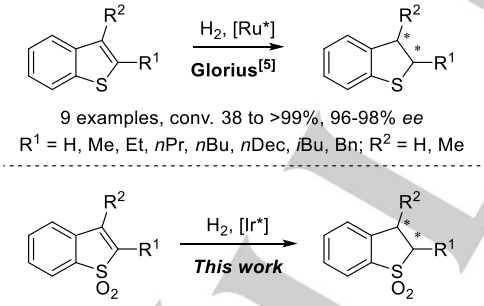
Iridium-catalyzed asymmetric hydrogenation of benzo[*b*]thiophene 1,1-dioxides

Paolo Tosatti, and Andreas Pfaltz*[a]

Abstract: An efficient iridium-catalyzed asymmetric hydrogenation of substituted benzothiophene 1,1-dioxides is described. The use of iridium complexes with chiral pyridyl phosphinite ligands provides access to highly enantiomerically enriched sulfones with substituents at the 2- and 3-position. Sulfones of this type are of interest as core structures of agrochemicals and pharmaceuticals. Moreover, they can be further reduced to access chiral 2,3-dihydrobenzothiophenes.

The asymmetric hydrogenation of heteroaromatic compounds is an attractive straightforward method for the synthesis of chiral heterocyclic compounds starting from readily available precursors that has recently received much attention.[1] Despite substantial progress in this area, efficient enantioselective catalysts for heteroarmatic substrates are still scarce.

During the last decade, several highly enantioselective hydrogenation methods for indoles[1,2] and benzofuranes[1,3] have been reported. However, related benzothiophenes have been rarely investigated as substrates. Only recently, the group of Glorius has reported an efficient chiral Ru-catalyst[4] for the enantioselective reduction of thiophenes and benzothiophenes[5] among other heteroaromatic compounds[1f] (Scheme 1). Although this work marks a breakthrough, the substrate scope is rather limited, especially in the case of benzothiophenes, as only primary alkyl substituents at either the 2- or the 3-position are tolerated.



Scheme 1. Enantioselective reduction of benzothiophenes and proposed asymmetric hydrogenation of benzothiophene 1,1-dioxides.

[a] Dr. Paolo Tosatti, Prof. Dr. Andreas Pfaltz
Department of Chemistry
University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)
Fax: (+41) 061-267-1103
E-mail: andreas.pfaltz@unibas.ch

Supporting information for this article is given via a link at the end of the document.

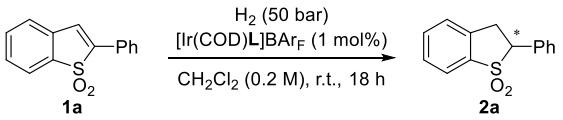
Subsequent to our studies of Ir N,P complexes as catalysts for the asymmetric hydrogenation of furans and benzofurans,[3b] we investigated benzothiophenes as substrates but without success. Consequently, we decided to study benzothiophene 1,1-dioxides as surrogates that could be converted to chiral 2,3-dihydrobenzothiophenes by reduction of the sulfone group. We reasoned that the reduced aromatic character and the absence of sulfur lone pairs, which could inhibit the catalyst by coordination, would facilitate hydrogenation. Moreover, Andersson *et al.* had demonstrated that unsaturated sulfones are suitable substrates for Ir-catalyzed asymmetric hydrogenation.[6] In addition, chiral 2,3-dihydrobenzothiophene 1,1-dioxides have found interest in agro and medicinal chemistry as herbicides, insecticides,[7] and inhibitors of the hypoxia-inducible factor HIF2α.[8]

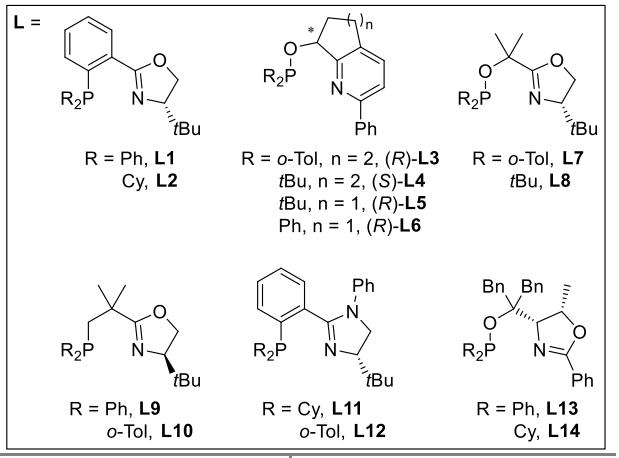
For initial studies we chose 2-phenylbenzothiophene 1,1-dioxide **1a** as test substrate for the screening of a series of Ir catalysts developed in our group (Table 1).[9] Under a H_2 atmosphere of 50 bar, most catalysts gave only moderate to low conversion with the exception of Ir complexes based on ligands **L5**, **L12** and **L14** (entries 5, 12 and 14). N,P-ligands with alkyl-substituted phosphine or phosphinite units showed higher activity than their aryl-substituted analogues (*cf.* entries 1, 3, 5 and 13 *vs.* 2, 4, 6 and 14 respectively). Pleasingly, the most active catalyst [Ir(COD)**L5**]BAr_F also induced the highest enantioselectivity, affording **2a** in 97% *ee* (entry 5).

With a promising catalyst in hand, we briefly tested six analogues of ligand **L5** with different substituents on the phosphorus atom (Cy, *t*-Bu) and the pyridine ring (H, Me, Ph). Both the presence of a di-*tert*-butyl phosphinite unit and a phenyl group on the pyridine ring proved to be essential to achieve high conversion and enantioselectivity (see Supporting Information). Lowering the hydrogen pressure from 50 to 10 bar reduced the conversion from 97% to 90% with no apparent effect on the enantioselectivity. Therefore, the original conditions specified in Table 1 were chosen for further studies using a variety of 2- and 3-arylbenzothiophene 1,1-dioxides as substrates (Table 2).

First substrate **1a** was compared with *para*-, *meta*-, and *ortho*-tolyl analogues. A *p*-Me group (substrate **1b**) had only marginal effects on conversion (97 *vs.* 95%) and enantioselectivity (97 *vs.* 98% *ee*), whereas a *m*-Me group (**1c**) slowed down the reaction significantly. However, at higher catalyst loading (2 mol%) full conversion and 97% *ee* were achieved. The *o*-Me derivative **1d**, on the other hand, gave only low conversion even with 2 mol% of catalyst, although the enantioselectivity remained high. Apparently the reaction is rather sensitive to steric hindrance in the 2-position. Both the *para*-fluoro and *para*-methoxy derivatives **1e** and **1f** reacted with high enantioselectivity. Compared to **1a**, the electron-withdrawing fluorophenyl group in **1e** lowered the reactivity while the opposite effect was observed for the *para*-methoxyphenyl derivative **1f**.

Table 1. Catalyst screening for the asymmetric hydrogenation of benzothiophene 1,1-dioxide **1a**.





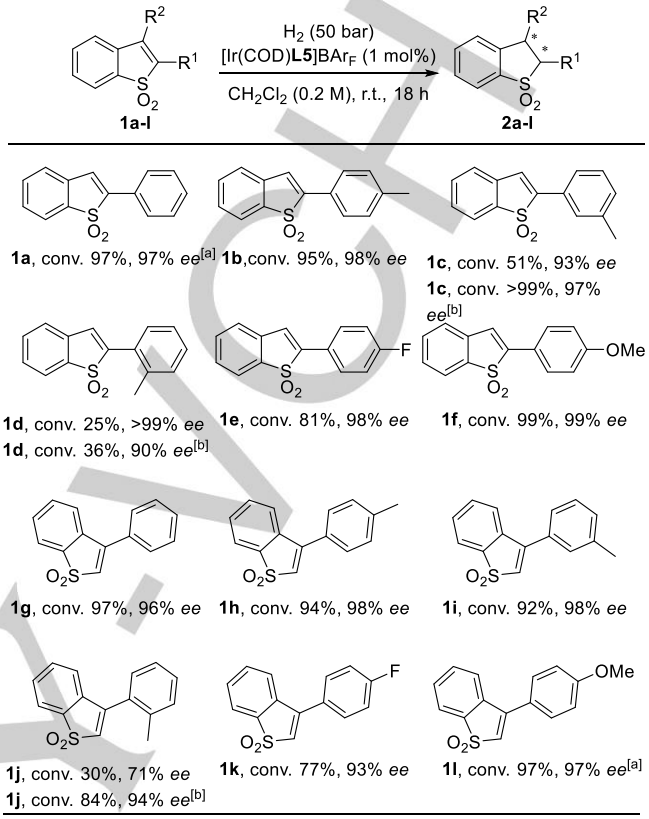
Entry	L	Conv. [%][a]	*ee* [%][b]	Entry	L	Conv. [%][a]	*ee* [%][b]
1	**L1**	45	32	8	**L8**	60	6
2	**L2**	70	24	9	**L9**	23	38
3	**L3**	29	74	10	**L10**	32	32
4	**L4**	68	24	11	**L11**	66	35
5	**L5**	97	97	12	**L12**	>99	54
6	**L6**	31	83	13	**L13**	29	42
7	**L7**	69	74	14	**L14**	90	91

BAr_F = (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; COD = 1,5-cyclooctadiene; [a] Determined by GC analysis (see the supporting information for details); [b] Determined by HPLC analysis.

The same catalyst [Ir(COD)**L5**]BAr_F also performed well in the asymmetric hydrogenation of analogous 3-aryl-substituted substrates. Benzothiophene 1,1-dioxides **1g** and **1h** reacted with high levels of conversion and enantioselectivity comparable to the 2-substituted isomers **1a** and **1b**. However, the increased steric hindrance of *meta*- and *ortho*-tolyl substituents seemed to have a less dramatic effect for 3-aryl benzothiophene 1,1-dioxides. In fact, compound **1i** reacted smoothly in the presence of 1 mol% of catalyst, affording **2i** with 92% conversion and 98% *ee*. Even compound **1j**, bearing an *o*-tolyl substituent at the 3-position, was reduced with 84% conversion and 94% *ee*, although in this case an increased catalyst loading (2 mol%) was necessary. Again, the electron-poor substrate **1k** gave lower conversion than the electron-rich analogue **1l** and also somewhat lower *ee*.

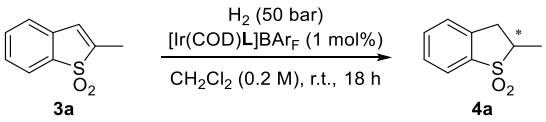
To examine the reactivity of alkyl-substituted substrates, 2-methylbenzothiophene 1,1-dioxide **3a** was hydrogenated under standard conditions used for substrates **1a-l** (Table 3). Although high conversion to **4a** (97%) was achieved, the level of enantioselectivity induced by the catalyst based on ligand **L5** was disappointing (entry 5). Consequently, screening of several other iridium complexes was carried out to identify a more selective catalyst for alkyl-substituted substrates (Table 3). Whilst most catalysts reduced **3a** with poor conversion and enantioselectivity, [Ir(COD)**L14**]BAr_F displayed high reactivity affording product **4a** with 99% conversion but poor enantioselectivity (entry 14). Surprisingly, the Ir-complex based on ligand **L4**, differing from **L5** only in the size of the carbocycle condensed to the pyridine ring, turned out to be the most active and selective catalyst, giving full conversion and 92% *ee* (entry 4). Further optimization of the reaction conditions (see the Supporting Information) revealed that for substrate **3a** full conversion and slightly higher stereoselectivity (93% *ee*) could be achieved in only 1 h at 2 bar H_2 pressure. In addition, variation of the substituents on ligand **L4** showed that both *tert*-butyl groups on the phosphorus atom and a phenyl group flanking the pyridine nitrogen atom are essential to get good results, paralleling the observations made earlier with **L5** (see the Supporting Information).

Table 2. Investigation of the substrate scope.



Reactions run on a 33 µmol scale. Conversions determined by GC analysis. *Ee*s determined by HPLC analysis. [a] (*S*) absolute configuration determined by single crystal X-ray analysis;[10] [b] 2 mol% of [Ir(COD)**L5**]BAr_F were used.

Table 3. Catalyst screening for the asymmetric hydrogenation of benzothiophene 1,1-dioxide **3a**.



3a **4a**

Entry	L	Conv. [%][a]	*ee* [%][b]	Entry	L	Conv. [%][a]	*ee* [%][b]
1	**L1**	9	13	8	**L8**	14	4
2	**L2**	20	28	9	**L9**	10	20
3	**L3**	25	17	10	**L10**	16	46
4	**L4**	>99[c]	93 (*S*)[d]	11	**L11**	25	2
5	**L5**	97	5	12	**L12**	58	3
6	**L6**	9	36	13	**L13**	9	37
7	**L7**	3	11	14	**L14**	99	42

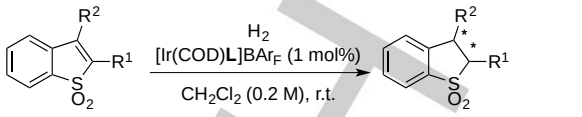
[a] Determined by GC analysis; [b] Determined by HPLC analysis; [c] Reaction also scaled up to 0.55 mmol scale (isolated yield 99%); [d] (*S*) absolute configuration according to the optical rotation of **5a** (see Scheme 2).

The results of further studies with a series of 2- and 3-alkyl-substituted benzothiophene 1,1-dioxides using [Ir(COD)**L4**]BAr_F as catalyst are shown in Table 4. Replacement of the methyl substituent in substrate **3a** by an ethyl group led to a decrease of reactivity and *ee*. Longer reaction times were necessary to reduce **3b** with 95% conversion, affording product **4b** with 84% *ee*. Lower temperatures resulted in drastically lower reactivity without affecting the enantioselectivity (see the Supporting Information). An *n*-propyl or benzyl group at the 2-position further reduced the enantioselectivity. For the benzyl-substituted substrate **3d** more forcing conditions had to be used (10 bar H_2 for 8 h) to attain **4d** in >90% conversion. The more sterically hindered 2-isopropyl derivative **3e** showed even lower reactivity and gave only 50% *ee*. Higher enantioselectivity was achieved with the catalyst derived from ligand **L5**.

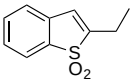
When substrate **3e** was hydrogenated using 2 mol% of [Ir(COD)**L5**]BAr_F under 50 bar hydrogen pressure, 75% conversion was achieved after 24 h with an *ee* of 84%. Notably, substrate **3f**, containing a protected alcohol functionality, displayed exceptionally high reactivity, being fully reduced within one hour under 2 bar of H_2, however, with only moderate enantioselectivity. Finally, we examined the 3-methyl-substituted benzothiophene 1,1-dioxide **3g**. Although this substrate proved far less reactive than the 2-methyl isomer **3a**, it was fully converted to product **4g** within 4 h under 50 bar H_2 with high enantiomeric excess of 93% *ee*.

To demonstrate the synthetic value of the hydrogenation products, we studied the reduction of selected chiral 2,3-dihdrobenzothiophene 1,1-dioxides to the corresponding 2,3-dihydrobenzothiophenes (Scheme 2). Using an excess of $LiAlH_4$ in THF, reactions proceeded smoothly in high yield with negligible or no loss of enantiomeric purity, thus providing access to highly enantiomerically enriched 2- and 3-substituted 2,3-dihydrobenzothiophenes **5a** and **5g**. Moreover, the acidity of the proton next to the SO_2 group allows the introduction of an additional substituent in the 2-position. As example we converted 3-methyl-2,3-dihydrobenzothiophene dioxide **5g** to the *trans*-2,3-dimethyl derivative **6** in high yield with a *dr* of 81:19 by deprotonation with *n*BuLi and subsequent methylation with dimethyl sulfate. In this way 2,3-disubstituted dihydrobenzothiophenes are accessible, which cannot be prepared by asymmetric hydrogenation because of the lack of reactivity of tetrasubstituted C=C bonds.

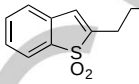
Table 4. Substrate scope of the asymmetric hydrogenation.



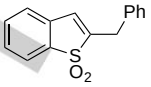
3b-g **4b-g**



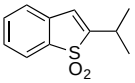
3b, conv. 95%, 84% *ee* (**L4**, 2 bar H_2, 2 h)



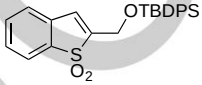
3c, conv. 94%, 74% *ee* (**L4**, 2 bar H_2, 2 h)



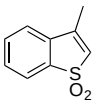
3d, conv. 93%, 69% *ee* (**L4**, 10 bar H_2, 8 h)



3e, conv. 22%, 50% *ee* (**L4**, 10 bar H_2, 1 h)
3e, conv. 18%, 86% *ee* (**L5**, 10 bar H_2, 1 h)
3e, conv. 22%, 86% *ee* (**L5**, 10 bar H_2, 8 h)
3e, conv. 75%, 84% *ee*[a] (**L5**, 50 bar H_2, 24 h)

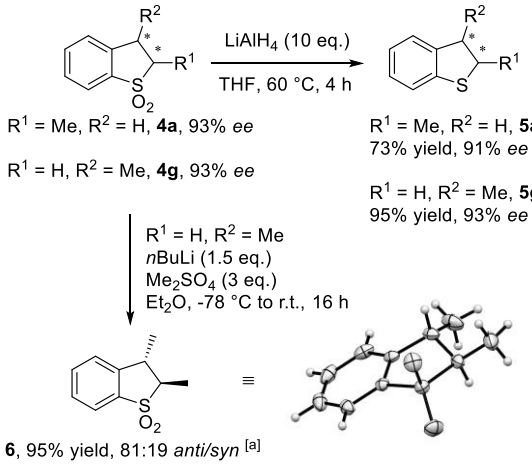


3f, conv. >99%, 71% *ee* (**L4**, 2 bar H_2, 1 h)



3g, conv. 84%, 93% *ee* (**L4**, 10 bar H_2, 4 h)
3g, conv. >99%, 93% *ee*[b,c] (**L4**, 50 bar H_2, 4 h)

Reactions run on a 33 µmol scale. Conversions determined by GC analysis. *Ee*s determined by HPLC analysis on a chiral stationary phase (see the supporting information for details); [a] 2 mol% of [Ir(COD)**L5**]BAr_F were used; [b] Reaction also scaled up to 1.63 mmol scale (99% yield of isolated product, 93% *ee*); [c] (*S*) absolute configuration determined by single crystal X-ray analysis.[10]



Scheme 2. Conversion of 2,3-dihydrobenzothiophene 1,1-dioxides into 2,3-dihydrobenzothiophenes, diastereoselective methylation of compound **4g**, and ORTEP view of (2*R*,3*S*)-**6**.[10] [a] The *dr* was determined by GC analysis of the crude reaction mixture.

In summary, we have identified two chiral Ir N,P-ligand complexes that enable the enantioselective hydrogenation of benzothiophene 1,1-dioxides. Excellent enantioselectivities and high yields were obtained for substrates bearing an aromatic substituent at either the 2- or the 3- position of the heterocyclic scaffold. Analogous alkyl-substituted derivatives proved to be more demanding substrates giving less consistent results (69-93% *ee*; 75-100% conversion). Subsequent reduction of the sulfone group gives access to highly enantiomerically enriched dihydrothiophenes. In this way 2- and 3-aryl-dihydro-benzothiophenes can be prepared that are not available by direct asymmetric hydrogenation of benzothiophenes as described by Glorius *et al.*,[5] because their method is not applicable to aryl substituted derivatives.

Acknowledgements

Financial support from the Swiss National Science Foundation is gratefully acknowledged. We thank Dr. Marcus Neuburger (University of Basel) for crystal structure analyses.

Keywords: Iridium • Asymmetric catalysis • N,P-ligands • Hydrogenation • Heterocyclic compounds

[1] Selected recent reviews: a) Z. Yu, W. Jin, Q. Jiang, *Angew. Chem. Int. Ed.* **2012**, 51, 6060–6072; *Angew. Chem.* **2012**, *124*, 6164–6177; b) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590; c) Y.-M. He, F.-T. Song, Q.-H. Fan, *Top. Curr. Chem.* **2014**, *343*, 145–190; d) V. Ratovelomanana-Vidal, P. Phansavath, T. Ayad, M. R. Vitale in *Comprehensive Organic Synthesis (2nd Ed.)*, *Vol. 8* (Eds. P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, pp. 741–793; e) T.J. Donohoe, C.R. Jones, C. Winter in *Comprehensive Organic Synthesis (2nd Ed.), Vol. 8* (Eds. P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, pp. 794–837; f) D. Zhao, L. Candish, D. Paul, F. Glorius, *ACS Catal.* **2016**, *6*, 5978–5988; g) Z.-P. Chen, Y.-G. Zhou, *Synthesis* **2016**, *48*, 1769–1781.

[2] Selected recent examples: a) A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 2036–2039; b) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909–8911; c) D.-S. Wang, J. Tang, Y.-G. Zhou, M.-W. Chen, C.-B. Yu, Y. Duan, G.-F. Jiang, *Chem. Sci.* **2011**, *2*, 803–806; d) C. Li, J. Chen, G. Fu, D. Liu, Y. Liu, W. Zhang, *Tetrahedron* **2013**, *69*, 6839–6844; e) Y. Duan, L. Li, M.-W. Chen, C.-B. Yu, H.-J. Fan, Y.-G. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 7688–7700; f) T. Touge, T. Arai, *J. Am. Chem. Soc.*, **2016**, *138*, 11299–11305; g) Z. Yang, F. Chen, Y. He, N. Yang, Q.-H. Fan, *Angew. Chem. Int. Ed.* **2016**, *55*, 13863–13866; *Angew.Chem.* **2016**, *128*,14067–14070.

[3] Selected recent examples: a) N. Ortega, S. Urban, B. Beiring, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 1710–1713; *Angew. Chem.* **2012**, *124*, 1742–1745; b) L. Pauli, R. Tannert, R. Scheil, A. Pfaltz, *Chem. Eur. J.* **2015**, *21*, 1482–1487.

[4] For an overview see D. Paul, B. Beiring, M. Plois, N. Ortega, S. Kock, D. Schlüns, J. Neugebauer, R. Wolf, F. Glorius, *Organometallics* **2016**, *35*, 3641–3646 and references therein.

[5] S. Urban, B. Beiring, N. Ortega, D. Paul, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 15241–15244.

[6] a) T. Zhou, B. Peters, M. F. Maldonado, T. Govender, P. G. Andersson, *J. Am. Chem. Soc.* **2012**, *134*, 13592–13595; b) B. K. Peters, T. Zhou, J. Rujirawanich, A. Cadu, T. Singh, W. Rabten, S. Kerdphon, P. G. Andersson, *J. Am. Chem. Soc.* **2014**, *136*, 16557–16562.

[7] a) H. Rempfler, A. Edmunds, A. De Mesmaeker, K. Seckinger (Novartis AG), WO 9909023, **1999**; c) M. Saitou, H. Sekiguchi, S. Ogawa (Idemitsu Kosan Co., Ltd.), WO 2000069853, **2000**; d) M. Saitou, H. Sekiguchi, S. Ogawa (Idemitsu Kosan Co., Ltd.), WO 2000020408, **2000**; e) R. G. Hall, O. Loiseleur, J. Pabba, S. Pal, A. Jeanguenat, A. Edmunds, A. Stoller (Syngenta AG), WO 2009010260, **2009**; f) A. Edmunds; M. Mühlebach; A. Stoller; O. Loiseleur; A. Buchholz; O. F. Hueter; A. Bigot; R. G. Hall; D. Emery; P. J. M. Jung; L. Lu; Y. Wu; R. Chen (Syngenta AG), WO 2015000715, **2015**.

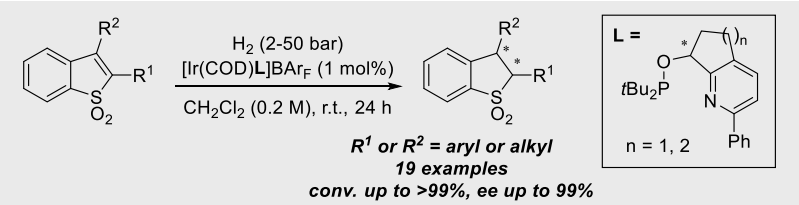
[8] a) D. D. Dixon, J. Grina, J. A. Josey, J. P. Rizzi, S. T. Schlachter, E. M. Wallace, B. Wang, P. When, R. Xu, H. Yang (Peloton Therapeutics, Inc.), WO 2015095048, **2015**; b) P. Wehn, H. Yang (Peloton Therapeutics, Inc.), US 20160362390, **2016**.

[9] a) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402–1411; b) D. H. Woodmansee, A. Pfaltz, *Chem. Commun.* **2011**, *47*, 7912–7916.

[10] CCDC-928151 (**2a**), CCDC-928152 (**2l**), CCDC-928153 (**4g**) and CCDC-928154 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Entry for the Table of Contents

COMMUNICATION



*Paolo Tosatti, Andreas Pfaltz**

Page No. – Page No.

Iridium-catalyzed asymmetric hydrogenation of benzo[*b*]thiophene 1,1-dioxides

Ir-catalyzed asymmetric hydrogenation of benzothiophene 1,1-dioxides gives access to highly enantiomerically enriched sulfones with substituents at the 2- and 3-position. Sulfones of this type are of interest as core structures of agrochemicals and pharmaceuticals. Moreover, they can be further reduced to provide chiral 2,3-dihydrobenzothiophenes.