OL Organic Letters

pubs.acs.org/OrgLett Letter

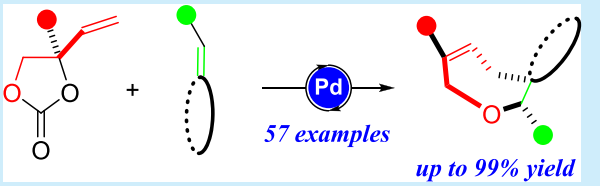
Palladium-Catalyzed [5 + 2] Annulation of Vinylethylene Carbonates with Barbiturate-Derived Alkenes

Xing Gao, Dongyu Zhu, Yuehua Chen, Hao Deng, Feng Jiang, Wei Wang, Yongjun Wu, and Hongchao Guo*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02508 Read Online

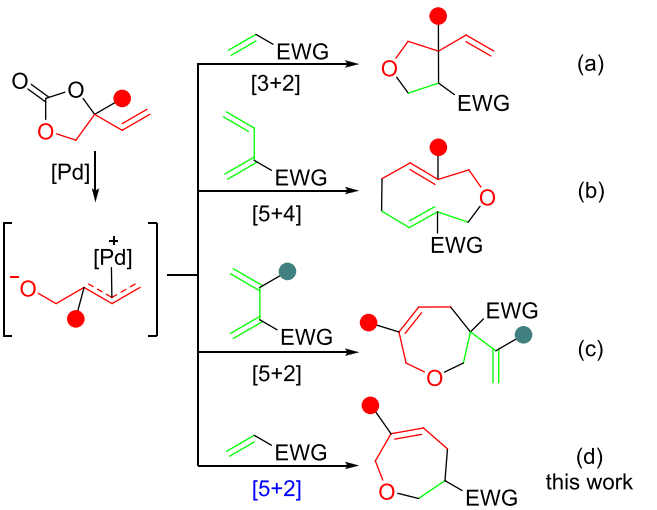
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A palladium/XantPhos-catalyzed [5 + 2] annulation of VECs with electron-deficient alkenes having an isolated carbon−carbon double bond has been developed to afford spirobarbiturate-tetrahydrooxepines. This study provides an expedient assembly of biologically interesting spirobarbiturate-tetrahydrooxepines. The easy scalability and versatile transformability of the reaction products were also exhibited.



Vinylethylene carbonates (VECs) have been demonstrated as a versatile synthon for the construction of cyclic and acyclic molecular scaffolds.[1] On the one hand, VECs have been used in allylic substitution reactions.[2] On the other hand, [3+*n*] and [5+*n*] cycloadditions of VECs are exceptional synthetic tools that provide efficient avenues toward the rapid synthesis of various cyclic molecules.[3] A broad range of substrates including aldehydes,[3a] alkenes,[3b−d] isocyanates,[3e] imines,[3f,g] azadienes,[3h] azomethine imines,[3i] benzoxazinanones,[3j] enals[3k] and electron-deficient conjugated 1,3-dienes[3o,p] have been exploited as the electrophilic reagents in diverse Pd-catalyzed annulation reactions of VECs. Among these electrophilic coupling reagents, alkenes are particularly fascinating for synthesis of oxygen-containing heterocycles and have attracted much attention. In principle, all types of electron-deficient alkenes can perform the cycloaddition reaction with VECs under palladium catalysis. In previous reports, electron-deficient alkenes having an isolated carbon−carbon double bond such as methylenemalononitriles,[3b] 3-cyanochromones,[3c] and *β*-nitroolefins[3d] have been used in Pd-catalyzed [3 + 2] annulation reactions of VECs to construct tetrahydrofuran derivatives (Scheme 1a). However, those alkenes having an isolated carbon−carbon double bond have not been successfully tamed in Pd-catalyzed [5 + 2] cycloaddition of VECs to construct medium-ring heterocycles, in which the zwitterionic palladium intermediates generated from VECs through decarboxylation serve as 1,5-dipoles. Due to their unfavorable transannular interactions[4] as compounds and competitive [3 + 2] annulation, Pd-catalyzed [5 + 2] annulation of VECs and the isolated carbon−carbon double bond represent a formidable challenge.[3k] In our previous work, we realized a Pd-catalyzed [5 + 4] annulation of electron-deficient conjugated 1,3-dienes with VECs via tandem [3 + 2] cycloaddition/Cope rearrangement to achieve synthesis of nine-membered cyclic compounds[3p] (Scheme 1b). Most recently, Peng and Han reported [5 + 4] and [5 + 2] annulations of VECs and conjugated 1,3-dienes for synthesis of seven- and nine-membered rings[3o] (Scheme 1b and 1c). As our continuous efforts on the cycloaddition reactions,[5] we herein describe an unprecedented palladium-catalyzed formal [5 + 2] cycloaddition of barbiturate-derived alkenes (BDAs) with VECs to synthesize functionalized spirobarbiturate-tetrahydrooxepines (Scheme 1d).

Scheme 1. Palladium-Catalyzed Annulation Reactions of VECs with Alkenes



Received: July 28, 2020

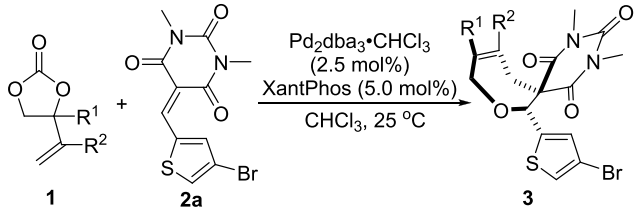
https://dx.doi.org/10.1021/acs.orglett.0c02508
Org. Lett. XXXX, XXX, XXX−XXX

As a readily accessible reaction partner[6] and pharmaceutically interesting skeleton,[7] barbiturate-derived alkenes were an ideal target for the current work. We chose the VEC **1a** with BDA **2a** as model reaction to investigate the optimal reaction conditions (Table S1). After an extensive investigation of reaction parameters, the optimal conditions for the [5 + 2] cycloaddition reaction were ultimately identified as follows: $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol %) as a catalyst and XantPhos (5.0 mol %) as a ligand in $CHCl_3$ at room temperature.

With the optimized reaction conditions in hand, the scope of VECs in this [5 + 2] annulation was examined first (Table 1). It is worth pointing out that the [3 + 2] cycloaddition product **4** has not been observed in all the following cases (see below). A wide range of substituted phenyl-VECs having different electronic and steric properties were well-tolerated and a number of spirobarbiturate-tetrahydrooxepines (**3aa**−**3ua**) were readily constructed (entries 1−21). Obviously, the steric hindrance makes much difference on the yield of corresponding products. For example, the VECs **1b** and **1i** bearing *o*-methyl- and *o*-fluorophenyl underwent the annulation reaction to afford the products **3ba** and **3ia** in 52% and 63% yield, respectively, in comparison, *meta*- and *para*-substituted substrates provided the corresponding products in >80% yield (entry 2 vs entries 3, 4 and entry 9 vs entries 10 and 11). The installation of a heterocycle in the spiro compounds was also workable (entry 24). The unsubstituted, methyl-, and *tert*-butyl-substituted VECs did not react with alkene **2a** (entries 25−27), probably due to instability of the corresponding seven-membered ring of products. Interestingly, the annulation product with a cyclohexyl group could be obtained in 65% yield through using a higher catalyst loading (7.5 mol % $Pd_2dba_3{\cdot}CHCl_3$) (entry 28). The vinyl-substituted VEC was also proved to be reactive to afford the product in 94% yield (entry 29). Additionally, the process also worked well for substrate VEC having a methyl group at alkenyl motif to furnish corresponding spiro compounds in 87% yield (entry 30). The structure of the product **3oa** was unequivocally determined through X-ray crystallographic data and that of other products was established by analogy.

In order to further amplify the scope of the reaction, we then systematically varied the BDAs to produce the annulation products **3** (Table 2). The alkene bearing a phenyl group led

Table 1. Scope of [5 + 2] Cycloaddition of VECs[a]

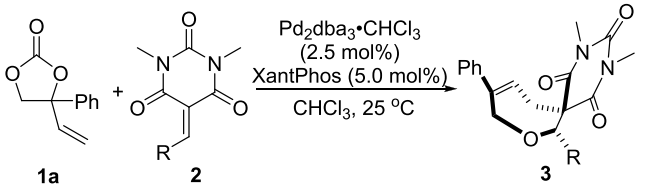


1 2a 3

entry	R^1	R^2	time (h)	3	yield[b] (%)
1	Ph	H	36	**3aa**	99
2	2-MeC_6H_4	H	36	**3ba**	52
3	3-MeC_6H_4	H	36	**3ca**	99
4	4-MeC_6H_4	H	36	**3da**	96
5	4-*t*-BuC_6H_4	H	36	**3ea**	99
6	2-$OMeC_6H_4$	H	80	**3fa**	78
7	3-$OMeC_6H_4$	H	46	**3ga**	82
8	4-$OMeC_6H_4$	H	24	**3ha**	86
9	2-FC_6H_4	H	70	**3ia**	63
10	3-FC_6H_4	H	36	**3ja**	99
11	4-FC_6H_4	H	36	**3ka**	85
12	2,4-$F_2C_6H_3$	H	60	**3la**	97
13	2-ClC_6H_4	H	72	**3ma**	83
14	3-ClC_6H_4	H	25	**3na**	97
15	4-ClC_6H_4	H	36	**3oa**	99
16	3,4-$Cl_2C_6H_3$	H	42	**3pa**	83
17	2-BrC_6H_4	H	52	**3qa**	94
18	3-BrC_6H_4	H	48	**3ra**	99
19	4-BrC_6H_4	H	36	**3sa**	99
20	4-CNC_6H_4	H	48	**3ta**	86
21	4-PhC_6H_4	H	49	**3ua**	84
22	1-naphthyl	H	72	**3va**	55
23	2-naphthyl	H	36	**3wa**	90
24	3-thienyl	H	12	**3xa**	99
25	H	H	93		NR[c]
26	Me	H	93		NR
27	*t*-Bu	H	72		NR
28	cyclohexyl	H	72	**3zc**	65[d]
29	vinyl	H	4	**3zd**	94
30	Ph	Me	72	**3ze**	87

[a]Unless noted otherwise, the reaction of **1** (0.15 mmol), **2a** (0.10 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol %), and XantPhos (5.0 mol %) was performed in 1.0 mL of $CHCl_3$ under the indicated reaction conditions. [b]Isolated yield. [c]No reaction. [d]The reaction was carried out with 7.5 mol % of $Pd_2dba_3{\cdot}CHCl_3$ and 15 mol % of XantPhos.

Table 2. Scope of [5 + 2] Cycloaddition of BDAs[a]



1a 2 3

entry	R	time (h)	3	yield[b] (%)
1	Ph	48	**3ab**	37, 69[c]
2	4-MeC_6H_4	48	**3ac**	NR[c,d,e]
3	4-$OMeC_6H_4$	42	**3ad**	35, 64[e]
4	3,4-$(OMe)_2C_6H_3$	42	**3ae**	73
5	4-FC_6H_4	48	**3af**	NR[c,e]
6	4-ClC_6H_4	48	**3ag**	NR[c,e]
7	2-naphthyl	48	**3ah**	NR, 43[c]
8	2-pyridyl	48	**3ai**	trace[c,e]
9	3-pyridyl	48	**3aj**	trace, 88[c]
10	4-pyridyl	48	**3ak**	NR[c,e]
11	2-furanyl	23	**3al**	82
12	3-furanyl	23	**3am**	30, 64[e]
13	2-thienyl	48	**3an**	trace[c,e]
14	3-thienyl	48	**3ao**	91
15	3-Me-2-thienyl	17	**3ap**	69
16	5-Me-2-thienyl	43	**3aq**	60
17	5-Cl-2-thienyl	23	**3ar**	46
18	2-benzofuran	12	**3as**	46
19[e]	cyclohexyl	24	**3au**	63

[a]Unless noted otherwise, the reaction of **1a** (0.15 mmol), **2** (0.10 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol %), and XantPhos (5.0 mol %) was performed in 1.0 mL of $CHCl_3$ under the indicated reaction conditions. [b]Isolated yield. [c]The reaction was performed with 5.0 mol % of $Pd_2dba_3{\cdot}CHCl_3$ and 20 mol % of PPh_3 in 1.0 mL of CH_2Cl_2. [d]No reaction. [e]5.0 mol % of $Pd_2dba_3{\cdot}CHCl_3$ and 10 mol % of XantPhos were used.

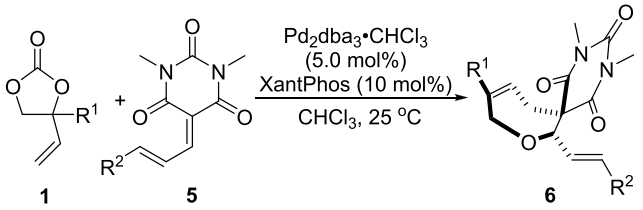
https://dx.doi.org/10.1021/acs.orglett.0c02508
Org. Lett. XXXX, XXX, XXX−XXX

to a 37% yield of the product (entry 1). In order to increase the yield, many experiments were carried out to tune reaction parameters. Out of various trials (see Table S2), the use of PPh_3 as ligand and dichloromethane as solvent led to an appreciable conversion, affording **3ab** in 69% isolated yield (entry 1). Surprisingly, BDAs bearing methyl- or electron-withdrawing substituents on the aromatic group failed to provide the desired products (entries 2, 5, and 6). Conversely, *p*-methoxyphenyl and 3,4-dimethoxyphenyl-substituted alkenes **2d** and **2e** were suitable for this transformation, delivering the products **3ad** and **3ae** (entries 3 and 4), indicating that the electron-rich group was beneficial to the reaction. Meaningfully, alkene with naphthyl was effective for this transformation (entry 7). Notably, the reaction of alkenes derived from picolinaldehyde and isonicotinaldehyde led to a trace amount of the seven-membered ring product, while the anti-Knoevenagel condensation/allylic alkylation product **11** was obtained as a major product (see Scheme S1). However, BDAs containing 3-pyridyl and furanyl moieties were tolerated under the reaction conditions to give the products in 64−88% yield (entries 9, 11, and 12). The alkenes from 2-thiophenecarboxaldehyde and benzofurancarboxaldehyde were also suitable for this transformation, giving the products **3ao**−**3as** (entries 14−18), whereas 2-thienyl olefin **2n** was unproductive (entry 13). The alkene having an aliphatic substituent was practicable, although a higher amount of Pd catalyst (5.0 mol %) was necessary (entry 19).

Following exploration of the substrate scope of olefins derived from aromatic and aliphatic aldehydes, we attempted to develop [5 + 2] annulation of cinnamaldehyde-derived olefins to construct alkenyl-substituted spiro seven-membered cyclic products and optimization was carried out (see Table S3). To our delight, the [5 + 2] annulation reaction of VEC **1a** with styryl olefin **5a** in the presence of $Pd_2dba_3{\cdot}CHCl_3$ at ambient temperature proceeded smoothly to afford the annulation product **6aa** in 72% yield. As outlined in Table 3, it can be seen that VECs with different electron-donating or electron-withdrawing substituents worked well to give the corresponding products in moderate to high yield (entries 2−4 and 9−18). When olefins **5d** and **5e**, which feature a methyl or a methoxy on phenyl group, respectively, were used as the material, the reaction failed to give the corresponding products under standard conditions (entries 7 and 8). Contrary to the results in Table 2, the electron-rich group in the substrate **5** was unfavorable for the reaction. Olefins bearing an electron-withdrawing group and thienyl were both competent substrates (entries 9−18). In addition, α-amylcinnamaldehyde-derived alkene favorably produced **6ai** in 98% yield (entry 19). We clearly determined the structure of **6of** by the single-crystal X-ray analysis and assigned that of the other products by analogy.

Subsequently, we attempted to develop an asymmetric variant of palladium-catalyzed [5 + 2] annulation reaction. Although different palladium salts, ligands, solvents, reaction temperatures, and substrates with different functional groups had been screened, attempts to increase the yield and improve enantioselectivity of the reaction failed and only trace amount of the desired product was observed in most cases. Overall, spiro seven-membered cyclic product **6aa** was obtained in 17% yield with 96% ee in the presence of $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol %) and the chiral phosphoramidite **L1** (10 mol %) (Scheme 2). The absolute configuration of the chiral product **6aa** had not been assigned. Since asymmetric annulation reaction gave the higher ratio of [3 + 2] cycloadduct **7aa** and

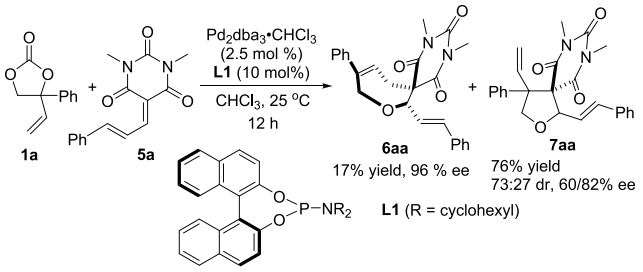
Table 3. Scope of Cinnamaldehyde-Derived Alkenes for Pd-Catalyzed [5 + 2] Cycloaddition of VECs[a]



entry	R^1	R^2	*t*/h	6	yield (%)[b]
1	Ph	Ph	10	**6aa**	72
2	4-MeC_6H_4	Ph	35	**6da**	52
3	4-$OMeC_6H_4$	Ph	35	**6ha**	48
4	4-PhC_6H_4	Ph	17	**6ua**	53
5	Ph	2-ClC_6H_4	18	**6ab**	53
6	Ph	4-ClC_6H_4	28	**6ac**	66
7	Ph	4-MeC_6H_4	12	**6ad**	trace
8	Ph	4-$OMeC_6H_4$	12	**6ae**	trace
9	4-ClC_6H_4	4-ClC_6H_4	46	**6oc**	48
10	4-ClC_6H_4	4-BrC_6H_4	46	**6of**	32
11	4-ClC_6H_4	4-Br-2-thienyl	48	**6og**	46
12	4-BrC_6H_4	4-ClC_6H_4	12	**6sc**	29
13	4-BrC_6H_4	4-BrC_6H_4	12	**6sf**	28
14	4-BrC_6H_4	4-Br-2-thienyl	12	**6sg**	34
15	4-PhC_6H_4	4-ClC_6H_4	48	**6uc**	37
16	4-PhC_6H_4	3-BrC_6H_4	38	**6uh**	49
17	4-PhC_6H_4	4-BrC_6H_4	38	**6uf**	44
18	4-PhC_6H_4	4-Br-2-thienyl	46	**6ug**	45
19	Ph		12	**6ai**	98

[a]Unless noted otherwise, the reaction of **1** (0.15 mmol), **5** (0.10 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (5.0 mol %), and XantPhos (10 mol %) was stirred in 1.0 mL of $CHCl_3$ under the indicated reaction conditions. [b]Isolated yield.

Scheme 2. Asymmetric Variant of [5 + 2] Annulation

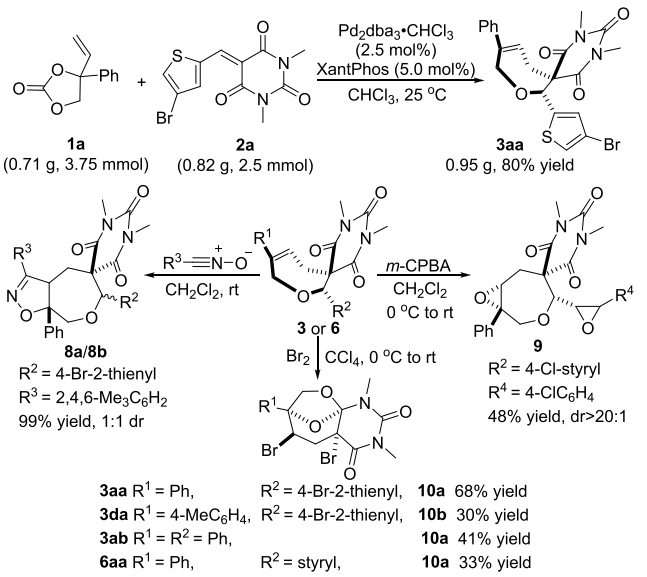


spirotetrahydrofurans are also biologically important compounds,[8] optimization was performed to explore stereoselective [3 + 2] annulation of **1a** and **5a** (see Table S4). Spiroketal-based diphosphine (SKP)[9] was found to be the optimal choice and afforded the product **7aa** in 95% yield with 99/96% ee and 83:17 dr. The reaction of a series of alkenes **2** and a range of VECs **1** gave products **7** with moderate to good yield with excellent enantioselectivity and good diastereoselectivity (see Table S5).

As shown in Scheme 3, to demonstrate the efficiency and the usefulness of this catalytic process, a gram-scale reaction of VEC **1a** and olefin **2a** was conducted under the optimized reaction conditions, furnishing the seven-membered spirocyclic product **3aa** in 80% yield (0.95 g). Importantly, **3aa** could undergo 1,3-dipolar cycloaddition reaction with nitrile oxides, producing a mixture of diastereoisomers of isoxazole-fused

https://dx.doi.org/10.1021/acs.orglett.0c02508
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Gram-Scale Reaction and Postfunctionalization



spirobarbiturate-tetrahydrooxepines **8a** and **8b** in 99% yield with the dr of 1:1. Furthermore, direct epoxidation of **6ah** provided **9** with two oxiranes ring in 48% yield with a single diastereomer. Interestingly, bromination of the product **3** or **6** resulted in a 6,8-dioxabicyclo[3.2.1]octane derivatives **10a** or **10b**. The configurations of the derivatives were unambiguously confirmed by single-crystal X-ray diffraction analysis.

In conclusion, we have developed a palladium-catalyzed [5 + 2] annulation of VECs with electron-deficient alkenes having an isolated carbon−carbon double bond, offering a useful tool for the synthesis of spirobarbiturate-tetrahydrooxepines. A broad range of VECs and BDAs were compatible in this procedure and were converted into the corresponding spiro seven-membered ring compounds in high yields. A gram-scale reaction and a series of synthetic transformations of these products were also demonstrated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02508.

Experimental procedure, characterization data, NMR spectra, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1985800−1985805 and 1991932 contain 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

Hongchao Guo − *Department of Chemistry and Innovation Center of Pesticide Research, China Agricultural University, Beijing 100193, P.R. China;* orcid.org/0000-0002-7356-4283; Email: hchguo@cau.edu.cn

Authors

Xing Gao − *Department of Chemistry and Innovation Center of Pesticide Research, China Agricultural University, Beijing 100193, P.R. China;* orcid.org/0000-0001-6254-2583

Dongyu Zhu − *Department of Chemistry and Innovation Center of Pesticide Research, China Agricultural University, Beijing 100193, P.R. China*

Yuehua Chen − *Department of Chemistry and Innovation Center of Pesticide Research, China Agricultural University, Beijing 100193, P.R. China*

Hao Deng − *Department of Chemistry and Innovation Center of Pesticide Research, China Agricultural University, Beijing 100193, P.R. China*

Feng Jiang − *Department of Chemistry and Innovation Center of Pesticide Research, China Agricultural University, Beijing 100193, P.R. China*

Wei Wang − *College of Public Health, Zhengzhou University, Zhengzhou 450001, P.R. China*

Yongjun Wu − *College of Public Health, Zhengzhou University, Zhengzhou 450001, P.R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02508

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the Natural Science Foundation of China (No. 21871293) and Chinese Universities Scientific Fund (Nos. 2018TC052, 2018TC055, and 2019TC085).

■ REFERENCES

(1) For a recent review of VECs, see: Guo, W.; Gómez, J. E.; Cristòfol, À.; Xie, J.; Kleij, A. W. Catalytic Transformations of Functionalized Cyclic Organic Carbonates. *Angew. Chem., Int. Ed.* **2018**, *57*, 13735−13747.

(2) Selected examples: (a) Trost, B. M.; Aponick, A. Palladium-catalyzed asymmetric allylic alkylation of meso- and dl-1,2-divinylethylene carbonate. *J. Am. Chem. Soc.* **2006**, *128*, 3931−3933. (b) Zhang, Y. J.; Yang, J. H.; Kim, S. H.; Krische, M. J. anti-Diastereo- and enantioselective carbonyl (hydroxymethyl)allylation from the alcohol or aldehyde oxidation level: allyl carbonates as allylmetal surrogates. *J. Am. Chem. Soc.* **2010**, *132*, 4562−4563. (c) Cai, A.; Guo, W.; Martinez-Rodriguez, L.; Kleij, A. W. Palladium-Catalyzed Regio- and Enantioselective Synthesis of Allylic Amines Featuring Tetrasubstituted Tertiary Carbons. *J. Am. Chem. Soc.* **2016**, *138*, 14194−14197. (d) Guo, W.; Martinez-Rodriguez, L.; Kuniyil, R.; Martin, E.; Escudero-Adan, E. C.; Maseras, F.; Kleij, A. W. Stereoselective and Versatile Preparation of Tri- and Tetrasubstituted Allylic Amine Scaffolds under Mild Conditions. *J. Am. Chem. Soc.* **2016**, *138*, 11970−11978. (e) Guo, W.; Martinez-Rodriguez, L.; Martin, E.; Escudero-Adan, E. C.; Kleij, A. W. Highly Efficient Catalytic Formation of (Z)-1,4-But-2-ene Diols Using Water as a Nucleophile. *Angew. Chem., Int. Ed.* **2016**, *55*, 11037−11040. (f) Khan, A.; Khan, S.; Khan, I.; Zhao, C.; Mao, Y.; Chen, Y.; Zhang, Y. J. Enantioselective Construction of Tertiary C-O Bond via Allylic Substitution of Vinylethylene Carbonates with Water and Alcohols. *J. Am. Chem. Soc.* **2017**, *139*, 10733−10741. (g) Miralles, N.; Gomez, J. E.; Kleij, A. W.; Fernandez, E. Copper-Mediated SN2' Allyl-Alkyl and Allyl-Boryl Couplings of Vinyl Cyclic Carbonates. *Org. Lett.* **2017**, *19*, 6096−6099. (h) Guo, W.; Kuniyil, R.; Gomez, J. E.; Maseras, F.; Kleij, A. W. A Domino Process toward Functionally Dense Quaternary Carbons through Pd-Catalyzed Decarboxylative C(sp(3))-C(sp(3)) Bond Formation. *J. Am. Chem. Soc.* **2018**, *140*, 3981−3987. (i) Wang, H.; Qiu, S.; Wang, S.; Zhai, H. Pd-Catalyzed Umpolung of π−

https://dx.doi.org/10.1021/acs.orglett.0c02508
Org. Lett. XXXX, XXX, XXX−XXX

Allylpalladium Intermediates: Assembly of All-Carbon α-Vinyl Quaternary Aldehydes through C(sp3)−C(sp3) Coupling. *ACS Catal.* **2018**, *8*, 11960−11965. (j) Khan, A.; Zhao, H.; Zhang, M.; Khan, S.; Zhao, D. Regio- and Enantioselective Synthesis of Sulfone-Bearing Quaternary Carbon Stereocenters by Pd-Catalyzed Allylic Substitution. *Angew. Chem., Int. Ed.* **2020**, *59*, 1340−1345.

(3) Selected examples: (a) Khan, A.; Zheng, R.; Kan, Y.; Ye, J.; Xing, J.; Zhang, Y. J. Palladium-catalyzed decarboxylative cycloaddition of vinylethylene carbonates with formaldehyde: enantioselective construction of tertiary vinylglycols. *Angew. Chem., Int. Ed.* **2014**, *53*, 6439−6442. (b) Khan, A.; Yang, L.; Xu, J.; Jin, L. Y.; Zhang, Y. J. Palladium-catalyzed asymmetric decarboxylative cycloaddition of vinylethylene carbonates with Michael acceptors: construction of vicinal quaternary stereocenters. *Angew. Chem., Int. Ed.* **2014**, *53*, 11257−11260. (c) Khan, I.; Zhao, C.; Zhang, Y. J. Pd-Catalyzed asymmetric decarboxylative cycloaddition of vinylethylene carbonates with 3-cyanochromones. *Chem. Commun.* **2018**, *54*, 4708−4711. (d) Liu, K.; Khan, I.; Cheng, J.; Hsueh, Y. J.; Zhang, Y. J. Asymmetric Decarboxylative Cycloaddition of Vinylethylene Carbonates with β-Nitroolefins by Cooperative Catalysis of Palladium Complex and Squaramide. *ACS Catal.* **2018**, *8*, 11600−11604. (e) Khan, A.; Xing, J.; Zhao, J.; Kan, Y.; Zhang, W.; Zhang, Y. J. Palladium-catalyzed enantioselective decarboxylative cycloaddition of vinylethylene carbonates with isocyanates. *Chem. - Eur. J.* **2015**, *21*, 120−124. (f) Yang, L.; Khan, A.; Zheng, R.; Jin, L. Y.; Zhang, Y. J. Pd-Catalyzed Asymmetric Decarboxylative Cycloaddition of Vinylethylene Carbonates with Imines. *Org. Lett.* **2015**, *17*, 6230−6233. (g) Park, J.-U.; Ahn, H.-I.; Cho, H.-J.; Xuan, Z.; Kim, J. H. Asymmetric Synthesis of N-Fused 1,3-Oxazolidines via Pd-Catalyzed Decarboxylative (3 + 2) Cycloaddition. *Adv. Synth. Catal.* **2020**, *362*, 1836−1840. (h) Yang, L. C.; Rong, Z. Q.; Wang, Y. N.; Tan, Z. Y.; Wang, M.; Zhao, Y. Construction of Nine-Membered Heterocycles through Palladium-Catalyzed Formal [5 + 4] Cycloaddition. *Angew. Chem., Int. Ed.* **2017**, *56*, 2927−2931. (i) Yuan, C.; Wu, Y.; Wang, D.; Zhang, Z.; Wang, C.; Zhou, L.; Zhang, C.; Song, B.; Guo, H. Formal [5 + 3] Cycloaddition of Zwitterionic Allylpalladium Intermediates with Azomethine Imines for Construction of N,O-Containing Eight-Membered Heterocycles. *Adv. Synth. Catal.* **2018**, *360*, 652−658. (j) Das, P.; Gondo, S.; Nagender, P.; Uno, H.; Tokunaga, E.; Shibata, N. Access to benzo-fused nine-membered heterocyclic alkenes with a trifluoromethyl carbinol moiety via a double decarboxylative formal ring-expansion process under palladium catalysis. *Chem. Sci.* **2018**, *9*, 3276−3281. (k) Singha, S.; Patra, T.; Daniliuc, C. G.; Glorius, F. Highly Enantioselective [5 + 2] Annulations through Cooperative N-Heterocyclic Carbene (NHC) Organocatalysis and Palladium Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 3551−3554. (l) Wei, Y.; Liu, S.; Li, M. M.; Li, Y.; Lan, Y.; Lu, L. Q.; Xiao, W. J. Enantioselective Trapping of Pd-Containing 1,5-Dipoles by Photogenerated Ketenes: Access to 7-Membered Lactones Bearing Chiral Quaternary Stereocenters. *J. Am. Chem. Soc.* **2019**, *141*, 133−137. (m) Zeng, R.; Li, J.-L.; Zhang, X.; Liu, Y.-Q.; Jia, Z.-Q.; Leng, H.-J.; Huang, Q.-W.; Liu, Y.; Li, Q.-Z. Diastereoselective Construction of 6,8-Dioxabicyclo[3.2.1]octane Frameworks from Vinylethylene Carbonates via Palladium-Organo Relay Catalysis. *ACS Catal.* **2019**, *9*, 8256−8262. (n) An, X.-T.; Du, J.-Y.; Jia, Z.-L.; Zhang, Q.; Yu, K.-Y.; Zhang, Y.-Z.; Zhao, X.-H.; Fang, R.; Fan, C.-A. Asymmetric Catalytic [4 + 5] Annulation of ortho-Quinone Methides with Vinylethylene Carbonates and its Extension to Stereoselective Tandem Rearrangement. *Chem. - Eur. J.* **2020**, *26*, 3803−3809. (o) Zhang, X.; Li, X.; Li, J.-L.; Wang, Q.-W.; Zou, W.-L.; Liu, Y.-Q.; Jia, Z.-Q.; Peng, F.; Han, B. Regiodivergent construction of medium-sized heterocycles from vinylethylene carbonates and allylidenemalononitriles. *Chem. Sci.* **2020**, *11*, 2888−2894. (p) Gao, X.; Xia, M.; Yuan, C.; Zhou, L.; Sun, W.; Li, C.; Wu, B.; Zhu, D.; Zhang, C.; Zheng, B.; Wang, D.; Guo, H. Enantioselective Synthesis of Chiral Medium-Sized Cyclic Compounds via Tandem Cycloaddition/Cope Rearrangement Strategy. *ACS Catal.* **2019**, *9*, 1645−1654.

(4) *Modern Physical Organic Chemistry*; Anslyn, E. V., Dougherty, D. A., Eds.; Higher Education Press: Beijing, 2009; pp 63−140.

(5) (a) Wu, Y.; Yuan, C.; Wang, C.; Mao, B.; Jia, H.; Gao, X.; Liao, J.; Jiang, F.; Zhou, L.; Wang, Q.; Guo, H. Palladium-Catalyzed [5 + 2] Cycloaddition of Vinyloxiranes with Sulfamate-Derived Cyclic Imines To Construct 1,3-Oxazepine Heterocycles. *Org. Lett.* **2017**, *19*, 6268−6271. (b) Mao, B.; Zhang, J.; Xu, Y.; Yan, Z.; Wang, W.; Wu, Y.; Sun, C.; Zheng, B.; Guo, H. Palladium-Catalyzed [3 + 2] Annulation of Allenyl Carbinol Acetates with C,N-cyclic Azomethine Imines. *Chem. Commun.* **2019**, *55*, 12841−12844. (c) Zhou, L.; Zeng, Y.; Gao, X.; Wang, Q.; Wang, C.; Wang, B.; Wang, W.; Wu, Y.; Zheng, B.; Guo, H. A Chiral Squaramide-Catalyzed Asymmetric Dearomative Tandem Annulation Reaction through A Kinetic Resolution of MBH Alcohols: Highly Enantioselective Synthesis of Three-Dimensional Heterocyclic Compounds. *Chem. Commun.* **2019**, *55*, 10464−10467. (d) Zhou, L.; Yuan, C.; Zeng, Y.; Wang, Q.; Wang, C.; Liu, M.; Wang, W.; Wu, Y.; Zheng, B.; Guo, H. Direct Activation of Unmodified Morita-Baylis-Hillman Alcohols through Phosphine Catalysis for Rapid Construction of Three-Dimensional Heterocyclic Compounds. *Org. Lett.* **2019**, *21*, 4882−4886. (e) Shi, W.; Mao, B.; Xu, J.; Wang, Q.; Wang, W.; Wu, Y.; Li, X.; Guo, H. Phosphine-Catalyzed Cascade Michael Addition/[4 + 2] Cycloaddition Reaction of Allenoates and 2-Arylidene-1,3-indanediones. *Org. Lett.* **2020**, *22*, 2675−2680. (f) Mao, B.; Liu, H.; Yan, Z.; Xu, Y.; Xu, J.; Wang, W.; Wu, Y.; Guo, H. Palladium-Catalyzed Asymmetric [4 + 2] Cycloaddition of 2-Methylidenetrimethylene Carbonate with Alkenes: Access to Chiral Tetrahydropyran-Fused Spirocyclic Scaffolds. *Angew. Chem., Int. Ed.* **2020**, *59*, 11316−11320.

(6) Selected examples: (a) Frankowski, S.; Gajda, T.; Albrecht, Ł. Isothiocyanate Strategy for the Synthesis of Quaternary α-Amino Acids Bearing a Spirocyclic Ring System. *Adv. Synth. Catal.* **2018**, *360*, 1822−1832. (b) Liu, H.; Liu, Y.; Yuan, C.; Wang, G.-P.; Zhu, S.-F.; Wu, Y.; Wang, B.; Sun, Z.; Xiao, Y.; Zhou, Q.-L.; Guo, H. Enantioselective Synthesis of Spirobarbiturate-Cyclohexenes through Phosphine-Catalyzed Asymmetric [4 + 2] Annulation of Barbiturate-Derived Alkenes with Allenoates. *Org. Lett.* **2016**, *18*, 1302−1305. (c) Liu, Y.; Yang, W.; Wu, Y.; Mao, B.; Gao, X.; Liu, H.; Sun, Z.; Xiao, Y.; Guo, H. Asymmetric Construction of Highly Functionalized Spirobarbiturate-Cyclopentenes through Chiral Phosphine-Catalyzed [3 + 2] Annulation of Morita−Baylis−Hillman Carbonates with Barbiturate-Derived Alkenes. *Adv. Synth. Catal.* **2016**, *358*, 2867−2872. (d) Gao, X.; Li, Z.; Yang, W.; Liu, Y.; Chen, W.; Zhang, C.; Zheng, L.; Guo, H. Phosphine-catalyzed [3 + 2] and [4 + 2] annulation reactions of ynones with barbiturate-derived alkenes. *Org. Biomol. Chem.* **2017**, *15*, 5298−5307.

(7) (a) Duan, J. J. W.; Chen, L.; Lu, Z.; Jiang, B.; Asakawa, N.; Sheppeck, J. E.; Liu, R.-Q.; Covington, M. B.; Pitts, W.; Kim, S.-H.; Decicco, C. P. Discovery of low nanomolar non-hydroxamate inhibitors of tumor necrosis factor-alpha converting enzyme (TACE). *Bioorg. Med. Chem. Lett.* **2007**, *17*, 266−271. (b) Girgis, A. S.; Farag, H.; Ismail, N. S. M.; George, R. F. Synthesis, hypnotic properties and molecular modeling studies of 1,2,7,9-tetraaza-spiro[4.5]dec-2-ene-6,8,10-triones. *Eur. J. Med. Chem.* **2011**, *46*, 4964−4969.

(8) (a) Heindel, N. D.; Minatelli, J. A. Synthesis and Antibacterial and Anticancer Evaluations of α-Methylene-γ-butyrolactones. *J. Pharm. Sci.* **1981**, *70*, 84−86. (b) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. Tetrahydrofuran-Containing Macrolides: A Fascinating Gift from the Deep Sea. *Chem. Rev.* **2013**, *113*, 4567−4610. (c) Taylor, R. D.; Maccoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845−5859.

(9) (a) Ding, K.; Han, Z.; Wang, Z. Spiro Skeletons: A Class of Privileged Structure for Chiral Ligand Design. *Chem. - Asian J.* **2009**, *4*, 32−41. (b) Wang, X.; Han, Z.; Wang, Z.; Ding, K. Catalytic Asymmetric Synthesis of Aromatic Spiroketals by SpinPhox/Iridium(I)-Catalyzed Hydrogenation and Spiroketalization of α,α′-Bis(2-hydroxyarylidene) Ketones. *Angew. Chem., Int. Ed.* **2012**, *51*, 936−940. (c) Wang, X.; Meng, F.; Wang, Y.; Han, Z.; Chen, Y.-J.; Liu, L.; Wang, Z.; Ding, K. Aromatic Spiroketal Bisphosphine Ligands: Palladium-Catalyzed Asymmetric Allylic Amination of Racemic Morita−Baylis−Hillman Adducts. *Angew. Chem., Int. Ed.* **2012**, *51*,

https://dx.doi.org/10.1021/acs.orglett.0c02508
Org. Lett. XXXX, XXX, XXX−XXX

9276−9282. (d) Wang, X.; Guo, P.; Wang, X.; Wang, Z.; Ding, K. Practical Asymmetric Catalytic Synthesis of Spiroketals and Chiral Diphosphine Ligands. *Adv. Synth. Catal.* **2013**, *355*, 2900−2907. (e) Wang, X.; Guo, P.; Han, Z.; Wang, X.; Wang, Z.; Ding, K. Spiroketal-Based Diphosphine Ligands in Pd-Catalyzed Asymmetric Allylic Amination of Morita−Baylis−Hillman Adducts: Exceptionally High Efficiency and New Mechanism. *J. Am. Chem. Soc.* **2014**, *136*, 405−411. (f) Liu, J.; Han, Z.; Wang, X.; Wang, Z.; Ding, K. Highly Regio- and Enantioselective Alkoxycarbonylative Amination of Terminal Allenes Catalyzed by a Spiroketal-Based Diphosphine/Pd(II) Complex. *J. Am. Chem. Soc.* **2015**, *137*, 15346−15349. (g) Liu, J.; Han, Z.; Wang, X.; Meng, F.; Wang, Z.; Ding, K. Palladium-Catalyzed Asymmetric Construction of Vicinal Tertiary and All-Carbon Quaternary Stereocenters by Allylation of *β*-Ketocarbonyls with Morita-Baylis-Hillman Adducts. *Angew. Chem., Int. Ed.* **2017**, *56*, 5050−5054. (h) Wang, X.; Wang, X.; Han, Z.; Wang, Z.; Ding, K. Palladium-Catalyzed Asymmetric Allylic AllylationofRacemic Morita−Baylis−HillmanAdducts. *Angew. Chem., Int. Ed.* **2017**, *56*, 1116−1119. (i) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. Highly Stereoselective Olefin Cyclopropanation of Diazooxindoles Catalyzed by a C2-Symmetric Spiroketal Bisphosphine/Au(I) Complex. *J. Am. Chem. Soc.* **2013**, *135*, 8197−8200. (j) Wang, H.; Yu, L.; Xie, M.; Wu, J.; Qu, G.; Ding, K.; Guo, H. Regio- and Enantioselective Allylic Amination of Aliphatic MBH Adducts with N-Heteroaromatics. *Chem. - Eur. J.* **2018**, *24*, 1425−1430.

https://dx.doi.org/10.1021/acs.orglett.0c02508
Org. Lett. XXXX, XXX, XXX−XXX