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Synergistic substrate and catalyst effects in the addition of trimethylsilylcyanide to imines derived from lactic acid.

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| ARTICLE INFO | ABSTRACT |
| Article history:ReceivedReceived in revised formAcceptedAvailable online | Trimethylsilylcyanide was added to various imines derived from (2*S*)-ethyl lactate in the presence of Lewis acids to provide both *syn-* and *anti-* *β-hydroxy-α-aminonitrile* stereoisomers. *Syn-* products were found to be the major in most instances, however, *anti*- products were formed in good yield and selectivity in the presence of ZnI2 & BF3.OEt2 and *N*-(-)-α-methylbenzyl substituents via double stereodifferentiation.2017 Elsevier Ltd. All rights reserved. |
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[[1]](#footnote-2)α-Amino nitriles are well known as products of the Strecker reaction and intermediates for the synthesis of α-amino acids. They are also synthetically useful as iminium and acyl anion equivalents under appropriate conditions, as well intermediates for other common functionalities, including 1,2-diamines.1 The high demand for enantiomerically pure α-amino acids has resulted in significant developments of the asymmetric Strecker reaction, which is especially useful for the preparation of enantioenriched non-proteinogenic α-amino acids. For example, Harada used α-methylbenzylamine as the amine component of a one-pot Strecker synthesis, giving the corresponding enantioenriched α-aminonitrile in up to a 3.3:1 diastereomeric ratio.2 Ojima *et al.* reported the use of trimethylsilyl cyanide as an alternative cyanide source for the Strecker reaction,3 adding this to imines bearing an α-methylbenzylamine stereodirecting group, giving *N*-chiral α-aminonitriles in a 2.3:1 diastereomeric ratio.4 Asymmetric trimethylsilylcyanation has been further developed using chiral catalysts5,6 and other *N*-chiral auxiliaries including *N*-sulfinylamines.7

In addition to nitrogen-based stereodirecting groups, an alternative strategy is to add cyanide to imines with an adjacent stereocentre bearing a hydroxyl group, giving access to diastereomerically enriched β-hydroxy-α-aminonitriles. Cainelli *et al.* reported the Lewis acid catalysed addition of trimethylsilyl cyanide to *N*-substituted imines derived from (2*S*)-lactaldehyde, proceeding with good diastereoselectivity (9:1) towards the corresponding (2*S*,3*S*)-2,3-*syn*-β-hydroxy-α-amino nitriles in the presence of ZnI2.8 Substrate control elements have also been employed in conjunction with chiral auxiliary approaches, examples including use of chiral *N*-sulfinyl imines with mandelate and valine derived substrates,7 and the *N*-α-methylbenzyl9 stereodirecting group with aromatic heterocycles. Building on these studies, this work explores the role of the stereogenic centres in controlling the stereoselectivity of the Lewis acid-catalyzed trimethylsilylcyanation reaction at a series of *N*-substituted imines derived from (*S*)-ethyl lactate.

1. Results

Imine substrates were prepared from commercially available (*S*)-ethyl lactate by first protecting as the *O*-benzyl and *O*-*t*-butyldimethylsilyl ethers. Benzyl protection of (*S*)-ethyl lactate was initially carried out using benzyl bromide and sodium hydride, but chiral phase HPLC indicated that the substrate had racemised under these conditions. Benzyl 2,2,2-trichloroacetimidate was initially used as a milder alternative methods until it was shown that using a weaker base, potassium *t*-butoxide, in conjunction with benzyl bromide, delivered the benzyl ether without racemization. This method was thus chosen as a more cost effective alternative. Lability of the proton at the hydroxyl stereocentre remained a concern. However, Gibson *et al.* recently demonstrated that epimerisation of lactic imines of this type is detectable by 1H NMR spectroscopy.10 This was confirmed for the imines synthesised in this study by comparison of their spectroscopic details with the corresponding analogous lactimines formed from racemic ethyl lactate.

Both *O-*Bn and *O-*Si protected derivatives were reduced to the corresponding aldehydes using di-isobutylaluminum hydride and immediately converted to the *N*-substituted imines using *p*-methoxyphenylamine and *p*-methoxybenzylamine (Scheme 1).



**Scheme 1.** Synthesis of lactate aldimines.

(*+*)-α-Methylbenzylamine and (*-*)-α-methylbenzylamine were used to form *N*-chiral-substituted imines for the *O*-Si derivatives only. Imines were confirmed to be a single isomer by 1H NMR spectroscopy. This was inferred to be the (*E*)-isomer in each case due to the well documented exclusive preference for this geometry at equilibrium.11 The *N*-PMP and *N*-PMB imines were found to be quite unstable, degrading rapidly after formation, even at low temperature, and could not be purified. Thus reactions of these were carried out immediately after imine formation. However, *N*-chiral-imines were significantly more stable, and were stored at 0 oC under a nitrogen atmosphere for up to 10 days without any noticeable degradation.

Trimethylsilyl cyanide addition reactions to the imines were then carried out for 24 hours at room temperature using trimethylsilyl cyanide (1.2 equiv.) in DCM and 10 mol% Lewis acid (Scheme 2). Each reaction was analyzed using 1H NMR spectroscopy, the conversion to product being assessed using an internal mesitylene reference, and the diastereoselectivity from comparison of the integrals from the doublet corresponding to the methine centre adjacent to the newly installed nitrile.



**Scheme 2.** TMSCN addition to lactimines **6**–**11**.

In general, higher conversion was observed for *O*-TBDMS than *O*-Bn-protected imines, whilst *N*-PMB substrates were broadly better tolerated than *N*-PMP ones. This result is reflective of the stability of the imine substrates. Previous work on the addition of TMSCN to aldehydes has established that coordination of the Lewis basic *N* atom of the imine to form a pentavalent silicate intermediate allows for facile formation of both cyanohydrins and α-aminonitriles.12 This may account for

**Table 1**

Conversion and diastereoselectivity of Lewis acid catalyzed to lactimines **6**–**9** according to Scheme 2.*a*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry** | **Imine** | **Lewis acid** | **Conversion (%)***b* | **Ratio***c* |
| 1 | **6** | BF3.OEt2 | 42% | 45 : 55 |
| 2 | **6** | SnCl4 | 50% | 42 : 58 |
| 3 | **6** | ZnI2 | 50% | 45 : 55 |
| 4 | **7** | BF3.OEt2 | 37% | 20 : 80 |
| 5 | **7** | SnCl4 | 19% | 24 : 76 |
| 6 | **7** | ZnI2 | 21% | 22 : 78 |
| 7 | **8** | BF3.OEt2 | 73% | 43 : 57 |
| 8 | **8** | SnCl4 | 93% | 42 : 58 |
| 9 | **8** | ZnI2 | 84% | 42 : 58 |
| 10 | **9** | BF3.OEt2 | 60% | 25 : 75*d* |
| 11 | **9** | SnCl4 | 44% | 40 : 60*d* |
| 12 | **9** | ZnI2 | 75% | 45 : 55*d* |
| 13 | **10** | no additive | 66% | 31 : 69*d* |
| 14 | **10** | BF3.OEt2 | 87% | 21 : 79*d* |
| 15 | **10** | ZnI2 | 96% | 29 : 78*d* |
| 16 | **10** | TfOH | 84% | 21 : 79*d* |
| 17 | **10** | La(OiPr)3 | 76% | 29 : 71*d* |
| 18 | **10** | TBAI | 99% | 32 : 68*d* |
| 19 | **10** | Zn(OAc)2 | 89% | 22 : 82*d* |
| 20 | **11** | no additive | 55% | 36 : 64*d* |
| 21 | **11** | BF3.OEt2 | 81% | 87 : 13*d* |
| 22 | **11** | ZnI2 | 89% | 90 : 10*d* |
| 23 | **11** | TfOH | 76% | 29 : 71*d* |
| 24 | **11** | La(OiPr)3 | 63% | 26 : 64*d* |
| 25 | **11** | TBAI | 86% | 34 : 66*d* |
| 26 | **11** | Zn(OAc)2 | 73% | 31 : 69*d* |

*a* Reactions were carried out at room temperature for 24 h using 10 mol% Lewis acid; *b* Conversion calculated by addition of mesitylene as an internal standard after reaction was complete; *c* Diastereomeric ratio was assessed by comparison of the integrals for the signals between 3.5 and 4.5 ppm for each diastereoisomer in the 1H NMR spectrum of the unpurified reaction mixture. The identity of each diastereisomer was not confirmed by further experiments for substrates **6**-**8**; *d* Refers to *anti* : *syn* ratio.

the reduced reactivity of the *N*-PMP derivatives due to the lower Lewis basicity of the nitrogen atom in these compounds.

Within the subset of imine substrates **6**-**9** lacking an additional stereogenic centre on the nitrogen atom, the identity of the major isomer formed from substrate **9** (Table 1, entries 10-12) was confirmed as *syn* by comparison of the analytical data to that in the literature.8 However, in all other cases within this subset, the identity of the major and minor isomers was not confirmed, but is likely to be similar. The *O*-TBDMS substrates consistently delivered the highest conversion to product compared to the *O*-benzyl substrates.

The best catalysts from this initial screen (ZnI2 and BF3.OEt2) were taken forward for further investigation with *N*-chiral imines **10** and **11**, together with TfOH and La(OiPr)3. This was due to the poor performance of SnCl4, and to monitor the effects of a Lewis acid with a larger coordination sphere in addition to a Brønsted acid. Additionally, only *O*-TBDMS derivatives were taken forward for further evaluation, as these were more stable and provided better results in the initial screening. Strategically, this also provides a more labile protecting group, orthogonal in reactivity to the additional -methylbenzyl group. Both reactions conducted without any additive on epimeric substrates **10** and **11** broadly delivered the same levels of selectivity in favor of the *syn* product as the major isomer (Table 1, entries 13 and 20), however in reduced conversion, consistent with the need of a catalytic ‘activator’ for the TMSCN. Furthermore, (*+*)-*N*-substituted substrate **10** exclusively provided the *syn* product in broadly similar ratios (Table 1, entries 13–19), while the selectivity of the (-)-*N*-substituted substrate **11** was found to be dependent on which Lewis acid was used (Table 1, entries 20-26). In particular, a switch of selectivity, delivering the 2,3-*anti-*α-aminonitrile was observed when using the (-)-substrate **11** and either ZnI2 or BF3.OEt2 (Table 1, entries 21 & 22). The excellent performance of ZnI2 was probed, first looking at the role of iodide by using TBAI, that does indeed accelerate the rate of the reaction with imines **10** and **11**, but with no stereoselectivity (Table 1, compare entries 15 & 18, 22 & 25). Similarly, Zn(OAc)2 was used as an alternate Zn(II) source (Table 1, entries 19 & 26). Neither of these additives surpassed ZnI2 in providing access to the *anti*-isomer. Use of TfOH (Table 1, entries 16 & 23) rules out the role of a hidden Brønsted acid.13 Thus, it is clear that additives have a significant effect on the reaction outcome, most likely through simultaneous activation of the TMSCN and imine.

The identity of each diastereoisomer was confirmed by deprotection of the *O*-TBS group and cyclisation using triphosgene to form the corresponding oxazolidinone (Scheme 3). The magnitude of the coupling constant for the α-amino proton signal at 4.0–4.5 ppm for each oxazolidinone was then compared. The 3*J* value for the oxazolidinones **25** and **27** was measured as 4.8–5.1 Hz, whilst the 3*J* value for oxazolidinones **29** and **31** was 7.7–7.8 Hz. These 3*J* values are in broad agreement with data previously reported for *cis-* and *trans*-oxazolidinones.14–17 The *trans* oxazolidinone therefore corresponds to the 2,3-*syn*-α-aminonitriles **21** and **23**, and the *cis* oxazolidinone corresponds to the 2,3-*anti*-α-aminonitriles **20** and **22**.



**Scheme 3.** Formation of oxazolidinones **25**, **27**, **29** and **31** to determine relative stereochemistry.

A possible model for the cyanide addition based on chelation control predicts the *syn*-isomer as the major product from addition to the *Si*-face (Fig. 1, **A**), whilst a Felkin-Anh model predicts the *anti-*isomer (Fig. 1, **B**). Unfortunately, this does not provide an adequate explanation for the majority of the reactions being *syn*- selective reactions, even those without additives. However, Cainelli *et al.* postulated a Felkin-Anh transition state in which the silyl group is coordinated to the imine *N* atom as cyanide is added to the C=N bond (Fig. 1, **C**).14 This effectively inverts the prediction of the standard model as the larger TMS group clashes with methyl group during *Re-*face addition, therefore favoring formation of the *syn-* product. However, this does not account for the role of any activator in this reaction.



**Figure 1.** Chelation and two Felkin-Anh models for the addition of TMSCN to *N*-chiral-(2*S*)-silyloxy imines.

The role of the chiral amine stereodirecting group is fairly minimal in all of these reactions, except for the switch in stereocontrol observed in very particular combinations of (-)-substrate **11** with either BF3.OEt2 or ZnI2 as additives (Table 1, entries 21 & 22). Clearly a powerful synergistic effect is in operation with this substrate, with a possible model depending upon interactions of the lactate derived stereogenic centre, the activator, and the chiral amine group. Although the exact role and mechanism of action of the activator is unclear, one could assume a coordinative model between the lactate oxygen and the imine nitrogen atoms that also activates the silyl group (Figure 2, shown with ZnI2 as the activator). This places the TMSCN in a similar geometry for addition as proposed by Cainelli. The -methyl benzyl group then would rotate to place the large phenyl group opposite the incoming TMSCN. In the absence of the -methyl benzyl group, addition opposite the methyl group of the lactate is slightly favored, leading to the *syn*-isomer. However, for the (*S*)-derived imine **11**, this mode of addition would lead to torsional A1,3 interactions between the -methyl group and imine, favoring the *anti*-isomer. For the (*R*)-imine **10**, this torsional interaction only exists when leading to the *anti*-isomer, thus favoring the *syn*-product.



**Figure 2.** Possible model for changes in selectivity through synergistic interactions.

1. Conclusion

2,3-*anti*-β-Hydroxy-α-aminonitriles have typically been reported as the minor product of asymmetric trimethylsilylcyanation. Trimethylsilyl cyanide addition to methyl ketimines derived from (*R*)-glyceraldehyde acetonide provided 2,3-*syn*-β-hydroxy-α-aminonitriles in excellent ratio (up to *syn:anti* = 98:2), but a far lower ratio for the 2,3-*anti­*-β-hydroxy-α-aminonitriles (up to *syn:anti =* 34:66).18 Addition to aldimines derived from (*R*)-glyceraldehyde have also been shown to proceed with *syn* diastereoselectivity.19 Addition of trimethylsilyl cyanide to *N*-substituted imines derived from (*S*)-ethyl lactate was shown to proceed with high selectivity toward (2*R*,3*R*)-2,3-*syn*-β-hydroxy-α-aminonitriles (*syn:anti* = 9:1) without the use of a chiral auxiliary.8 The high selectivity for (2*R*,3*S*)-2,3-*anti*-β-hydroxy-α-aminonitriles reported herein (Table 1, entries 21 & 22) is therefore particularly interesting. The (2*R*,3*S*)-2,3-*anti*-β-hydroxy-α-amino motif – which corresponds to that found in the non-proteinogenic amino acid, *allo*-threonine – is often difficult to access. Total syntheses containing this motif often proceed via inversion of (2*R*,3*R*)-2,3-*syn*-β-hydroxy-α-hydroxy configurations.19,20,21 This strategy provides efficient access to an orthogonally protected (2*R*,3*S*)-*anti* configuration in high overall yield and good diastereoselectivity.

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1. Experimental
	1. General information

Dry solvents were obtained either from the Grubbs dry solvent system or by distillation. All other reagents were used as supplied without purification, unless specified. Glassware was flame dried and cooled under vacuum before use. Thin layer chromatography was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F254). Plates were visualised using UV light or by dipping in KMnO4 solution, followed by exposure to heat. Flash column chromatography was performed on silica gel (Merck Kieselgel 60 F254 230-400 mesh), unless otherwise stated. 1H and 13C NMR spectra were measured using CDCl3 as solvent unless otherwise stated, on a Bruker AV-250 or AV-400 MHz machine with an automated sample changer. Chemical shifts for carbon and hydrogen are given, on the  scale. Coupling constants were measured in Hertz (Hz). 13C NMR spectra were recorded using the DEPT method. Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na line). [**]D Values are given in 10-1 deg cm2 g-1. Infrared spectra were recorded on a Perkin-Elmer 100 FT-IR machine using attenuated total reflectance (ATR). Mass spectra were recorded on a micromass autospec (EI+) or Waters LCT Classic (TOF ES+). HPLC was carried out on a Gilson analytical system using chiral phase analytical columns (4.8 mm × 250 mm).

* 1. **(2S)-2-(Phenylmethoxy)-propanoic acid ethyl ester 2**22

A solution of the alcohol **1** (1.00 g, 8.47 mmol) in DCM (10 mL) was cooled to 0 oC and *t*-BuOK (0.95 g, 8.47 mmol) was added portion-wise over 10 min. After complete dissolution of the *t*-BuOK, BnBr (1.45 g, 8.47 mmol) was added dropwise over 10 min. The reaction was then warmed to room temperature and stirred for 14 h before being quenched with sat. NH4Cl(aq) (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried over MgSO4 filtered and concentrated under reduced pressure to give a yellow oil which was purified by flash column chromatography on silica gel eluting with petroleum ether 40/60 and ethyl acetate (4:1) as the eluent to give the benzyl ether **2** (1.39 g, 79%) as a colourless oil; $[a]\_{D}^{24}$ -68.9 (*c* 1.01, CHCl3), [lit.22 -69.3 (*c* 1.00, CHCl3)]; *δ*H (400 MHz; CDCl3) 7.41–7.30 (5H, m, ArC*H*), 4.72 (1H, d, *J* 11.6, PhCH*H*), 4.48 (1H, d, *J* 11.6, PhC*H*H), 4.25–4.22 (2H, m, OC*H*2CH3), 4.08 (1H, q, *J* 6.8, C*H*O), 1.46 (3H, d, *J* 6.8, C*H*3CH), 1.32 (3H, t, *J* 7.1, CH2C*H*3); *δ*C (100 MHz, CDCl3) 173.3 (*C*), 137.6 (Ar*C*), 128.4 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 127.9 (Ar*C*H), 74.1 (*C*HO), 72.0 (*C*H2O), 60.9 (*C*H2O), 18.7 (*C*H3), 14.3 (*C*H3); *m/z* (ESI+) 226 (100%, [M+NH4]+), 209.1171 (66, [M+H]+ C12H17O3 requires 209.1172), 181 (13), 117 (6). All data in accordance with literature.

* 1. **Ethyl (2S)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-propanoate 3**22

Imidazole (6.00 g, 87.5 mmol) was added in a single portion to a solution of the alcohol **1** (8.62 g, 72.9 mmol) in DCM (50 mL). After complete dissolution of the imidazole, TBDMSCl (11.0 g, 72.9 mmol) was added and the reaction mixture was stirred at room temperature for 16 h before being quenched with H2O (60 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried with MgSO4, filtered, and concentrated under reduced pressure to give the silyl ether **3** (15.8 g, 67.8 mmol, 93%) as a colourless oil which did not require any further purification; $[a]\_{D}^{21}$ -31.3(*c* 1.98 in CHCl3) [lit.22. -31.1 (*c* 1.0 in CHCl3)]; *δ*H (400 MHz; CDCl3) 4.32 (1H, q, *J* 6.7, C*H*O), 4.22–4.15 (2H, m, OC*H2*), 1.40 (3H, d, *J* 6.7, C*H3*CH), 1.28 (3H, t, *J* 7.1, C*H*2CH3), 0.91 [9H, s, (C*H*3)3C], 0.09 (3H, s, C*H3*Si), 0.08 (3H, s, C*H3*Si); *δ*C (100 MHz; CDCl3) 174.2 (*C*), 68.4 (*C*HO), 60.7 (O*C*H2), 25.7 [(*C*H3)3C], 21.3 (CH2*C*H3), 18.3 [(CH3)3*C*], 14.2 (*C*H3CH), -5.0 (*C*H3Si), -5.3 (*C*H3Si); *m/z* (ESI+) 233.1569 (13%, M+H+.C11H25O3Si requires 233.1567), 217 (100), 189 (6), 173 (1), 156 (39). All data in accordance with literature.

* 1. **(2S)-2-(Phenylmethoxy)-propanal 4**23

A solution of the ethyl ester **2** (2.90 g, 14.0 mmol) in diethyl ether (30 mL) was cooled to -78 oC. DIBAL-H (1M in hexane, 19.6 mmol, 19.6 mL) was added cautiously dropwise over 1 h. The solution was stirred for a further 4 h at -78 oC before being quenched with MeOH (20 mL) and warmed to room temperature. Saturated aqueous potassium sodium tartrate solution (50 mL) was added and the mixture left to stir for 12 h before being extracted with diethyl ether (3 × 10 mL). The organic extracts were dried with MgSO4, and concentrated under reduced pressure to give the crude aldehyde **4** as a clear oil (2.18 g, 95%) which was used immediately without further purification; $[a]\_{D}^{23}$ -52.6 (*c* 1.00 in CHCl3) [lit.24 -50.2 (*c* 1.00 in CHCl3)]; *δ*H (400 MHz; CDCl3) 9.69 (1H, d, *J* 1.8, C*H*O), 7.40-7.31 (5H, m, ArC*H*), 4.68 (1H, d, *J* 11.7, PhC*H*H), 4.63 (1H, d, *J* 11.7, PhCH*H*), 3.92 (1H, qd, *J* 6.9, 1.8, C*H*OBn), 1.36 (3H, d, *J* 6.9, C*H*3CHO); *δ*C (100 MHz; CDCl3) 203.4 (*C*HO), 137.4 (Ar*C*), 128.6 (2 × Ar*C*H), 128.1 (Ar*C*H), 128.0 (2 × Ar*C*H), 79.5 (CH3*C*H), 72.0 (*C*H2Ph), 15.3 (*C*H3CHO). All data in accordance with the literature.

* 1. **(2S)-2-[(1,1-Dimethylethyl)dimethylsilyl]oxy-propanal 5**25

A solution of the ethyl ester **3** (4.00 g, 17.2 mmol) in diethyl ether (70 mL) and cooled to -78 oC. DIBAL-H (1M in hexane, 20 mmol, 20 mL) was added cautiously dropwise over 1 h. The solution was stirred for a further 4 h at -78 oC before being quenched with MeOH (40 mL) and warmed to room temperature. Saturated potassium sodium tartrate solution (60 mL) was added and the mixture left to stir for 12 h before being extracted with diethyl ether (3 × 15 mL). The organic extracts were dried with MgSO4, filtered, and concentrated under reduced pressure to give the crude aldehyde **5** (3.22 g, 99%) as a clear oil which was used without further purification; $[a]\_{D}^{20}$ -12.0 (*c* 1.00 in CHCl3) [lit.25 -12.6 (*c* 1.1 in CHCl3)]; max/cm-1 (film) 2954, 2858, 1750, 1735; *δ*H (400 MHz; CDCl3) 9.64 (1H, d, *J* 1.2, C*H*O), 4.12 (1H, qd, *J* 6.9, 1.2, C*H*O), 1.30 (3H, d, *J* 6.9, C*H3*), 0.94 [9H, s, (C*H*3)3C], 0.12 (3H, s, C*H*3Si), 0.11 (3H, s, C*H*3Si); *δ*C (100 MHz; CDCl3) 204.2 (*C*HO), 73.8 (CH3*C*H), 25.7 [(*C*H3)3C], 18.5 (*C*H3), 18.2 [(CH3)3*C*], -4.8 (*C*H3Si), -4.8 (*C*H3Si); *m/z* (ESI+) 217 (100%, M+K+), 211.1131 (67, M+Na+ C9H20O2SiNa+ requires 211.1130). All data in accordance with literature.

* 1. **[N(E),αR]-N-[(2S)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propylidene]-α-methyl-benzenemethanamine 10**

(*R*)-(+)-α-Methylbenzylamine (0.46 g, 3.76 mmol) was added to a stirred solution of the aldehyde 5 (0.71 g, 3.76 mmol) in diethyl ether (5 mL) at 0 oC, followed by MgSO4 (0.50 g). After stirring for 16 h, the reaction mixture was filtered and concentrated to give the title compound 10 as a light brown oil (0.88 g, 85%) which was used without further purification; $[a]\_{D}^{22}$ +47.0 (*c* 1.18 in CHCl3) [lit.26 +46.2 (*c* 1.20 in CHCl3); max/cm-1 (film) 2929, 2856, 1671; *δ*H (400 MHz; CDCl3) 7.62 (1H, d, *J* 5.2, *H*C=N), 7.36–7.23 (5H, m, ArC*H*), 4.37–4.33 (2H, m, 2 × CH3C*H*), 1.51 (3H, d, *J* 6.6, C*H*3CH), 1.32 (3H, d, *J* 6.5, C*H*3CH), 0.86 [9H, s, (C*H*3)3C], 0.04 (3H, s, C*H*3Si), -0.01 (3H, s, C*H*3Si); *δ*C (100 MHz; CDCl3) 166.3 (*C*=N), 144.6 (Ar*C*), 128.4 (2 × Ar*C*H), 126.9 (Ar*C*H), 126.6 (2 × Ar*C*H), 70.7 (*C*H), 69.0 (*C*H), 25.8 [(*C*H3)3C], 24.2 (*C*H3), 21.7 (*C*H3), 18.2 [(CH3)3*C*Si], -4.7 (*C*H3Si), -4.8 (*C*H3Si); *m/z* (ESI+) 305 (100%, M+Na+), 292.2093 (69%, M+H+. C17H30NOSi+ requires 292.2097), 290 (4). All data in accordance with literature.26

* 1. **[N(E),αS]-N-[(2S)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propylidene]-α-methyl-benzenemethanamine 11**

(*S*)-(*-*)-α-Methylbenzylamine (0.46 g, 3.76 mmol) was added to a stirred solution of the aldehyde **5** (0.71 g, 3.76 mmol) in diethyl ether (5 mL) at 0 oC, followed by MgSO4 (0.50 g). After 16 h, the reaction mixture was filtered and concentrated to give the title compound **11** as a light brown oil (0.93 g, 89%) which was used without further purification; $[a]\_{D}^{20}$ -54.8 (*c* 1.18 in CHCl3) [lit.26 -55.2 (*c* 1.20 in CHCl3); max/cm-1 (film) 2929, 2856, 1673; *δ*H (400 MHz; CDCl3) 7.64 (1H, d, *J* 5.2, *H*C=N), 7.37–7.23 (5H, m, ArC*H*), 4.40 (1H, qd, *J* 6.5, 5.2, C*H*O), 4.33 (1H, q, *J* 6.6, CH3C*H*), 1.52 (3H, d, *J* 6.6, C*H*3CH), 1.28 (3H, d, *J* 6.5, C*H*3CO), 0.93 [9H, s, (C*H*3)3C], 0.11 (6H, s, 2 × C*H*3Si); *δ*C (100 MHz; CDCl3) 166.5 (*C*=N), 144.6 (Ar*C*), 128.4 (2 × Ar*C*H), 126.8 (Ar*C*H), 126.5 (2 × Ar*C*H), 70.7 (*C*H), 69.0 (*C*H), 25.8 [(*C*H3)3CSi], 24.2 (*C*H3), 21.8 (*C*H3), 18.5 [(CH3)3*C*Si], -4.5 (*C*H3Si), -4.7 (*C*H3Si); *m/z* (ESI+) 305 (55%, M+Na+), 292.2094 (100, M+H+. C17H30NOSi+ requires 292.2097). All data in accordance with literature.26

* 1. **(2R, 3S) and (2S, 3S)-3-(Benzyloxy)-2-N-[(p-methoxybenzyl)amino]butanenitrile 12 & 13**

MgSO4 (1.00 g) was added in a single portion to a solution of the aldehyde **4** (0.11 g, 0.66 mmol) in DCM (1 mL). *p*-Methoxybenzyl amine (0.08 g, 0.60 mmol) was added and the mixture was stirred at room temperature for 16 h before filtration and concentration to give the crude imine which was immediately dissolved in DCM (1 mL). ZnI2 (0.02 g, 0.06 mmol) was added, followed by TMSCN (0.11 mL, 0.79 mmol), and the mixture was left to stir for 24 h. The reaction mixture was quenched with saturated aqueous NH4Cl (1 mL), extracted with DCM (4 × 2 mL), dried with MgSO4, filtered and concentrated to give the crude α-aminonitrile as a dark brown oil (0.10 g, 50%, 1 : 1.2 ratio of diastereoisomers) which was purified by flash column chromatography on silica eluting with petroleum ether 40/60 and ethyl acetate (4:1) to give an analytically pure mixture of diastereoisomers **12** & **13** (45 : 55 ratio) as a clear oil; $[a]\_{D}^{23}$+8.8 (*c* 2.40 in CHCl3); *v*max/cm-1 (film) 2933, 2228, 1673, 1611; *δ*H (400 MHz; CDCl3) 7.40–7.28 (7H, m, ArC*H*), 6.92–6.88 (2H, m, ArC*H*), 4.71–4.66 (1H, m, C*H* major & minor), 4.59 (1H, d, *J* 13.1, CH major), 4.01 (1H, d, *J* 13.1, CH minor), 4.04–4.10 (1H, m, C*H*), 3.88–3.72 (5H, m, C*H*3 & 2 × C*H*), 3.83 (3H, s, C*H*3), 3.53 (1H, d, *J* 4.0, C*H* major), 3.46 (1H, d, *J* 4.0, C*H* minor), 1.37–1.35 (3H, m, C*H*3 major & minor); *δ*C (100 MHz; CDCl3) 159.1 (Ar*C*), 137.7 (2 × Ar*C*), 130.3 (Ar*C*), 130.3 (2 × Ar*C*), 129.7 (Ar*C*H), 129.6 (Ar*C*H), 128.5 (Ar*C*H), 127.9 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 127.8 (Ar*C*H), 119.0 (*C*N major), 118.2 (*C*N minor), 114.0 (ArC*H*), 74.6 (*C*H minor), 74.5 (C*H* major), 71.5 (C*H*3O major), 71.2 (C*H*3O minor), 55.3 (*C*H major), 54.3 (*C*H minor), 50.9 (*C*H2 minor), 50.8 (*C*H2 major), 16.8 (*C*H3 minor), 16.2 (*C*H3 major); *m/z* (ESI+) 311.1751 (20%, M+H+.C19H23N2O2 requires 311.1754), 164 (35), 121 (100).

* 1. **(2R, 3S) and (2S, 3S)-3-(Benzyloxy)-2-N-[(p-methoxyphenyl)amino]butanenitrile 14 & 15**

MgSO4 (1.00 g) was added in a single portion to a solution of the aldehyde **4** (0.11 g, 0.66 mmol) in DCM (1 mL). *p*-Methoxyphenyl amine (0.07 g, 0.66 mmol) was added and the mixture was stirred at room temperature for 16 hours before being filtered and concentrated to give the crude imine which was immediately dissolved in DCM (1 mL). ZnI2 (0.02 g, 0.06 mmol) was added, followed by TMSCN (0.11 mL, 0.79 mmol), and the mixture was left to stir for 24 hours. The reaction mixture was quenched with NH4Cl(aq) (1 mL), extracted with DCM (4 × 2 mL), dried with MgSO4, filtered and concentrated to give the crude α-aminonitrile as a brown oil (0.04 g, 0.14 mmol, 21 %, 22 : 78) which was purified by column chromatography on silica using petroleum ether 40/60 and ethyl acetate (19:1) to give an analytically pure mixture of diastereoisomers **14** & **15** as a clear oil: $[a]\_{D}^{23}$ -17.6 (*c* 2.30); *v*max/cm-1 (film) 2977, 2232, 2194, 1679; *δ*H (400 MHz; CDCl3) 7.45–7.34 (5H, m, ArC*H*), 6.88–6.83 (2H, m, ArC*H*), 6.73–6.66 (2H, m, ArC*H*), 4.80 (1H, d, *J* 16.3, C*H* minor),4.78 (1H, d, *J* 16.3, C*H* major),4.68 (1H, d, *J* 16.3, C*H* major),4.56 (1H, d, *J* 16.3, C*H* minor), 4.15–4.11 (1H, m, C*H*), 4.03–4.09 (1H, m, C*H*), 4.00–3,92 (1H, m, N*H*), 3.79 (3H, s, OC*H*3 major), 3.78 (3H, s, OC*H*3 minor), 1.48 (3H, d, *J* 6.2, C*H*3 minor), 1.43 (3H, d, *J* 6.2, C*H*3 major); *δ*C (100 MHz; CDCl3) 153.9 (Ar*C*), 138.9 (Ar*C* major), 137.3 (Ar*C* minor), 128.6 (Ar*C*H), 128.2 (Ar*C*H), 128.0 (2 × Ar*C*H), 118.9 (*C*N), 116.4 (ArCH minor), 116.1 (Ar*C*H), 115.0 (Ar*C*H), 74.1 (*C*H major), 73.8 (*C*H minor), 71.8 (*C*H2 major), 71.2 (*C*H2 minor), 55.7 (*C*H), 53.1 (*C*H minor), 51.9 (*C*H major), 16.7 (*C*H3 minor), 16.6 (*C*H3 major); *m/z* (ESI+) 297.1597 (100%, M+H+.C18H21N2O2 requires 296.1598), 180 (30).

* 1. **(2R, 3S) and (2S, 3S)-3-[(t-Butyldimethylsilyl)oxy]-2-N-[(p-methoxybenzyl)amino]butanenitrile 16 & 17**

MgSO4 (1.00 g) was added in a single portion to a solution of the aldehyde **5** (0.29 g, 1.56 mmol) in DCM (2.5 mL). *p*-Methoxybenzyl amine (0.21 g, 1.50 mmol) was added and the mixture was stirred at room temperature for 16 hours before being filtered and concentrated to give the crude imine which was immediately dissolved in DCM (2.5 mL). ZnI2 (0.05 g, 0.16 mmol) was added, followed by TMSCN (0.23 mL, 1.87 mmol), and the mixture was left to stir for 24 hours. The reaction mixture was quenched with NH4Cl(aq) (2.5 mL), extracted with DCM (4 × 2 mL), dried with MgSO4, filtered and concentrated to give the crude α-aminonitriles as a brown oil (0.44 g, 84%, 42 : 58) which was purified by column chromatography on silica using petroleum ether 40/60 and ethyl acetate (4:1) to give analytically pure diastereoisomers **16** & **17** as clear oils: minor isomer **16** (assumed to be *anti*);$[a]\_{D}^{20}$ +40.0 (*c* 2.5 in CHCl3); *v*max/cm-1 (film) 2955, 2931, 2857, 2228, 1683, 1612, 1513; *δ*H (400 MHz; CDCl3) 7.30 (2H, d, *J* 8.6 Hz, ArC*H*), 6.90 (2H, d, *J* 8.6 Hz, ArC*H*), 4.14–4.07 (2H, m, C*H*H and C*H*), 3.83 (3H, s, C*H*3), 3.77 (1H, d, *J* 12.8 Hz, C*H*H), 3.38 (1H, d, *J* 3.4, C*H*), 1.81 (1H, br s, N*H*), 1.30 [3H, d, *J* 6.2, C*H*3], 0.92 [9H, s, (C*H*3)3C], 0.14 (3H, s, C*H*3Si), 0.11 (3H, s, C*H*3Si); *δ*C (100 MHz; CDCl3) 159.0 (Ar*C*), 130.0 (Ar*C*), 129.5 (2 × Ar*C*H), 119.3 (*C*N), 113.9 (2 × Ar*C*H), 68.8 (*C*HOSi), 56.1 (*C*H3), 55.3 (*C*H), 50.9 (*C*H2), 25.7 [(*C*H3)3C], 20.1 (*C*H3), 18.0 [ (CH3)3*C*], -4.5 (*C*H3Si), -4.9 (*C*H3Si); *m/z* (ESI+) 357 (5%), 335.2165 (20, M+H+.C18H31N2O2Si requires 335.2149), 188 (70), 121 (100): major isomer **17** (assumed to be *syn*) $[a]\_{D}^{21}$ +135.0 (*c* 2.80 in CHCl3); *v*max (cm-1) 2932, 2955, 2857, 2228, 1682, 1613, 1514; *δ*H (400 MHz; CDCl3) 7.33–7.28 (2H, m, Ar*H*), 6.92 (2H, m, Ar*H*), 4.11–4.05 (2H, m, C*H*H and C*H*), 3.85 (1H, m, C*H*H), 3.82 (3H, s, C*H*3), 3.40 (1H, d, *J* 3.0, C*H*), 1.32 (3H, d, *J* 6.2, C*H*3), 0.92 [9H, s, (C*H*3)3C], 0.13 (3H, s, C*H*3Si), 0.12 (3H, s, C*H*3Si); *δ*C (100 MHz; CDCl3) 161.3 (Ar*C*), 139.4 (Ar*C*), 129.8 (2 × Ar*C*H), 122.9 (*C*N), 114.0 (2 × Ar*C*H), 68.8 (*C*H), 56.8 (*C*H3), 55.3 (*C*H), 50.8 (*C*H2), 25.7 [(*C*H3)3C], 21.0 (*C*H3), 17.2 [(CH3)3*C*], -4.3 (*C*H3Si), -4.7 (*C*H3Si); *m/z* (ESI+) 357 (5%), 335.2158 (17, M+H+.C18H31N2O2Si requires 335.2149), 188 (69), 121 (100).

* 1. **(2R, 3S) and (2S, 3S)-3-(t-Butyldimethylsilyloxy)-2-N-[(p-methoxyphenyl)amino]butanenitrile 18 & 19**

MgSO4 (1.00 g) was added in a single portion to a solution of the aldehyde **5** (0.29 g, 1.56 mmol) in DCM (2.5 mL). *p*-Methoxyphenyl amine (0.19 g, 1.50 mmol) was added and the mixture was stirred at room temperature for 16 hours before being filtered and concentrated to give the crude imine which was immediately dissolved in DCM (2.5 mL). ZnI2 (0.05 g, 0.16 mmol) was added, followed by TMSCN (2.3 mL, 1.87 mmol), and the mixture was left to stir for 24 hours. The reaction mixture was quenched with NH4Cl(aq) (1.0 mL), extracted with DCM (4 × 2.0 mL), dried with MgSO4, filtered, and concentrated to give the crude major and minor diastereoisomers of the α-aminonitrile as a pink oil (0.38 g, 1.17 mmol, 75 %, 45 : 55) which was purified by column chromatography on silica using petroleum ether 40/60 and ethyl acetate (19:1) to give an analytically pure mixture of diastereoisomers **18** & **19** as a clear oil: $[a]\_{D}^{22}$ +46.1 (*c* 3.40 in CHCl3); *v*max/cm-1 (film) 2957, 2930, 2858, 2229, 1493, 1471, 1452;*δ*H (400 MHz; CDCl3) 6.88–6.84 (2H, m, ArC*H*), 6.75–6.70 (2H, m, ArC*H*), 4.33 (1H, qd, *J* 6.2, 2.8,C*H* major), 4.18 (1H, qd, *J* 6.2, 3.6, C*H* minor), 3.97-3.91 (1H, m, N*H*), 3.79 (3H, s, C*H*3), 1.43 (3H, d, *J* 6.2, C*H*3 minor), 1.38 (3H, d, *J* 6.2, C*H*3 major), 0.98 [9H, s, C(C*H*3)3 minor], 0.97 [9H, s, C(C*H*3)3 major], 0.21 [3H, s, (C*H*3)2Si major], 0.19 [3H, s, (C*H*3)2Si minor], 0.18 [3H, s, (C*H*3)2Si]; *δ*C (100 MHz; CDCl3) 153.9 (Ar*C*), 139.0 (Ar*C*), 119.1 (*C*N major), 118.7 (*C*N minor), 116.4 (Ar*C*H), 116.1 (2 × Ar*C*H), 115.0 (2 × Ar*C*H), 68.8 (*C*H major), 68.6 (*C*H minor), 55.7 (*C*H3), 54.7 (*C*H minor), 53.5 (*C*H major), 25.8 [(*C*H3)3C], 21.0 (*C*H3 minor), 20.5 (*C*H3 major), 18.0 [(CH3)3*C*], -4.4 (*C*H3Si), -4.9 (*C*H3Si); *m/z* (ESI+) 321.1996 (100% M+H+.C17H29N2O2Si requires 321.1993).

* 1. **(2R,3S) and (2S,3S)-3-[(t-Butyldimethylsilyl)oxy]-2-{[(1R)-1-phenylethyl]amino}butanenitrile 20 & 21**

TMSCN (0.26 mL, 2.06 mmol) was added to a solution of imine 10 (0.50 g, 1.71 mmol) in DCM (3 mL) followed by ZnI2 (0.05 g, 0.17 mmol). The reaction mixture was stirred at room temperature for 24 h, then quenched with NH4Cl(aq) (10 mL) and extracted with DCM (3 × 5 mL). The combined organic extracts were dried with MgSO4, filtered, and concentrated under reduced pressure to give the crude α-aminonitrile (0.53 g) as a mixture of diastereoisomers (*syn* : *anti* 78:29) which was purified by flash column chromatography on silica gel eluting with toluene to give the individual diastereoisomers 20 & 21 as clear oils. Diastereoisomer 20; $[a]\_{D}^{22}$ +56.2 (*c* 1.00 in CHCl3); max/cm-1 (film) 3057, 2987, 2305, 1760, 1398; *δ*H (400 MHz; CDCl3) 7.40–7.21 (5H, m, ArC*H*), 4.12–3.98 (2H, m, C*H*N and C*H*O), 3.52 (d, 1H, *J* 3.8 Hz, C*H*CN), 1.37 (3H, d, *J* 6.5, C*H*3), 1.34 (d, *J* 6.2, C*H3*), 0.87 [9H, s, (C*H*3)3C], 0.12 (s, 3H, C*H3*Si), 0.10 (s, 3H, C*H3*Si); *δ*C (100 MHz; CDCl3) 144.6 (Ar*C*), 128.6 (2 × Ar*C*H), 127.5 (Ar*C*H), 126.6 (2 × Ar*C*H), 118.2 (*C*N), 68.6 (*C*H), 55.9 (*C*H), 55.8 (*C*H), 25.8 [(*C*H3)3CSi], 22.4 (*C*H3), 21.1 (*C*H3), 18.0 [(CH3)3*C*Si], -4.3 (*C*H3Si), -4.9 (*C*H3Si); *m/z* (ESI+) 319.2196 (100 %, M+H+.C18H31N2OSi requires 319.2200), 292 (3), 215 (1), 188 (50). Diastereoisomer 21; $[a]\_{D}^{23}$ +36.5 (*c* 1.00 in CHCl3); max/cm-1 (film) 3329, 2956, 2930, 2886, 2857, 2232, 1493, 1471; *δ*H (400 MHz; CDCl3) 7.39–7.30 (5H, m, ArC*H*), 4.13 – 4.01 (2H, m, C*H*N and C*H*O), 3.13 (1H, d, *J* 3.6, C*H*CN), 1.44 (3H, d, *J* 6.5, C*H*3), 1.28 (3H, d, *J* 6.2, C*H*3), 0.92 [9H, s, (C*H*3)3C], 0.11 (3H, s, C*H*3Si), 0.09 (3H, s, C*H*3Si); *δ*C (100 MHz; CDCl3) 143.5 (Ar*C*), 128.7 (2 × Ar*C*H), 127.6 (Ar*C*H), 126.8 (2 × Ar*C*H), 119.6 (*C*N), 68.8 (*C*H), 56.1 (*C*H), 54.9 (*C*H), 25.8 [(*C*H3)3CSi], 25.1 (*C*H3) 20.0 (*C*H3), 18.0 [(CH3)3*C*Si], -4.5 (*C*H3Si), -5.0 (*C*H3Si); *m/z* (ESI+) 319.2230 (100%, M+H+. C18H31N2OSi requires 319.2225), 188 (36).

* 1. **(2R,3S) and (2S,3S)-3-[(t-Butyldimethylsilyl)oxy]-2-{[(1S)-1-phenylethyl]amino}butanenitrile 22 & 23**

TMSCN (0.26 mL, 2.06 mmol) was added to a solution of the imine **11** (0.50 g, 1.71 mmol) in DCM(3 mL) followed by ZnI2 (0.05 g, 0.17 mmol). The reaction mixture was stirred at room temperature for 24 h, then quenched with NH4Cl(aq) (10 mL) and extracted with DCM(3 × 5 mL). The combined organic extracts were dried with MgSO4, filtered, and concentrated under reduced pressure to give the crude α-aminonitrile (0.51 g) as a mixture of diastereoisomers (*syn* : *anti* 10:90) which was purified by flash column chromatography on silica gel eluting with toluene to give the individual diastereoisomers **22** & **23** as clear oils: major isomer *anti-***22**;$ $ $[a]\_{D}^{23}$ -9.2 (*c* 1.00 in CHCl3); max/cm-1 (film) 2963, 2932, 2860, 2163, 1452, 1254, 835; *δ*H (400 MHz; CDCl3) 7.41–7.21 (5H, m, ArC*H*), 4.11 (1H, q, *J* 6.5, C*H*N), 3.80 (1H, qd, *J* 6.2, 3.8, C*H*O), 3.07 (1H, br s, C*H*CN), 1.85 (1H, br d, *J* 5.2, N*H*), 1.40 (3H, d, *J* 6.5, C*H*3), 1.26 (3H, d, *J* 6.3, C*H*3), 0.93 [9H, s, (C*H*3)3C], 0.18 (3H, d, C*H*3Si), 0.14 (3H, s, C*H*3Si); *δ*C (100 MHz; CDCl3) 143.6 (Ar*C*), 128.7 (2 × Ar*C*H), 127.6 (Ar*C*H), 126.7 (2 × Ar*C*H), 118.5 (*C*N), 69.1 (*C*H), 56.1 (*C*H), 56.0 (*C*H), 25.8 [(*C*H3)3C], 25.0 (*C*H3), 21.0 (*C*H3), 18.0 [(CH­3)3 *C*Si], -4.3 (*C*H3Si), -4.8 (*C*H3Si); *m/z* (ESI+) 319.2202 (100%, M+H+. C18H31N2OSi requires 319.2225), 188 (35): minor isomer *syn-***23**; $[a]\_{D}^{23}$ -18.0 (c 1.0 in CHCl3); max/cm-1 (film) 2959, 2932, 2860, 2160, 1467, 1467, 1254, 839; *δ*H (400 MHz; CDCl3) 7.42–7.28 (5H, m, ArC*H*), 4.14 (1H, qd, *J* 6.2, 3.9, C*H*O), 4.05 (1H, q, *J* 6.4, CH3C*H*), 3.60 (1H, d, *J* 3.9, C*H*CN), 1.82 (1H, br s, N*H*), 1.37 (3H, d, *J* 6.4, C*H*3CHN), 1.34 (3H, d, *J* 6.2, C*H3*CHO), 0.91 [9H, s, (C*H*3)3C], 0.14 (3H, s, SiC*H*3), 0.12 (3H, s, SiC*H*3); *δ*C (100 MHz; CDCl3) 144.6 (Ar*C*), 128.7 (2 × Ar*C*H), 127.6 (Ar*C*H), 126.7 (2 × Ar*C*H), 119.2 (*C*N), 68.9 (*C*H), 56.2 (*C*H), 55.1 (*C*H), 25.7 [(*C*H3)3C], 22.1 (*C*H3), 20.0 (*C*H3), 18.0 [(CH3)3*C*], -4.5 (*C*H3Si), -4.9 (*C*H3Si); *m/z* (ESI+) 319.2196 (100%, M+H+. C18H31N2OSi requires 319.2200), 188 (45).

* 1. **(2S,3S)-3-Hydroxy-2-{[(1R)-1-phenylethyl]amino}-butanenitrile 24**

A solution of the silyl ether 21 (0.80 g, 2.50 mmol) in THF was cooled to 0 oC and TBAF (1M in THF, 2.5 mL, 2.5 mmol) was added dropwise. The reaction mixture was stirred for 3 h before being concentrated, and adding DCM (5 mL) and H2O (10 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 5 mL). The combined organic extracts were washed with K2CO3(aq) (10 mL), dried with MgSO4, filtered, and concentrated under reduced pressure to give a yellow oil. This was purified by flash column chromatography on silica gel eluting with petroleum ether 40/60 and ethyl acetate (4:1) to give the alcohol 24 (0.43 g, 83%) as a colourless oil; $[a]\_{D}^{23}$+29.0 (*c* 0.30 in CHCl3); max/cm-1 (film) 3428, 3325, 3029, 2976, 2929, 2231, 1493, 1452; *δ*H (400 MHz; CDCl3) 7.39-7.28 (5H, m, ArC*H*), 4.13 (1H, q, *J* 6.5, C*H*), 3.89 (1H, quin, *J* 6.4, C*H*), 3.04 (1H, d, *J* 7.0, C*H*), 2.96 (1H, br s, N*H*), 1.74 (1H, br s, O*H*), 1.45 (3H, d, *J* 6.5, C*H*3), 1.31 (3H, d, *J* 6.4, C*H*3); *δ*C (100 MHz; CDCl3) 142.6 (Ar*C*), 128.9 (2 × Ar*C*H), 127.9 (Ar*C*H), 126.9 (2 × Ar*C*H), 119.0 (*C*N), 68.0 (*C*H), 56.5 (*C*H), 54.6 (*C*H), 24.9 (C*H*3), 19.0 (C*H*3); *m/z* (ESI+) 205.1343 (75%, M+H+. C12H17N2O requires 205.1335), 105 (70), 74 (100).

* 1. **(4S,5S)-5-Methyl-2-oxo-3-[(1R)-1-phenylethyl]-1,3-oxazolidine-4-carbonitrile 25**

Triphosgene (0.10 g, 0.29 mmol) and Et3N (0.13 g, 1.31 mmol) were added sequentially to a solution of the alcohol **24** (0.18 g, 0.87 mmol) in DCM (3 mL) at 0 oC. The reaction mixture was stirred at room temperature for 48 hours before being quenched with NH4Cl(aq) (4 mL) and extracted with DCM (5 × 4 mL). The combined organic extracts were dried with MgSO4 and concentrated under reduced pressure to give a brown oil which was purified by column chromatography on silica using petroleum ether 40/60 and ethyl acetate (3:1) as the eluent to give the oxazolidinone **25** (0.17 g, 85%) as a white solid: $[a]\_{D}^{23}$ +25.6 (c 1.0 in CHCl3); max/cm-1 (film) 3058, 2987, 2940, 2306, 1763; δH (400 MHz; CDCl3) 7.47–7.36 (5H, m, ArCH), 5.15 (1H, q, J 7.1, CH3CH), 4.72 (1H, qd, J 6.2, 5.1, CH3CH), 4.05 (1H, d, J 5.1, CHCN), 1.75 (3H, d, J 7.1, CH3CH), 1.50 (3H, d, J 6.2, CH3CH); δC (100 MHz; CDCl3) 155.4 (CO), 138.3 (ArC), 129.0 (2 × ArCH), 128.9 (ArCH), 127.5 (2 × ArCH), 115.2 (CN), 73.5 (CH), 53.3 (CH), 50.2 (CH), 20.1 (CH3), 16.8 (CH3); m/z (ESI+) 231.1126 (100%, M+H+. C13H15N2O2 requires 231.1128), 127 (20), 106 (4), 105 (56).

* 1. **(2S,3S)-3-Hydroxy-2-{[(1S)-1-phenylethyl]amino}-butanenitrile 26**

A solution of the silyl ether 23 (0.89 g, 2.8 mmol) in THF was cooled to 0 oC and TBAF (1M in THF, 2.8 mL, 2.8 mmol) was added dropwise. The reaction mixture was stirred for 3 h then concentrated, DCM (5 mL) and H2O (10 mL) added, and the organic layer separated. The aqueous layer was extracted with DCM (3 × 5 mL), the combined organic extracts washed with K2CO3(aq) (10 mL), dried with MgSO4, filtered, and concentrated under reduced pressure. The resultant yellow oil was purified by flash column chromatography on silica gel eluting with petroleum ether 40–60 / ethyl acetate (4:1) to give the alcohol 26 (0.49 g, 85 %) as a colourless oil; $[a]\_{D}^{23}$ -3.6 (*c* 0.35 in CHCl3); νmax/cm-1 (film) 3450, 3324, 2975, 2928, 2232, 1494, 1453; *δ*H (400 MHz; CDCl3) 7.42–7.31 (5H, m, ArC*H*), 4.08 (1H, q, *J* 6.5, C*H*), 3.72–3.68 (1H, m, C*H*), 3.40 (1H, d, *J* 8.2, C*H*), 3.14 (1H, br s, C*H*), 1.77 (1H, br s, N*H*), 1.42 (3H, d, *J* 6.5, C*H*3), 1.37 (3H, d, *J* 6.1, C*H*3); *δ*C (100 MHz; CDCl3) 143.9 (Ar*C*), 128.9 (2 × Ar*C*H), 128.0 (Ar*C*H), 126.6 (2 × Ar*C*H), 118.4 (*C*N), 67.7 (*C*H), 56.5 (*C*H), 55.1 (*C*H), 22.2 (C*H*3), 19.0 (C*H*3); *m/z* (ESI+) 205.1342 (75%, M+H+.C12H17N2O requires 205.1335), 105 (70), 74 (100).

* 1. **(4S,5S)-5-Methyl-2-oxo-3-[(1S)-1-phenylethyl]-1,3-oxazolidine-4-carbonitrile 27**

Triphosgene (0.10 g, 0.29 mmol) and Et3N (0.13 g, 1.31 mmol) were added sequentially to a solution of the alcohol **26** (0.18 g, 0.87 mmol) in DCM (3 mL) at 0 oC. The reaction mixture was stirred at room temperature for 48 h before being quenched with NH4Cl(aq) (4 mL) and extracted with DCM (5 × 4 mL). The combined organic extracts were dried with MgSO4, filtered, and concentrated under reduced pressure to give a brown oil. This was purified by flash column chromatography on silica gel eluting with petroleum ether (40–60) / ethyl acetate (3:1) to give the oxazolidinone **27** (0.18 g, 90%) as a white solid; m.p. 113–116 oC; $[a]\_{D}^{23}$-6.4 (*c* 1.02 in CHCl3); max/cm-1 (film) 3055, 2987, 2306, 1765, 1266; *δ*H (400 MHz; CDCl3) 7.48–7.38 (5H, m, ArC*H*), 5.37 (1H, q, *J* 7.3, CH3C*H*), 4.73 (1H, qd, *J* 6.3, 4.8, CH3C*H*), 3.55 (1H, d, *J* 4.8, C*H*CN), 1.83 (3H, d, *J* 7.3, C*H*3CH), 1.31 (3H, d, *J* 6.3, C*H*3CH); *δ*C (100 MHz; CDCl3) 155.5 (*C*O), 137.4 (Ar*C*), 129.3 (2 × Ar*C*H), 128.9 (Ar*C*H), 127.4 (2 × Ar*C*H), 117.0 (*C*N), 73.5 (*C*H), 53.2 (*C*H), 48.9 (*C*H), 20.1 (*C*H3), 16.4 (*C*H3); *m/z* (ESI+) 253 (15%), 231.1127 (100%, M+H+. C13H15N2O2 requires 231.1128), 127 (18), 105 (35).

* 1. **(2S,3R)-3-Hydroxy-2-{[(1R)-1-phenylethyl]amino}-butanenitrile 28**

A solution of the silyl ether 20 (0.89 g, 2.8 mmol) in THF was cooled to 0 oC and TBAF (1M in THF, 2.8 mL, 2.8 mmol) was added dropwise. The reaction mixture was stirred for 3 hours before being concentrated, dissolved in DCM (5 mL), quenched with H2O (10 mL), and extracted with DCM (3 × 5 mL). The combined organic extracts were washed with K2CO3(aq) (10 mL) and extracted with DCM (3 × 5 mL), dried, and concentrated under reduced pressure to give a yellow oil which was purified by column chromatography on silica using petroleum ether 40/60 and ethyl acetate (4:1) as the eluent to give the alcohol 28 (0.49 g, 85 %) as a colourless oil: $[a]\_{D}^{23}$ +4.5 (*c* 0.30 in CHCl3); νmax/cm-1 (film) 3455, 3325, 2973, 2926, 2232, 1494, 1453; *δ*H (400 MHz; CDCl3) 7.40–7.28 (5H, m, ArC*H*), 4.07-4.02 (2H, m, 2 × C*H*), 3.62 (1H, d, *J* 3.5, C*H*), 2.17 (1H, br s, O*H*), 2.07 (1H, br s, N*H*), 1.40 (6H, d, *J* 6.4, 2 × C*H*3); *δ*C (100 MHz; CDCl3) 144.0 (Ar*C*), 128.8 (2 × Ar*C*H), 127.8 (Ar*C*H), 126.7 (2 × Ar*C*H), 118.0 (*C*N), 67.5 (*C*H), 56.1 (*C*H), 54.9 (*C*H), 22.2 (C*H*3), 20.0 (C*H*3); *m/z* (ESI+) 205.1340 (75%, M+H+. C12H17N2O requires 205.1335), 105 (75), 74 (100).

* 1. **(4R,5S)-5-Methyl-2-oxo-3-[(1R)-1-phenylethyl]-1,3-oxazolidine-4-carbonitrile 29**

Triphosgene (0.10 g, 0.29 mmol) and Et3N (0.13 g, 1.31 mmol) were added sequentially to a solution of the alcohol 28 (0.18 g, 0.87 mmol) in DCM (3 mL) at 0 oC. The reaction mixture was stirred at room temperature for 48 hours before being quenched with NH4Cl(aq) (4 mL) and extracted with DCM (5 × 4 mL). The combined organic extracts were dried with MgSO4 and concentrated under reduced pressure to give a brown oil which was purified by column chromatography on silica using petroleum ether 40/60 and ethyl acetate (3:1) as the eluent to give the oxazolidinone 29 (0.16 g, 80%) as a white solid; m.p. 111–114 oC; $[a]\_{D}^{23}$ +1.03 (*c* 1.05 in CHCl3); max/cm-1 (film)3058, 2987, 2306, 1763; *δ*H (400 MHz; CDCl3) 7.46–7.36 (5H, m, ArC*H*), 5.30 (1H, q, *J* 7.2, CH3C*H*), 4.58 (1H, dq, *J* 7.8, 6.4, CH3C*H*), 4.08 (1H, d, *J* 7.8, C*H*CN), 1.82 (3H, d, *J* 7.2,C*H*3CH), 1.60 (3H, d, *J* 6.4, C*H*3CH); *δ*C (100 MHz; CDCl3) 155.6 (*C*O), 137.8 (Ar*C*), 129.3 (2 × Ar*C*H), 128.8 (Ar*C*H), 127.4 (2 × Ar*C*H), 115.4 (*C*N), 70.8 (*C*H), 53.3 (*C*H), 48.8 (*C*H), 17.2 (*C*H3), 16.2 (*C*H3); *m/z* (ESI+) 253 (20%), 231.1127 (100, M+H+. C13H15N2O2 requires 231.1128), 127 (19), 105 (43).

* 1. **(2R,3S)-3-Hydroxy-2-{[(1S)-1-phenylethyl]amino}-butanenitrile 30**

A solution of the silyl ether 22 (0.89 g, 2.8 mmol) in THF was cooled to 0oC and TBAF (1M in THF, 2.8 mL, 2.8 mmol) was added dropwise. The reaction mixture was stirred for 3 hours before being concentrated, dissolved in DCM (5 mL), quenched with H2O (10 mL), and extracted with DCM (3 × 5 mL). The combined organic extracts were washed with K2CO3(aq) (10 mL) and extracted with DCM (3 × 5 mL), dried with MgSO4, filtered, and concentrated under reduced pressure to give a yellow oil which was purified by column chromatography on silica using petroleum ether 40/60 and ethyl acetate (4:1) as the eluent to give the alcohol 30 (0.50 g, 88 %) as a colourless oil: $[a]\_{D}^{23}$ -18.0 (*c* 0.30 in CHCl3); max/cm-1 (film)3460, 3324, 2973, 2925, 2231, 1493, 1452; *δ*H (400 MHz; CDCl3) 7.38–7.29 (5H, m, ArC*H*), 4.11 (1H, q, *J* 6.5, C*H*), 3.96 (1H, qd, *J* 6.4, 3.5, C*H*), 3.18 (1H, d, *J* 3.5, C*H*), 2.10 (1H, br s, N*H*), 1.69 (1H, br s, O*H*), 1.44 (3H, d, *J* 6.5, C*H*3), 1.33 (3H, d, *J* 6.4, C*H*3); *δ*C (100 MHz; CDCl3) 143.1 (Ar*C*), 128.8 (2 × Ar*C*H), 127.8 (Ar*C*H), 127.0 (2 × Ar*C*H), 118.3 (*C*N), 68.2 (*C*H), 56.4 (*C*H), 55.3 (*C*H), 24.9 (*C*H3), 20.3 (C*H*3); *m/z* (ESI+) 205.1336 (70%, M+H+. C12H17N2O requires 205.1335), 105 (60), 74 (100).

* 1. **(4R,5S)-5-Methyl-2-oxo-3-[(1S)-1-phenylethyl]-1,3-oxazolidine-4-carbonitrile 31**

Triphosgene (0.10 g, 0.29 mmol) and Et3N (0.13 g, 1.31 mmol) were added sequentially to a solution of the alcohol **30** (0.18 g, 0.87 mmol) in DCM (3 mL) at 0 oC. The reaction mixture was stirred at room temperature for 48 h before being quenched with NH4Cl(aq) (4 mL) and extracted with DCM (5 × 4 mL). The combined organic extracts were dried with MgSO4, filtered, and concentrated under reduced pressure to give a brown oil. This was purified by flash column chromatography on silica gel eluting with petroleum ether (40–60) / ethyl acetate (3:1) to give the oxazolidinone **31** (0.18 g, 92%) as a white solid; m.p. 112–113 oC; $[a]\_{D}^{23}$ -11.5 (*c* 1.21 in CHCl3); max/cm-1(film)3055, 2987, 2306, 1765, 1266; *δ*H (400 MHz; CDCl3) 7.47–7.37 (5H, m, ArC*H*), 5.12 (1H, q, *J* 7.1, CH3C*H*), 4.72 (1H, dq, *J* 7.7, 6.4, CH3C*H*), 4.50 (1H, d, *J* 7.7, C*H*CN), 1.77 (3H, d, *J* 7.1, C*H*3CH), 1.60 (3H, d, *J* 6.4, C*H*3CH); *δ*C (100 MHz; CDCl3) 155.6 (*C*O), 138.4 (Ar*C*), 129.0 (2 × Ar*C*H), 128.9 (Ar*C*H), 127.5 (2 × Ar*C*H), 113.4 (*C*N), 70.6 (*C*H), 53.6 (*C*H), 50.1 (*C*H), 17.6 (*C*H3), 17.3 (*C*H3); *m/z* (ESI+) 248 (10%), 231.1128 (100, M+H+.C13H15N2O2 requires 231.1128), 127 (15), 105 (40).

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