Hot off the Press

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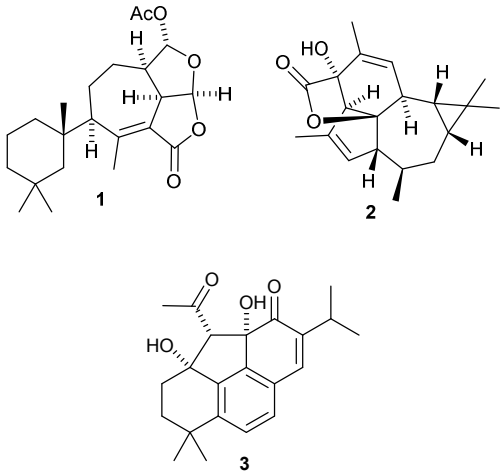
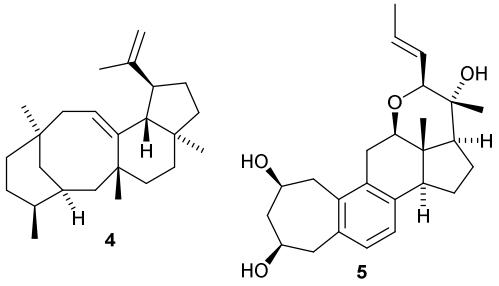
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as euphorikanin A from *Euphorbia kansui*.

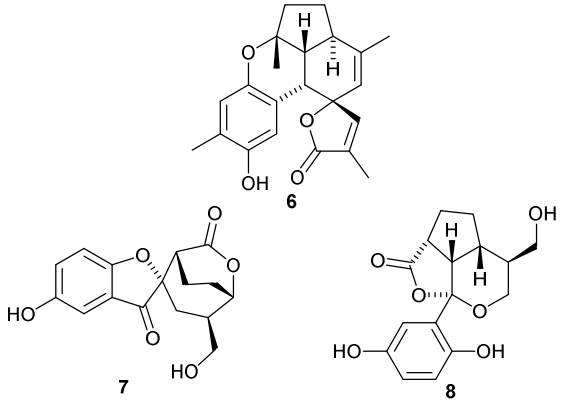
Darwinolide **1**, from the Antarctic sponge *Dendrilla membranosa*, shows interesting activity against methicillin-resistant *Staphylococcus aureus.*[1] The novel diterpenoid structure of darwinolide **1** was confirmed by X-ray analysis. A biosynthetic pathway for darwinolide **1**, from a spongiane precursor, has been proposed. The structure of euphorikanin A **2**, from *Euphorbia kansui*, was also confirmed by X-ray analysis.[2] The authors suggest that the new skeleton of euphorikanin A **2** is formed from an ingenane diterpenoid precursor. Perovskiaol **3**, from *Perovskia atriplicifolia*, may be formed by condensation of acetoacetyl CoA with a 20-norabietane diterpenoid.[3]



Genome mining of a terpene synthase gene from *Emericella variecolor* and its functional expression in *Aspergillus oryzae* led to the isolation of the sesterterpenoid astellifadiene **4** which has a new skeleton.[4] The structure and absolute configuration of astellifadiene **4**, which exists as an oil, were established by the crystalline sponge method. A biosynthetic pathway to astellifadiene **4** has been proposed based on the results of acetate labelling studies. Phomarol **5**, with a novel 1(10→19)*abeo* steroid skeleton, is a metabolite of a *Phoma* species isolated from the giant jellyfish *Nemopilema nomurai*.[5]

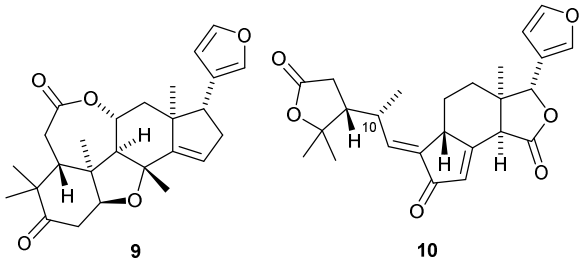


The meroterpenoid verrubenzospirolactone **6**, from the soft coral *Sinularia verruca*, has a new carbon skeleton.[6] Applanatumols A **7** and B **8**, from *Ganoderma applanatum*, are further meroterpenoids with new skeletons.[7] Biosynthetic pathways to applanatumols A **7** and B **8** have been proposed.



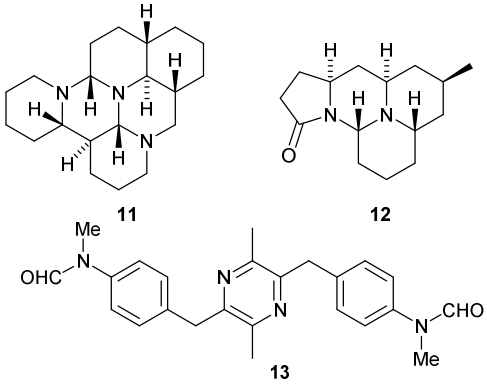
The structural diversity of the limonoid family, or the tetranortriterpenoids, is enormous. Two additional examples with unusual structures are ciliatonoid A **9**, from *Toona ciliata*,[8] and perforanoid A **10**, from *Harrisonia perforata*.[9] The structure of

ciliatonoid A **9**, was confirmed by X-ray analysis whereas the structure of perforanoid A **10**, including the stereochemistry at C-10, was confirmed by total synthesis.



9 **10**

Myritonine A **11**, from *Myrioneuron tonkinensis*, has a novel heterohexacyclic ring system.[10] The structure of myritonine A was confirmed by X-ray analysis. Another new ring system is present in palcernuine **12** which has been isolated from *Palhinhaea cernua* f. *sikkimensis*.[11] A biosynthetic pathway for the formation of the five-membered ring of palcernuine **12** from a cernuane alkaloid precursor has been proposed. The symmetrical pyrazine grizeusrazin A **13**, a metabolite of marine-derived *Streptomyces griseus* ssp. *griseus*, shows interesting anti-inflammatory properties.[12]

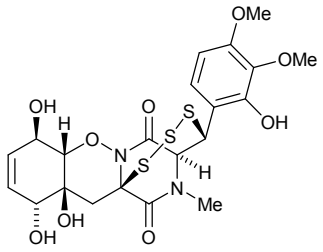


11 **12**

13

Outovirins A – C are epipolythiodiketopiperazines isolated from *Penicillium raciborskii*, an endophytic fungus isolated from *Rhododendron tomentosum*.[13] Outovirin C **14** is the first reported trisulfide of the gliovirin family of alkaloids. The first cyclopentachromone with a sulfide chain, chromosulfine **15**, has been isolated from a marine-derived *Penicillium purpurogenum*.[14] Chromosulfine **15** is produced by

a silent biosynthetic pathway that was induced after the introduction of neomycin resistance.



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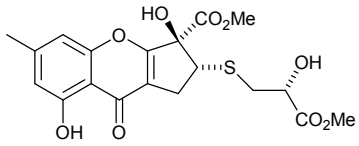
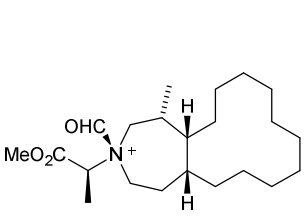


15

Callyazepin **16**, from a sponge of the genus *Callyspongia*, has a new skeleton and includes a chiral quaternary nitrogen.[15] Callyazepin **16** is of mixed biogenetic origin and appears to be derived from a polyketide and alanine. Antalid **17**, a metabolite of a *Polyangium* species, is also of mixed biosynthetic origin.[16] *In silico* analysis of the biosynthetic gene cluster for antalid **17** has established the biosynthetic origin of this PKS-NRPS hybrid natural product. The structure of antalid **17** was confirmed by crystal structure analysis and total synthesis.



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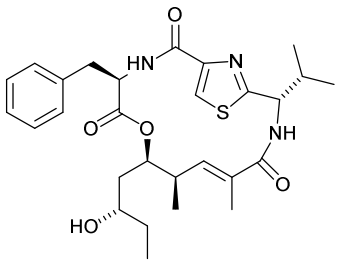
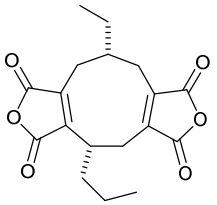


17

Cox and co-workers have recreated the biosynthesis of maleidrides such as byssochlamic acid **18** in a heterologous host.[17] Gene disruption and heterologous expression experiments identified two proteins with homology to ketosteroid isomerases involved in the key stage of C_9-maleic anhydride monomer dimerisation.

The Cox group have also reported the elucidation of the gene cluster responsible for the biosynthesis of squalestatin S1 **19**, a lead compound in the 1990s for the treatment of hypercholestermia.[18] An acyltransferase gene from the cluster was expressed in *E. coli*, with the resulting protein MfM4 found to be responsible for loading acyl groups from coenzyme A (CoA) onto the squalestatin core. The broad substrate specificity of MfM4 for acyl CoA substrates allowed the *in vitro* preparation of novel squalestatins.



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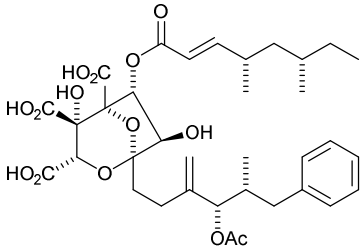
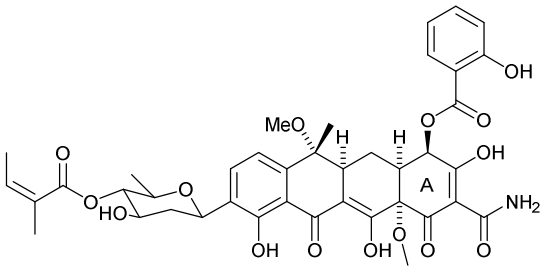


19

In vitro and *in vivo* studies of the biosynthesis of SF2575 **20**, a tetracycline antibiotic produced by *Streptomyces* sp. *SF2575* have identified an ATP-dependent acyl-CoA ligase responsible for the Claisen cyclisation of the A-ring.[19] The authors propose that the reaction proceeds by the ligase-mediated adenylation of a tricyclic carboxylic acid substrate followed by Claisen cyclisation. The spirotetronate cyclase AbyU, a key enzyme for the biosynthesis of the antibiotic abyssomicin C **21** has been fully characterised and shown to be a cofactor-independent Diels-Alderase.[20] A combination of enzyme assays, X-ray crystallography and molecular modelling has established the binding mode of the linear substrate as well as the catalytic mechanism of the [4+2] cycloaddition.



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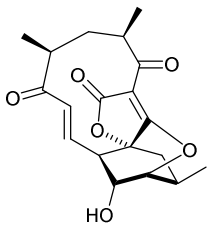
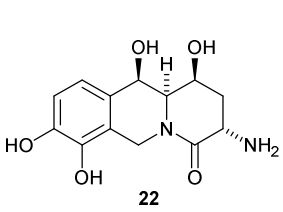


21

Comparative metabolomics of the human pathogen *Aspergillus fumigatus* have revealed the *fsq* gene cluster which features a non-ribosomal peptide synthetase gene (*fsqF*) that lacks a condensation domain.[21] The *fsqF* gene is responsible for the production of a series of novel isoquinoline alkaloids (e.g. fumisoquin A **22**) that are formed *via* a carbon-carbon bond forming reaction between L-serine and L-tyrosine. The late stage biosynthesis of sesterterpenes such as ophiobolin F **23** have been investigated by the heterologous expression of four candidate genes from ophiobolin gene clusters in *Aspergillus oryzae*.[22] The resulting transformant was shown to catalyse a four-step oxidative process, converting ophiobolin F to ophiobolin C. One of the enzymes OblB, a cytochrome P450 was found to be responsible for the introduction of oxygen functionality at C-5 and C-21.



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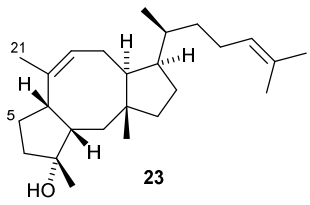
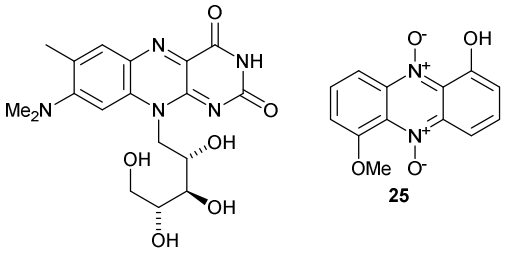


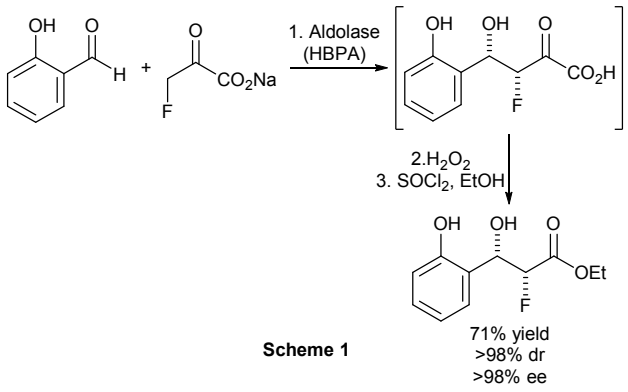
23

A combination of systematic gene deletion, heterologous gene expression and biochemical studies have revealed the key enzyme involved in the biosynthesis of roseoflavin **24**, the only known natural riboflavin analogue with antibiotic activity.[23] This key enzyme produced from gene BN159_7989 from *Streptomyces davawensis* was shown to convert riboflavin-5'-phosphate via a series of reactions to 8-demethyl-8-aminoriboflavin-5'-phosphate, an advanced intermediate of roseoflavin biosynthesis. Six phenazine antibiotics including four *N*-oxides (e.g. myxin **25**) have been isolated from *Lysobacter antibioticus* OH13.[24] Identification of the phenazine gene cluster has led to the characterisation of the enzyme LaPhzNO1, which although homologous to Baeyer-Villiger flavoproteins performs the *N*-oxidation of phenazines.

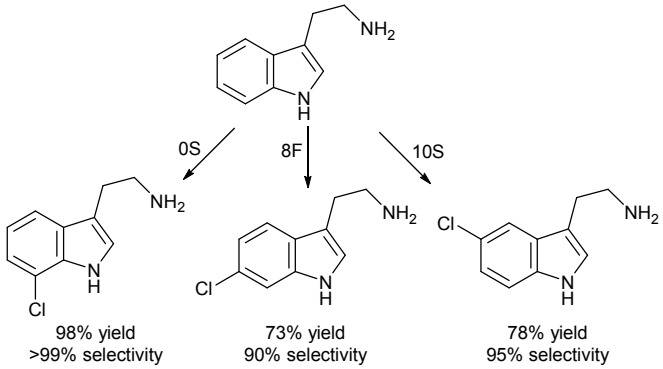


24 25

A chemoenzymatic synthesis of α-fluoro β-hydroxy carboxylic esters has been developed using a *trans-o*-hydroxybenzylidene pyruvate aldolase catalysed reaction between fluoropyruvate and various aromatic aldehydes (Scheme 1).[25] Following the aldolase reaction, hydrogen peroxide was used to facilitate decarboxylation, yielding the target compounds after esterification with excellent yields and enantioselectivity. Deuterium-substituted probe substrates in combination with mass spectrometry have been used to discover variants of rebeccamycin halogenase for the chlorination of indoles.[26] This evolution strategy identified enzymes that could selectivity produce *ortho*-, *meta*- or *para*-substituted products in high yields (Scheme 2).

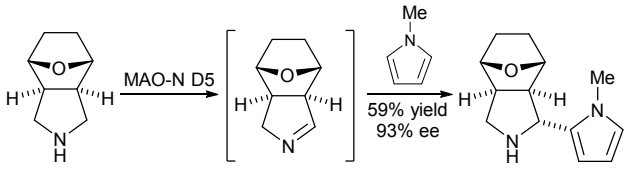


Scheme 1

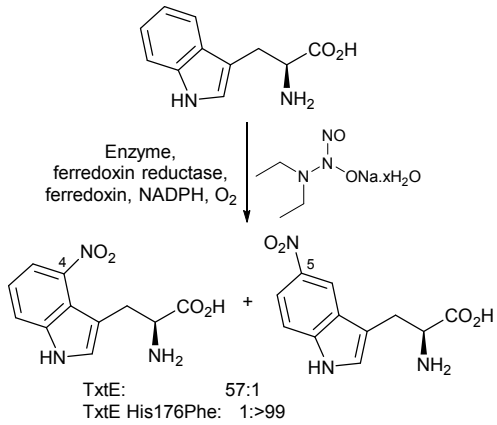


Scheme 2

A one-pot chemoenzymatic oxidative aza-Friedel-Crafts reaction for the α-functionalisation of pyrrolidines has been developed.[27] Oxidation of *meso*-pyrrolidines by an engineered monoamine oxidase, followed by reaction with a range of *C*-nucleophiles gave the substitution products as single diastereomers with high enantioselectivity (Scheme 3). Experimental and computation work have identified a single mutation in the F/G loop of the nitrating cytochrome P450 TxtE enzyme that alters the regioselectivity of the reaction.[28] Rather than forming the wild-type C-4 nitration product with L-tyrosine, mutation of this single residue which interacts with the substrate and contributes to active site organisation produced instead the C-5 product (Scheme 4).



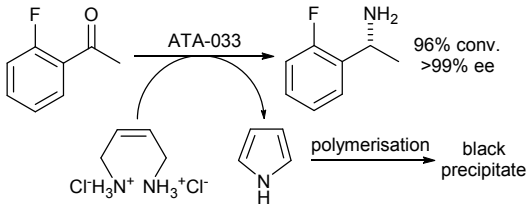
Scheme 3



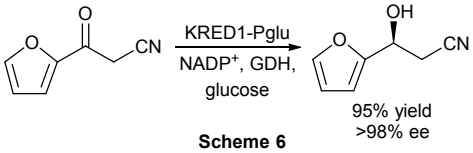
Scheme 4

Lavandera and co-workers have shown that *cis*- and *trans*-but-2-ene-1,4-diamines can be used as sacrificial co-substrates in enzymatic transamination reactions.[29] Following amino group transfer, the resulting ω-amino aldehyde intermediate undergoes an intramolecular cyclisation, providing the driving force for the efficient production of optically active amines with excellent enantioselectivity (Scheme 5). The recombinant

ketoreductase KRED1-Pglu isolated from the yeast *Pichia glucozyma* CBS 5766 has been shown to be an effective biocatalyst for the asymmetric reduction of β-hydroxynitriles (Scheme 6) and α-haloketones.[30] Using a glucose/glucose dehydrogenase recycling system for the $NADP^+$ cofactor gave chiral synthetic building blocks in excellent yields.

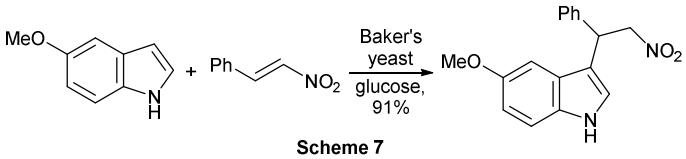


Scheme 5

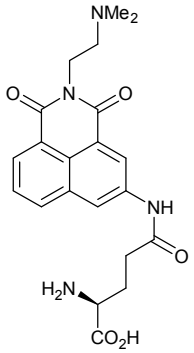


Scheme 6

Baker's yeast has been shown to catalyse the highly regioselective 1,4-conjugate addition reaction of indoles with nitroalkenes.[31] The operationally simple procedure was found to be tolerant of a wide range of substitution patterns for both substrates, giving the addition products in high yields (Scheme 7). A two-photon fluorescent probe **26** has been reported that has the potential to act as a visual tool in the real-time dynamic imaging of DNA damage.[32] The probe operates through sequential intramolecular charge transfer (ICT) processes and allows in vivo visualisation of DNA damage in cancer cells either by one/two photon microscopic imaging or using a hand-held UV lamp.



Scheme 7



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References

1 J. L. von Salm, C. G. Witowski, R. M. Fleeman, J. B. McClintock, C. D. Amsler, L. N. Shaw and B. J. Baker, *Org. Lett*., 2016, **18**, 2596.

2 D.-Q. Fei, L.-L. Dong, F.-M. Qi, G.-X. Fan, H.-H. Li, Z.-Y. Li and Z.-X. Zhang, *Org. Lett*., 2016, **18**, 2844.

3 Z.-Y. Jiang, L.-Y. Zhu, J. Zhou, Q.-F. Hu, G.-Y. Yang, X.-Z. Huang, W.-X. Liu, L. Gao, G.-P. Li and F.-T. Xia, *Helv. Chim. Acta*, 2016, **99**, 452.

4 Y. Matsuda, T. Mitsuhashi, S. Lee, M. Hoshino, T. Mori, M. Okada, H. Zhang, F. Hayashi, M. Fujita and I. Abe, *Angew. Chem. Int. Ed*., 2016, **55**, 5785.

5 E. L. Kim, J. L. Li, J. Hong, W. D. Yoon, H. S. Kim, Y. Liu, X. Wei and J. H. Jung, *Tetrahedron Lett*., 2016, **57**, 2803.

6 W. Yuan, S. Cheng, W. Fu, M. Zhao, X. Li, Y. Cai, J. Dong, K. Huang, K. R. Gustafson and P. Yan, *J. Nat. Prod*., 2016, **79**, 1124.

7 Q. Luo, L. Di, X.-H. Yang and Y.-X. Cheng, *RSC Adv*., 2016, **6**, 45963.

8 C.-P. Liu, G.-C. Wang, L.-S. Gan, C.-H. Xu, Q.-F. Liu, J. Ding and J.-M. Yue, *Org. Lett*., 2016, **18**, 2894.

9 C. Lv, X. Yan, Q. Tu, Y. Di, C. Yuan, X. Fang, Y. Ben-David, L. Xia, J. Gong, Y. Shen, Z. Yang and X. Hao, *Angew. Chem. Int. Ed*., 2016, **55**, 7539.

10 X.-H. Li, Y. Zhang, J.-H. Zhang, X.-N. Li, M.-M. Cao, Y.-T. Di, Z.-G. Peng, J.-D. Jiang and X.-J. Hao, *J. Nat. Prod*., 2016, **79**, 1203.

11 Y. Tang, J. Xiong, Y. Zou, B. Nay, L.-J. Wang and J.-F. Hu, *Chin. Chem. Lett*., 2016, **27**, 969.

12 D.-S. Lee, C.-S. Yoon, Y.-T. Jung, J.-H. Yoon, Y.-C. Kim and H. Oh, *J. Nat. Prod*., 2016, **79**, 1105.

13 M. Kajula, J. M. Ward, A. Turpeinen, M. V. Tejesvi, J. Hokkanen, A. Tolonen, H. Häkkänen, P. Picart, J. Ihalainen, H.-G. Sahl, A. M. Pirttilä and S. Mattila, *J. Nat. Prod*., 2016, **79**, 685.

14 L. Yi, C.-B. Cui, C.-W. Li, J.-X. Peng and Q.-Q. Gu, *RSC Adv*., 2016 **6**, 43975.

15 C.-K. Kim, J.-K. Woo, Y.-J. Lee, H.-S. Lee, C. J. Sim, D.-C. Oh, K.-B. Oh and J. Shin, *J. Nat. Prod*., 2016, **79**, 1179.

16 T. Tautz, J. Hoffmann, T. Hoffmann, H. Steinmetz, P. Washausen, B. Kunze, V. Huch, A. Kitsche, H. Reichenbach, G. Höfle, R. Müller and M. Kalesse, *Org. Lett*., 2016, **18**, 2560.

17 K. Williams, A. J. Szwalbe, N. P. Mulholland, J. L. M. Bailey, C. L. Willis, T. J. Simpson and R. J. Cox, *Angew. Chem. Int. Ed*., 2016, **55**, 6784.

18 B. Bonsch, V. Belt, C. Bartel, N. Duensing, M. Koziol, C. M. Lazarus, A. M. Bailey, T. J. Simpson and R. J. Cox, *Chem. Commun*., 2016, **52**, 6777.

19 W. Xu, L. B. Raetz, P. Wang and Y. Tang, *Tetrahedron*, 2016, **72**, 3599.

20 M. J. Byrne, N. R. Lees, L.-C. Han, M. W. van der Kamp, A. J. Mulholland, J. E. M. Stach, C. L. Willis and P. R. Race, *J. Am. Chem. Soc*., 2016, **138**, 6095.

21 J. A. Baccile, J. E. Spraker, H. H. Le, E. Brandenburger, C. Gomez, J. W. Bok, J. Macheleidt, A. A. Brakhage, D. Hoffmeister, N. P. Keller and F. C. Schroeder, *Nat. Chem. Biol*., 2016, **12**, 419.

22 K. Narita, R. Chiba, A. Minami, M. Kodama, I. Fujii, K. Gomi and H. Oikawa, *Org. Lett*., 2016, **18**, 1980.

23 J. Schwarz, V. Konjik, F. Jankowitsch, R. Sandhoff and M. Mack, *Angew. Chem. Int. Ed*., 2016, **55**, 6103.

24 Y. Zhao, G. Qian, Y. Ye, S. Wright, H. Chen, Y. Shen, F. Liu and L. Du, *Org. Lett*., 2016, **18**, 2495.

25 J. K. Howard, M. Müller, A. Berry and A. Nelson, *Angew. Chem. Int. Ed*., 2016, **55**, 6767.

26 M. C. Andorfer, H. J. Park, J. Vergara-Coll and J. C. Lewis, *Chem. Sci*., 2016, **7**, 3720.

27 C. de Graaff, B. Oppelaar, O. Péruch, C. M. L. Vande Velde, B. Bechi, N. J. Turner, E. Ruijter and R. V. A. Orru, *Adv. Synth. Catal*., 2016, **358**, 1555.

28 S. C. Dodani, G. Kiss, J. K. B. Cahn, Y. Su, V. S. Pande and F. H. Arnold, *Nat. Chem*., 2016, **8**, 419.

29 L. Martínez-Montero, V. Gotor, V. Gotor-Fernández and I. Lavandera, *Adv. Synth. Catal*., 2016, **358**, 1618.

30 M. L. Contente, I. Serra, F. Molinari, R. Gandolfi, A. Pinto and D. Romano, *Tetrahedron*, 2016, **72**, 3974.

31 A. Mane, T. Lohar and R. Salunkhe, *Tetrahedron Lett*., 2016, **57**, 2341.

32 H. Zhang, K. Wang, X. Xuan, Q. Lv, Y. Nie and H. Guo, *Chem. Commun*., 2016, **52**, 6308.