ChemComm

Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: N. Shimada, N. Takahashi, N. Ohse, M. Koshizuka and K. Makino, *Chem. Commun.*, 2020, DOI: 10.1039/D0CC05630H.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/D0CC05630H

COMMUNICATION

Synthesis of Weinreb amides using diboronic acid anhydride-catalyzed dehydrative amidation of carboxylic acids

Naoyuki Shimada,* Naoya Takahashi, Naoki Ohse, Masayoshi Koshizuka and Kazuishi Makino

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

The first successful example of the direct synthesis of Weinreb amides using catalytic hydroxy-directed dehydrative amidation of carboxylic acids using diboronic acid anhydride catalyst is described. The methodology is applicable to the concise syntheses of eight α-hydroxyketone natural products, namely, sattabacin, 4-hydroxy sattabacin, kurasoins A and B, soraphinols A and B, and circumcins B and C.

N-Methoxy-*N*-methylamides (i.e., Weinreb amides[1]) are widely used as versatile building blocks in organic synthesis for their conversion to aldehydes or modified ketones.[2,3] Recently, Weinreb amides have also been used as directing groups for transition metal-catalyzed C–H functionalization.[4] Although a number of methods for the preparation of Weinreb amides using esters, amides, imides, aldehydes, alcohols, aromatic halides, and acid chlorides as starting materials have been reported, the most straightforward approach is the dehydrative condensation of corresponding carboxylic acids with *N*,*O*-dimethylhydroxylamine.[2] However, the common methods for dehydrative condensation require a stoichiometric amount of coupling reagents,[5] which causes problems associated with poor atom economy (Fig 1a: conventional method). This drawback can be overcome using catalytic dehydrative amidation[6] of carboxylic acids (Fig 1a: ideal method). Following the pioneering work by Yamamoto on dehydrative amidation of carboxylic acids using electron-deficient group-substituted aromatic boronic acids as catalysts,[7] a wide variety of modified aromatic boronic acid catalysts has been developed.[8] Recently, other classes of organoboron catalysts have been developed such as alkylboronic acid,[9] boronate ester,[10] 1,3-dioxa-5-aza-2,4,6-triborinane (DATB),[11] and diboron.[12] Most recently, based on the revised amidation mechanism that the intermediate with a B–O–B motif by the dimerization of boronic acid is the real active species reported by Whiting et al.,[13] Takemoto has developed *gem*-diboronic acid (*gem*-DBA) composed of a B–C–B active intermediate and found it to be an efficient catalyst in direct dehydrative amidation or peptide bond formation.[14] However, there are no examples of the direct synthesis of Weinreb amides using catalytic dehydrative condensation.

Hydroxy-directed reaction triggered by the interaction between hydroxy functional group of substrate and catalyst is an attractive strategy for molecular transformations.[9,15,16] We developed a newly designed biphenyl-based diboronic acid anhydride (DBAA) possessing a B–O–B motif, which showed high catalytic activity for the series of β-hydroxy-directed amidation of carboxylic acids.[17] Herein, we report a successful DBAA-catalyzed dehydrative amidation of α-hydroxycarboxylic acids with *N*,*O*-dimethylhydroxylamine, which has never been used for catalytic dehydrative amidation as an amine nucleophile because of its poor nucleophilicity. Notably, this is the first report on the catalytic synthesis of Weinreb amides using direct dehydrative amidation of carboxylic acids. Furthermore, this catalysis enabled concise syntheses of biologically active α-hydroxyketone natural products (Fig 1b).

Initially, we explored the reaction of (*S*)-2-hydroxy-3-phenylpropanoic acid (**2a**) with *N*,*O*-dimethylhydroxylamine (**3**)

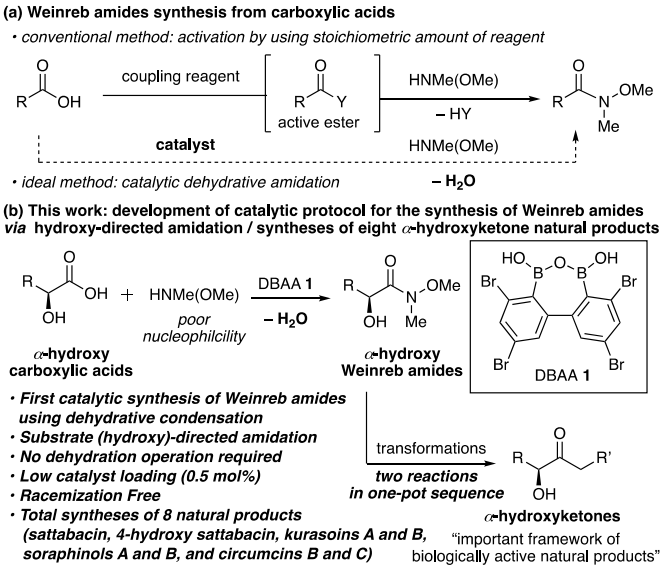


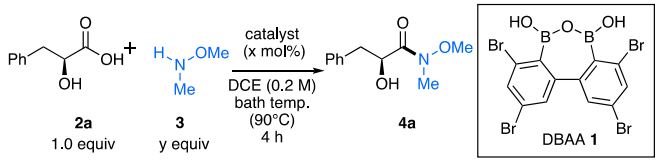
Fig 1. Overview of this work

Department of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minatao-ku, Tokyo 108-8641, Japan. E-mail: shimadan@pharm.kitasato-u.ac.jp, makinok@pharm.kitasato-u.ac.jp

† Electronic Supplementary Information (ESI) available: Experimental details, characterization data, copies of ^{1}H- and ^{13}C-NMR spectra for all new compounds. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/D0CC05630H

Table 1 Optimization of dehydrative amidation conditions[a]



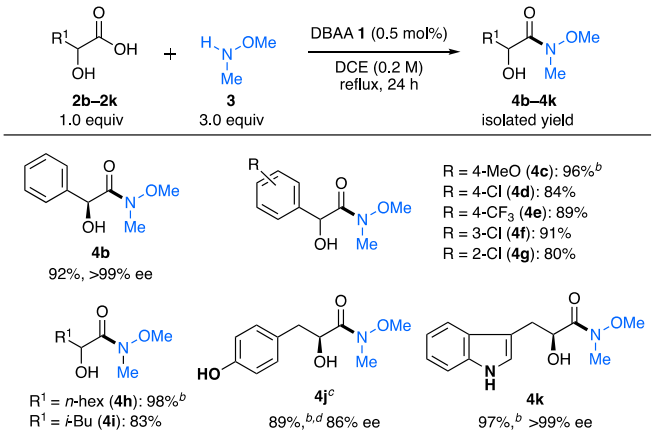
Entry	Catalyst [mol%]	3 [equiv]	Yield[b] [%]
1	DBAA **1** (2.0)	1.0	78
2[c]	DBAA **1** (2.0)	1.0	64
3	DBAA **1** (2.0)	3.0	98
4	DBAA **1** (0.5)	3.0	96 [94][d]
5	3,4,5-F_3-$C_6H_2B(OH)_2$ (0.5)	3.0	6
6	2-(i-Pr)$_2$NCH$_2$-$C_6H_4B(OH)_2$ (0.5)	3.0	3
7	2-I-5-MeO-$C_6H_3B(OH)_2$ (0.5)	3.0	15
8	2,4-$(CF_3)_2$-$C_6H_3B(OH)_2$ (0.5)	3.0	33
9	$MeB(OH)_2$ (0.5)	3.0	4
10	$B_2(NMe_2)_4$ (0.5)	3.0	2
11	$B(OCH_2CF_3)_3$ (0.5)	3.0	12
12	DATB (0.5)	3.0	25
13	*gem*-DBA (0.5)	3.0	4
14[e]	–	3.0	1

[a]The reactions were carried out in the presence of acid **2a** (0.40 mmol, 1.0 equiv), HNMe(OMe) (**3**), and catalyst in solvent (0.2 M) at 90°C (bath temp) for 4 h. [b]Determined by ^{1}H NMR of a crude reaction mixture of products using 1,1,2,2-tetrachloroethane as an internal standard. [c]Performed in toluene (0.2 M). [d]Isolated yield. The optical purity of amides **4a** was determined to be >99% by chiral HPLC analysis. [e]In the absence of catalyst.

in the presence of DBAA **1** (Table 1). The reaction of an equimolar mixture of **2a** and **3** with 2.0 mol% of **1** in DCE proceeded at 90°C to afford the corresponding Weinreb amide **4a** in 78% yield after 4 h (entry 1). Switching the solvent to toluene slightly decreased product yield (entry 2), whereas the use of 3.0 equiv of amine **3** in DCE increased product yield to 98% (entry 3). An excellent isolated yield of 94% was maintained even when reducing the catalyst loading of DBAA **1** to 0.5 mol% (entry 4). When other organoboron compounds[7-12,14] that are known as efficient dehydrative amidation catalysts were used under the same conditions, only low to moderate product yields were observed (2%–33% yields, entries 5–13).[18] A trace amount of product was obtained in the absence of **1** (entry 14).

After identifying the suitability of DBAA **1** as the catalyst for the Weinreb amide synthesis using dehydrative amidation, next, we investigated the reaction of a range of α-hydroxycarboxylic acids (Scheme 1). The reaction of chiral (*S*)-mandelic acid (**2b**) with amine **3** in the presence of 0.5 mol% of catalyst **1** afforded corresponding α-hydroxyamide **4b** in 92% yield. We found that α-aryl substrates possessing either electron-donating or electron-withdrawing groups provided corresponding amides**4c**–**4e** in high to excellent yields (84%–96%). The use of substrates with a *meta*- or *ortho*-substituent afforded amides **4f** and **4g** in 91% and 80% yield, respectively. Carboxylic acids containing not only an aromatic ring but also an alkyl side chain at the α-position were also applicable, and **4h**–**4k** were obtained in satisfactory yields (83%–98%). Notably, loss of optical purity was not observed during the synthesis of α-hydroxy Weinreb amides **4b**, **4j**, and **4k** from chiral carboxylic acids **2b**, **2j**, and **2k**.

Scheme 1. Diboronic acid anhydride-catalyzed synthesis of β-hydroxy Weinreb amides[a]



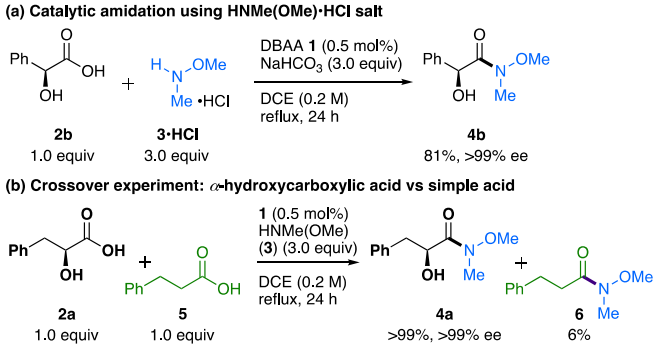
[a]The reactions were carried out in the presence of acid **2** (0.40 mmol, 1.0 equiv), HNMe(OMe) (**3**) (1.20 mmol, 3.0 equiv), and DBAA **1** (2.00 µmol, 0.5 mol%) in DCE (0.2 M) under reflux (bath temperature, 90°C). The optical purity of amides **4b**, **4j**, and **4k** was determined by chiral HPLC analysis. [b]Performed with 2.0 mol% of **1**. [c]Performed using acid **2j** with 86% optical purity as a substrate. [d]Performed in DCE (0.1 M).

For the reaction using a commercially available *N*,*O*-dimethylhydroxylamine hydrochloride salt (**3**•HCl), the desired amide **4b** was obtained in a 81% yield without racemization by the reaction of carboxylic acid **2b** with amine **3** generated in situ in the presence of sodium hydrogen carbonate (Scheme 2a). This protocol is advantageous in terms of practical operation. Competition experiments using an equimolar mixture of α-hydroxycarboxylic acid **2a** and simple carboxylic acid **5** revealed that DBAA **1** showed high chemoselectivity for α-hydroxycarboxylic acid and afforded α-hydroxyamide **4a** in quantitative yield along with simple amide **6** in low yield (6%) (Scheme 2b). This indicates the characteristic features of hydroxy-directed reaction.

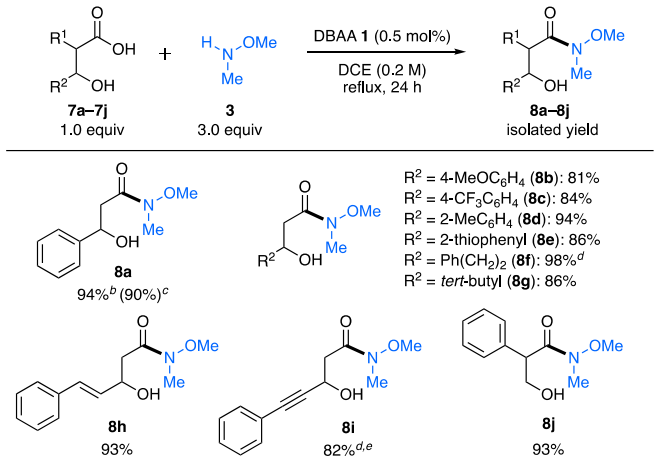
DBAA **1** was also applicable to the catalytic synthesis of β-hydroxy Weinreb amides (Scheme 3). The reaction of β-aryl-substituted carboxylic acids afforded corresponding Weinreb amides **8a**–**8c** in 81%–94% yields. High yields were also obtained with an *ortho*-substituted aryl group or heteroaromatic ring at the β-position to provide **8d** and **8e**. Carboxylic acids containing an aliphatic side chain such as phenylethyl or the bulky *tert*-butyl group at the β-position were also applicable, giving amides **8f** and **8g** in high to excellent yields (98 and 86%). Alkenyl or alkynyl substituents at the β-position of carboxylic acid substrates were tolerated, and the corresponding amides **8h** and **8i** were obtained in 93% and 82% yields, respectively. A phenyl substituent at α-position could be also applied, giving**8j**

in 93% yield, whereas more hindered α,α- or β,β-disubstituted substrates were not suitable for the present catalysis.[18]

Scheme 2. Diboronic acid anhydride-catalyzed amidation



Scheme 3. Diboronic acid anhydride-catalyzed synthesis of β-hydroxy Weinreb amides[a]



[a]The reactions were carried out in the presence of acid **7** (0.40 mmol, 1.0 equiv), HNMe(OMe) (**3**) (1.20 mmol, 3.0 equiv), and DBAA **1** (2.00 μmol, 0.5 mol%) in DCE (0.2 M) under reflux (bath temperature, 90°C). [b]Performed with 1.0 mmol scale. [c]Performed with HCl salt of amine **3** (3.0 equiv) in the presence of $NaHCO_3$ (3.0 equiv). [d]Performed with 2.0 mol% of **1**. [e]Performed at 60°C.

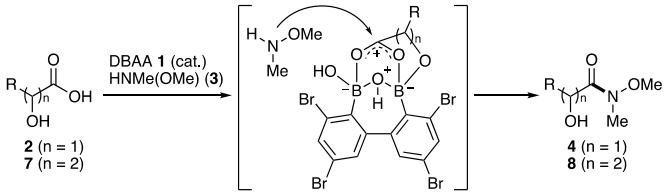
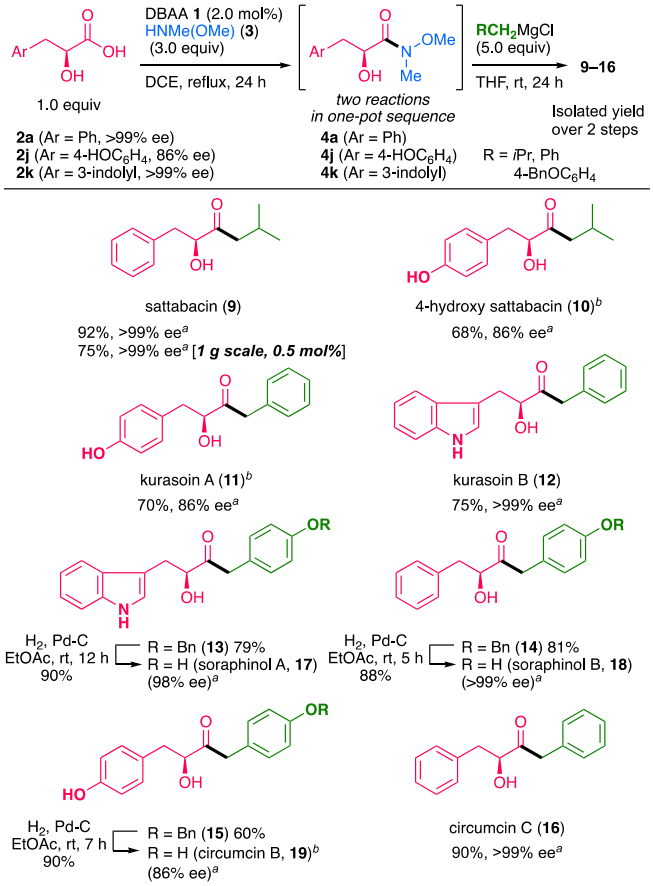


Fig 2. Plausible reaction pathway

Plausible reaction pathway is depicted in Fig 2. Based on Whiting's proposed mechanism of boronic acid-catalyzed amidation,[13] our hydroxy-directed reaction might proceed through a bicyclic acyloxydiboronate intermediate via dehydrative B–O bond formation with the hydroxy substituent in carboxylic acids.[17]

α-Hydroxyketone structures are widely found in some potent antiviral agents, in protein farnesylatranferase inhibitors, or in some antitumor antibiotics, and therefore their versatile and efficient synthetic method is required.[19] Because water is the only byproduct in the catalysis, we designed a one-pot

Scheme 4. Concise syntheses of α-hydroxyketone natural products



[a]The optical purity was determined by chiral HPLC analysis. [b]Performed using acid **2j** with 86% optical purity as a substrate.

sequence of two reactions[20] that comprised Grignard addition after the DBAA-catalyzed dehydrative amidation without the workup or purification of the Weinreb amide intermediate (Scheme 4). Thus, the catalytic dehydrative amidation of chiral carboxylic acid **2a** and amine **3** without a workup, followed by treatment with isopropyl magnesium chloride after switching the solvent, afforded optically pure sattabacin (**9**)[21] in 92% yield in two steps. Notably, this sequential protocol with low catalyst loading (0.5 mol%) of **1** can be easily applied to the gram-scale synthesis of the natural product, affording **9** in 75% yield without any racemization. Using analogous two-step sequences, 4-hydroxy sattabacin (**10**)[21a], and kurasoin A (**11**)[22a,b] were synthesized from chiral carboxylic acid **2j**, and kurasoin B (**12**)[22a,c,e] was synthesized from carboxylic acid **2k** in good to high yield (68%–75%). Furthermore, exposure of carboxylic acids **2k** and **2a** to amidation conditions, followed by the treatment with 4-(benzyloxy)benzylmagnesium chloride resulted in α-hydroxyketones **13** and **14**, which, upon deprotection of phenolic benzyl ether, afforded soraphinol A (**17**)[23a] and soraphinol B (**18**)[24], respectively. This is the first

example of the total synthesis of soraphinol B (**18**). These protocols were also applicable to the synthesis of circumcin B (**19**)[23a] and circumcin C (**16**).[23b]

In conclusion, we successfully developed a catalytic method for the synthesis of Weinreb amides derived from α- or β-hydroxycarboxylic acids using diboronic acid anhydride as the catalyst. This distinctive hydroxy-directed amidation reaction is the first example of the synthesis of Weinreb amides by the catalytic dehydrative condensation of carboxylic acids with *N*,*O*-dimethylhydroxylamine. This catalytic reaction proceeded in high to excellent yields with low catalytic loading without racemization and any dehydration protocols such as the addition of molecular sieves or azeotropic reflux using a Dean–Stark apparatus. Its synthetic utility was demonstrated by the concise syntheses of eight biologically active α-hydroxyketone natural products. Efforts to expand the utility of DBAA catalysis are currently underway in our laboratory.

This research was supported in part by JSPS KAKENHI Grant Numbers 19K07000 (N.S.) for Scientific Research (C). We thank Dr. K. Nagai and Ms. N. Sato at Kitasato University for instrumental analyses.

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1 S. Nahm and S. M. Weinreb, *Tetrahedron Lett.,* 1981, **22**, 3815–3818.

2 For reviews, see: (a) S. Balasubramaniam and I. S. Aidhen, *Synthesis*, 2008, 3707–3738; (b) R. Senatore, L. Ielo, S. Monticelli, L. Castoldi and V. Pace, *Synthesis*, 2019, **51**, 2792–2808.

3 For selected recent examples, see: (a) S. T. Heller, J. N. Newton, T. Fu and R. Sarpong, *Angew. Chem. Int. Ed.*, 2015, **54**, 9839–9843; (b) M. Giannerini, C. Vila, V. Hornillos and B. L. Feringa, *Chem. Commun.*, 2016, **52**, 1206–1209; (c) V. Pace, I. Murgia, S. Westermayer, T. Langer and W. Holzer, *Chem. Commun.*, 2016, **52**, 7584–7587; (d) G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degennaro, V. Pace and R. Luisi, *J. Am. Chem. Soc.*, 2017, **139**, 13648–13651; (e) R. Senatore, L. Castoldi, L. Ielo, W. Holzer and V. Pace, *Org. Lett.*, 2018, **20**, 2685–2688; (f) M. Miele, A. Citarella, N. Micale, W.Holzer and V. Pace, *Org. Lett.*, 2019, **21**, 8261–8265.

4 For a review, see: J. Kalepu and L. Pilarski, *Molecules*, 2019, **24**, 830–851.

5 For selected examples, see: (a) J. C. S. Woo, E. Fenster and G. R. Dake, *J. Org. Chem.*, 2004, **69**, 8984–8986; (b) K. Hiroki, H. Kobayashi, R. Ohkihara, S. Tani and M. Kunishima, *Chem. Pharm. Bull.*, 2004, **52**, 470–472; (c) T. Niu, W. Zhang, D. Huang, C. Xu, H. Wang and Y. Hu, *Org. Lett.*, 2009, **11**, 4474–4477; (d) E. Morisset, A. Chardon, J. Rouden and J. Blanchet, *Eur. J. Org.*, 2020, 388–392.

6 For selected reviews, see: (a) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471–479; (b) H. Lundberg, F. Tinnis, N. Selander and H. Adolfsson, *Chem. Soc. Rev.*, 2014, **43**, 2714–2742; (c) R. M. de Figueiredo, J.-S. Suppo and J.-M. Campagne, *Chem. Rev.*, 2016, **116**, 12029–12122.

7 K. Ishihara, S. Ohara and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4196–4197.

8 For selected examples, see: (a) T. Maki, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2005, **7**, 5043–5046; (b) K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith and A. Whiting, *Adv. Synth. Catal.*, 2006, **348**, 813–820; (c) K. Arnold, B. Davies, D. Hérault and A. Whiting, *Angew. Chem. Int. Ed.*, 2008, **47**, 2673–2676; (d) R. M. Al-Zoubi, O. Marion and D. G. Hall, *Angew. Chem. Int. Ed.*, 2008, **47**, 2876–2879; (e) K. Arnold, A. S. Batsanov, B. Davies and A. Whiting, *Green Chem.*, 2008, **10**, 124–134; (f) N. Gernigon, R. M. Al-Zoubi and D. G. Hall, *J. Org. Chem.*, 2012, **77**, 8386–8400; (g) S. Liu, Y. Yang, X. Liu, F. K. Ferdousi, A. S. Batsanov and A. Whiting, *Eur. J. Org. Chem.*, 2013, 5692–5700 (h) S. Fatemi, N. Gernigon and D. G. Hall, *Green Chem.*, 2015, **17**, 4016–4028. (i) T. M. El Dine, W. Erb, Y. Berhaunt, J. Rouden and J. Blanchet, *J. Org. Chem.*, 2015, **80**, 4532–4544; (j) T. M. El Dine, J. Rouden and J. Blanchet, *Chem. Commun.*, 2015, **51**, 16084–16087. (k) K. Ishihara and Y. Lu, *Chem. Sci.*, 2016, **7**, 1276–1280; (l) K. Wang, Y. Lu and K. Ishihara, *Chem. Commun.*, 2018, **54**, 5410–5413; (m) Y. Du, T. Barber, S. E. Lim, H. S. Rzepa, I. R. Baxendale and A. Whiting, *Chem. Commun.*, 2019, **55**, 2916–2919.

9 R. Yamashita, A. Sakakura and K. Ishihara, *Org. Lett.*, 2013, **15**, 3654–3657.

10 (a) M. T. Sabatini, L. T. Boulton and T. D. Sheppard, *Sci. Adv.*, 2017, **3**, e1701028; (b) M. T. Sabatini, V. Karaluka, R. M. Lanigan, L. T. Boulton, M. Badland and T. D. Sheppard, *Chem. Eur. J.*, 2018, **24**, 7033–7043.

11 (a) H. Noda, M. Furutachi, Y. Asada, M. Shibasaki and N. Kumgai, *Nat. Chem.*, 2017, **9**, 571–577; (b) Z. Liu, H. Noda, M. Shibasaki and N. Kumagai, *Org. Lett.*, 2018, **20**, 612–615; (c) H. Noda, Y. Asada, M. Shibasaki and N. Kumagai, *J. Am. Chem. Soc.*, 2019, **141**, 1546–1554; (d) C. R. Opie, H. Noda, M. Shibasaki and N. Kumagai, *Chem. Eur. J.*, 2019, **25**, 4648–4653.

12 D. N. Sawant, D. B. Bagal, S. Ogawa, K. Selvam and S. Saito, *Org. Lett.*, 2018, **20**, 4397–4400.

13 S. Arkhipenko, M. T. Sabatini, A. S. Batsanov, V. Karaluka, T. D. Sheppard, H. S. Rzepa and A. Whiting, *Chem. Sci.*, 2018, **9**, 1058–1072.

14 K. Michigami, T. Sakaguchi and Y. Takemoto, *ACS Catal.*, 2020, **10**, 683–688.

15 Selected reviews for substrate-directed reactions, see: (a) A. H. Hoveyda, D. A. Evans and G. C. Fu, *Chem. Rev.*, 1993, **93**, 1307–1370; (b) S. Bhadra and H. Yamamoto, *Chem. Rev.*, 2018, **118**, 3391–3446; (c) T. Sawano and H. Yamamoto, *J. Org. Chem.*, 2018, **83**, 4889–4904.

16 (a) H. Tsuji and H. Yamamoto, *J. Am. Chem. Soc.*, 2016, **138**, 14218–14221; (b) W. Muramatsu, H. Tsuji and H. Yamamoto, *ACS Catal.*, 2018, **8**, 2181–2187.

17 N. Shimada, M. Hirata, M. Koshizuka, N. Ohse, R. Kaito and K. Makino, *Org. Lett.*, 2019, **21**, 4303–4308.

18 See details in Electronic Supplementary Information (ESI).

19 P. Hoyos, J.-V. Sinisterra, F. Molinari, A. R. Alcántara and P. D. De María, *Acc. Chem. Res.*, 2010, **43**, 288–299.

20 Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866–880.

21 For the synthesis of sattabacins, see: (a) M. R. Aronoff, N. A. Bourjaily, and K. A. Miller, *Tetrahedron Lett.*, 2010, **51**, 6375–6377; (b) K. Bailadi, A. Talakokkula and A. V. Narsaiah, *Arkivoc*, 2019, **vi**, 167–173.

22 For the synthesis of kurasoins, see: (a) R. Uchida, K. Shiomi, T. Sunazuka, J. Inokoshi, A. Nishizawa, T. Hirose, H. Tanaka, Y. Iwai and S. Ōmura, *J. Antibiot.*, 1996, **49**, 886–889; (b) M. B. Andrus, E. J. Hicken, J. C. Stephens and D. K. Bedke, *J. Org. Chem.*, 2006, **71**, 8651–8654; (c) S. Tsuchiya, T. Sunazuka, T. Shirahata, T. Hirose, E. Kaji and S. Ōmura, *Heterocycles*, 2007, **72**, 91–94; (d) R. A. Fernandes, *Tetrahedron: Asymmetry*, 2008, **19**, 15–18; (e) M. A. Christiansen, A. W. Butler, A. R. Hill and M. B. Andrus, *Synlett*, 2009, 653–657.

23 For the synthesis of soraphinol A and circumsins, see: (a) E. P. Balskus and C. T. Walsh, *J. Am. Chem. Soc.*, 2008, **130**, 15260–

View Article Online
DOI: 10.1039/D0CC05630H

15261; (b) T. Ooi, A. Saito and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 3220–3221.
24 For the isolation of soraphinol B, see: J.-W. Ahn, X. Li and O.-P. Zee, *Bull. Korean Chem. Soc.*, 2007, **28**, 1215–1216.