Organic LETTERS

Letter

pubs.acs.org/OrgLett

Reagent-Controlled Tandem Reactions of Vinyl Epoxides: Access to Functionalized γ-Butenolides

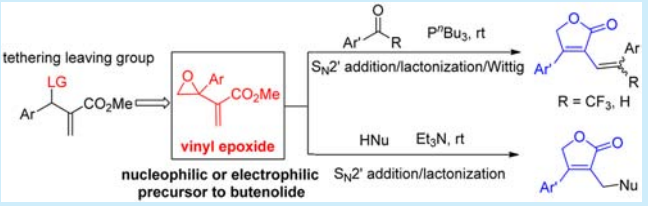
Juan Ma,[†] Zhe-zhe Yuan,[†] Xiang-wen Kong,[†] Huai Wang,[†] Yi-ming Li,[†] Hua Xiao,*[,†,‡] and Gang Zhao[‡]

[†]Department of Pharmaceutical Engineering, Hefei University of Technology, 193 Tunxi Road, Hefei 230009, P. R. China

[‡]Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China

Supporting Information

ABSTRACT: A new approach to functionalized γ-butenolides based on reagent-controlled tandem reaction sequences of Morita−Baylis−Hillman-type vinyl epoxides is described. The nucleophilic addition of a tertiary phosphine to the electron-deficient alkene led to ring-opening of the epoxide followed by lactonization to produce phosphonium ylides, which could undergo Wittig olefination with aryl trifluoromethyl ketones and aryl aldehydes to give 3-alkenyl γ-butenolides in moderate to good yields and high *E*/*Z* selectivity. Tertiary amine promoted the Michael-type addition of carbon- and nitrogen-based nucleophiles to the vinyl epoxides followed by lactonization to provide diverse 3-substituted γ-butenolides.



The γ-butenolide is a structural motif of wide occurrence in biologically significant natural products and pharmaceutically important molecules.[1] For instance, lead structure PD 156707 is a nonpeptide-selective ET_A receptor antagonist with high endothelin receptor affinity. Strigol functions as a germination and shoot-branching phytohormone. Rubriflordilactone B, isolated from *Schisandra rubriflora*, also has been traditionally used in Chinese herbal medicine. All share this five-membered oxygenated heterocycle structure (Figure 1).[2] A number of synthetic approaches have been developed for the construction of butenolides, which primarily fall into two major strategies. One is the use of synthetic building blocks with a masked γ-butenolide skeleton such as nucleophilic silyloxy furan or furanone analogues.[3] The other strategy utilizes linear starting materials and performs halolactonization or ring-closing metathesis of linear molecules or metal-mediated addition−cyclization and aldol-type condensations.[4] Despite these advances, the development of a convenient method for the preparation of γ-butenolides with broad functionality compatibility, under mild metal-free conditions, is still highly desirable.

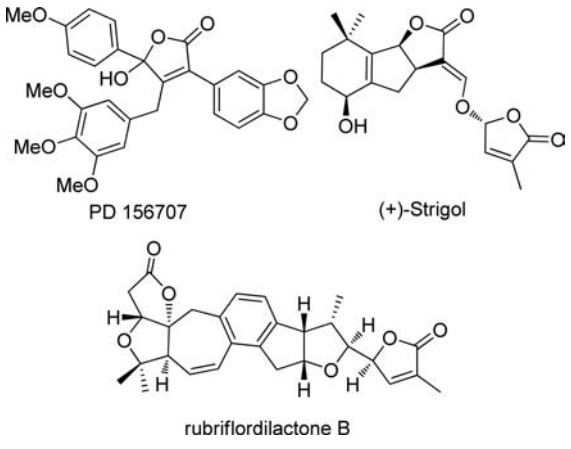


Figure 1. Representative natural compounds with butenolide structure.

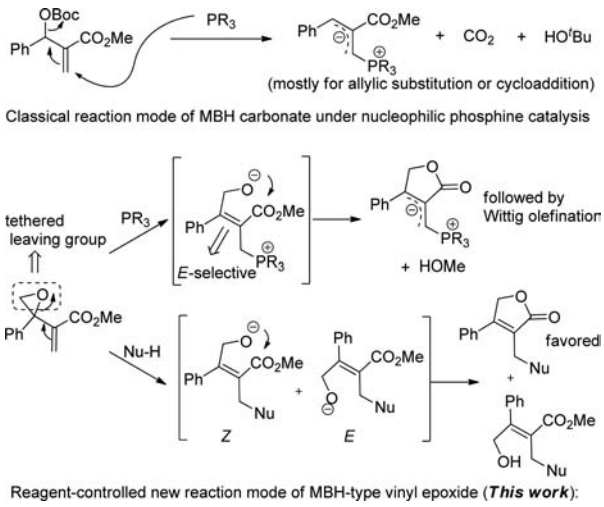
In recent decades, transformations of Morita−Baylis−Hillman (MBH) adducts under the nucleophilic catalysis of a tertiary amine or phosphine have emerged as powerful tools for accessing all sorts of unsaturated cyclic compounds in an asymmetric[5] or nonasymmetric manner.[6] In this regard, the major reported reactivity pattern of MBH adducts under such catalysis involves the formation of a key zwitterion, enabled by the presence of the leaving group at the allylic position, which may be used for various allylic substitutions (Scheme 1).[7] Notably, several recent examples have demonstrated that structural modifications of MBH adducts can readily be accomplished.[8]

In this context, we reasoned that the use of substrate **1a** bearing an epoxide[9] as a tethered leaving group under the usual activation mode of nucleophilic catalysis might generate novel reactive intermediates with reactivities different from classical ones (Scheme 1). Herein, we report two reagent-controlled novel reaction modes with such substrates. In the first, the use of a stoichiometric amount of tertiary phosphine[10,11] enables a tandem S_N2'-type ring-opening/lactonization/Wittig olefination sequence of vinyl epoxides[12] with aryl trifluoromethyl ketones or aryl aldehydes to give 3-vinyl γ-butenolide products in moderate-to-good yields and with high *E*/*Z* selectivity. In the

Received: February 9, 2016
Published: March 4, 2016

DOI: 10.1021/acs.orglett.6b00392
Org. Lett. 2016, 18, 1450−1453

Scheme 1. Reactivity Patterns of MBH Adduct and Vinyl Epoxide

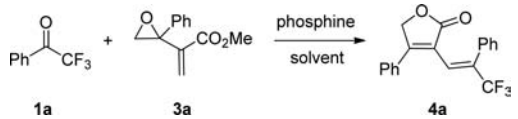


second, a tertiary amine allows for a tandem S_N2'-type ring-opening/lactonization sequence of vinyl epoxides with carbon or nitrogen-based nucleophiles to deliver 3-substituted butenolide products with moderate-to-good yields and good chemoselectivity.

The vinyl epoxides employed in this research were easily prepared from commercially available α-bromo aryl ketones in two steps following a literature method.[13] The tandem reaction between phenyl trifluoromethyl ketone **1a** and vinyl epoxide **3a** was selected as a model reaction for optimization of the reaction conditions (Table 1). A screen of several tertiary phosphines showed ^{n}Bu$_3$P to be the best reagent for this reaction. Examination of other reaction parameters such as the ratio of **1a** and **3a**, solvent, and concentration revealed that the reaction was best performed by reacting trifluoromethyl ketone **1a** (2 equiv) with vinyl epoxide **3a** in the presence of ^{n}Bu$_3$P (1 equiv) at room temperature in CH_2Cl_2 as the solvent (Table 1, entry 6). Notably, the phosphine-mediated ring opening/lactonization sequence[12a,14] of vinyl epoxide took place smoothly to give the γ-butenolide-containing phosphine ylide intermediate, which underwent Wittig olefination with trifluoromethyl ketone **1a** without the need for an external base. The corresponding 3-vinyl butenolide product **4a** was isolated in good chemical yield and with high *E*-selectivity at the newly generated trifluoromethyl-substituted alkene bond. The configuration of *E*-isomer was determined by comparison with literature analogues,[11e] and the configurations of the other congeners were assigned accordingly.

The substrate generality of the tandem ring-opening/lactonization/Wittig reaction of vinyl epoxides and carbonyl compounds was then probed and summarized in Table 2. Different 4-substituted aryl trifluoromethyl ketones were well tolerated to produce the desired trifluoromethylated vinyl butenolides in moderate-to-good yields and with generally high *E*-selectivities. In the cases of the heterocyclic 2-thienyl CF_3 ketone **1h** (Table 2, entry 8) and one with a strongly electron-donating substituents **1e** (Table 2, entry 5), reduced yields were obtained, probably due to their lower reactivity for the Wittig reaction. The substituent on the oxirane could also tolerate a chloro-substituted phenyl group, which provided the butenolide product in an acceptable yield and satisfying geometrical selectivity (Table 2, entry 9). To our delight, the

Table 1. Survey of Conditions for the Ring-Opening/Lactonization/Wittig Tandem Reaction of Vinyl Epoxide and Trifluoromethyl Ketone[a]



1a **3a** **4a**

entry	concn	phosphine	solvent	**1a**/**3a**	**4a**[b] (%)	*E*/*Z* ratio[c]
1	0.1	Me_3P	CH_2Cl_2	2/1	37	ND[e]
2	0.1	Ph_3P	CH_2Cl_2	2/1	8	ND[e]
3	0.1	dppp	CH_2Cl_2	2/1	15	ND[e]
4	0.1	^{n}Bu$_3$P	CH_2Cl_2	1/1	64	11/1
5	0.1	^{n}Bu$_3$P	CH_2Cl_2	3/1	76	10/1
6	0.1	^{n}Bu$_3$P	CH_2Cl_2	2/1	88	11/1
7	0.2	^{n}Bu$_3$P	CH_2Cl_2	2/1	80	11/1
8	0.05	^{n}Bu$_3$P	CH_2Cl_2	2/1	76	10/1
12	0.1	^{n}Bu$_3$P	toluene	2/1	84	9/1
13[d]	0.1	^{n}Bu$_3$P	toluene	2/1	36	8/1
14	0.1	^{n}Bu$_3$P	$CHCl_3$	2/1	79	12/1
15	0.1	^{n}Bu$_3$P	Et_2O	2/1	40	9/1
16	0.1	^{n}Bu$_3$P	acetone	2/1	45	5/1
17	0.1	^{n}Bu$_3$P	ethyl acetate	2/1	78	7/1
18	0.1	^{n}Bu$_3$P	EtOH	2/1	15	ND[e]
19	0.1	^{n}Bu$_3$P	DMF	2/1	35	ND[e]
20	0.1	^{n}Bu$_3$P	*n*-hexane	2/1	45	6/1

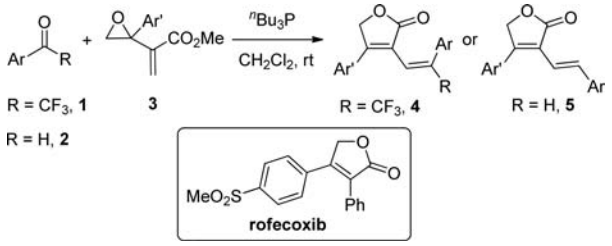
[a]Unless otherwise noted, ketone **1a** and vinyl epoxide **3a** (0.05 mmol) were stirred in the presence of phosphine at room temperature; the use of triarylphosphine proved fruitless. [b]Yields of isolated products. [c]Determined by ^{1}H NMR of crude product. [d]Reaction was carried out at 100 °C. [e]Not determined. Dppp = 1,3-bis(diphenylphosphino)-propane.

tandem reaction also worked well for a range of aryl aldehydes. A range of 3-vinyl butenolides were isolated with good *E*-selectivities, albeit with marginally diminished yields compared to those obtained with trifluoromethyl ketones. The presence of electron-donating substituents at the *ortho* position of phenyl ring was detrimental to the chemical yield but seemingly had a negligible influence on the *E*/*Z* selectivity of the reaction (Table 2, entry 15). The heteroaryl aldehyde **2h** and sterically demanding substrate **2i** were also amenable to our protocol (Table 2, entry 16, 17). However, neither aliphatic CF_3 ketone nor aliphatic aldehyde were suitable substrates. These tended to deliver a messy outcome, and considerable starting material remained unchanged. Noteworthy is the fact that the styrenyl-substituted butenolide product **5a** may be viewed as a vinylogous congener of rofecoxib, a widely used nonsteroidal anti-inflammatory drug that was withdrawn from the market.[15]

Recently, Ramachandran's group reported a catalyst-free tandem amination−lactonization reaction for the synthesis of α-aminomethyl lactones with excellent yields and diastereoselectivities.[16] Inspired by this elegant work, further efforts were devoted to carrying out the tandem ring-opening/lactonization directly initiated by the Michael addition of a secondary amine or other nitrogen nucleophiles to vinyl epoxide **3** (Scheme 2). When the vinyl epoxide **3a** and cyclic secondary amine morpholine were reacted in the presence of triethylamine at room temperature for 12 h, the desired aminolactonization product **7a** was obtained in 81% yield, together with Michael adduct *E*-**7a**′ in 11% yield. The vinyl epoxide with a 3-chlorophenyl group was compatible with this transformation

DOI: 10.1021/acs.orglett.6b00392
Org. Lett. 2016, 18, 1450−1453

Table 2. Reaction Scope of the Tandem Ring-Opening/Lactonization/Wittig Reactions[a]



entry	1 or 2, R, Ar	3, Ar′	time (h)	product	yield[b] (%)	E/Z[c]
1	**1a**, CF_3, Ph	**3a**, Ph	10	**4a**	88	11/1
2	**1b**, CF_3, 4-BrC_6H_4	**3a**, Ph	10	**4b**	76	9/1
3	**1c**, CF_3, 4-FC_6H_4	**3a**, Ph	10	**4c**	76	>19/1
4	**1d**, CF_3, 4-ClC_6H_4	**3a**, Ph	10	**4d**	75	>19/1
5	**1e**, CF_3, 4-$MeOC_6H_4$	**3a**, Ph	10	**4e**	58	10/1
6	**1f**, CF_3, 4-EtC_6H_4	**3a**, Ph	10	**4f**	79	14/1
7	**1g**, CF_3, 4-MeC_6H_4	**3a**, Ph	10	**4g**	74	>19/1
8	**1h**, CF_3, 2-thienyl	**3a**, Ph	12	**4h**	57	8/1
9	**1a**, CF_3, Ph	**3b**, 3-ClC_6H_4	10	**4ab**	62	10/1
10	**2a**, H, Ph	**3a**, Ph	15	**5a**	61	9/1
11	**2b**, H, 3-ClC_6H_4	**3a**, Ph	15	**5b**	66	15/1
12	**2c**, H, 4-FC_6H_4	**3a**, Ph	15	**5c**	75	19/1
13	**2d**, H,2-ClC_6H_4	**3a**, Ph	15	**5d**	73	19/1
14	**2f**, H, 3-$MeOC_6H_4$	**3a**, Ph	15	**5f**	69	>19/1
15	**2g**, H, 2-$MeOC_6H_4$	**3a**, Ph	15	**5g**	55	11/1
16	**2h**, H, 2-thienyl	**3a**, Ph	15	**5h**	68	9/1
17	**2i**, H, 2-naphthyl	**3a**, Ph	15	**5i**	76	19/1

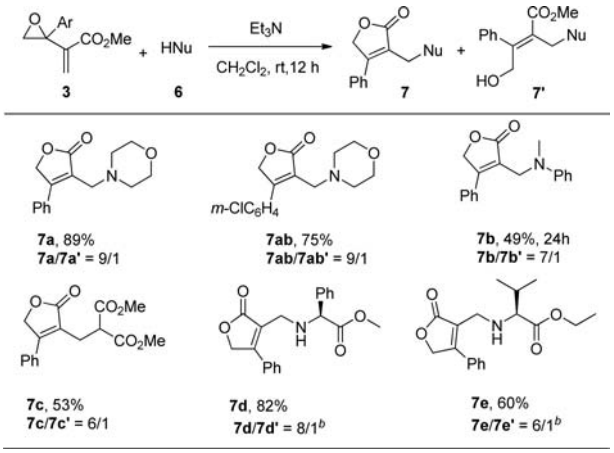
[a]Unless otherwise noted, all reactions were carried out with **1** or **2** (0.1 mmol) and **3** (0.05 mmol) in the presence of phosphine (0.05 mmol) in CH_2Cl_2 (1.0 mL) for the indicated time at room temperature. [b]Yields of isolated product. [c]Determined by ^1H NMR analysis of crude products.

and afforded the expected compounds with a moderate yield and an acceptable chemoselectivity. Use of *N*-methylaniline resulted in a diminished yield, which may be explained by its unfavorable sterics in comparison to morpholine. In addition, the carbon-based nucleophile dimethyl malonates also underwent the reaction smoothly to provide the desired product **7c** in acceptable yields and selectivity. More importantly, α-amino acid esters performed well in this transformation, with ethanol as solvent, which led to the formation of γ-butenolide-containing amino acid derivatives in 60−82% yields with moderate chemoselectivities.

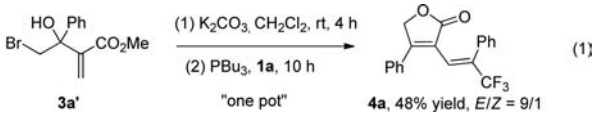
To further simplify the procedure, a tandem ring-closing/ring-opening/lactonization/Wittig four-step sequence directly from the bromohydrin **8** (the direct precursor to the vinyl epoxide **3a**) was realized in a one-pot fashion, albeit in a moderate chemical yield (eq 1).

In summary, we have disclosed two novel tandem reaction sequences of vinyl epoxides possessing the backbone of MBH adducts. They are mediated by simple tertiary phosphine or

Scheme 2. Tandem Michael Addition/Ring-Opening/Lactonization of Vinyl Epoxide 3 with Various Nucleophilic Reagents 6[a]



[a]Unless otherwise noted, all reactions were carried out with **6** (0.1 mmol) and **3** (0.05 mmol) in the presence of triethylamine (0.05 mmol) in CH_2Cl_2 (1.0 mL) at room temperature; yields of isolated product provided; chemoselectivity ratios were based on the isolated yields. [b]The reaction was conducted in ethanol as solvent.



amines and provide a mild metal-free path to functionalized γ-butenolides in moderate to good yields and good to excellent chemo- and stereoselectivities. In the presence of tertiary phosphine, the ring-opening/lactonization/Wittig cascade of vinyl epoxides with CF_3 ketone or aryl aldehyde occurred while in the presence of amine-based nucleophiles or malonates, and a tandem Michael addition/ring-opening/lactonization reaction took place. Further elaboration of the vinyl epoxides to other types of nucleophilic catalysis reactions as well as the development of their enantioselective versions are being actively pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00392.

Experimental procedures; characterization data of **4**, **5**, and **7** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xiaohua@hfut.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the National Natural Science Foundation of China (Grant Nos. 21302034 and 21372058), the Fundamental Research Funds for the

DOI: 10.1021/acs.orglett.6b00392
Org. Lett. 2016, 18, 1450−1453

Central Universities, and the supporting fund for young researchers of the Hefei University of Technology.

REFERENCES

(1) (a) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426. (b) Patt, W. C.; Cheng, X.-M.; Repine, J. T.; Lee, C.; Reisdorph, B. R.; Massa, M. A.; Doherty, A. M.; Welch, K. M.; Bryant, J. W.; Flynn, M. A.; Walker, D. M.; Schroeder, R. L.; Haleen, S. J.; Keiser, J. A. *J. Med. Chem.* **1999**, *42*, 2162.

(2) (a) Michel, K.; Büther, K.; Law, M. P.; Wagner, S.; Schober, O.; Hermann, S.; Schäfers, M.; Riemann, B.; Höltke, C.; Kopka, K. *J. Med. Chem.* **2011**, *54*, 939. (b) Fukui, K.; Ito, S.; Ueno, K.; Yamaguchi, S.; Kyozuka, J.; Asami, T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4905. (c) Li, J.; Yang, P.; Yao, M.; Deng, J.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 16477.

(3) (a) Yang, H.; Gao, Y.; Qiao, X.; Xie, L.; Xu, X. *Org. Lett.* **2011**, *13*, 3670. (b) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (c) Zheng, Y.-C.; Duan, Y.-C.; Ma, J.-L.; Xu, R.-M.; Zi, X.; Lv, W.-L.; Wang, M.-M.; Ye, X.-W.; Zhu, S.; Mobley, D.; Zhu, Y.-Y.; Wang, J.-W.; Li, J.-F.; Wang, Z.-R.; Zhao, W.; Liu, H.-M. *J. Med. Chem.* **2013**, *56*, 8543.

(4) (a) Mao, B.; Geurts, K.; Fañanás-Mastral, M.; van Zijl, A. W.; Fletcher, S. P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2011**, *13*, 948. (b) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1775. (c) Lee, D.; Newman, S. G.; Taylor, M. S. *Org. Lett.* **2009**, *11*, 5486.

(5) (a) Liu, T.-Y.; Xie, M.; Chen, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4101. (b) Wang, Q.-L.; Peng, L.; Wang, F.-Y.; Zhang, M.-L.; Jia, L.-N.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2013**, *49*, 9422. (c) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202.

(6) (a) Zhang, Q.; Meng, L.-G.; Wang, K.; Wang, L. *Org. Lett.* **2015**, *17*, 872. (b) Chen, Z.; Zhang, J. *Chem. - Asian J.* **2010**, *5*, 1542.

(7) (a) Mao, J.; Lin, A.; Shi, Y.; Mao, Z.; Zhu, X.; Li, W.; Hu, H.; Cheng, Y.; Zhu, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 6288. (b) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 172.

(8) (a) Gu, Y.; Li, F.; Hu, P.; Liao, D.; Tong, X. *Org. Lett.* **2015**, *17*, 1106. (b) Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 13183.

(9) For nucleophilic phosphine-promoted reactions of small rings, see: (a) Li, Y.; Su, X.; Zhou, W.; Li, W.; Zhang, J. *Chem. - Eur. J.* **2015**, *21*, 4224. (b) Yang, Y.-L.; Zhang, Z.; Zhang, X.-N.; Wang, D.; Wei, Y.; Shi, M. *Chem. Commun.* **2014**, *50*, 115.

(10) For latest examples of nucleophilic catalysis, see: (a) Wang, F.; Luo, C.; Shen, Y.-Y.; Wang, Z.-D.; Li, X.; Cheng, J.-P. *Org. Lett.* **2015**, *17*, 338−341. (b) Gicquel, M.; Zhang, Y.; Aillard, P.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 5470. (c) Fan, Y. C.; Kwon, O. *Org. Lett.* **2015**, *17*, 2058. (d) Zhao, W.; Yan, P. K.; Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, *137*, 616. (e) Lee, C.-J.; Tsai, C.-C.; Hong, S.-H.; Chang, G.-H.; Yang, M.-C.; Möllmann, L.; Lin, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 8502. (f) Dong, X.; Liang, L.; Li, E.; Huang, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 1621. (g) Fang, Y.-Q.; Tadross, P. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 17966.

(11) For our previous work on phosphine catalysis, see: (a) Xiao, H.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4467. (b) Xiao, H.; Chai, Z.; Wang, H.- F.; Wang, X.-W.; Cao, D.-D.; Liu, W.; Lu, Y.-P.; Yang, Y.-Q.; Zhao, G. *Chem. - Eur. J.* **2011**, *17*, 10562. (c) Xiao, H.; Chai, Z.; Cao, D.; Wang, H.; Chen, J.; Zhao, G. *Org. Biomol. Chem.* **2012**, *10*, 3195. (d) Xiao, H.; Chai, Z.; Yao, R.-S.; Zhao, G. *J. Org. Chem.* **2013**, *78*, 9781. (e) Xiao, H.; Duan, H.; Ye, J.; Yao, R.; Ma, J.; Yuan, Z.; Zhao, G. *Org. Lett.* **2014**, *16*, 5462.

(12) For vinyl epoxide chemistry, see: (a) He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, 8037. (b) Ilardi, E. A.; Njardarson, J. T. *J. Org. Chem.* **2013**, *78*, 9533. (c) Ohno, H. *Chem. Rev.* **2014**, *114*, 7784. (d) Jiao, L.; Yu, Z.-X. *J. Org. Chem.* **2013**, *78*, 6842. (e) Feng, J.; Garza, V. J.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8911.

(13) Ramachandran, P. V.; Krzeminski, M. P. *Tetrahedron Lett.* **1999**, *40*, 7879.

(14) For related expansion reaction of oxirane, see: (a) Kondoh, A.; Odaira, K.; Terada, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11240. (b) Davoust, M.; Cantagrel, F.; Metzner, P.; Brière, J.-F. *Org. Biomol. Chem.* **2008**, *6*, 1981.

(15) Bombardier, C.; Laine, L.; Reicin, A.; Shapiro, D.; Burgos-Vargas, R.; Davis, B.; Day, R.; Ferraz, M. B.; Hawkey, C. J.; Hochberg, M. C.; Kvien, T. K.; Schnitzer, T. J. *N. Engl. J. Med.* **2000**, *343*, 1520.

(16) Ramachandran, P. V.; Nicponski, D. R. *Chem. Commun.* **2014**, *50*, 15216.

DOI: 10.1021/acs.orglett.6b00392
Org. Lett. 2016, 18, 1450−1453