Check for updates

View Article Online
View Journal

# ChemComm

## Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Sun, F. He, Z. Wang, D. Pan, P. Zheng, C. Mou, Z. JIN and Y. R. Chi, *Chem. Commun.*, 2018, DOI: 10.1039/C8CC03017K.


This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Please do not adjust margins

View Article Online
DOI: 10.1039/C8CC03017K

Journal Name

COMMUNICATION

# Carbene-catalyzed enal γ-carbon addition to α-ketophosphonates for enantioselective access to bioactive 2-pyranylphosphonates

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jun Sun,[a] Fangcheng He,[a] Zhongyao Wang,[a] Dingwu Pan,[a] Pengcheng Zheng,[a] Chengli Mou,[c] Zhichao Jin*[a] and Yonggui Robin Chi*[a,b]

**A carbene-catalyzed enantioselective [4+2] cycloaddition reaction between α,β-unsaturated aldehydes and α-ketophosphonates is developed. The reaction affords chiral 2-pyranylphosphonates with excellent enantioselectivities. The optically enriched phosphonate products bear multiple functional groups, including unsaturated lactone and phosphonate moieties that often lead to unique bio-activities. Preliminary studies show that the prodcuts from our reactions exhibit anti-bacterial (*X. oryzae pv. oryzae*) and anti-viral (Tobacco Mosaic Virus) activities for potential use in plant protections.**

Phosphonate-containing molecules exhibit ubiquitous biological activities with proven applications in medicines and agriculture chemicals.[1] For example, chiral phosphonate compounds could be used as renin inhibitors,[1a,b] anti-viral,[1f] and anti-bacterial reagents[1g,i] (Figure 1a). Over the years, several types of methods have been developed for the incorporation of phosphonate moieties in enantioselective manners to realize various chiral functional molecules (Figure 1b). One of the most straightforward methods is based on the Pudovik-type reaction.[2] A stereoselective Carbon-Phosphine (C-P) bond is directly formed under the catalysis of chiral bases or transition metal catalysts (Figure 1b-1). Another important approach is to use functionalized phosphonates (such as acylphosphonates) as electrophiles in asymmetric catalytic reactions (Figure 1b-2).[3,4] For example, Scheidt and co-workers reported the asymmetric addition of the β-carbons of cinamylaldehydes to ketophosphonates via a formal [3+2] process to afford 5-membered lactone products with 78-91% ee under the catalysis of rationally designed chiral N-heterocyclic carbene (abbreviated as NHC or carbene) organic catalysts.[5]

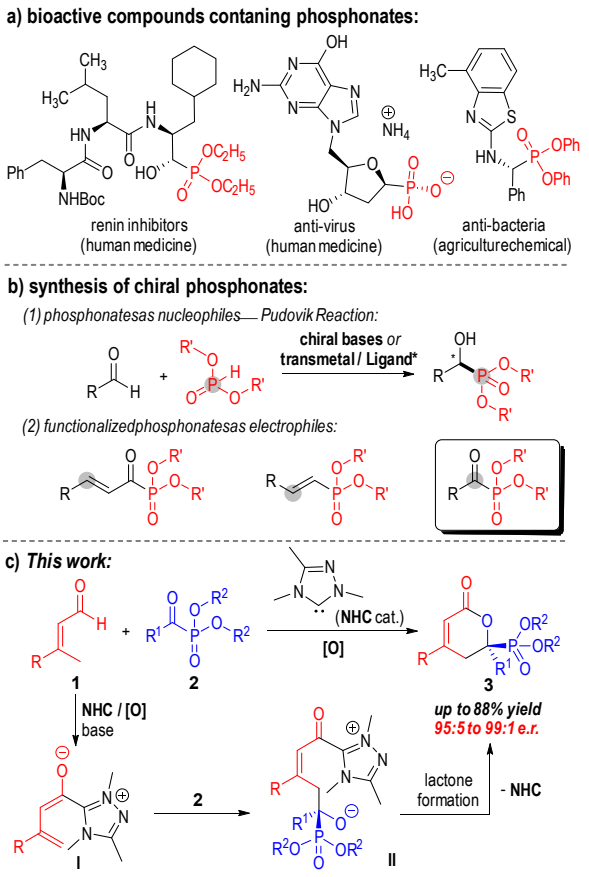



**Figure 1.** Asymmetric Catalytic Methodologies for Chiral Phosphonate Synthesis.

We are interested in developing new activation and reaction modes enabled by NHC catalysts for quick access to functional

[a] Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China.
[b] Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore
[c] School of Pharmacy, Guiyang College of Traditional Chinese Medicine, Huaxi District, Guiyang 550025, China.
E-mail: zcjin@gzu.edu.cn; robinchi@ntu.edu.sg

Electronic Supplementary Information (ESI) available: For ESI and crystallographic data in CIF or other electronic format. See DOI: 10.1039/x0xx00000x

Published on 14 May 2018. Downloaded by Universite Pierre et Marie Curie on 14/05/2018 16:49:11.

ChemComm Accepted Manuscript



Please do not adjust margins

View Article Online
DOI: 10.1039/C8CC03017K

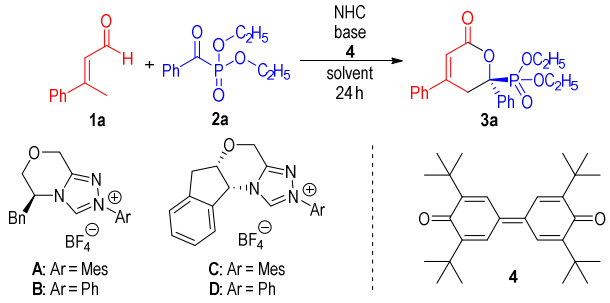

Published on 14 May 2018. Downloaded by Universite Pierre et Marie Curie on 14/05/2018 16:49:11.

molecules. One element that caught our attention is phosphine as it is widely present in functional molecules ranging from catalysts / ligands to medicines. We have recently reported an efficient access to P-stereogenic phosphinates via NHC-catalyzed desymmetrization of bisphenols.[6] Here we report a highly enantioselective synthesis of 2-pyranylphosphonates bearing a phosphonate moiety directly connected to a chiral carbon centre under oxidative NHC catalysis (Figure 1c). The reaction of enal with an NHC catalyst in the presence of an oxidant generates a vinyl enolate intermediate (**I**) with a nucleophilic carbon.[7] Addition of the γ-carbon of **I** to α-ketophosphonate substrate (**2**) affords intermediate **II** that subsequently undergoes a lactone formation process to furnish the final product (**3**). In our earlier reaction between enal γ-carbon and trifluromethylketone under oxidative NHC catalysis, the use of a Lewis acid co-catalyst is necessary in order to achieve high enantioselectivities.[7b] In our present studies, the use of NHC catalyst alone is sufficient for high enantioselectivities. This is likely due to the unique stereo-electronic properties of the α-ketophosphonate substrates. The chiral phosphonate-containing compounds obtained through our method showed anti-bacterial (*X. oryzae pv. oryzae*) and anti-viral (Tobacco Mosaic Virus) activities in our preliminary studies searching for new scaffolds of plant-protecting chemicals.

The asymmetric [4+2] cycloaddition reaction between the α,β-unsaturated aldehyde **1a** and α-ketophosphonate **2a** was selected as the model reaction for condition optimization (Table 1). To our delight, the aminoindanol-derived NHC catalyst **C**[8] could give the desired product in low but promising isolated yield with good enantioselectivity (Table 1, entry 3). Other NHC catalysts we tested were not effective for this transformation (eg., entries 1, 2 and 4). Both of the product yield and enantioselectivity could be dramatically increased when switching the basic additives to the ones with weaker basicities (entries 5 to 8). The 2-pyranylphosphonate product **3a** could be afforded in 63% yield with 97:3 e.r. valule when carrying out the reaction using NHC catalyst **C** with NaOAc as the base in THF (entry 8). Investigations on the solvent effect did not result in further improvements of the reaction outcome (entries 9 to 10).

With an optimized reaction condition at hand (as stated in Table 1, entry 8), we then tested the substrate scope for this [4+2] reaction using substrates **1** and **2** with different substitution patterns (Table 2). Both electron-donating and electron-withdrawing groups were well tolerated on the β-benzene rings of the α,β-unsaturated aldehydes **1**. All the chiral lactone products could be afforded in moderate to good yields with excellent enantioselectivities (**3b** to **3m**). Notably, installing steric hindered substituents on the 2-position of the β-benzene groups would lead to drops on the product yields (**3f** to **3g**). The substituted β-benzene groups on substrates **1** could also be replaced with a napthynyl group (**3n**) or a hetero aromatic group (**3o** to **3p**) without deteriorating the product yields and e.r. values. Substituents with various electronic properties could also be installed on the phenyl group attached to the ketone motif of the phosphonate **2a**, with the 2-pyranylphosphonate products afforded in good yields and e.r. values (**3q** to **3s**). Phosphonates derived from different alcohols also worked well in this catalytic process, affording the corresponding chiral phosphonates in moderate yields with excellent enantioselectivies (**3t** to **3u**). It should be noted that no or trace products could be isolated when switching the aryl groups on either of the substrates **1** or **2** to alkyl groups (**3v** to **3x**).

**Table 1.** Condition optimization.[a]




| Entry | Cat. | Base | Solvent | Yield [%][b] | *e.r.*[c] |
|---|---|---|---|---|---|
| 1 | **A** | $Cs_2CO_3$ | THF | 0 | -- |
| 2 | **B** | $Cs_2CO_3$ | THF | < 5 | -- |
| 3 | **C** | $Cs_2CO_3$ | THF | 10 | 90:10 |
| 4 | **D** | $Cs_2CO_3$ | THF | < 5 | -- |
| 5 | **C** | $K_2CO_3$ | THF | 26 | 89:11 |
| 6 | **C** | $Et_3N$ | THF | 42 | 97:3 |
| 7 | **C** | DMAP | THF | 31 | 97:3 |
| 8 | **C** | NaOAc | THF | 63 | 97:3 |
| 9 | **C** | NaOAc | toluene | 23 | 95:5 |
| 10 | **C** | NaOAc | $CH_3CN$ | <10 | -- |

[a]Reaction conditions: **1a** (0.12 mmol). **2a** (0.1 mmol), NHC (0.02 mmol), base (0.12 mmol), **4** (0.12mmol), THF (2 mL), 30 °C, 48 h. [b]Yields were isolated yields after purification by $SiO_2$ column chromatography. [c]E.r. values were determined *via* HPLC using a chiral stationary phase.

The optically enriched phosphonate products were evaluated for their plant disease-relevant anti-bacteria and anti-virus activities.[9] Bacterial blight disease (abbreviated as BB) is a widespread rice infection disease that can lead to big economic loss.[10] This disease is caused by *X. oryzae pv. oryzae*.[11] We tested the in-vitro anti-bacterial activity of our chiral products (**3)** against *X. oryzae* through turbidimeter test with bismerthiazol and DMSO used as the positive and negative controls respectively (Table 3).[12] Several of our optically enriched 2-pyranylphosphonate products were found to show promising activities. For example, products **3f** and **3u** exhibited similar inhibitory rate against *X. oryzae pv. oryzae*

ChemComm Accepted Manuscript

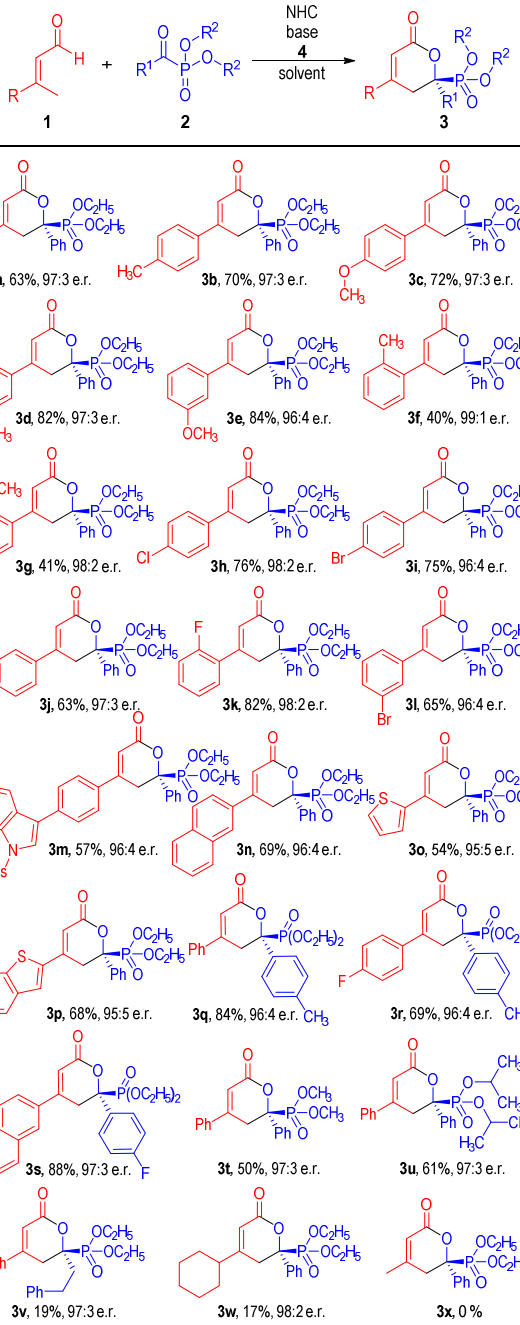

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins
View Article Online
DOI: 10.1039/C8CC03017K


Published on 14 May 2018. Downloaded by Universite Pierre et Marie Curie on 14/05/2018 16:49:11.

when compared to the commercially available bactericide bismerthiazol at the concentrations of both 100 μg/mL and 200 μg/mL.

**Table 2.** Substrate scope.[a]




[a]Reactions were carried out under condition as in Table 1, entry 8. Yields were isolated yields after purification by $SiO_2$ column chromatography. E.r. values were determined *via* HPLC using a chiral stationary phase.

Tobacco mosaic virus (abbreviated as TMV) is a damaging plant virus that is difficult to be controlled.[13] We carried out anti-viral studies of our phosphonates (**3**) against TMV (Table 4).[14] Comparing with the commercially available anti-viral drug of ningnanmycin,[15] products **3i**, **3o** and **3u** showed similar curative effects, and products **3p** and **3r** showed comparable protective effects.

**Table 3.** Anti-bacterial activity of our products (**3**).

| Compound | *X. oryzae pv. oryzae* inhibition rate (%)[a] | |
|---|---|---|
| | 100 μg/mL | 200 μg/mL |
| **3b** | 10.8 ± 3.0 | 45.8 ± 1.5 |
| **3f** | 54.2 ± 2.0 | 60.8 ± 1.2 |
| **3u** | 44.4 ± 4.2 | 59.9 ± 4.4 |
| bismerthiazol[b] | 47.1 ± 4.7 | 72.7 ± 5.8 |
| DMSO[c] | 0 | 0 |

[a]All data were average data of three replicates. [b]Commercial bactericide, used as the positive control. [c]DMSO was used as the negative control.

**Table 4.** *In vivo* inhibitory effects of our products (**3**) against TMV.[a]

| Compound | Curative effect (%) | Protective effect (%) |
|---|---|---|
| **3i** | 44.8 ± 2.9 | 24.3 ± 3.5 |
| **3o** | 43.1 ± 4.4 | 24.1 ± 2.9 |
| **3p** | 30.4 ± 3.4 | 44.8 ± 2.7 |
| **3r** | 27.6 ± 5.6 | 44.4 ± 7.9 |
| **3u** | 50.4 ± 3.2 | 23.6 ± 1.8 |
| ningnanmycin[b] | 45.5 ± 2.3 | 44.6 ± 1.3 |

[a]All data were average data of three replicates at the concentrations of 500 μg/mL. [b]Commercially available anti-viral drug, used as positive control.

## Conclusions

In summary, we have developed an NHC-catalyzed enantioselective formal [4 + 2] reaction of α,β-unsaturated aldehydes and α-ketophosphonates. A variety of chiral 2-pyranylphosphonates were afforded as the final products with excellent enantioselectivities. Several of the optically enriched phosphonate compounds generated from our reactions exhibited anti-bacterial and anti-viral activities in our preliminary studies searching for new plant-protection agents. Further studies for quick access to phosphine-containing chiral molecules and their applications are in progress.

## Conflicts of interest

There are no conflicts to declare.

ChemComm Accepted Manuscript


Please do not adjust margins

View Article Online
DOI: 10.1039/C8CC03017K


Published on 14 May 2018. Downloaded by Universite Pierre et Marie Curie on 14/05/2018 16:49:11.

## Acknowledgements

We acknowledge financial support by the National Natural Science Foundation of China (No. 21772029, 21472028), National Key Technologies R&D Program (No. 2014BAD23B01), "Thousand Talent Plan", The 10 Talent Plan (Shicengci) of Guizhou Province, Guizhou Province Returned Oversea Student Science and Technology Activity Program, Guizhou University (China) and Singapore National Research Foundation (NRF-NRFI2016-06), the Ministry of Education of Singapore (MOE2013-T2-2-003; MOE2016-T2-1-032; RG108/16), A*STAR Individual Research Grant (A1783c0008), Nanyang Research Award Grant, and Nanyang Technological University.

## Notes and references

1 (*a*) J. F. Dellaria, Jr., R. G. Maki, H. H. Stein, J. Cohen, D. Whittern, K. Marsh, D. J. Hoffman, J. J. Plattner, T. J. Perun, *J. Med. Chem*., 1990, **33**, 534; (*b*) D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, C. A. Free, W. L. Rogers, S. A. Smith, J. M. DeForrest, R. S. Oehl, E. W. Petrillo, Jr., *J. Med. Chem.,* 1995, **38**, 4557; (*c*) M. Tao, R. ihovsky, G. J. Wells, J. P. Mallamo, *J. Med. Chem*., 1998, **41**, 3912; (*d*) M. Collinsova, J. Jiracek, *Curr. Med. Chem*., 2000, **7**, 629; (*e*) P. Kafarski, B. Lejczak, *Curr. Med. Chem.: Anti-Cancer Agents,* 2001, **1**, 301; (*f*) M. Bubenik, R. Rej, N. Nguyen-Ba, G. Attardo, F. Ouellet, L. Chan, *Bioorg. Med. Chem. Lett.,* 2002, **12**, 3063; (*g*) L. H. Jin, B. A. Song, G. P. Zhang, R. Q. Xu, S. M. Zhang, X. W. Gao, D. Y. Hu, S. Yang, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 1537; (*h*) Mucha, A. Kafarski, P. Berlicki, L. *J. Med. Chem*., 2011, **54**, 5955; (*i*) G. Zhang, G. Hao, J. Pan, J. Zhang, D. Hu, B. Song, *J. Agric. Food Chem.,* 2016, **64**, 4207.

2 For reviews see: (*a*) A. N. Pudovik, I. V. Konovalova, *Synthesis,* 1979, 81; (*b*) O. I. Kolodiazhnyi, *Tetrahedron*: *Asymmetry,* 1998, **9**, 1279; (*c*) J.-A. Ma, *Chem. Soc. Rev.,* 2006, **35**, 630; (*d*) P. Merino, E. M. López, R. P. Herrera, *Adv. Synth. Catal.,* 2008, **350**, 1195.

3 (a) L. A. Telan, C.-D. Poon, S. A. Evans, Jr. *J. Org. Chem.,* 1996**, 61**, 7455; (*b*) D. F. Wiemer, *Tetrahedron*, 1997, **53**, 16609; (c) D. A. Evans, J. S. Johnson, *J. Am. Chem. Soc*., 1998, **120**, 4895; (*d*) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.,* 2000, **122**, 1635; (*e*) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc*., 2003, **125**, 10780; (*f*) M. C. Fernández, A. Díaz, J. J. Guillín, O. Blanco, M. Ruiz, V. Ojea, *J. Org. Chem.*, 2006, **71**, 6958; (*g*) N. Takenaka, J. P. Abell, H. Yamamoto, *J. Am. Chem. Soc.,* 2007, **129**, 742; (*h*) S. Samanta, J. Krause, T. Mandal, C.-G. Zhao, *Org. Let.,* 2007, **9**, 2745; (*i*) C. F. Weise, V. H. Lauridsen, R. S. Rambo, E. H. Iversen, M.-L. Olsen, K. A. Jørgensen, *J. Org. Chem.*, 2014, **79**, 3537; (j) S. R. Smith, S. M. Leckie, R. Holmes, J. Douglas, C. Fallan, P. Shapland, D. Pryde, A M. Z. Slawin, A. D. Smith, *Org. Let*., 2014, **16**, 2506.

4 (*a*) S. Samanta, C.-G. Zhao*, J. Am. Chem. Soc*.**,** 2006, **128**, 7442; (*b*) V. B. Gondi, K. Hagihara, V. H. Rawal, *Angew. Chem., Int. Ed*., 2009, **48**, 776; (*c*) N. S. Goulioukina, G. N. Bondarenko, A. V. Bogdanov, K. N. Gavrilov, I. P. Beletskaya, *Eur. J. Org. Chem.,* 2009, 510; (*d*) S. Perera, V. K. Naganaboina, L. Wang, B. Zhang, Q. Guo, L. Rout, C. G Zhao, *Adv. Synth. Catal.,* 2011, **353**, 1729; (*e*) S. M. Leckie, C. Fallan, J. E. Taylor, T. B. Brown, D. Pryde, T. Lébl, A. M. Z. Slawin, A. D. Smith, *Synlett.,* 2013*,* **24**, *1243;* (*f*) M. T. Corbett, J. S. Johnson, *J. Am. Chem. Soc.*, 2013, **135**, 594; (*g*) Q. Li, C. J. Hou, Y. J. Liu, R. F. Yang, X. P. Hu *Tetrahedron: Asymmetry*, 2015*,* **26**, 617; (*h*) M. Sun, J. Campbell, G. Kang, H. Wang, B. Ni, *J. Organomet. Chem.,* 2016*,* **810**, 12.

5 K. P. Jang, G. E. Hutson, R. C. Johnston, E. O. McCusker, P. H.-Y. Cheong, K. A. Scheidt, *J. Am. Chem. Soc.,* 2014, **136**, 76.

6 Z. Huang, X. Huang, B. Li, C. Mou, S. Yang, B. A. Song, Y. R. Chi, *J. Am. Chem. Soc.*, 2016, **138**, 7524.

7 For pioneering studies on NHC catalyzed nucleophilic γ-carbon activation, see: (a) L.-T. Shen, P.-L. Shao, S. Ye, *Adv. Synth. Catal.,* 2011, **353**, 1943; (b) J. Mo, X. Chen, Y. R. Chi, *J. Am. Chem. Soc.,* 2012, **134**, 8810.

8 (*a*) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.,* 2006, **128**, 8418; (*b*) J. R. Struble, J. W. Bode, *Org. Synth*., 2010, **87**, 362.

9 (*a*) K. Namitharan, T. Zhu, J. Chen, P. Zheng, X. Li, S. Yang, B.-A. Song, Y. R. Chi, *Nat. Commun*., 2014, **5**, 3982. (*b*) P. Zheng, J. Cheng, S. Su, Z. Jin, Y. Wang, S. Yang, L. Jin, B.-A. Song, Y. R. Chi, *Chem. Eur. J.,* 2015, **21**, 9984; (*c*) X. Chen, H. Wang, K. Doitomi, C. Oil, P. Zheng, W. Liu, H. Guo, S. Yang, B.-A. Song, H. Hirao, Y. R. Chi, *Nat. Commun.,* 2017, **8**, 15598; (*d*) H. Wang, X. Chen, Y. Li, J. Wang, S. Wu, W. Xue, S. Yang, Y. R. Chi. *Org. Lett.*, 2018, **20**, 333.

10 (*a*) T. W Mew, *Ann. Rev. Phytopath.* 1987, **25**, 359; (*b*) J. Swings, M. Van Den Mooter, L. Vauterin, B. Hoste, M. Gillis, T. W. Mew, K. Kersters, *Intl. J. Syst. Bacteriol.* 1990, **40**, 309; (*c*) A. Kala, S. Soosairaj, S. Mathiyazhagan, P. Raja, *Asian J. Plant Sci. Res.*, 2015, **5**, 80; (*d*) P. Balanagouda, G. B. Jagadeesh, C. Karegowda, R. M. Revathi, N. Seema, *Int. J. Chem. Stud.,* 2017, **5**, 232.

11 M. Reichman, Y. Devash, R. J. Suhadolnik, I. Sela, *Virology* 1983, **128**, 240.

12 (*a*) W.-M. Xu, F.-F. Han, M. He, D.-Y. Hu, J. He, S. Yang, B.-A. Song, *J. Agric. Food Chem.,* 2012, **60**, 1036; (*b*) X. Wang, P. Li, Z. Li, J. Yin, M. He, W. Xue, Z. Chen, B. Song, *J. Agric. Food Chem*., 2013, **61**, 9575.

13 A. N. Craeger, K. B. Scholthof, V. Citovsky, H. B. Scholthof, *Plant Cell*, 1999, **11**, 301.

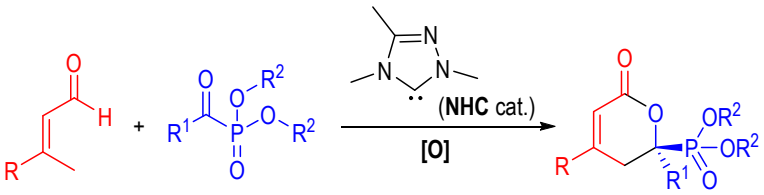
14 (*a*) G. V. Gooding, Jr., T. T. Hebert, *Phytopathology,* 1967, **57**, 1285; (*b*) B.-A. Song, H.-P. Zhang, H. Wang, S. Yang, L.-H. Jin, D.-Y. Hu, L.-L. Pang, W. Xue, *J. Agric. Food Chem*., 2005, **53**, 7886; (*c*) F. Wu, P. Li, D.-Y. Hu, B.-A. Song, *Res. Chem. Intermed.,* 2016, **42**, 7153.

15 (*a*) H. Z. Hu, G. X. Xiang, J. R. Chen, China Patent CN 1093869, 1994; (*b*) M. H. Chen, Z. Chen, B. A. Song, P. S. Bhadury, S. Yang, X. -J. Cai, D. Y. Hu, W. Xue, S. Zeng, *J. Agric. Food Chem.,* 2009, **57**, 1383.

ChemComm Accepted Manuscript


This journal is © The Royal Society of Chemistry 20xx

View Article Online
DOI: 10.1039/C8CC03017K




***up to 88% yield, 95:5 to 99:1 e.r.***

**anti-bacterial** (*X. oryzae pv. oryzae*) & **anti-viral** (Tobacco Mosaic Virus)

A carbene-catalyzed [4+2] reaction of enals and α-ketophosphonates is developed to afford chiral 2-pyranylphosphonates with potential use in plant protections.

Published on 14 May 2018. Downloaded by Universite Pierre et Marie Curie on 14/05/2018 16:49:11.

ChemComm Accepted Manuscript