



CrossMark
click for updates

Cite this: *Chem. Sci.*, 2014, 5, 4216

Received 30th June 2014
Accepted 21st July 2014

DOI: 10.1039/c4sc01940g

www.rsc.org/chemicalscience

Asymmetric synthesis of *N,O*-heterocycles via enantioselective iridium-catalysed intramolecular allylic amidation†

Depeng Zhao, Martín Fañanás-Mastral, Mu-Chieh Chang, Edwin Otten and Ben L. Feringa*

Chiral *N,O*-heterocycles were synthesized in high yields and excellent enantioselectivity up to 97% ee via iridium-catalysed intramolecular allylic substitution with nucleophilic attack by the amide oxygen atom. The resulting benzoxazine derivatives were further transformed into challenging chiral *N,O*-ketals bearing both a tertiary and a quaternary center with excellent diastereoselectivities.

Introduction

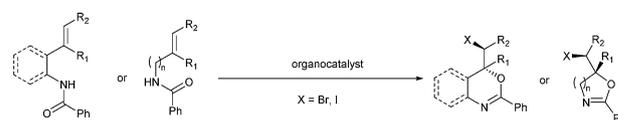
Chiral *N,O*-heterocycles are important structural motifs found in a variety of natural products which exhibit significant biological activities including anti-tumor, antifungal and antibacterial properties.¹ Among these heterocycles, oxazolines, oxazines, benzoxazines and their derivatives are of particular importance. Efavirenz (Sustiva), which features a 4*H*-3,1-benzoxazin-2-one core, is a non-nucleoside reverse transcriptase inhibitor and is used for the treatment of human immunodeficiency virus (HIV) type 1.² 4*H*-3,1-benzoxazin-4-one derivatives are able to inhibit C1r serine protease.^{2b} Furthermore, *N,O*-heterocycles play a prominent role in asymmetric synthesis as they are core structures of several chiral ligands used in asymmetric catalysis.³ The preparation of this class of heterocycles and their derivatives usually relies on the use of chiral amino alcohols.^{2,4} However, direct catalytic asymmetric syntheses of these chiral heterocycles remain challenging. As far as we know, it was not until very recently that the first catalytic methods were reported, which are all based on asymmetric halocyclization of amides (Scheme 1a).⁵ In order to expand chiral space in heterocyclic chemistry, the development of complementary asymmetric routes to *N,O*-heterocycles with diverse functional groups is highly desirable.

Asymmetric allylic substitution (AAS) represents a powerful transformation for the assembly of congested chiral architectures.⁶ In particular, Ir-catalysed AAS features high reactivity and allows stereoselective construction of chiral branched

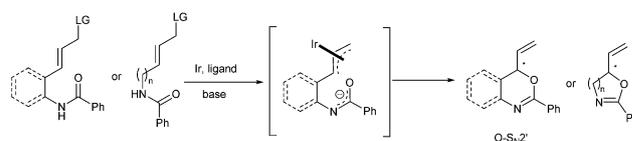
allylic compounds.⁷ Since the pioneering work of Helmchen⁸ and Hartwig,⁹ several iridium-catalysed asymmetric allylic substitution reactions with phosphoramidites¹⁰ as chiral ligands have been developed. To date, a variety of nucleophiles including C-,¹¹ N-,¹² O-¹³ and S-nucleophiles¹⁴ have been used in this type of reaction. We recently developed the first intramolecular Ir-catalysed asymmetric allylic amidation.¹⁵ Through nucleophilic attack by the amide nitrogen atom, chiral tetrahydroisoquinolines and saturated *N*-heterocycles could be obtained with high enantioselectivities. However, to the best of our knowledge, transition metal-catalysed asymmetric allylic substitution with nucleophilic attack by the amide oxygen atom is unprecedented.¹⁶

In view of our continuing interest in developing new catalytic methodologies for the construction of chiral heterocycles,¹⁷ we decided to study the asymmetric synthesis of *N,O*-heterocyclic derivatives. We envisioned that reversing the selectivity of the ambidentate amide nucleophile in the iridium-catalysed intramolecular AAS could provide a versatile method to access chiral oxazolines, oxazines and benzoxazines (Scheme 1b). Herein, we

a) Asymmetric halocyclization (ref 5)



b) This work: Ir-catalyzed AAS



Scheme 1 Protocols for catalytic asymmetric synthesis of *N,O*-heterocycles.

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands. E-mail: b.l.feringa@rug.nl; Web: <http://www.benferinga.com>; Fax: +31 50 363 4278; Tel: +31 50 3634296

† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. CCDC 957090 and 957091. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4sc01940g



Table 1 Screening of ligands

L1 Ar = Ph
 L2 Ar = 2-MeO-C₆H₄
 L3 Ar = 1-naphthyl
 L4 (S,R,R)
 L5 (S,R,R)
 L6 (S,S)
 L7 (S,S)
 L8 (S,R,R)

Entry ^a	Ligand	T (°C)	Time (h)	Conv. ^b (%)	ee ^{c,e} (%)
1	L1	50	14	90	-31
2	L2	50	14	90	-57
3	L3	50	14	75	-53
4	L4	50	14	21	-7
5	L5	50	14	80	-1
6	L6	50	14	>95	27
7 ^d	L2	RT	16	40	-79
8	L7	50	14	>95	88
9	L7	RT	40	>95	95
10	L8	RT	40	>95	91

^a Reaction conditions: 5 mol % [Ir(cod)Cl]₂, 10 mol % of ligand, 0.2 mmol of **1a**, 0.2 mmol of base in 2.0 mL THF (0.1 M) unless otherwise noted. ^b Determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis. ^d Reaction was performed with 4.0 mL THF (0.05 M). ^e Negative value indicates that opposite enantiomer was obtained. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

report the successful realization of this catalytic transformation *i.e.* iridium-catalysed intramolecular allylic substitution with nucleophilic attack by the amide oxygen atom. The resulting *N,O*-heterocyclic derivatives can be readily obtained in high yields and excellent enantioselectivities (up to 97% ee).

Results and discussion

Our preliminary studies started with the intramolecular reaction of 2-benzamido cinnamyl carbonate **1a** with 5 mol% of [Ir(cod)Cl]₂ in the presence of 10 mol% of phosphoramidite **L1** at 50 °C. We were pleased to find that the anticipated reaction proceeded smoothly to provide the benzoxazine product **2a** with 31% ee, without formation of any S_N2 by-products resulting from attack by either *N* or *O* atoms (Table 1, entry 1).

Encouraged by this result, we examined a series of related phosphoramidite ligands **L2–L6** (Table 1, entries 2–6). It turned out that the reaction with **L2** (ref. 18) at RT led to a promising

increase in ee, however, only modest conversion was achieved (entry 7, 79% ee). It has been reported that in allylic substitution with the iridium catalysts derived from commonly used ligands **L1** and **L2**, *ortho*-substituted cinnamyl substrates in general are not tolerated, with much decreased enantioselectivities observed in many cases.^{9a,11h,13d,19} The use of tetrahydroquino-line-derived phosphoramidite ligand **L7** gave rise to full conversion and furnished the cyclization product with 88% ee at 50 °C and 95% ee at RT (entries 8, 9). Related ligand **L8**, which features an additional stereogenic center and was reported to give good results in AAS of cinnamyl substrates,²⁰ provided a slightly lower ee in the present transformation (entry 10). It should be noted that the active catalyst generated from **L1** or **L2** features an Ir–C(sp³) bond in accordance with the structure shown by Hartwig,⁹ while the active catalyst derived from **L7** or **L8**, introduced by You's group, incorporates an Ir–C(sp²) bond instead.²⁰

With a highly selective catalyst based on ligand **L7** in hand, we further optimized the reaction conditions (Table 2). Evaluation of several bases indicated that the reaction was slower with inorganic bases such as Cs₂CO₃ and K₂CO₃, probably due to poor solubility (Table 2, entries 2 and 3), whereas the use of DABCO as a base led to a slightly higher ee (97% ee vs. 95% ee) and a similar reaction rate as compared with DBU (entries 1 and 4). With DABCO as the optimal base, the reaction was then performed with 2.5 mol% of [Ir(cod)Cl]₂ at room temperature (entry 5). However, the reaction turned out to be very slow and did not reach full conversion under these conditions. Gratifyingly, when the reaction was performed at 35 °C with 5 mol% (2.5 mol% of [Ir(cod)Cl]₂) catalyst, the ee was not affected and the reaction was complete when 3 equiv. of DABCO were used

Table 2 Optimization of base and reaction conditions

Entry ^a	[Ir(cod)Cl] ₂ (mol%)	T (°C)	Base (equiv.)	Time (h)	Conv. ^b (%)	ee ^c (%)
1	5%	RT	DBU (1)	40	>95	95
2	5%	RT	Cs ₂ CO ₃ (1)	40	75	94
3	5%	RT	K ₂ CO ₃ (1)	40	87	96
4	5%	RT	DABCO (1)	40	>95	97
5	2.5%	RT	DABCO (1)	24	31	ND
6	2.5%	35	DABCO (1)	48	90	96
7	2.5%	35	DABCO (3)	48	>95	97
8	2.5%	50	DABCO (3)	24	>95 (81) ^d	97
9	2.5%	50	DBU (3)	24	>95	89

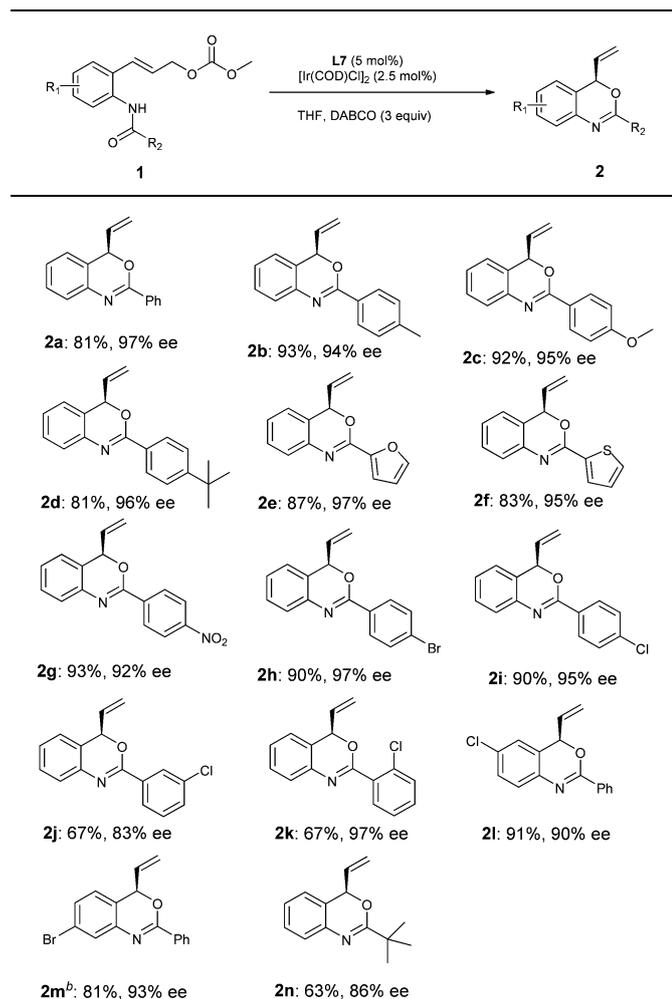
^a Reaction was performed on a 0.2 mmol scale in 2.0 mL THF. ^b Determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis. ^d Value in parenthesis is the yield of isolated **2a**. DABCO = 1,4-diazabicyclo[2.2.2]octane. ND = Not determined.



(Table 2, entries 6 and 7). Importantly, the enantioselectivity could be maintained and the reaction was completed in a shorter time when carried out at 50 °C (Table 2, entry 8, 81% yield, 97% ee). As shown in Table 2, the enantioselectivity and reaction rate can both be enhanced with additional equivalents of DABCO. It seems that this catalytic conversion tolerates higher temperature when DABCO is used as the base. In contrast, the use of DBU as the base under the same conditions led to **2a** with only 89% ee (Table 2, entry 9).

Under the optimized reaction conditions (Table 2, entry 8), we explored the substrate scope of this new catalytic allylic cyclization (Table 3). High tolerance for substituents at the *para*-position of the benzamide aryl group was observed, irrespective of the electronic and steric properties (Table 3, **2b–2d** and **2g–2i**). Substrates **1j** and **1k** with substituents at the *meta*- and *ortho*-position of the benzamide aryl group were also tested,

Table 3 Ir-catalysed synthesis of chiral benzoxazines **2a–n**^a

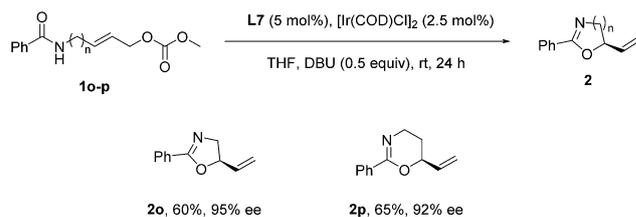


^a Reaction conditions: 2.5 mol % [Ir(cod)Cl]₂, 5.0 mol % of ligand, 0.2 mmol of **1**, 0.6 mmol DABCO in 2.0 mL THF at 50 °C for 24 h. Yields of isolated products after column chromatography; enantiomeric excess determined by HPLC or GC analysis (see the ESI†). ^b The absolute configuration of **2m** was determined as *R* by X-ray crystallographic analysis (Fig. 1).²¹

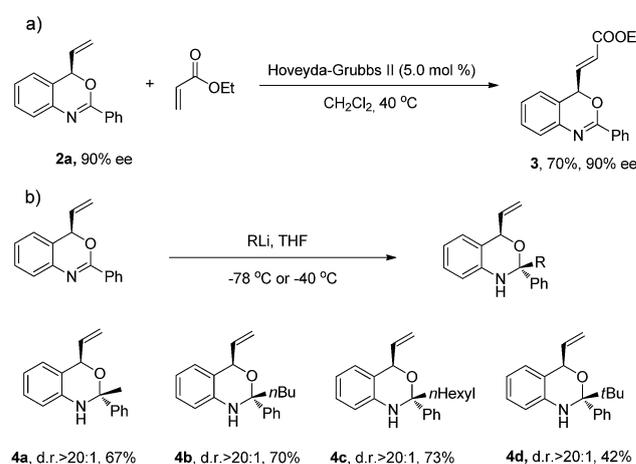
and it was shown that **2j** with *meta*-Cl gave a reduced ee, while *ortho*-Cl substituted substrate **1k** provided **2k** with 97% ee. Heteroarylamides **1e** and **1f** were also suitable substrates for the present cyclization reaction. Benzoxazine **2n** with a *t*-butyl substituent at the 2-position could be obtained under standard reaction conditions in 63% yield and 86% ee. Notably, substrates **1l** and **1m** with substituents at the C4 and C5 position of the cinnamyl carbonate gave the desired products **2l** and **2m** in good yields and enantioselectivities.

To further demonstrate the versatility of the reaction, we examined some aliphatic substrates to provide the corresponding chiral oxazoline and oxazine. Under the optimized reaction conditions for the enantioselective synthesis of benzoxazines **2**, the reaction of aliphatic substrates **1o** and **1p** gave rise to a complex mixture of products. However, through a slight modification of the reaction conditions, *i.e.* running the reaction at room temperature and using DBU (0.5 equiv.) as the base instead of DABCO, the corresponding chiral oxazoline **2o** and oxazine **2p** were obtained with excellent ee (Scheme 2).

In order to evaluate the synthetic applicability of this new catalytic method, a number of transformations of the benzoxazine products were carried out (Scheme 3). The allylation products of this transformation feature a terminal double bond which allows for further functionalization. As an example, the vinyl moiety of **2a** underwent cross-metathesis with ethyl acrylate in the presence of the Grubbs–Hoveyda II catalyst without compromising the enantiomeric excess of product **3**.



Scheme 2 Ir-catalysed synthesis of chiral oxazoline **2o** and oxazine **2p**.



Scheme 3 Transformations of benzoxazine **2a**.



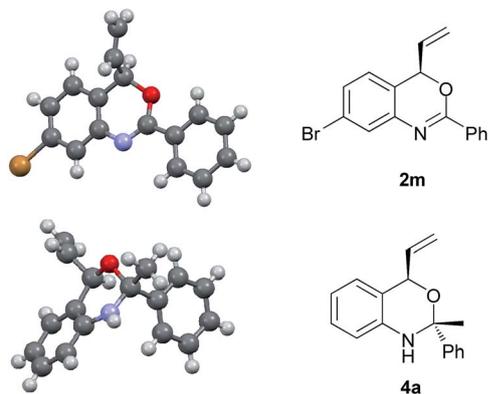
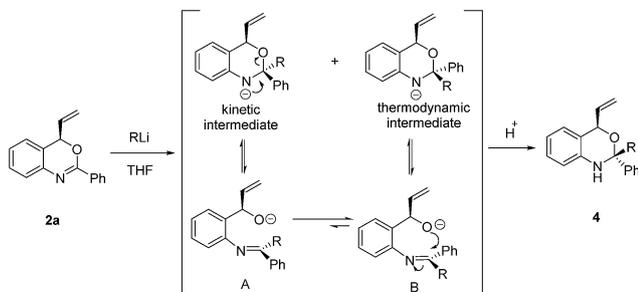


Fig. 1 X-ray crystal structures of **2m** and **4a**.



Scheme 4 Proposed mechanism for the addition of organolithium reagents to benzoxazines.

In view of the synthetic challenges to prepare chiral hemiaminals,²² we also explored the 1,2-addition of organolithium reagents to chiral benzoxazine **2a**.²³ As shown in Scheme 3, a series of linear and branched organolithium reagents were successfully employed, furnishing the chiral *N,O*-ketals **4a–4d** bearing both a tertiary and a quaternary stereogenic center with excellent diastereoselectivities. The relative configurations of **4a** and **4d** were determined by NOESY studies.²⁴ Surprisingly, the X-ray analysis of **4a** (ref. 21) confirmed that the methyl group is installed *cis* to the vinyl group (Fig. 1). It is expected that under kinetic control, the alkyl nucleophile would prefer to attack from the opposite side of the vinyl group due to steric hindrance.^{23,25} While the detailed mechanism is as yet unclear, on the basis of control experiments,²⁶ we propose that there is an equilibrium between the closed acetal form and open imine form of the product formed in the reaction (Scheme 4). Through the ring opening and subsequent closing, the kinetically favored intermediate epimerizes *in situ* to the thermodynamically more stable intermediate, although alternative pathways cannot be excluded.

Conclusions

In conclusion, we have developed the first enantioselective iridium-catalyzed intramolecular allylic substitution reaction with nucleophilic attack by the amide oxygen atom. A series of *N,O*-heterocycles, *i.e.*, oxazolines, oxazines and benzoxazine

derivatives, could be readily obtained with high enantioselectivities. Furthermore, the resulting benzoxazine derivatives were transformed into chiral *N,O*-ketals bearing tertiary and quaternary centers with excellent diastereoselectivities. This methodology offers excellent opportunities to explore the “3rd dimension” in common planar *N,O*-heterocycles.

Acknowledgements

The Netherlands Organization for Scientific Research (NWO-CW), the National Research School of Catalysis (NRSC-C), the European Research Council (ERC advanced grant 227897 to BLF), the Royal Netherlands Academy of Arts and Sciences (KNAW) and the Ministry of Education Culture and Science (Gravity program 024.601035) are acknowledged for financial support.

Notes and references

- (a) G. Pattenden, *J. Heterocycl. Chem.*, 1992, **29**, 607; (b) E. J. Corey, B. Czako and L. Kürti, *Molecules and Medicine*, Wiley, Hoboken, 2007; (c) *Comprehensive Heterocyclic Chemistry III*, Ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, 2008, vol. 4 and 8.
- (a) N. Chinkov, A. Warm and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2011, **50**, 2957; (b) S. J. Hays, B. W. Caprathe, J. L. Gilmore, N. Amin, M. R. Emmerling, W. Michael, R. Nadimpalli, R. Nath, K. J. Raser, D. Stafford, D. Watson, K. Wang and J. C. Jaen, *J. Med. Chem.*, 1998, **41**, 1060.
- (a) G. Helmchen and A. Pfaltz, *Acc. Chem. Res.*, 2000, **33**, 336; (b) A. Pfaltz and W. J. Drury III, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5723; (c) G. Desimoni, G. Faita and K. A. Jørgensen, *Chem. Rev.*, 2006, **106**, 3561; (d) G. C. Hargaden and P. J. Guiry, *Chem. Rev.*, 2009, **109**, 2505.
- A. Solladié-Cavallo, P. Lupattelli, C. Bonini, V. Ostuni and N. D. Blasio, *J. Org. Chem.*, 2006, **71**, 9891.
- (a) V. Rauniyar, A. D. Lackner, G. L. Hamilton and F. D. Toste, *Science*, 2011, **334**, 1681; (b) Y.-M. Wang, J. Wu, C. Hoong, V. Rauniyar and F. D. Toste, *J. Am. Chem. Soc.*, 2012, **134**, 12928; (c) A. Jaganathan, A. Garzan, D. C. Whitehead, R. J. Staples and B. Borhan, *Angew. Chem., Int. Ed.*, 2011, **50**, 2593; (d) Q. Yin and S.-L. You, *Org. Lett.*, 2013, **15**, 4266.
- (a) *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*, Ed. U. Kazmaier, Springer, 2012; (b) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; (c) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 258; (d) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (e) S. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824.
- For recent reviews, see: (a) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies and R. Weihofen, *Chem. Commun.*, 2007, 675; (b) G. Helmchen, in *Iridium Complexes in Organic Synthesis*, Ed. OroL. A. and ClaverC., Wiley-VCH, Weinheim, 2009, p. 211; (c) J. F. Hartwig and M. J. Pouy, *Top. Organomet. Chem.*, 2011, **34**, 169; (d) P. Tosatti,



- A. Nelson and S. P. Marsden, *Org. Biomol. Chem.*, 2012, **10**, 3147; (e) W.-B. Liu, J.-B. Xia and S.-L. You, *Top. Organomet. Chem.*, 2012, **38**, 155.
- 8 (a) J. P. Janssen and G. Helmchen, *Tetrahedron Lett.*, 1997, **38**, 8025; (b) B. Bartels and G. Helmchen, *Chem. Commun.*, 1999, 741; (c) B. Bartels, C. García-Yebra and G. Helmchen, *Eur. J. Org. Chem.*, 2003, 1097.
- 9 (a) T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 15164; (b) C. A. Kiener, C. T. Shu, C. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 14272; (c) D. Marković and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 11680; (d) S. T. Madrahimov, D. Marković and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 7228.
- 10 For reviews, see: (a) J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486; (b) B. L. Feringa, *Acc. Chem. Res.*, 2000, **33**, 346.
- 11 For selected examples, see: (a) J. Y. Hamilton, D. Sarlah and E. M. Carreira, *J. Am. Chem. Soc.*, 2013, **135**, 994; (b) J. Y. Hamilton, D. Sarlah and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2013, **52**, 7532; (c) G. Lipowsky, N. Miller and G. Helmchen, *Angew. Chem., Int. Ed.*, 2004, **43**, 4595; (d) S. Streiff, C. Welter, M. Schelwies, G. Lipowsky, N. Miller and G. Helmchen, *Chem. Commun.*, 2005, 2957; (e) T. Graening and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 17192; (f) D. J. Weix and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 7720; (g) Q.-F. Wu, H. He, W.-B. Liu and S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 11418; (h) W.-B. Liu, H. He, L.-X. Dai and S.-L. You, *Org. Lett.*, 2008, **10**, 11815; (i) C.-X. Zhuo, Q.-F. Wu, Q. Zhao, Q.-L. Xu and S.-L. You, *J. Am. Chem. Soc.*, 2013, **135**, 8169; (j) A. Alexakis, S. E. Hajjaji, D. Polet and X. Rathgeb, *Org. Lett.*, 2007, **9**, 3393; (k) D. Polet, X. Rathgeb, C. A. Falciola, J.-B. Langlois, S. E. Hajjaji and A. Alexakis, *Chem.-Eur. J.*, 2009, **15**, 1205; (l) S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, *Science*, 2013, **340**, 1065.
- 12 For selected examples, see: (a) M. Lafrance, M. Roggen and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2012, **51**, 3470; (b) C. Shu, A. Leitner and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2004, **43**, 4797; (c) M. J. Pouy, L. M. Stanley and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 11312; (d) S. Spiess, C. Welter, G. Franck, J.-P. Taquet and G. Helmchen, *Angew. Chem., Int. Ed.*, 2008, **47**, 7652; (e) R. Weihofen, O. Tverskoy and G. Helmchen, *Angew. Chem., Int. Ed.*, 2006, **45**, 5546; (f) O. V. Singh and H. Han, *J. Am. Chem. Soc.*, 2007, **129**, 774.
- 13 For selected examples, see: (a) C. Fischer, C. Defieber, T. Suzuki and E. M. Carreira, *J. Am. Chem. Soc.*, 2004, **126**, 1628; (b) L. M. Stanley, C. Bai, M. Ueda and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 8918; (c) C. Shu and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2004, **43**, 4794; (d) F. Lopez, T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 3426; (e) I. Lyothier, C. Defieber and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2006, **45**, 6204; (f) D. Kim, J. S. Lee, S. B. Kong and H. Han, *Angew. Chem., Int. Ed.*, 2013, **52**, 4203.
- 14 For selected examples, see: (a) M. Ueda and J. F. Hartwig, *Org. Lett.*, 2010, **12**, 92; (b) Q. L. Xu, L. X. Dai and S.-L. You, *Org. Lett.*, 2010, **12**, 800; (c) Q. L. Xu, W. B. Liu, L. X. Dai and S.-L. You, *J. Org. Chem.*, 2010, **75**, 4615.
- 15 J. F. Teichert, M. Fañanás-Mastral and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2011, **50**, 688.
- 16 For examples of intramolecular oxazine formation employing chiral allylic substrates, see: (a) J. E. Joo, K. Y. Lee, V. T. Pham, Y. S. Tian and W. H. Ham, *Org. Lett.*, 2007, **9**, 3627; (b) Y. Mu, T. Jin, G. W. Kim, J. S. Kim, S. S. Kim, Y. S. Tian, C. Y. Oh and W. H. Ham, *Eur. J. Org. Chem.*, 2012, 2614; (c) V. T. Pham, J. E. Joo, K. Y. Lee, T. W. Kim, Y. Mu and W. H. Ham, *Tetrahedron*, 2010, **66**, 2123.
- 17 For selected examples, see: (a) A. Rudolph, P. H. Bos, A. Meetsma, A. J. Minnaard and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2011, **50**, 5834; (b) J. F. Teichert, S. Zhang, A. W. van Zijl, J. W. Slaa, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2010, **12**, 4658; (c) B. Mao, Y. Ji, M. Fañanás-Mastral, G. Caroli, A. Meetsma and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2012, **51**, 3168; (d) B. Mao, K. Geurts, M. Fañanás-Mastral, A. W. van Zijl, S. P. Fletcher, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2011, **13**, 948; (e) B. Mao, M. Fañanás-Mastral, M. Lutz and B. L. Feringa, *Chem.-Eur. J.*, 2013, **19**, 761.
- 18 K. Tissot-Croset, D. Polet and A. Alexakis, *Angew. Chem., Int. Ed.*, 2004, **43**, 2426.
- 19 (a) A. Alexakis and D. Polet, *Org. Lett.*, 2004, **6**, 3529; (b) D. Polet, A. Alexakis, K. Tissot-Croset, C. Corminboeuf and K. Ditrich, *Chem.-Eur. J.*, 2006, **12**, 3596; (c) Y. Yamashita, A. Gopalathnam and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 7508; (d) L. M. Stanley and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 8971.
- 20 W.-B. Liu, C. Zheng, C.-X. Zhuo, L.-X. Dai and S.-L. You, *J. Am. Chem. Soc.*, 2012, **134**, 4812.
- 21 CCDC 957090 (**4a**) and 957091 (**2m**) contain the supplementary crystallographic data for this paper.
- 22 (a) M. Miyashita, M. Sasaki, I. Hattori, M. Sakai and K. Tanino, *Science*, 2004, **305**, 495; (b) Y. Takahashi, F. Yoshimura, K. Tanino and M. Miyashita, *Angew. Chem., Int. Ed.*, 2009, **48**, 8905; (c) J. Kim and M. Movassaghi, *J. Am. Chem. Soc.*, 2010, **132**, 14376.
- 23 For transformations of benzoxazines, see: R. R. Schmidt and B. Beitzke, *Chem. Ber.*, 1983, **116**, 2115.
- 24 For details, see the ESI.†
- 25 B. H. Lipshutz, J. A. Kozlowski and R. S. Wilhelm, *J. Org. Chem.*, 1983, **48**, 546.
- 26 When the reaction of **2a** was performed with 3 equiv. of MeLi at RT, formation of compound **5** was observed. This might proceed *via* attack of MeLi on the open imine structure.

