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Organocatalytic, enantioselective synthesis of benzoxaboroles *via* Wittig/oxa-Michael reaction Cascade of α -formyl boronic acids†

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An unprecedented enantioselective synthesis of 3-substituted benzoxaboroles has been developed. An *in situ* generated *ortho*-boronic acid containing chalcone provides the chiral benzoxaboroles *via* an asymmetric oxa-Michael addition of hydroxyl group attached to the boronic acid triggered by the cinchona alkaloid based chiral amino-squaramide catalysts. In general, good yields with good to excellent enantioselectivities (up to 99%) were obtained. The resulting benzoxaboroles were converted to the corresponding chiral β -hydroxy ketones without affecting the enantioselectivity.

Introduction

Benzoxaboroles, an important class of boron containing molecules, has recently acquired significant attention towards its applications for the development of new drugs.^{1,2} The Lewis acidity of the boron and its easy conversion from trigonal to tetrahedral geometry enables benzoxaboroles to bind to the active site of various enzymes and thereby inhibit their activity.^{1,3} Ever since the discovery of the exceptional sugar-binding properties at physiological conditions⁴ as well as the finding of anti-fungal activity of AN2690 (Fig. 1),⁵ benzoxaboroles have been extensively studied for therapeutic applications. This leads to the development of benzoxaboroles with antibacterial,⁶ antiviral,⁷

anti-parasitic,⁸ anti-inflammatory,⁹ and antimalarial¹⁰ activities as well as β -lactamase inhibitor.¹

Very recently, KERYDIN was approved for onychomycosis treatment,¹¹ AN2728 (ref. 12) and AN2898 (ref. 13) are currently under clinical trials for psoriasis. SCYX-7158/AN5568 entered into clinical trials for the treatment of human African trypanosomiasis.¹⁴ Thus, the intrinsic reactivity and metabolic stability of benzoxaborole motif have made it a new “privileged scaffold” for the design of new drugs.¹⁵ Furthermore, the materials conjugated with benzoxaborole exhibit a unique structural assembly which enables to unfold multidentate interactions to improve selective binding.¹⁶ This property has extended their applications in supramolecular¹⁷ and materials chemistry.¹⁸ Apart from these, benzoxaboroles are versatile building blocks for the synthesis of organic molecules of higher complexity.¹⁹ Despite the surging applications of benzoxaboroles in various fields and handful attempts directed towards their achiral synthesis, we report herein, for the first time, the catalytic enantioselective synthesis of this class of compounds. In this reaction, the 2-formyl aryl boronic acids react *via* a Wittig reaction followed by an enantioselective oxa-Michael addition of a hydroxyl group attached to the boronic acid using chiral bifunctional organocatalysts (Scheme 1).

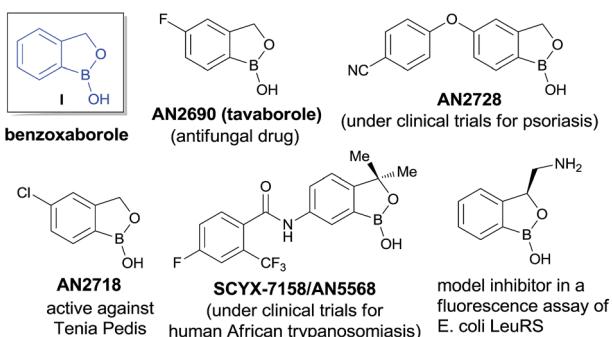
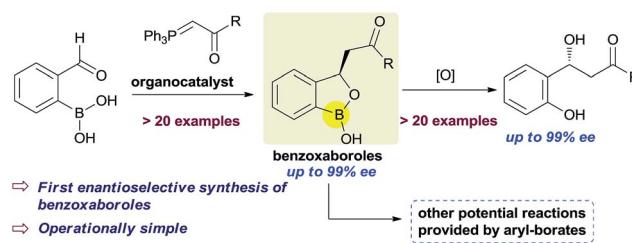


Fig. 1 Pharmaceuticals featuring benzoxaborole moiety.

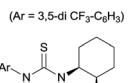
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† Electronic supplementary information (ESI) available. CCDC 1487136. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc04522g



Scheme 1 Catalytic enantioselective synthesis of benzoxaboroles.

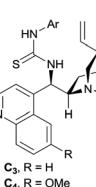
Table 1 Optimization of the reaction conditions^a

Entry	Catalyst	Solvent	Yield ^b (%)	(% ee) ^c	
				(%) ee ^c	(%) ee ^c
1	C ₁	CH ₂ Cl ₂	12	56	
2	C ₂	CH ₂ Cl ₂	<5	ND	
3	C ₃	CH ₂ Cl ₂	26	70	
4	C ₄	CH ₂ Cl ₂	16	–62	
5	C ₅	CH ₂ Cl ₂	26	86	
6	C ₆	CH ₂ Cl ₂	53	90	
7	C ₇	CH ₂ Cl ₂	55	91	
8	C ₇	Toluene	70	90	
9	C ₇	PhCF ₃	85	90	
10	C ₇	THF	15	80	
11	C ₇	Chlorobenzene	86	91	

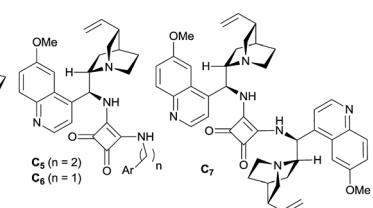


C₁

(Ar = 3,5-di CF₃-C₆H₃)



(DHQ)₂PHAL (C₂)



C₃, R = H; C₄, R = OMe

C₅ (n = 2); C₆ (n = 1)

C₇

^a Reactions were performed on a 0.05 mmol scale of aldehyde **1a**, 1.5 equiv. of **2a**. ^b Yield was calculated based on ¹H NMR spectroscopy of the crude reaction mixture using diphenyl acetonitrile as the internal standard. ^c Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase after oxidative deborylation.

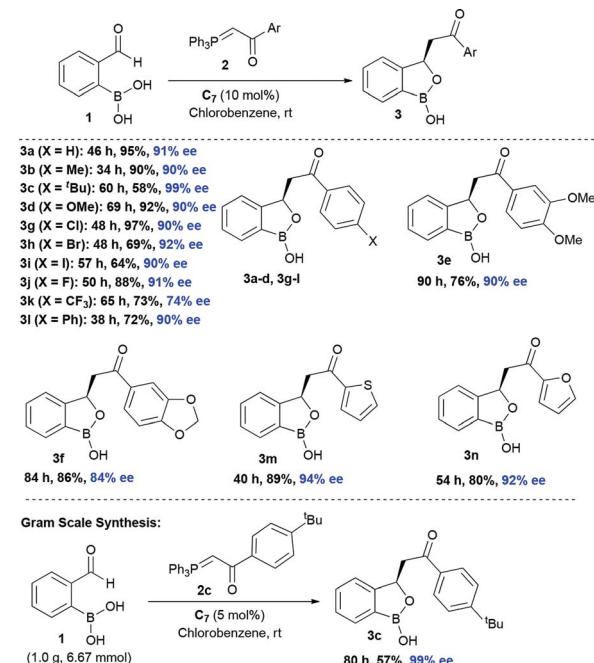
Our strategy is leveraged from the asymmetric oxa-Michael addition using bifunctional organocatalyst consisting of squaramide/thiourea moiety attached to a tertiary nitrogen on a chiral scaffold and the oxo-nucleophilicity of the hydroxy group of organoboronic acids, revealed by Falck *et al.*²⁰ We hypothesized to utilize an *in situ* generated *ortho*-boronic acid containing chalcones (II, Table 1) as the substrate wherein the asymmetric oxa-Michael reaction of hydroxy group of boronic acid is involved in the simultaneous coordination of the carbonyl with squaramide/thiourea (the pull) moiety and the tertiary nitrogen to boron (the push).

Results and discussion

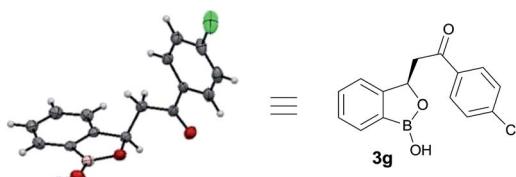
At the outset, we began our investigation with *ortho*-formyl phenyl boronic acid **1a** and benzoyl Wittig olefin **2a** aiming towards the synthesis of chiral benzoxaborole **3a** (Table 1). A variety of chiral amino-thiourea (**C₁**) and cinchona alkaloid-derived catalysts (**C₂–C₇**) were surveyed in dichloromethane at room temperature (entries 1–7) (see ESI†). As shown in entry 7, catalyst **C₇** was found to catalyze the reaction cleanly to furnish the benzoxaborole **3a** (55% NMR yield with 91% ee). A notable increase in yield was observed when the reaction was performed in toluene and trifluoro-toluene (entry 8 and 9, respectively). An

immediate solvent study consoled that chlorobenzene was the optimal one, affording 91% ee with 86% yield (entry 11). Under these optimal reaction conditions, we examined the substrate scope of this reaction, and the results are shown in Scheme 2. The effect of substitution on the aryl moiety of Wittig-olefins was first examined. To our delight, electron-donating substituents such as Me– (**3b**), ^tBu– (**3c**) and MeO– (**3d–e**) underwent smooth cyclization, affording the desired products in good to excellent yields and with excellent enantioselectivities (58–95% yields, 84–99% ee). Similarly, electron-withdrawing substituents such as Cl– (**3g**), Br– (**3h**), I– (**3i**), F– (**3j**), F₃C– (**3k**) and Ph– (**3l**), also furnished the desired products with high stereo-induction (64–97% yields, 74–92% ee). Hetero-aromatic groups such as 2-thiophenyl as well as 2-furyl were also well tolerated to provide the corresponding benzoxaboroles **3m** (89% yield, 94% ee) and **3n** (80% yield, 92% ee), respectively. To illustrate the practical utility of this methodology, a gram scale (1.0 g, 6.67 mmol) reaction was performed to provide the product **3c**. Interestingly, it was observed that even 5 mol% of catalyst was enough to complete the reaction without losing any enantioselectivity (57% yield, 99% ee). The absolute stereochemistry (*R*) of the product **3g** was determined by X-ray crystallography (Fig. 2) and the other compounds were assigned by analogy.

Next, the substitution on the central aryl moiety was examined which was quite general (Scheme 3) concerning enantioselectivities as well as yields. Electron-donating substituents such as Me– (**3o–p**), MeO– (**3q**), as well as electron-withdrawing substituents such as F– (**3r–t**), CN– (**3u**) and Cl– (**3v**), worked smoothly, affording the desired benzoxaborole with excellent

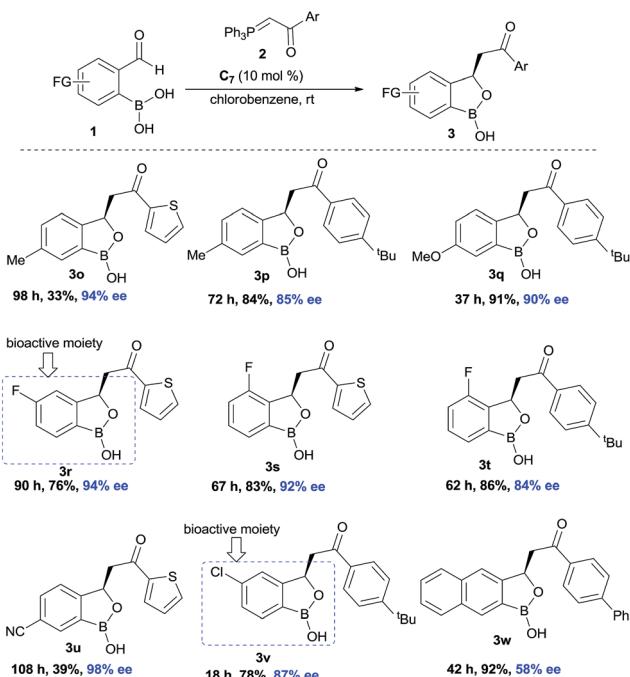


Scheme 2 Exploration of the scope with Wittig olefines^{a,b,c}. ^aReaction conditions: **1** (0.2 mmol), Wittig olefin **2** (0.3 mmol, 1.5 equiv.), **C₇** (0.02 mmol, 10 mol%). ^bEnantiomeric excess was determined by chiral HPLC analysis of the corresponding oxidative deborylation product. ^cAll are isolated yields.

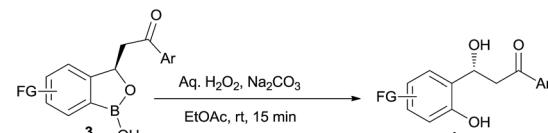
Fig. 2 Crystal structure of **3g** (CCDC 1487136).

enantioselectivities. Instead of central phenyl moiety, naphthyl moiety (**3w**) remained less efficient regarding enantioselectivity. Notably, the F- and Cl-substituted (**3r** and **3v**) benzoxaborole moieties are known to have bioactivity as mentioned in Fig. 1.

The synthesis of chiral β -hydroxy carbonyls has remained an attractive area of research because of their prevalence in organic synthesis and medicinal chemistry.²¹ Chiral benzylic alcohol containing phenols were used as chiral precursor for asymmetric synthesis, ligand and chiral auxiliary in asymmetric catalysis.²² However, there are limited methods in literature for the synthesis of such chiral alcohols.²³ Moreover, synthesis of chiral β -hydroxy ketones has remained elusive so far. Therefore, we also emphasized on the oxidative deborylation of the products **3** (Scheme 4). Interestingly, the corresponding chiral benzyl alcohol **4** was obtained smoothly after oxidative deborylation of **3** with high yields and excellent enantioselectivities. Thus, *via* this benzoxaborolane pathway, the synthesis of β -hydroxy ketones shows a considerable advantage with respect to enantioselectivity and substrate generality.



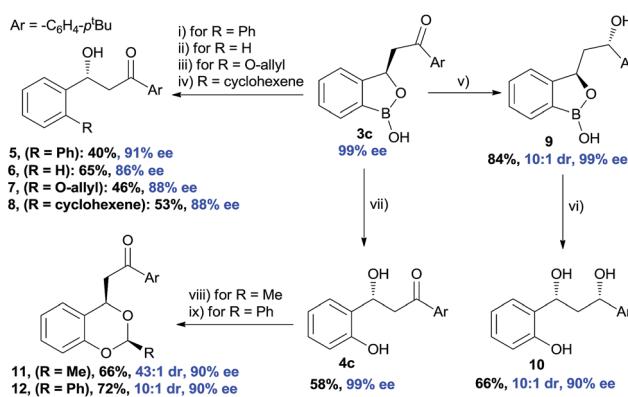
Scheme 3 Exploration of the scope with *o*-formyl aryl boronic acid **3**^{a,b,c}. ^aReaction conditions: **1** (0.2 mmol), Wittig olefin **2** (0.3 mmol, 1.5 equiv.), **C**₇ (0.02 mmol, 10 mol %). ^bEnantiomeric excess was determined by chiral HPLC analysis of the corresponding oxidative deborylation product. ^cAll are isolated yields.



4a: 78%, 91% ee	4i: 78%, 90% ee	4q: 61%, 90% ee
4b: 65%, 90% ee	4j: 73%, 91% ee	4r: 62%, 94% ee
4c: 88%, 99% ee	4k: 83%, 74% ee	4s: 58%, 92% ee
4d: 68%, 90% ee	4l: 85%, 90% ee	4t: 67%, 86% ee
4e: 76%, 90% ee	4m: 71%, 94% ee	4u: 62%, 98% ee
4f: 75%, 84% ee	4n: 69%, 92% ee	4v: 53%, 87% ee
4g: 85%, 90% ee	4o: 86%, 94% ee	4w: 72%, 58% ee
4h: 80%, 92% ee	4p: 88%, 85% ee	

Scheme 4 Synthesis of chiral β -hydroxy ketones^{a,b,c}. ^aReaction conditions: **3** (0.1 mmol), Aq. H_2O_2 (0.1 mL), Aq. Na_2CO_3 (1 mL). ^bEnantiomeric excess was determined by HPLC analysis on a chiral stationary phase. ^cAll are isolated yields.

The synthetic potential of the benzoxaborolanes was briefly investigated using oxaborol **3** (Scheme 5). Subjecting **3c** to a Pd-catalyzed Suzuki reaction conditions using bromobenzene afforded product **5** in 40% yield and 91% ee. Similarly, Ag-catalyzed deborylation provided the compound **6** and Cu-catalyzed deborylation in the presence of allyl alcohol produced **7** with high ee. A palladium catalyzed olefination with alkenyl triflate furnished the desired **8** with 88% ee. A substantial stereo-induction was observed during the NaBH_4 reduction of keto functionality of **3c**, an excellent diastereoselectivity (10 : 1) was achieved in the compound **9**. Further, oxidative deborylation of the product **9** produced chiral 1,3-diol²⁴ **10** with high enantioselectivity and good diastereoselectivity. Finally, chiral benzylic alcohol **4c** was treated with aldehydes in the presence of acids which furnished the acetals (**11** and **12**) with excellent diastereoselectivity (43 : 1 and 10 : 1, respectively), albeit a small reduction of enantioselectivity.



Scheme 5 Functional group transformation of the product^a. Reaction conditions: (i) PhBr (1.1 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (2 mol %), K_2CO_3 (2 equiv.), dry dioxane, 80 °C. (ii) AgNO_3 (10 mol %), Et_3N (0.1 equiv.), $\text{EtOH} : \text{H}_2\text{O}$ (1 : 1), rt. (iii) Allyl alcohol, $\text{Cu}(\text{OAc})_2$ (2 equiv.), Et_3N (4 equiv.), rt. (iv) Cyclohexenyl trifluoromethanesulfonate (1.2 equiv.), $\text{Pd}(\text{dpf})\text{Cl}_2$ (0.1 equiv.), DME , EtOH , Na_2CO_3 80 °C. (v) NaBH_4 (1.1 equiv.), MeOH , -5°C to -10°C . (vi) $\text{Pd}(\text{PPh}_3)_4$ (2 mol %), K_2CO_3 (20 mol %), 1,4-dioxane, 80 °C. (vii) Aq. H_2O_2 , NaHCO_3 , EtOAc , rt. (viii) CH_3CHO (1.2 equiv.), PTSA (20 mol %), CH_2Cl_2 , rt. (ix) $\text{PhCH}(\text{OMe})_2$ (1.2 equiv.), PTSA (20 mol %), CH_2Cl_2 , rt. ^aAll are isolated yields.



To explain the observed absolute stereochemical outcome a bifunctional mechanism similar to those previously proposed for the squaramide/thiourea-catalyzed oxa-Michael reaction of enones may be invoked.²⁵

Conclusions

In summary, a sequential Wittig olefination followed by an enantioselective intramolecular oxa-Michael reaction of *ortho*-boronic acid containing chalcones have been developed using chiral bifunctional organocatalysts. This process provides the very first and promising approach for the synthesis of benzoxaboroles with excellent enantioselectivities and with a broad substrate scope. The resulting products were converted to the corresponding chiral β -hydroxy ketones without affecting the enantioselectivity.

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Notes and references

- (a) A. Adamczyk-Wozniak, K. M. Borys and A. Sporzyński, *Chem. Rev.*, 2015, **115**, 5224; (b) C. T. Liu, J. W. Tomsho and S. J. Benkovic, *Bioorg. Med. Chem.*, 2014, **22**, 4462; (c) D. C. McKinney, F. Zhou, C. J. Eyermann, A. D. Ferguson, D. B. Prince, J. Breen, R. A. Giacobbe, S. Lahiri and J. C. Verheijen, *ACS Infect. Dis.*, 2015, **1**, 310; (d) V. M. Chellat, L. Raguž and R. Riedl, *Angew. Chem.*, 2016, **128**, 6710; *Angew. Chem., Int. Ed.*, 2016, **55**, 6600; (e) S. G. Kurz, S. Hazra, C. R. Bethel, C. Romagnoli, E. Caselli, F. Prati, J. S. Blanchard and R. A. Bonomo, *ACS Infect. Dis.*, 2015, **1**, 234.
- For drug delivery: (a) G. A. Ellis, M. J. Palte and R. T. Raines, *J. Am. Chem. Soc.*, 2012, **134**, 3631; (b) A. Matsumoto, N. Sato, K. Kataoka and Y. Miyahara, *J. Am. Chem. Soc.*, 2009, **131**, 12022; (c) A. Matsumoto, H. Cabral, N. Sato, K. Kataoka and Y. Miyahara, *Angew. Chem.*, 2010, **122**, 5626; *Angew. Chem., Int. Ed.*, 2010, **49**, 5494; (d) Q. Peng, F. Chen, Z. Zhong and R. Zhuo, *Chem. Commun.*, 2010, **46**, 5888; (e) S. Biswas, K. Kinbara, T. Niwa, H. Taguchi, N. Ishii, S. Watanabe, K. Miyata, K. Kataoka and T. Aida, *Nat. Chem.*, 2013, **5**, 613.
- S. J. Baker, J. W. Tomsho and S. J. Benkovic, *Chem. Soc. Rev.*, 2011, **40**, 4279.
- (a) M. Dowlut and D. G. Hall, *J. Am. Chem. Soc.*, 2006, **128**, 4226; (b) M. Bérubé, M. Dowlut and D. G. Hall, *J. Org. Chem.*, 2008, **73**, 6471.
- (a) S. J. Baker, Y.-K. Zhang, T. Akama, A. Lau, H. Zhou, V. Hernandez, W. Mao, M. R. K. Alley, V. Sanders and J. J. Plattner, *J. Med. Chem.*, 2006, **49**, 4447; (b) F. L. Rock, W. Mao, A. Yaremchuk, M. Tukalo, T. Crepin, H. Zhou, Y. K. Zhang, V. Hernandez, T. Akama, S. J. Baker, J. J. Plattner, L. Shapiro, S. A. Martinis, S. J. Benkovic, S. Cusack and M. R. K. Alley, *Science*, 2007, **316**, 1759; (c) E. Seiradake, W. Mao, V. Hernandez, S. J. Baker, J. J. Plattner, M. R. K. Alley and S. Cusack, *J. Mol. Biol.*, 2009, **390**, 196.
- X. Li, S. M. Zhang, Y.-K. Zhang, Y. D. Liu, Z. Charles, Y. Zhou, J. J. Plattner, S. J. Baker, W. Bu, L. Liu, W. M. Kazmierski, M. S. Duan, R. M. Grimes, L. L. Wright, G. K. Smith, R. L. Jarvest, J. J. Ji, J. P. Cooper, M. D. Tallant, R. M. Crosby, K. Creech, J. Z. Ni, W. X. Zou and J. Wright, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2048.
- Y. Xia, K. Cao, Y. Zhou, M. R. K. Alley, F. Rock, M. Mohan, M. Meewan, S. J. Baker, S. Lux, C. Z. Ding, G. F. Jia, M. Kully and J. Plattner, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2533.
- R. T. Jacobs, B. Nare, S. A. Wring, M. D. Orr, D. Chen, J. M. Sligar, M. X. Jenks, R. A. Noe, T. S. Bowling, L. T. Mercer, C. Rewerts, E. Gaukel, J. Owens, R. Parham, R. Randolph, B. Beaudet, C. J. Bacchi, N. Yarlett, J. J. Plattner, Y. Freund, C. Ding, T. Akama, Y.-K. Zhang, R. Brun, M. Kaiser, I. Scandale and R. Don, *PLoS Neglected Trop. Dis.*, 2011, **5**, e1151.
- T. Akama, C. Virtucio, C. Dong, R. Kimura, Y.-K. Zhang, J. A. Nieman, R. Sharma, X. Lu, M. Sales, R. Singh, A. Wu, X.-Q. Fan, L. Liu, J. J. Plattner, K. Jarnagin and Y. R. Freund, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1680.
- For antimalarial activity: Y.-K. Zhang, J. J. Plattner, E. E. Easom, R. T. Jacobs, D. Guo, V. Sanders, Y. R. Freund, B. Campo, P. J. Rosenthal, W. Bu, F.-J. Gamo, L. M. Sanz, M. Ge, L. Li, J. Ding and Y. Yang, *J. Med. Chem.*, 2015, **58**, 5344.
- Press release, July 8, 2014; <http://investor.anacor.com/>.
- T. Akama, S. J. Baker, Y.-K. Zhang, V. Hernandez, H. Zhou, V. Sanders, Y. R. Freund, R. Kimura, K. R. Maples and J. J. Plattner, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2129.
- Y. R. Freund, T. Akama, M. R. K. Alley, J. Antunes, C. Dong, K. Jarnagin, R. Kimura, J. A. Nieman, K. R. Maples, J. J. Plattner, F. Rock, R. Sharma, R. Singh, V. Sanders and Y. Zhou, *FEBS Lett.*, 2012, **586**, 3410.
- R. T. Jacobs, J. J. Plattner, B. Nare, S. A. Wring, D. Chen, Y. Freund, E. G. Gaukel, M. D. Orr, J. B. Perales, M. Jenks, R. A. Noe, J. M. Sligar, Y.-K. Zhang, C. J. Bacchi, N. Yarlett and R. Don, *Future Med. Chem.*, 2011, **3**, 1259.
- (a) M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347; (b) S. Sene, J. McLane, N. Schaub, S. Bégu, H. Mutin, L. Ligon, R. J. Gilbert and D. Laurencin, *J. Mater. Chem. B*, 2016, **4**, 257.
- (a) T. A. Houston, *ChemBioChem*, 2010, **11**, 954; (b) S. Burroughs and B. Wang, *ChemBioChem*, 2010, **11**, 2245; (c) H. Kim, Y. J. Kang, S. Kang and K. T. Kim, *J. Am. Chem. Soc.*, 2012, **134**, 4030; (d) Y. Kotsuchibashi, R. V. C. Agustin, J.-Y. Lu, D. G. Hall and R. Narain, *ACS Macro Lett.*, 2013, **2**, 260; (e) Y. Zhang, W. Ma, D. Li, M. Yu, J. Guo and C. Wang, *Small*, 2013, **10**, 1379; (f) D. Dechtrirat, N. Gajovic-Eichelmann, F. Wojcik,



L. Hartmann, F. F. Bier and F. W. Scheller, *Biosens. Bioelectron.*, 2014, **58**, 1.

17 (a) P. Rodriguez-Cuamatzi, G. Vargas-Diaz and H. Höpfl, *Angew. Chem.*, 2004, **116**, 3103; *Angew. Chem., Int. Ed.*, 2004, **43**, 3041; (b) P. Rogowska, M. K. Cyrański, A. Sporzyński and A. Ciesielski, *Tetrahedron Lett.*, 2006, **47**, 1389; (c) A. Adamczyk-Woźniak, M. K. Cyrański, M. Jakubczyk, P. Klimentowska, A. Koll, J. Kołodziejczak, G. Pojmaj, A. Żubrowska, G. Z. Żukowska and A. Sporzyński, *J. Phys. Chem. A*, 2010, **114**, 324.

18 S. Sene, S. Bégu, C. Gervais, G. Renaudin, A. Mesbah, M. E. Smith, P. H. Mutin, A. van der Lee, J.-M. Nedelec, C. Bonhomme and D. Laurencin, *Chem. Mater.*, 2015, **27**, 1242.

19 A. Adamczyk-Woźniak, M. K. Cyrański, A. Żubrowska and A. Sporzyński, *J. Organomet. Chem.*, 2009, **694**, 3533.

20 For the nucleophilic oxa-addition of organoboronic acids: (a) K. Oshima and Y. Aoyama, *J. Am. Chem. Soc.*, 1999, **121**, 2315; (b) J. R. Falck, M. Bondlela, S. K. Venkataraman and D. Srinivas, *J. Org. Chem.*, 2001, **66**, 7148; (c) D. R. Li, A. Murugan and J. R. Falck, *J. Am. Chem. Soc.*, 2008, **130**, 46.

21 For the synthesis of chiral β -hydroxy carbonyls: (a) R. Mahrwald, *Chem. Rev.*, 1999, **99**, 1095; (b) B. Schetter and R. Mahrwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7506; (c) D. A. Evans, S. A. Siska and V. J. Cee, *Angew. Chem.*, 2003, **115**, 1803; *Angew. Chem., Int. Ed.*, 2003, **42**, 1761.

22 For the use of chiral benzylic alcohol containing phenols: (a) I. Cho, L. Meimetis and R. Britton, *Org. Lett.*, 2009, **11**, 1903; (b) I. Cho, L. Meimetis, L. Belding, M. J. Katz, T. Dudding and R. Britton, *Beilstein J. Org. Chem.*, 2011, **7**, 1315; (c) A. Kišić, M. Stephan and B. Mohara, *Adv. Synth. Catal.*, 2014, **356**, 3193.

23 For the synthesis of chiral benzylic alcohol: (a) T. Kitanosono and S. Kobayashi, *Asian J. Org. Chem.*, 2013, **2**, 961; (b) M. Sai and H. Yamamoto, *J. Am. Chem. Soc.*, 2015, **137**, 7091; (c) S. Kobayashi, P. Xu, T. Endo, M. Ueno and T. Kitanosono, *Angew. Chem.*, 2012, **124**, 12935; *Angew. Chem., Int. Ed.*, 2012, **51**, 12763; (d) L. Zhu, T. Kitanosono, P. Xu and S. Kobayashi, *Chem. Commun.*, 2015, **51**, 11685; (e) S. G. Davies, E. W. Hume, P. M. Roberts and J. E. Thomson, *Tetrahedron*, 2010, **66**, 8076; (f) D. B. Ramachary and R. Sakthidevi, *Chem.-Eur. J.*, 2009, **15**, 4516; (g) M. A. Ariger and E. M. Carreira, *Org. Lett.*, 2012, **14**, 4522.

24 For the synthesis of chiral 1,3-diol: (a) S. E. Bode, M. Wolberg and M. Müller, *Synthesis*, 2006, **4**, 557; (b) K. Baer, M. Kraußer, E. Burda, W. Hummel, A. Berkessel and H. Gröger, *Angew. Chem.*, 2009, **121**, 9519; *Angew. Chem., Int. Ed.*, 2009, **48**, 9355; (c) P. Gogoi, T. Kotipalli, K. Indukuri, S. Bondalapati, P. Saha and A. K. Saikia, *Tetrahedron Lett.*, 2012, **53**, 2726; (d) Y. Shimoda, S. Kotani, M. Sugiura and M. Nakajima, *Chem.-Eur. J.*, 2011, **17**, 7992.

25 Asymmetric oxa-Michael addition *via* push/pull-type bifunctional organocatalysis: (a) J. P. Malerich, K. Hagibara and V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416; (b) K. Asano and S. Matsubara, *J. Am. Chem. Soc.*, 2011, **133**, 16711; (c) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma and Y. Takemoto, *Angew. Chem.*, 2013, **125**, 11320; *Angew. Chem., Int. Ed.*, 2013, **52**, 11114; (d) R. Miyaji, K. Asano and S. Matsubara, *Org. Biomol. Chem.*, 2014, **12**, 119; (e) B. Ravindra, B. G. Das and P. Ghorai, *Org. Lett.*, 2014, **16**, 5580; (f) B. Ravindra, S. Maity, B. G. Das and P. Ghorai, *J. Org. Chem.*, 2015, **80**, 7008; (g) S. Maity, B. Parhi and P. Ghorai, *Angew. Chem.*, 2016, **128**, 7854; *Angew. Chem., Int. Ed.*, 2016, **55**, 7723; (h) N. Molleti and V. K. Singh, *Org. Biomol. Chem.*, 2015, **13**, 5243; (i) S. Agrawal, N. Molleti and V. K. Singh, *Chem. Commun.*, 2015, **51**, 9793; (j) S. Kayal and S. Mukherjee, *Org. Lett.*, 2015, **17**, 5508; (k) R. R. Reddy, S. S. Gudup and P. Ghorai, *Angew. Chem.*, 2016, **128**, 15339; *Angew. Chem., Int. Ed.*, 2016, **55**, 15115.

