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Enantioselective total synthesis of parnafungin A1 and 10a-*epi*-hirtusneanine†

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The first and enantioselective total synthesis of the heterodimeric biaryl antifungal natural product parnafungin A1 as well as complex biaryl tetrahydroxanthone 10a-*epi*-hirtusneanine is accomplished, by employing cross-coupling through the benzoxaborole strategy to construct their sterically hindered biaryl cores. Besides the powerful Suzuki–Miyaura cross-coupling, the synthesis of parnafungin A1 also features a highly diastereoselective oxa-Michael addition to construct a tetrahydroxanthone skeleton, and an effective Zn-mediated reductive cyclization-Mitsunobu sequence to furnish the isoxazolidinone structure. Key innovations in total synthesis of 10a-*epi*-hirtusneanine include the employment of DTBS protection for functional group manipulation on the tetrahydroxanthone skeleton, stereoselective methylations, and complete reversal of the stereochemistry of the C5-hydroxy group using oxidation/Evans–Saksena reduction, as well as the strategy of preparing both complex tetrahydroxanthone monomers from the same chiral intermediate **25**.

Introduction

Dimeric tetrahydroxanthones exist widely in fungi and bacteria as secondary metabolites with rich pharmacological properties.[1,2] In particular, biaryl dimeric tetrahydroxanthones have gained significant interest recently, not only because of their intriguing antibacterial and anticancer activities, but also owing to the synthetic challenges posed by their structures. Recent work from the groups of Bräse,[3–7,21,22] Nicolaou,[8] Tietze,[9–11,18,19] Porco,[12,15–17] Kumamoto,[13] and Gao[14,20] *et al.* has shown significant progress in the synthesis of tetrahydroxanthone monomers[3–14] or homodimeric tetrahydroxanthones.[15–22] To the best of our knowledge, heterodimeric biaryl tetrahydroxanthones have rarely been synthesized, largely due to the synthetic challenges in assembling their sterically hindered biaryls.

Parnafungin A1 (**1**), A2 (**2**), B1 (**3**), and B2 (**4**) are both structurally and biologically interesting heterodimeric tetrahydroxanthones isolated by a Merck team in 2008 from the lichenicolous fungi *Fusarium larvarum* as an equilibrating mixture of four interconverting species[23] (Fig. 1A). Biologically, parnafungins specifically inhibit the activity of fungal polyadenosine polymerase (PAP) and have shown a broad spectrum of antifungal activities.[24–27] Structurally, besides the interconversion between four species of parnafungins, the uniqueness of parnafungins also resides in the presence of an unprecedented isoxazolidinone unit, which is responsible for their broad spectrum of antifungal activity and selectivity. Under basic or neutral conditions, the cleavage of the sensitive isoxazolidinone can take place readily, leading to the inactive, ring-opened phenathridine isomers.

The significant antifungal activities as well as intriguing structure of parnafungins have attracted attention from a number of synthetic groups.[28–33] In 2010, Zhou and Snider[28–30] described the synthesis of hexacyclic parnafungin A and C models and further revealed the sensitivity of the isoxazolidinone structure. Later, Tietze,[31] Gao,[32] and Porco[33] groups also reported their efforts on this elusive molecule in related dissertations, but with no success in completing the synthesis. It appears that "the ready isomerization of parnafungins and their propensity to rapidly decompose to phenathridines under neutral or basic conditions make these natural products especially challenging synthetic targets.[1]"

Hirtusneanoside (**5**) is an L-rhamnose-glycosylated biaryl heterodimeric tetrahydroxanthone (Fig. 1B), first isolated from the lichen *Usnea hirta* in 2007 by Rezanka and Sigler.[34] Biologically, it inhibits the growth of *Staphylococcus aureus* and *Bacillus subtilis* at the nanomolar level (LD_{50} = 3.4 nM and LD_{50} = 14.0 nM, respectively), but is inactive against Gram-negative bacteria and yeast. This heterodimer bears a unique chemical structure which contains a rare L-rhamnopyranoside and an additional peripheral methyl group compared to secalonic acid D,[15] and rugulotrosin A[17] (Fig. 1C). The biosynthetic origin of this methyl group is yet to be elucidated, and the rotation along

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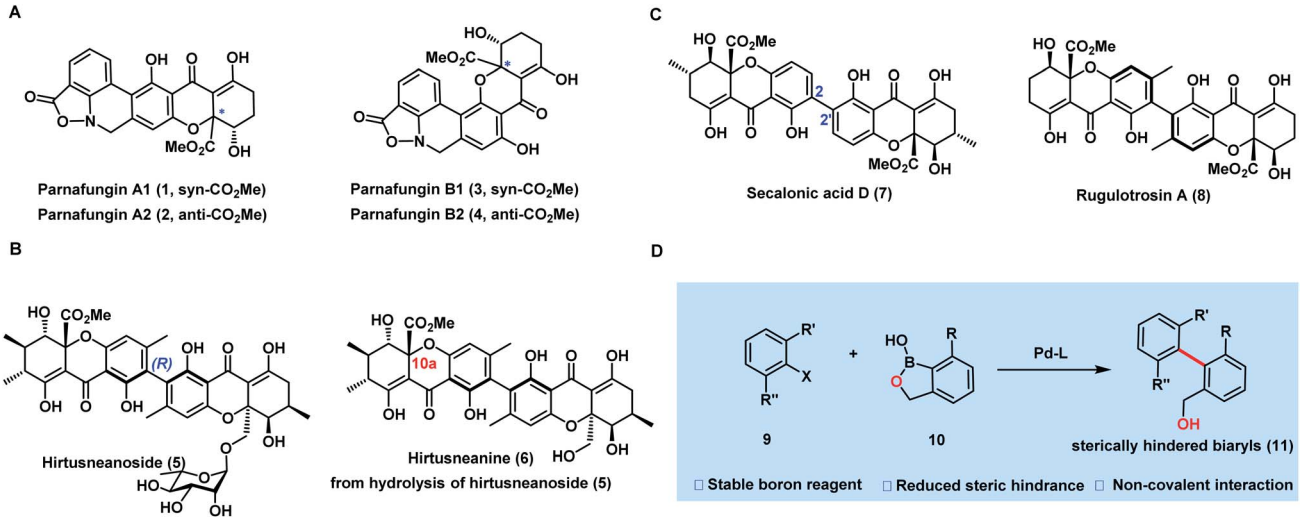


Fig. 1 Dimeric tetrahydroxanthones and the cross-coupling strategy. (A) Parnafungins A1, A2, B1, and B2. (B) Hirtusneanoside and hirtusneanine. (C) Symmetrical biaryl dimeric tetrahydroxanthones. (D) Biaryl construction by cross-coupling through the benzoxaborole strategy.

the biaryl axis is restricted by the bulky *ortho*-substituents, forming an axial chirality similarly to rugulotrosin A. Since its isolation, no synthetic studies have been reported towards hirtusneanoside (**5**) or its aglycon, hirtusneanine (**6**). We envision that the most challenging tasks in synthesizing **5** and **6** are the construction of complex tetrahydroxanthone monomers with up to four contiguous stereocenters and the installation of the sterically hindered axially chiral tetra-*ortho*-substituted biaryl unit.

Considering the synthetic challenges within the structures of both parnafungins and hirtusneanine, we believe that the paramount goal in our synthetic studies toward these elusive heterodimeric biaryl tetrahydroxanthones is to develop an efficient cross-coupling strategy for constructing the sterically hindered biaryls of these structures. Because of its excellent stability, less steric hindrance, and good ability in providing non-covalent interactions, benzoxaborole is recognized as one of most ideal and successful cross-coupling partners for the construction of sterically hindered biaryls[35] (Fig. 1D). Herein, we report the employment of cross-coupling through the benzoxaborole strategy in accomplishing the first and enantioselective synthesis of the parnafungin A1 and 10a-*epi*-hirtusneanine.

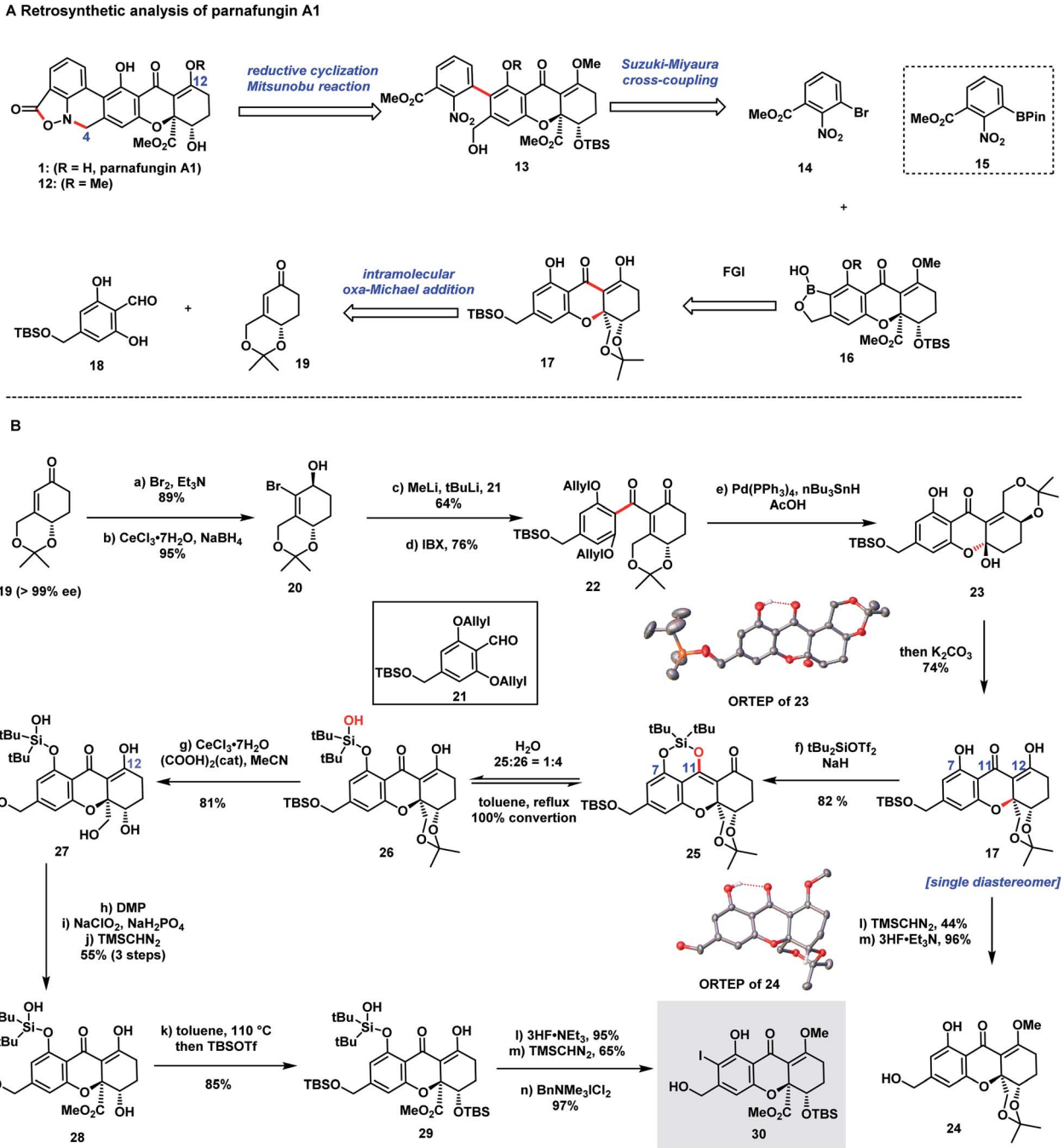
Results and discussion

(a) Total synthesis of the parnafungin A1 (1)

Our retrosynthetic analysis of the parnafungin A1 (**1**) is depicted in Scheme 1A. Structure **12**, the methylated form of parnafungin A1, proved to be stable and was characterized by X-ray crystallography.[23] Because of its sensitive nature, the isoxazolidinone structure was planned to be installed at a late stage through the reduction of the nitro group followed by ring-closure. The formation of the biaryl linkage proved to be a challenge since a previous attempt on Suzuki–Miyaura cross-coupling between boronic ester **15** and an aryl halide containing the tetrahydroxanthone moiety failed to obtain the desired coupling product,[32] possibly due to the issue of severe protodeboronation. We envisioned that benzoxaborole **16** would be more resistent to protodeboronation and suitable for the key cross-coupling.[35] And benzoxaborole **16** could be derived from tetrahydroxanthone monomer **17**. Although several effective strategies are developed by Bräse,[3–7] Nicolaou,[8] Tietze,[9–11] Porco,[12] Kumamoto[13] and Gao[14] groups in the preparation of the chiral tetrahydroxanthone structure, a highly enantioselective and diastereoselective version would be highly desirable. We anticipated that **17** could be efficiently synthesized from **18** and a known chiral intermediate **19** (ref. 36) through an oxa-Michael addition.[8] Besides serving as a protecting group, the acetonide moiety in the structure of **19** was anticipated to be an anchor to forge a highly diastereoselective oxa-Michael addition.

Our synthesis commenced with the preparation of tetrahydroxanthone monomer **30** from known compound **19** (Scheme 1B). Bromination of **19** and a subsequent Luche reduction afforded **20**, which was subjected to Li–Br exchange, treatment with aldehyde **21**, and IBX oxidation providing diketone **22**. Next, a Pd-catalyzed deallylation-intramolecular oxa-Michael addition cascade was explored to form **17**. Surprisingly, instead of forming **17**, a hemiketal **23** resulting from intramolecular 1,2-addition was isolated, whose structure was confirmed by X-ray crystallography. To our delight, **23** was smoothly converted to **17** as a single diastereomer under basic conditions (K_2CO_3/MeOH) and its stereochemistry (15*R*,15a*R*) was confirmed by **24** which was prepared from the methylation of **17** followed by desilylation. The perfect diastereoselectivity of the oxa-Michael reaction, likely due to the rigid conformation of the bicyclic ring system, was in contrast to the unsatisfactory diastereoselectivities (1 : 2 to 2 : 1 dr) observed in Nicolaou's report.[8]

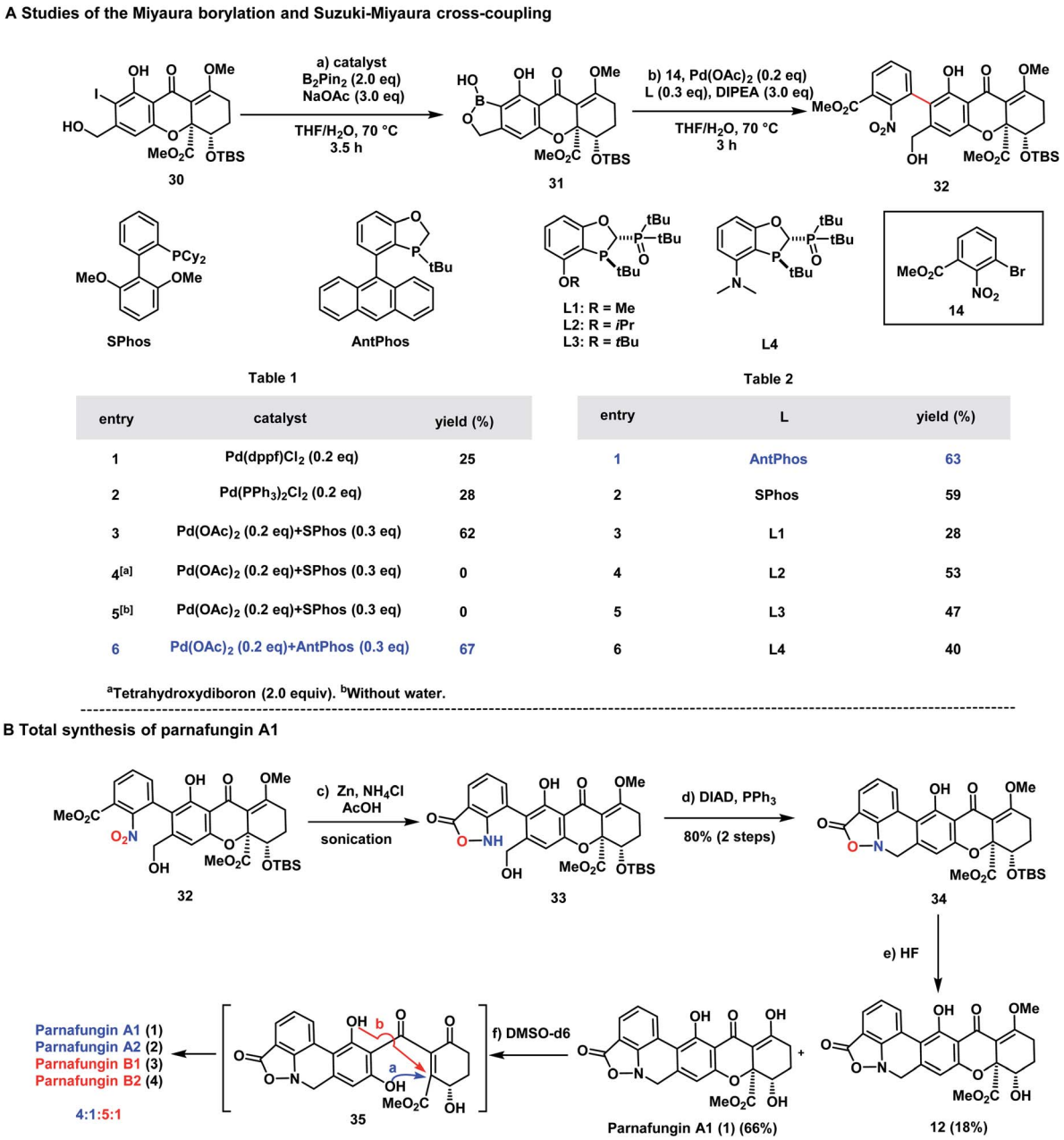
We next turned our attention to furnish the ester moiety of the tetrahydroxanthone structure (Scheme 1B). Because of the labile nature of the tetrahydroxanthone once the ester was incorporated, the choice of the protecting group for the



Scheme 1 (A) Retrosynthetic analysis of parnafungin A1. (B) Synthesis of tetrahydroxanthone **30**.

following manipulation was essential. We chose di-*tert*-butylsilylene (DTBS) protection for diol **17**. The selective installation of the DTBS group at both C7-hydroxyl and C11-enol hydroxyl groups was successfully accomplished under conditions of $DTBS(OTf)_2$/NaH to form **25**. Owning to the labile nature of the vinylogous silyl ether, the ring opening of the DTBS protection occurred readily to give a mixture of **26** and **25** at 4 : 1 ratio. Interestingly, **26** was transformed back to **25** by heating in toluene with azeotropical removal of water. Next, selective removal of the acetonide protection was accomplished by treatment of **26** with $CeCl_3 \cdot 7H_2O$ and $(COOH)_2$ (5 mol%),[37] affording **27** in 81% yield. Subsequent Dess–Martin oxidation, Pinnick oxidation, and methylation with $TMSCHN_2$ delivered ester **28** in 55% overall yield. Treatment of **28** in toluene at 110 °C resulted in DTBS ring closure, followed by selective TBS protection of the hydroxyl group adjacent to the ester group gave **29** in 85% yield. Selective desilylation, methylation with $TMSCHN_2$, and *ortho*-iodination with $BnMe_3NICl_2$ successfully led to **30**.

We then looked into the key Suzuki–Miyaura cross-coupling for the formation of biaryl moiety. Initial experiments on sterically hindered cross-coupling between aryl iodide **30** and



entry	catalyst	yield (%)
1	$Pd(dppf)Cl_2$ (0.2 eq)	25
2	$Pd(PPh_3)_2Cl_2$ (0.2 eq)	28
3	$Pd(OAc)_2$ (0.2 eq)+SPhos (0.3 eq)	62
4[a]	$Pd(OAc)_2$ (0.2 eq)+SPhos (0.3 eq)	0
5[b]	$Pd(OAc)_2$ (0.2 eq)+SPhos (0.3 eq)	0
6	$Pd(OAc)_2$ (0.2 eq)+AntPhos (0.3 eq)	67

entry	L	yield (%)
1	AntPhos	63
2	SPhos	59
3	L1	28
4	L2	53
5	L3	47
6	L4	40

[a]Tetrahydroxydiboron (2.0 equiv). [b]Without water.

Scheme 2 (A) Studies of the Miyaura borylation (Table 1); studies of the Suzuki–Miyaura cross-coupling reaction (Table 2). (B) Total synthesis of parnafungin A1.

boronic ester **15** proved to be futile and significant formation of protodeboronation and deiodination side-products was observed. We envisioned that benzoxaborole **31** would be stable and more resistant to protodeboronation. Thus, Miyaura borylation of **30** to form **31** was studied. As depicted in Scheme 2, $Pd(dppf)Cl_2$ (Scheme 2, Table 1, entry 1) and $Pd(PPh_3)_2Cl_2$ (Scheme 2, Table 1, entry 2), commonly used catalysts for borylation led to unsatisfactory yields (25% and 28% respectively). Encouragingly, SPhos (Scheme 2, Table 1, entry 3) provided an improved yield (62%). The use of tetrahydroxydiboron (Scheme 2, Table 1, entry 4) did not provide any activities. Surprisingly, the addition of water turned out to be crucial for the transformation and AntPhos, a prominent ligand for both Miyaura borylation and Suzuki coupling with sterically hindered substrates,[38–41] providing the best yield for this transformation (67% yield) (Scheme 2, Table 1, entry 5 and 6). With **31** in hand, the Pd-catalyzed cross-coupling between **31** and **14** was carried out in THF/H_2O with DIPEA as the base (Scheme 2, Table 2). AntPhos proved to be the most prominent ligand, providing coupling product **32** as an atropisomeric mixture (1.5 : 1 dr) in 63% yield with protodeboronation as the major side-product (Scheme 2, Table 2, entry 1). SPhos was similarly effective (Scheme 2, Table 2, entry 2). A series of P,P=O ligands[42,43] were also applicable and **L2** delivered a moderate yield (53%) (Scheme 2, Table 2, entry 3–6).

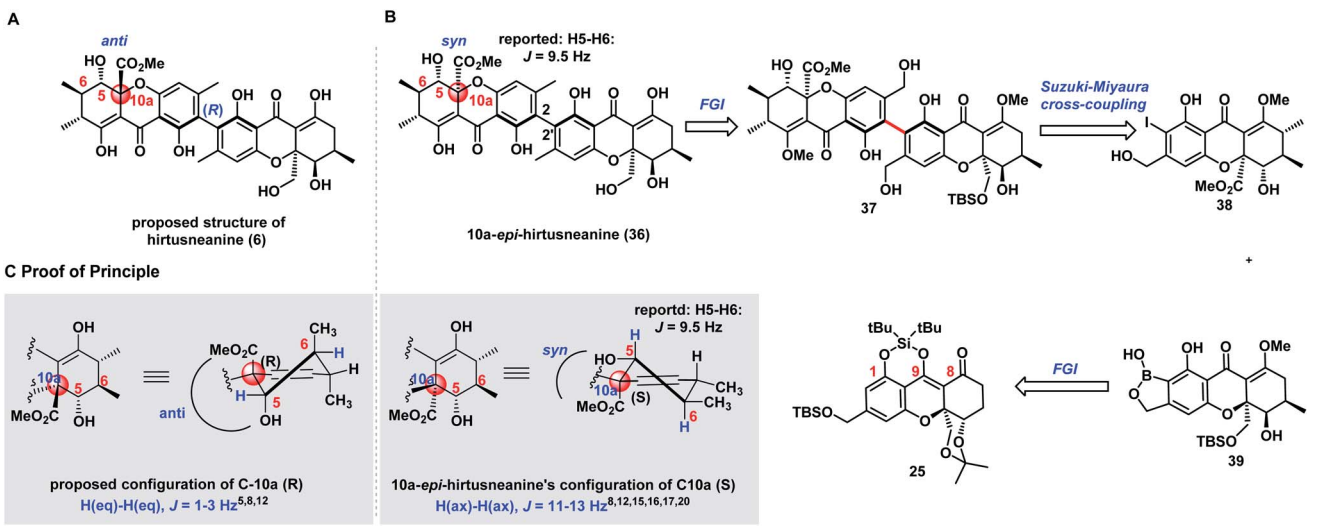
The stage was set for generating the sensitive isoxazolidinone structure (Scheme 2B). Reported methods such as Zn reduction and reduction with RANEY® Ni/H_2 (ref. 44) failed to provide the desired product. When the reductive cyclization was performed with Zn and using acetic acid as an additive,[29] the target product **33** was successfully formed as an inseparable mixture (1.3 : 1) from both atropisomers of **33**. Next, ring closure of **33** to form **34** was studied. Extensive experiments revealed that this transformation was successfully accomplished under Mitsunobu conditions (DIAD/PPh_3) and **34** was formed in an excellent yield (80%). Finally, a global deprotection of **34** provided parnafungin A1 (**1**) in 66% yield along with the methylated form of parnafungin A1 (**12**) in 18% yield. Thus, we accomplished for the first time the total synthesis of the parnafungin A1. Because the interconversion of parnafungins proceeded slowly in $CDCl_3$ solution, the pure spectra of parnafungin A1 (**1**) were acquired successfully for the first time.

Experiments revealed that the interconversion between parnafungins A1, A2, B1, and B2 took place more facilely in DMSO and an instant conversion from parnafungin A1 (**1**) to B1 (**3**) was observed. The formation of parnafungins A2 (**2**) and B2 (**4**) occurred after several hours. The NMR spectra of the interconverting mixture of the four parnafungin A1, A2, B1, and B2 in DMSO (the equilibrium ratio 4 : 1 : 5 : 1) was consistent with the reported data.[23] Thus, we accomplished the total synthesis of the parnafungins for the first time.

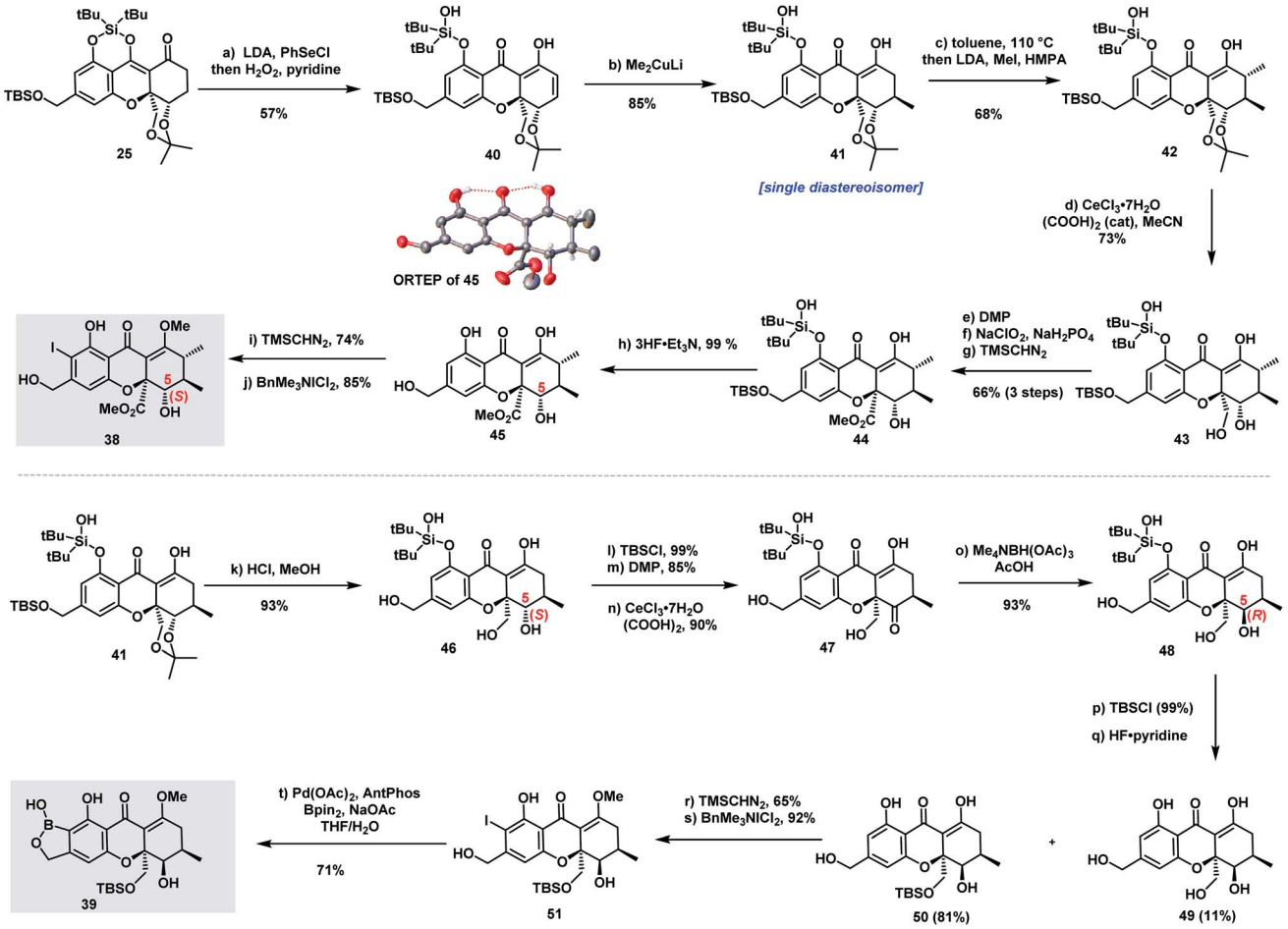
(b) Total synthesis of 10a-*epi*-hirtusneanine

The successful diastereoselective synthesis of tetrahydroxanthone monomers such as **25** and the development of a reliable cross-coupling for biaryl formation in complex structure synthesis prompted us to explore the synthesis of hirtusneanine (**6**) (Scheme 3A). The absolute configuration of hirtusneanine was assigned as **6** in Rezanka and Sigler's original reports based on spectroscopic data and chemical degradation. Nevertheless, no original NMR spectra of hirtusneanoside (**5**) and hirtusneanine (**6**) could be provided by either the authors or the journal office, which significantly increases the difficulties of their total syntheses. As we meticulously compared the ^{1}H NMR data of both hirtusneanoside (**5**) and hirtusneanine (**6**) provided by Rezanka and Sigler,[34] with the reported 2,2′-linked tetrahydroxanthones dimers [secalonic acid D (H5, dd, J = 11.3, 1.6 Hz),[15] rugulotrosin A (H5, dd, J = 12.3, 5.0 Hz),[17] ascherxanthone A (H5, d, J = 10.3 Hz)[20]], the large H-5/H-6 coupling constant (d, J = 9.5 Hz) indicated that H-5 of hirtusneanine (**6**) should occupy an axial position and, thus, be in the *syn*-position (and not in the *anti*-position) with respect to the methyl carboxylate moiety at C10a (Scheme 3C).Taken together, we speculated that 10a-*epi*-hirtusneanine (**36**) should be the feasible structure that would match the reported NMR data. Therefore, our attention was concentrated on the total synthesis of 10a-*epi*-hirtusneanine (**36**), which could be the real natural product. Our synthetic plan toward 10a-*epi*-hirtusneanine (**36**) is outlined in Scheme 3B. We anticipated that the tetra-*ortho*-substituted biaryl could be formed from the coupling between benzoxaborole **39** and iodide **38**. We expected that the presence of the benzyl hydroxyl group could be crucial for the synthesis of benzoxaborole **39** as well as the subsequent cross-coupling. More importantly, both fragments (benzoxaborole **39** and iodide **38**) could be derived from a single intermediate **25**.

Thus, our first task was to synthesize iodide **38** from **25** with the expectation that the formation of cyclic DTBS ether within **25** would enable the keto form at C8 and be beneficial to subsequent methylations. Compound **25** was treated under dehydrogenation conditions in order to produce dihydroxanthone **40** (Scheme 4). The conditions of Saegusa oxidation and Nicolaou dehydrogenation led to severe decompositions, while the employment of Mukaiyama's protocol (*N*-*tert*-butylphenylsulfinimidoyl chloride)[45] and Grieco elimination[46] gave product **40** in 40% and 57% yield, respectively. Direct exposure of **40** to dimethylcopperlithium (3.0 equiv.) furnished the



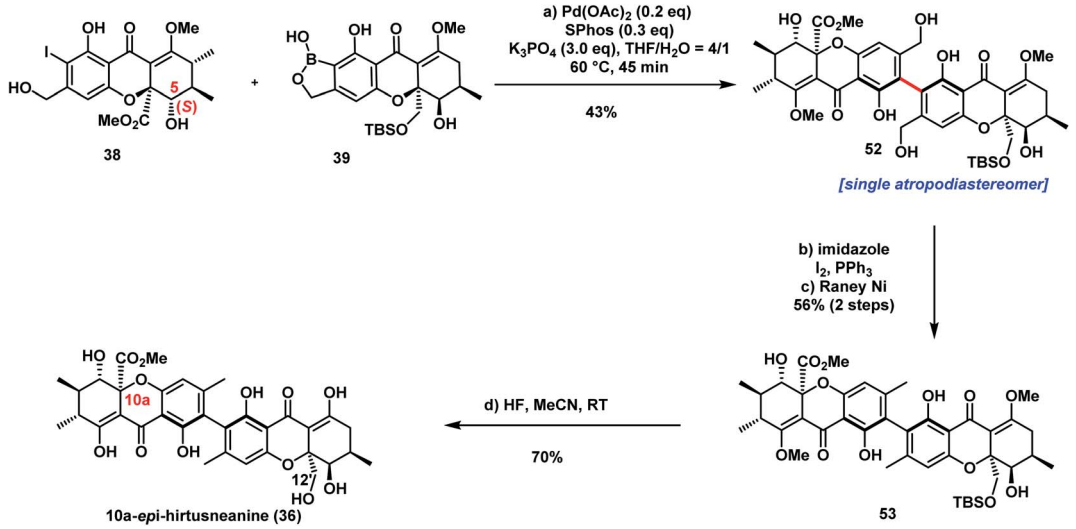
Scheme 3 Comparison of the NMR coupling constants of H5/H6 and retrosynthetic analysis of 10a-*epi*-hirtusneanine (**36**). (A) Proposed structure of hirtusneanine (**6**). (B) 10a-*epi*-Hirtusneanine and retrosynthetic analysis. (C) Proof of principle.



Scheme 4 Synthesis of iodide **38** and benzoxaborole **39**.

desired Michael addition product **41** as a single diastereoisomer in 85% yield. The perfect diastereoselectivity could be attributed to the steric bulk of acetonide at the si face. Installation of the second methyl group provided **42** which was elaborated to **45** through the well-developed five-step sequence in parnafungin syntheses: (1) removal of the acetonide protection with $CeCl_3 \cdot 7H_2O$ and $(COOH)_2$ (cat); (2) selective oxidation of primary alcohol; (3) Pinnick oxidation; (4) methylation of the resulting acid with $TMSCHN_2$; (5) removal of silyl groups with $3HF \cdot Et_3N$. The relative stereochemistry of **45** was confirmed by its X-ray structure. As shown in Scheme 4, H-5 of compound **45** was at axial orientation, and the coupling constants (H-5/H6, $J = 11.1$ Hz) in DMSO-d_6 were consistent with the H-5/H-6 coupling constant (9.5 Hz) reported by Rezanka and Sigler, indicating the correctness of our proposal on 10a-*epi*-hirtusneanine. Selective methylation of **45** with $TMSCHN_2$ (74% yield) and *ortho*-iodination with $BnMe_3NICl_2$ afforded iodide **38** in 92% yield.

We then turned our attention to construct benzoxaborole **39** (Scheme 4). Different from iodide **38**, the structure of benzoxaborole **39** has *R* configuration at the C5 position. Our immediate mission was to inverse the configuration of the C5–OH functionality of the mono-methylated tetrahydroxanthone intermediate **41**. Attempts of employing the Mitsunobu protocol failed to provide the desired outcome. We then explored the strategy of the hydroxyl-directed Evans–Saksena reduction.[47] Removal of both acetonide and TBS protection with HCl/MeOH (93% yield), followed by selective protection of **46** with TBSCl (99% yield), a subsequent Dess–Martin oxidation to form the ketone functionality (85% yield), and finally selective TBS deprotection to release the primary hydroxyl group (90% yield), afforded ketone **47**. It was noteworthy that ketone **47** could undergo aromatization easily under acidic conditions. Fortunately, the mild conditions [$CeCl_3 \cdot 7H_2O/(COOH)_2$] previously employed for acetonide deprotection also applied effectively for TBS deprotection, therefore minimizing the formation of side-products. Pleasingly, ketone **47** facilitated Evans–Saksena reduction[47] smoothly to give alcohol **48** with an inversed *R* configuration at the C5 position. Treatment of alcohol **48** with TBSCl followed by selective removal of the silyl protecting groups at both phenol and benzyl alcohol positions with $HF \cdot Py$ provided compound **50** in 81% yield, along with a fully-deprotected product **49** in 11% yield. Further transformation of **50** to iodide **51** was achieved through selective methylation with $TMSCHN_2$ (65% yield) and *ortho*-iodination with $BnMe_3NICl_2$ (92% yield). A palladium-catalyzed Miyaura borylation of iodide **51** affected by Pd-AntPhos successfully furnished benzoxaborole **39**.



Scheme 5 Synthesis of 10a-*epi*-hirtusneanine (**36**).

With iodide **38** and benzoxaborole **39** in hand, we came to the stage of the key sterically hindered Suzuki–Miyaura cross-coupling (see Table S1†). Use of the reaction conditions (Pd-AntPhos, DIPEA) applied in the synthesis of parnafungins did not provide any desired coupling product. Realizing that the steric hindrance of this cross-coupling is even greater than those reported for rugulotrosin A[17] and ascherxanthone A,[20] we further screened various commercially available ligands and found that SPhos was one among the most effective ligands. With $Pd(OAc)_2$/SPhos as the catalyst, the desired tetra-*ortho*-substituted biaryl **52** was isolated in 43% yield and an atropodiastereomerically pure form (Scheme 5).

With the heterodimeric biaryl tetrahydroxanthone skeleton **52** successfully assembled, the final task of the total synthesis was the deoxygenation of the two primary alcohols as well as the deprotection of TBSO- and MeO-functionalities. Treatment of **52** with iodine and triphenylphosphine led to the formation of iodide, which underwent dehalogenation with RANEY® nickel to form compound **53**. The CD spectroscopic data of compound **53** revealed the *R* configuration of the axial chirality. Finally, a global deprotection of the protecting group with HF (aq) accomplished the total synthesis of 10a-*epi*-hirtusneanine **36**. Unfortunately, our acquired spectroscopic data of **36** did not match those reported by Rezanka and Sigler.[34] Although the H-5/H-6 coupling constant (11.1 Hz) of 10a-*epi*-hirtusneanine was close to the reported data of hirtusneanine (9.5 Hz), marked differences of chemical shifts were observed for enolic and phenolic protons, as well as C(12′)–H (see ESI Table 13†). It was unfortunate that the authors could not provide original NMR spectra of hirtusneanine or hirtusneanoside for further comparison. Efforts are currently in progress to elucidate the real structure of hirtusneanine or hirtusneanoside.

Conclusions

In summary, we have accomplished the first and enantioselective total synthesis of the heterodimeric biaryl antifungal natural product parnafungin A1 as well as complex biaryl tetrahydroxanthone 10a-*epi*-hirtusneanine, using cross-coupling through the benzoxaborole strategy to construct their key sterically hindered biaryl cores. Besides the powerful Suzuki–Miyaura cross-coupling, the synthesis of parnafungin A1 also features a highly diastereoselective oxa-Michael addition to construct the tetrahydroxanthone skeleton, and an effective Zn-mediated reductive cyclization-Mitsunobu sequence to furnish the isoxazolidinone structure. Key innovations in total synthesis of 10a-*epi*-hirtusneanine include the employment of DTBS protection for functional group manipulation on the tetrahydroxanthone skeleton, the stereoselective methylations, complete reversal of the stereochemistry of the C5-hydroxy group using oxidation/Evans–Saksena reduction, as well as the strategy of preparing both complex tetrahydroxanthone monomers from the same chiral intermediate **25**. We strongly believe that the strategy of cross-coupling through benzoxaborole for sterically hindered biaryl cross-coupling should be applicable to the total syntheses of a number of heterodimeric biaryl tetrahydroxanthones.

Data availability

The authors declare that all data supporting the findings of this study are available within the paper and its supplementary information files, including experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra of all new compounds.

Author contributions

W. T. designed the research and experiments. J. S., H. Y. and W. G. conducted the synthetic work. W. T. and H. Y. wrote the manuscript. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 K.-S. Masters and S. Bräse, *Chem. Rev.*, 2012, **112**, 3717–3776.
2 T. Wezeman, S. Bräse and K.-S. Masters, *Nat. Prod. Rep.*, 2015, **32**, 6–28.
3 B. Lesch and S. Bräse, *Angew. Chem., Int. Ed.*, 2004, **43**, 115–118.
4 C. F. Nising, U. K. Ohnemüller and S. Bräse, *Angew. Chem., Int. Ed.*, 2006, **45**, 307–309.
5 E. M. C. Gérard and S. Bräse, *Chem.–Eur. J.*, 2008, **14**, 8086–8089.
6 M. C. Bröhmer, E. Bourcet, M. Nieger and S. Bräse, *Chem.–Eur. J.*, 2011, **17**, 13706–13711.
7 A. C. Meister, A. Encinas, H. Sahin, E. M. Singer, C. F. Nising, M. Nieger and S. Bräse, *Eur. J. Org. Chem.*, 2014, **2014**, 4861–4875.
8 K. C. Nicolaou and A. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 6579–6582.
9 L. F. Tietze, S. Jackenkroll, C. Raith, D. A. Spiegl, J. R. Reiner and M. C. Ochoa Campos, *Chem.–Eur. J.*, 2013, **19**, 4876–4882.
10 L. F. Tietze, L. Ma, J. R. Reiner, S. Jackenkroll and S. Heidemann, *Chem.–Eur. J.*, 2013, **19**, 8610–8614.
11 L. F. Tietze, S. Jackenkroll, J. Hierold, L. Ma and B. Waldecker, *Chem.–Eur. J.*, 2014, **20**, 8628–8635.
12 T. Qin, R. P. Johnson and J. A. Porco Jr, *J. Am. Chem. Soc.*, 2011, **133**, 1714–1717.
13 K. Adachi, S. Hasegawa, K. Katakawa and T. Kumamoto, *Tetrahedron Lett.*, 2017, **58**, 4479–4482.
14 J. Chen, Y. Li, Z. Xiao, H. He and S. Gao, *Org. Lett.*, 2020, **22**, 1485–1489.
15 T. Qin and J. A. Porco Jr, *Angew. Chem., Int. Ed.*, 2014, **53**, 3107–3110.
16 T. Qin, T. Iwata, T. T. Ransom, J. A. Beutler and J. A. Porco Jr, *J. Am. Chem. Soc.*, 2015, **137**, 15225–15233.
17 T. Qin, S. L. Skraba-Joiner, Z. G. Khalil, R. P. Johnson, R. J. Capon and J. A. Porco, *Nat. Chem.*, 2015, **7**, 234–240.
18 D. Ganapathy, J. R. Reiner, L. E. Löffler, L. Ma, B. Gnanaprakasam, B. Niepoetter, I. Koehne and L. F. Tietze, *Chem.–Eur. J.*, 2015, **21**, 16807–16810.
19 D. Ganapathy, J. R. Reiner, G. Valdomir, S. Senthilkumar and L. F. Tietze, *Chem.–Eur. J.*, 2017, **23**, 2299–2302.
20 Z. Xiao, Y. Li and S. Gao, *Org. Lett.*, 2017, **19**, 1834–1837.
21 S. Lindner, M. Nieger and S. Braese, *Adv. Synth. Catal.*, 2015, **357**, 3303–3308.
22 L. Geiger, M. Nieger and S. Bräse, *Adv. Synth. Catal.*, 2017, **359**, 3421–3427.
23 C. A. Parish, S. K. Smith, K. Calati, D. Zink, K. Wilson, T. Roemer, B. Jiang, D. Xu, G. Bills and G. Platas, *J. Am. Chem. Soc.*, 2008, **130**, 7060–7066.
24 D. Overy, K. Calati, J. N. Kahn, M.-J. Hsu, J. Martín, J. Collado, T. Roemer, G. Harris and C. A. Parish, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1224–1227.
25 B. Jiang, D. Xu, J. Allocco, C. Parish, J. Davison, K. Veillette, S. Sillaots, W. Hu, R. Rodriguez-Suarez and S. Trosok, *Chem. Biol.*, 2008, **15**, 363–374.
26 G. F. Bills, G. Platas, D. P. Overy, J. Collado, A. Fillola, M. R. Jimenez, J. Martin, A. G. del Val, F. Vicente and J. R. Tormo, *Mycologia*, 2009, **101**, 449–472.
27 G. C. Adam, C. A. Parish, D. Wisniewski, J. Meng, M. Liu, K. Calati, B. D. Stein, J. Athanasopoulos, P. Liberator and T. Roemer, *J. Am. Chem. Soc.*, 2008, **130**, 16704–16710.
28 Q. Zhou and B. B. Snider, *J. Org. Chem.*, 2010, **75**, 8224–8233.
29 Q. Zhou and B. B. Snider, *Org. Lett.*, 2009, **11**, 2936–2939.
30 Q. Zhou, PhD thesis, Brandeis University, 2011.
31 S. Heidemann, PhD thesis, Georg-August University of Göttingen, 2016.
32 Y. Li, MSc thesis, East China Normal University, 2017.
33 X. Wu, PhD thesis, Boston University, 2020.
34 T. Rezanka and K. Sigler, *J. Nat. Prod.*, 2007, **70**, 1487–1491.
35 A. Adamczyk-Woźniak, M. K. Cyrański, A. Żubrowska and A. Sporzyński, *J. Organomet. Chem.*, 2009, **694**, 3533–3541.
36 E. Corey and H. Kigoshi, *Tetrahedron Lett.*, 1991, **32**, 5025–5028.
37 X. Xiao and D. Bai, *Synlett*, 2001, 535–537.
38 W. Tang, A. G. Capacci, X. Wei, W. Li, A. White, N. D. Patel, J. Savoie, J. J. Gao, S. Rodriguez and B. Qu, *Angew. Chem., Int. Ed.*, 2010, **49**, 5879–5883.
39 G. Xu, W. Fu, G. Liu, C. H. Senanayake and W. Tang, *J. Am. Chem. Soc.*, 2014, **136**, 570–573.
40 H. Yang, J. Sun, W. Gu and W. Tang, *J. Am. Chem. Soc.*, 2020, **142**, 8036–8043.
41 G. Xu, C. H. Senanayake and W. Tang, *Acc. Chem. Res.*, 2019, **52**, 1101–1112.
42 C. Li, T. Chen, B. Li, G. Xiao and W. Tang, *Angew. Chem., Int. Ed.*, 2015, **54**, 3792–3796.
43 B. Li, T. Li, M. A. Aliyu, Z. H. Li and W. Tang, *Angew. Chem., Int. Ed.*, 2019, **131**, 11477–11481.
44 W. Wierenga, B. Evans and G. Zurenko, *J. Med. Chem.*, 1984, **27**, 1212–1215.
45 T. Mukaiyama, J.-i. Matsuo and H. Kitagawa, *Chem. Lett.*, 2000, **29**, 1250–1251.
46 H. J. Reich, J. M. Renga and I. L. Reich, *J. Org. Chem.*, 1974, **39**, 2133–2135.
47 D. Evans, K. Chapman and E. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560–3578.