RESEARCH ARTICLE

Check for updates

Synthesis of chiral seven-membered cyclic sulfonamides through palladium-catalyzed arylation of cyclic imines†

Zi-Biao Zhao, [a,b] Lei Shi, [*a] Fan-Jie Meng,[a] Yaming Li[a] and Yong-Gui Zhou [*a,b]

An enantioselective palladium-catalyzed addition of arylboronic acids to seven-membered cyclic *N*-sulfonyl aldimines and ketimines has been developed, giving the chiral cyclic sulfonamides with excellent yields and up to 99% ee.

Sulfonamide moieties can serve as valuable pharmacophores that play an important role in improving the pharmacological effect and pharmacokinetic profiles.[1] Medium-sized cyclic amines, especially seven-membered cyclic amines, possess unique structural characteristics and have been widely applied in biologically active molecules and pharmaceuticals.[2] For example, seven-membered cyclic sulfonamides (**I**, Fig. 1) can be used as apical sodium co-dependent bile acid transporter (ASTB) inhibitors that exhibit potencies in treating hyperlipidemia.[3] In addition, they can also be used as an inhibitor (**II**) of HIV-1 protease,[4] a glucokinase activator[5] (**III**) and an extracellular calcium-sensing receptor (CaSR)[6] (**IV**).
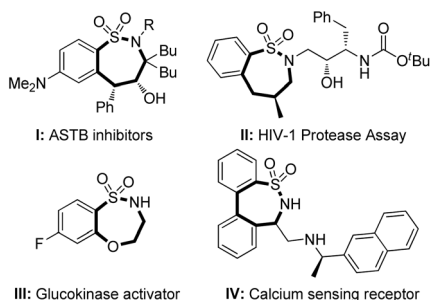

Fig. 1 Some bioactive molecules containing seven-membered cyclic sulfonamide moieties.

[a]State Key Laboratory of Fine Chemicals, School of Chemistry, Dalian University of Technology, 2 Linggong Road, Dalian 116024, P. R. China.
E-mail: shileichem@dlut.edu.cn
[b]State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China. E-mail: ygzhou@dicp.ac.cn
†Electronic supplementary information (ESI) available: Experimental details, compound characterization, NMR and HPLC spectra. CCDC 1877280. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8qo01323c

Owing to the remarkable importance of seven-membered cyclic sulfonamides, a variety of synthetic methods for this kind of compound were developed, such as intramolecular cyclization including ring-closing metathesis,[7] metal-catalyzed reaction,[8] radical cyclization,[9] *etc*.[10] However, many of these methods generally involve achiral transformations. A limited number of methods are also available for enantioselective synthesis.[11–13] In 2017, Zhou and co-workers developed a Pd-catalyzed intramolecular reductive amination of ketones with sulfonamides in the presence of a Brønsted acid, providing the chiral ε-sultams with excellent enantioselectivities (Scheme 1a).[11] Shortly afterwards, Baudoin's group developed new chiral bifunctional ligands for palladium-catalyzed enantioselective C–H arylation, yielding a seven-membered cyclic product with 34% ee (Scheme 1b).[12] Recently, Zhang's group has reported an elegant method to synthesize seven-membered chiral sulfonamides *via* a nickel(II)-catalyzed asymmetric alkenylation/rearrangement cascade of five-membered cyclic ketimines (Scheme 1c).[13] Despite these examples, given the great significance of the chiral seven-membered cyclic sulfonamides, the development of new and effective approaches for the synthesis of chiral ε-sultams is still highly desirable.

Metal-catalyzed addition of arylboron reagents to activated imines has emerged as a powerful tool to prepare diversely substituted amines in an enantioselective fashion.[14–24] Initiated by the pioneering work of the Hayashi group,[15] several groups such as Lam,[16] Xu[17] and Lin[18] have made a great contribution to the rhodium-catalyzed asymmetric addition of arylboron reagents to imines. It is worth noting that using palladium catalysts in the same reaction is more attractive owing to the relatively low cost.[19] Considering this advantage, Lu's group has pioneered the palladium-catalyzed asymmetric addition of arylboronic acids to aldimines.[20] Later, other groups including Zhang,[21] Hayashi[22] and Zhou[23] have also conducted related studies using chiral palladium cata-
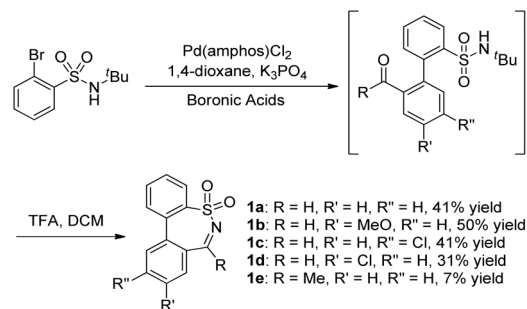
1572 | *Org. Chem. Front.*, 2019, **6**, 1572–1576

This journal is © the Partner Organisations 2019
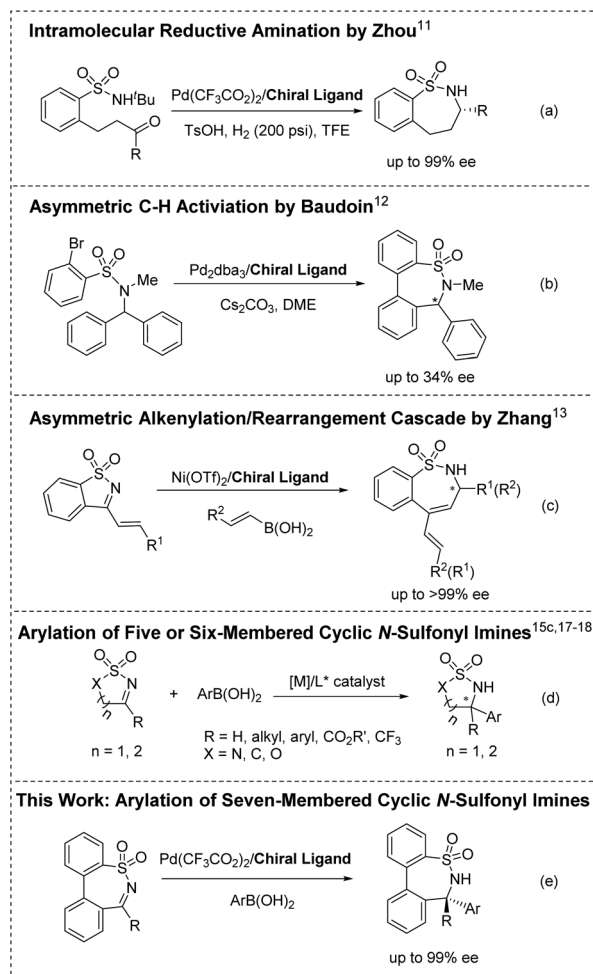
Scheme 1 Catalytic asymmetric synthesis of chiral cyclic sulfonamides.

Scheme 2 Synthesis of the seven-membered cyclic *N*-sulfonyl imines.

Table 1 Optimization of the reaction conditions[a]

Entry	Solvent	L*	Yield[b] (%)	ee[c] (%)
1	DCM	**L1**	62	71
2	TFE	**L1**	93	72
3	Toluene	**L1**	41	80
4	THF	**L1**	34	78
5	1,4-Dioxane	**L1**	12	79
6	TFE	**L2**	99	81
7	TFE	**L3**	99	99
8	TFE	**L4**	97	99
9	TFE	**L5**	93	67
10	TFE	**L6**	90	93
11[d]	TFE	**L3**	98	99

[a] Conditions: **1a** (0.10 mmol), PhB(OH)$_2$ (0.30 mmol), Pd(CF$_3$CO$_2$)$_2$ (5.0 mol%), ligand (7.5 mol%), solvent (3.0 mL), 40 °C, 4–32 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] **1a** (0.20 mmol), PhB (OH)$_2$ (0.60 mmol), Pd(CF$_3$CO$_2$)$_2$ (5.0 mol%), **L3** (7.5 mol%), TFE (3.0 mL), 40 °C, 4 h. TFE: 2,2,2-trifluoroethanol.

lysts. In the last few years, cyclic *N*-sulfonyl imines have attracted attention because of the general high reactivity and high enantioselectivity in the arylation process.[22] To date, the existing studies have mostly focused on five-membered rings and six-membered rings (Scheme 1d).[15c,17,18] We envisaged that enantioselective addition of arylboronic acids to seven-membered *N*-sulfonyl imines would be one straightforward way for the synthesis of chiral ε-sultams. Herein, we present a palladium-catalyzed asymmetric arylation of seven-membered cyclic *N*-sulfonyl imines, giving the chiral ε-sultams with excellent yields and up to 99% of enantioselectivities.

Initially, we designed strained seven-membered cyclic *N*-sulfonyl imines **1** containing a biphenyl motif, which could be conveniently synthesized in two steps (Scheme 2).[25] The main steps include a palladium-catalyzed Suzuki coupling reaction and trifluoroacetic acid-promoted intramolecular cyclization.

Subsequently, we chose compound **1a** as the model substrate for the palladium-catalyzed asymmetric addition reaction and the results of the optimization of the reaction conditions are depicted in Table 1. To our delight, when we use pyridine-oxazoline type **L1** as the chiral ligand and Pd (CF$_3$CO$_2$)$_2$ as the metal precursor, the addition of phenyl-

boronic acid **2a** to substrate **1a** proceeded smoothly in dichloromethane at 40 °C, affording the desired chiral cyclic ε-sultams **3aa** in 62% yield and 71% ee (Table 1, entry 1). After this, various solvents were extensively examined (entries 2–5). Although moderate enantioselectivities can be obtained in most solvents, only trifluoroethanol (TFE) exhibited excellent reactivity; the reaction almost completed in 24 hours with 93% isolated yields (entry 2). This solvent effect was probably due to TFE promoting the transmetallation and protonation steps of the catalytic cycle well. Next, a series of chiral ligands were

This journal is © the Partner Organisations 2019

Org. Chem. Front., 2019, **6**, 1572–1576 | **1573**

explored in TFE. The chiral bipyridine ligand **L2** developed by the Zhou group[26] proved to be beneficial for this process with 99% yield and 81% ee (entry 6). The phosphino-oxazoline-type ligands such as **L3** and **L4** were also tested (entries 7 and 8). Fortunately, these two ligands gave the products with 99% ee in a nearly full conversion. In addition, the commercially available N–P ligand Quinap (**L5**) and diphospine-type ligand Binap (**L6**) also performed well (entries 9 and 10), for example, **L6** could furnish the desired product with 93% ee and 90% yield. We selected **L3** as the optimal ligand in terms of enantioselectivity and reactivity. Thus, the optimal conditions were established: Pd(CF$_3$CO$_2$)$_2$/**L3** as the catalyst, TFE as the solvent and the reaction temperature at 40 °C.

With the optimal reaction conditions in hand, we next explored the substrate scope of this addition reaction. As summarized in Scheme 3, in most cases, the corresponding products were able to be furnished with high yields and excellent enantioselectivities. In detail, a series of electron-rich arylboronic acids (**3ab**–**3ad**) performed very well under the above standard reaction conditions. Considering the steric effect of alkyl substituents, a methyl group at the *ortho*-position or *meta*-position had a marginal effect on the enantioselectivities and reactivities (**3ae**–**3af**). The electron-deficient arylboronic acids containing halo- or trifluoromethyl were also well tolerated (**3ag**–**3aj**). It is worth noting that the reaction time was prolonged to 3 days to give 94% isolated yield when using the strong electron-withdrawing CF$_3$-substituted phenylboronic acid (**3aj**). Fused-ring aryl or disubstituted aryl boronic acids as the nucleophile would result in a slight decrease of reactivity and enantioselectivity (**3ak**–**3an**). But for 2,6-dimethyl substituted arylboronic acid, only a trace amount of the product was observed, and the reason may be the obvious steric effect. In addition, we also investigated heterocyclic boronic acids (**3ao**–**3ap**). For example, 3-furanboronic acid could provide the corresponding product in 64% yield and 98% ee. Benzofuran-2-boronic acid could lead to excellent enantioselectivities, but the reactivity was low. For 3-pyridylboronic acid and 3,5-dimethylisoxazole-4-boronic acid under the standard conditions for 24 h, unfortunately, no desired products were observed. The position and electronic properties of the substituents on the biphenyl motif had little influence on the reactivity and enantioselectivity (**3ba**–**3da**).

The construction of chiral quaternary stereocenters is extremely important and challenging in chemical synthesis. To the best of our knowledge, palladium-catalyzed asymmetric addition of aryl boronic nucleophiles to N-sulfonyl ketimines to construct a chiral quaternary carbon center is rare due to the relatively weak nucleophilicity of the aryl-Pd active intermediate. Gratifyingly, Pd-catalyzed addition of arylboronic acid to the strained cyclic N-sulfonyl ketimine **1e** proceeded smoothly under the standard conditions, providing the corresponding cyclic chiral ε-sultams containing a quaternary stereocenter with excellent enantioselectivities of 99% and 84–95% yields (Scheme 3, **3ea**–**3ee**). When a methyl group was introduced to the *para*-position or *meta*-position, the corresponding products could be obtained with high yields and excellent enantioselectivities.
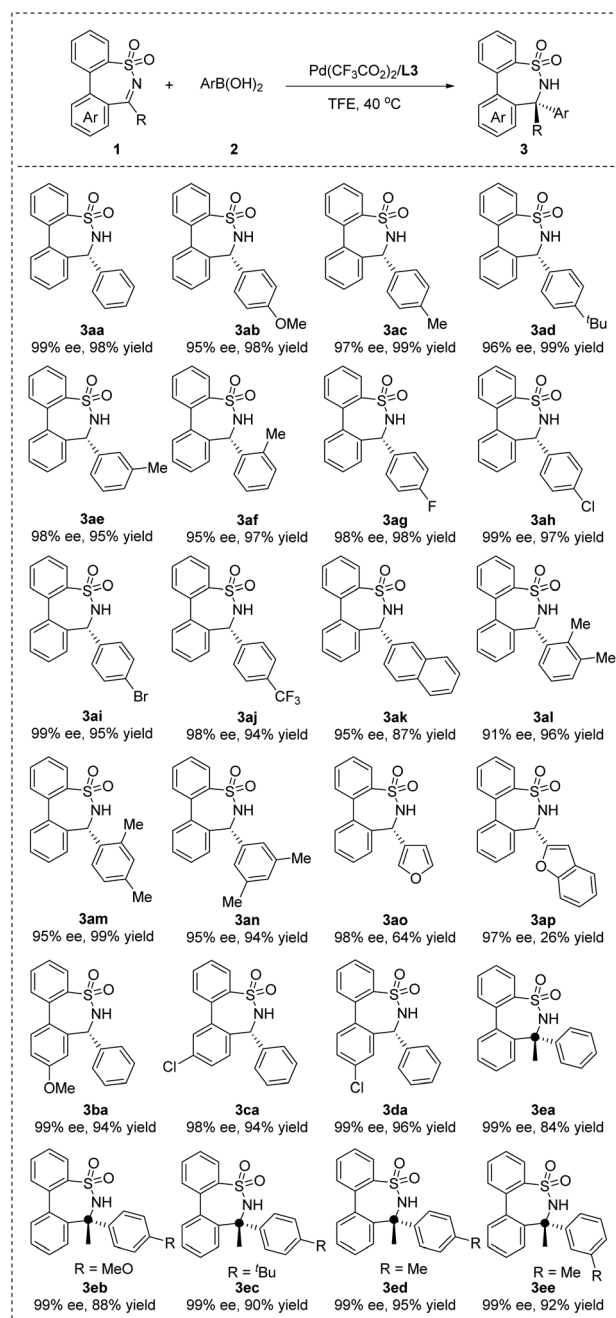
Scheme 3 Substrate scope: N-Sulfonyl imines and boronic acids.

The absolute configuration of the addition product (+)-**3aa** was unambiguously assigned to be R by X-ray crystallographic analysis after simple recrystallization with ethyl acetate and n-hexane (Fig. 2). Interestingly, the axial chirality of the biphenyl scaffold exists in the solid state, the dihedral angle of the biphenyl is 44.5° and the absolute configuration of the axis was determined to be S. The central-to-axial chirality transfer along the strained seven-membered cyclic structure might result in a preferential helical structure.

The stereochemistry of this reaction can be explained by the stereochemical model as shown in Fig. 3. The seven-mem-
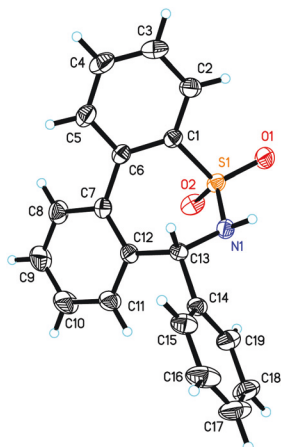
1574 | *Org. Chem. Front.*, 2019, **6**, 1572–1576

This journal is © the Partner Organisations 2019

Fig. 2   X-ray crystal structure of the addition product (+)-**3aa**.
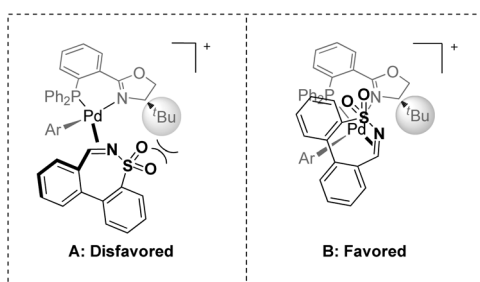

Fig. 3   Stereochemical model.

bered *N*-sulfonyl imine bound to the palladium center is *trans* to the diphenylphosphine group of the ligand, and the aryl group is *cis* to the diphenylphosphine group. One of the two possible orientations (**A**), that is, the steric interaction between the *t*-butyl group and the –SO₂ group is obvious. The alternative orientation (**B**), avoiding such interactions, could lead to the products with the observed absolute configuration.

Conclusion

In summary, we have successfully developed an efficient method for the synthesis of chiral seven-membered cyclic sulfonamides through the Pd-catalyzed asymmetric addition of arylboronic acids to the strained cyclic *N*-sulfonyl aldimines and ketimines in excellent yields with up to 99% ee. Further investigations on the central-to-axial chirality transfer phenomena of the chiral seven-membered cyclic sulfonamides and other macrocyclic structures are underway in our laboratory.

Experimental

A typical procedure for Pd-catalyzed asymmetric arylation of seven-membered cyclic *N*-sulfonyl imines

The ligand (*S*)-^{t}Bu-Phox (5.8 mg, 0.015 mmol) and Pd(OCOCF₃)₂ (3.3 mg, 0.01 mmol) were placed in a dried Schlenk

tube under a nitrogen atmosphere and degassed anhydrous acetone (1 mL) was added. The mixture was stirred at room temperature for 1 hour. The solvent was removed under vacuum to give the catalyst. Under a nitrogen atmosphere, to the mixture of seven-membered cyclic *N*-sulfonyl imines (0.20 mmol) and arylboronic acids (0.60 mmol) was added the above catalyst with 2,2,2-trifluoroethanol (3.0 mL). The solution was stirred at 40 °C for 4 h. The reaction mixture was cooled to room temperature, and the solvent was removed by rotary evaporation. Flash chromatography on silica gel using hexanes/ethyl acetate as the eluent gave the chiral products **3aa** as a white solid (63 mg, 98% yield, 99% ee). Enantiomeric excess was determined by HPLC (AD-H column, *n*-hexane/i-PrOH 80/20, 1.0 mL min^{-1}, 220 nm, 30 °C), t_1 = 12.7 min (minor), t_2 = 18.3 min (major).

Conflicts of interest

There are no conflicts to declare.

References

1 For some selected reviews, see: A. Scozzafava, T. Owa, A. Mastrolorenzo and C. T. Supuran, *Curr. Med. Chem.*, 2003, **10**, 925. For selected examples, see: (*a*) P. R. Hanson, D. A. Probst, R. E. Robinson and M. Yau, *Tetrahedron Lett.*, 1999, **40**, 4761.

2 For selected examples, see: (*a*) Y. Liao, B. J. Venhuis, N. Rodenhuis, W. Timmerman and H. Wikström, *J. Med. Chem.*, 1999, **42**, 2235; (*b*) G. R. Cook, P. S. Shanker and S. L. Peterson, *Org. Lett.*, 1999, **1**, 615; (*c*) K. Gao, B. Wu, C.-B. Yu, Q.-A. Chen, Z.-S. Ye and Y.-G. Zhou, *Org. Lett.*, 2012, **14**, 3890; (*d*) R.-N. Guo, K. Gao, Z.-S. Ye, L. Shi, Y. Li and Y.-G. Zhou, *Pure Appl. Chem.*, 2013, **85**, 843; (*e*) P. Li, Y. Huang, X. Hu, X.-Q. Dong and X. Zhang, *Org. Lett.*, 2017, **19**, 3855.

3 M. B. Tollefson, S. A. Kolodziej, T. R. Fletcher, W. F. Vernier, J. A. Beaudry, B. T. Keller and D. B. Reitz, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3727.

4 (*a*) A. K. Ganguly, S. S. Alluri, D. Caroccia, D. Biswas, C.-H. Wang, E. Kang, Y. Zhang, A. T. McPhail, S. S. Carroll, C. Burlein, V. Munshi, P. Orth and C. Strickland, *J. Med. Chem.*, 2011, **54**, 7176; (*b*) A. K. Ganguly, S. S. Alluri, C.-H. Wang, A. Antropow, A. White, D. Caroccia, D. Biswas, E. Kang, L.-K. Zhang, S. S. Carroll, C. Burlein, J. Fay, P. Orth and C. Strickland, *Tetrahedron*, 2014, **70**, 2894.

5 D. McKerrecher, K. G. Pike and M. J. Waring, *Patent Appl* WO 2006125972A1, 2006.

6 L. Kiefer, T. Gorojankina, P. Dauban, H. Faure, M. Ruat and R. H. Dodd, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7483.

7 For some selected examples, see: (*a*) R. D. Brown, J. Castro and J.-D. Moriggi, *Tetrahedron Lett.*, 2000, **41**, 3681; (*b*) S. Hanessian, H. Sailes and E. Therrien, *Tetrahedron*, 2003, **59**, 7047; (*c*) J.-D. Moriggi, L. J. Brown, J. L. Castro and R. C. D. Brown, *Org. Biomol. Chem.*, 2004, **2**, 835; (*d*) S. Karsch, D. Freitag, P. Schwab and P. Metz, *Synthesis*, 2004, 1696; (*e*) P. Gilleron, N. Wlodarczyk, R. Houssin, A. Farce, G. Laconde, J. Goossens, A. Lemoine, N. Pommery, J. Hénichart and R. Millet, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5465; (*f*) L. D. Sasiambarrena, A. S. Cánepa, C. N. Luna and R. D. Bravo, *Tetrahedron Lett.*, 2015, **56**, 2054.

8 For some selected examples, see: (*a*) D. K. Rayabarapu, A. Zhou, K. O. Jeon, T. Samarakoon and A. Rolfe, *Tetrahedron*, 2009, **65**, 3180; (*b*) C. B. Bheeter, J. K. Bera and H. Doucet, *Adv. Synth. Catal.*, 2012, **354**, 3533; (*c*) C. B. Bheeter, R. Jin, J. K. Bera and H. Doucet, *RSC Adv.*, 2013, **3**, 5987; (*d*) J. K. Laha, N. Dayal, R. Jain and K. Patel, *J. Org. Chem.*, 2014, **79**, 10899; (*e*) S. Joardar, S. Chakravorty and S. Das, *Synlett*, 2015, **26**, 359; (*f*) S. M. C. Balgobin, D. J. Brookes, J. Jiang, R. G. Pritchard and T. W. Wallace, *Org. Biomol. Chem.*, 2017, **15**, 10184; (*g*) Y. Tanji, N. Mitsutake, T. Fujihara and Y. Tsuji, *Angew. Chem., Int. Ed.*, 2018, **57**, 10314.

9 F. Ujjainwalla, M. L. Mata, A. M. Pennell, C. Escolano, W. B. Motherwell and S. Vázquez, *Tetrahedron*, 2015, **71**, 6701.

10 For other syntheses of sultams, see: (*a*) Z. Liu and Y. Takeuchi, *Heterocycles*, 2002, **56**, 693; (*b*) K. C. Majumdar and S. Mondal, *Chem. Rev.*, 2011, **111**, 7749.

11 B. Song, C.-B. Yu, Y. Ji, M.-W. Chen and Y.-G. Zhou, *Chem. Commun.*, 2017, **53**, 1704.

12 L. Yang, M. Neuburger and O. Baudoin, *Angew. Chem., Int. Ed.*, 2018, **57**, 1394.

13 M. Quan, X. Wang, L. Wu, I. D. Gridnev, G. Yang and W. Zhang, *Nat. Commun.*, 2018, **9**, 2258.

14 For some reviews, see: (*a*) G. K. Friestad and A. K. Mathies, *Tetrahedron*, 2007, **63**, 2541; (*b*) C. S. Marques and A. J. Burke, *ChemCatChem*, 2011, **3**, 635; (*c*) S. Kobayashi, Y. Mori, J. S. Fossey and M. M. Salter, *Chem. Rev.*, 2011, **111**, 2626; (*d*) P. Tian, H.-Q. Dong and G.-Q. Lin, *ACS Catal.*, 2012, **2**, 95; (*e*) M. Quan, L. Wu, G. Yang and W. Zhang, *Chem. Commun.*, 2018, **54**, 10394.

15 For some selected examples, see: (*a*) R. Shintani, M. Takeda, T. Tsuji and T. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 13168; (*b*) R. Shintani, M. Takeda, Y.-T. Soh, T. Ito and T. Hayashi, *Org. Lett.*, 2011, **13**, 2977; (*c*) T. Nishimura, A. Noishiki, G. C. Tsui and T. Hayashi, *J. Am. Chem. Soc.*,

2012, **134**, 5056; (*d*) T. Nishimura, A. Noishiki, Y. Ebe and T. Hayashi, *Angew. Chem., Int. Ed.*, 2013, **52**, 1777.

16 For selected examples, see: (*a*) Y. Luo, A. J. Carnell and H. W. Lam, *Angew. Chem., Int. Ed.*, 2012, **51**, 6762; (*b*) Y. Luo, H. B. Hepburn, N. Chotsaeng and H. W. Lam, *Angew. Chem., Int. Ed.*, 2012, **51**, 8309.

17 For selected examples, see: (*a*) H. Wang, T. Jiang and M.-H. Xu, *J. Am. Chem. Soc.*, 2013, **135**, 971; (*b*) H. Wang, Y. Li and M.-H. Xu, *Org. Lett.*, 2014, **16**, 3962; (*c*) Y. Li, Y.-N. Yu and M.-H. Xu, *ACS Catal.*, 2016, **6**, 661; (*d*) Y. Li, B. Liu and M.-H. Xu, *Org. Lett.*, 2018, **20**, 2306.

18 Y.-J. Chen, Y.-H. Chen, C.-G. Feng and G.-Q. Lin, *Org. Lett.*, 2014, **16**, 3400.

19 For reviews, see: Y.-W. Sun, P.-L. Zhu, Q. Xu and M. Shi, *RSC Adv.*, 2013, **3**, 3153.

20 For selected examples, see: (*a*) H. Dai and X. Lu, *Org. Lett.*, 2007, **9**, 3077; (*b*) H. Dai, M. Yang and X. Lu, *Adv. Synth. Catal.*, 2008, **350**, 249; (*c*) Q. Dai and X. Lu, *Tetrahedron Lett.*, 2009, **50**, 3478.

21 For selected examples, see: (*a*) G. Yang and W. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 7540; (*b*) M. Quan, G. Yang, F. Xie, I. D. Gridnev and W. Zhang, *Org. Chem. Front.*, 2015, **2**, 398; (*c*) Q. He, L. Wu, X. Kou, N. Butt, G. Yang and W. Zhang, *Org. Lett.*, 2016, **18**, 288.

22 C. Jiang, Y. Lu and T. Hayashi, *Angew. Chem., Int. Ed.*, 2014, **53**, 9936.

23 (*a*) X. Gao, B. Wu, Z. Yan and Y.-G. Zhou, *Org. Biomol. Chem.*, 2016, **14**, 55; (*b*) Z. Yan, B. Wu, X. Gao and Y.-G. Zhou, *Chem. Commun.*, 2016, **52**, 10882.

24 (*a*) G.-N. Ma, T. Zhang and M. Shi, *Org. Lett.*, 2009, **11**, 875; (*b*) C. S. Marques and A. J. Burke, *Eur. J. Org. Chem.*, 2010, 1639; (*c*) J. Chen, X. Lu, W. Lou, Y. Ye, H. Jiang and W. Zeng, *J. Org. Chem.*, 2012, **77**, 8541; (*d*) C. Schrapel and R. Peters, *Angew. Chem., Int. Ed.*, 2015, **54**, 10289; (*e*) T. Beisel and G. Manolikakes, *Org. Lett.*, 2015, **17**, 3162; (*f*) Y. Álvarez-Casao, D. Monge, E. álvarez and R. Fernández, *Org. Lett.*, 2015, **17**, 5104; (*g*) W. Chen, D. Meng, B. N'Zemba and W. J. Morris, *Org. Lett.*, 2018, **20**, 1265.

25 (*a*) C. Burlein, C. Wang, M. Xu, T. Bhatt, M. Stahlhut, Y. Ou, G. C. Adam, J. Heath, D. J. Klein, J. Sanders, K. Narayan, P. Abeywickrema, M. R. Heo, S. S. Carroll, J. A. Grobler, S. Sharma, T. L. Diamond, A. Converso and D. J. Krosky, *ACS Chem. Biol.*, 2017, **12**, 2858; (*b*) S. P. France, G. A. Aleku, M. Sharma, J. Mangas-Sanchez, R. M. Howard, J. Steflik, R. Kumar, R. W. Adams, I. Slabu, R. Crook, G. Grogan, T. W. Wallace and N. J. Turner, *Angew. Chem., Int. Ed.*, 2017, **56**, 15589; (*c*) C. Ni, D. Zha, H. Ye, Y. Hai, Y. Zhou, E. V. Anslyn and L. You, *Angew. Chem., Int. Ed.*, 2018, **57**, 1300.

26 X. Gao, B. Wu, W.-X. Huang, M.-W. Chen and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2015, **54**, 11956.