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Disulfonimide-Catalyzed Asymmetric Reduction of *N*-Alkyl Imines

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Abstract: *A chiral disulfonimide (DSI)-catalyzed asymmetric reduction of N-alkyl imines with Hantzsch esters as a hydrogen source in the presence of Boc_2O has been developed. The reaction delivers Boc-protected N-alkyl amines with excellent yields and enantioselectivity. The method tolerates a large variety of alkyl amines, thus illustrating potential for a general reductive cross-coupling of ketones with diverse amines, and it was applied in the synthesis of the pharmaceuticals (S)-Rivastigmine, NPS R-568 Hydrochloride, and (R)-Fendiline.*

Enantiomerically pure amines, in particular α-chiral *N*-alkyl amines, represent a privileged pharmacophore that can be found in a vast number of pharmaceutical and agrochemical substances, including (*S*)-Rivastigmine (Alzheimer's and Parkinson's diseases), NPS *R*-568 (hyperparathyroidism), and (*R*)-Fendiline (angina pectoris; Figure 1).[1]

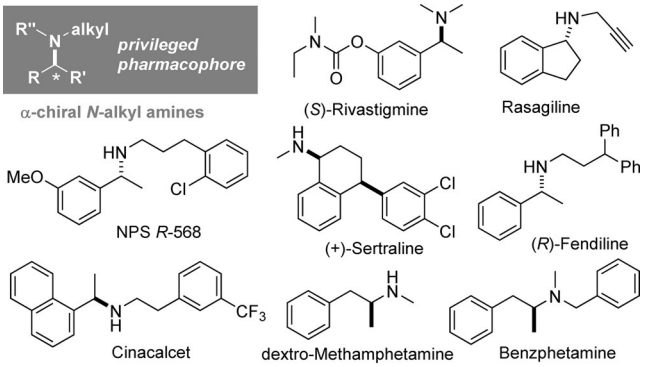
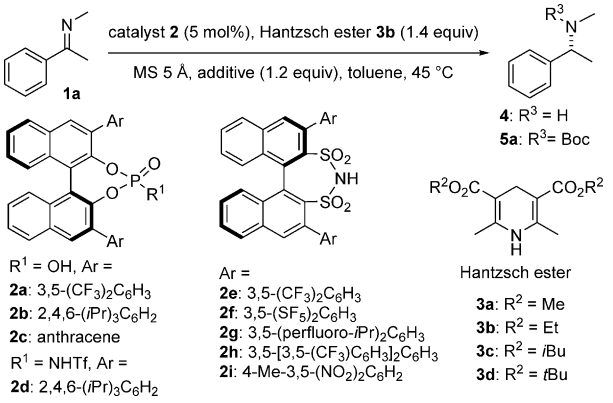


Figure 1. α-Chiral *N*-alkyl amine pharmaceuticals.

Catalytic asymmetric imine reductions and reductive aminations of carbonyl compounds represent efficient approaches for the construction of optically pure amines.[2] Recently, we developed a Brønsted acid catalyzed asymmetric imine reduction and reductive amination of ketones using Hantzsch esters as hydrogen source,[3] and independent variations and applications have appeared.[4–8] Despite these advances, however, such reductions have been limited to *N*-aryl imines. We now report a highly enantioselective chiral disulfonimide (DSI)-catalyzed Hantzsch ester mediated reduction of *N*-alkyl imines.

N-Alkyl imines are highly attractive substrates for asymmetric reductions since they would directly furnish the *N*-alkyl amine pharmacophore. Chiral phosphoric acids typically fail in the corresponding Hantzsch ester mediated imine reductions and alternative approaches have only rarely been investigated and remain a major challenge.[3b,6,9,10] At the onset of our work, we hypothesized that owing to the high basicity of the desired *N*-alkyl amine products, a stronger Brønsted acid catalyst may be required for Hantzsch ester reductions to achieve high turnover and enantioselectivity. Indeed, we found that both phosphoric acids (**2a**–**c**) and *N*-triflyl phosphoramide **2d** promoted the reduction of *N*-methyl imine **1a** with Hantzsch ester **3b** to give amine **4** with only disappointing conversion and enantioselectivity (Table 1, entries 1–4). Recently, we introduced chiral disulfonimides (DSIs) as effective precatalysts in silicon-based

Table 1: Reaction development.[a]



Entry	Cat.	Hantzsch ester	additive	*t* [h]	Conv.[%][b]	e.r.[c]
1	**2a**	**3b**	–	72	18	51.5:48.5
2	**2b**	**3b**	–	72	6	63:37
3	**2c**	**3b**	–	72	25	51.5:48.5
4	**2d**	**3b**	–	72	50	51:49
5	**2e**	**3b**	–	48	84	77:23
6	**2f**	**3b**	–	72	86	70:30
7	**2g**	**3b**	–	72	80	76:24
8	**2h**	**3b**	–	48	83	85:15
9	**2i**	**3b**	–	48	83	88:12
10	**2i**	**3a**	–	48	40	89.5:10.5
11	**2i**	**3c**	–	48	81	88.5:11.5
12	**2i**	**3d**	–	24	99	88:12
13[d]	**2i**	**3d**	–	48	88	93:7
14[d,e]	**2i**	**3d**	–	48	60	95.5:4.5
15[d–f]	***2i***	***3d***	Boc_2O	*48*	*99*	*95.5:4.5*
16[d–f]	**2b**	**3d**	Boc_2O	48	80	62:38

[a] Reactions were run on a 0.1 mmol scale. [b] Determined by GC–MS. [c] Determined by GC or HPLC with a chiral stationary phase. [d] Reactions were run at 10°C. [e] Mesitylene was used as a solvent. [f] Obtained product **5a**.

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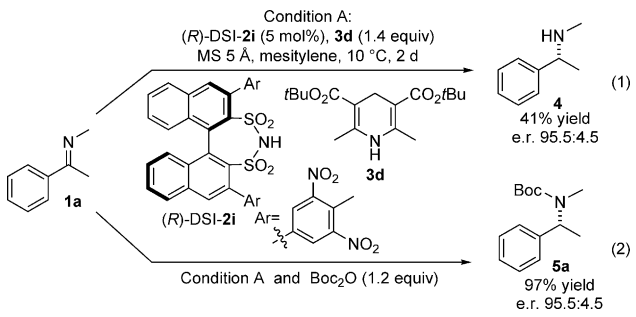
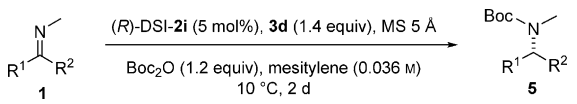
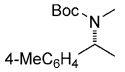
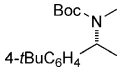
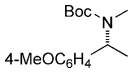
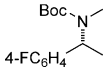
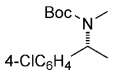
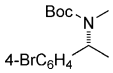
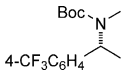
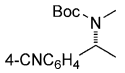
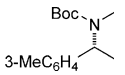
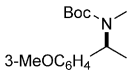
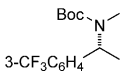
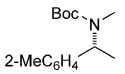
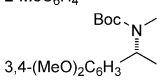
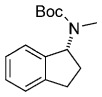
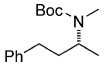
Lewis acid catalysis[11] and also as strong Brønsted acid catalysts.[12] Indeed, our chiral DSIs (**2e**–**i**) catalyzed the transformation more rapidly than the alternative phosphoric acid based catalysts and also afforded amine **4** with higher enantioselectivity (entries 5–9). After careful investigation, we identified reaction conditions in which the reduction of imine **1a** is performed using 5 mol% of catalyst (*R*)-DSI-**2i**, Hantzsch ester **3d** (1.4 equiv), and 5 Å molecular sieves in mesitylene at 10 °C for 2 days. Amine **4** was obtained with a high enantiomeric ratio (e.r.) of 95.5:4.5, however the reaction was still rather sluggish and the product was isolated in only 41% yield [Eq. (1)]. We speculated that the poor yield of isolated product was still due to catalyst deactivation through salt formation with the highly basic amine **4**. It has previously been reported that related product inhibition pathways can be eliminated by in situ protection.[10c,d,13] Encouraged by these reports, we investigated the effect of running the reaction in the presence of di-*tert*-butyl dicarbonate (Boc_2O). Remarkably, we found that full conversion into the desired *N*-Boc-protected product **5a** in 97% yield with an identical e.r. of 95.5:4.5 was observed under these conditions [Eq. (2)].



Other reagents, such as acetic anhydride and dibenzyl dicarbonate (Cbz_2O), could also be used and afforded the corresponding *N*-Ac product in 90% yield with an e.r. of 94.5:5.5 and the *N*-Cbz product in 92% yield with an e.r. of 95:5, respectively (see the Supporting Information). Encouraged by this result, the scope of the enantioselective reduction of *N*-methyl imines was next investigated (Table 2). A variety of *N*-methyl imines were efficiently reduced in the presence of (*R*)-DSI-**2i** (5.0 mol%) to afford the corresponding Boc-protected *N*-methyl amines with high yields and enantioselectivity. Electron-donating *para* substituents are well tolerated (entries 1–4). For example, *tert*-butyl-substituted imine **1c** provided amine **5c** in 91% yield with an e.r. of 98.5:1.5 (entry 3). A *p*-methoxy group in imine **1d** decreased the reactivity and required 5 days to achieve high yield and 96:4 e.r. (entry 4). Electron-withdrawing *para* substituents such as fluorine, chlorine, bromine, or trifluoromethyl groups have no significant influence on enantioselectivity or reactivity (entries 5–8). However, the *p*-cyano group in imine **1i** decreased the reactivity and also required a longer reaction time to achieve full conversion with an e.r. of 95:5 (entry 9). Substitutions at the *meta* position are equally well tolerated and both electron-donating and electron-withdrawing groups

Table 2: Substrate scope of the asymmetric reduction of *N*-methyl imines.[a]



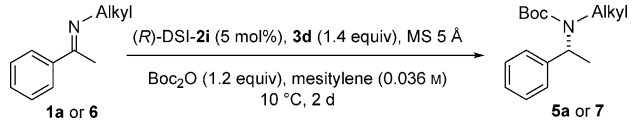
Entry	Products		Yield [%]	e.r.[b]
1		**5a**	97	95.5:4.5
2		**5b**	88	95:5
3		**5c**	91	98.5:1.5
4[c]		**5d**	93	96:4
5		**5e**	94	95:5
6		**5f**	96	95.5:4.5
7		**5g**	95	96:4
8		**5h**	96	97:3
9[c]		**5i**	95	95:5
10		**5j**	90	95:5
11[d,e]		**5k**	92	94:6
12		**5l**	94	95:5
13[c]		**5m**	67	67.5:33.5
14[c]		**5n**	95	97:3
15		**5o**	92	95.5:4.5
16		**5p**	89	90.5:9.5
17[d]		**5q**	74	52.5: 47.5
18[c]		**5r**	63	53.5:46.5
19		**5s**	90	71:29

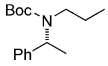
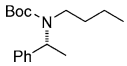
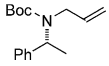
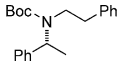
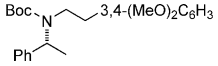
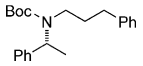
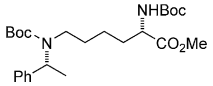
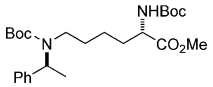
[a] Reactions were run on a 0.25 mmol scale. [b] Determined by HPLC with a chiral stationary phase. The absolute configuration was determined by preparing an authentic sample of **5a** and by comparing various known optical rotation values (see the Supporting Information). [c] Reaction time 5 d. [d] Reaction time 3 d. [e] The *S*-enantiomer of disulfonimide **2i** was used.

provided the corresponding amines in high yields and enantioselectivity (entries 10–12). *ortho* Substitution proved detrimental to both reactivity and selectivity, while *meta*,*para* disubstitution led to good results with an e.r. of 97:3 (entries 13 and 14). Interestingly, *N*-methyl imine **1o**, which is derived from α-tetralone, was reduced in high yield with an e.r. of 95.5:4.5 (entry 15). *N*-Methyl imine **1p**, which is derived from 1-indanone, gave less satisfactory results (entry 16). An aliphatic imine can also be employed but gave poor enantioselectivity (entries 17 and 18). Propiophenone-derived imine **1s** was reduced in 90% yield with an e.r. of 71:29 (entry 19).

An additional strength of our method is revealed upon exploring longer and substituted *N*-alkyl groups. Gratifyingly, the reduction of *N*-ethyl imine **6a** proceeded in 83% yield and with an e.r. of 97:3 (Table 3, entry 2). Remarkably, even

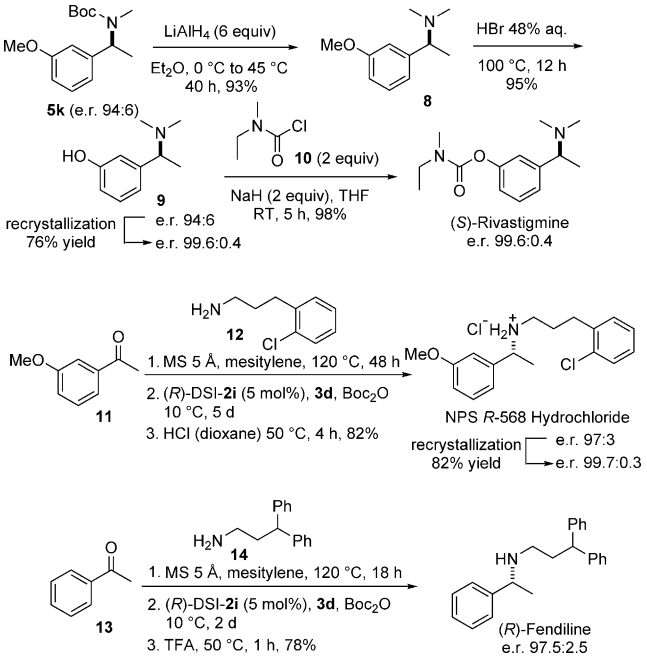
Table 3: Scope of the asymmetric reduction of *N*-alkyl imines.[a]



Entry	Products		Yield [%]	e.r./d.r.[b]
1		**5a**	97	95.5:4.5
2		**7a**	83	97:3
3		**7b**	90	97.5:2.5
4		**7c**	82	97.5:2.5
5		**7d**	77	95.5:4.5
6		**7e**	94	97:3
7[c]		**7f**	83	95.5:4.5
8		**7g**	94	97.5:2.5
9[c]		**7h**	75	93:7
10[c,d]		*ent*-**7h**	79	97.5:2.5

[a] Reactions were run on a 0.25 mmol scale. [b] Determined by HPLC with a chiral stationary phase. [c] Reaction time 3 d. [d] The *S*-enantiomer of disulfonimide **2i** was used.

the *N*-*n*-propyl, *N*-*n*-butyl, *N*-allyl, *N*-2-phenylethyl, *N*-2-(3,4-dimethoxy)-phenylethyl, and *N*-3-phenylpropyl imine substrates (**6b**–**6g**) are well tolerated and reacted with excellent enantioselectivity (entries 3–8). Interestingly, the reduction of imine **6h**, which is derived from methyl (tert-butoxycarbonyl)-L-lysinate, with (*R*)-DSI-**2i** resulted in a d.r. of 93:7, while (*S*)-DSI-**2i** gave a d.r. of 97.5:2.5, which is indicative of a matched combination (entries 9 and 10).



Scheme 1. Synthesis of (*S*)-Rivastigmine, NPS *R*-568 Hydrochloride, and (*R*)-Fendiline.

To illustrate the synthetic utility of our method, several marketed pharmaceuticals were prepared (Scheme 1). For example, a short synthesis of (*S*)-Rivastigmine, which is currently used for treating Alzheimer's disease, was realized.[14] Boc-protected *N*-methyl amine **5k** (Table 2, entry 11) was converted into *N*,*N*-dimethyl amine **8** in 93% yield upon $LiAlH_4$ reduction. This transformation illustrates an additional benefit of the Boc moiety, which not only enables turnover in the asymmetric reduction but also introduces a useful *N*-methyl precursor. Next, cleavage of the *O*-methyl group using aqueous HBr provided (*S*)-3-(1-dimethylaminoethyl)phenol **9** in 95% yield. A single recrystallization from CH_2Cl_2/pentane gave product **9** in 76% yield with an e.r. of 99.6:0.4. Finally, carbamoylation of alcohol (*S*)-**9** with commercially available *N*-ethyl-*N*-methylcarbamoyl chloride **10** in the presence of sodium hydride furnished (*S*)-Rivastigmine in 98% yield with an e.r. of 99.6:0.4.

Furthermore, the calcimimetic compound NPS *R*-568 hydrochloride, which has been shown to be effective against both primary and secondary hyperparathyroidism, was synthesized.[15] In this case, imine generation from commercially available ketone **11** and amine **12**, asymmetric reduction, and Boc deprotection, were all performed in one pot, thereby providing NPS *R*-568 in 82% yield with an e.r. of 97:3. A single recrystallization of the corresponding HCl salt from CH_2Cl_2/MTBE gave NPS *R*-568 hydrochloride in 82% yield with an e.r. of 99.7:0.3.

In a similar manner, an enantioselective synthesis of (*R*)-Fendiline, an effective antianginal drug for the treatment of coronary heart diseases, was achieved in 78% yield with an e.r. of 97.5:2.5.[16]

In summary, we have developed a highly enantioselective Brønsted acid catalyzed reduction of *N*-alkyl imines. The

reaction is catalyzed by a disulfonimide catalyst with a Hantzsch ester as a hydrogen source in the presence of Boc_2O, and it provides facile access to several enantioenriched Boc-protected *N*-alkyl amines. The in situ protection of the basic *N*-alkyl amine product with the easily removable Boc group not only solves the problem of product inhibition but also introduces a convenient *N*-methyl precursor. Our method was applied to the synthesis of the pharmaceuticals (*S*)-Rivastigmine, NPS *R*-568 hydrochloride, and (*R*)-Fendiline. The high tolerance for various *N*-alkyl amines immediately suggests the potential of our method as a general approach for the reductive cross-coupling of ketones with diverse amines. Our explorations of disulfonimide-catalyzed reactions continue.

Acknowledgements

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Keywords: Brønsted acids · disulfonimide · *N*-alkyl amines · organocatalysis · reduction

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Angew. Chem. **2015**, *127*, 12019–12023

[1] *Chiral Amine Synthesis: Methods, Developments and Applications* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**.

[2] Reviews on asymmetric reduction of imines and reductive amination of ketones: a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3070; b) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151; c) V. I. Tararov, A. Börner, *Synlett* **2005**, 203–211; d) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236; e) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753–819; f) N. Fleury-Brégeot, V. de La Fuente, S. Castillón, C. Claver, *ChemCatChem* **2010**, *2*, 1346–1371; g) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760; h) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590.

[3] a) S. Hoffmann, A. Seayad, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424–7427; *Angew. Chem.* **2005**, *117*, 7590–7593; b) for attempts towards phosphoric acid catalyzed Hantzsch ester reductions of *N-benzyl* imines, see: V. N. Wakchaure, M. Nicoletti, L. Ratjen, B. List, *Synlett* **2010**, 2708–2710.

[4] Selected examples of other organocatalytic asymmetric imine reductions and reductive aminations: a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781–3783; b) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86; c) S. Singh, U. K. Batra, *Indian J. Chem. Sect. B* **1989**, *28*, 1–2; selected examples of organocatalytic asymmetric α-imino ester reductions: d) G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830–5831; e) Q. Kang, Z.-A. Zhao, S.-L. You, *Adv. Synth. Catal.* **2007**, *349*, 1657–1660; for a theoretical study, see: f) L. Simón, J. M. Goodman, *J. Am. Chem. Soc.* **2008**, *130*, 8741–8747; for reviews, see: g) S.-L. You, *Chem. Asian J.* **2007**, *2*, 820–827; h) S. J. Connon, *Org. Biomol. Chem.* **2007**, *5*, 3407–3417; i) S. G. Ouellet, A. M. Walji, D. W. C. MacMillan, *Acc. Chem. Res.* **2007**, *40*, 1327–1339; j) C. Wang, X. Wu, J. Xiao, *Chem. Asian J.* **2008**, *3*, 1750–1770; k) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2010**, 852–865; l) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chem.* **2011**, *13*, 1084–1105; m) J. G. de Vries, N. Mršić, *Catal. Sci. Technol.* **2011**, *1*, 727–735; n) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498–2518; organocatalytic asymmetric enamide reductions: o) G. Li, J. C. Antilla, *Org. Lett.* **2009**, *11*, 1075–1078; selected examples of Lewis base catalyzed asymmetric imine reductions and reductive aminations using silanes: p) F. Iwasaki, O. Onomura, K. Mishima, T. Kanematsu, T. Maki, Y. Matsumura, *Tetrahedron Lett.* **2001**, *42*, 2525–2527; q) A. V. Malkov, A. Mariani, K. N. MacDougall, P. Kočovský, *Org. Lett.* **2004**, *6*, 2253–2556; r) A. V. Malkov, S. Stončius, K. N. MacDougall, A. Mariani, G. D. McGeoch, P. Kočovský, *Tetrahedron* **2006**, *62*, 264–284; s) Z. Wang, X. Ye, S. Wei, P. Wu, A. Zhang, J. Sun, *Org. Lett.* **2006**, *8*, 999–1001; t) D. Pei, Y. Zhang, S. Wei, M. Wang, J. Sun, *Adv. Synth. Catal.* **2008**, *350*, 619–623; u) P. Wu, Z. Wang, M. Cheng, L. Zhou, J. Sun, *Tetrahedron* **2008**, *64*, 11304–11312; v) F.-M. Gautier, S. Jones, S. J. Martin, *Org. Biomol. Chem.* **2009**, *7*, 229–231; w) S. Guizzetti, M. Benaglia, F. Cozzi, S. Rossi, G. Celentano, *Chirality* **2009**, *21*, 233–238; x) F.-M. Gautier, S. Jones, X. Li, S. J. Martin, *Org. Biomol. Chem.* **2011**, *9*, 7860–7868; for structural and mechanistic studies, see: y) Z. Zhang, P. Rooshenas, H. Hausmann, P. R. Schreiner, *Synthesis* **2009**, 1531–1544. Also see: z) S. Ortial, R. Dave, Z. Benfodda, D. Bénimélis, P. Meffre, *Synlett* **2014**, 569–573.

[5] A review on organocatalytic asymmetric reductive aminations and reduction of imines using benzothiazolines as reducing agents: a) C. Zhu, K. Saito, M. Yamanaka, T. Akiyama, *Acc. Chem. Res.* **2015**, *48*, 388–398; for a theoretical study, see: b) Y. Shibata, M. Yamanaka, *J. Org. Chem.* **2013**, *78*, 3731–3736.

[6] Asymmetric reductions of imines using catecholborane: D. Enders, A. Rembiak, M. Seppelt, *Tetrahedron Lett.* **2013**, *54*, 470–473.

[7] a) G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta* **2008**, *41*, 31–39; for pioneering studies on the use of chiral phosphoric acid catalysts, see: b) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; *Angew. Chem.* **2004**, *116*, 1592–1594; c) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357; comprehensive reviews on asymmetric Brønsted acid catalysis: d) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010; e) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395–456; f) M. Terada, *Synthesis* **2010**, 1929–1982; g) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603–614.

[8] a) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074–13075; b) V. N. Wakchaure, J. Zhou, S. Hoffmann, B. List, *Angew. Chem. Int. Ed.* **2010**, *49*, 4612–4614; *Angew. Chem.* **2010**, *122*, 4716–4718.

[9] Selected examples of metal-catalyzed and organocatalytic hydrosilylation of *N*-alkyl imines: a) X. Verdaguer, U. E. W. Lange, M. T. Reding, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 6784–6785; b) C. Wang, X. Wu, L. Zhou, J. Sun, *Chem. Eur. J.* **2008**, *14*, 8789–8792; c) S. Guizzetti, M. Benaglia, G. Celentano, *Eur. J. Org. Chem.* **2009**, 3683–3687; d) C. Wang, X. Wu, L. Zhou, J. Sun, *Org. Biomol. Chem.* **2015**, *13*, 577–582.

[10] Selected examples of metal-catalyzed asymmetric hydrogenations of *N*-alkyl imines: a) A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 4003–4009; b) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem. Int. Ed.* **2009**, *48*, 5345–5349; *Angew. Chem.* **2009**, *121*, 5449–5453; c) F. Chen, T. Wang, Y. He, Z. Ding, Z. Li, L. Xu, Q.-H. Fan, *Chem. Eur. J.* **2011**, *17*, 1109–1113; d) F. Chen, Z. Ding, Y. He, J. Qin, T. Wang, Q.-H. Fan, *Tetrahedron* **2012**, *68*, 5248–5257.

[11] Recent articles on asymmetric catalysis with disulfonimides: a) M. van Gemmeren, F. Lay, B. List, *Aldrichimica Acta* **2014**, *47*, 3–13; for selected applications, see: b) P. García-García, F. Lay, P. García-García, C. Rabalakos, B. List, *Angew. Chem. Int. Ed.*

2009, *48*, 4363 – 4366; *Angew. Chem.* **2009**, *121*, 4427 – 4430; c) L. Ratjen, P. García-García, F. Lay, M. E. Beck, B. List, *Angew. Chem. Int. Ed.* **2011**, *50*, 754 – 758; *Angew. Chem.* **2011**, *123*, 780 – 784; d) J. Guin, C. Rabalakos, B. List, *Angew. Chem. Int. Ed.* **2012**, *51*, 8859 – 8863; *Angew. Chem.* **2012**, *124*, 8989 – 8993; e) M. Mahlau, P. García-García, B. List, *Chem. Eur. J.* **2012**, *18*, 16283 – 16287; f) S. Gandhi, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 2573 – 2576; *Angew. Chem.* **2013**, *125*, 2633 – 2636; g) Q. Wang, M. Leutzsch, M. van Gemmeren, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 15334 – 15337; h) Q. Wang, M. van Gemmeren, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 13592 – 13595; *Angew. Chem.* **2014**, *126*, 13810 – 13813; i) J. Guin, Q. Wang, M. van Gemmeren, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 355 – 358; *Angew. Chem.* **2015**, *127*, 362 – 365; j) Q. Wang, B. List, *Synlett* **2015**, 807 – 809; k) Q. Wang, B. List, *Synlett* **2015**, 1525 – 1527.

[12] The asymmetric Torgov cyclization: a) S. Prévost, N. Dupré, M. Leutzsch, Q. Wang, V. Wakchaure, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 8770 – 8773; *Angew. Chem.* **2014**, *126*, 8915 – 8918; For other examples, see: b) H. He, L.-Y. Chen, W.-Y. Wong, W.-H. Chan, A. W. M. Lee, *Eur. J. Org. Chem.* **2010**, 4181 – 4184; c) L.-Y. Chen, H. He, W.-H. Chan, A. W. M. Lee, *J. Org. Chem.* **2011**, *76*, 7141 – 7147; d) M. Treskow, J. Neudörfl, R. Giernoth, *Eur. J. Org. Chem.* **2009**, 3693 – 3697.

[13] a) K. B. Hansen, T. Rosner, M. Kubryk, P. G. Dormer, J. D. Armstrong, *Org. Lett.* **2005**, *7*, 4935 – 4938; b) F. Chen, Z. Ding, J. Qin, T. Wang, Y. He, Q.-H. Fan, *Org. Lett.* **2011**, *13*, 4348 – 4351; c) N. Mittal, D. X. Sun, D. Seidel, *Org. Lett.* **2014**, *16*, 1012 – 1015.

[14] a) P.-C. Yan, G.-L. Zhu, J.-H. Xie, X.-D. Zhang, Q.-L. Zhou, Y.-Q. Li, W.-H. Shen, D.-Q. Che, *Org. Process Res. Dev.* **2013**, *17*, 307 – 312, and references therein; b) C. M. Spencer, S. Noble, *Drugs Aging* **1998**, *13*, 391 – 411.

[15] R. Rao, M. P. Shewalkar, R. Nandipati, J. S. Yadav, M. Khagga, D. B. Shinde, *Synth. Commun.* **2012**, *42*, 589 – 598, and references therein.

[16] A review of the pharmacological and clinical properties: R. Bayer, R. Mannhold, *Pharmatherapeutica* **1987**, *5*, 103 – 136.

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