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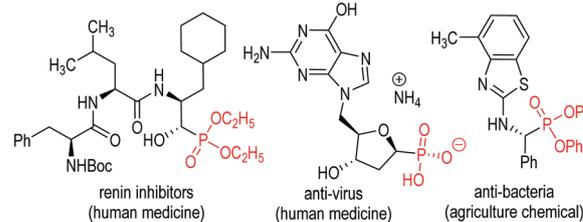
Carbene-catalyzed enal γ -carbon addition to α -ketophosphonates for enantioselective access to bioactive 2-pyranylphosphonates†

Jun Sun,^a Fangcheng He,^a Zhongyao Wang,^a Dingwu Pan,^a Pengcheng Zheng,^{id}^a Chengli Mou,^{id}^b Zhichao Jin^{id}^{*a} and Yonggui Robin Chi^{*ac}

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 products from our reactions exhibit anti-bacterial (*X. oryzae pv. oryzae*) and anti-viral (Tobacco Mosaic Virus) activities for potential use in plant protection.

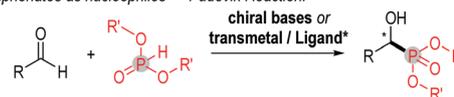
Phosphonate-containing molecules exhibit ubiquitous biological activities with proven applications in medicines and agriculture chemicals.¹ For example, chiral phosphonate compounds can be used as renin inhibitors,^{1a,b} and anti-viral,^{1f} and anti-bacterial reagents^{1g,i} (Fig. 1a). Over the years, several types of methods have been developed for the incorporation of phosphonate moieties in enantioselective manners to realize various chiral functional molecules (Fig. 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 (Fig. 1b(1)). Another important approach is to use functionalized phosphonates (such as acylphosphonates) as electrophiles in asymmetric catalytic reactions (Fig. 1b(2)).^{3,4} For example, Scheidt and co-workers reported the asymmetric addition of the β -carbons of cinnamaldehydes 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

a) bioactive compounds containing phosphonates:

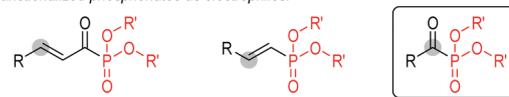


b) synthesis of chiral phosphonates:

(1) phosphonates as nucleophiles—Pudovik Reaction:



(2) functionalized phosphonates as electrophiles:



c) This work:

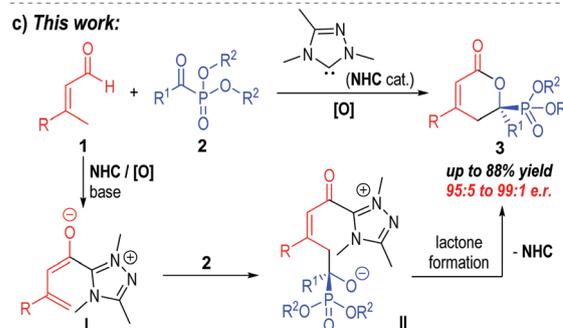


Fig. 1 Asymmetric catalytic methodologies for chiral phosphonate synthesis.

^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. E-mail: zcjin@gzu.edu.cn

^b School of Pharmacy, Guiyang College of Traditional Chinese Medicine, Huaxi District, Guiyang 550025, China

^c Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. E-mail: robinchi@ntu.edu.sg

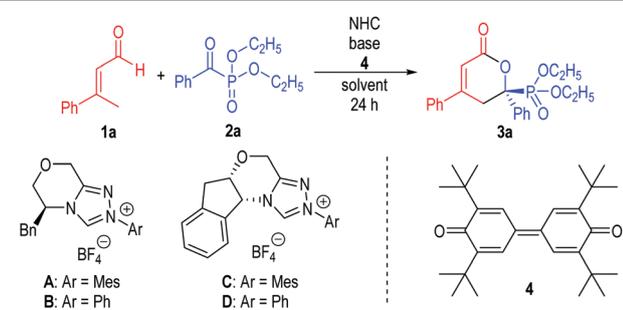
† Electronic supplementary information (ESI) available. CCDC 1813384. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc03017k

N-heterocyclic carbene (abbreviated as NHC or carbene) organic catalysts.⁵

We are interested in developing new activation and reaction modes enabled by NHC catalysts for quick access to functional 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 (Fig. 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 an α -ketophosphonate substrate (**2**) affords intermediate **II**, which subsequently undergoes a lactone formation process to furnish the final product (**3**). In our earlier reaction between enal γ -carbon and trifluoromethylketone 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 an 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 for plant-protecting chemicals.

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

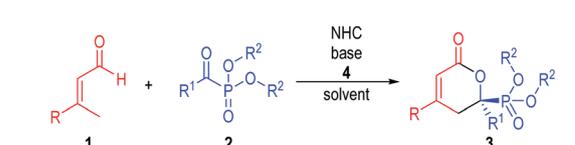
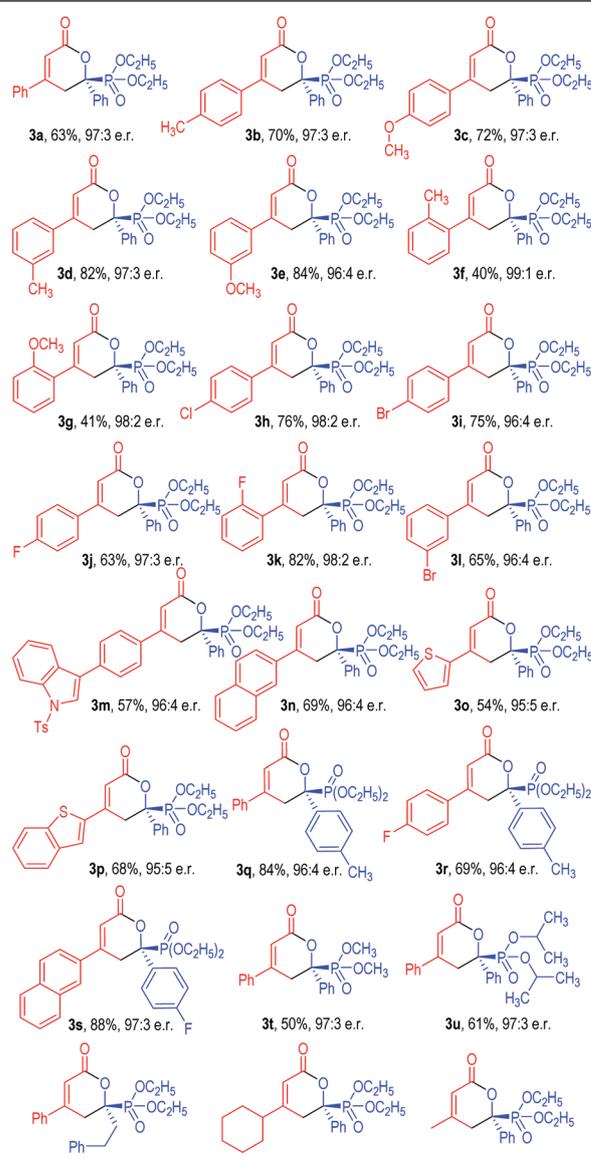
Table 1 Condition optimization^a


Entry	Cat.	Base	Solvent	Yield ^b [%]	e.r. ^c
1	A	CS ₂ CO ₃	THF	0	—
2	B	CS ₂ CO ₃	THF	<5	—
3	C	CS ₂ CO ₃	THF	10	90:10
4	D	CS ₂ CO ₃	THF	<5	—
5	C	K ₂ CO ₃	THF	26	89:11
6	C	Et ₃ N	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 ₃ CN	<10	—

^a Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), NHC (0.02 mmol), base (0.12 mmol), **4** (0.12 mmol), THF (2 mL), 30 °C, 48 h. ^b Yields were isolated yields after purification *via* SiO₂ column chromatography. ^c E.r. values were determined *via* HPLC using a chiral stationary phase.

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 the optimized reaction conditions in 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

Table 2 Substrate scope^a



Product	Yield [%]	e.r.
3a	63%	97:3 e.r.
3b	70%	97:3 e.r.
3c	72%	97:3 e.r.
3d	82%	97:3 e.r.
3e	84%	96:4 e.r.
3f	40%	99:1 e.r.
3g	41%	98:2 e.r.
3h	76%	98:2 e.r.
3i	75%	96:4 e.r.
3j	63%	97:3 e.r.
3k	82%	98:2 e.r.
3l	65%	96:4 e.r.
3m	57%	96:4 e.r.
3n	69%	96:4 e.r.
3o	54%	95:5 e.r.
3p	68%	95:5 e.r.
3q	84%	96:4 e.r.
3r	69%	96:4 e.r.
3s	88%	97:3 e.r.
3t	50%	97:3 e.r.
3u	61%	97:3 e.r.
3v	19%	97:3 e.r.
3w	17%	98:2 e.r.
3x	0%	—

^a Reactions were carried out under the conditions as in Table 1, entry 8. Yields were isolated yields after purification *via* SiO₂ column chromatography. E.r. values were determined *via* HPLC using a chiral stationary phase.

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 sterically hindered substituents on the 2-position of the β -benzene groups would lead to drops in the product yields (**3f** to **3g**). The substituted β -benzene groups on substrates **1** could also be replaced with a naphthyl 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 enantioselectivities (**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**).

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 the turbidimeter test with bismethiazol 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 a similar inhibitory rate against *X. oryzae pv. oryzae* when compared to the commercially available bactericide bismethiazol at the concentrations of both 100 $\mu\text{g mL}^{-1}$ and 200 $\mu\text{g mL}^{-1}$.

Tobacco mosaic virus (abbreviated as TMV) is a damaging plant virus that is difficult to control.¹³ We carried out anti-viral studies of our phosphonates (**3**) against TMV (Table 4).¹⁴ Compared 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.

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

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

Compound	<i>X. oryzae pv. oryzae</i> inhibition rate ^a (%)	
	100 $\mu\text{g mL}^{-1}$	200 $\mu\text{g mL}^{-1}$
3b	10.8 \pm 3.0	45.8 \pm 1.5
3f	54.2 \pm 2.0	60.8 \pm 1.2
3u	44.4 \pm 4.2	59.9 \pm 4.4
Bismethiazol ^b	47.1 \pm 4.7	72.7 \pm 5.8
DMSO ^c	0	0

^a All data are 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 \pm 2.9	24.3 \pm 3.5
3o	43.1 \pm 4.4	24.1 \pm 2.9
3p	30.4 \pm 3.4	44.8 \pm 2.7
3r	27.6 \pm 5.6	44.4 \pm 7.9
3u	50.4 \pm 3.2	23.6 \pm 1.8
Ningnanmycin ^b	45.5 \pm 2.3	44.6 \pm 1.3

^a All data are average data of three replicates at the concentration of 500 $\mu\text{g mL}^{-1}$. ^b Commercially available anti-viral drug, used as the positive control.

new plant-protection agents. Further studies for quick access to phosphine-containing chiral molecules and their applications are in progress.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) J. F. Dellaria, Jr., R. G. Maki, H. H. Stein, J. Cohen, D. Whittern, K. Marsh, D. J. Hoffman, J. J. Plattner and 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 and E. W. Petrillo, Jr., *J. Med. Chem.*, 1995, **38**, 4557; (c) M. Tao, R. Bihovsky, G. J. Wells and J. P. Mallamo, *J. Med. Chem.*, 1998, **41**, 3912; (d) M. Collinsova and J. Jiracek, *Curr. Med. Chem.*, 2000, **7**, 629; (e) P. Kafarski and B. Lejczak, *Curr. Med. Chem.: Anti-Cancer Agents*, 2001, **1**, 301; (f) M. Bubenik, R. Rej, N. Nguyen-Ba, G. Attardo, F. Ouellet and 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 and S. Yang, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1537; (h) A. Mucha, P. Kafarski and L. Berlicki, *J. Med. Chem.*, 2011, **54**, 5955; (i) G. Zhang, G. Hao, J. Pan, J. Zhang, D. Hu and B. Song, *J. Agric. Food Chem.*, 2016, **64**, 4207.
- For reviews see: (a) A. N. Pudovik and 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 and R. P. Herrera, *Adv. Synth. Catal.*, 2008, **350**, 1195.
- (a) L. A. Telan, C.-D. Poon and S. A. Evans, Jr., *J. Org. Chem.*, 1996, **61**, 7455; (b) D. F. Wiemer, *Tetrahedron*, 1997, **53**, 16609; (c) D. A. Evans and J. S. Johnson, *J. Am. Chem. Soc.*, 1998, **120**, 4895; (d) D. A. Evans, J. S. Johnson and E. J. Olhava, *J. Am. Chem. Soc.*, 2000, **122**, 1635; (e) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam and J. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 10780; (f) M. C. Fernández, A. Diaz, J. J. Guillín, O. Blanco, M. Ruiz and V. Ojea, *J. Org. Chem.*, 2006, **71**, 6958; (g) N. Takenaka, J. P. Abell and H. Yamamoto, *J. Am. Chem. Soc.*, 2007, **129**, 742; (h) S. Samanta, J. Krause, T. Mandal and C.-G. Zhao, *Org. Lett.*, 2007, **9**, 2745; (i) C. F. Weise, V. H. Lauridsen, R. S. Rambo, E. H. Iversen, M.-L. Olsen and 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 and A. D. Smith, *Org. Lett.*, 2014, **16**, 2506.
- 4 (a) S. Samanta and C.-G. Zhao, *J. Am. Chem. Soc.*, 2006, **128**, 7442; (b) V. B. Gondli, K. Hagihara and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2009, **48**, 776; (c) N. S. Goulioukina, G. N. Bondarenko, A. V. Bogdanov, K. N. Gavrilov and I. P. Beletskaya, *Eur. J. Org. Chem.*, 2009, 510; (d) S. Perera, V. K. Naganaboina, L. Wang, B. Zhang, Q. Guo, L. Rout and 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 and A. D. Smith, *Synlett*, 2013, 1243; (f) M. T. Corbett and J. S. Johnson, *J. Am. Chem. Soc.*, 2013, **135**, 594; (g) Q. Li, C. J. Hou, Y. J. Liu, R. F. Yang and X. P. Hu, *Tetrahedron: Asymmetry*, 2015, **26**, 617; (h) M. Sun, J. Campbell, G. Kang, H. Wang and 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 and K. A. Scheidt, *J. Am. Chem. Soc.*, 2014, **136**, 76.
- 6 Z. Huang, X. Huang, B. Li, C. Mou, S. Yang, B. A. Song and 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 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.
- 8 (a) M. He, J. R. Struble and J. W. Bode, *J. Am. Chem. Soc.*, 2006, **128**, 8418; (b) J. R. Struble and 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 and 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 and 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 and Y. R. Chi, *Nat. Commun.*, 2017, **8**, 15598; (d) H. Wang, X. Chen, Y. Li, J. Wang, S. Wu, W. Xue, S. Yang and Y. R. Chi, *Org. Lett.*, 2018, **20**, 333.
- 10 (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.
- 11 M. Reichman, Y. Devash, R. J. Suhadolnik and I. Sela, *Virology*, 1983, **128**, 240.
- 12 (a) W.-M. Xu, F.-F. Han, M. He, D.-Y. Hu, J. He, S. Yang and 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 and B. Song, *J. Agric. Food Chem.*, 2013, **61**, 9575.
- 13 A. N. Craeger, K. B. Scholthof, V. Citovsky and H. B. Scholthof, *Plant Cell*, 1999, **11**, 301.
- 14 (a) G. V. Gooding, Jr. and 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 and W. Xue, *J. Agric. Food Chem.*, 2005, **53**, 7886; (c) F. Wu, P. Li, D.-Y. Hu and B.-A. Song, *Res. Chem. Intermed.*, 2016, **42**, 7153.
- 15 (a) H. Z. Hu, G. X. Xiang and J. R. Chen, *China Pat.*, 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 and S. Zeng, *J. Agric. Food Chem.*, 2009, **57**, 1383.