Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Li, Y. Fu, C. Qin, Y. Yu, H. Li and W. Wang, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB01527E.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB01527E

Organic & Biomolecular Chemistry

COMMUNICATION

Asymmetric Synthesis of Isoquinolinonaphthyridines Catalyzed by a Chiral Brønsted Acid

Jianjun Li,[a] Yiwei Fu,[a] Cong Qin,[a] Yang Yu,[a] Hao Li,*[a] and Wei Wang*[a,b]

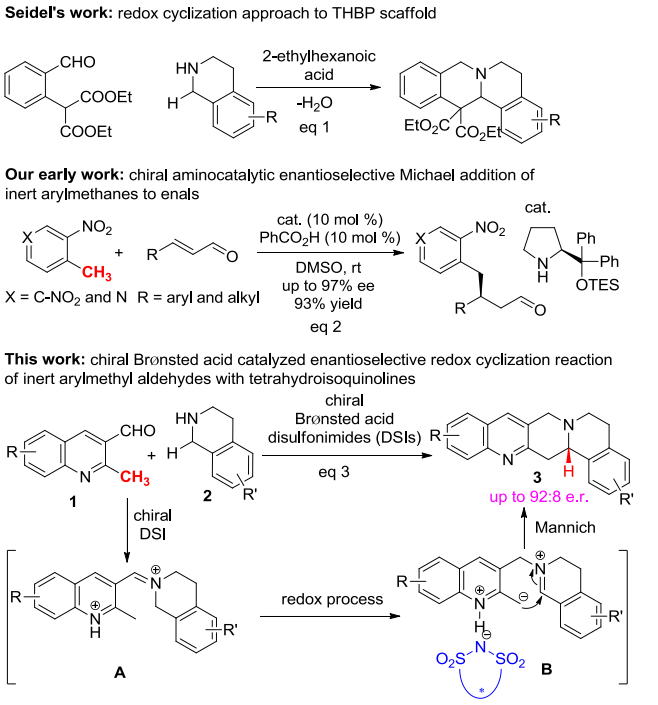
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

A catalytic asymmetric method for the synthesis of chiral isoquinolinonaphthyridines has been developed. A chiral disulfonimide catalyzes a redox cyclization between 2-methyl-3-aldehydeazaarenes and 1,2,3,4-tetrahydroisoquinolines to deliver a range of isoquinolinonaphthyridines with good to high yields (up to 91%) and up to 92:8 e.r..

Tetrahydroprotoberberines (THPBs) containing a quinolizine core possess a broad spectrum of appealing biological properties.[1] They display antifungal,[2] antimicrobial,[3] antiepileptic,[4] anti-inflammatory,[5] antihypertensive,[6] antiviral,[7] antitumor[8] bioactivities. Therefore, the synthesis of THPB analogues has been a long-standing interest to synthetic and medicinal community. The classic approaches to THPBs employ the Bischler-Napieralski[9] and the Pictet-Spengler reactions.[10] Recently, the THPBs derivatives containing N, O and S atoms have been efficiently synthesized from readily accessible tetrahydroisoquinolines with 2-hetreoatom (eg., N, O and S) substituted benzaldehydes via redox cyclization strategy, significantly contributed from Seidel and his team.[11] Reactions involving C-C bond instead of C-heteroatom bond formation representing direct approach to the tetrahydroisoquinoline scaffold also have been elegantly realized by the same group (Scheme 1, eq 1).[12] In these studies, easily enolizable melanonate, keto- or nitroalkyl aldehydes have been used for effective transformations. In addition, it is noted that these processes are carried out in a non-asymmetric manner or by employing chiral substrates to make chiral products. Catalytic



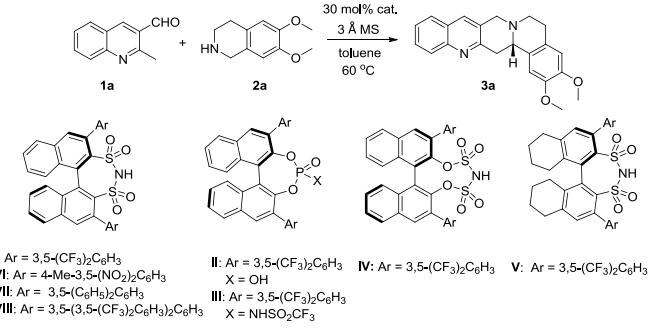
Scheme 1. Brønsted acid catalyzed enantioselective redox Mannich cyclization reaction of inert arylmethyl aldehydes with tetrahydroisoquinolines.

enantioselective process is particularly appealing for the synthesis of chiral tetrahydroisoquinolines, but remains elusive. Recently, we have developed a non-classic class of carbon centered nucleophiles for asymmetric organocatalysis.[13] We successfully implemented inert aryl methane as nucleophiles for chiral amine catalyzed Michael addition and cascade reactions (Scheme 1, eq. 2).[13a] Very recently, we developed a Lewis acid catalyzed annulation for the synthesis of achiral tetrahydroisoquinolines.[14,15] In our continuing efforts on advancing the useful chemistry, herein we report a chiral Brønsted acid catalyzed redox cyclization method[16] for the synthesis of chiral tetrahydroisoquinolines **3** (eq. 3). In this new process, we successfully imple-mented 2-methyl-3-

[a] State Key Laboratory of Bioengineering Reactor, Shanghai Key Laboratory of New Drug Design, and School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China
Email: hli77@ecust.edu.cn
[b] Department of Chemistry and Chemical Biology
University of New Mexico, Albuquerque, NM 87131-0001, USA
Email: wwang@unm.edu

†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1. Catalyst screening for the asymmetric annulation reactions[a]



Entry	cat.	t (d)	Yield[b] (%)	e.r.[c]
1	**I**	1.5	51	77:23
2	**II**	2.5	trace	-
3	**III**	2.5	42	55:45
4	**IV**	2.5	50	53:47
5	**V**	4	40	75:25
6	**VI**	2.5	55	72:28
7	**VII**	0.75	91	86:14
8	**VIII**	2.5	20	71:29
9[d]	**VII**	2.5	trace	-
10[e]	**VII**	7.5	50	82:18

[a] Unless specified, a mixture of **1a** (0.1 mmol) and cat. (30 mol%) in toluene (1.0 mL) was stirred for 30 min at rt. Then 3Å MS, **2a** (0.13 mmol) was added sequentially before the reaction was carried out at 60 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] The reaction mixture was stirred at 40 °C. [e] **VII** (15 mol%) was used.

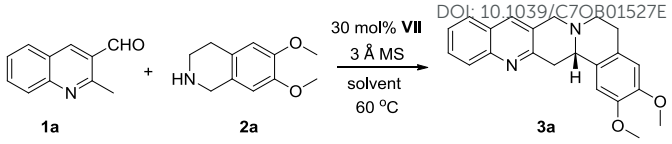
aldehydeazaarenes **1** as a new coupling partner for reacting with tetrahydroisoquinolines **2**.

In searching suitable chiral activators for the newly proposed process, we feel that chiral Brønsted acids may be of possible choice.[17] An acid promotes the formation of imine **A** from **1** and **2** to form the corresponding substrate-Brønsted acid complexes, such as the well-explored catalyst-iminium ions,[18,19] and subsequent redox neutral process to generate chiral dipolar complex B with a chiral Brønsted acid,[12c] which undergoes an intramolecular Mannich reaction to give chiral products **3**. The chiral Brønsted acid play a dual role in this process: promoting the reaction and forming chiral complex with positively charged "N" to control enantioselectivity.

To demonstrate the feasibility of the designed process, 2-methylquinoline-3-carbaldehyde (**1a**) and 1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinoline (**2a**) were selected as the model substrates. Initially, the reaction was performed in the presence of 30 mol% of DSI **I**[20] and 3 Å molecular sieves (MS) in toluene at 60 °C for 1.5 d. To our delight, the desired product **3a** was obtained in 51% yield with a promising 77:23 e.r. (Table 1, entry 1). Next, different kinds of chiral Brønsted acids (**II**-**V**) were screened. When the commercially available chiral phosphoric acid **II**[18] was probed, the reaction failed to give the desired product even after longer reaction time (2.5 d, entry 2). N-Triflyl phosphoramide **III**[21] and disulfurylimide (JINGLE) **IV**[22] could provide the product **3a** in moderate yields (42% and 50%) but low enantiomeric ratios (55:45 and 53:47 e.r., entries 3 and 4). Enlightened by these results, we turned our attention to chiral DSIs.

Table 2. Solvent Screening for the asymmetric annulation reactions[a]

View Article Online
DOI: 10.1039/C7OB01527E



Entry	Solvent	t (d)	Yield[b] (%)	e.r.[c]
1	toluene	0.75	91	86:14
2	*o*-xylene	2.5	62	79:21
3	*p*-xylene	2.5	70	78:22
4	chlorobenzene	1.5	87	76:24
5	DCE	14	60	63:37
6	dioxane	4	71	75:25
7	EtOH	6	50	58:42
8	DMF	30	trace	50:50
9[d]	toluene	0.75	81	83:17

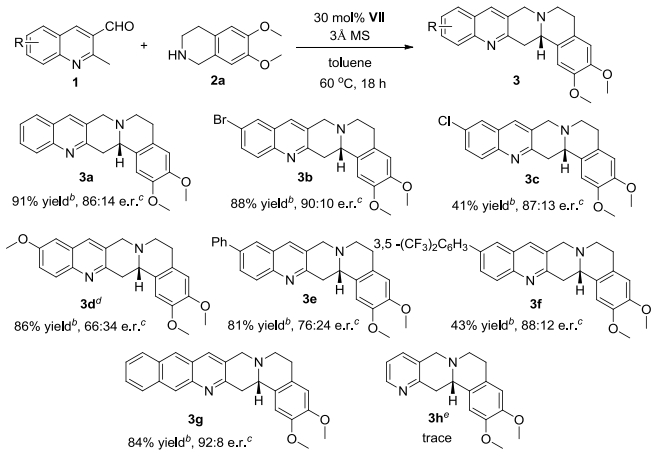
[a] Unless specified, a mixture of **1a** (0.1 mmol) and **VII** (30 mol%) in the solvent (1.0 mL) was stirred for 30 min at rt. Then 3Å MS, **2a** (0.13 mmol) was added before the reaction was carried out at 60 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] 0.5 mL toluene was used.

H8-BINOL-based disulfonimide **V**, had no significant influence on this reaction with only 40% yield and 75:25 e.r. (entry 5). It is well known that the introduction of bulky and electron-deficient groups into the 3,3'-positions of the BINOL structure could result in a sterically demanding environment.[17] Then we screened more hindered DSIs (**VI**-**VIII**) to improve reaction yields and enantioselectivities. DSI **VI**, with even more electron deficient aryl substituents, gave worse results than **I** (55% yield, 72:28 e.r., entry 6). Gratifyingly, when bulkier DSI **VII** was employed, product **3a** was produced with a dramatic increase in the enantioselectivity and higher yield (86:14 e.r., 91%, entry 7). However, more sterically demanding DSI **VIII** gave much lower yield and poor enantioselectivity (21%, 71: 29 e.r., entry 8). We also found that lower reaction temperature (40 °C) diminished the reaction efficiency (entry 9). When the catalyst loading was reduced to 15 mol%, the reaction became sluggish with loss of yield (7.5 d, 50%, entry 10). Therefore, the high catalyst loading is the limitation of this reaction.

Moreover, the solvent screening results were listed in Table 2. The reactions in less polar solvents, such as *o*-xylene, *p*-xylene and chlorobenzene, gave the products with lower reaction yields and enantioselectivities than that in toluene (entries 2-4). The reaction gave much lower enantioselectivity when dichloroethane (DCE) was used as solvent (entry 5). The reaction in dioxane afforded the product with similar result as that in *p*-xylene (entry 6). However, the reactions gave almost racemic products when the polar solvents were used (entries 7 and 8). Interestingly, only trace amount of racemic product was achieved when the reaction was carried out in DMF. When the reaction concentration was enhanced, the lower reaction yield was achieved (entry 9). The solvent screening revealed that toluene was the choice for this reaction in both reaction yield and enantiocontrol.

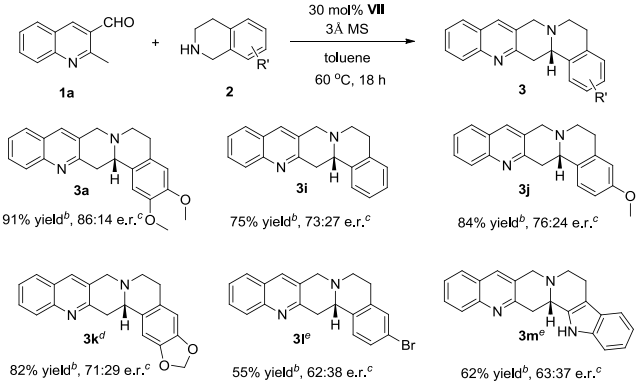
With the optimal reaction conditions in hand, the structural generality and limitation of 2-methylquinoline-3-carbaldehydes was then investigated. As shown in Scheme 2, 6-Br substituent

View Article Online
DOI: 10.1039/C7OB01527F



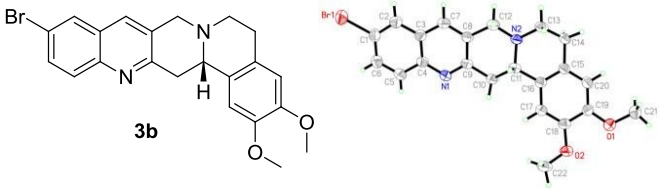
Scheme 2. Scope of 2-methylquinoline-3-carbaldehydes.[a] [a] Reaction conditions: unless otherwise specified, see footnote a of Table 1 and the Experimental Section in the Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] The reaction mixture was stirred for 2 d. [e] The reaction mixture was stirred for 4 d.

product **3b** was obtained in both good yield and enantioselectivity (88% yield, 90:10 e.r.). Interestingly, 6-Cl substituent **1c** delivered product **3c** with similar enantioselectivity but in much lower yield (87:13 e.r., 41%). When the electron-donating methoxy group was introduced at the 6-position of quinoline, the enantioselectivity dropped dramatically but without loss of yield after much longer reaction time (86% yield, 66:34 e.r., 2 d). A similar result was obtained for 6-phenyl quinoline **1e**, giving product **3e** in high yield but poor enantiocontrol (81%, 76:24 e.r.). A branched 3,5-bis(trifluoromethyl)-phenyl group at the 6-position furnished product **3f** with good enantioselectivity but lower yield (88:12 e.r., 43%). When more rigid substrate 2-methylbenzo[g]quinoline-3-carbaldehyde **1g** was examined, both high yield and enantioselectivity were obtained (84% yield, 92:8 e.r.). Moreover, we evaluated a less reactive substrate 2-methylnicotinaldehyde (**1h**). Not surprisingly, the cyclization reaction went sluggishly and only gave a trace amount of product after 4 d.



Scheme 3. Scope of secondary amines.[a] [a] Reaction conditions: unless otherwise specified, see footnote a of Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] **2d** (0.05 mmol) was added every 2 d, and the reaction mixture was stirred for 14 d. [e] The reaction mixture was stirred for 5 d.

Next, we probed the reaction scope by variation of amines components (Scheme 3). 1,2,3,4-Tetrahydroisoquinoline **2b** enabled to afford the product **3i** with both moderate yield and enantioselectivity (75% yield, 73:27 e.r.). Slightly better results for the formation of product **3j** (84%, 76:24 e.r.) were obtained with 6-methoxy **2c**. 6,7-Dioxolo 1,2,3,4-tetrahydroisoquinoline **2d** gave similar efficiency but requiring portion addition of **2d** and longer reaction time. Tetrahydroisoquinoline **2e** bearing electron-withdrawing 6-bromo group was tolerated with the moderate yield and low enantioselectivity (55% yield, 62:38 e.r.). Finally, more pharmaceutically relevant indole derived tetrahydroisoquinoline **2m** was applicable for this reaction and gave the desired product **3m** in 62% yield and with 63:37 e.r).



Scheme 4. X-Ray crystalstructure of compound **3b**.

The absolute configuration of the products was determined to be *S* on the basis of single-crystal X-ray diffraction analysis of compound **3b** (Scheme 4).[23]

Conclusions

We have developed the first chiral Brønsted acid promoted enantioselective reaction of 2-methylquinoline-3-carbaldehydes with 1,2,3,4-tetrahydroisoquinolines. A range of substituted 2-methylquinoline-3-carbaldehydes and 1,2,3,4-tetrahydroisoquinoline derivatives are tolerated for the process with good to high yields (up to 91%) and up to 92:8 e.r.. The structures of the produced products are highly close to those of biologically interesting tetrahydroprotoberberines. Therefore, exploration of their biological activities and the catalysis strategy for further improving enantioselectivity of the process and new organic transformations are under investigation in our laboratories.

This work was supported by the National Science Foundation of China (21372073, 21572054 and 21572055), the Fundamental Research Funds for the Central Universities and the China 111 Project (Grant B07023).

Notes and references

1 For selected examples: *(a)* F. Šantavý, in *The Alkaloids: Chemistry and Physiology*, *Vol. 17* (Eds.: R. H. F. Manske, R. G. A. Rodrigo), Academic Press, New York, 1979, pp. 385; *(b)* D. S. Bhakuni and S. Jain in *The Alkaloids: Chemistry and Pharmacology*, *Vol. 28* (Ed.: A. Brossi), Academic Press, New York, 1986, pp. 95; *(c)* K. Iwasa, W. Cui, M. Sugiura, A. Takeuchi, M. Moriyasu and K. Takeda, *J. Nat. Prod.,* 2005, **68**, 992; *(d)* M. Hesse, *Alkaloids: Nature's Curse or Blessing*; Wiley-VCH, Weinheim; Chichester, UK, 2002.
2 Y. Han, and J. H. Lee, *Biol. Pharm. Bull.*, 2005, **28**, 541.

3 A. H. Amin, T. V. Subbaiah and K. M. Abbasi, *Can. J. Microbiol*., 1969, **15**, 1067; *(b)* T. V. Subbaiah and A. H. Amin, *Nature,* 1967, **215**, 527; *(c)* P. Cheng, B.Wang, X. Liu, W. Liu, W. Kang, J. Zhou and J. Zeng, *Nat. Prod. Res*., 2014, **28**, 413.

4 *(a)* G. Memetzidis, J. F. Stambach, L. Jung, C. Schott, C. Heitz and J. C. Stoclet, *Eur. J. Med. Chem*., 1991, **26**, 605; *(b)* M. T. Lin, J. J. Wang and M. S. Young, *Neurosci. Lett*., 2002, **320**, 113.

5 Z. M. Zhang, B. Jiang and X. X. Zheng, *China J. Chin. Mater. Med*., 2005, **30**, 861; *(b)* C. L. Kuo, C. W. Chi and T. Y. Liu, *Cancer Lett*., 2004, **203**, 127.

6 M. T. Lin, F. Y. Chuch, M. T. Hsieh and C. F. Chen, *Clin. Exp. Pharmacol. Physiol*., 1996, **23**, 738.

7 C. E. Cecil, J. M. Davis, N. B. Cech and S. M. Laster, *Int. Immunopharmacol*., 2011, **11**, 1706.

8 *(a)* W. D. Wilson, A. N. Gough, J. J. Doyle and M. W. Davison, *J. Med. Chem*., 1976, **19**, 1261; *(b)* R. K. Y. Zee-Cheng and C. C. Cheng, *J. Med. Chem*., 1976, **19**, 882; *(c)* M. Cushman, F. W. Dekow and L. B. Jacobsen, *J. Med. Chem*., 1979, **22**, 331.

9 For selected examples: *(a)* A. Bischler and B. Napieralski, *Ber. Dtsch. Chem Ges*., 1893, **26**, 1903; *(b)* R. D. Larsen, R. A. Reamer, E. G. Corley, P. Davis, E. J. J. Grabowski, P. J. Reider and I. Shinkai, *J. Org. Chem*., 1991, **56**, 6034; *(c)* A. P. Venkov and I. I. Ivanov, *Tetrahedron,* 1996, **52**, 12299; *(d)* X. J. Wang, J. Tan and K. Grozinger, *Tetrahedron Lett.,* 1998, **39**, 6609; *(e)* T. L. Ho and Q. X. Lin, *Tetrahedron,* 2008, **64**, 10401.

10 For selected examples: a review: *(a)* E. D. Cox and J. M. Cook, *Chem. Rev*., 1995, **95**, 1797; *(b)* A. Pictet and T. Spengler, *Ber*., 1911, **44**, 2030; *(c)* A. I. Meyers, M. Boes and D. A. Dickman, *Angew. Chem. Int. Ed*., 1984, **23**, 458; *(d)* R. B. Miller and T. Tsang, *Tetrahedron Lett*., 1988, **29**, 6715; *(e)* D. J. Mergott, S. J. Zuend and E. N. Jacobsen, *Org. Lett*., 2008, **10**, 745; *(f)* C. N. Eid, J. Shin, J. Bikker and M. Lin, *J. Org. Chem*., 2009, **74**, 423.

11 For selected examples: *(a)* C. Zhang, C. K. De, R. Mal and D. Seidel, *J. Am. Chem. Soc*., 2008, **130**, 416; *(b)* M. T. Richers, M. Breugst, A. Y. Platonova, A. Ullrich, A. Dieckmann, K. N. Houk and D. Seidel, *J. Am. Chem. Soc*., 2014, **136**, 6123; *(c)* C. L. Jarvis, M. T. Richers, M. Breugst, K. N. Houk and D. Seidel, *Org. Lett.,* 2014, **16**, 3556.

12 *(a)* Y. Kang, W. Chen, M. Breugst and D. Seidel, *J. Org. Chem*., 2015, **80**, 9628; *(b)* W. Chen and D. Seidel, *Org. Lett*., 2016, **18**, 1024; *(c)* L. Ma and D. Seidel, *Chem. Eur. J*., 2015, **21**, 12908.

13 *(a)* T. F. Li, J. Zhu, D. Y. Wu, X. M. Li, S. N. Wang, H. Li, J. Li and W. Wang, *Chem. Eur. J*., 2013, **19**, 9147; *(b)* X. M. Li, S. N. Wang, T. F. Li, J. Li, H. Li and W. Wang, *Org. Lett.,* 2013, **15**, 5634.

14 J. J. Li, C. Qin, Y. Yu, H. Q. Fan, Y. W. Fu, H. Li and W. Wang, *Adv. Synth. Catal.,* 2017, DOI: 10.1002/adsc.201601423.

15 During the preparation of this manuscript, the similar achiral reaction was reported: Z. B. Zhu and D. Seidel, *Org. Lett*., 2017, **19**, 2841.

16 Studies from our laboratories, see: *(a)* Z. Q. Zou, Z. J. Deng, X. H. Yu, M. M. Zhang, S. H. Zhao, T. Luo, X. Yin, H. Xu and W. Wang, *Sci. China-Chem*., 2012, **55**, 43; *(b)* S. C. Wu, N. Liu, G. Q. Dong, L. Ma, S. Z. Wang, W. C. Shi, K. Fang, S. Q. Chen, J. Li, W. N. Zhang, C. Q. Sheng and W. Wang, *Chem. Commun*., 2016, **52**, 9593.

17 For reviews: *(a)* T. Akiyama, *Chem. Rev.,* 2007, **107**, 5744; *(b)* M. Terada, *Synthesis,* 2010, **12**, 1929; *(c)* D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.,* 2014, **114**, 9047; *(d)* T. Akiyama and K. Mori, *Chem. Rev.,* 2015, **115**, 9277; *(e)* T. James, V. M. Gemmeren and B. List, *Chem. Rev.,* 2015, **115**, 9388.

18 *(a)* J. Itoh, K. Yokota, K. Fuchibe and T. Akiyama, *Angew. Chem. Int. Ed*., 2004, **43**, 1566; *(b)* D. Uraguchi and M. Terada, *J. Am. Chem. Soc*., 2004, **126**, 5356.

19 For selected examples of chiral Brønsted acids activating aldimines, see: *(a)* D. Uraguchi, K. Sorimachi and M. Terada, *J. Am. Chem. Soc*. 2004, **126**, 11804; *(b)* M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc*., 2004, **126**, 10558; *(c)* M. Rueping, E. Sugiono and C. Azap, *Angew. Chem. Int. Ed*., 2006, **45**, 2617; *(d)* Q. Kang, Z. A. Zhao and S. L. You, *J. Am. Chem. Soc*., 2007, **129**, 1484; *(e)* M. Yamanaka, J. Itoh, K. Fuchibe and T. Akiyama, *J. Am. Chem. Soc*., 2007, **129**, 6756; *(f)* Q. X. Guo, H. Liu, C. Guo, S. W. Luo, Y. Gu and L. Z. Gong, *J. Am. Chem. Soc*., 2007, **129**, 3790; *(g)* X. Cheng, S. Vellalath, R. Goddard and B. List, *J. Am. Chem. Soc*., 2008, **130**, 15786.

20 *(a)* L. Y. Chen, H. He, W. H. Chan and A. W. M. Lee, *J. Org. Chem*., 2011, **76**, 7141; *(b)* S. Prévost, N. Dupré, M. Leutzsch, Q. Wang, V. Wakchaure and B. List, *Angew. Chem. Int. Ed.,* 2014, **53**, 8770.

21 For selscted examples of chiral *N*-triflyl phosphoramides: *(a)* D. Nakashima and H. Yamamoto, *J. Am. Chem. Soc*., 2006, **128**, 9626; *(b)* M. Rueping, W. Ieawsuwan, A. P. Antonchick and B. J. Nachtsheim, *Angew. Chem. Int. Ed*., 2007, **46**, 2097; *(c)* J. N. Johnston, *Angew. Chem. Int. Ed*., 2011, **50**, 2890; *(d)* L. P. Liu, S. J. Kaib Philip, A. Tap and B. List, *J. Am. Chem. Soc*., 2016, **138**, 10822.

22 For selected examples of chiral disulfurylimides (JINGLEs): *(a)* A. Berkessel, P. Christ, N. Leconte, J. M. Neudörfl and M. Schäfer, *Eur. J. Org. Chem*., 2010, 5165; *(b)* S. J. Ni, V. R. Naidu and J. Franzén, *Eur. J. Org. Chem*., 2016, 1708.

23 CCDC-1515185 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk.