral tertiary 1,3-diols involve the asymmetric Aldol reaction of ketones, followed by a reduction or asymmetric allylation/alkenylation of ketones and further manipulations.[5] Oxa-Michael addition followed by reduction is also an effective protocol for the synthesis of chiral 1,3-diols.[6] However, oxa-Michael addition to β,β-disubstituted Michael acceptors for the construction of tertiary C−O bond are largely underdeveloped.[7] Transition-metal-catalyzed asymmetric allylic etherification is one of the most powerful methods for the C−O bond formation to provide chiral allylic ethers,[8] which could be converted to 1,3-diols by further manipulations. However, regioselective construction of tertiary C−O bond using this transformation remains a significant challenge.[9] In contrast, only a few methods for more directly accessing chiral tertiary 1,3-diols have been reported, including asymmetric dihydroxylation of functionalized olefins[10] and kinetic resolution of diols via asymmetric acetalization.[11] Therefore, the development of efficient catalytic methods, which allows rapid access to enantioenriched tertiary 1,3-diols, is highly appealing.

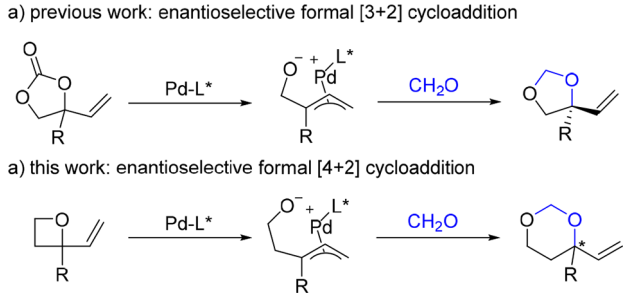
Pd-catalyzed cycloaddition reactions through zwitterionic allylpalladium intermediates have recently emerged as an important strategy for the construction of various cyclic frameworks.[12] Various allylic donors have successfully been applied to this transformation with diverse unsaturated electrophiles. Among them, vinyl epoxides[13] and vinylethylene carbonates (VECs)[14,15] have served as efficient 1,3- or 1,5-*C*,*O*-dipoles in the Pd-catalyzed allylic cycloaddition reactions to afford oxo-cyclic compounds. (See Scheme 1.) However, the analogous vinyl oxetanes[16] as *C*,*O*-dipoles for the cycloaddition have been largely underdeveloped.[17]

There is only one report of Pd-catalyzed allylic cycloaddition of vinyl oxetanes with isocyanates/carbodiimides to afford 1,3-oxazines in a racemic form.[18] During our studies on this work,

Received: November 16, 2018

DOI: 10.1021/acs.orglett.8b03665
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Enantioselective Cycloaddition of Vinyloxetanes with Formaldehyde

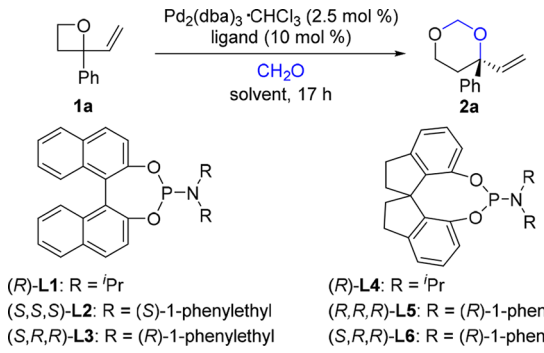


Zhao and co-workers reported Pd-catalyzed asymmetric formal [6 + 4] cycloaddition of vinyl oxetanes with azadienes to prepare 10-membered heterocycles.[19] Most recently, we developed VECs as more stable and readily accessible allylic donors and achieved the Pd-catalyzed asymmetric decarboxylative allylic cycloaddition of VECs with various unsaturated electrophiles to afford diverse heterocycles with tetrasubstituted stereocenters in high efficiencies.[14] In our previous studies, we developed an efficient process of Pd-catalyzed asymmetric allylc cycloaddition of VECs with formaldehyde to access chiral 1,3-dioxolanes as methylene acetal protected tertiary 1,2-diols.[14e] Based on our continuous efforts to develop efficient methods for the enantioselective construction of tertiary alcohols with diverse functionalities, we are interested in the possibility of using vinyl oxetanes in an enantioselective allylic cycloaddition with formaldehyde to access enantioenriched tertiary 1,3-diol derivatives. In this communication, we report Pd-catalyzed asymmetric allylic cycloaddition of vinyl oxetanes with formaldehyde, which is an efficient method that allows rapid access to valuable chiral 1,3-dioxanes as methylene acetal protected tertiary 1,3-diols in high yields with high levels of enantioselectivities.

Initial studies focused on the cycloaddition of vinyloxetane **1a** as a standard substrate with formaldehyde (Table 1). Based on our previous studies on the cycloaddition of VECs,[14] we began our investigation by examining the cycloaddition of **1a** with formaldehyde (37% aqueous solution) in the presence of a Pd(0)-catalyst with different phosphoramidite ligands. First, we tried the reactions using phosphoramidites derived from binol[20] in tetrahydrofuran (THF) at 20 °C for 17 h. The reactions proceeded well to give desired 1,3-dioxane **2a** in good yields (Table 1, entries 1−3), and the reaction with ligand **L3** revealed the best enantioselectivity (80% enantiomeric excess (ee)). The Zhou ligand[21] **L4** is also effective for the reaction, but the yield slightly decreased (Table 1, entry 4). The reaction using ligand **L6** gave the cycloadduct **2a** in 98% ee, whereas the yield is poor (Table 1, entry 6). The yields can be improved without significant deterioration of enantioselectivities when the reactions proceeded at 40 °C (Table 1, entries 7−9). Further increasing the reaction temperature to 60 °C (Table 1entries 10 and 11), the yields decreased instead. Based on these results, we tried to further screen reaction solvent with **L3** as a ligand at 40 °C (Table 1entries 12−18).[22] As a result, we found that the reaction proceeded smoothly in the different solvents, and the reaction in diethyl ether showed the best results, affording 1,3-dioxane **2a** in 86% yield with 92% ee (Table 1, entry 15).

With the optimal conditions in hand (Table 1, entry 15), the generality of this process was evaluated by the reaction of

Table 1. Condition Optimizations[a]



entry	ligand	solvent	temperature, T (°C)	yield[b] (%)	ee (%)[c]
1	**L1**	THF	20	79	−35
2	**L2**	THF	20	72	44
3	**L3**	THF	20	75	80
4	**L4**	THF	20	63	81
5	**L5**	THF	20	–	–
6	**L6**	THF	20	8	−98
7	**L3**	THF	40	91	80
8	**L4**	THF	40	67	70
9	**L6**	THF	40	49	−94
10	**L3**	THF	60	75	79
11	**L6**	THF	60	12	−97
12	**L3**	CH_2Cl_2	40	82	68
13	**L3**	toluene	40	63	86
14	**L3**	cyclohexane	40	53	89
15	**L3**	Et_2O	40	86	92
16	**L3**	1,4-dioxane	40	79	74
17	**L3**	CPME[d]	40	66	93
18	**L3**	MeCN	40	68	77

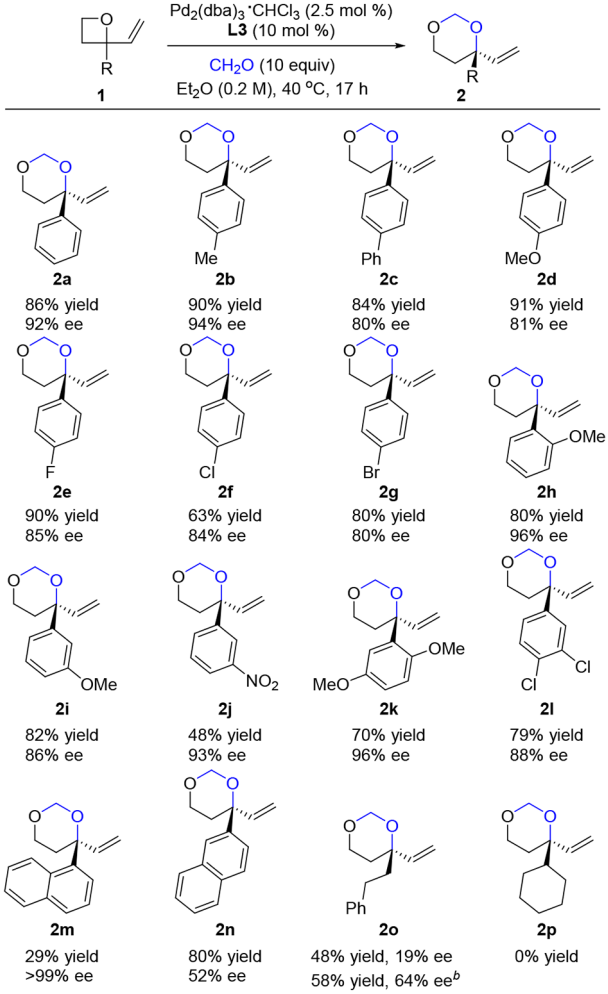
[a]Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), ligand (10 mol %), **1a** (0.2 mmol), formaldehyde (2.0 mmol, 37% aqueous solution), solvent (1.0 mL), 17 h. [b]Isolated yields. [c]ee = enantiomeric excess. Determined by chiral HPLC. The absolute configuration was confirmed by X-ray crystallography of **4** elaborated from **2a** (Scheme 3). [d]CPME = cyclopentyl methyl ether.

various substituted vinyl oxetanes **1** with formaldehyde. As shown in Scheme 2 , a wide range of aryl-substituted vinyl oxetanes bearing different electronic and steric properties was tolerated under the reaction conditions, affording the corresponding 1,3-dioxanes **2a−2l** in moderate to high yields with good to high enantioselectivities. For the cycloaddition of 2-(1-naphthyl)-2-vinyloxetane (**1m**), high enantioselectivity (>99% ee) was observed, but the yield was poor. The cycloaddition of 2-(2-naphthyl)-2-vinyloxetane (**1n**) proceeded smoothly to afford corresponding 1,3-dioxane **2n** in high yield with moderate enantioselectivity (52% ee). Unfortunately, the reaction conditions were not compatible for the aliphatic-substituted vinyloxetane **1o**: only poor yield and enantioselectivity were observed. When using ligand **L4** instead of **L3** under otherwise identical conditions, the reaction efficiency can be improved to afford corresponding 1,3-dioxane **2o** in 58% yield with moderate enantioselectivity (64% ee). The reaction of 2-cyclohexyl-2-vinyloxetane (**1p**) was ineffective under these reaction conditions.

Next, we tried vinyl carbonate **3a**, which is synthesized from the corresponding 1,3-diol, instead of vinyl oxetane **1a** for this cycloaddition reaction. As shown in Scheme 3, the reaction conditions were also effective for the cycloaddition of vinyl

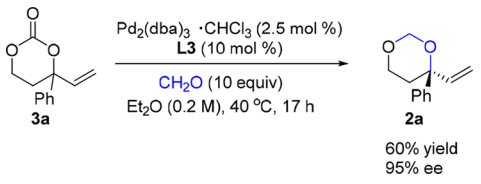
DOI: 10.1021/acs.orglett.8b03665
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope for Pd-Catalyzed Asymmetric Cycloaddition of Vinyloxetanes 1 with Formaldehyde[a]



[a]Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), ligand (10 mol %), **1a** (0.2 mmol), formaldehyde (2.0 mmol, 37% aqueous solution), solvent (1.0 mL), 17 h. Yields are isolated yields. The enantioselectivities were determined by chiral HPLC. The absolute configuration was confirmed by X-ray crystallography of **4** elaborated from **2a** (Scheme 3); those of the other products were assigned by analogy. [b]The results were obtained by using **L4** as a ligand under otherwise identical conditions.

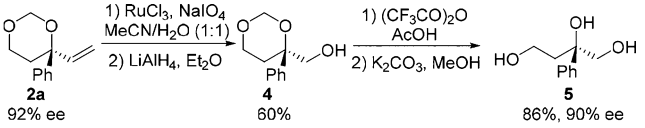
Scheme 3. Pd-Catalyzed Asymmetric Cycloaddition of Vinyl Carbonate 3a with Formaldehyde



carbonate **3a** with formaldehyde to furnish 1,3-dioxane **2a** in 60% yield with high enantioselectivity (95% ee).

The synthetic versatility of the present protocol was demonstrated by the elaboration of 1,3-dioxane **2a** into triol **5** (Scheme 4). Oxidation of **2a** with $RuCl_3$ and $NaIO_4$ and subsequent reduction with $LiAlH_4$ gave compound **4** in 60% yield for two steps. The absolute configuration of **4** was

Scheme 4. Elaboration of 2a To Form Triol 5



unambiguously assigned by X-ray crystallography (see the Supporting Information). Deprotection of methylene acetal of compound **4** was performed with trifluoroacetic anhydride and acetic acid, followed by transesterification under basic conditions in methanol to give triol **5** in 86% yield without a significant loss of enantioselectivity (90% ee).

In conclusion, we have developed an efficient method for the enantioselective construction of methylene acetal protected tertiary 1,3-diols via Pd-catalyzed asymmetric allylic cycloaddition of vinyloxetanes with an abundant feedstock: formaldehyde. The reactions proceeded smoothly in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and phosphoramidite **L3** under mild conditions, providing 4-substituted 4-vinyl-1,3-dioxanes **2** in high yields with good to excellent enantioselectivities. The synthetic utility was demonstrated by the elaboration of 1,3-dioxane **2a** into corresponding triol **5** bearing a tetrasubstituted stereocenter. Further studies on the the extending of the scope of the cycloaddition of vinyloxetanes with other unsaturated electrophiles are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03665.

Detailed experimental procedures; characterization data of all the new compounds; copies of HPLC chromatographies, ^1H and ^{13}C NMR spectra of the products (PDF)

Accession Codes

CCDC 1876159 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yjian@sjtu.edu.cn.

ORCID

Yong Jian Zhang: 0000-0001-5808-1745

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 21572130 and 21871179). We thank the Instrumental Analysis Center of Shanghai Jiao Tong University for HRMS analysis.

DOI: 10.1021/acs.orglett.8b03665
Org. Lett. XXXX, XXX, XXX−XXX

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(22) The examination of the solvent screen was also conducted by using **L6** as ligand, but the yield cannot further improve; see the Supporting Information.

DOI: 10.1021/acs.orglett.8b03665
Org. Lett. XXXX, XXX, XXX−XXX