



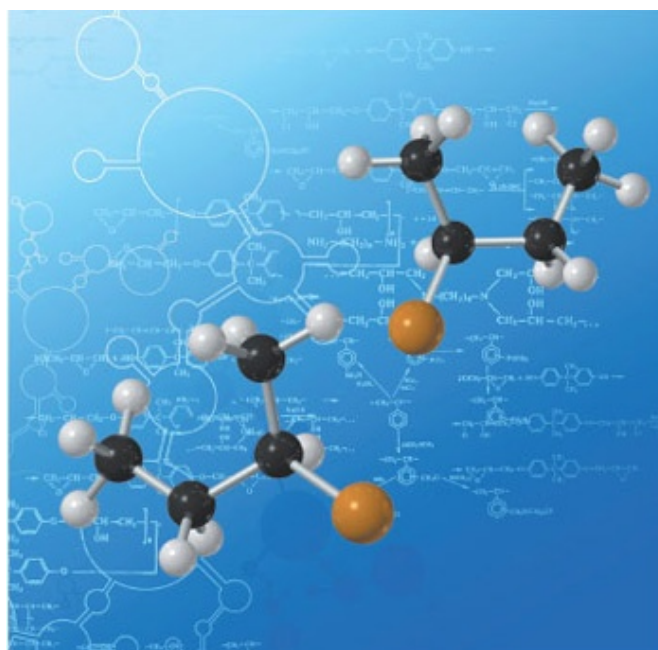
This article is part of the

Organocatalysis

web themed issue

Guest editors: Professors Keiji Maruoka, Hisashi Yamamoto, Liu-Zhu Gong and Benjamin List

All articles in this issue will be gathered together online at
www.rsc.org/organocatalysis



Catalyst development for organocatalytic hydrosilylation of aromatic ketones and ketimines†‡§

 Andrei V. Malkov,^{*a,b} Angus J. P. Stewart-Liddon,^a Grant D. McGeoch,^a Pedro Ramírez-López^{¶a} and Pavel Kočovský^{**a}

Received 4th March 2012, Accepted 24th April 2012

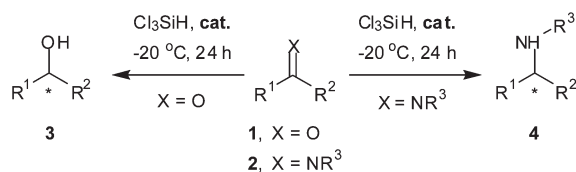
DOI: 10.1039/c2ob25472g

A new family of Lewis basic 2-pyridyl oxazolines have been developed, which can act as efficient organocatalysts for the enantioselective reduction of prochiral aromatic ketones and ketimines with trichlorosilane, a readily available and inexpensive reagent. 1-Isoquinolyl oxazoline, derived from mandelic acid, was identified as the most efficient catalyst of the series, capable of delivering high enantioselectivities in the reduction of both ketones (up to 94% ee) and ketimines (up to 89% ee).

Introduction

Asymmetric reduction of carbonyl and heterocarbonyl functionalities arguably belongs to the class of fundamental organic transformations. In the racemic realm, the reducing reagents, such as metal hydrides, are usually competent to reduce both ketones and ketimines.¹ However, the asymmetric methods that work well for ketones, are often considerably less efficient for ketimines, and *vice versa*.² There are only a limited number of catalytic systems that exhibit high selectivity with both compound classes, *e.g.*, a highly efficient Cu-catalysed hydrosilylation of ketones and ketimines developed by Lipshutz *et al.*³

Asymmetric reduction of ketones **1** and ketimines **2** with trichlorosilane, catalysed by chiral Lewis bases (Scheme 1),



Scheme 1

recently emerged as an efficient methodology⁴ capable of competing with the traditional, transition metal-mediated processes² and other organocatalytic methods.^{5,6} The field has witnessed an exponential growth in the last decade after Matsumura *et al.*⁷ had reported on useful enantioselectivities in the reduction of ketones (up to 43% ee) and ketimines (up to 66% ee), employing the proline-derived formamide **5b** as a chiral catalyst (Chart 1). Formamides **5–8**,^{8,9} picolinamides **9–11**,¹⁰ and sulfinamides **12** and **13**¹¹ represent the major catalyst types for the asymmetric reduction of ketimines with trichlorosilane (Chart 1). Of these, the commercially available valine-derived Kenamide **6a** and Sigamide **6b**, developed by us,⁸ are among the most versatile catalysts, delivering high enantioselectivity over a broad substrate range.

In a preliminary communication¹² we have reported on a novel design of organocatalysts based on the pyridyl-oxazoline core, such as **14** and **16**, which proved equally efficient in the reduction of aromatic ketones **1** and ketimines **2** (Scheme 1 and Chart 2). Later, Sun *et al.*^{9e} introduced catalyst **7c**, which also shared that ability. Herein, we present a full account of the development of pyridyl-oxazoline type catalysts **14–28** and reveal new applications.

Results and discussion

Catalyst design and synthesis

Design of our catalysts has its origin in the successful series of chelating nitrogen ligands containing pyridine and oxazoline fragments;^{13,14} their selection is shown in Chart 2. The oxazolines derived from pyridine (**14–21**), quinoline (**26**), and isoquinoline (**27**) were synthesised following the method described by Brunner and Obermann as follows (Scheme 2):¹⁵ 2-cyano pyridines **29a–e** were first converted into the corresponding imidates **30a–e** by the reaction with a catalytic quantity of sodium methoxide in methanol. Acid-catalysed cyclisation of the latter

^aDepartment of Chemistry, WestChem, Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, Scotland, UK. E-mail: pavelk@chem.gla.ac.uk

^bDepartment of Chemistry, Loughborough University, Leics.LE11 3TU, UK. E-mail: a.malkov@lboro.ac.uk

† This article is part of the joint ChemComm–Organic & Biomolecular Chemistry ‘Organocatalysis’ web themed issue.

‡ Dedicated to Professor Bruce H. Lipshutz on the occasion of his 60th birthday.

§ Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob25472g

¶ Current address: Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain.

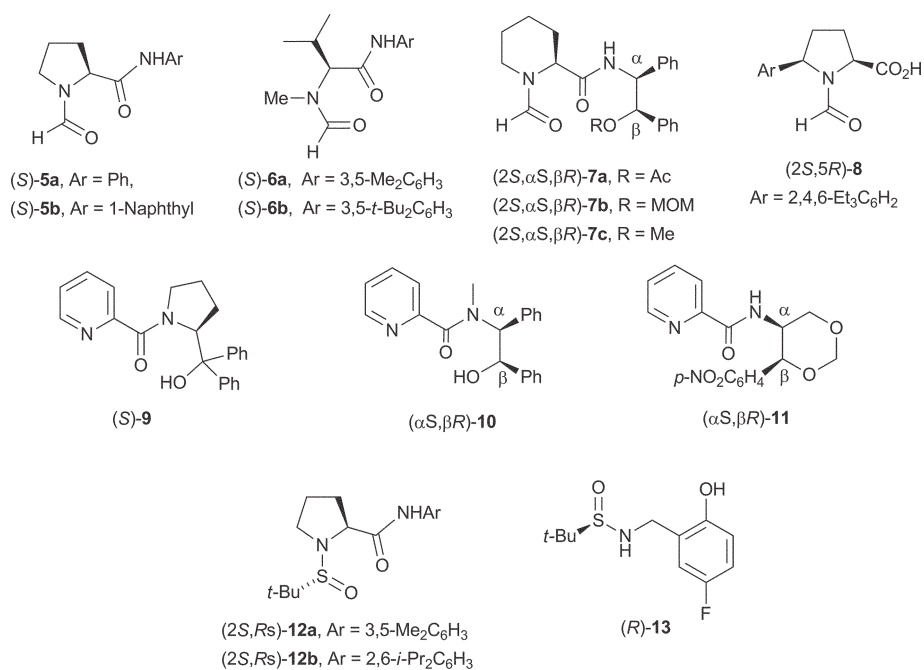


Chart 1 The most successful Lewis-basic organocatalysts for asymmetric reduction of ketimines with trichlorosilane.

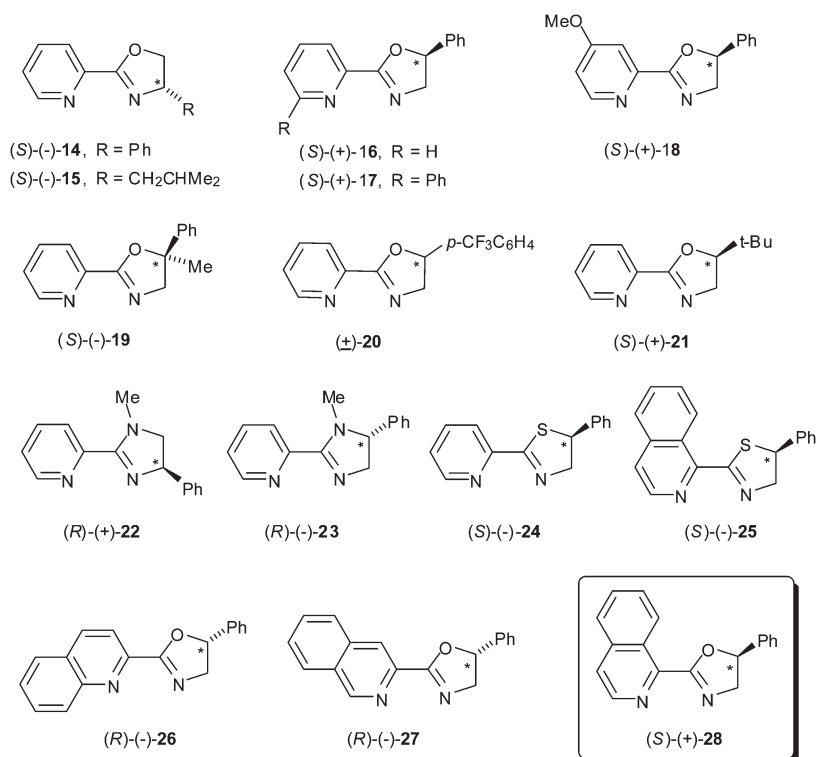
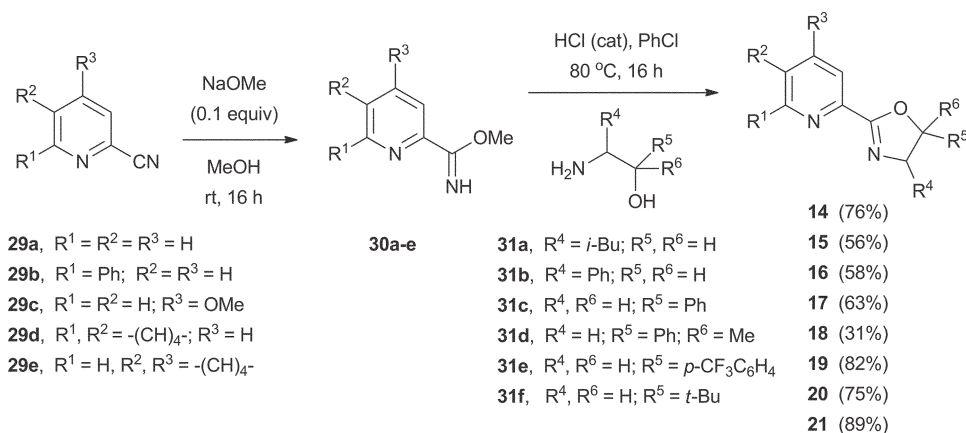
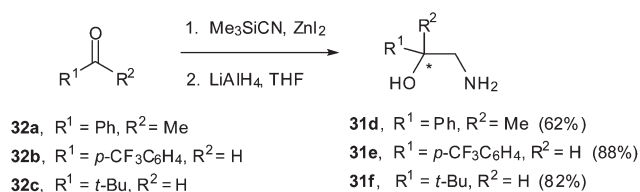


Chart 2 Pyridine-derived catalysts for asymmetric reduction of ketones and ketimines with trichlorosilane.

imidates **30a–e** with the appropriate amino alcohols **31a–f** afforded the desired oxazolines **14–21** in the yields ranging from 31% (**18**) to 89% (**21**). The preparation of **14–16**^{12,15} and **26**, **27**¹² was described earlier.

The reaction of chiral amino alcohols **31** with imidates **30** proceeds with retention of configuration at the stereogenic centre(s)

as both amino and hydroxy groups of the amino alcohol act as nucleophiles, with methanol and ammonia being displaced from the imidate. In order to drive the equilibrium towards the oxazoline product, the reaction was carried out at an elevated temperature with argon bubbling through the reaction mixture to remove methanol and ammonia from the system.

Scheme 2 For R¹–R⁶ in 19–21, see Chart 2.

Scheme 3

The requisite amino alcohols **31** were synthesised in our laboratory, except for the commercially available (*S*)-leucinol **31a** and (*S*)-phenylglycinol **31b**. Thus, (*S*)-**31c** and (*R*)-**31c** were prepared from the (*S*) and (*R*) enantiomers of mandelic acid, respectively, which were first converted to the enantiomeric amides, followed by reduction with LiAlH₄.¹² The synthesis of amino alcohols **31d–f** was accomplished in two steps *via* cyanation of the carbonyl compounds **32a–c**, followed by reduction of the resulting nitriles (Scheme 3). Under the optimised conditions, the zinc(II)-catalysed cyanosilylation¹⁶ of the carbonyl functionality was carried out in neat trimethylsilyl cyanide to give the trimethylsilyl protected cyanohydrins, which were then *in situ* reduced with LiAlH₄ to afford racemic amino alcohols **31d–f**.

Amino alcohol **31d** was resolved by co-crystallisation with (*S*)-(+)-mandelic acid from hot ethanol. After two crystallisations, (+)-**31d** was obtained in 92% ee, as revealed by chiral GC analysis. Resolution of the other amino alcohols was not attempted; however, the enantiomerically pure oxazoline **21** was obtained from a racemate by preparative chiral HPLC.

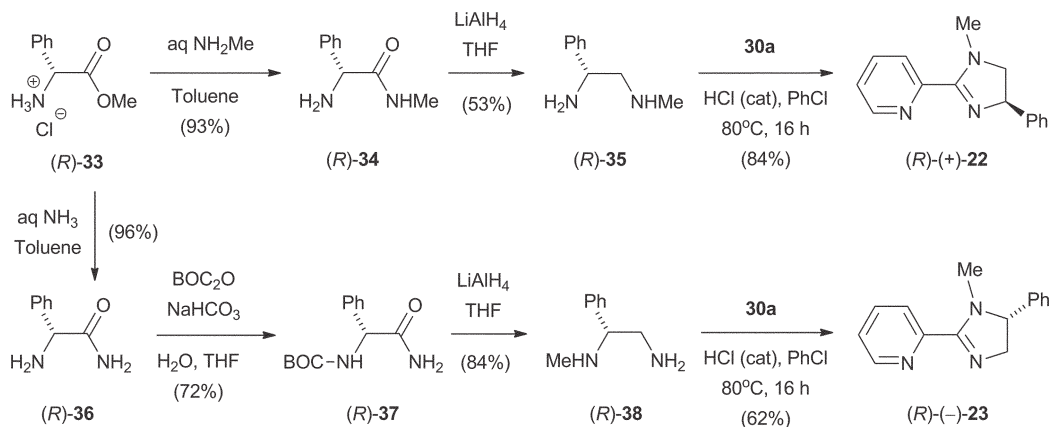
The synthesis of imidazolines (*R*)-**22** and (*R*)-**23** was achieved by the reaction of imidate **30a** and diamines (*R*)-**35** and (*R*)-**38**, respectively (Scheme 4). The latter diamines were synthesised from methyl phenylglycinate hydrochloride (*R*)-**33** as follows: the latter starting material was converted into diamine (*R*)-**35** in two steps by first forming amide (*R*)-**34** with *N*-methylamine, followed by reduction with lithium aluminium hydride. To obtain amine (*R*)-**38**, ester (*R*)-**33** was first converted into amide (*R*)-**36** on reaction with aqueous ammonia. Amide (*R*)-**36** was then treated with di-*tert*-butyl carbonate to give the Boc-derivative (*R*)-**37**, which was subsequently reduced with lithium aluminium hydride to afford diamine (*R*)-**38**.

For the synthesis of 1-isoquinolinoxazoline **28**, a different strategy was employed due to the high cost of 1-isoquinoline carbonitrile (Scheme 5). The preparation commenced with amidation of the commercially available 1-isoquinoline carboxylic acid **39** with mandelamine (*R*)-**31c** using the mixed anhydride method. The resulting amide (*R*)-**40** (89%) was then treated with mesyl chloride in the presence of triethylamine to effect cyclization, which proceeded with inversion of configuration at the stereogenic centre. The desired 1-isoquinoline oxazoline (*S*)-**28** was recrystallised from ethanol and isolated as a white solid in 95% yield.

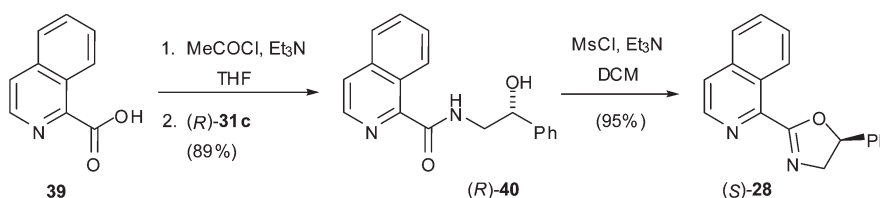
Synthetic sequences towards thiazolines **24** and **25** (as analogues of **16** and **28**), are shown in Scheme 6. The synthesis of pyridyl-thiazoline **24** began with the preparation of thioester **42** from 2-chloromethylpyridine **41** on reaction with sulfur, followed by treatment with methyl iodide.¹⁷ The resulting thioester **42** was then coupled with amino alcohol (*R*)-**31c** in THF in the presence of triethylamine to afford thioamide (*R*)-**43** (78%). Cyclization was then achieved by treating the latter thioamide with mesyl chloride, furnishing thiazoline (*S*)-**24** (82%). Hydroxy amide (*R*)-**40** was chosen as a starting material for the synthesis of catalyst (*S*)-**25**. First, thionation of the latter amide with Lawesson *et al.*'s reagent in HMPA¹⁸ was attempted but the conversion was very low and the desired thioamide could not be isolated from the crude reaction mixture. In a modified protocol, hydroxy amide (*R*)-**40** was first converted into the TBDMS ether (*R*)-**44**; subsequent treatment with the Lawesson's reagent in toluene at 85 °C overnight, followed by acidic work-up and flash chromatography, was successful and furnished thiazoline (*S*)-**25** in 78% yield. The latter thionation of **44** is accompanied by removal of the TBDMS protecting group and the resulting intermediate alcohol is then presumably derivatized by Lawesson's reagent,¹⁹ to generate a leaving group (*via* a P–O bond formation), followed by cyclisation to produce (*S*)-**25** with inversion of configuration.

Asymmetric reduction of ketones with trichlorosilane

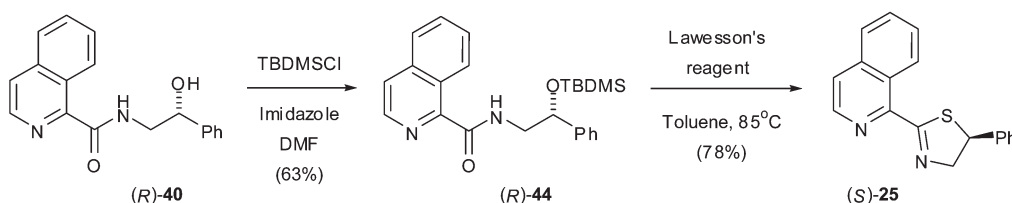
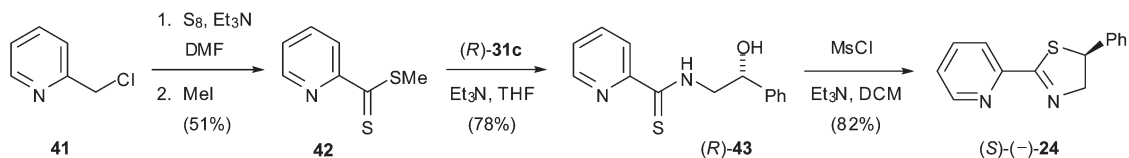
Our preliminary investigation focused on the reduction of aromatic ketones with trichlorosilane in the presence of 20 mol% of 2-pyridyl oxazolines (Table 1). Oxazolines (*S*)-**14** and (*S*)-**15**, derived from phenylglycine and leucine, respectively, exhibited



Scheme 4



Scheme 5



Scheme 6

modest conversion and enantioselectivity in the reduction of acetophenones **1a** at $-20\text{ }^{\circ}\text{C}$ in chloroform (entries 1 and 2). Interestingly, under the same conditions, the isomeric oxazoline (*S*)-**16**, derived from mandelic acid, and with the chiral centre further away from the (presumably) coordinating nitrogen, catalysed the formation of alcohol (*R*)-**3a** at a better conversion (85%) and with an improved enantiomeric excess (78% ee, entry 4). A brief investigation of the solvent effect revealed a minor decrease in enantioselectivity for dichloromethane compared to chloroform (*cf.* entries 7 and 4); in THF, further drop in ee was accompanied by low conversion (entry 8), whereas in acetonitrile and toluene both conversion and ee were negligible. The reaction temperatures of $-20\text{ }^{\circ}\text{C}$ or $-30\text{ }^{\circ}\text{C}$ appear to be optimal in terms of performance (entries 4 and 5) but $-20\text{ }^{\circ}\text{C}$ is preferred for operational convenience. An expected fall in enantioselectivity was observed at room temperature (entry 3). On the other hand,

decreasing the temperature to $-40\text{ }^{\circ}\text{C}$ had a detrimental effect on both the conversion and enantioselectivity (entry 6).

The influence of steric and electronic properties of the pyridine moiety on the catalyst efficiency was investigated with the aid of 2-pyridyl oxazolines **17** and **18**. It turned out that introduction of a phenyl substituent at the 6-position of the pyridine ring, as in **17**, rendered the catalyst completely inactive (entry 20), presumably as a result of increasing the steric hindrance in the vicinity of the anticipated coordination site. Increasing the Lewis basicity of the pyridine nitrogen by incorporating the electron-donating 4-methoxy substituent (**18**) did not improve the catalyst activity either (entry 21).

The initial screening identified 2-pyridyl oxazoline (*S*)-**16** as the best catalyst and CHCl_3 at $-20\text{ }^{\circ}\text{C}$ as the optimal reaction conditions. Next, the reaction scope was assessed by employing a range of ketones **1a–I** (Table 1). Propiophenone **1b** (entry 9)

Table 1 Reduction of ketones with trichlorosilane^a

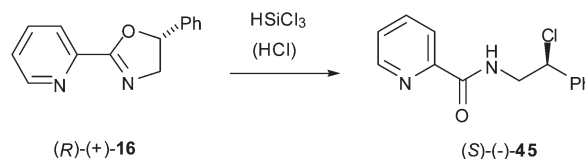
Reaction scheme: Ketone **1** (R¹-C(=O)-R²) reacts with Cl₃SiH, cat. in solvent at temperature T (°C) for 16 h to yield alcohol **3** (R¹-CH(OH)-R²).

Entry	Catalyst	Ketone	R ¹ , R ²	Solvent	Temp (°C)	Conversion ^a (%)	3 , ee (%)
1	(<i>S</i>)- 14	1a	Ph, Me	CHCl ₃	-20	29	66 (<i>S</i>)
2	(<i>S</i>)- 15	1a	Ph, Me	CHCl ₃	-20	34	54 (<i>S</i>)
3	(<i>S</i>)- 16	1a	Ph, Me	CH ₂ Cl ₂	rt	40	64 (<i>R</i>)
4	(<i>S</i>)- 16	1a	Ph, Me	CHCl ₃	-20	85	78 (<i>R</i>)
5	(<i>S</i>)- 16	1a	Ph, Me	CHCl ₃	-30	94	78 (<i>R</i>)
6	(<i>S</i>)- 16	1a	Ph, Me	CHCl ₃	-40	6	69 (<i>R</i>)
7	(<i>S</i>)- 16	1a	Ph, Me	CH ₂ Cl ₂	-20	83	74 (<i>R</i>)
8	(<i>S</i>)- 16	1a	Ph, Me	THF	-20	30	70 (<i>R</i>)
9	(<i>S</i>)- 16	1b	Ph, Et	CHCl ₃	-20	91	80 (<i>R</i>)
10	(<i>S</i>)- 16	1c	Ph, <i>i</i> -Pr	CH ₂ Cl ₂	-20	0	—
11	(<i>S</i>)- 16	1d	2-Naphthyl, Me	CHCl ₃	-20	99	80 (<i>R</i>)
12	(<i>S</i>)- 16	1e	6'-Me-Naphth-2-yl, Me	CHCl ₃	-20	99	83 (<i>R</i>)
13	(<i>S</i>)- 16	1f	4-Me-C ₆ H ₄ , Me	CHCl ₃	-20	96	80 (<i>R</i>)
14	(<i>S</i>)- 16	1g	2-MeO-C ₆ H ₄ , Me	CHCl ₃	-20	99	77 (<i>R</i>)
15	(<i>S</i>)- 16	1h	4-MeO-C ₆ H ₄ , Me	CH ₂ Cl ₂	-20	65	43 (<i>R</i>)
16	(<i>S</i>)- 16	1i	2-F-C ₆ H ₄ , Me	CHCl ₃	-20	30	70 (<i>R</i>)
17	(<i>S</i>)- 16	1j	2-Br-C ₆ H ₄ , Me	CH ₂ Cl ₂	-20	0	—
18	(<i>S</i>)- 16	1k	4-CF ₃ -C ₆ H ₄ , Me	CHCl ₃	-20	47	71 (<i>R</i>)
19	(<i>S</i>)- 16	1l	<i>c</i> -Hex, Me	CH ₂ Cl ₂	-20	67	0
20	(<i>S</i>)- 17	1a	Ph, Me	CH ₂ Cl ₂	0	0	—
21	(<i>S</i>)- 18	1a	Ph, Me	CH ₂ Cl ₂	0	10	25 (<i>R</i>)

^a The reactions were carried out at 0.4 mmol scale using 20 mol% catalyst loading. Conversion and ee's were determined by chiral GC.

reacted similarly to acetophenone **1a** (*cf.* entries 9 and 4) but the more sterically demanding isopropylphenyl ketone **1c** proved unreactive (entry 10). 2-Acetylnaphthalenes **1d** and **1e**, and 4-methylacetophenone **1f** were more reactive than **1a**, showing enantioselectivities around 80% ee (entries 11–13). Reduction of 4-methoxy acetophenone **1h** (entry 15) turned out to be less enantioselective (43% ee), which may stem from partial racemisation of the scalemic product under the reaction conditions or during the workup. This reaction was also accompanied by a notable formation of by-products. The latter effect, however, was not manifested in the case of the 2-methoxy isomer **1g** (entry 14), which gave the product of practically the same enantiopurity as **1a**. Electron-withdrawing substituents in **1i** and **1k** had a detrimental effect on the reaction rates and led to lower enantioselectivities (entries 16, 18). 2-Bromoacetophenone **1j**, which represents a combination of the unfavourable electronic and steric factors, was found to be completely inactive (entry 17). Finally, the non-aromatic ketone **1l** gave a racemic product (entry 19).

The encouraging level of enantioselectivities attained with catalyst **16** set the scene for further development. First, we focused on lowering the relatively high catalyst loading (20 mol%). Since we observed that the oxazoline moiety of (*R*)-**16** was undergoing a slow, chloride-promoted ring opening, giving rise to the chloro derivative (*S*)-**45** (Scheme 7), we initially focused on this problem. It can be assumed that in the reaction mixture the oxazoline ring is strongly activated towards nucleophilic attack either by protonation (originating from the HCl that is always present in Cl₃SiH as a contaminant) or by coordination of the Lewis-acidic silicon,²⁰ either of which could

**Scheme 7**

facilitate the undesired gradual ring-opening at the benzylic position.

In an attempt to discourage the chloride-promoted ring opening of the oxazoline moiety, 2-pyridyloxazolines **19–21** (Chart 2) were synthesised.²¹ The ring opening *via* an S_N2 mechanism should be blocked in **19**, although the susceptibility to S_N1 would be increased. Ring opening *via* S_N1 mechanism would be disfavoured in the case of **20**, where the electron-withdrawing trifluoromethyl group in the aryl ring should destabilise the carbocation intermediate. This does however increase the electrophilicity of the benzylic carbon and thus the likelihood of an S_N2 reaction. Finally, a neopentyl carbon centre, as in the *t*-butyl substituted oxazoline **21**, should disfavour the ring opening by either mechanism. However, neither of the new catalysts **19–21** (Table 2) turned out to be able to bring any advantage over the mandelic acid-derived **16** (compare entry 1 with entries 2–4). The drop in enantioselectivity for (*S*)-**19** is likely to originate in the steric hindrance introduced by the methyl to the bottom face of the catalyst. Only the oxazoline (*S*)-**21**, carrying a *t*-Bu group, performed comparably to **16** (entry 4). Anyway, in all three cases, the oxazoline moiety was found to undergo gradual decomposition.

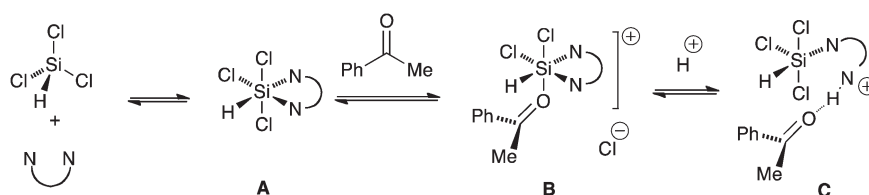
Next, we reasoned that replacing the oxazoline moiety with imidazoline or thiazoline fragments (**22–25**) would prevent the chloride-promoted ring-opening as the decreased electronegativity of nitrogen and sulfur should reduce the propensity for a nucleophilic attack at the benzylic position. Pyridine imidazolines (*R*)-**22** and (*R*)-**23** and thiazoline (*S*)-**24** can be viewed as analogues of 2-pyridyl oxazolines (*R*)-**14** and (*R*)-**16**, whereas thiazoline (*S*)-**25** represents an analogue with an extended aromatic system. However, catalysts **22–24** turned out to be considerably less reactive than the parent oxazoline **16** (Table 2, entries 5–7). Only thiazoline **24** showed acceptable enantioselectivity (entry 7), whereas imidazolines **22** and **23** produced much lower ee and the isoquinoline-derived oxazoline **25** was found to be inert (entry 8). Thus, although these new catalysts did not bring about any improvement in terms of activity, the imidazoline and thiazoline moieties proved to be stable (compared to the oxazolines), as no decomposition was observed under the reaction conditions.

The reactivity of ketones in the reduction with trichlorosilane catalysed by **16** displays a good correlation with their Brønsted basicity (pK_{HB}): 2-MeO-C₆H₄COMe (1.34) > PhCOMe (1.11) > 2-F-C₆H₄COMe (0.90).²² Assuming that this trend can be extrapolated to Lewis basicity, this behaviour suggests that, in the transition state, the carbonyl oxygen is either coordinated to the weakly Lewis acidic trichlorosilane or connected to the catalytically active species *via* hydrogen bonding (originating from the omnipresent traces of HCl).²³ A linear relationship observed between the enantiopurity of the catalyst and the product of the reduction of acetophenone **1a** with trichlorosilane catalysed by **16** indicates that only one molecule of the catalyst is actively participating in the enantiodiscriminating step.¹² Based on the available experimental data, we can tentatively suggest possible transition structures (Scheme 8): *N,N*-Chelation of trichlorosilane

Table 2 Reduction of **1a** with trichlorosilane catalysed by 5-substituted oxazolines^a

Entry	Catalyst	Solvent	Temp (°C)	Conversion ^a (%)	3 , ee (%)
1	(<i>S</i>)- 16	CH ₂ Cl ₂	–20	83	74 (<i>R</i>)
2	(<i>S</i>)- 19	CH ₂ Cl ₂	rt	63	34 (<i>R</i>)
3	(±)- 20 ^{b,c}	CHCl ₃	–20	72	—
4	(<i>S</i>)- 21 ^b	CH ₂ Cl ₂	–20	85	68 (<i>R</i>)
5	(<i>R</i>)- 22 ^b	CHCl ₃	–20	51	34 (<i>R</i>)
6	(<i>R</i>)- 23 ^b	CHCl ₃	–20	17	34 (<i>S</i>)
7	(<i>S</i>)- 24	CHCl ₃	–20	25 ^d	64 (<i>R</i>)
8	(<i>S</i>)- 25	CH ₂ Cl ₂	–20	0	—

^a The reactions were carried out at 1 mmol scale using 20 mol% catalyst loading. Conversion and ee's were determined by chiral GC. ^b 10 mol% catalyst loading. ^c Racemic catalyst. ^d Isolated yield.



Scheme 8

by the catalyst can be predicted to generate an activated hyper-valent species **A**, which then coordinates the carbonyl group upon replacement of a chloride atom to form **B**. Alternatively, the catalyst could act in a monodentate fashion, whereby the protonated second nitrogen serves as a hydrogen bond donor for the incoming ketone (**C**). The lack of enantioselectivity for non-aromatic ketones may also suggest a potential role of arene–arene interactions in the enantiodiscrimination event.²⁴ In the related Lewis base-catalysed addition of allyltrichlorosilanes to aromatic aldehydes, computational analysis indicated a substantial contribution of arene–arene interactions between the catalyst and the substrate to the stereochemical outcome of the process.²⁵ Therefore, quinoline (**26**) and isoquinoline (**27** and **28**) derivatives, featuring an extended π -system, were synthesised. The results of the catalytic reduction of ketones with trichlorosilane employing these catalysts are presented in Table 3.

No reduction was observed with quinoline (*R*)-**26** (Table 3, entry 1), presumably due to the steric constraints in the frontal part,²⁶ imposed by the quinoline moiety, mirroring the behaviour of the pyridine analogue **17** substituted at the 6-position (Table 1, entry 20). The 3-isoquinoline catalyst (*R*)-**27** was approximately as efficient as the parent pyridine catalyst **16** (Table 3, entry 2). A real improvement was attained with the 1-isoquinoline catalyst (*S*)-**28** (entries 3 and 4). The enhanced reactivity of 1-isoquinoline (*S*)-**28** allowed to reduce the catalyst loading to 10 mol% with no adverse effect on enantioselectivity (Table 3, entry 5). This trend was consistent across a range of aromatic ketones (entries 6–11) with the highest enantioselectivity of 94% ee attained for the reduction of 2-acetylnaphthalene **1d** (entry 7). Similarly to the results obtained with the pyridine analogue **16**, 2-fluoroacetophenone **1i** was reduced with lower selectivity (entry 11), whereas the aliphatic ketone **1l** afforded a racemic product (entry 12). Reduction of benzylidene acetone **1m** gave solely the product of 1,2-addition, albeit in low enantioselectivity (entry 13). Furthermore, the reaction was accompanied by dimerisation of the resulting alcohol to give a mixture of diastereoisomeric ethers **48** (entry 13). Formation of ethers **47**, though in smaller quantities, was also observed for the reduction of **1g** (entry 10).

Asymmetric reduction of ketimines with trichlorosilane

Significantly, 2-pyridyl oxazolines were also found to be active in the reduction of *N*-aryl ketimines.¹² Preliminary results demonstrated that the pyridine-derived catalyst **16** (Table 4, entry 1) promoted the reduction of ketimine **2a** derived from acetophenone with good yield and moderate enantioselectivity. The asymmetric induction was improved dramatically by employing the isoquinoline-derived catalyst (*S*)-**28**. The optimal

Table 3 Reduction of ketones **1** with trichlorosilane catalyzed by **25–28**^a

Entry	Catalyst (mol%)	Ketone	R ¹ , R ²	Yield ^b (%)	ee ^{c,d} (%)
1	(<i>R</i>)- 26 (20)	1a	Ph, Me	0 ^e	—
2	(<i>R</i>)- 27 (20)	1a	Ph, Me	41 ^e	73
3	(<i>S</i>)- 28 (20)	1a	Ph, Me	80 ^e	76
4	(<i>S</i>)- 28 (20)	1a	Ph, Me	72	84
5	(<i>S</i>)- 28 (10)	1a	Ph, Me	85	84
6	(<i>S</i>)- 28 (10)	1b	Ph, Et	55	86
7	(<i>S</i>)- 28 (10)	1d	2-Naphth, Me	93	94
8	(<i>S</i>)- 28 (10)	1e	6-Me-2-Naphth, Me	93	92
9	(<i>S</i>)- 28 (10)	1f	4-Me-C ₆ H ₄ , Me	90	85
10	(<i>S</i>)- 28 (10)	1g	2-MeO-C ₆ H ₄ , Me	50 ^f	87
11	(<i>S</i>)- 28 (10)	1i	2-F-C ₆ H ₄ , Me	35	70
12	(<i>S</i>)- 28 (10)	1l	Cyclohexyl, Me	77	0
13	(<i>S</i>)- 28 (10)	1m	Cinnamyl, Me	52 ^g	16

^a The reactions were carried out on 0.4 mmol scale with 2.1 equiv. of HSiCl₃ in CHCl₃ in the presence of the catalyst for 24 h (unless stated otherwise). ^b Isolated yield (product pure by ¹H NMR). ^c All products **3** were of (*R*)-configuration (unless stated otherwise) as revealed by the comparison of their optical rotation with the literature data. ^d Enantiomeric excess was determined by chiral GC or HPLC. ^e The solvent was CH₂Cl₂. ^f 19% of di[1-(2-methoxy-phenyl)-ethyl]ether (**47**) was also isolated as a 55 : 45 diastereoisomeric mixture. ^g 42% of di(1-phenyl-1-buten-3-yl)ether (**48**) was also isolated as a 1 : 1 diastereoisomeric mixture.

Table 4 Reduction of ketimines **2** with trichlorosilane catalyzed by (*S*)-**28**^a

Entry	Imine	R ¹ , R ² , R ³	Solvent	4 , Yield ^b (%)	4 , ee ^{c,d} (%)
1 ^e	2a	Ph, Me, Ph	CHCl ₃	94	54
2	2a	Ph, Me, Ph	CHCl ₃	65	87
3	2a	Ph, Me, Ph	MeCN ^f	50	34
4	2a	Ph, Me, Ph	THF ^f	77	65
5	2a	Ph, Me, Ph	Toluene ^f	27	79
6	2a	Ph, Me, Ph	CH ₂ Cl ₂ ^f	34	82
7	2b	Ph, Me, PMP	CHCl ₃	60	85
8	2c	Ph, Et, PMP	CHCl ₃	90	79
9	2d	Naphth, Me, Ph	CHCl ₃	67	87(98 ^g)
10	2e	Naphth, Me, PMP	CHCl ₃	67	86
11	2f	4-CF ₃ -C ₆ H ₄ , Me, PMP	CHCl ₃	65	87
12	2g	4-MeO-C ₆ H ₄ , Me, PMP	CHCl ₃	51	87
13	2h	2-furyl, Me, PMP	CHCl ₃	73	55
14	2i	2-benzofuryl, Me, PMP	CHCl ₃	77	75
15	2j	2-thienyl, Me, PMP	CHCl ₃	77	60
16	2k	4-pyridyl, Me, PMP	CHCl ₃	70	82
17	2l	2-pyridyl, Me, PMP	CHCl ₃	88	79
18	2m	C ₆ H ₅ , CH ₂ Cl, PMP	CHCl ₃	90	88
19	2n	4-Cl-C ₆ H ₅ , CH ₂ Cl, PMP	CHCl ₃	47	88
20	2o	4-F-C ₆ H ₅ , CH ₂ Cl, PMP	CHCl ₃	70	89

^a The reactions were carried out on 0.4 mmol scale with 2.0 equiv. of HSiCl₃ in CHCl₃ in the presence of catalyst (*S*)-**28** (20 mol%) at –20 °C for 24 h (unless stated otherwise). ^b Isolated yield (product pure by ¹H NMR). ^c Amines **5** were of (*R*)-configuration (except for entries 1, 12, 13) as revealed by the comparison of their optical rotation and their HPLC retention times with the literature data. ^d Enantiomeric excess was determined by HPLC using Chiralcel OD-H, IB or AD columns. ^e Catalyst (*R*)-**16** was used. ^f The reaction time was 12 h. ^g After one recrystallization from methanol.

conditions mirrored those identified for the reduction of ketones: chloroform emerged as the best solvent (compare entries 2–5), while running the reaction at –20 °C provided a good balance

between reactivity and enantioselectivity. The enantioselectivity remained consistently high for a range of imines including heterocyclic substrates (entries 7–20). Significantly, even the

pyridine-derived substrates **2k** and **2l**, notoriously known to be difficult to reduce enantioselectively,^{8g} were efficiently reduced by employing (*S*)-**28** (entries 16, 17). Reduction of imines **2m–2o** derived from α -chloroketones proceeded in high enantioselectivity to afford the respective chloroamines **4m–4o** (entries 18–20), which serve as precursors in the synthesis of terminal aziridines showing pesticide activity.^{8d}

The sense of asymmetric induction for the reaction of imines is similar to that observed in the case of ketones, so that a similar mechanism can be envisaged. The coordination of trichlorosilane to the nitrogen of the imine is unlikely, as this would create a very crowded environment. Hence, a hydrogen-bonding interaction with the catalyst, similar to structure **C** shown in Scheme 8, with the C=N–R³ group of the imine **2** in place of the C=O group, can be envisioned. However, in the absence of comprehensive kinetic and computational data we are currently unable to provide a more detailed mechanistic picture.

Conclusions

We have developed a new family of Lewis-basic 2-pyridyl oxazolines, which can act as efficient organocatalysts for the enantioselective reduction of prochiral aromatic ketones and ketimines with trichlorosilane, a readily available and inexpensive reagent. 1-Isoquinoline derivative **28** was identified as the most efficient catalyst of the series capable of delivering high enantioselectivities in the reduction of both ketones (up to 94% ee) and ketimines (up to 89% ee) and we propose to name it “Angusoline” in appreciation of the contribution made by one of us (A.J.P.S.L.).

Experimental section

General methods

All reactions, unless otherwise stated, were run under an inert atmosphere in oven dried glassware. Room temperature refers to ambient room temperature (20–22 °C), 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by thin layer chromatography (TLC) using aluminium backed silica gel 60 (F₂₅₄) plates, visualised using UV_{254 nm} and potassium permanganate, phosphomolybdic acid or Dragendorff dips as appropriate. Flash chromatography was carried out routinely using 60 Å silica gel (Fischer). Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded at 25 °C unless otherwise indicated with an error of < ±0.1. The $[\alpha]_D$ values are given in 10⁻¹ deg cm² g⁻¹. The NMR spectra were recorded for CDCl₃ solutions, ¹H at 400 MHz and ¹³C at 100.6 MHz with chloroform-d₁ (δ 7.26, ¹H; δ 77.0, ¹³C) as an internal standard unless otherwise indicated. Coupling patterns are designated as follows: s – singlet, d – doublet, t – triplet, dd – doublet of doublets, ddd – doublet of doublet of doublets, tt – triplet of triplets, hept – heptet, m – multiplet, br – broad. Various 2D techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film between NaCl plates, in a solid by the Golden Gate technique, or as a KBr disc. The mass spectra (EI and/or CI) were measured on a

high resolution, dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. Enantiomeric excess was determined by GC (Supelco β -DEXTM 120 fused capillary column, 30 m × 0.25 mm × 0.25 μ m film thickness) or HPLC analysis as specified.

Materials

All solvents for the reactions were of reagent grade and were dried and distilled under argon or nitrogen immediately before use as follows: tetrahydrofuran, diethyl ether and toluene from sodium–benzophenone, dichloromethane from calcium hydride, chloroform from phosphorous pentoxide, methanol from magnesium turnings. Petroleum ether refers to the fraction boiling in the range 40–60 °C. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR spectra. Imines **2a–2o** are known compounds and were prepared according to literature method.^{8g} Oxazolines **14–16**,^{12,14} **26**¹⁴ and **27**¹⁴ are known compounds.

General procedure for the asymmetric reduction of ketones **1** with trichlorosilane

Trichlorosilane (86 μ L, 0.84 mmol, 2.1 equiv.) was slowly added dropwise to a solution of the catalyst (21.9 mg, 0.08 mmol or 11.0 mg, 0.04 mmol) and the ketone (0.40 mmol, 1.0 equiv.) in CHCl₃ (2 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 24 h, after which time saturated aqueous NaHCO₃ (1 mL) was added to quench the reaction. The mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic extracts were dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography on silica gel with CH₂Cl₂ afforded *sec*-alcohols **3a**, **3b**, **3d–3i**, **3k**, **3l**. Configuration of alcohols **3a**, **3b**, **3d–3i**, **3k** was established by comparison of their optical rotations and their HPLC (Chiracel OD-H or AD columns) and GC retention times with the literature data and with the behaviour of authentic samples. Enantioenriched alcohols **3a**, **3b**, **3d–3i**, **3k**, **3l** were described by us previously,¹² alcohol **3m** is also a known compound.²⁷

General procedure for the asymmetric reduction of imines **2** with trichlorosilane

Trichlorosilane (82 μ L, 0.80 mmol, 2.0 equiv.) was slowly added dropwise to a solution of the catalyst (21.9 mg, 0.08 mmol) and the imine (0.40 mmol, 1.0 equiv.) in CHCl₃ (2 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 24 h, after which time saturated aqueous NaHCO₃ (1 mL) was added to quench the reaction. The mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic extracts were dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography on silica gel afforded amines **4a–4o**. Configuration of the amines (where known) was established by comparison of their optical rotations and their HPLC (Chiracel OD-H, IB or AD columns) retention times with the literature data and with the

behaviour of authentic samples. All amines **4a–4o** are known compounds.^{8d,g}

(S)-(+)-2-(6'-Phenyl-2'-pyridyl)-5-phenyl-1,3-oxazoline (S)-(+)-17. Sodium methoxide (20 mg, 0.37 mmol, 0.13 equiv.) was added to a solution of 6-phenyl-2-cyanopyridine **29b**²⁸ (500 mg, 2.78 mmol, 1.0 equiv.) in MeOH (15 mL) and the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with glacial acetic acid (2 drops) and the mixture was concentrated *in vacuo*. Warm ether was then added and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in chlorobenzene (4 mL). (*S*)-Aminoalcohol (+)-**31d** was then added, followed by conc. HCl (1 drop). The mixture was stirred at 80 °C for 3 days, with argon gas bubbled through the solution. Concentration *in vacuo* followed by purification *via* flash chromatography on silica gel, eluting with a hexane–ethyl acetate–triethylamine mixture (2 : 1 : 0.03) gave the pyridine oxazoline (*S*)-**17** (523 mg, 63%): mp 60–62 °C (CH₂Cl₂); [α]_D +104.6 (*c* 1.1, CHCl₃); IR (KBr) ν 1637 (C=N), 2873, 2932 (CH–CH₂), 3032, 3060 (Ar–H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ _H 4.03 (dd, *J* = 15.2, 8.2 Hz, 1H), 4.50 (dd, *J* = 15.2, 10.2 Hz, 1H), 5.69 (dd, *J* = 10.2, 8.2 Hz, 1H), 7.24–7.43 (m, 8H), 7.77–7.79 (m, 2H), 7.84–7.94 (m, 1H), 8.00–8.03 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ _C 63.8 (CH₂), 82.1 (CH), 122.7 (CH), 122.8 (CH), 126.3 (2 × CH), 127.6 (2 × CH), 128.8 (CH), 129.1 (2 × CH), 129.2 (2 × CH), 129.7 (CH), 137.8 (CH), 139.0 (C), 141.2 (C), 147.0 (C), 158.1 (C), 163.9 (C); EI MS *m/z* (%) 300 (M⁺, 65), 193 (100), 154 (15), 127 (16), 118 (12), 77 (8); HRMS (EI) 300.1260 (C₂₀H₁₆N₂O requires 300.1263).

(S)-(+)-2-(4'-Methoxy-2'-pyridyl)-5-phenyl-1,3-oxazoline (S)-(+)-18. Sodium methoxide (18 mg, 0.33 mmol, 0.12 equiv.) was added to a solution of 4-methoxy-2-cyanopyridine **29c** (361 mg, 2.69 mmol, 1.0 equiv.) in MeOH (15 mL) and the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with glacial acetic acid (2 drops) and the mixture was concentrated *in vacuo*. Warm ether was then added and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in chlorobenzene (4 mL). (*S*)-(+)-Amino alcohol (*S*)-**31c** (392 mg, 2.86 mmol, 1.1 equiv.) was then added, followed by conc. HCl (1 drop). The reaction mixture was stirred at 80 °C for 3 days, with argon gas bubbled through the solution. Concentration *in vacuo*, followed by purification *via* flash chromatography on silica gel (ethyl acetate–methanol, 25 : 1), gave pyridine-oxazoline (*S*)-**18** (215 mg, 31%) as a clear oil: [α]_D +74.9 (*c* 0.9, CHCl₃); IR (neat) ν 2873, 2939 (CH–CH₂–CH₃), 3030, 3063 (Ar–H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ _H 3.84 (s, 3H), 4.01 (dd, *J* = 15.2, 8.2 Hz, 1H), 4.47 (dd, *J* = 15.2, 10.2 Hz, 1H), 5.67 (dd, *J* = 10.2, 8.3 Hz, 1H), 6.85 (dd, *J* = 5.7, 2.6 Hz, 1H), 7.24–7.31 (m, 5H), 7.55 (d, *J* = 2.6 Hz, 1H), 8.46 (d, *J* = 5.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ _C 55.9 (CH₃), 63.5 (CH₂), 82.3 (CH), 109.8 (CH), 112.7 (CH), 126.4 (2 × CH), 128.2 (CH), 129.2 (2 × CH), 140.9 (C), 148.6 (C), 151.4 (C), 163.7 (C), 166.5 (C); EI MS *m/z* (%) 254 (M⁺, 100), 195 (7), 166 (8), 148 (95), 108 (72), 84 (65), 77 (9), 47 (11); HRMS (EI) 254.1054 (C₁₅H₁₄N₂O₂ requires 254.1055).

(S)-(-)-2-(2'-Pyridyl)-5-methyl-5-phenyl-1,3-oxazoline (S)-(-)-19. Adapting the protocol of Brunner and Obermann¹⁵ amino alcohol (–)-**31d** (570 mg, 4.17 mmol, 1.0 equiv.) was added to a solution of methyl pyridine-2-carboxyimide **30a** (567 mg, 4.17 mmol, 1.0 equiv.) in chlorobenzene (5 mL). A drop of conc. HCl was added and the reaction mixture was stirred at 80 °C overnight with argon bubbled through the solvent. The solvent was then removed and purification *via* column chromatography (ethyl acetate–methanol, 40 : 1) afforded (–)-**19** (812 mg, 82%) as a clear oil: [α]_D –171.5 (*c* 1.07, CHCl₃); IR ν (KBr) 1673 (C=N); 2869, 2930, 2975 (CH–CH₂–CH₃), 3027 (aryl-H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ _H 1.89 (s, 3H), 4.22 (d, *J* = 14.8 Hz, 1H), 4.23 (d, *J* = 14.8 Hz, 1H), 7.29–7.45 (m, 6H), 7.84 (td, *J* = 8.0, 2.0 Hz, 1H), 8.13 (d, *J* = 7.6 Hz, 1H), 8.80 (d, *J* = 4.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ _C 28.1 (CH₃), 69.1 (CH), 87.7 (C), 123.8 (CH), 124.3 (2 × CH), 125.5 (CH), 127.4 (CH), 128.5 (2 × CH), 136.6 (CH), 145.1 (C), 146.9 (C), 149.9 (CH), 162.3 (C); EI MS *m/z* (%) 238 (M⁺, 20), 118 (100), 91 (15), 78 (80), 77 (10), 51 (10); HRMS (EI) 238.1107 (C₁₅H₁₄N₂O requires 238.1106).

(±)-2-(2'-Pyridyl)-5-(4''-Trifluoromethylphenyl)-1,3-oxazoline (±)-20. Adapting the procedure of Bruner,¹⁵ 2-amino-1-phenylethanol (±)-**31e** (754 mg, 3.68 mmol, 1.0 equiv.) was added to a solution of imide **30a** (500 mg, 3.68 mmol, 1.0 equiv.) in chlorobenzene (5 mL). A drop of conc. HCl was added and the reaction mixture was stirred at 80 °C overnight with argon bubbled through the solvent. The solvent was then removed *in vacuo* and purification of the residue *via* column chromatography on silica gel (ethyl acetate–triethylamine, 10 : 0.1) afforded oxazoline **20** (809 mg, 75%) as a yellow solid: mp 68–70 °C (CH₂Cl₂); IR ν (KBr) 1643 (C=N), 2867, 2963 (CH–CH₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ _H 3.98 (dd, *J* = 15.4, 8.0 Hz, 1H), 4.53 (dd, *J* = 15.4, 10.4 Hz, 1H), 5.73 (dd, *J* = 10.4, 8.0 Hz, 1H), 7.37 (ddd, *J* = 7.6, 4.8, 0.8 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.76 (td, *J* = 8.0, 2.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 8.69 (dd, *J* = 4.8, 0.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ _C 63.3 (CH₂), 80.9 (CH), 124.0 (q, ¹*J*_{CF} = 246 Hz, [CF₃]), 124.0 (2 × CH), 125.8 (C), 125.9 (CH), 125.9 (CH), 126.1 (2 × CH), 130.6 (q, ²*J*_{CF} = 32 Hz, [C]), 136.8 (CH), 144.6 (C), 146.3 (C), 150.0 (CH); EI MS *m/z* (%) 292 (M⁺, 75), 273 (5), 186 (10), 159 (7), 118 (100), 106 (7), 78 (98), 51 (10); HRMS (EI) 292.0822 (C₁₅H₁₁F₃N₂O requires 292.0823).

(+)-2-(2'-Pyridyl)-5-tert-butyl-1,3-oxazoline (+)-21. Adapting the protocol of Brunner and Obermann,¹⁵ 1-amino-3,3-dimethylbutan-2-ol (±)-**31f** (430 mg, 3.68 mmol, 1.0 equiv.) was added to a solution of methyl pyridine-2-carboxyimide (500 mg, 3.68 mmol, 1.0 equiv.) in chlorobenzene (5 mL). A drop of conc. HCl was added and the reaction mixture was stirred at 80 °C overnight with argon bubbled through the solvent. The solvent was then removed *in vacuo* and purification of the residue *via* column chromatography on silica gel (ethyl acetate–methanol, 20 : 1) afforded oxazoline (±)-**21** (671 mg, 89%) white solid: mp 73–75 °C (CH₂Cl₂); IR (KBr) ν 1644 (C=N), 2869, 2958 (CH–CH₂–CH₃), 3066 (aryl-H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ _H 0.91 (s, 9H), 3.81 (dd, *J* = 15.2, 8.0 Hz, 1H), 3.98 (dd, *J* = 15.2, 10.4 Hz, 1H), 4.44 (dd, *J* = 10.4,

8.0 Hz, 1H), 7.31 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 7.70 (td, $J = 7.6, 1.6$ Hz, 1H), 7.92 (d, $J = 7.6$ Hz, 1H), 8.66 (dd, 4.0, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 24.8 ($3 \times \text{CH}_3$), 34.0 (C), 55.9 (CH_2), 88.4 (CH), 123.6 (CH), 125.4 (CH), 136.6 (CH), 146.9 (C), 149.9 (CH), 163.5 (C); EI MS m/z (%) 204 (M^+ , 15), 147 (100), 119 (35), 92 (50), 78 (55), 51 (10); HRMS (EI) 204.1261 ($\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$ requires 204.1263). The racemate was resolved by preparative chiral HPLC on a Chiralpak AD column (Heptane-2-Propanol, 98 : 2, 1 mL min^{-1}) to give (+)-**21**: $[\alpha]_{\text{D}}^{25} +24.0$ (c 0.9, CHCl_3) and the respective (–)-**21**.

(R)-(+)-2-(2'-Pyridyl)-1-methyl-4-phenyl-imidazoline (R)-(+)-(22).

A solution of diamine (*R*)-**35** (500 mg, 3.7 mmol, 1.0 equiv.) in PhCl (5 mL) was added to a solution of imidate **30a** (500 mg, 3.7 mmol, 1.0 equiv.) in chlorobenzene (10 mL). The reaction mixture was stirred at 80 °C overnight with argon bubbling through the solution. The solvent was then removed from the resultant dark brown paste under reduced pressure and the crude product was purified *via* flash chromatography on silica gel (ethyl acetate–methanol–triethylamine, 9 : 1 : 0.1) to give imidazoline (*R*)-**22** (732 mg, 84%) as a yellow oil: $[\alpha]_{\text{D}}^{25} +11.9$ (c 1.0, CHCl_3); IR (KBr) ν 1522, 1670 (aryl ring), 2797, 2848, 2937 ($\text{CH}-\text{CH}_2-\text{CH}_3$), 3029, 3059 (Ar–H) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.12 (s, 3H), 3.40 (t, $J = 9.4$, 1H), 4.01 (dd, $J = 10.9, 9.4$ Hz, 1H), 5.21 (dd, $J = 10.7, 9.7$ Hz, 1H), 7.28–7.29 (m, 1H), 7.35–7.40 (m, 5H), 7.79 (td, $J = 7.6, 1.6$ Hz, 1H), 7.91 (dt, $J = 7.6, 0.8$ Hz, 1H), 8.69 (dd, $J = 4.8, 1.6, 0.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 36.2 (CH_3), 62.5 (CH_2), 68.0 (CH), 124.9 (CH), 125.0 (CH), 127.2 ($2 \times \text{CH}$), 127.5 (CH), 128.9 ($2 \times \text{CH}$), 137.1 (CH), 144.5 (C), 149.0 (CH), 150.9 (C), 165.5 (C); CI MS m/z (%) 238 ($[\text{M} + \text{H}]^+$, 100); HRMS (CI) 238.1341 ($\text{C}_{15}\text{H}_{16}\text{N}_3$ requires 238.1344).

(R)-(–)-2-(2'-Pyridyl)-1-methyl-5-phenyl-imidazoline (R)-(–)-(23).

Diamine (*R*)-**38** (926 mg, 6.13 mmol, 1.0 equiv.) was added to a solution of imidate **30a** (840 mg, 6.13 mmol, 1.0 equiv.) in chlorobenzene (2.0 mL) and the reaction mixture was stirred at 60 °C overnight with argon bubbling through the solution. The solvent was then removed from the resultant dark brown paste under reduced pressure and the crude product was purified *via* flash chromatography on silica gel (ethyl acetate) to give imidazoline (*R*)-**23** (906 mg, 62%) as a yellow oil: $[\alpha]_{\text{D}}^{25} -86.2$ (c 0.67, CHCl_3); IR (KBr) ν 1671, 1590, 1495 (aryl ring), 2858, 2920 ($\text{CH}-\text{CH}_2\text{CH}_3$), 3029, 3060 (Ar–H) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 2.88 (s, 3H), 3.67 (dd, $J = 14.8, 10.8$ Hz, 1H), 4.29 (dd, $J = 14.8, 10.8$ Hz, 1H), 4.53 (t, $J = 10.8$ Hz, 1H), 7.22–7.34 (m, 6H), 7.72 (td, 7.6, 0.4 Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 8.60 (d, $J = 4.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 34.2 (CH_3), 62.7 (CH_2), 70.4 (CH), 124.6 ($2 \times \text{CH}$), 127.2 ($2 \times \text{CH}$), 127.8 (C), 128.8 ($2 \times \text{CH}$), 136.7 (CH), 147.5 (C), 148.7 (CH), 150.5 (C), 165.1 (C); EI MS m/z (%) 237 (M^+ , 75), 236 (10), 222 (6), 207 (4), 160 (15), 133 (100), 118 (50), 78 (80), 77 (12), 51 (10); HRMS (EI) 237.1268 ($\text{C}_{15}\text{H}_{15}\text{N}_3$ requires 237.1266).

(S)-(–)-2-(2'-Pyridyl)-5-phenyl-thiazoline (S)-(–)-(24). Mesyl chloride (0.57 mL, 7.01 mmol) and triethylamine (2.15 mL, 14.3 mmol) were added to a solution of (*S*)-**43** (1.29 g, 4.99 mmol) in THF (15 mL) at 0 °C and the reaction mixture was allowed to stir at room temperature for 48 h. Water (10 mL)

was then added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The organic layer was washed with water (2×20 mL) and dried over MgSO_4 and the solvent removed *in vacuo*. The crude solid was purified by chromatography on a column of silica gel (20 g) with a mixture of petroleum ether and AcOEt (1 : 1) to afford an off white solid, which was recrystallised from EtOH to afford thiazoline (*S*)-(–)-**24** as a white crystalline solid (0.98 g, 82%); mp 105–106 °C; $[\alpha]_{\text{D}}^{25} -77.50$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.60 (dd, $J = 16.4, 5.8$ Hz, 1H), 4.82 (dd, $J = 16.4, 9.1$ Hz, 1H), 4.99 (dd, $J = 9.1, 5.8$ Hz, 1H), 7.17–7.33 (m, 6H), 7.73 (dt, $J = 7.8, 1.8$ Hz, 1H), 8.05 (dt, $J = 7.8, 1.0$ Hz, 1H), 8.60 (ddd, $J = 4.8, 1.0, 0.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 53.5 (CH), 73.9 (CH_2), 121.6 (CH), 125.5 (CH), 127.2 (CH), 127.7 (CH), 128.9 (CH), 136.6 (CH), 142.2 (C), 149.4 (CH), 151.2 (C), 170.2 (C); MS EI m/z (%) 240.1 (M+, 100), 118.0 (49), 78.0 (74), 51.0 (20); HRMS (EI) 240.0721 ($\text{C}_{14}\text{H}_{12}\text{N}_2\text{S}$ requires 240.0718).

(S)-(–)-2-(1'-Isoquinolyl)-5-phenyl-thiazoline (S)-(–)-(25).

A solution of amide (*R*)-**44** (253 mg, 0.71 mmol) and Lawesson's reagent (344 mg, 0.85 mmol) in toluene (20 mL) was heated at 85 °C overnight. The reaction mixture was then allowed to cool to room temperature, aqueous 2 M HCl (20 mL) was added, and the precipitate was removed by filtration. After separation of the organic layer, the aqueous phase was extracted with CH_2Cl_2 (3×30 mL) and the combined organic phases were washed with water (3×15 mL) and dried over MgSO_4 . The solvent was then evaporated *in vacuo* and the residue was purified by chromatography on a column of silica gel with a mixture of petroleum ether and AcOEt (5 : 1) to afford (*S*)-(–)-**25** as a yellow oil (161 mg, 74%); $[\alpha]_{\text{D}}^{25} -22.9$ ($c = 1.0, \text{CHCl}_3$); ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.78 (1H, dd, $J = 4.3, 15.2$ Hz, 2-H), 4.83–4.89 (1H, m, 1 α -H), 5.02–5.06 (1H, m, 1 β -H), 7.17 (m, 1H), 7.21–7.25 (m, 2H), 7.33–7.35 (m, 2H), 7.59–7.66 (m, 3H), 7.89–7.97 (m, 1H), 8.52 (d, $J = 5.6$ Hz, 1H), 9.42 (dd, $J = 1.5, 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 52.2 (CH, C-2), 75.2 (CH_2 , C-1), 123.2 (CH), 126.4 (C-3), 127.0 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 128.9 (CH), 130.4 (CH), 136.9 (C-14), 141.5 (CH), 142.4 (CH), 149.2 (C-9), 168.1 (C-8), 170.9 (C-7); MS EI m/z (%) 290.1 (M+, 100), 186.0 (44), 128.0 (92), 91.0 (28); HRMS (EI) 290.0878 ($\text{C}_{18}\text{H}_{14}\text{N}_2\text{S}$ requires 290.0879).

(S)-(+)-2-(1'-Isoquinolyl)-5-phenyl-1,3-oxazoline (S)-(+)-(28).

Triethylamine (2.5 mL, 17.78 mmol, 5.2 equiv.) was added to a solution of (*R*)-**40** (1.00 g, 3.42 mmol, 1.0 equiv.) in CH_2Cl_2 (65 mL). The mixture was then cooled to 0 °C and a solution of methanesulfonyl chloride (0.62 mL, 7.87 mmol, 2.3 equiv.) in CH_2Cl_2 (10 mL) was added dropwise over 15 min. The reaction mixture was then allowed to attain room temperature and stirred overnight. The reaction mixture was poured onto crushed ice, the aqueous layer was extracted with CH_2Cl_2 , and the combined organic phase was washed with 5% aqueous HCl (3×40 mL), water (1×40 mL), saturated aqueous NaHCO_3 (3×40 mL), and brine (1×40 mL) and dried over MgSO_4 . Concentration *in vacuo* then afforded a residue, which was purified *via* column chromatography on silica gel (petroleum ether–ethyl acetate, 1 : 1) to give **28** (0.89 g, 95%) as a white solid: mp 78–80 °C (CH_2Cl_2); $[\alpha]_{\text{D}}^{25} +83.5$ (c 0.5, CHCl_3); IR (KBr) 700, 759, 838

(aryl), 1645 (C=N), 2866, 2931 (CH-CH₂), 3064 (aryl-H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ_H 4.29 (dd, *J* = 15.2, 8.0 Hz, 1H), 4.74 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.84 (dd, *J* = 10.4, 8.0 Hz, 1H), 7.35–7.55 (m, 5H), 7.71–7.80 (m, 2H), 7.83 (d, *J* = 5.6 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 8.71 (d, *J* = 5.6 Hz, 1H), 9.28 (d, *J* = 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ_C 63.9 (CH₂), 80.7 (CH), 123.5 (CH), 126.1 (2 × CH), 127.2 (CH), 127.3 (CH), 127.4 (C), 128.4 (CH), 128.6 (CH), 128.9 (2 × CH), 130.5 (CH), 136.8 (C), 140.7 (C), 141.9 (CH), 146.3 (C), 162.7 (C); EI MS *m/z* (%) 274 (M⁺, 65), 168 (70), 128 (100), 101 (15), 82 (35), 77 (10), 47 (5); HRMS (EI) 274.1105 (C₁₈H₁₄N₂O requires 274.1106).

2-Cyano-4-methoxy-pyridine (29c). Adapting the method of Fife,^{28a} Me₃SiCN (1.55 mL, 1.15 g, 11.7 mmol, 1.25 equiv.) was added to a solution of 4-methoxypyridine-*N*-oxide (1.17 g, 9.36 mmol, 1.0 equiv.) in CH₂Cl₂ (100 mL) at room temperature. A solution of dimethylcarbamoyl chloride (0.73 mL, 1.26 g, 11.7 mmol, 1.25 equiv.) in CH₂Cl₂ (20 mL) was then added dropwise over 30 min and the reaction mixture was stirred at room temperature for 6 days. Satd Na₂CO₃ (aq) (50 mL) was then added and the mixture was stirred for a further 10 min. The organic phase was then separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo* to give the crude product, which was purified *via* column chromatography on silica gel (ethyl acetate) to give **29c** (932 mg, 74%) as a pale yellow solid: mp 115–117 °C (CH₂Cl₂); IR (KBr) ν 1528, 1586, 1657 (aryl ring), 2888, 2929, 2954 (CH₃), 2996 (Ar-H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ_H 3.84 (s, 3H), 6.93 (dd, *J* = 5.6, 2.4 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 8.44 (d, *J* = 5.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ_C 56.2 (CH₃), 113.1 (CH), 115.8 (CH), 117.5 (C), 135.5 (C), 152.7 (CH), 166.3 (C); EI MS *m/z* (%) 134 (M⁺, 100), 119 (5), 104 (50), 104 (50), 83 (20), 77 (25), 64 (10), 51 (10), 50 (9); HRMS (EI) 134.0479 (C₇H₆N₂O requires 134.0480).

1-Amino-2-phenylpropan-2-ol (31d).²⁹ Adapting the protocol of Fleming,¹⁶ Me₃SiCN (6.1 mL, 45.0 mmol, 1.1 equiv.) and anhydrous ZnI₂ (80 mg, 0.25 mmol, 0.6 mol%) were added to a Schlenk tube containing acetophenone **32a** (4.85 mL, 41.6 mmol, 1.0 equiv.) and the mixture was stirred at 50 °C for 16 h. The neat reaction mixture was then diluted with THF (200 mL) and added *via* cannula to a suspension of LiAlH₄ (4.75 g, 125 mmol, 3.0 equiv.) in THF (200 mL). After heating at reflux for 3 h the reaction was quenched with Na₂SO₄·10H₂O and filtered through a pad of celite (eluting with ether). Concentration of the filtrate *in vacuo* afforded **31d** (3.90 g, 62%) as a clear oil: ¹H NMR (400 MHz, CDCl₃) δ_H 1.34 (s, 3H), 2.65 (d, *J* = 12.8 Hz, 1H), 2.95 (d, *J* = 12.8 Hz, 1H), 7.25–7.29 (m, 1H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ_C 27.8 (CH₃), 52.7 (CH₂), 73.4 (C), 125.1 (2 × CH), 126.7 (CH), 128.2 (2 × CH), 146.5 (C); CI MS *m/z* (%) 152 ([M + H]⁺, 100), 134 (64), 121 (11), 97 (4), 71 (7); HRMS (CI) 152.1078 (C₉H₁₄NO requires 152.1075), in agreement with the literature.²⁹

Resolution

The resolution of **31d** was carried out by recrystallising racemic **31d** (3.90 g, 25.8 mmol, 1.0 equiv.) and (+)-mandelic acid (3.93 g, 25.8 mmol, 1.0 equiv.) from hot ethanol three times. The resultant salt was then basified with 2 M NaOH (30 mL) and extracted with ether (2 × 30 mL), dried over MgSO₄ and concentrated *in vacuo* to give (–)-**31d** (688 mg, 35%); [α]_D –13.6 (*c* 1.2, CHCl₃).

GC analysis

A portion of (–)-**31d** (50 mg) in CH₂Cl₂ (1 mL) was treated with TFAA (1 mL) and stirred for 30 min. After concentration *in vacuo* the crude residue was passed through a plug column of silica gel (ethyl acetate) to provide a chiral GC sample: Chiral GC (β-DEXTM); carrier gas, He (flow 2 mL min⁻¹); injection temp, 200 °C; column temp: initial temperature, 80 °C; rate, 1.5 °C min⁻¹; final temperature, 200 °C, *t*₍₊₎ 48.62 min, *t*_(–) 48.72 min, showed 92% ee.

2-Amino-1-(4'-trifluoromethylphenyl)-ethanol (31e). Adapting the protocol of Fleming,¹⁶ Me₃SiCN (1.37 mL, 10.3 mmol, 1.4 equiv.) and anhydrous ZnI₂ (15 mg, 0.05 mmol, 0.6 mol%) were added to a Schlenk tube containing 4-trifluoromethyl benzaldehyde (1.0 mL, 7.33 mmol, 1.0 equiv.) and the mixture was stirred at 50 °C for 16 h. The neat reaction mixture was then diluted with THF (150 mL) and added *via* cannula to a suspension of LiAlH₄ (1.66 g, 43.8 mmol, 3.0 equiv.) in THF (100 mL). After heating at reflux for 4 h the reaction was quenched with Na₂SO₄·10H₂O and the mixture was filtered through a pad of Celite (eluting with ether). Concentration *in vacuo* afforded **31e** (1.32 g, 88%) as a yellow solid: mp 70–72 °C; IR ν (KBr) 1330 (C–O), 2923 (CH–CH₂), 3095 (Ar–H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ_H 2.53 (bs, 3H), 2.66–2.71 (m, 1H), 2.89–2.92 (m, 1H), 4.61 (dd, *J* = 7.6, 3.6 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ_C 48.0 (CH₂), 72.2 (CH), 123.1 (q, ¹*J*_{CF} = 270 Hz, [CF₃]), 124.4 (2 × CH), 125.1 (2 × CH), 128.7 (q, ²*J*_{CF} = 32 Hz, [C]), 145.6 (C); CI MS *m/z* (%) 206 ([M + H]⁺, 100), 188 (10), 121 (1) 71 (2); HRMS (CI) 206.0791 (C₉H₁₁F₃NO requires 206.0793).

1-Amino-3,3-dimethylbutan-2-ol (31f).³⁰ Adapting the protocol of Fleming,¹⁶ Me₃SiCN (4.33 mL, 32.5 mmol, 1.4 equiv.) and anhydrous ZnI₂ (40 mg, 0.125 mmol, 0.5 mol%) were added to a Schlenk tube containing pivaldehyde (2.57 mL, 23.2 mmol, 1.0 equiv.) and the reaction mixture was stirred at 50 °C for 16 h. The neat reaction mixture was then diluted with THF (250 mL) and added *via* cannula to a suspension of LiAlH₄ (2.66 g, 70.0 mmol, 3.0 equiv.) in THF (150 mL). After heating at reflux for 3 h, the reaction was quenched with Na₂SO₄·10H₂O and the mixture was filtered through a pad of Celite (eluting with ether). The filtrate was concentrated by evaporation *in vacuo* to afford **31f** (2.23 g, 82%) as a yellow solid: mp 55–57 °C (CH₂Cl₂); IR (KBr) ν 2956 (CH–CH₂–CH₃), 3281 (N–H) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ_H 0.76 (s, 9H), 1.78 (bs, 3H), 2.33 (dd, *J* = 12.4, 10.4 Hz, 1H), 2.77 (dd, *J* = 12.4, 2.8 Hz, 1H), 3.00 (dd, *J* = 10.4, 2.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ_C 24.4 (3 × CH₃), 32.4 (C), 41.1 (CH₂), 78.1 (CH);

CI MS m/z (%) 118 ($[M + H]^+$, 100), 91 (2), 71 (2); HRMS (CI) 118.1230 ($C_6H_{16}NO$ requires 118.1232), in agreement with the literature.³⁰

(R)-2-Amino-1-methylamino-2-phenylethane (R)-(35).³¹ A solution of (R)-34³¹ (5.17 g, 32.0 mmol, 1.0 equiv.) in THF (200 mL) was added to a suspension of $LiAlH_4$ (6.0 g, 158.0 mmol, 5.0 equiv.) in THF (300 mL) at 0 °C and the reaction mixture was heated to reflux overnight. After quenching with $Na_2SO_4 \cdot 10H_2O$, the suspension was passed through a pad of Celite, eluting with ether. The solvent was then removed *in vacuo* to give diamine (R)-35 (2.56 g, 53%) as a yellow oil: 1H NMR (400 MHz, $CDCl_3$) δ_H 2.37 (s, 3H), 2.63–2.73 (m, 2H), 3.98 (dd, $J = 7.8, 5.3$ Hz, 1H), 7.17–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 36.8 (CH₃), 55.8 (CH), 60.4 (CH₂), 126.8 (2 × CH), 127.6 (CH), 128.9 (2 × CH), 145.1 (C), in accordance with the literature.³¹

(R)-(-)-2(tert-Butylcarbamido)-2-phenylacetamide (R)-(-)(37). A solution of di-*tert*-butyl carbonate (2.9 g, 13.3 mmol, 1.0 equiv.) in THF (50 mL) was added to a solution of amine (R)-36³² (2.0 g, 13.3 mmol, 1.0 equiv.) and $NaHCO_3$ (1.5 g, 17.9 mmol, 1.3 equiv.) in H_2O (50 mL) and the reaction mixture was stirred at room temperature overnight. The volatile solvent was then removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 100 mL) and dried over $MgSO_4$. Concentration *in vacuo* afforded (R)-37 as a white solid (2.39 g, 72%): mp 119–121 °C (CH_2Cl_2); $[\alpha]_D -170.7$ (c 0.3, $CHCl_3$), IR (neat) ν 1685 (C=O), 2832, 2945, 2984 (CH–CH₃), 3055 (Ar–H); 1H NMR (400 MHz, $CDCl_3$) δ_H 1.34 (s, 9H), 5.11 (s, 1H), 5.46 (s, 1H), 5.62 (s, 1H), 5.71 (s, 1H), 7.24–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 27.8 (CH), 28.7 (3 × CH₃), 58.8 (C), 127.7 (2 × CH), 128.9 (CH), 129.5 (2 × CH), 138.6 (C), 172.6 (C); CI MS m/z (%) 251 ($[M + H]^+$, 38), 195 (100), 151 (15), 106 (5); HRMS (CI) 251.1398 ($C_{13}H_{19}N_2O_3$ requires 251.1396).

(R)-(-)-1-Amino-2-methylamino-2-phenylethane (R)-(-)(38).³³ A solution of amide (R)-37 (2.76 g, 11.0 mmol, 1.0 equiv.) in THF (200 mL) was added to a suspension of $LiAlH_4$ (2.5 g, 66.0 mmol, 6.0 equiv.) in THF (300 mL) at 0 °C and the reaction mixture was then heated to reflux overnight. After quenching with $Na_2SO_4 \cdot 10H_2O$, the suspension was passed through a pad of Celite, eluting with ether. The solvent was then removed to give diamine (R)-38 (1.39 g, 84%) as a viscous oil: $[\alpha]_D -31.2$ (c 1.0, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ_H 2.21 (s, 3H), 2.70 (dd, $J = 12.8, 7.2$ Hz, 1H), 2.79 (dd, $J = 12.8, 5.6$ Hz, 1H), 3.37 (dd, $J = 6.8, 5.6$ Hz, 1H), 7.13–7.26 (m, 5H) in accordance with the literature.³³

(R)-(-)-N-(2'-Hydroxy-2'-phenylethyl)-1-isoquinolyl-carboxamide (R)-(-)(40). Methyl chloroformate (1.56 mL, 19.82 mmol, 1.2 equiv.) was added dropwise to a stirred solution of 1-isoquinoline carboxylic acid 39 (2.86 g, 16.52 mmol, 1.0 equiv.) and triethylamine (2.76 mL, 19.82 mmol, 1.2 equiv.) in anhydrous THF (80 mL) at 0 °C under an argon atmosphere and the solution was stirred at that temperature for 2 h. The precipitate was removed by filtration *in vacuo* and the filtrate was added dropwise to a solution of (R)-31c (2.72 g, 19.82 mmol, 1.2 equiv.) and triethylamine (2.76 mL, 19.82 mmol, 1.2 equiv.) in

anhydrous THF (80 mL) at 0 °C under an argon atmosphere and the mixture was allowed to attain room temperature and stirred overnight. The solvent was removed under reduced pressure and the residue was purified *via* column chromatography on silica gel (petroleum ether–ethyl acetate, 1 : 1) to afford 40 (4.30 g, 89%) as a white amorphous solid: $[\alpha]_D -78.6$ ($c = 0.5, CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ_H 3.48 (ddd, $J_{1\alpha,1\beta} = 13.9$ Hz, $J_{1\alpha,2} = 8.6$ Hz, $J_{1\alpha,NH} = 5.3$ Hz, 1H), 3.85 (ddd, $J_{1\alpha,1\beta} = 13.9$ Hz, $J_{1\beta,NH} = 7.1$ Hz, $J_{1\beta,2} = 3.3$ Hz, 1H), 5.08 (dd, $J_{1\alpha,2} = 8.6$ Hz, $J_{1\beta,2} = 3.3$ Hz, 1H), 7.15–7.26 (m, 3H), 7.37 (d, $J = 7.1$ Hz, 2H), 7.49–7.57 (m, 2H), 7.59 (d, $J = 5.3$ Hz, 2H), 7.70 (d, $J = 7.6$ Hz, 1H), 8.17 (d, $J = 5.6$ Hz, 1H), 8.67 (t, $J = 5.8$ Hz, 1H), 9.30 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 47.9 (CH, 1-C), 74.2 (CH₂, 2-C), 124.6 (CH), 125.9 (CH), 126.9 (CH), 127.1 (C, 3-C), 127.7 (CH), 127.9 (CH), 128.6 (CH), 128.8 (CH), 130.6 (CH), 137.4 (C, 11-C), 140.28 (CH), 141.9 (C, 16-C), 147.9 (C, 10-C), 167.5 (C, 9-C) CI MS m/z (%) 293 ($[M + H]^+$, 100), 275 (15), 186 (7), 173 (5), 123 (4), 107 (5); HRMS (CI) 293.1288 ($C_{18}H_{17}N_2O_2$ requires 293.1290).

(R)-N-(2'-Hydroxy-2'-phenylethyl)-2-pyridyl-carbothioamide (R)-(43). Prepared by modification of the protocol developed by Masson and co-workers.³⁴ Amino alcohol 31c (1.20 g, 8.5 mmol) and triethylamine (1.12 mL, 8.5 mmol) were added to a solution of thioester 42 (1.05 g, 6.4 mmol) in THF and the reaction mixture was allowed to stir at room temperature for 18 h, after which time the solvent was removed *in vacuo*. The residue was passed through a column of silica gel (35 g) with a petroleum ether–AcOEt mixture (1 : 1) to afford 43 as a colourless oil (1.289 g, 78%): 1H NMR (400 MHz, $CDCl_3$) δ_H 3.82 (ddd, $J = 10.1$ Hz, $J = 8.8$ Hz, $J = 4.8$ Hz, 1H) 4.35 (ddd, $J = 13.9$ Hz, $J = 7.1$ Hz, $J = 3.3$ Hz, 1H) 5.11 (dd, $J = 8.8$ Hz, $J = 3.3$ Hz, 1H), 7.24–7.42 (m, 6H), 7.77 (dt, $J = 7.8$ Hz, $J = 1.7$ Hz, 1H), 8.42 (ddd, $J = 4.8$ Hz, $J = 1.8$ Hz, $J = 1.0$ Hz, 1H), 8.63 (dt, 8.1 Hz, $J = 1.0$ Hz, 1H), 10.50 (bs, 1H). The compound was used in the next step without further purification.

(R)-(-)-N-(2'-tert-Butyldimethylsilyloxy-2'-phenylethyl)-1-isoquinolyl-carboxamide (R)-(-)(44). A solution of alcohol (R)-40 (500 mg, 1.71 mmol), *tert*-butyldimethylsilyl chloride (309 mg, 2.05 mmol), and imidazole (291 mg, 4.28 mmol) in DMF (5 mL) was stirred at room temperature overnight. The mixture was then diluted with aqueous NH_4Cl and extracted with CH_2Cl_2 . The organic phase was washed with brine (3 × 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford (R)-(-)-44 as a colourless oil (63%); $[\alpha]_D -23.7$ (c 1.00, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ_H 0.01 (s, 6H), 0.82 (s, 9H), 3.36 (ddd, $J = 13.89$ Hz, $J = 8.4$ Hz, $J = 4.8$ Hz, 1H), 3.90 (ddd, $J = 13.6$ Hz, $J = 8.0$ Hz, $J = 4.0$ Hz, 1H), 4.90 (dd, $J = 8.4$ Hz, $J = 4.0$ Hz, 1H), 7.31–7.41 (m, 5H), 7.65–7.84 (m, 3H), 8.44 (d, $J = 5.6$ Hz, 1H), 8.62 (bs, 1H), 9.61 (d, $J = 5.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C -4.6 (CH₃, C-19), -3.6 (CH₃, C-20), 18.2 (C-21), 25.7 (CH₃, C-22), 47.9 (CH₂, C-1), 74.0 (CH, C-2); MS EI m/z (%) 406.14 (M^+ , 5), 349.11 (42), 221.1 (100), 185.1 (35), 128.0 (54), 73.0 (60); HRMS 406.2077 ($C_{24}H_{30}O_2N_2Si$ requires 406.2076); Anal. Calcd for $C_{24}H_{30}N_2O_2Si$: C 70.90 H 7.44 N 6.89. Found C 70.81 H 7.44 N 6.69.

(S)-(–)-N-(2'-Chloro-2'-phenylethyl)-2-pyridyl-carboxamide (S)-(–)-(45). Trichlorosilane (367 μ L, 3.6 mmol, 8.1 equiv.) was added to a solution of oxazoline (S)-16 (100 mg, 0.45 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C and the mixture was stirred at room temperature overnight. The reaction was quenched with satd NaHCO_3 (aq) (10 mL) and the mixture was extracted with CH_2Cl_2 (3 \times 20 mL) and the combined organic extracts were dried over MgSO_4 . Concentration under reduced pressure, followed by purification *via* column chromatography on silica gel (hexane–ethyl acetate, 1 : 1), gave (–)-45 (63 mg, 54%) as a white solid: mp 74–75 °C (ethyl acetate–hexane); $[\alpha]_{\text{D}} -45.3$ (c 0.4, CHCl_3); IR (KBr) ν 1523, 1656 (amide C=O), 2938 (CH/CH_2), 3034 (Ar-H), 3336, 3373 (amide N-H) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.74–3.81 (m, 1H), 4.03–4.10 (m, 1H), 5.06 (dd, $J = 9.2, 5.2$ Hz, 1H), 7.25–7.41 (m, 6H), 7.78 (td, $J = 8.0, 1.6$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 8.38 (br s, 1H), 8.49 (d, $J = 4.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 47.5 (CH_2), 62.5 (CH), 122.7 (CH), 126.8 (CH), 127.6 (2 \times CH), 129.2 (2 \times CH), 137.8 (CH), 138.5 (C), 139.2 (C), 148.6 (CH), 149.9 (C), 164.9 (C); EI MS m/z (%) 262 (M^+ , $\{^{37}\text{Cl}\}$, 3), 260 (M^+ , $\{^{35}\text{Cl}\}$, 10), 224 (10), 135 (100), 118 (15), 106 (90), 78 (98), 51 (18), 50 (4); HRMS (EI) 260.0714 and 262.0689 ($\text{C}_{14}\text{H}_{13}^{35}\text{ClN}_2\text{O}$ requires 260.0716, $\text{C}_{14}\text{H}_{13}^{37}\text{ClN}_2\text{O}$ requires 262.0691).

Di[1-(2'-methoxyphenyl)-ethyl]ether (47). Obtained from the reduction of **1f** (Table 3, entry 9) as a 55 : 45 mixture of diastereoisomers by elution from silica gel as a less polar fraction than the main product using a petroleum ether–AcOEt mixture (20 : 1): colourless oil; ^1H -NMR (400 MHz, CDCl_3) δ_{H} 1.30 (m, d, $J = 6.4$ Hz, 6H, 2Me), 1.34 (M, d, $J = 6.4$ Hz, 6H, 2Me), 3.64 (m, s, 6H, 2OMe), 3.67 (M, s, 6H, 2OMe), 4.10 (m, q, $J = 6.4$ Hz, 2H, 2CH), 4.16 (M, q, $J = 6.4$ Hz, 2H, 2CH), 6.71 (M, d, $J = 8.4$ Hz, 2H), 6.76 (m, d, $J = 8.0$ Hz, 2H), 6.82 (M, t, $J = 7.6, 2\text{H}$), 6.96 (m, t, $J = 7.2, 2\text{H}$), 7.10 (M, td, $J = 8.0, 1.6$ Hz, 2H), 7.17 (m, td, $J = 8.0, 1.6$ Hz, 2H), 7.39 (M, dd, $J = 7.6, 1.6$ Hz, 2H), 7.50 (m, dd, $J = 7.2, 1.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 22.8 (2 \times CH_3), 25.4 (CH), 45.5 (CH_2), 65.4 (CH), 79.7 (CH_2), 123.9 (CH), 125.4 (CH), 136.6 (CH), 149.7 (CH), 162.5 (C), 165.1 (C); IR (CHCl_3) ν 1216 (C–O), 3019 (Aryl C–H) cm^{-1} ; EI MS m/z (%) 286 (M^+ , 6), 271 (4), 178 (4), 151 (6) 135 (100), 105 (13), 84 (9), 49 (11); HRMS (EI) 286.1569 ($\text{C}_{18}\text{H}_{22}\text{O}_3$ requires 286.1568).

Di(1-phenyl-1-buten-3-yl)ether (48).³⁵ Obtained from the reduction of **1m** (Table 3, entry 13) as a 1 : 1 mixture of diastereoisomers by elution from silica gel as a less polar fraction than the main product using a petroleum ether–AcOEt mixture (75 : 1): ^1H -NMR (400 MHz, CDCl_3) δ_{H} 1.26 and 1.28 (2 \times d, $J = 6.4$ Hz, 2 \times 6H, 2 \times 2Me), 4.10 and 4.16 (2 \times m, 2 \times 2H, 2 \times 2 CH_3CH), 6.04 and 6.11 (2 \times dd, 2 \times $J = 16.0, 7.6$ Hz, 2 \times 2H, 2 \times 2 $\text{CHCH}=\text{}$), 6.42 and 6.46 (2 \times d, 2 \times $J = 16.0$ Hz, 2 \times 2H, 2 \times 2 $\text{PhCH}=\text{}$), 7.12–7.36 (m, 2 \times 10H, 2 \times 2Ph) in agreement with literature data.³⁵

Acknowledgements

We thank the EPSRC for grant No. GR/S87294/01, GSK and EPSRC for an industrial CASE awards to A. J. P. S. L., the

Ministry of Education and Science of Spain for a fellowship to P. R.-L., the Loughborough University, the University of Glasgow and Dr Alfred Bader for additional support. We acknowledge COST-ORCA action (CM0905) for creating networking and exchange opportunities.

References

- (a) M. Hudlický, *Reductions in Organic Chemistry*, Ellis Horwood Limited, Chichester, 1984; (b) J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, Wiley-VCH, New York, 1997.
- For a general overview of the asymmetric reduction methods, see: (a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, 1994; (b) I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley & Sons, New York, 2nd edn, 2000; (c) B. R. James, *Catal. Today*, 1977, **37**, 209; (d) S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069; (e) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Springer, vol. I–III, 1999; (f) T. C. Nugent, *Chiral Amine Synthesis*, Wiley-VCH Verlag GmbH, Weinheim, 2010; (g) J. C. Moore, D. J. Pollard, B. Kosjek and P. N. Devine, *Acc. Chem. Res.*, 2007, **40**, 1412; (h) T. C. Nugent and M. El-Shazly, *Adv. Synth. Catal.*, 2010, **352**, 753; (i) J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713.
- (a) B. H. Lipshutz, K. Noson, W. Chrisman and A. Lower, *J. Am. Chem. Soc.*, 2003, **125**, 8779; (b) B. H. Lipshutz and H. Shimizu, *Angew. Chem., Int. Ed.*, 2004, **43**, 2228; (c) B. H. Lipshutz, *Synlett*, 2009, 509; (d) A. V. Malkov, *Angew. Chem., Int. Ed.*, 2010, **49**, 9814.
- (a) P. Kočovský and A. V. Malkov, *Chiral Lewis bases as catalysts*, in *Enantioselective Organocatalysis*, ed. P. I. Dalko, Wiley-VCH Verlag GmbH, Weinheim, 2007, p. 255; (b) A. Weickgenannt and M. Oestreich, *ChemCatChem*, 2011, **3**, 1527; (c) S. Guizzetti and M. Benaglia, *Eur. J. Org. Chem.*, 2010, 5529; (d) P. Kočovský and S. Stončius, *Reduction of imines with trichlorosilane catalyzed by chiral Lewis bases*, in *Chiral Amine Synthesis (Methods, Developments and Applications)*, ed. T. Nugent, J. Wiley & Sons, Chichester, 2010, p. 131; (e) S. Jones and C. J. A. Warner, *Org. Biomol. Chem.*, 2012, **10**, 2189.
- H. Kagan, *Organocatalytic enantioselective reduction of olefins, ketones, and imines*, in *Enantioselective Organocatalysis*, ed. P. I. Dalko, Wiley-VCH Verlag GmbH, Weinheim, 2007, p. 391.
- (a) S. Singh and U. K. Batra, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1989, **28**, 1; (b) M. Rueping, E. Sugiono, C. Azap, T. Theissmann and M. Bolte, *Org. Lett.*, 2005, **7**, 3781; (c) S. Hoffman, A. M. Seayad and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 7424; (d) S. Hoffmann, M. Nicoletti and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 13074; (e) R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 84; (f) S. G. Ouellet, A. M. Walji and D. W. C. MacMillan, *Acc. Chem. Res.*, 2007, **40**, 1327; (g) C. Zheng and S.-L. You, *Chem. Soc. Rev.*, 2012, **41**, 2498.
- (a) F. Iwasaki, O. Onomura, K. Mishima, T. Maki and Y. Matsumura, *Tetrahedron Lett.*, 1999, **40**, 7507; (b) F. Iwasaki, O. Onomura, K. Mishima, T. Kanematsu, T. Maki and Y. Matsumura, *Tetrahedron Lett.*, 2001, **42**, 2525; (c) Y. Matsumura, K. Ogura, Y. Kouchi, F. Iwasaki and O. Onomura, *Org. Lett.*, 2006, **8**, 3789.
- (a) A. V. Malkov, A. Mariani, K. N. MacDougall and P. Kočovský, *Org. Lett.*, 2004, **6**, 2253; (b) A. V. Malkov, S. Stončius, K. N. MacDougall, A. Mariani, G. D. McGeoch and P. Kočovský, *Tetrahedron*, 2006, **62**, 264; (c) A. V. Malkov, M. Figlus, S. Stončius and P. Kočovský, *J. Org. Chem.*, 2007, **72**, 1315; (d) A. V. Malkov, S. Stončius and P. Kočovský, *Angew. Chem., Int. Ed.*, 2007, **46**, 3722; (e) A. V. Malkov, S. Stončius, K. Vranková, M. Arndt and P. Kočovský, *Chem.–Eur. J.*, 2008, **14**, 8082; (f) A. V. Malkov, M. Figlus and P. Kočovský, *J. Org. Chem.*, 2008, **73**, 3985; (g) A. V. Malkov, K. Vranková, S. Stončius and P. Kočovský, *J. Org. Chem.*, 2009, **74**, 5839; (h) A. V. Malkov, K. Vranková, R. Sigerson, S. Stončius and P. Kočovský, *Tetrahedron*, 2009, **65**, 9481; (i) A. V. Malkov, K. Vranková, M. Černý and P. Kočovský, *J. Org. Chem.*, 2009, **74**, 8425; (j) A. V. Malkov, M. Figlus, G. Cooke, S. T. Caldwell, G. Rabani, M. R. Prestly and P. Kočovský, *Org. Biomol. Chem.*, 2009, **7**, 1878; (k) A. V. Malkov, M. Figlus, M. R. Prestly, G. Rabani, G. Cooke and P. Kočovský, *Chem.–Eur. J.*, 2009, **15**, 9651; (l) M. Figlus, S. T. Caldwell, D. Wálas, G. Yesilbag, G. Cooke,

- P. Kočovský, A. V. Malkov and A. Sanyal, *Org. Biomol. Chem.*, 2010, **8**, 137.
- 9 (a) Z. Wang, X. Ye, S. Wei, P. Wu, A. Zhang and J. Sun, *Org. Lett.*, 2006, **8**, 999; (b) Z. Wang, M. Cheng, P. Wu, S. Wei and J. Sun, *Org. Lett.*, 2006, **8**, 3045; (c) P. Wu, Z. Wang, M. Cheng, L. Zhou and J. Sun, *Tetrahedron*, 2008, **64**, 11304; (d) Z. Wang, S. Wei, C. Wang and J. Sun, *Tetrahedron: Asymmetry*, 2007, **18**, 705; (e) L. Zhou, Z. Wang, S. Wei and J. Sun, *Chem. Commun.*, 2007, 2977; (f) J. F. Collados, M. L. Quiroga-Feijóo and C. Alvarez-Ibarra, *Eur. J. Org. Chem.*, 2009, 3357; (g) Y.-C. Xiao, C. Wang, Y. Yao, J. Sun and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2011, **50**, 10661.
- 10 (a) O. Onomura, Y. Kouchi, F. Iwasaki and Y. Matsumura, *Tetrahedron Lett.*, 2006, **47**, 3751; (b) H. Zheng, J. Deng, W. Lin and X. Zhang, *Tetrahedron Lett.*, 2007, **48**, 7934; (c) H.-J. Zheng, W. B. Chen, Z.-J. Wu, J.-G. Deng, W.-Q. Lin, W.-C. Yuan and X.-M. Zhang, *Chem.-Eur. J.*, 2008, **14**, 9864; (d) S. Guizzetti, M. Benaglia, F. Cozzi, S. Rossi and G. Celentano, *Chirality*, 2009, **21**, 233; (e) Z.-Y. Xue, Y. Jiang, W.-C. Yuan and X.-M. Zhang, *Eur. J. Org. Chem.*, 2010, 616; (f) Z.-Y. Xue, Y. Jiang, X.-Z. Peng, W.-C. Yuan and X.-M. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 2132; (g) X. Chen, Y. Zheng, C. Shu, W. Yuan, B. Liu and X. Zhang, *J. Org. Chem.*, 2011, **76**, 9109; (h) Y. Jiang, X. Chen, Y. Zheng, Z. Xue, C. Shu, W. Yuan and X. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 7304; (i) S. Guizzetti, M. Benaglia, M. Bonsignore and L. Raimondi, *Org. Biomol. Chem.*, 2011, **9**, 739. For related *N*-methyl imidazole derivatives, see (j) F. M. Gautier, S. Jones and S. J. Martin, *Org. Biomol. Chem.*, 2009, **7**, 229; (k) S. Jones and X. Li, *Org. Biomol. Chem.*, 2011, **9**, 7860.
- 11 (a) D. Pei, Z. Wang, S. Wei, Y. Zhang and J. Sun, *Org. Lett.*, 2006, **8**, 5913; (b) C. Wang, X. Wu, L. Zhou and J. Sun, *Chem.-Eur. J.*, 2008, **14**, 8789; (c) D. Pei, Y. Zhang, S. Wei, M. Wang and J. Sun, *Adv. Synth. Catal.*, 2008, **350**, 619; (d) X. Wu, Y. Li, C. Wang, L. Zhou, X. Lu and J. Sun, *Chem.-Eur. J.*, 2011, **17**, 2846. See also (e) M. Bonsignore, M. Benaglia, R. Annunziata and G. Celentano, *Synlett*, 2011, 1085.
- 12 A. V. Malkov, A. J. P. Stewart-Liddon, P. Ramírez-López, L. Bendová, D. Haigh and P. Kočovský, *Angew. Chem., Int. Ed.*, 2006, **45**, 1432.
- 13 (a) G. Desimoni, G. Faita and P. Quardelli, *Chem. Rev.*, 2003, **103**, 3119; (b) H.-L. Kwong, H.-L. Yeung, C.-T. Yeung, W.-S. Lee, C.-S. Lee and W.-L. Wong, *Coord. Chem. Rev.*, 2007, **251**, 2188.
- 14 Note that pyridine coordination to chlorosilanes is well established: (a) G. W. Fester, J. Wagler, E. Brendler, U. Böhme, D. Gerlach and E. Kroke, *J. Am. Chem. Soc.*, 2009, **131**, 6855; (b) G. W. Fester, J. Wagler, E. Brendler and E. Kroke, *Eur. J. Inorg. Chem.*, 2008, 5020. See also ref. 8g.
- 15 H. Brunner and U. Obermann, *Chem. Ber.*, 1989, **122**, 499.
- 16 I. Fleming and M. Woolias, *J. Chem. Soc., Perkin Trans. 1*, 1979, 829.
- 17 For the method, see: C. Lempereur, N. Ple, A. Turck, G. Queguiner, F. Corbin, C. Alayrac and P. Metzner, *Heterocycles*, 1998, **48**, 2019.
- 18 S. Scheibye, B. S. Pederson and S.-O. Lawesson, *Bull. Soc. Chim. Belg.*, 1978, **87**, 229.
- 19 M. P. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061.
- 20 For analogous oxazoline ring opening reactions, see: (a) T. G. Gant and A. I. Meyers, *Tetrahedron*, 1994, **50**, 2297; (b) D. A. Klumpp, R. Rendy and A. McElrea, *Tetrahedron Lett.*, 2004, **45**, 7959.
- 21 The exact ee of **45** has not been established, therefore, we assumed that the mechanism of the ring opening might be a mix of S_N2 and S_N1 .
- 22 F. Besseau, M. Luçon, C. Laurence and M. Berthelot, *J. Chem. Soc., Perkin Trans. 2*, 1998, 101.
- 23 Note that hydrochloric acid, which is always present in trace amounts in commercial trichlorosilane due to partial hydrolysis, appears to play a crucial role in the catalytic process since in the presence of 1,8-bis-(dimethylamino)-naphthalene and related bases the reaction completely shuts down.
- 24 For a recent overview of the arene–arene interaction, see: L. M. Salonen, M. Ellermann and F. Diederich, *Angew. Chem., Int. Ed.*, 2011, **50**, 4808.
- 25 A. V. Malkov, P. Ramírez-López, L. Biedermannová, L. Rulišek, L. Duřková, M. Kotora, F. Zhu and P. Kočovský, *J. Am. Chem. Soc.*, 2008, **130**, 5341.
- 26 For impaired coordination of transition metals, resulting from the steric hindrance in the frontal part of the related bipyridine-type ligands, see: A. V. Malkov, I. R. Baxendale, M. Bella, V. Langer, J. Fawcett, D. R. Russell, D. J. Mansfield, M. Valko and P. Kočovský, *Organometallics*, 2001, **20**, 673.
- 27 (a) H. J. Reich, F. Chow and S. K. Shah, *J. Am. Chem. Soc.*, 1979, **101**, 6638; (b) I. Starý and P. Kočovský, *J. Am. Chem. Soc.*, 1989, **111**, 4981; (c) I. Starý, J. Zajiček and P. Kočovský, *Tetrahedron*, 1992, **48**, 7229; (d) A. V. Malkov, I. R. Baxendale, D. Dvořák, D. J. Mansfield and P. Kočovský, *J. Org. Chem.*, 1999, **64**, 2737.
- 28 (a) W. K. Fife, *J. Org. Chem.*, 1983, **48**, 1375; (b) A. V. Malkov, J. B. Hand and P. Kočovský, *Chem. Commun.*, 2003, 1948.
- 29 O. Tsuge, S. Kanemasa, A. Hatada and K. Matsuda, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2537.
- 30 T. Ziegler, B. Hörsch and F. Effenberger, *Synthesis*, 1990, 575.
- 31 N. Halland, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 8331.
- 32 A. V. Malkov, P. Spoor, V. Vinader and P. Kočovský, *Tetrahedron Lett.*, 2001, **42**, 509.
- 33 G. Buono and C. Triantaphylides, *Synthesis*, 1982, 1030.
- 34 I. Abrunhosa, M. Gulea, J. Levillain and S. Masson, *Tetrahedron: Asymmetry*, 2001, **12**, 2851.
- 35 A. V. Malkov, P. Spoor, V. Vinader and P. Kočovský, *J. Org. Chem.*, 1999, **64**, 5308.