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Enantioselective access to multi-cyclic α-amino phosphonates *via* carbene-catalyzed cycloaddition reactions between enals and six-membered cyclic imines†

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A carbene-catalyzed enantioselective cycloaddition reaction between enals and cyclic ketiminophosphonates is disclosed. α-Amino phosphonates bearing sophisticated fused heterocycles and quaternary carbons are afforded with excellent enantioselectivities. The α-amino phosphonate products from our approach exhibit encouraging anti-bacterial activities against *X. oryzae pv. oryzae*, the bacteria that cause serious diseases to rice and other plants.

Phosphonic analogues of naturally occurring amino acids have strong affinities with amino peptidase[1] and therefore exhibit diverse biological activities.[2] These amino phosphonates can be used as medicines for humans such as renin inhibitors[3] and anti-cancer agents.[4] In the field of pesticides, Song and co-workers have developed a novel amino phosphonate (Dufulin) with strong anti-virus activity and broad commercial applications for plant protection.[5] Considerable attention has been paid to the synthesis of α-amino phosphonic acids and their derivatives, especially in their optically pure forms.[6]

Transition-metal-free organic catalysis is a promising approach as it offers excellent enantioselectivity control and the conditions are typically mild and green.[7] We are interested in developing N-heterocyclic carbene (abbreviated as NHC or carbene)[8] organic catalysis for new or more efficient reactions. Despite the rapid progress of NHC catalysis, access to chiral phosphonic acid derivatives *via* this class of catalysis is rare.[9] The only two reports are from Scheidt's and our laboratories. Scheidt and co-workers showed that optically enriched tetrahydrofurans bearing phosphonate units could be synthesized under the catalysis of a rationally designed chiral imidazolium-derived NHC catalyst (Fig. 1a, eqn (1)).[10] We recently showed that the addition of enals to α-ketophosphonates could afford 2-pyranylphosphonates with anti-bacterial and anti-viral activities (Fig. 1a, eqn (2)).[11] It is also worth noting that cyclic sulfonyl imines have been previously used by us in the [4 + 2] cycloaddition reactions with β-methyl enals to synthesize chiral tricyclic sulfonyl amides with antimicrobial activities (Fig. 1b).[12] However, carbene-catalyzed methods for the synthesis of chiral amino phosphonates that are likely more useful remain undeveloped. Here we disclose that the addition of enal γ-carbon[13] to cyclic ketiminophosphonates **2** under oxidative NHC catalysis can afford α-amino phosphonates **3** with exceptionally high er values in most cases (Fig. 1c). The key steps involve the formation of vinyl enolate intermediate **I** from enal and the catalyst, and subsequent addition of **I** to ketiminophosphonates **2** to form **II**. The overall process is an asymmetric formal aza-[4 + 2] cycloaddition reaction. One fully substituted carbon center is formed with excellent stereo-controls. The catalytic reactions are amenable for large scale synthesis. Preliminary studies on the bioactivities showed that our products can provide encouraging anti-bacterial activities against *X. oryzaepv. oryzae*[14] that cause serious diseases to rice and other plants.

The β-methyl-α,β-unsaturated aldehyde **1a** and the cyclic ketiminophosphonate **2a** are selected as the model substrates to evaluate the catalytic conditions of the [4 + 2] cycloaddition reaction with the dibenzoquinone **4** used as the external oxidant. Various NHC catalysts were first examined for this transformation (Table 1, entries 1 to 5). *N*-Mesityl substituted triazolium NHC catalysts derived from chiral amino-indanol

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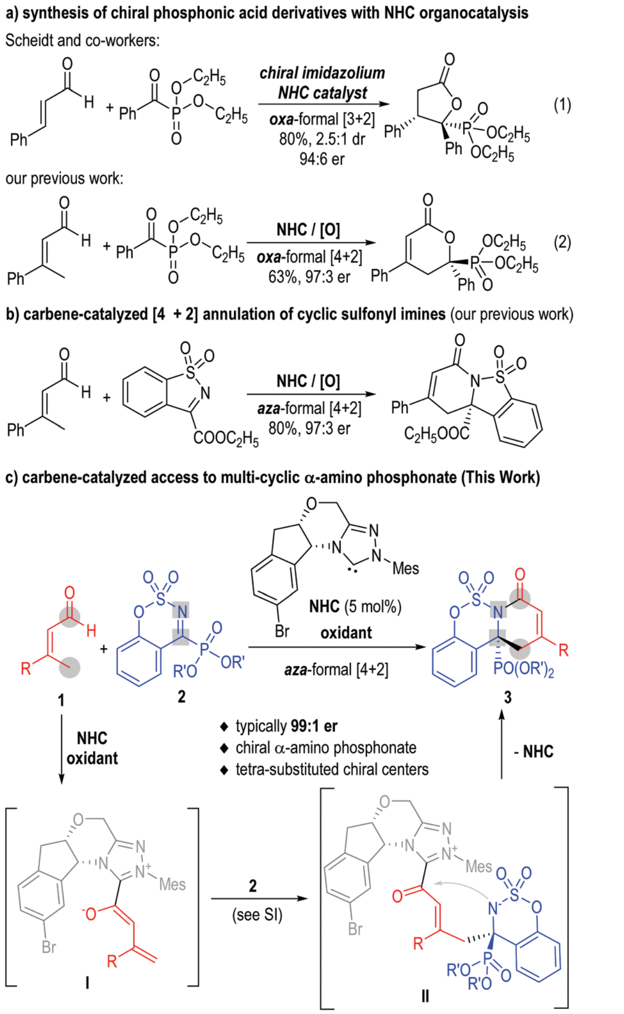
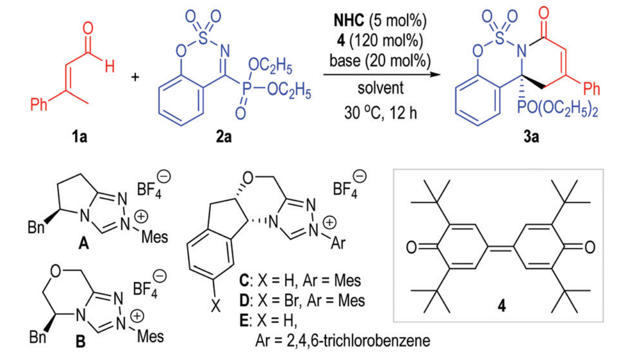


Fig. 1 Synthesis of chiral phosphonate compounds through NHC organocatalysis.

Table 1 Condition optimization[a]



Entry	Cat.	Base	Solvent	Yield[b] [%]	er[c]
1	**A**	Cs_2CO_3	THF	<5	—
2	**B**	Cs_2CO_3	THF	<5	—
3	**C**	Cs_2CO_3	THF	34	98 : 2
4	**D**	Cs_2CO_3	THF	73	99 : 1
5	**E**	Cs_2CO_3	THF	<5	—
6	**D**	K_2CO_3	THF	60	99 : 1
7	**D**	NaOAc	THF	93	>99 : 1
8	**D**	DBU	THF	34	97 : 3
9	**D**	DMAP	THF	<5	—
10	**D**	NaOAc	EtOAc	58	>99 : 1
11	**D**	NaOAc	CH_2Cl_2	32	99 : 1

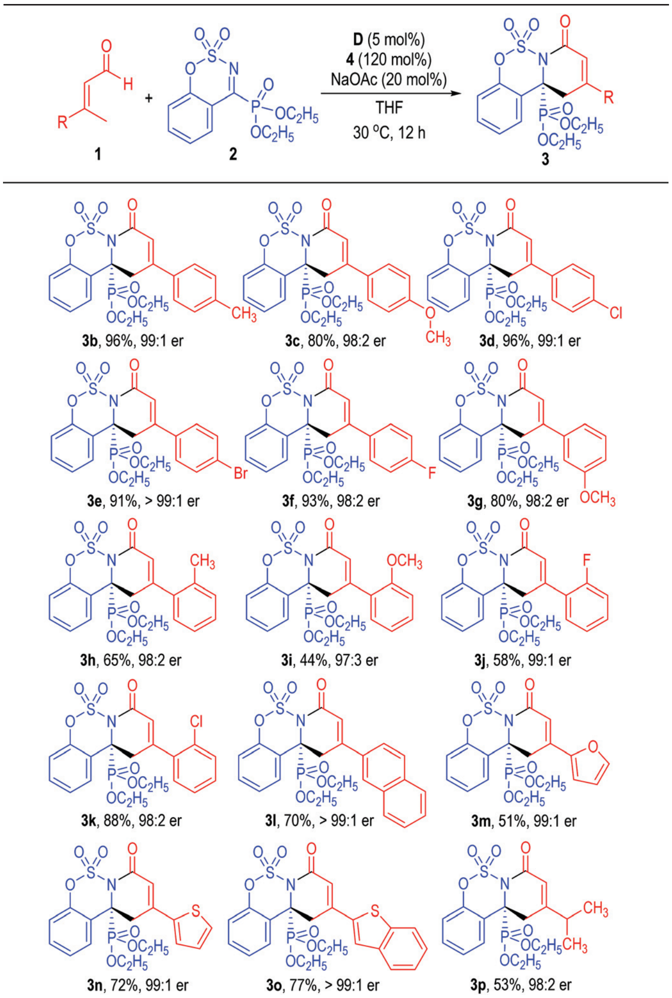
[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), NHC (0.005 mmol), base (0.02 mmol), **4** (0.12 mmol), THF (2 mL), 30 °C, 12 h. [b] Yields were isolated yields after purification by SiO_2 column chromatography. [c] er values were determined *via* HPLC using a chiral stationary phase.

scaffolds could give the desired α-amino phosphonate product **3a** in promising yields and enantioselectivities (entries 3–4). The other NHC catalysts that we tested could not effectively facilitate product formation (*e.g.*, entries 1, 2 and 5). NHC catalyst **D** [15] was then selected to test the base and solvent effects on this catalytic transformation. Inorganic bases with different basicities could give the products in moderate to excellent yields with excellent optical purities (*e.g.*, entries 6–7), while the organic bases that we tested gave the desired products in poor yields (*e.g.*, entries 8 to 9). A variety of organic solvents could be used as the reaction medium without obvious erosion of the enantioselectivities, though the product yields are generally lower (entries 10 to 11). Therefore, the optimized reaction conditions were identified: using NHC **D** as the chiral catalyst, NaOAc as the base and THF as the solvent, the desired α-amino phosphonate product **3a** formed in 93% yield and >99 : 1 er value (entry 7).

With the optimized reaction conditions in hand (as stated in Table 1, entry 7), we then examined the reaction scope using enal substrates **1** with various substitution patterns (Table 2). Both of the electron-donating and the electron-withdrawing groups could be installed at the 4- and 3-positions of the β-benzene ring on enal **1a**, with the chiral α-amino phosphonates afforded in good to excellent yields and excellent enantioselectivities (**3a** to **3g**). Substitutions at the 2-position of the β-benzene ring on enal **1a** gave the products in lower yields, although the er values of the products were still excellent (**3h** to **3k**). The β-benzene ring on enal **1a** could also be switched to various electron-rich aromatic or heteroaromatic groups, with the corresponding products obtained in moderate to good yields in their optically pure forms (**3l** to **3o**). Interestingly, aliphatic enal substrates could also give the desired products in a highly enantioselective manner through this transformation, although the yields were relatively lower under the current catalytic conditions (*e.g.*, **3p**).

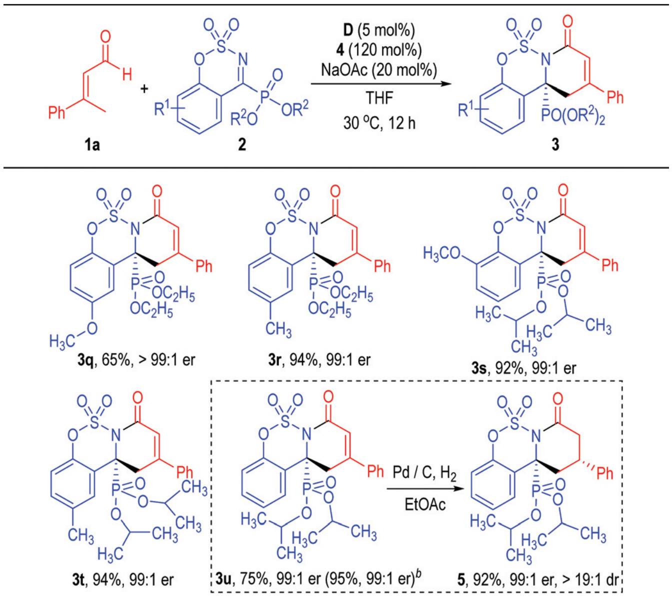
Various ketiminophosphonates **2** bearing different substituents on both of the benzene rings and the phosphonate units also worked well in this process, with all the α-amino phosphonate products afforded in good to excellent yields with excellent optical purities (Table 3, **3q** to **3u**). It is worth noting that the developed catalytic [4 + 2] transformation could be smoothly carried out at gram-scales, with the desired α-amino phosphonates afforded in even higher yields without erosion of the enantioselectivities (*e.g.*, **3u**). The α-amino phosphonate product **3u** obtained from this methodology could be further reduced to give tetrahydropyridine-derived phosphonate **5** in a

Table 2 Scope of enals[a]



[a] Reactions were carried out under conditions as in Table 1, entry 7. Yields were isolated yields. er values were determined *via* HPLC using a chiral stationary phase.

Table 3 Scope of ketiminophosphonates.[a]



[a] Reactions were carried out under conditions as in Table 1, entry 7. Yields were isolated yields. er values were determined *via* HPLC using a chiral stationary phase. [b] The reaction was carried out at the 1.5 mmol scale.

Table 4 Anti-bacterial activity of products **3**

	X. oryzaepv. oryzae inhibition rate[a] (%)	
Compound	100 μg mL^{-1}	200 μg mL^{-1}
3d	17.1 ± 4.8	46.0 ± 1.9
3e	45.6 ± 3.8	80.0 ± 2.5
3l	69.3 ± 3.8	88.8 ± 3.1
Bismerthiazol[b]	45.4 ± 1.9	73.6± 1.4
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.

quantitative yield with the retention of the optical purity as a single diastereomer (Table 3, **3u** to **5**).

Since the afforded chiral α-amino phosphonate products **3** are analogous to a variety of bio-active molecules, we are very much interested in their potential applications in the development of novel agrichemicals. *X. oryzaepv. oryzae*[14] is the cause of a serious disease in rice named bacterial blight (abbreviated as BB),[16] which can lead to an enormous loss of rice production. We therefore tested the anti-bacterial activities of our products **3** against *X. oryzaepv. oryzae* with bismerthiazol and DMSO used as the positive and negative controls respectively (Table 4).[17] To our delight, many of our products with various substitution patterns have exhibited encouraging anti-bacterial activities against *X. oryzaepv. oryzae* (*e.g.*, **3d**, **3e**, **3l**, for more details, see the ESI†). It is worth noting that some of the products obtained by this methodology have exhibited even better anti-bacterial activities than the commercialized bactericide of bismerthiazol (*e.g.*, **3l**).

Conclusions

In summary, we have developed an NHC-catalyzed oxidative enantioselective [4 + 2] reaction for the preparation of chiral α-amino phosphonates. A variety of substituted α-amino phosphonates bearing sophisticated multi-cyclic scaffolds were afforded in generally good to excellent yields with excellent enantioselectivities. The α-amino phosphonate products afforded by this methodology exhibited promising anti-bacterial activities against *X. oryzaepv. oryzae*. Further investigations into the biological activities of the chiral amino phosphonates, as well as the quick access to sophisticated chiral functional molecules by assembly of simple substrates through NHC organocatalysis, are currently in progress in our laboratories.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) A. P. Kaplan and P. A. Bartlett, *Biochemistry*, 1991, **30**, 8165; (*b*) P. Kafarski and B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1991, **63**, 193; (*c*) J. Bird, R. C. De Mello, G. P. Harper, D. J. Hunter, E. H. Karran, R. E. Markwell, A. J. Miles-Williams, S. S. Rahman and R. W. Ward, *J. Med. Chem.*, 1994, **37**, 158; (*d*) R. Hirschmann, A. B. Smith III, C. M. Taylor, P. A. Benkovic, S. D. Taylor, K. M. Yager, P. A. Sprengler and S. J. Benkovics, *Science*, 1994, **265**, 234; (*e*) T. R. Burke Jr., H. K. Kole and P. P. Roller, *Biochem. Biophys. Res. Commun.*, 1994, **204**, 129; (*f*) J. Ding, M. E. Fraser, J. H. Meyer, P. A. Bartlett and M. N. G. James, *J. Am. Chem. Soc.*, 1998, **120**, 4610; (*g*) W. W. Smith and P. A. Bartlett, *J. Am. Chem. Soc.*, 1998, **120**, 4622; (*h*) M. Collinsová and J. Jirácek, *Curr. Med. Chem.*, 2000, **7**, 629; (*i*) M. Emgenbroich and G. Wulff, *Chem. – Eur. J.*, 2003, **9**, 4106; (*j*) F. Orsini, G. Sello and M. Sisti, *Curr. Med. Chem.*, 2010, **17**, 264; (*k*) K.-W. Yang, X. Cheng, C. Zhao, C.-C. Liu, C. Jia, L. Feng, J.-M. Xiao, L.-S. Zhou, H.-Z. Gao, X. Yang and L. Zhai, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 7224.

2 (*a*) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassal, S. W. Holmes, R. W. Lambert, L. J. Nisbet and P. S. Ringrose, *Nature*, 1978, **272**, 56; (*b*) F. R. Atherton, C. H. Hassall and R. W. Lambert, *J. Med. Chem.*, 1986, **29**, 29; (*c*) R. F. Pratt, *Science*, 1989, **246**, 917; (*d*) F. R. Atherton, C. H. Hassall and R. W. Lambert, *J. Med. Chem.*, 1991, **34**, 1998; (*e*) A. P. Kaplan and P. A. Bartlett, *Biochemistry*, 1991, **30**, 8165; (*f*) J. Hiratake and J. Oda, *Biosci., Biotechnol., Biochem.*, 1997, **61**, 211; (*g*) E. Alonso, A. Solis and C. del Pozo, *Synlett*, 2000, 698.

3 (*a*) R. L. Johnson, *J. Med. Chem.*, 1984, **27**, 1351; (*b*) J. Boger, L. S. Payne, D. S. Perlow, N. S. Lohr, M. Poe, E. H. Blaine, E. Ulm, T. Schorn, B. I. LaMont, T.-Y. Lin, M. Kawai, D. H. Rich and D. F. Veber, *J. Med. Chem.*, 1985, **28**, 1779; (*c*) F. G. Salituro, N. Agarwal, T. Hofmann and D. H. Rich, *J. Med. Chem.*, 1987, **30**, 286; (*d*) J. R. Luly, G. Bolis, N. BaMaung, J. Soderquist, J. F. Dellaria, H. Stein, J. Cohen, T. J. Perun, J. Greer and J. J. Plattner, *J. Med. Chem.*, 1988, **31**, 532; (*e*) S. Thaisrivongs, D. T. Pals, S. R. Turner and L. T. Kroll, *J. Med. Chem.*, 1988, **31**, 1369; (*f*) P. Buhlmayer, A. Caselli, W. Fuhrer, R. Goschke, V. Rasetti, H. Rueger, J. L. Stanton, L. riscione and J. M. Wood, *J. Med. Chem.*, 1988, **31**, 1839; (*g*) M. G. Bock, R. M. DiPardo, B. E. Evans, R. M. Freidinger, K. E. Rittle, L. S. Payne, J. Boger, W. L. Whitter, B. I. LaMont, E. H. Ulm, E. H. Blaine, T. W. Schorn and D. F. Veber, *J. Med. Chem.*, 1988, **31**, 1918; (*h*) M. C. Allen, W. Fuhrer, B. Tuch, R. Wade and J. M. Wood, *J. Med. Chem.*, 1989, **32**, 1652.

4 (*a*) A. Mucha, P. Kafarski and L. Berlicki, *J. Med. Chem.*, 2011, **54**, 5955; (*b*) A. Kril, M. Topashka-Ancheva, I. Iliev, T. Gerasimova, I. Kraicheva, I. Tsacheva, E. Vodenicharova and K. Troev, *Z. Naturforsch. C Bio. Sci.*, 2012, **67**, 473; (*c*) S. S. Prasad, K. S. Kumar, S. H. Jayaprakash, B. S. Krishna, C. S. Sundar, P. V. Rao, T. M. Babu, W. Rajendra and C. S. Reddy, *Arch. Pharm. Chem. Life Sci.*, 2013, **346**, 380.

5 (*a*) L. H. Jin, B. A. Song, G. P. Zhang, R. Q. Xu, S. M. Zhang, X. W. Gao, D. Y. Hu and S. Yang, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1537; (*b*) G. Zhang, G. Hao, J. Pan, J. Zhang, D. Hu and B. Song, *J. Agric. Food Chem.*, 2016, **64**, 4207.

6 (*a*) M. Sawamura, H. Hamashima and Y. Ito, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 2559; (*b*) A. Fadel and N. Tesson, *Eur. J. Org. Chem.*, 2000, 2153; (*c*) L. Bernardi and W. Zhuang, *J. Am. Chem. Soc.*, 2005, **127**, 5772; (*d*) J. C. Wilt, M. Pinkzb and J. N. Johnston, *Chem. Commun.*, 2008, 4177; (*e*) C. B. Tripathi, S. Kayal and S. Mukherjee, *Org. Lett.*, 2012, **14**, 3296.

7 For selected reviews on organocatalysis, see: (*a*) B. List and J. W. Yang, *Science*, 2006, **313**, 1584; (*b*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304; (*c*) E. Arceo and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2012, **51**, 5290; (*d*) C. C. J. Loh and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 46; (*e*) S. J. Connon, *Angew. Chem., Int. Ed.*, 2014, **53**, 1203; (*f*) L. C. Morrill and A. D. Smith, *Chem. Soc. Rev.*, 2014, **43**, 6214; (*g*) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047; (*h*) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, 2014, **114**, 9219; (*i*) A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson and D. J. Dixon, *Chem. Soc. Rev.*, 2016, **45**, 5474; (*j*) S. Vellalath and D. Romo, *Angew. Chem., Int. Ed.*, 2016, **55**, 13934; (*k*) L. Klier, F. Tur, P. H. Poulsen and K. A. Jøergensen, *Chem. Soc. Rev.*, 2017, **46**, 1080.

8 For selected reviews on NHC catalysis, see: (*a*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (*b*) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988; (*c*) V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev.*, 2008, **37**, 2691; (*d*) A. T. Biju, N. Kuhl and F. Glorius, *Acc. Chem. Res.*, 2011, **44**, 1182; (*e*) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose and V. Sreekumar, *Chem. Soc. Rev.*, 2011, **40**, 5336; (*f*) J. Izquierdo, G. E. Hutson, D. T. Cohen and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2012, **51**, 11686; (*g*) S. J. Ryan, L. Candish and D. W. Lupton, *Chem. Soc. Rev.*, 2013, **42**, 4906; (*h*) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485; (*i*) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307; (*j*) S. R. Yetra, A. Patra and A. T. Biju, *Synthesis*, 2015, **47**, 1357.

9 For racemic NHC-catalyzed routes to organophosphorus compounds, see: (*a*) S. C. Cullen and T. Rovis, *Org. Lett.*, 2008, **10**, 3141; (*b*) A. Patra, A. Bhunia and A. Biju, *Org. Lett.*, 2014, **16**, 4798.

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

11 J. Sun, F. He, Z. Wang, D. Pan, P. Zheng, C. Mou, Z. Jin and Y. R. Chi, *Chem. Commun.*, 2018, **54**, 6040.

12 P.-C. Zheng, J. Cheng, S. Su, Z. Jin, T.-H. Wang, S. Yang, L.-H. Jin, B.-A. Song and Y. R. Chi, *Chem. – Eur. J.*, 2015, **21**, 9984.

13 (*a*) L.-T. Shen;, P.-L. Shao and S. Ye, *Adv. Synth. Catal.*, 2011, **353**, 1943; (*b*) J. Mo, X. Chen and Y. R. Chi, *J. Am. Chem. Soc.*, 2012, **134**, 8810; (*c*) J. Xu, Z. Jin and Y. R. Chi, *Org. Lett.*, 2013, **15**, 5028; (*d*) T. Zhu, P. Zheng, C. Mou, S. Yang, B.-A. Song and Y. R. Chi, *Nat. Commun.*, 2014, **5**, 5027; (*e*) M. Wang, Z. Huang, J. Xu and Y. R. Chi, *J. Am. Chem. Soc.*, 2014, **136**, 1214.

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

15 S. Lu, S. B. Poh and Y. Zhao, *Angew. Chem., Int. Ed.*, 2014, **53**, 11041.

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

17 (*a*) K. Namitharan, T. Zhu, J. Cheng, P. Zheng, X. Li, S. Yang, B.-A. Song and Y. R. Chi, *Nat. Commun.*, 2014, **5**, 3982; (*b*) X. Chen, H. Wang, K. Doitomi, C. Ooi, P. Zheng, W. Liu, H. Guo, S. Yang, B.-A. Song, H. Hirao and Y. R. Chi, *Nat. Commun.*, 2017, **8**, 15598.