Catalyst Development for Organocatalytic Hydrosilylation of Aromatic Ketones and Ketimines[†,‡]

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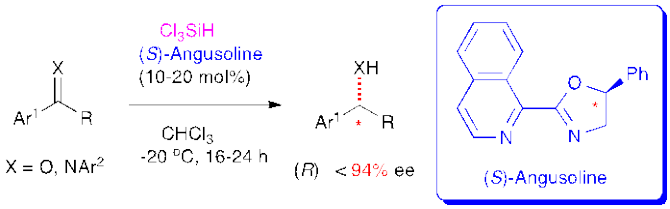
TOC entry: Angusoline, the organocatalyst derived from mandelic acid, delivered high enantioselectivities in the reduction of both ketones and ketimines (≤ 94% ee).

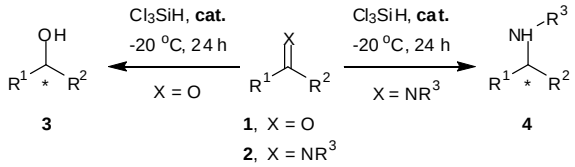


Introduction

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.[3]

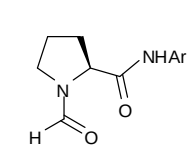
Asymmetric reduction of ketones **1** and ketimines **2** with trichlorosilane, catalysed by chiral Lewis bases (Scheme 1), recently emerged as an efficient methodology[4] capable of competing with the traditional, transition metal-mediated processes[2] and other organocatalytic methods.[5,6] The field has witnessed an exponential growth in the last decade after Matsumura[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 (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.

Scheme 1

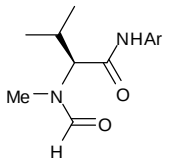


In a preliminary communication [12] we have reported on a novel design of organocatalysts based on the pyridyl-oxazoline core, such as **14** and **16**,[13] which proved equally

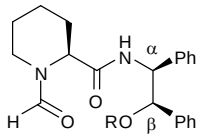
efficient in the reduction of aromatic ketones **1** and ketimines **2** (Scheme 1 and Chart 2). Later, Sun[9e] introduced catalyst **7c**, which also shared that ability. Herein, we present a full account of the development of pyridyl-oxazoline type catalysts **14**-**28** and reveal new applications.



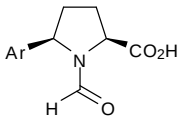
(*S*)-**5a**, Ar = Ph,
(*S*)-**5a**, Ar = 1-Naphthyl



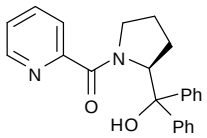
(*S*)-**6a**, Ar = 3,5-$Me_2C_6H_3$
(*S*)-**6b**, Ar = 3,5-*t*-$Bu_2C_6H_3$



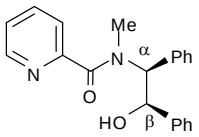
(2*S*,αS,β*R*)-**7a**, R = Ac
(2*S*,αS,β*R*)-**7b**, R = MOM
(2*S*,αS,β*R*)-**7c**, R = Me



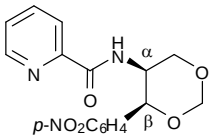
(2*S*,5*R*)-**8**
Ar = 2,4,6-$Et_3C_6H_2$



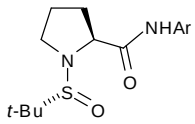
(*S*)-**9**



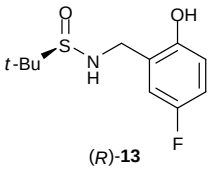
(αS,β*R*)-**10**



(αS,β*R*)-**11**



(2*S*,*R*s)-**12a**, Ar = 3,5-$Me_2C_6H_3$
(2*S*,*R*s)-**12b**, Ar = 2,6-*i*-$Pr_2C_6H_3$



(*R*)-**13**

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

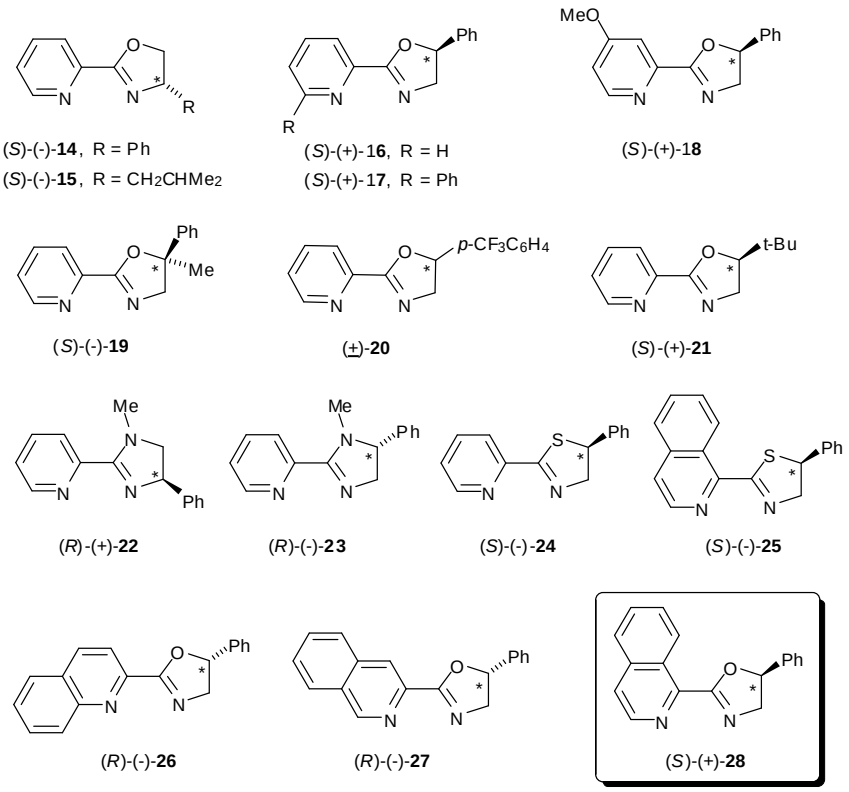
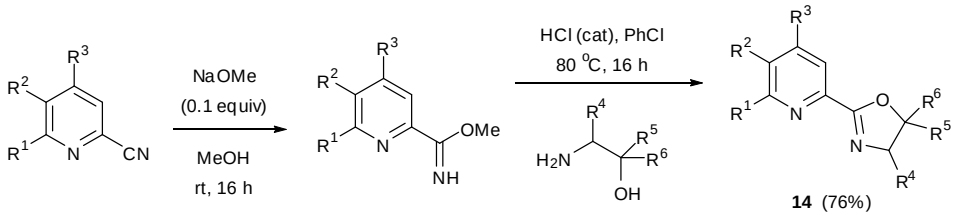


Chart 2. Pyridine-derived catalysts for asymmetric reduction of ketones and ketimines with trichlorosilane.

Results and Discussion

Catalyst design and synthesis. Design of our catalysts takes its origin in the successful series of chelating nitrogen ligands containing pyridine and oxazoline fragments;[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 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 cyclization of the latter 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**[12,14] and **26**, **27**[12] was described earlier.

Scheme 2



29a, $R^1 = R^2 = R^3 = H$
29b, $R^1 = Ph$; $R^2 = R^3 = H$
29c, $R^1 = R^2 = H$; $R^3 = OMe$
29d, $R^1, R^2 = -(CH)_4-$; $R^3 = H$
29e, $R^1 = H$, $R^2, R^3 = -(CH)_4-$

30a-e

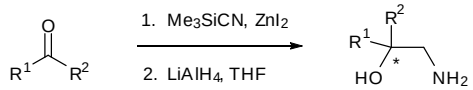
31a, $R^4 = i\text{-Bu}$; $R^5, R^6 = H$
31b, $R^4 = Ph$; $R^5, R^6 = H$
31c, $R^4, R^6 = H$; $R^5 = Ph$
31d, $R^4 = H$; $R^5 = Ph$; $R^6 = Me$
31e, $R^4, R^6 = H$; $R^5 = p\text{-}CF_3C_6H_4$
31f, $R^4, R^6 = H$; $R^5 = i\text{-Bu}$

14 (76%)
15 (56%)
16 (58%)
17 (63%)
18 (31%)
19 (82%)
20 (75%)
21 (82%)

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

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 into the enantiomeric amides, followed by reduction with $LiAlH_4$.[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 cyanosilylation[16] of the carbonyl functionality was carried out in neat trimethylsilyl cyanide to give the trimethylsilyl protected cyanohydrins, which were then *in situ* reduced with $LiAlH_4$ to afford racemic amino alcohols **31d-f**.

Scheme 3



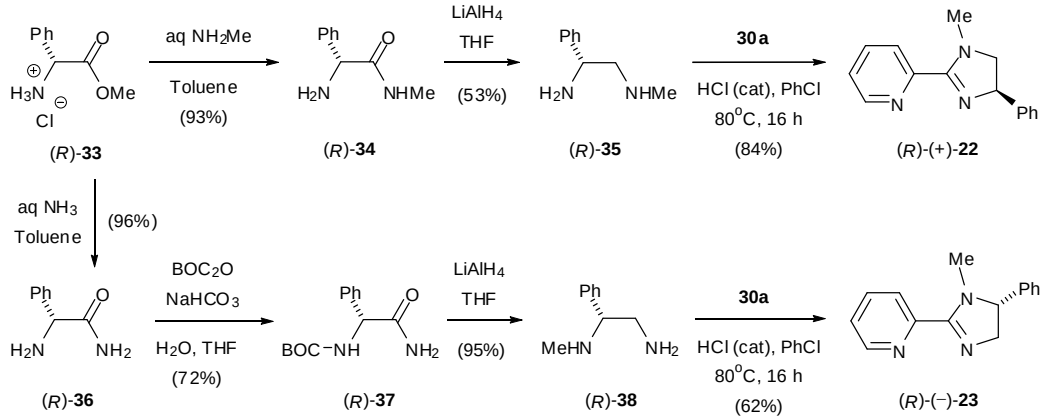
32a, $R^1 = Ph$, $R^2 = Me$
32b, $R^1 = p\text{-}CF_3C_6H_4$, $R^2 = H$
32c, $R^1 = t\text{-Bu}$, $R^2 = H$

31d, $R^1 = Ph$, $R^2 = Me$ (62%)
31e, $R^1 = p\text{-}CF_3C_6H_4$, $R^2 = H$ (88%)
31f, $R^1 = t\text{-Bu}$, $R^2 = H$ (82%)

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.

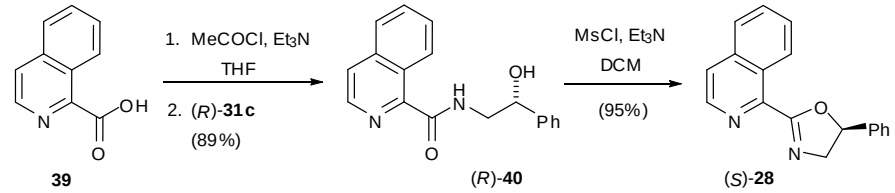
The synthesis of imidazolines (*R*)-**22** and (*R*)-**23** was achieved by the reaction of imidate **30a** and diamines (*R*)-**35** and (*R*)-**38**, respectively (Scheme 4). The latter diamines were synthesised from methyl phenylglycinate hydrochloride (*R*)-**33** as follows: the latter starting 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**.

Scheme 4



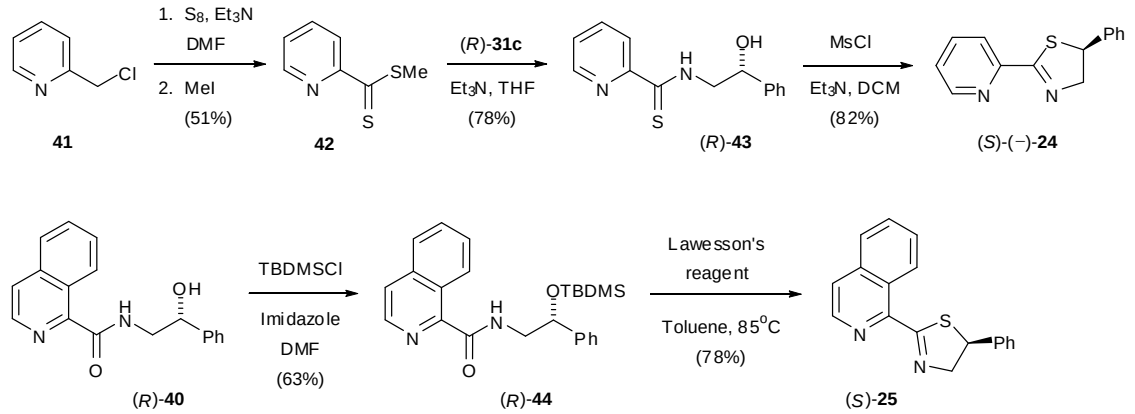
For the synthesis of 1-isoquinolyloxazoline **28**, a different strategy was employed due to the high cost of 1-isoquinolinecarbonitrile (Scheme 5). The preparation commenced with amidation of the commercially available 1-isoquinoline carboxylic acid **39** with mandelamine (*R*)-**31c** using the mixed 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.

Scheme 5



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's reagent in HMPA[18] 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.

Scheme 6



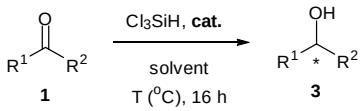
Asymmetric reduction of ketones with trichlorosilane. Our preliminary investigation focused on the reduction of aromatic ketones with trichlorosilane in the presence of 20 mol% of 2-pyridyl oxazolines (Table 1). Oxazolines (*S*)-**14** and (*S*)-**15**, derived from phenylglycine and leucine, respectively, exhibited modest conversion and enantioselectivity in the reduction of acetophenones **1a** at -20 °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 °C or -30 °C appear to be optimal in terms of performance (entries 4 and 5) but -20 °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 °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 catalysts and $CHCl_3$ at -20 °C as the optimal reaction conditions. Next, the reaction scope was assessed by employing a range of ketones **1a-l** (Table 1). Propiophenone **1b** (entry 9) 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 **1j** 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).

Table 1. Reduction of Ketones with Trichlorosilane.[a]



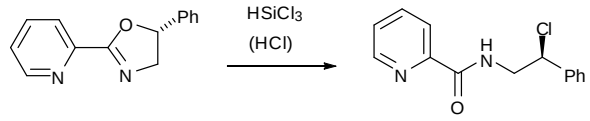
Entry	Catalyst	Ketone	R^1, R^2	Solvent	Temp (°C)	Conversion (%)[a]	**3**, ee (%)
1	(*S*)-**14**	**1a**	Ph, Me	$CHCl_3$	−20	29	66 (*S*)
2	(*S*)-**15**	**1a**	Ph, Me	$CHCl_3$	−20	34	54 (*S*)
3	(*S*)-**16**	**1a**	Ph, Me	CH_2Cl_2	rt	40	64 (*R*)
4	(*S*)-**16**	**1a**	Ph, Me	$CHCl_3$	−20	85	78 (*R*)
5	(*S*)-**16**	**1a**	Ph, Me	$CHCl_3$	−30	94	78 (*R*)
6	(*S*)-**16**	**1a**	Ph, Me	$CHCl_3$	−40	6	69 (*R*)
7	(*S*)-**16**	**1a**	Ph, Me	CH_2Cl_2	−20	83	74 (*R*)
8	(*S*)-**16**	**1a**	Ph, Me	THF	−20	30	70 (*R*)
9	(*S*)-**16**	**1b**	Ph, Et	$CHCl_3$	−20	91	80 (*R*)
10	(*S*)-**16**	**1c**	Ph, *i*-Pr	CH_2Cl_2	−20	0	-
11	(*S*)-**16**	**1d**	2-Naphthyl, Me	$CHCl_3$	−20	99	80 (*R*)
12	(*S*)-**16**	**1e**	6'-Me-Naphth-2-yl, Me	$CHCl_3$	−20	99	83 (*R*)
13	(*S*)-**16**	**1f**	4-Me-C_6H_4, Me	$CHCl_3$	−20	96	80 (*R*)
14	(*S*)-**16**	**1g**	2-MeO-C_6H_4, Me	$CHCl_3$	−20	99	77 (*R*)
15	(*S*)-**16**	**1h**	4-MeO-C_6H_4, Me	CH_2Cl_2	−20	65	43 (*R*)
16	(*S*)-**16**	**1i**	2-F-C_6H_4, Me	$CHCl_3$	−20	30	70 (*R*)
17	(*S*)-**16**	**1j**	2-Br-C_6H_4, Me	CH_2Cl_2	−20	0	-
18	(*S*)-**16**	**1k**	4-CF_3-C_6H_4, Me	$CHCl_3$	−20	47	71 (*R*)
19	(*S*)-**16**	**1l**	*c*-Hex, Me	CH_2Cl_2	−20	67	0
20	(*S*)-**17**	**1a**	Ph, Me	CH_2Cl_2	0	0	-
21	(*S*)-**18**	**1a**	Ph, Me	CH_2Cl_2	0	10	25 (*R*)

[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.

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 Cl_3SiH as a contaminant) or by coordination of the Lewis-acidic silicon,[20] either of which could facilitate the undesired gradual ring-opening at the benzylic position.

Scheme 7



(*R*)-(+)-**16** (*S*)-(-)-**45**

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.

***Table 2*.** Reduction of **1a** with Trichlorsilane Catalysed by 5-Subtituted Oxazolines.[a]

Entry	Catalyst	Solvent	Temp (°C)	Conversion (%)[a]	**3**, ee (%)
1	(*S*)-**16**	CH_2Cl_2	−20	83	74 (*R*)
2	(*S*)-**19**	CH_2Cl_2	rt	63	34 (*R*)
3	(±)-**20**[b,c]	$CHCl_3$	−20	72	-
4	(*S*)-**21**[b]	CH_2Cl_2	−20	85	68 (*R*)
5	(*R*)-**22**[b]	$CHCl_3$	−20	51	34 (*R*)
6	(*R*)-**23**[b]	$CHCl_3$	−20	17	34 (*S*)
7	(*S*)-**24**	$CHCl_3$	−20	25[d]	64 (*R*)
8	(*S*)-**25**	CH_2Cl_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.

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-C_6H_4COMe (1.34) > PhCOMe (1.11) > 2-F-C_6H_4COMe (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 by the catalyst can be predicted to generate an activated hypervalent 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.

Scheme 8.

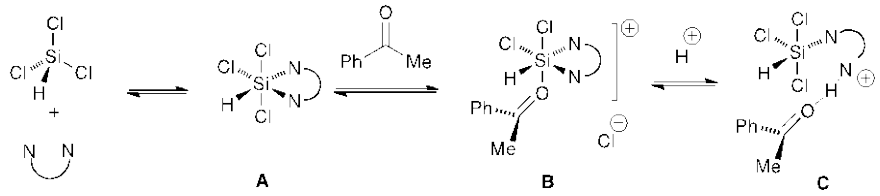
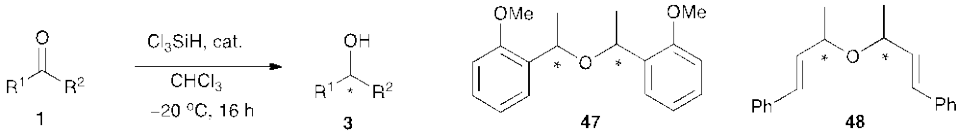


Table 3: Reduction of Ketones **1** with Trichlorosilane Catalyzed by **25-28**.[a]



entry	Catalyst (mol%)	ketone	R^1, R^2	yield (%)[b]	*ee* (%)[c,d]
1	(*R*)-**26** (20)	**1a**	Ph, Me	0[e]	-
2	(*R*)-**27** (20)	**1a**	Ph, Me	41[e]	73
3	(*S*)-**28** (20)	**1a**	Ph, Me	80[e]	76
4	(*S*)-**28** (20)	**1a**	Ph, Me	72	84
5	(*S*)-**28** (10)	**1a**	Ph, Me	85	84
6	(*S*)-**28** (10)	**1b**	Ph, Et	55	86
7	(*S*)-**28** (10)	**1d**	2-Naphth, Me	93	94
8	(*S*)-**28** (10)	**1e**	6-Me-2-Naphth, Me	93	92
9	(*S*)-**28** (10)	**1f**	4-Me-C_6H_4, Me	90	85
10	(*S*)-**28** (10)	**1g**	2-MeO-C_6H_4, Me	50[f]	87
11	(*S*)-**28** (10)	**1i**	2-F-C_6H_4, Me	35	70
12	(*S*)-**28** (10)	**1l**	Cyclohexyl, Me	77	0
13	(*S*)-**28** (10)	**1m**	Cinnamyl, Me	52[g]	16

[a] The reactions were carried out on 0.4 mmol scale with 2.1 equiv. of $HSiCl_3$ in $CHCl_3$ in the presence of catalyst **7** for 24 h (unless stated otherwise). [b] Isolated yield (product pure by ^1H NMR). [c] All products **2** 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 CH_2Cl_2. [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.

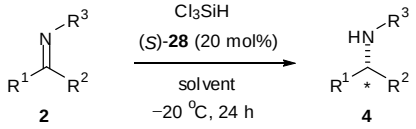
No reduction was observed with quinoline (*R*)-**26** (Table 3, entry 1), presumably due to the steric constraints in the frontal part,[26] imposed by the quinoline moiety, mirroring the behaviour of the pyridine analogue **17** substituted at the 6-position (Table 1, entry 20). The 3-isoquinoline catalyst (*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 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 ^{o}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 precursor 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*–R^3 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.

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_2Cl_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_6H_4, Me, PMP	$CHCl_3$	65	87
12	**2g**	4-MeO-C_6H_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_6H_5, CH_2Cl, PMP	$CHCl_3$	90	88
19	**2n**	4-Cl-C_6H_5, CH_2Cl, PMP	$CHCl_3$	47	88
20	**2o**	4-F-C_6H_5, CH_2Cl, PMP	$CHCl_3$	70	89

[a] The reactions were carried out on 0.4 mmol scale with 2.0 equiv. of $HSiCl_3$ in $CHCl_3$ in the presence of catalyst (*S*)-**28** (20 mol%) at -20 °C for 24 h (unless stated otherwise). [b] Isolated yield (product pure by ^{1}H 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 Chiracel 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.

In conclusion: 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 apreciation 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 (F_{254}) plates, visualised using $UV_{254\,nm}$ and potassium permanganate, phosphomolybdic acid or Dragendorf 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 cm^2 g^{-1}. The NMR spectra were recorded for $CDCl_3$ solutions, ^1H at 400 MHz and ^{13}C at 100.6 MHz with chloroform-d_1 (δ 7.26, ^1H; δ 77.0, ^{13}C) 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-DEX™ 120 fused capillary column, 30 m × 0.25 mm ×0.25 μm 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 μL, 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 eq) in $CHCl_3$ (2 mL) at –20 ˚C. The reaction mixture was stirred at -20 ˚C for 24 h, after which time saturated aqueous $NaHCO_3$ (1 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography on silica gel with CH_2Cl_2 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 μL, 0.80 mmol, 2.0 eq) was slowly added dropwise to a solution of the catalyst (21.9 mg, 0.08 mmol) and the imine (0.40 mmol, 1.0 eq) in $CHCl_3$ (2 mL) at –20 ˚C. The reaction mixture was stirred at -20 ˚C for 24 h, after which time saturated aqueous $NaHCO_3$ (1 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. 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,8g]

(*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 (CH_2Cl_2); $[\alpha]_D$ +104.6 (*c* 1.1, $CHCl_3$); IR (KBr) ν 1637 (C=N), 2873, 2932 (CH/CH_2), 3032, 3060 (Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 63.8 (CH_2), 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 ($M^{+\bullet}$, 65), 193 (100), 154 (15), 127 (16), 118 (12), 77 (8); HRMS (EI) 300.1260 ($C_{20}H_{16}N_2O$ 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*)-**31d** (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** (215mg, 31%) as a clear oil: $[\alpha]_D$ +74.9 (*c* 0.9, $CHCl_3$); IR (neat) ν 2873, 2939 ($CH/CH_2/CH_3$), 3030, 3063 (Ar-H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 55.9 (CH_3), 63.5 (CH_2), 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 ($M^{+\bullet}$, 100), 195 (7), 166 (8), 148 (95), 108 (72), 84 (65), 77 (9), 47 (11); HRMS (EI) 254.1054 ($C_{15}H_{14}N_2O_2$ requires 254.1055).

(*S*)-(–)-2-(2'-Pyridyl)-5-phenyl-1,3-oxazoline (*S*)-(–)-(19). Adapting the protocol of Brunner[14] amino alcohol (–)-**31d** (570 mg, 4.17 mmol, 1.0 equiv) was added to a solution of methyl pyridine-2-carboxyimidate **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: $[\alpha]_D$ –171.5 (*c* 1.07, $CHCl_3$); IR ν (KBr) 1673 (C=N); 2869, 2930, 2975 ($CH/CH_2/CH_3$), 3027 (aryl-H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.1 (CH_3), 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 ($M^{+\bullet}$, 20), 118 (100), 91 (15), 78 (80), 77 (10), 51 (10); HRMS (EI) 238.1107 ($C_{15}H_{14}N_2O$ requires 238.1106).

(±)-2-(2'-Pyridyl)-5-(4''-Trifluoromethylphenyl)-1,3-oxazoline (±)-(20). Adapting the procedure of Bruner,[14] 2-amino-1-phenylethanol (±)-**31e** (754 mg, 3.68 mmol, 1.0 equiv) was added to a solution of imidate **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 (CH_2Cl_2); IR ν (KBr) 1643 (C=N), 2867, 2963 (CH/CH_2) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 63.3 (CH_2), 80.9 (CH), 124.0 (q, $^1J_{CF}$ = 246 Hz, [CF_3], 124.0 (2 × CH), 125.8 (C), 125.9 (CH), 125.9 (CH), 126.1 (2 × CH), 130.6 (q, $^2J_{CF}$ = 32 Hz, [C]), 136.8 (CH), 144.6 (C), 146.3 (C), 150.0 (CH); EI MS *m/z* (%) 292 ($M^{+\bullet}$, 75), 273 (5), 186 (10), 159 (7), 118 (100), 106 (7), 78 (98), 51 (10); HRMS (EI) 292.0822 ($C_{15}H_{11}F_3N_2O$ requires 292.0823).

(+)-2-(2'-Pyridyl)-5-*tert*-butyl-1,3-oxazoline (+)-(21). Adapting the protocol of Brunner,[14] 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-carboxyimidate (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** (671mg, 89%) white solid: mp 73-75 ˚C (CH_2Cl_2);; IR (KBr) ν 1644 (C=N), 2869, 2958 (CH/CH_2/CH_3), 3066 (aryl-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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 × 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 ($M^{+\bullet}$, 15), 147 (100), 119 (35), 92 (50), 78 (55), 51 (10); HRMS (EI) 204.1261 ($C_{12}H_{16}N_2O$ requires 204.1263). The racemate was resolved by preparative chiral HPLC on a Chiralpak AD column (Heptane–2-Propanol, 98:2, 1mL/min) to give (+)-**21**: $[\alpha]_D$ +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: $[\alpha]_D$ +11.9 (*c* 1.0, $CHCl_3$); IR (KBr) ν 1522, 1670 (aryl ring), 2797, 2848, 2937 (CH/CH_2/CH_3), 3029, 3059 (Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.12 (s, 3H), 3.40 (t, *J* = 9.4, 1H), 4.01 (dd, *J* = 10.9, 9.4Hz, 1H), 5.21 (dd, *J* = 10.7, 9.7Hz, 1H), 7.28-7.29 (m, 1H), 7.35-7.40 (m, 5H), 7.79 (td, *J* = 7.6, 1.6Hz, 1H), 7.91 (dt, *J* = 7.6, 0.8Hz, 1H), 8.69 (dd, *J* = 4.8, 1.6, 0.8Hz, 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 × CH), 127.5 (CH), 128.9 (2 × CH), 137.1 (CH), 144.5 (C), 149.0 (CH), 150.9 (C), 165.5 (C); CI MS *m/z* (%) 238 ($[M+H]^+$, 100); HRMS (CI) 238.1341 ($C_{15}H_{16}N_3$ 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: $[\alpha]_D$ –86.2 (*c* 0.67, $CHCl_3$); IR (KBr) ν 1671, 1590, 1495 (aryl ring), 2858, 2920 (CH/CH_2CH_3), 3029, 3060 (Ar-H) cm^{-1}; ^{1}H 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 × CH), 127.2 (2 × CH), 127.8 (C), 128.8 (2 × CH), 136.7 (CH), 147.5 (C), 148.7 (CH), 150.5 (C), 165.1 (C); EI MS *m/z* (%) 237 ($M^{+\bullet}$, 75), 236 (10), 222 (6), 207 (4), 160 (15), 133 (100), 118 (50), 78 (80), 77 (12), 51 (10); HRMS (EI) 237.1268 ($C_{15}H_{15}N_3$ 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 ^{o}C and the reaction 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 x 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 ^{o}C; $[\alpha]_D$–77.50 (*c* 1.0, $CHCl_3$); ^{1}H 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 ($C_{14}H_{12}N_2S$ 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 ^{o}C overnight. The reaction mixture was then allowed to cool to room temperature, aqueous 2M 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 x 30 mL) and the combined organic phases were washed with water (3 x 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 (152 mg, 74%): $[\alpha]_D$ -22.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ_H 4.78 (1H, dd, *J* = 4.3, 15.2 Hz, 2-H), 4.83 – 4.89 (1H, m, 1α-H), 5.02 – 5.06 (1H, m, 1β-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 ($C_{18}H_{14}N_2S$ requires 290.0879).

(*S*)-(+)-2-(1'-Isoquinolinyl)-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 vessel 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); $[\alpha]_D$ +83.5 (*c* 0.5, $CHCl_3$); IR (KBr) 700, 759, 838 (aryl), 1645 (C=N), 2866, 2931 (CH/CH_2), 3064 (aryl-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100MHz, $CDCl_3$) δ_C 63.9 (CH_2), 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 ($M^{+\bullet}$, 65), 168 (70), 128 (100), 101 (15), 82 (35), 77 (10), 47 (5); HRMS (EI) 274.1105 ($C_{18}H_{14}N_2O$ requires 274.1106).

2-Cyano-4-methoxy-pyridine (**29c**)**.** Adapting the method of Fife,[28a] Me_3SiCN (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 CH_2Cl_2 (100 mL) at room temperature. A solution of dimethylcarbamoyl chloride (0.73 mL, 1.26 g, 11.7 mmol, 1.25 equiv) in CH_2Cl_2 (20 mL) was then added dropwise over 30 min and the reaction mixture was stirred at room temperature for 6 days. Satd. Na_2CO_3 (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 CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ 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 (CH_2Cl_2); IR (KBr) ν 1528, 1586, 1657 (aryl ring), 2888, 2929, 2954 (CH_3), 2996 (Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 56.2 (CH_3), 113.1 (CH), 115.8 (CH), 117.5 (C), 135.5 (C), 152.7

(CH), 166.3 (C); EI MS *m/z* (%) 134 ($M^{+\bullet}$, 100), 119 (5), 104 (50), 104 (50), 83 (20), 77 (25), 64 (10), 51 (10), 50 (9); HRMS (EI) 134.0479 ($C_7H_6N_2O$ requires 134.0480).

1-Amino-2-phenylpropan-2-ol (31d).[29] Adapting the protocol of Fleming,[16] Me_3SiCN (6.1 mL, 45.0 mmol, 1.1 equiv) and anhydrous ZnI_2 (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 $LiAlH_4$ (4.75 g, 125 mmol, 3.0 equiv) in THF (200 mL). After heating at reflux for 3 h the reaction was quenched with $Na_2SO_4{\cdot}10H_2O$ 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: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 27.8 (CH_3), 52.7 (CH_2), 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 ($C_9H_{14}NO$ requires 152.1075), in agreement with the literature.[29]

Resolution: The resolution of **31d** was carried out by recrystalising 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 2M NaOH (30 mL) and extracted with ether (2 × 30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give (–)-**31d** (688 mg, 35%): $[\alpha]_D$ -13.6 (*c* 1.2, $CHCl_3$).

GC Analysis: A portion of (–)-**31d** (50 mg) in CH_2Cl_2 (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-DEX^{TM}); carrier gas, He (flow 2 mL/min); injection temp, 200 ˚C; column temp: initial temperature, 80 ˚C; rate, 1.5 ˚C/min; 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 Flemming,[16] Me_3SiCN (1.37 mL, 10.3 mmol, 1.4 equiv) and anhydrous ZnI_2 (15 mg, 0.05 mmol, 0.6 mol%) were added to a Schlenk tube containing 4-trifluomethyl 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 $LiAlH_4$ (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 $Na_2SO_4{\cdot}10H_2O$ 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/CH_2), 3095 (Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 48.0 (CH_2), 72.2 (CH), 123.1 (q, $^1J_{CF}$ = 270 Hz, [CF_3]), 124.4 (2 × CH), 125.1 (2 × CH), 128.7 (q, $^2J_{CF}$ = 32 Hz, [C]), 145.6 (C); CI MS *m/z* (%) 206 ($[M+H]^+$, 100), 188 (10), 121 (1) 71 (2); HRMS (CI) 206.0791 ($C_9H_{11}F_3NO$ requires 206.0793).

1-Amino-3,3-dimethylbutan-2-ol (31f).[30] Adapting the protocol of Fleming,[16] Me_3SiCN (4.33 mL, 32.5 mmol, 1.4 equiv) and anhydrous ZnI_2 (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 $LiAlH_4$ (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 $Na_2SO_4{\cdot}10H_2O$ and the mixture was filtered through a pad of celite (eluting with ether). The filtrate was concentrated by evaporation *in vacuo* to afford **31f** (2.23g, 82%) as a yellow solid: mp 55-57˚C (CH_2Cl_2); IR (KBr) ν 2956 ($CH/CH_2/CH_3$), 3281 (N-H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 24.4 (3 × CH_3), 32.4 (C), 41.1 (CH_2), 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*)-**34**[31] (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 (CH_3), 55.8 (CH), 60.4 (CH_2), 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*)-**36**[32] (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/CH_3), 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 × CH_3), 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-Methylmino-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, $CHCl_3$); ^{1}H 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-isoquinolinyl-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 ^{o}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 ^{o}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, $CHCl_3$); ^{1}H 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 (CH_2, 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.[34] Amino alcohol **31b** (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 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%): ^{1}H 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*-Butyldimethylsilanoxy-2'-phenylethyl)-1-isoquinolinyl-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 x 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, $CHCl_3$); ^{1}H 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 (CH_3, C-19), -3.6 (CH_3, C-20), 18.2 (C-21), 25.7 (CH_3, C-22), 47.9 (CH_2, 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 μL, 3.6 mmol, 8.1 equiv) was added to a solution of oxazoline (*S*)-**17** (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 × 20 mL) and the combined organic fractions 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); $[\alpha]_D$ –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}; ^{1}H 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 × CH), 129.2 (2 × CH), 137.8 (CH), 138.5 (C), 139.2 (C), 148.6 (CH), 149.9 (C), 164.9 (C); EI MS *m/z* (%) 262 ($M^{+\bullet}${^{37}Cl}, 3), 260 ($M^{+\bullet}${^{35}Cl}, 10), 224 (10), 135 (100), 118 (15), 106 (90), 78 (98), 51 (18), 50 (4); HRMS (EI) 260.0714 and 262.0689 ($C_{14}H_{13}{}^{35}ClN_2O$ requires 260.0716, $C_{14}H_{13}{}^{37}ClN_2O$ 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; ^{1}H-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, 2H), 6.96 (*m*, t, *J* = 7.2, 2H), 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 × 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 ($M^{+\bullet}$, 6), 271 (4), 178 (4), 151 (6) 135 (100), 105 (13), 84 (9), 49 (11); HRMS (EI) 286.1569 ($C_{18}H_{22}O_3$ 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 mixturwe of diastereoisomers by elution from silica gel as a less polar fraction than the main product using a petroleum ether-AcOEt mixture (75:1): ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.26 and 1.28 (2 x d, *J* = 6.4 Hz, 2 x 6H, 2 x 2Me), 4.10 and 4.16 (2 x m, 2 x 2H, 2 x 2CH_3C*H*), 6.04 and 6.11 (2 x dd, 2 x *J* = 16.0, 7.6 Hz, 2 x 2H, 2 x 2CHC*H*=), 6.42 and 6.46 (2 x d, 2 x *J* = 16.0 Hz, 2 x 2H, 2 x 2PhC*H*=), 7.12-7.36 (m, 2 x 10H, 2 x 2Ph) in agreement with literature data.[35]

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