OL | Organic Letters

pubs.acs.org/OrgLett Letter

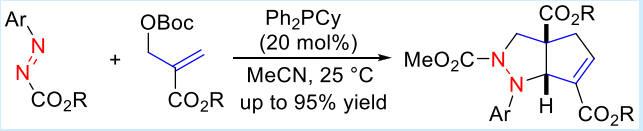
Phosphine-Catalyzed Cascade Annulation of MBH Carbonates and Diazenes: Synthesis of Hexahydrocyclopenta[c]pyrazole Derivatives

Hongxiang Li,[#] Wangyu Shi,[#] Chang Wang, Hao Liu, Wei Wang, Yongjun Wu, and Hongchao Guo*

Cite This: *Org. Lett.* 2021, 23, 5571−5575 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

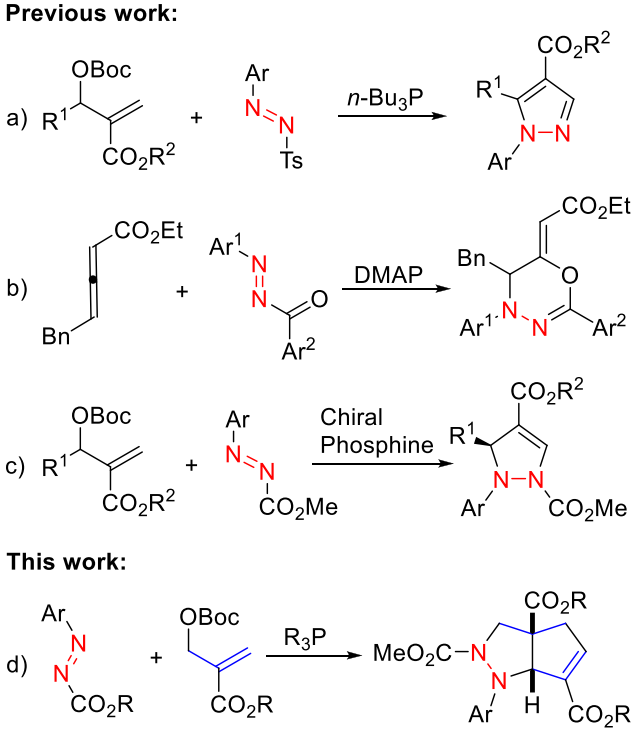
ABSTRACT: A phosphine-catalyzed cascade annulation of Morita−Baylis−Hillman (MBH) carbonates and diazenes was achieved, giving tetrahydropyrazole-fused heterocycles bearing two five-membered rings in moderate to excellent yields. The reaction underwent an unprecedented reaction mode of MBH carbonates, in which two molecules of MBH carbonates were fully merged into the ring system.



Pyrazole, dihydropyrazole, and tetrahydropyrazole are among the most widespread motifs in agrochemicals and drugs.[1] The related heterocycles are privileged structures in agrochemical and medicinal chemistry.[2] Therefore, their synthesis is highly desirable and has attracted much attention.

In the past two decades, phosphine-catalyzed annulation reactions have been developed as a powerful tool for synthesis of carbo- and heterocycles.[3] Among them, the annulation reactions with Morita−Baylis−Hillman (MBH) carbonates as phosphine acceptor have been extensively investigated.[3h,j,4−11] MBH carbonates often worked as a three-membered synthon to achieve [3 + 2],[5] [3 + 3],[6] [3 + 4],[7] and [3 + 6][8] annulation reactions and sometimes functioned as a C1 synthon to furnish [1 + 4] annulation reactions.[9] In these reactions, electron-deficient carbon−carbon,[5a−g] carbon−nitrogen,[5h,i] carbon−oxygen,[5j] and nitrogen−nitrogen[11] double bonds are widely used as electrophiles to accomplish numerous annulation reactions. Obviously, the annualtion reactions of nitrogen−nitrogen double bond with MBH carbonates are a concise synthetic tool for pyrazole, dihydropyrazole, and tetrahydropyrazole compounds (Scheme 1).[11] At an early stage, in the presence of an equivalent of phosphine, azodicarboxylates were used as phosphine acceptor for synthesis of dinitrogen-fused compounds.[12] In 2015, Meng and Wang developed a Bu_3P-catalyzed desulfonylative [3 + 2] cycloaddition of MBH carbonates with arylazosulfones for synthesis of pyrazole derivatives in good to excellent yields (Scheme 1a).[11a] With the use of 4-dimethylaminopyridine (DMAP) as the catalyst, Meng and Wang also achieved a similar [3 + 2] cycloaddition of isatin-derived MBH carbonates with diazenes for the construction of 3-spiropyrazole-2-oxindoles in good to excellent yields.[11c] The same research group also reported a DMAP-catalyzed [2 + 4] cycloaddition of allenoates and *N*-acyldiazenes to generate 1,3,4-oxadiazine derivatives in moderate to good yields (Scheme 1b).[11b] In 2019, we accomplished a phosphine-catalyzed asymmetric [3 + 2] cycloaddition of diazenes with MBH carbonates to give chiral

Scheme 1. Lewis Base-Catalyzed Annulation Reactions of Diazenes



Received: June 14, 2021
Published: July 7, 2021

https://doi.org/10.1021/acs.orglett.1c01975
Org. Lett. 2021, 23, 5571−5575

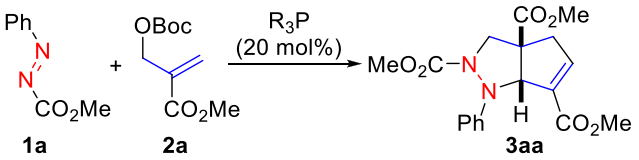
dihydropyrazoles in high yields with excellent enantioselectivities (Scheme 1c).[11d] On the basis of our previous work,[11d,13] we herein disclose an unprecedented phosphine-catalyzed cascade annulation of MBH carbonates and diazenes for synthesis of hexahydrocyclopenta[c]pyrazole derivatives (Scheme 1d). Different from previous annulation reactions involving MBH carbonates, two molecules of MBH carbonates were merged into two five-membered rings in the current reaction.

Initially, we began our investigation of cascade annulation between diazene **1a** and MBH carbonate **2a** in dichloromethane at room temperature (Table 1). A variety of phosphine catalysts were explored (entries 1−7). The Ph_3P with a low nucleophilicity did not efficiently catalyze the reaction, leading to only a trace of the desired product (entry 1). Other phosphines having at least one alkyl group displayed certain catalytic activity, leading to the desired product in moderate to high yields (entries 2−7). Among these phosphines, $CyPh_2P$ demonstrated relatively good catalytic ability, resulting in the product in 64% yield (entry 4). With the use of $CyPh_2P$ as the catalyst, a concise solvent screening was performed (entries 8−13). The chlorinated solvent 1,2-dichloroethane was compatible with the reaction and provided a 67% yield close to that obtained in the solvent CH_2Cl_2 (entry 8 vs entry 4). Toluene and THF gave inferior results (entries 9 and 10). Polar solvent acetonitrile was efficient, offering a high 82% yield (entry 11). Another two polar solvents, 1,4-dioxane and methanol, were incompatible, affording only a trace of products (entries 12 and 13). Increasing the ratio of MBH carbonate to diazene resulted in a slightly higher 84% yield (entry 14), but further increasing the ratio of MBH carbonate to diazene **1a** did not help enhance the yield (entry 15). The effect of temperature was also explored. Increasing reaction temperature to 40 °C reduced the yield (entry 16), while decreasing reaction temperature to 0 °C had no negative effect on the yield but required longer reaction time (entry 17). On the basis of the above screening, the optimal reaction conditions were determined as follows: 0.1 mmol of diazenes and 0.3 mmol of MBH carbonates with 20 mol % $CyPh_2P$ in 2 mL of MeCN at 25 °C.

Under the optimized reaction conditions, we examined reactions between various diazenes **1** with MBH carbonate **2a** (Table 2, entries 1−16). Diazenes with both electron-donating and -withdrawing groups on the phenyl ring were well tolerated to produce the corresponding annulation products in moderate to good yields. Various diazenes bearing functional groups such as methoxy (**1f** and **1g**), fluorine (**1j**−**1l**), chlorine (**1m**) and bromine (**1n** and **1o**) behaved properly in this catalytic system. The substrates having an *ortho*-substituted phenyl (**1b** and **1n**) gave relatively low yields of the corresponding products, indicating that steric hindrance has a remarkable influence on the reactivity of the substrates (entries 1 and 13). Diazenes with disubstituted phenyl such as **1e** and **1l** were proven to be suitable substrates for the cascade cycloaddition, giving the hexahydrocyclopenta[c]pyrazole derivatives in good yields (entries 4 and 11). To our delight, 2-naphthyl and substituted naphthyl group (**1p** and **1q**) were also carried out, and the corresponding products (**3pa** and **3qa**) were obtained in high yields (entries 15 and 16). The relative configuration of the annulation products has been confirmed by X-ray crystallography of the product **3aa**.

As shown in Table 3, the scope of MBH carbonates was also evaluated (entries 1−7). The reactions of several MBH carbonates with different alkyl groups in the ester moiety

Table 1. Optimization of Reaction Conditions[a]

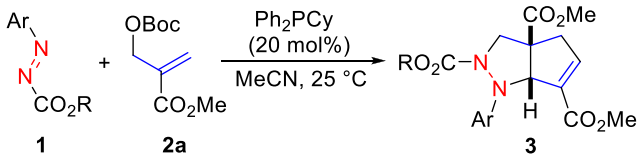


1a 2a 3aa

entry	R_3P	solvent	T (°C)	yield (%)[b]
1	Ph_3P	CH_2Cl_2	25	trace
2	$MePh_2P$	CH_2Cl_2	25	48
3	$BnPh_2P$	CH_2Cl_2	25	42
4	$CyPh_2P$	CH_2Cl_2	25	64
5	Bn_3P	CH_2Cl_2	25	62
6	Cy_3P	CH_2Cl_2	25	58
7	Bu_3P	CH_2Cl_2	25	44
8	$CyPh_2P$	$(CH_2Cl)_2$	25	67
9	$CyPh_2P$	THF	25	42
10	$CyPh_2P$	toluene	25	37
11	$CyPh_2P$	MeCN	25	82
12	$CyPh_2P$	1,4-dioxane	25	trace
13	$CyPh_2P$	MeOH	25	trace
14[c]	$CyPh_2P$	MeCN	25	84
15[d]	$CyPh_2P$	MeCN	25	82
16	$CyPh_2P$	MeCN	40	68
17[e]	$CyPh_2P$	MeCN	0	82

[a]Unless otherwise indicated, reactions of **1a** (0.10 mmol) and **2a** (0.24 mmol) were carried out in the presence of phosphine (0.02 mmol) in 2 mL of the solvent for 3 h. [b]Isolated yield, >20:1 dr. [c]0.3 mmol of **2a** was used in the reaction. [d]0.4 mmol of **2a** was used in the reaction. [e]The reaction time was 13 h.

Table 2. Scope of Diazenes[a]



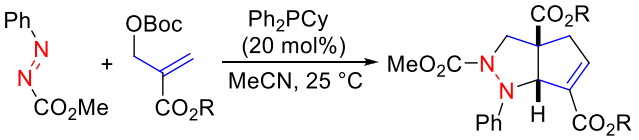
1 2a 3

entry	R/Ar in **1**	t (h)	**3**	yield (%)[b]
1	Me/2-MeC_6H_4 (**1b**)	2	**3ba**	45
2	Me/3-MeC_6H_4 (**1c**)	2	**3ca**	84
3	Me/4-MeC_6H_4 (**1d**)	5	**3da**	61
4	Me/2,4-$Me_2C_6H_3$ (**1e**)	2	**3ea**	65
5	Me/3-$MeOC_6H_4$ (**1f**)	2	**3fa**	82
6	Me/4-$MeOC_6H_4$ (**1g**)	3	**3ga**	59
7	Me/4-EtC_6H_4 (**1h**)	2	**3ha**	89
8	Me/4-*i*-PrC_6H_4 (**1i**)	5	**3ia**	88
9	Me/3-FC_6H_4 (**1j**)	3	**3ja**	48
10	Me/4-FC_6H_4 (**1k**)	1	**3ka**	63
11	Me/3,4-$F_2C_6H_3$ (**1l**)	2	**3la**	61
12	Me/4-ClC_6H_4 (**1m**)	2	**3ma**	55
13	Me/2-BrC_6H_4 (**1n**)	2	**3na**	46
14	Me/4-BrC_6H_4 (**1o**)	3	**3oa**	70
15	Me/2-naphthyl (**1p**)	3	**3pa**	77
16	Me/6-Br-2-naphthyl (**1q**)	6	**3qa**	63
17	*t*-Bu/C_6H_5 (**1r**)	2	**3ra**	68

[a]Unless otherwise indicated, all reactions were carried out with **1** (0.1 mmol), **2a** (0.3 mmol), and $CyPh_2P$ (0.02 mmol) in 2 mL of MeCN at 25 °C. [b]Isolated yield, >20:1 dr.

https://doi.org/10.1021/acs.orglett.1c01975
Org. Lett. 2021, 23, 5571−5575

Table 3. Scope of MBH Carbonates[a]



1a 2 3

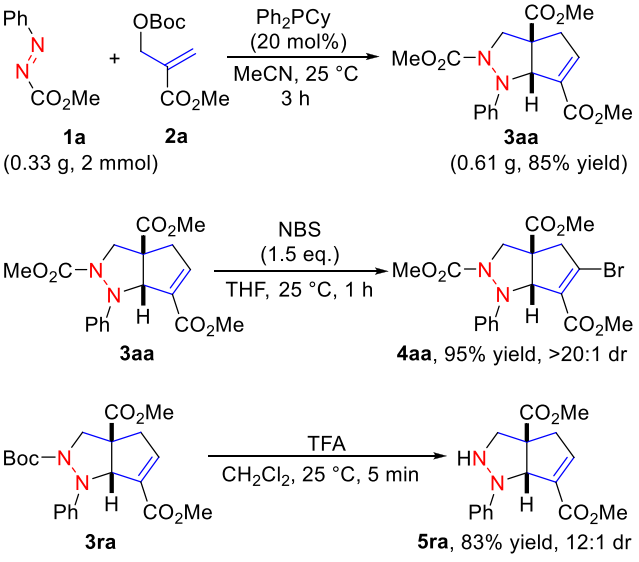
entry	R	*t* (h)	3	yield (%)[b]
1	Et (**2b**)	2	**3ab**	71
2	*n*-Pr (**2c**)	2	**3ac**	59
3	Cy (**2d**)	2	**3ad**	95
4	Bn (**2e**)	2	**3ae**	57
5	*i*-Pr (**2f**)	2	**3af**	60
6	Ad (**2g**)	2	**3ag**	53
7	*t*-Bu (**2h**)	24	**3ah**	trace

[a]Unless otherwise indicated, all reactions were carried out with **1a** (0.1 mmol), **2** (0.3 mmol), and $CyPh_2P$ (0.02 mmol) in 2 mL of MeCN at 25 °C. Ad: 1-adamantyl. [b]Isolated yield, >20:1 dr.

(**2b**–**2g**) proceeded smoothly to give the desired products (**3ab**–**3ag**) in moderate to high yields (entries 1–6). Particularly, when the cyclohexyl-bearing MBH carbonate **2d** was used, 95% yield of the annulation product **3ad** was obtained (entry 3). The *tert*-butyl substituted MBH carbonate **2h** was not reactive, leading to only a trace of product **3ah** (entry 7), probably because of its steric hindrance. It should be noted that those MBH carbonates derived from other aldehydes, such as benzaldehyde, did not work in this reaction.

To our delight, the scale-up reaction still worked well under standard reaction conditions. As indicated in Scheme 2, 2

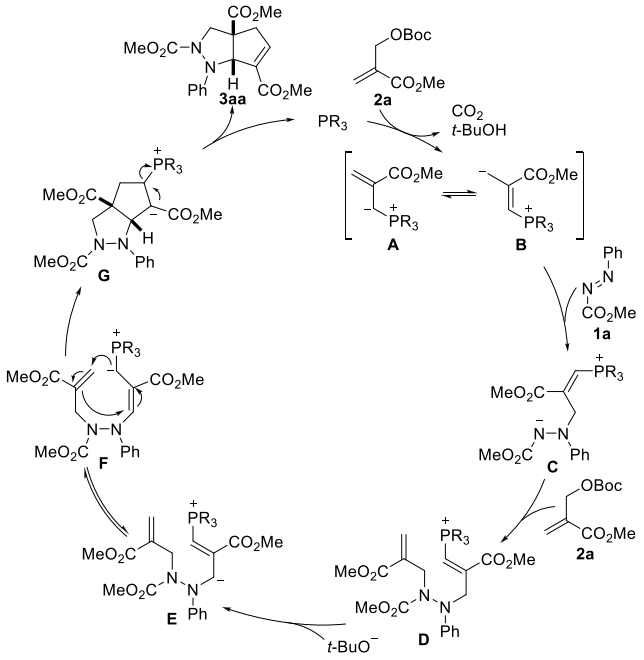
Scheme 2. Scale-up Reaction and Further Transformations of the Products



mmol of the diazene **1a** (0.33 g) reacted with MBH carbonate **2a** (6 mmol, 1.30 g) in acetonitrile at room temperature for 3 h, leading to the cycloaddition product **3aa** in 85% yield (0.61 g). No loss of yield was observed in the scale-up reaction, compared with the reaction at 0.1 mmol scale. Further transformations of the product **3** also were investigated (Scheme 2). Treatment of **3aa** with N-bromosuccinimide (NBS) gave the brominated product **4aa** in excellent yield with >20:1 dr. In the presence of trifluoroacetic acid (TFA), the Boc group in the product **3ra** was easily removed to give the derivative **5ra** in high yield with good dr.

On the basis of phosphine catalysis principles, a plausible mechanism was proposed for this cascade annulation reaction (Scheme 3). Initially, the phosphine catalyst attacks the MBH

Scheme 3. A Plausible Mechanism



carbonate **2a** to form zwitterionic intermediate **A**. Its tautomeric isomer **B** then attacks the diazene **1a** to give the ylide **C**, which reacts with another molecule of MBH carbonate **2a** to generate the intermediate **D**. Subsequent deprotonation of the intermediate **D** through *tert*-butoxy anion from decarboxylation of the substrate **2a** leads to the ylide **E**, which performs an isomerization to afford the intermediate **F**. Consequent intramolecular nucleophilic addition triggers highly diastereoselective cascade annulation to furnish the intermediate **G** having two five-membered rings. Subsequent formation of the carbon–carbon double bond with simultaneous regeneration of phosphine catalyst produces the final product **3aa**.

In summary, we achieved the cascade annulation of MBH carbonates with diazenes under mild reaction conditions. A variety of tetrahydropyrazole-fused heterocycles were obtained in moderate to excellent yields. The reaction undergoes a very interesting reaction pathway and demonstrates an unprecedented reaction mode of MBH carbonates under phosphine catalysis conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01975.

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

Accession Codes

CCDC 2055670 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge

https://doi.org/10.1021/acs.orglett.1c01975
Org. Lett. 2021, 23, 5571–5575

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

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

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

Chang Wang − *Department of Chemistry and Innovation Center of Pesticide Research, China Agricultural University, Beijing 100193, P.R. China;* orcid.org/0000-0003-2870-6518

Hao Liu − *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.1c01975

Author Contributions

#H.L. and W.S. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work is supported by the Natural Science Foundation of China (Nos. 21871293 and 22071264).

REFERENCES

(1) (a) Ardiansah, B. Recent reports on pyrazole-based bioactive compounds as candidate for anticancer agents. *Asian J. Pharm. Clin. Res.* **2017**, *10*, 45−51. (b) Ardiansah, B. Pharmaceutical importance of pyrazoline derivatives: A mini review. *J. Pharm. Sci. Res.* **2017**, *9*, 1958−1960. (c) Muralidharan, V.; Asha Deepti, C.; Raja, S. A Review on Anticancer Potential of Substituted Pyrazoline Derivatives. *Eur. J. Biomed. Pharm. Sci.* **2018**, *5*, 1−13.

(2) (a) Gigante, A.; Tagarro, I. Non-Steroidal Anti-Inflammatory Drugs and Gastroprotection with Proton Pump Inhibitors A Focus on Ketoprofen/Omeprazole. *Clin. Drug Invest.* **2012**, *32*, 221−233. (b) Faria, J. V.; Vegi, P. F.; Miguita, A. G. C.; dos Santos, M. S.; Boechat, N.; Bernardino, A. M. R. Recently reported biological activities of pyrazole compounds. *Bioorg. Med. Chem.* **2017**, *25*, 5891−5903. (c) Raymer, B.; Bhattacharya, S. K. Lead-like Drugs: A Perspective. *J. Med. Chem.* **2018**, *61*, 10375−10384. (d) Giray, B.; Karadag, A. E.; Ipek, O. S.; Pekel, H.; Guzel, M.; Kucuk, H. B. Design and synthesis of novel cylopentapyrazoles bearing 1,2,3-thiadiazole moiety as potent antifungal agents. *Bioorg. Chem.* **2020**, *95*, 103509.

(3) For selected reviews, see: (a) Wang, Z.; Xu, X.; Kwon, O. Phosphine Catalysis of Allenes with Electrophiles. *Chem. Soc. Rev.* **2014**, *43*, 2927−2940. (b) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. Chiral Phosphines in Nucleophilic Organocatalysis. *Beilstein J. Org. Chem.* **2014**, *10*, 2089−2121. (c) Xiao, Y.; Guo, H.; Kwon, O. Nucleophilic Chiral Phosphines: Powerful and Versatile Catalysts for Asymmetric Annulations. *Aldrichimica Acta* **2016**, *49*, 3−13. (d) Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. Amino Acid-Derived Bifunctional Phosphines for Enantioselective Transformations. *Acc. Chem. Res.* **2016**, *49*, 1369−1378. (e) Li, W.; Zhang, J. Recent Developments in the Synthesis and Utilization of Chiral *β*-Aminophosphine Derivatives as Catalysts or Ligands. *Chem. Soc. Rev.* **2016**, *45*, 1657−1677. (f) Wei, Y.; Shi, M. Lu's [3 + 2] Cycloaddition of Allenes with Electrophiles: Discovery, Development and Synthetic Application. *Org. Chem. Front.* **2017**, *4*, 1876−1890. (g) Ni, H.; Chan, W.-L.; Lu, Y. Phosphine Catalyzed Asymmetric Organic Reactions. *Chem. Rev.* **2018**, *118*, 9344−9411. (h) Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. Phosphine Organocatalysis. *Chem. Rev.* **2018**, *118*, 10049−10293. (i) Li, E.-Q.; Huang, Y. Recent Advances in Phosphine Catalysis Involving *γ*-Substituted Allenoates. *Chem. Commun.* **2020**, *56*, 680−694. (j) Huang, Y.; Liao, J.; Wang, W.; Liu, H.; Guo, H. Synthesis of heterocyclic compounds through nucleophilic phosphine catalysis. *Chem. Commun.* **2020**, *56*, 15235−15281.

(4) For reviews, see: (a) Xie, P.; Huang, Y. Morita-Baylis-Hillman Adduct Derivatives (MBHADs): Versatile Reactivity in Lewis base-promoted Annulation. *Org. Biomol. Chem.* **2015**, *13*, 8578−8595. (b) Chen, Z.-C.; Chen, Z.; Du, W.; Chen, Y.-C. Transformations of Modified Morita-Baylis-Hillman Adducts from Isatins Catalyzed by Lewis Bases. *Chem. Rec.* **2020**, *20*, 541−555.

(5) For [3 + 2] annulation of carbon−carbon double bond, see: (a) Du, Y.; Lu, X.; Zhang, C. A catalytic carbon−phosphorus ylide reaction: Phosphane-catalyzed annulation of allylic compounds with electron-deficient alkenes. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035−1037. (b) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. Phosphine-catalyzed intramolecular formal [3 + 2] cycloaddition for highly diastereoselective synthesis of bicyclo[n.3.0] compounds. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951−5954. (c) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. Highly enantioselective [3 + 2] annulation of Morita−Baylis−Hillman adducts mediated by L-threonine−derived phosphines: Synthesis of 3-spirocyclopentene-2-oxindoles having two contiguous quaternary centers. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837−7841. (d) Zhan, G.; Shi, M. L.; He, Q.; Lin, W. J.; Ouyang, Q.; Du, W.; Chen, Y. C. Catalyst-controlled switch in chemo- and diastereoselectivities: Annulations of Morita−Baylis−Hillman carbonates from isatins. *Angew. Chem., Int. Ed.* **2016**, *55*, 2147−2151. (e) 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. (f) Wu, Y.; Liu, Y.; Yang, W.; Liu, H.; Zhou, L.; Sun, Z.; Guo, H. Chiral phosphine-catalyzed enantioselective [3 + 2] annulation of Morita−Baylis−Hillman carbonates with cyclic 1-azadienes: Synthesis of functionalized cyclopentenes. *Adv. Synth. Catal.* **2016**, *358*, 3517−3521. (g) Wang, C.; Gao, Z.; Zhou, L.; Wang, Q.; Wu, Y.; Yuan, C.; Liao, J.; Xiao, Y.; Guo, H. Multifunctional chiral phosphine-catalyzed [3 + 2] annulation of Morita−Baylis−Hillman carbonates with cyclopentenones: Asymmetric synthesis of 4-oxo-hexahydropentalenes. *Chem. Commun.* **2018**, *54*, 279−282. For [3 + 2] annulation of carbon−nitrogen double bond, see: (h) Zheng, S.; Lu, X. A phosphine-catalyzed [3 + 2] annulation reaction of modified allylic compounds and N-tosylimines. *Org. Lett.* **2008**, *10*, 4481−4484. (i) Zhang, L.; Yu, H.; Yang, Z.; Liu, H.; Li, Z.; Guo, J.; Xiao, Y.; Guo, H. Phosphine-catalyzed [3 + 2] cycloaddition of Morita−Baylis−Hillman carbonates with sulfamate-derived cyclic imines. *Org. Biomol. Chem.* **2013**, *11*, 8235−8240. For [3 + 2] annulation of carbon−oxygen double bond, see: (j) Duan, H.-Y.; Ma, J.; Yuan, Z.-Z.; Yao, R.-S.; Tao, W.; Xu, F.; Xiao, H.; Zhao, G. Phosphine-promoted [3 + 2] cycloaddition between nonsubstituted MBH carbonates and trifluoromethyl ketones. *Chin. Chem. Lett.* **2015**, *26*, 646−648.

(6) (a) Zheng, S.; Lu, X. Phosphine-catalyzed [3 + 3] annulation reaction of modified tert-butyl allylic carbonates and substituted alkylidenemalononitriles. *Tetrahedron Lett.* **2009**, *50*, 4532−4535. (b) Zhang, L.; Liu, H.; Qiao, G.; Hou, Z.; Liu, Y.; Xiao, Y.; Guo, H. Phosphine-catalyzed highly enantioselective [3 + 3] cycloaddition of Morita−Baylis−Hillman carbonates with C,N-cyclic azomethine imines. *J. Am. Chem. Soc.* **2015**, *137*, 4316−4319. (c) Zhang, L.; Yang, W.; Zhou, L.; Liu, H.; Huang, J.; Xiao, Y.; Guo, H. Phosphine-catalyzed diastereoselective [3 + 3] annulation of Morita−Baylis−Hillman carbonates with C,N-cyclic azomethine imines. *J. Heterocycl. Chem.* **2017**, *54*, 3377−3388. (d) Zhou, L.; Yuan, C.; Zhang, C.; Zhang, L.; Gao, Z.; Wang, C.; Liu, H.; Wu, Y.; Guo, H. Enantioselective synthesis of quinazoline-based heterocycles through phosphine-catalyzed asymmetric [3 + 3] annulation of Morita−Baylis−Hillman carbonates with azomethine imines. *Adv. Synth. Catal.* **2017**, *359*, 2316−2321. (e) Yang, W.; Sun, W.; Zhang, C.; Wang, Q.; Guo, Z.; Mao, B.; Liao, J.; Guo, H. Lewis-base-catalyzed asymmetric [3 + 3] annulation reaction of Morita−Baylis−Hillman carbonates: enantioselective synthesis of spirocyclohexenes. *ACS Catal.* **2017**, *7*, 3142−3146. (f) Jin, H. X.; Lai, J. X.; Huang, Y. Phosphine-Catalyzed Domino [3 + 3] Cyclization of para-Quinamines with Morita-Baylis-Hillman Carbonates: Access to Hydroquinoline Derivatives. *Org. Lett.* **2019**, *21*, 2843−2846.

(7) (a) Zheng, S.; Lu, X. Phosphine-catalyzed [4 + 3] annulation for the synthesis of highly functionalized bicyclo[3.2.2]nonadienes. *Org. Lett.* **2009**, *11*, 3978−3981. (b) Zhou, R.; Wang, J.; Duan, C.; He, Z. Phosphine-triggered tandem annulation between Morita−Baylis−Hillman carbonates and dinucleophiles: Facile syntheses of oxazepanes, thiazepanes, and diazepanes. *Org. Lett.* **2012**, *14*, 6134−6137. (c) Chen, J.; Huang, Y. Phosphine-catalyzed sequential [4 + 3] domino annulation/allylic alkylation reaction of MBH carbonates: Efficient construction of seven-membered heterocycles. *Org. Lett.* **2017**, *19*, 5609−5612. (d) Chen, J. L.; Yin, Z. M.; Huang, Y. Phosphine-Catalyzed Divergent [4 + 3] Domino Annulations of CF_3-Containing Imines with MBH Carbonates: Construction of Perfluoroalkylated Benzazepines. *Org. Lett.* **2019**, *21*, 7060−7064.

(8) Du, Y.; Feng, J.; Lu, X. A phosphine-catalyzed [3 + 6] annulation reaction of modified allylic compounds and tropone. *Org. Lett.* **2005**, *7*, 1987−1989.

(9) (a) Xie, P.; Huang, Y.; Chen, R. Phosphine-catalyzed domino reaction: Highly stereoselective synthesis of trans-2,3-dihydrobenzofurans from salicyl N-thiophosphinyl imines and allylic carbonates. *Org. Lett.* **2010**, *12*, 3768−3771. (b) Zhang, X.-N.; Deng, H.-P.; Huang, L.; Wei, Y.; Shi, M. Phosphine-catalyzed asymmetric [4 + 1] annulation of Morita−Baylis−Hillman carbonates with dicyano-2-methylenebut-3-enoates. *Chem. Commun.* **2012**, *48*, 8664−8666. (c) Hu, F.-L.; Wei, Y.; Shi, M. Phosphine-catalyzed asymmetric [4 + 1] annulation of activated α,β-unsaturated ketones with Morita−Baylis−Hillman carbonates: Enantioselective synthesis of spirooxindoles containing two adjacent quaternary stereocenters. *Chem. Commun.* **2014**, *50*, 8912−8914. (d) Li, H.; Luo, J.; Li, B.; Yi, X.; He, Z. Enantioselective [4 + 1]-annulation of α,β-unsaturated imines with allylic carbonates catalyzed by a hybrid P-chiral phosphine oxide−phosphine. *Org. Lett.* **2017**, *19*, 5637−5640. (e) Cheng, Y.; Han, Y.; Li, P. Organocatalytic enantioselective [1 + 4] annulation of Morita−Baylis−Hillman carbonates with electron-deficient olefins: Access to chiral 2,3-dihydrofuran derivatives. *Org. Lett.* **2017**, *19*, 4774−4777. (f) Zhou, T.; Xia, T.; Liu, Z. L.; Liu, L.; Zhang, J. L. Asymmetric Phosphine-Catalyzed [4 + 1] Annulations of o-Quinone Methides with MBH Carbonates. *Adv. Synth. Catal.* **2018**, *360*, 4475−4479. (g) Zhang, P. F.; Guo, X.; Liu, C.; Li, W. J.; Li, P. F. Enantioselective Construction of Pyridine N-Oxides Featuring 2,3-Dihydrofuran Motifs via Phosphine-Catalyzed [4 + 1]-Annulation of 2-Enoylpyridine N-Oxides with Morita-Baylis-Hillman Carbonates. *Org. Lett.* **2019**, *21*, 152−155.

(10) For tandem annulations, see: (a) Zhou, R.; Wang, J.; Song, H.; He, Z. Phosphine-catalyzed cascade [3 + 2] cyclization−allylic alkylation, [2 + 2+1] annulation, and [3 + 2] cyclization reactions between allylic carbonates and enones. *Org. Lett.* **2011**, *13*, 580−583. (b) Zheng, J.; Huang, Y.; Li, Z. Phosphine-catalyzed sequential annulation domino reaction: Rapid construction of bicyclo[4.1.0]-heptene skeletons. *Chem. Commun.* **2014**, *50*, 5710−5713. (c) Ma, S.; Yu, A.; Zhang, S.; Zhang, L.; Meng, X. Construction of [6−5-5−6-6] Pentacyclic Skeleton via a Phosphine-Catalyzed Domino Reaction and Mechanism Study. *J. Org. Chem.* **2020**, *85*, 7884−7895.

(11) (a) Zhang, Q.; Meng, L.-G.; Wang, K.; Wang, L. ^{n}Bu$_3$P-catalyzed desulfonylative [3 + 2] cycloadditions of allylic carbonates with arylazosulfones to pyrazole derivatives. *Org. Lett.* **2015**, *17*, 872−875. (b) Zhang, Q.; Meng, L.-G.; Zhang, J.; Wang, L. DMAP-catalyzed [2 + 4] cycloadditions of allenoates with N-acyldiazenes: direct method to 1,3,4-oxadiazine derivatives. *Org. Lett.* **2015**, *17*, 3272−3275. (c) Ren, Y.; Meng, L.-G.; Peng, T.; Zhu, L.; Wang, L. 4-Dimethylaminopyridine-catalyzed regioselective [3 + 2] cycloaddition of isatin-derived Morita−Baylis− Hillman adducts with azo esters: a simple protocol to access 3-spiro-pyrazole-2-oxindoles. *Adv. Synth. Catal.* **2018**, *360*, 3176−3180. (d) Wang, C.; Chen, Y.; Li, J.; Zhou, L.; Wang, B.; Xiao, Y.; Guo, H. Phosphine-Catalyzed Asymmetric Cycloaddition Reaction of Diazenes: Enantioselective Synthesis of Chiral Dihydropyrazoles. *Org. Lett.* **2019**, *21*, 7519−7523.

(12) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. Engaging zwitterions in carbon−carbon and carbon−nitrogen bond-forming reactions: a promising synthetic strategy. *Acc. Chem. Res.* **2006**, *39*, 520−530.

(13) (a) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. Phosphine-catalyzed annulations of azomethine imines: allene-dependent [3 + 2], [3 + 3], [4 + 3], and [3 + 2+3] pathways. *J. Am. Chem. Soc.* **2011**, *133*, 13337−13348. (b) Jing, C.; Na, R.; Wang, B.; Liu, H.; Zhang, L.; Liu, J.; Wang, M.; Zhong, J.; Kwon, O.; Guo, H. Phosphine-Catalyzed [3 + 2] and [4 + 3]Annulation Reactions of C,N-Cyclic Azomethine Imines with Allenoates. *Adv. Synth. Catal.* **2012**, *354*, 1023−1034. (c) Zhou, L.; Yuan, C.; Zeng, Y.; Liu, H.; Wang, C.; Gao, X.; Wang, Q.; Zhang, C.; Guo, H. Phosphine-catalyzed [5 + 1] annulation of δ-sulfonamido-substituted enones with *N*-sulfonylimines: a facile synthesis of tetrahydropyridines. *Chem. Sci.* **2018**, *9*, 1831−1835. (d) 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. (e) 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.

https://doi.org/10.1021/acs.orglett.1c01975
Org. Lett. 2021, 23, 5571−5575