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Catalytic, asymmetric Strecker reactions catalysed by titanium^{IV} and vanadium^{V}(salen) complexes

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Abstract—Vanadium^{V}(salen) complex **3** has been found to be an effective catalyst for the asymmetric addition of hydrogen cyanide (generated in situ from trimethylsilyl cyanide) to imines. The best results (up to 81% enantiomeric excess) were obtained for aromatic imines in which the nitrogen atom is protected with a benzyl group and in which the imine bond is not sterically encumbered.
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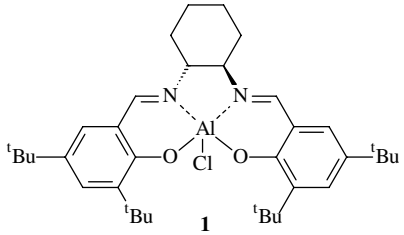
1. Introduction

The asymmetric addition of cyanide to aldehydes to form nonracemic cyanohydrins was first reported[1] in 1908 and is now a well established method for the asymmetric synthesis of a carbon–carbon bond.[2] Successful catalysts based on transition metal complexes,[2] organocatalysts[2] and enzymes[3] have been developed and some of these are now used commercially. In contrast, the asymmetric addition of cyanide to imines (the Strecker reaction) has proven to be a much more difficult task due to the lower electrophilicity of a carbon nitrogen double bond and the added complication of the substituent on the nitrogen.

The first asymmetric catalyst for a Strecker reaction was not reported until 1996 when Lipton described the use of a diketopiperazine to catalyse the asymmetric addition of hydrogen cyanide to imines.[4] The efficacy of this catalyst has since been disputed,[5] but it did spur the subsequent development of other organocatalysts[6–8] and metal based catalysts[9–15] for Strecker reactions[16] and related processes such as the addition of cyanide to hydrazones[17] and Reissert reactions.[18] Notable amongst these procedures was the report by Jacobsen of the screening of a number of metal(salen) complexes as catalysts for the asymmetric addition of hydrogen cyanide to imines.[12] This study resulted in the discovery that 5 mol % of aluminium(salen) complex **1** would catalyse the asymmetric addition of hydrogen cyanide (generated in situ from trimethylsilyl cyanide and methanol) to imines with 37–95% enantiomeric excess.



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In recent work, we have developed titanium(salen) complex **2** and vanadium(salen) complex **3** as catalysts for asymmetric cyanohydrin synthesis.[19] Complexes **2** and **3** were found to be compatible with a wide range of different cyanide sources (including trimethylsilyl cyanide,[20] ethyl cyanoformate,[21] acetyl cyanide[22] and potassium cyanide[23]) and to catalyse the asymmetric addition of cyanide to both aldehydes and ketones[24] at high substrate to catalyst ratios and under mild reaction conditions. It was, therefore, of

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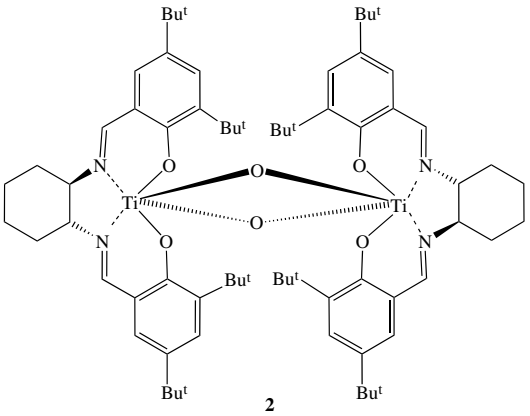
interest to investigate the use of these two complexes and related transition metal(salen) complexes as asymmetric catalysts for the Strecker reaction. Herein we report the results of this study.



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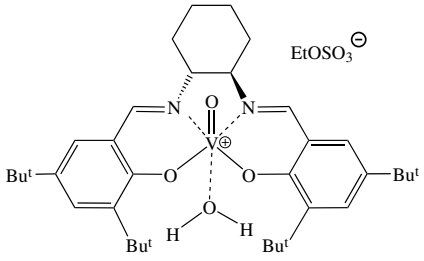

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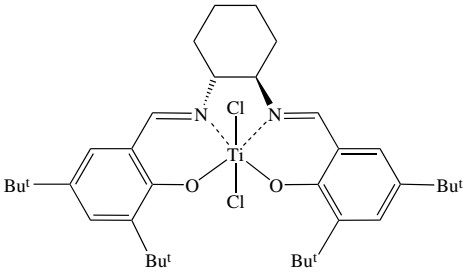

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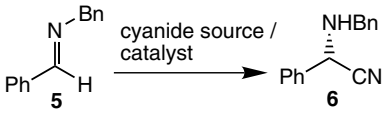
2. Results and discussion

Since titanium complexes had previously been found to be effective asymmetric catalysts for both cyanohydrin synthesis[2] and Strecker reactions,[10,13–15] it was anticipated that complex **2** might be an effective catalyst for the Strecker reaction. However, Jacobsen reported[12] that titanium(salen) dichloride[25] **4** was only a poor catalyst for the asymmetric addition of trimethylsilyl cyanide to *N*-allyl benzylimine; 5 mol % of complex **4** inducing just a 19% conversion to the corresponding α-amino nitrile with 24% enantiomeric excess after 15 h at room temperature. As a model system, we chose to investigate the addition of cyanide to commercially available *N*-benzyl benzylimine **5** (Scheme 1) since the enantiomeric excess of the resulting α-amino nitrile **6** could easily be determined by ^{1}H NMR spectroscopy in the presence of (*R*)-camphor sulfonic acid.[15]



Scheme 1.

All attempts to catalyse the reaction shown in Scheme 1 using 5 mol % of bimetallic titanium complex **2** as a catalyst were unsuccessful. The use of ethyl cyanoformate as the cyanide source resulted in a 55% conversion to racemic amino nitrile after 42 h reaction at room temperature in dichloromethane. The conversion could be improved (100% conversion after 48 h) by adding excess potassium cyanide to the above reaction,[26] but the product was again racemic. The use of trimethylsilyl cyanide as the cyanide source allowed the reaction temperature to be reduced to −40 °C, however again only racemic product was obtained (100% conversion) after a reaction time of 48 h. Similarly, use of titanium dichloride complex **4** (5 mol %) to catalyse the addition of trimethylsilyl cyanide to imine **5** at −40 °C gave only racemic product **6**. Under the reaction conditions used for this series of experiments, control reactions indicated that there was no background reaction between imine **5** and trimethylsilyl cyanide at temperatures up to 0 °C. Even when imine **5** and trimethylsilyl cyanide were mixed in the absence of solvent at room temperature, only 28% conversion of imine **5** into amino nitrile **6** occurred after 24 h. Thus, it appeared that complexes **2** and **4** were catalysing the formation of α-amino nitrile **6**, but were doing so without inducing any asymmetric induction into the reaction.

All previous reports[10,13–15] of the successful use of titanium complexes as catalysts for asymmetric Strecker reactions have generated the catalytically active complex in situ from the ligand and titanium tetra-isopropoxide. Therefore we investigated the use of the in situ prepared complex[27] obtained from titanium tetra-isopropoxide and *N*,*N*′-bis(3,5-di-*tert*-butyl-salicylidene)-(*R*,*R*)-cyclohexane-1,2-diamine as a catalyst for the reaction shown in Scheme 1. The results obtained using this catalyst system with trimethylsilyl cyanide as the cyanide source are summarised in Table 1. This system was catalytically active, though in dichloromethane, the enantioselectivity was very low even at −78 °C; at this temperature the reaction was also very slow. Changing the solvent to toluene was beneficial to both the rate of reaction and the enantioselectivity. This solvent effect is consistent with previous work on asymmetric Strecker reactions using titanium complexes.[10,13–15] Increasing the reaction temperature to −40 °C increased the rate of reaction, and more surprisingly also increased the enantioselectivity to 30% in favour of the (*S*)-enantiomer of the α-amino nitrile. Doubling the mol % of catalyst to 20 mol % further increased the rate of reaction, but had a detrimental effect on the enantioselectivity. Finally, conducting the reaction at room temperature in the presence of 10 mol % of catalyst allowed the reaction to go to completion over-

Table 1. The asymmetric addition of trimethylsilyl cyanide to imine **5** catalysed by an in situ generated titanium(salen) complex[a]

Catalyst (mol %)	Solvent	Temperature (°C)	Time (h)	Conversion (%)	ee (%)
10	CH_2Cl_2	−78	46	52	7
10	Toluene	−78	46	79	15
10	Toluene	−40	42	100	30 (*S*)[b]
20	Toluene	−40	23	100	16
10	Toluene	25	18	100	30 (*S*)[b]

[a] All reactions were carried out using 2 equiv of trimethylsilyl cyanide and equimolar amounts of the salen ligand and titanium tetra-isopropoxide.
[b] Determined from the sign of the specific rotation of product **6**.

Table 2. The asymmetric addition of trimethylsilyl cyanide to imine **5** catalysed by vanadium^{V}(salen) complex **3**[a]

Entry	Catalyst (mol %)	Solvent	Temperature (°C)	Time (h)	ee (%)
1	5	Toluene	−40	20	30 (*R*)[b]
2	10	Toluene	−40	23	77 (*R*)[b]
3	15	Toluene	−40	20	70 (*R*)[b]
4	10	Toluene	0	19	54 (*R*)[b]
5	10	Toluene	−78	21	54 (*R*)[b]
6	10	CH_2Cl_2	−40	22	27 (*R*)[b]

[a] All reactions were carried out using 2 equiv of trimethylsilyl cyanide and had gone to completion in the time specified.
[b] For reactions carried out using the (*S*,*S*)-enantiomer of complex **3** and determined from the sign of the specific rotation of product **6**.

night, whilst still giving a product with 30% enantiomeric excess.

Other attempts to increase the enantioselectivity of this process were unsuccessful. Replacement of the *N*-benzyl substituent by the larger benzhydryl protecting group[14,15] resulted in the formation of racemic product. The use of the salen ligand with no *tert*-butyl groups attached to the aromatic rings in conjunction with imine **5** was also detrimental, with a maximum 3% enantiomeric excess being obtained at −40 °C when using 10 mol % of the in situ generated catalyst. Tridentate amino alcohol derived ligands have previously been reported to give higher enantioselectivities in asymmetric Strecker reactions than the corresponding imine derivatives.[10,15] However, reduction of the di-*tert*-butyl salen ligand using sodium cyanoborohydride and complexation of the resulting salan ligand to titanium tetra-isopropoxide gave a catalyst which quantitatively converted imine **5** into α-amino nitrile **6**, but with just 6% enantiomeric excess after 22 h at room temperature.

As titanium(salen) complexes had not produced an effective asymmetric catalyst for Strecker reactions, the use of vanadium(salen) complexes was investigated. It was anticipated that the positively charged vanadium of a vanadium^{V}(salen) complex such as **3** would coordinate more strongly to an imine than the uncharged titanium ions, thus resulting in a more active catalyst and higher asymmetric induction. This theory was confirmed by the use of 5 mol % of complex **3** to catalyse the asymmetric addition of trimethylsilyl cyanide to imine **5** at −40 °C. After 20 h, this reaction resulted in the quantitative formation of **6** with 30% enantiomeric excess (Table 2, entry 1). The importance of the vanadium oxidation state was demonstrated by the use of the analogous vanadium^{IV}(salen) complex, which resulted in the formation of racemic α-amino nitrile **6** under identical reaction conditions.

Encouragingly, by increasing the loading of catalyst **3** to 10 mol %, the enantiomeric excess of α-amino nitrile **6** could be increased to 77% (Table 2, entry 2). However, a further increase in the catalyst loading (to 15 mol %) was not beneficial (Table 2, entry 3). Attempts to carry out the Strecker reaction at higher (Table 2, entry 4) or lower temperatures (Table 2, entry 5) were also detrimental to the enantioselectivity, as was an attempt to change the solvent to dichloromethane (Table 2, entry 6).

The unusual temperature dependence of the enantioselectivity, coupled with a decrease in the enantioselectivity when the reaction was scaled up from 0.5 to 2.5 mmol of imine **5** suggested that trimethylsilyl cyanide might not be the active cyanating agent, but might be reacting with protic species to generate hydrogen cyanide in situ. In many previous asymmetric Strecker reactions, the cyanide source has been shown to be hydrogen cyanide rather than trimethylsilyl cyanide.[9,12,14,15] To investigate this hypothesis, reactions were carried out in the presence of various additives (Table 3).

Table 3. The effect of proton sources on the asymmetric addition of cyanide to imine **5** catalysed by vanadium^{V}(salen) complex **3**

Entry	Additive/conditions	Time (h)	Temperature (°C)	Yield (%)	ee (%)
1[a]	Anhydrous solvent	20	−40	100	48 (*R*)
2[a]	4 Å Molecular sieves	19	−40	100	62 (*R*)
3[a,b]	Undried solvent	19	−40	100	81 (*R*)
4[a,b,c]	Undried solvent	19	−40	100	57 (*R*)
5[a,b]	MeOH (1.2 equiv)	19	−40	100	79 (*R*)
6[a,b,c]	MeOH (1.2 equiv)	18	−40	100	75 (*R*)
7[d]	Water (10 μL)	16	25	74	61 (*S*)
8[d]	Water (20 μL)	16	25	93	64 (*S*)
9[d]	Water (30 μL)	16	25	100	61 (*S*)
10[d]	Water (40 μL)	16	25	100	62 (*S*)
11[d]	Water (20 μL)	2	25	85	52 (*S*)
12[d]	Water (20 μL)	3	25	77	66 (*S*)
13[d]	Water (20 μL)	4	25	89	69 (*S*)
14[d]	Water (20 μL)	16	−10	74	76 (*S*)
15[d]	Water (20 μL)	16	−20	77	79 (*S*)
16[d]	Water (20 μL)	16	−30	85	80 (*S*)

[a] Reaction carried out in toluene using 10 mol % of the (*S*,*S*)-enantiomer of complex **3**, 0.5 mmol of imine **5** and 2 equiv of trimethylsilyl cyanide.
[b] As (a) but using 1.2 equiv of trimethylsilyl cyanide.
[c] As (a) but using 1 mmol of imine **5**.
[d] Reaction carried out using 4 mol % of the (*R*,*R*)-enantiomer of complex **3** and 1.2 equiv of trimethylsilyl cyanide.

Under strictly anhydrous conditions, a significant drop in the enantioselectivity of the reaction was observed (Table 3, entry 1). The addition of undried molecular sieves to the reaction mixture partially restored the enantioselectivity (Table 3, entry 2), while reducing the amount of trimethylsilyl cyanide to 1.2 equiv fully restored the enantioselectivity for small scale reactions (Table 3, entry 3).

However, when the latter reaction was carried out on twice the scale, the enantioselectivity was again severely reduced (Table 3, entry 4). Since undried molecular sieves can act as a source of a limited amount of water and trimethylsilyl cyanide can sequester water by formation of bis-trimethylsilyl ether, these results were again an indication of the importance of a protic additive. Finally, the addition of methanol (1.2 equiv) to the reaction mixture was found to reliably restore the enantioselectivity for both small (Table 3, entry 5) and large (Table 3, entry 6) scale reactions and allowed the amount of trimethylsilyl cyanide used to be reduced to just 1.2 equiv. Since trimethylsilyl cyanide is known to react rapidly with methanol to generate hydrogen cyanide,[28] it appears that hydrogen cyanide is the active cyanide source in these reactions. It is likely that this is also the case for the titanium(salen) catalysed reactions which would explain why only the in situ prepared catalyst was active, as this would have liberated isopropanol which could then generate the hydrogen cyanide.

In a further study (Table 3, entries 7–16), water was used as the proton source for reactions carried out at room temperature in the presence of just 4 mol % of catalyst **3**. Under these conditions, the enantioselectivity is lower than that observed at −40 °C, but the effect of the protic additive on the rate of reaction is illustrated as increasing the amount of water present (from 10 to 30 μL) increased the conversion observed after a 16 h reaction time. This study also illustrated that the reactions were extremely rapid, as after a reaction time of just four hours, similar yields and enantioselectivities were obtained to those observed after 16 h (Table 3, entries 8 and 11–13). By lowering the reaction temperature to −30 °C, the enantioselectivity of these reactions could be increased to 80% (Table 3, entries 8 and 14–16).

Under the conditions of Table 3, entry 8, titanium based catalysts **2** and **4** were reinvestigated and were found to catalyse the reaction shown in Scheme 1, with enantioselectivities of 54% and 43% respectively, and with 90% conversion in both cases. Under the conditions of Table 3, entry 5, complex **2** catalysed the formation of α-amino nitrile **6** with just 16% enantiomeric excess, though in quantitative yield. As these enantioselectivities were still inferior to those obtainable with complex **3**, no further studies were carried out with titanium based catalysts. Reactions carried out using the vanadium^{IV}(salen) complex analogous to complex **3** still gave only racemic product under these conditions.

Under the optimised reaction conditions (Table 3, entry 5), the effect of the solvent on the enantioselectivity was again investigated. Both THF and dichloromethane gave a lower enantioselectivity (50–52% ee), whilst methanol and hexane gave racemic product, though in all four solvents >90% conversion of imine **5** to α-amino nitrile **6** was observed. The effect of the nitrogen protecting group on enantioselectivity was also investigated. *N*-Allyl benzylimine was converted into the corresponding amino nitrile with 47% enantiomeric excess under the conditions of Table 3, entry 5, and with 45% enantiomeric excess using 5 mol % of catalyst **3** at room temperature. *N*-Benzhydryl benzylimine gave racemic amino nitrile under the conditions of Table 3, entry 5, a result which is in contrast to previous studies where this protecting group has been found to enhance the enantioselectivity.[14,15] Thus it appeared that increasing or decreasing the size of the nitrogen protecting group was detrimental to the enantioselectivity and subsequent studies were conducted exclusively on *N*-benzyl derivatives.

Having optimised the various experimental parameters, the application of this chemistry to the asymmetric cyanation of a range of *N*-benzyl imines was investigated. These reactions were all carried out under the conditions of Table 3, entry 5, with the results summarised in Table 4.

Table 4. The asymmetric addition of trimethylsilyl cyanide to *N*-benzyl imines catalysed by vanadium^{V}(salen) complex **3**[a]

Entry	Imine	Isolated yield	ee (%)
1	$PhCH{=}NCH_2Ph$	88	75 (*R*)[b]
2	$4\text{-}MeC_6H_4CH{=}NCH_2Ph$	65	70 (*S*)[c]
3	$3\text{-}MeC_6H_4CH{=}NCH_2Ph$	77	74 (*S*)[c]
4	$2\text{-}MeC_6H_4CH{=}NCH_2Ph$	46	52 (*S*)[c]
5	*N*-Benzyl-2-naphthylimine	46	72 (*S*)[c]
6	*N*-Benzyl-1-naphthylimine	82	34 (*S*)[c]
7	$3\text{-}MeOC_6H_4CH{=}NCH_2Ph$	70	59 (*R*)[b]
8	$4\text{-}MeOC_6H_4CH{=}NCH_2Ph$	50	51 (*S*)[c]
9	$3\text{-}ClC_6H_4CH{=}NCH_2Ph$	76	57 (*R*)[b]
10	$4\text{-}ClC_6H_4CH{=}NCH_2Ph$	48	41 (*S*)[c]
11	$4\text{-}CF_3C_6H_4CH{=}NCH_2Ph$	65	31 (*S*)[c]
12	$Me_3CCH{=}NCH_2Ph$	85	16 (*S*)[c]
13	$PhC(Me){=}NCH_2Ph$	92	43 (*R*)[b]

[a] Reaction carried out at −40 °C in toluene using 10 mol % of complex **3** and 1.2 equiv of trimethylsilyl cyanide. All reactions had gone to completion within 3 h.
[b] Using the (*S*,*S*)-enantiomer of complex **3**.
[c] Using the (*R*,*R*)-enantiomer of complex **3**.

The introduction of a methyl group onto the *meta*- or *para*-position of the imine had no significant effect on the enantioselectivity of the reaction (Table 4, compare entries 1–3). However, when the methyl group was *ortho*- to the imine, a significant drop in enantioselectivity was apparent (Table 4, entry 4), suggesting that the asymmetric Strecker reaction catalysed by complex **3** was sensitive to steric effects around the imine bond. This was further supported by reactions involving the *N*-benzyl imines of 1- or 2-naphthaldehyde as substrate, since the 2-isomer (which is only substituted *meta*- and *para*- to the imine) displayed a similar enantioselectivity to the benzaldehyde derived imine (Table 4, compare entries 1 and 5), whilst the 1-isomer (which is substituted *ortho*- to the imine) displayed much lower enantioselectivity (Table 4, entry 6). Both electron donating (Table 4, entries 7 and 8) and electron withdrawing (Table 4, entries 9–11) substituents in the *meta*- or *para*-position were found to have a detrimental effect on the enantioselectivity of the Strecker reaction. The *N*-benzyl imine of pivaldehyde gave a very low enantioselectivity (Table 4, entry 12), again consistent with the detrimental influence of substituents close to the imine. The ketimine derived from acetophone also gave a Strecker adduct with a rather low enantiomeric excess of 43% (Table 4, entry 13).

3. Conclusions

Vanadium^{V}(salen) complex **3**, which has previously been reported to catalyse asymmetric cyanohydrin synthesis[19] has also been found to catalyse the asymmetric addition of cyanide to imines, giving α-amino nitriles with up to 81% enantiomeric excess. Despite the apparent similarities between the two reactions, there are some notable differences between the two processes. The asymmetric cyanohydrin synthesis occurs most effectively in dichloromethane,[19] whereas the asymmetric Strecker reactions are most effective in toluene. For asymmetric cyanohydrin synthesis, the active cyanating agent is trimethylsilyl cyanide,[19] whilst for asymmetric Strecker reactions this is converted in situ into hydrogen cyanide which is then the source of cyanide. Asymmetric Strecker reactions are much faster than the corresponding cyanohydrin syntheses; as the former reactions are complete within three hours at −40 °C, whilst the latter require reaction times of 16 h at room temperature, though the asymmetric cyanohydrin synthesis is carried out with just 0.1 mol % of catalyst as opposed to the 5–10 mol % required for asymmetric Strecker reactions. However, the enantioselectivity of the Strecker reactions is not as high as that obtainable in asymmetric cyanohydrin synthesis, and appears to be highly sensitive to steric effects associated with substituents at either end of the imine bond as both large nitrogen protecting groups and substituents close to the imine carbon significantly reduce the enantioselectivity.

Further studies are currently underway to optimise the structure of the vanadium based catalysts and to investigate the mechanism of the Strecker reactions.

4. Experimental

4.1. Synthesis of imines

N-Benzyl benzylimine is commercially available. *N*-Benzyl 1-phenylethanimine was prepared by the literature method.[29] All other imines were prepared by the following procedure:

To a stirred solution of the aldehyde (1 equiv) and magnesium sulfate (anhydrous) (2 g) in dichloromethane (10 mL), under nitrogen at room temperature, was added benzyl amine (1 equiv). The reaction mixture was stirred for 21 h, then the magnesium sulfate was removed by filtration and the solvent removed in vacuo to give the *N*-benzyl imine as a clear/pale yellow oil or a white/pale yellow solid. The imines were sufficiently pure for use without further purification, and had analytical data which was consistent with the literature.[30]

4.2. Synthesis of racemic α-aminonitriles

Racemic samples of the α-amino nitriles were required to authenticate the enantiomeric excess determinations and were prepared by using a method reported by Reddy et al.[31]

4.3. General procedure for the asymmetric synthesis of α-aminonitriles using catalyst 3 with methanol as the proton source

To a stirred solution of (*S*,*S*)- or (*R*,*R*)-**3** (0.1 equiv) in toluene (10 mL/mmol of imine), under nitrogen at −40 °C, was added trimethylsilyl cyanide (1.2 equiv) and methanol (1.2 equiv). The solution was stirred for 1 h, then the imine (1.0 equiv) was added and the reaction allowed to stir at −40 °C for 4 h. The reaction was then passed through a plug of silica gel, eluting with hexane–ethyl acetate and the eluent evaporated in vacuo. The residue was purified by chromatography on silica gel using hexane–ethyl acetate as eluent unless otherwise stated.

4.3.1. *N*-Benzyl (*R*)-2-amino-phenylacetonitrile.[10,32] Purified by silica gel chromatography using 9:1 hexane–ethyl acetate as eluent to give the product in 88% yield as a yellow oil. $[\alpha]_D^{20} = +64.0$ (*c* 1, $CHCl_3$) {lit.[32] $[\alpha]_D^{20} = -75$ for (*S*)-enantiomer with >97% ee}; ν_{max} (neat) 3322 s, 3062 s, 3030 s, 2846 s, 2227 m and 1701 cm^{-1} s; δ_H ($CDCl_3$) 1.84 (1H, br s, NH), 3.98 (1H, d, *J* 13.0 Hz, NCH_2), 4.14 (1H, d, *J* 13.0 Hz, NCH_2), 4.78 (1H, s, NCHCN), 7.3–7.9 (10H, m, ArH); *m*/*z* (EI) 223 (MH^+, 100).

4.3.2. *N*-Benzyl (*S*)-2-amino-(4-methylphenyl)acetonitrile.[10] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 65% yield as a yellow oil. $[\alpha]_D^{20} = -32.2$ (*c* 1, $CHCl_3$) {lit.[32] $[\alpha]_D^{20} = -57$ (*c* 1, CCl_4)}; ν_{max} (neat) 3223 m, 3061 m, 2848 m, 2226 w and 1736 cm^{-1} s; δ_H ($CDCl_3$) 1.85 (1H, br s, NH), 2.39 (3H, s, $ArCH_3$), 3.97 (1H, d, *J* 13.0 Hz, NCH_2), 4.15 (1H, d, *J* 13.0 Hz, NCH_2), 4.74 (1H, s, NCHCN), 7.2–7.5 (9H, m, ArH); *m*/*z* (CI) 237 (MH^+, 12), 210 (100).

4.4. Asymmetric synthesis of *N*-benzyl (*R*)-2-amino-phenylacetonitrile hydrochloride using catalyst 3 with water as the proton source

(*S*,*S*)-**3** (43.3 mg, 0.057 mmol) and *N*-benzylidene benzylamine (0.195 g, 1 mmol) were dissolved in toluene (20 mL) in an oven dried round bottom flask. Water (20 μL) was added followed by trimethylsilyl cyanide (0.119 g, 1.20 mmol) and the reaction stirred for 4 h. The reaction was then acidified using hydrogen chloride in ether (1 mL of 1.0 M solution, 1 mmol) and filtered under reduced pressure to yield *N*-benzyl (*R*)-2-amino-phenylacetonitrile hydrochloride as a white solid (0.23 g, 89%). δ_H ($CDCl_3$): 2.32 (2H, br s, NH_2^+), 4.15 (2H, s, CH_2), 5.40 (1H, br s, CH), 7.4–7.5 (8H, m, ArH), 7.7–7.8 (2H, m, ArH).

4.4.1. *N*-Benzyl (*S*)-2-amino-(3-methylphenyl)acetonitrile.[33] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 77% yield as a yellow oil. $[\alpha]_D^{20} = -58.0$ (*c* 1, $CHCl_3$); ν_{max} (neat) 3326 m, 3061 m, 2856 m, 2227 w and 1702 cm^{-1} w; δ_H ($CDCl_3$) (1H, br s, NH), 2.43 (3H, s, $ArCH_3$), 4.02 (1H, d, *J* 13.0 Hz, NCH_2), 4.14 (1H, d, *J* 13.0 Hz, NCH_2), 4.77 (1H, s, NCHCN), 7.2–7.5 (9H, m, ArH); *m*/*z* (CI) 237 (MH^+, 14), 210 (100), 120 (19), 108 (7), 91 (3).

4.4.2. *N*-Benzyl (*S*)-2-amino-(2-methylphenyl)acetonitrile.[33] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 46% yield as a yellow oil. $[\alpha]_D^{20} = -72.1$ (*c* 1, $CHCl_3$); ν_{max} (neat) 3322 s, 3063 s, 2846 s, 2225 w and 1734 cm^{-1} s; δ_H ($CDCl_3$) 1.73 (1H, s, NH), 2.38 (3H, s, CH_3), 3.98 (1H, d, *J* 13.0 Hz, NCH_2), 4.15 (1H, d, *J* 13.0 Hz, NCH_2), 4.79 (1H, s, NCHCN), 7.2–7.6 (9H, m, ArH); *m*/*z* (EI) 236 (M^+, 63), 235 (100), 218 (27).

4.4.3. *N*-Benzyl (*S*)-2-amino-(2-naphthyl)acetonitrile.[11,34] Purified by recrystallisation from chloroform–hexane to give the product in 46% yield as a white solid. Mp 56–57 °C (lit.[34] mp 57–58 °C); $[\alpha]_D^{20} = -4.0$ (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3327 m, 2846 m, 2229 w and 1602 m, cm^{-1}; δ_H ($CDCl_3$) 1.78 (1H, br s, NH), 4.03 (1H, d, *J* 13.0 Hz, NCH_2), 4.11 (1H, d, *J* 13.0 Hz, NCH_2), 7.3–8.1 (12H, m, ArH); *m*/*z* (CI) 273 (MH^+, 6), 246 (100).

4.4.4. *N*-Benzyl (*S*)-2-amino-(1-naphthyl)acetonitrile.[35] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 82% yield as a white solid. Mp 79–80 °C (lit.[35] 78–79 °C); $[\alpha]_D^{20} = -112.0$ (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 3325 w, 2849 w, 2227 w and 1600 cm^{-1} w; δ_H ($CDCl_3$) 1.99 (1H, br s, NH), 4.11 (1H, d, *J* 13.0 Hz, NCH_2), 4.20 (1H, d, *J* 13.0 Hz, NCH_2), 5.39 (1H, s, NCHCN), 7.2–7.9 (12H, m, ArH); *m*/*z* (EI) 272 (M^+, 100).

4.4.5. *N*-Benzyl (*R*)-2-amino-(3-methoxyphenyl)acetonitrile.[36] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 70% yield as a yellow oil. $[\alpha]_D^{20} = +25.9$ (*c* 1, $CHCl_3$); ν_{max} (neat) 3321 m, 3029 m, 2837 m and 2227 cm^{-1} w; δ_H ($CDCl_3$) 1.93 (1H, br s, NH), 3.85 (3H, s, OCH_3), 3.97 (1H, d, *J* 13.0 Hz, NCH_2), 4.09 (1H, d, *J* 13.0 Hz, NCH_2), 4.75 (1H, s, NCHCN), 6.9–7.5 (9H, m, ArH); *m*/*z* (EI) 252 (M^+, 12), 91 (100), 77 (23), 65 (30).

4.4.6. *N*-Benzyl (*S*)-2-amino-(4-methoxyphenyl)acetonitrile.[10] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 50% yield as a yellow oil. $[\alpha]_D^{20} = -12.0$ (*c* 0.6, $CHCl_3$); ν_{max} 3320 m, 2838 m, 2226 w and 1682 cm^{-1} s; δ_H ($CDCl_3$) 1.84 (1H, br s, NH), 3.83 (3H, s, OCH_3), 3.97 (1H, d, *J* 13.0 Hz, NCH_2), 4.07 (1H, d, *J* 12.9 Hz, NCH_2), 4.72 (1H, s, NCHCN), 6.94 (2H, d, *J* 8.6 Hz, ArH), 7.3–7.5 (7H, m, ArH); *m*/*z* (CI) 253 (MH^+, 21), 226 (100).

4.4.7. *N*-Benzyl (*R*)-2-amino-(3-chlorophenyl)acetonitrile.[10] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 76% yield as a white solid. $[\alpha]_D^{22} = +2.4$ (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3323 m, 3085 m, 3063 m, 3029 m, 2924 m, 2849 m and 2228 cm^{-1} w; δ_H ($CDCl_3$) 1.94 (1H, s, NH), 3.96 (1H, d, *J* 13.0 Hz, NCH_2), 4.12 (1H, d, *J* 13.0 Hz, NCH_2), 4.74 (1H, s, NCHCN), 7.3–7.6 (9H, m, ArH); *m*/*z* (CI) 257 ((^{35}Cl)MH^+, 7), 230 (100), 52 (53).

4.4.8. *N*-Benzyl (*S*)-2-amino-(4-chlorophenyl)acetonitrile.[10] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 48% yield as a yellow oil. $[\alpha]_D^{20} = -19.7$ (*c* 0.8, $CHCl_3$); ν_{max} (neat) 3324 m, 3087 m, 2853 m, 2228 w and 1732 cm^{-1} s; δ_H ($CDCl_3$) 1.80 (1H, br s, NH), 3.85 (1H, d, *J* 13.0 Hz, NCH_2), 4.05 (1H, d, *J* 13.0 Hz, NCH_2), 4.64 (1H, s, NCHCN), 7.1–7.9 (9H, m, ArH); *m*/*z* (EI) 256 (M^+, 13), 228 (100).

4.4.9. *N*-Benzyl (*S*)-2-amino-(4-trifluoromethylphenyl)acetonitrile.[37] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 65% yield as a yellow oil. $[\alpha]_D^{20} = -28.3$ (*c* 1, $CHCl_3$); ν_{max} (neat) 3327 m, 3064 m, 2851 m, 2230 w, 1619 s and 1329 cm^{-1} s; δ_H ($CDCl_3$) 2.0 (1H, br s, NH), 4.03 (1H, d, *J* 12.9 Hz, NCH_2), 4.16 (1H, d, *J* 13.6 Hz, NCH_2), 4.84 (1H, s, NCHCN), 7.2–7.7 (9H, m, ArH); *m*/*z* (CI) 291 (MH^+, 7), 264 (100).

4.4.10. *N*-Benzyl (*S*)-2-amino-3,3-dimethyl butanonitrile.[7] Purified by silica gel chromatography using 9:1 hexane–ethyl acetate as eluent to give the product in 85% yield as a yellow oil. $[\alpha]_D^{20} = -29.3$ (*c* 1, $CHCl_3$); ν_{max} (neat) 3340 m, 3086 s, 2802 s, 2223 m and 1604 cm^{-1} m; δ_H ($CDCl_3$) 1.00 (9H, s, $C(CH_3)_3$), 3.03 (1H, s, NCHCN), 3.74 (1H, d, *J* 13.2 Hz, NCH_2), 4.07 (1H, d, *J* 13.2 Hz, NCH_2), 7.2–7.3 (5H, m, ArH); *m*/*z* (CI) 203 (MH^+, 3), 176 (100).

4.4.11. *N*-Benzyl (*R*)-2-amino-2-phenylpropanonitrile.[11] Purified by silica gel chromatography using 6:1 hexane–ethyl acetate as eluent to give the product in 92% yield as a yellow oil. $[\alpha]_D^{21} = +16.6$ (*c* 0.5, $CHCl_3$); ν_{max} (neat) 3343 m, 3029 m, 2859 m, 2222 w and 1685 cm^{-1} m; δ_H ($CDCl_3$) 1.49 (1H, br s, NH), 1.72 (3H, s, CH_3), 3.49 (1H, d, *J* 12.2 Hz, NCH_2), 3.81 (1H, d, *J* 12.2 Hz, NCH_2), 7.1–7.6 (10H, m, ArH); *m*/*z* (ES) 237 (MH^+, 4), 210 (100), 244 (87), 232 (38). Found (ES) 259.1203, $C_{16}H_{16}N_2Na^+$ ($M+Na^+$) requires 259.1206.

4.4.12. *N*-Benzhydryl (*RS*)-2-amino-phenylacetonitrile.[15] Prepared using the general procedure (Section 4.3) except that toluene was used as eluent and the compound was purified by recrystallisation from chloroform/hexane to give the product in 22% yield as a white solid. Mp 99–100 °C (lit.[38] mp 98–100 °C); ν_{max} ($CHCl_3$) 3087 s, 3020 s, 2230 w and 1601 cm^{-1} w; δ_H ($CDCl_3$) 1.53 (1H, s, NH), 4.58 (1H, s, $NCHPh_2$), 5.23 (1H, s, NCHCN), 7.2–7.6 (15H, m, ArH); *m*/*z* (CI) 299 (100, MH^+). Found (CI) 299.1537, $C_{21}H_{19}N_2$ (MH^+) requires 299.1543.

4.4.13. *N*-Allyl (*S*)-2-amino-phenylacetonitrile.[8] Purified by silica gel chromatography using 4:1 hexane–ethyl acetate as eluent to give the product in 85% yield as a yellow oil. $[\alpha]_D^{22} = -65.5$ (*c* 0.5, $CHCl_3$); ν_{max} (neat) 3321 s, 3066 m, 3032 m, 2926 m, 2841 m and 2227 cm^{-1} w; δ_H ($CDCl_3$) 1.86 (1H, s, NH), 3.5–3.6 (2H, m, NCH_2), 4.83 (1H, s, NCHCN), 5.24 (1H, d, *J* 10.2 Hz, CH=CH_2), 5.36 (1H, d, *J* 17.2 Hz, CH=CH_2), 5.92 (1H, m, C*H*=CH_2), 7.2–7.6 (5H, m, ArH); *m*/*z* (EI) 171 ($M-H^+$, 5), 144 (67), 116 (100), 104 (42).

4.5. *N*-Allyl-*N*-trifluoroacetyl (*S*)-2-amino-phenylacetonitrile[8]

To a sample of *N*-allyl-(*S*)-2-amino-phenylacetonitrile (0.01 g, 5.85×10^{-5} mol) in dichloromethane (1 mL) was added trifluoroacetic anhydride (0.018 g, 8.78×10^{-5} mol). The resulting solution was stirred for 1 h, then the solvent was removed in vacuo to give the trifluoroacetyl-protected α-amino nitrile which was analysed without purification. δ_H ($CDCl_3$) 3.91 (1H, dd, *J* 6.0, 17.0 Hz, NCH_2), 4.15 (1H, dd, *J* 4.7, 17.0 Hz, NCH_2), 5.13 (1H, d, *J* 17.0 Hz, $CH{=}CH_2$), 5.19 (1H, d, *J* 10.2 Hz, $CH{=}CH_2$), 5.66 (1H, m, $CH{=}CH_2$), 6.65 (1H, s, NCHCN), 7.4–7.5 (5H, m, ArH); chiral GC conditions (γ-CD butyryl column): initial temperature 100 °C, hold at initial temperature for 5 min then ramp rate 3 °C/min. t_R 22.8 min (major) and 22.7 min (minor).

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