Design and synthesis of a tetradentate '3-amine-1-carboxylate' ligand to mimic the metal binding environment at the non-heme iron(II) oxidase active site†

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Non-heme iron(II) oxidases (NHIOs) catalyse a diverse array of oxidative chemistry in Nature. As part of ongoing efforts to realize biomimetic, iron-mediated C–H activation, we report the synthesis of a new 'three-amine-one-carboxylate' ligand designed to complex with iron(II) and mimic the NHIO active site. The tetradentate ligand has been prepared as a single enantiomer in nine synthetic steps from *N*-Cbz-L-alanine, pyridine-2,6-dimethanol and diphenylamine, using Seebach oxazolidinone chemistry to control the stereochemistry. X-Ray crystal structures are reported for two important intermediates, along with variable temperature NMR experiments to probe the hindered interconversion of conformational isomers of several key intermediates, 2,6-disubstituted pyridine derivatives. The target ligand and an *N*-Cbz-protected precursor were each then complexed with iron(II) and tested for their ability to promote alkene dihydroxylation, using hydrogen peroxide as the oxidant.

Introduction

Chemists have for some time looked to Nature for inspiration in the design of new oxidation catalysts.[1–6] Non-heme iron oxidase enzymes (NHIOs) catalyse the oxidation of a wide range of substrates to give hydroxylated, oxygenated, oxidatively cleaved and oxidatively cyclised products.[7–16] The active site environment is highly conserved across the NHIO family, and sees the iron(II) cofactor coordinated by two histidine residues, an aspartate or glutamate residue and a water molecule, the so-called '2-His-1-carboxylate triad' (Fig. 1a).[17,18]

A number of small-molecule iron-based systems designed to mimic NHIO catalysis have been reported in recent times, some of which demonstrate the ability to oxidize hydrocarbon substrates with impressive activity and selectivity.[15,19–23] The most effective of these iron(II) complexes are those based upon tetradentate nitrogen ligands such as tris(2-pyridylmethyl)amine (TPA, **1**), *N*,*N*′-bis(2-pyridylmethyl)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (BPMCN, **2**) and 2-({2-[1-(pyridin-2-ylmethyl)-pyrrolidin-2-yl]pyrrolidin-1-yl}methyl)pyridine (PDP, **3** also known as 'bispyridyl-bispyrrolidine' BPBP) and their derivatives (Fig. 1b).[20–24] These ligands combine with hydrogen peroxide to effect oxidative reactivity that mirrors the ability of NHIOs to carry out stereoselective dihydroxylation, epoxidation and hydroxylation reactions on simple unactivated alkene and alkane substrates. These complexes have also been used as mechanistic probes to trap high-valent iron-oxo intermediates similar to those proposed to mediate NHIO catalytic pathways.[25,26]

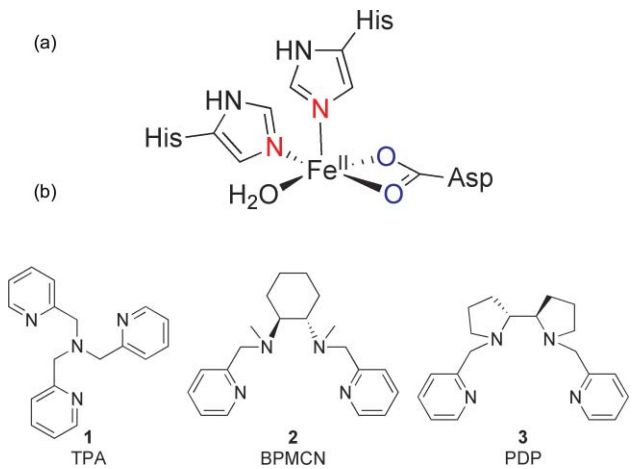

Fig. 1 **a.** Generalised NHIO active site; **b.** tetradentate amine ligands that form the basis of the most effective functional mimics of the NHIO active site: TPA (tris(2-pyridylmethyl)amine) **1**, BPMCN (*N*,*N*′-bis(2-pyridylmethyl)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine) **2**, and PDP (2-({2-[1-(pyridin-2-ylmethyl)pyrrolidin-2-yl]pyrrolidin-1-yl}-methyl)pyridine) **3** (also known as 'bispyridyl-bispyrrolidine' BPBP).

We have recently reported a new class of tetradentate ligand that mimics the structure of the NHIO active site, 'two-nitrogen-two-oxygen' ligands such as **4** (Fig. 2).[27,28] These ligands incorporate two nitrogen donors and a carboxylic acid to recreate the '2-His-1-carboxylate triad' of the NHIO active site, and an alcohol to replicate the water ligand at iron. Ligand **4a** (R = Et) combines with iron(II) acetate and hydrogen peroxide to oxidize a range of simple alkenes to epoxide and *cis*-diol products, although yields of these oxidized products are low due to competing radical chemistry and Fenton reaction pathways.[29]

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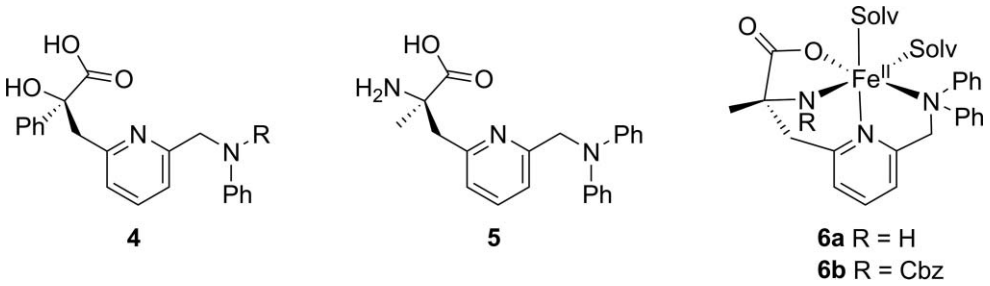


Fig. 2 'Two-nitrogen-two oxygen' ligands **4** that we have reported previously, the new ligand **5** described in this paper, and its proposed iron(II) complex **6**.

In this paper, we report the design and synthesis of a new tetradentate biomimetic ligand system **5**, a 'three-nitrogen-one-oxygen' ligand modified from **4**. Ligand **5** retains the '2-nitrogen-1-carboxylate' motif of **4**, but also an additional nitrogen donor: the primary amine of amino acid L-alanine. It was envisaged that this change in donor ligand would increase the binding affinity of the ligand for iron and thus increase the stability of the iron(II) complex to suppress the competing Fenton pathways.

Results and discussion

Ligand design and synthesis

The ligand **5** is designed to form a tetradendate complex **6** with iron(II), leaving two sites vacant for dioxygen binding. It has been demonstrated previously that for *cis*-dihydroxylation to occur in systems such as these, the catalyst must include two labile sites *cis* to each other at the iron(II) centre.[30] Ligand **5** includes three nitrogen donors—a pyridine, a substituted aniline and a primary amine derived from L-alanine—and the carboxylate oxygen of the amino acid to model the aspartic/glutamic acid residue of the NHIO active site. The pyridine and aniline moieties bring bulk to the system to counter the propensity of iron complexes to form bridged products (*e.g.* Fe(III)–O–Fe(III) species) *via* competing intermolecular oxidation pathways.

Synthesis of ligand **5** (Scheme 1) begins with selective protection[31] and activation[32] of pyridine-2,6-dimethanol **7** as the mono-*tert*-butyldimethylsilyl (TBDMS) ether/mono-bromide **8** as we have reported previously.[27,28]

N-Cbz-L-Alanine **9** was converted to the oxazolidinone **10** following the procedure of Kapadia *et al.* who used zinc(II) chloride and thionyl chloride to mediate condensation with benzaldehyde dimethyl acetal.[33] This afforded the desired *cis* diastereomer **10** in moderate yield (56%). The *cis* configuration was confirmed by ^{1}H NMR and the X-ray crystal structure, which shows the methyl and phenyl groups on the same face of the ring (Fig. 3).

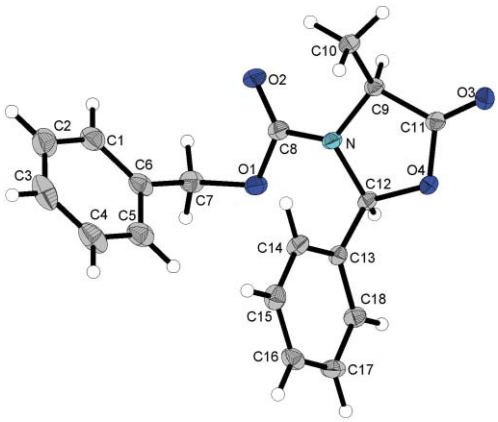
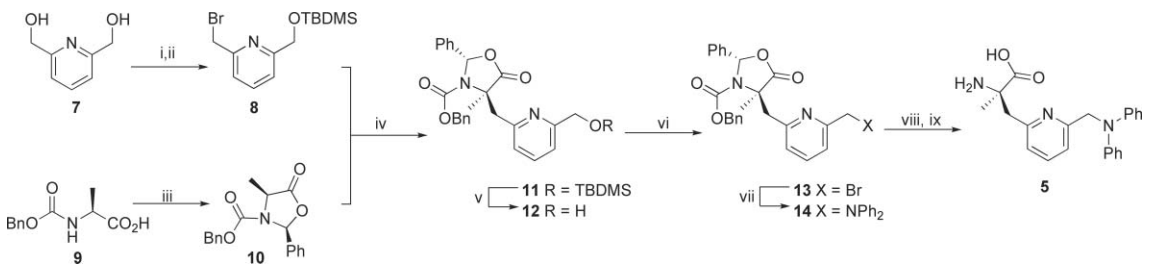


Fig. 3 X-Ray crystal structure of oxazolidinone **10**; thermal ellipsoids are drawn on the 50% probability level.

Oxazolidinone **10** was introduced stereoselectively, *via* α-alkylation of the cyclic enolate derived from **10** by treatment with lithium hexamethyldisilazide (LHMDS). This route exploits the principle of 'self-reproduction of chirality centres' introduced by Seebach and Fadel.[34] Thus, the benzaldehyde-derived phenyl group of the oxazolidinone directs the incoming electrophile **8** to the opposite face of the planar enolate, giving the enantiopure product **11** in which the stereochemistry is retained from the original oxazolidinone—*i.e.* the phenyl and methyl groups remain *cis* to each other (Fig. 4a). Attempts to generate the enolate **10a** using lithium diisopropylamide (LDA) at −78 °C gave only an intractable mixture of products, as observed by Seebach,



Scheme 1 Synthesis of ligand **5**; i. NaH, THF, rt, 45 min, then TBDMSCl, THF, rt, 45 min, 65%; ii. CBr_4, PPh_3, DCM, rt, 90 min, 71%; iii. $PhC(OMe)_2$, $ZnCl_2$, $SOCl_2$, THF, 0 °C, 4 h, 56%; iv. **10**, LHMDS, THF, −78 °C, 30 min, then **8**, THF, −78 °C, 3 h, 85%; v. TBAF, THF, rt, 90 min, 77%; vi. CBr_4, PPh_3, DCM, rt, 2 h, 77%; vii. pre-combined $NHPh_2$, *n*-BuLi/DMPU, THF, 0 °C, 40 min, then **13**, THF −15 °C, 5 h and rt o/n, 87%; viii. 2M LiOH, methanol, 45 °C, 2 h, then 1M HCl, 32%; ix. 10% Pd/C, HCO_2NH_4, methanol, reflux, 2 h, 95%.

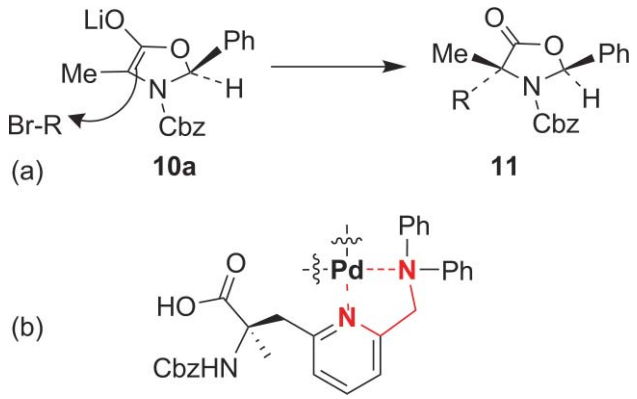


Fig. 4 **a.** α-Alkylation of the enolate derived from oxazolidinone **10**: approach of the incoming electrophile (RBr) to the top face is hindered by the phenyl group, so the electrophile approaches the enolate from below. **b.** Compound **15** poisons the palladium catalyst, binding through its pyridyl and aniline nitrogen atoms.

while lithium diethylamide (LDEA), recommended by Seebach for systems of this type,[34] also failed to yield the desired alkylation product **11**. Moreover, test reactions using oxazolidinone **10**, LDEA and benzyl bromide or methyl iodide as model electrophiles gave only complex mixtures. Gratifyingly, the bulkier LHMDS proved more successful: treatment of **10** with LHMDS at –78 °C, followed by introduction of bromide **8** (also at –78 °C) gave **11** in excellent yield (85%).

The TBDMS group was removed simply using tetra-*n*-butylammonium fluoride (TBAF) to give **12** in high yield (77%) and bromination was achieved using the same procedure as used to prepare mono-bromide **8**. This afforded **13** as a white crystalline solid in good yield (77%). The X-ray crystal structure of **13** (Fig. 5) confirmed that alkylation of the enolate **10a** had occurred stereoselectively as anticipated to give the (2*R*,4*S*)-oxazolidinone product.

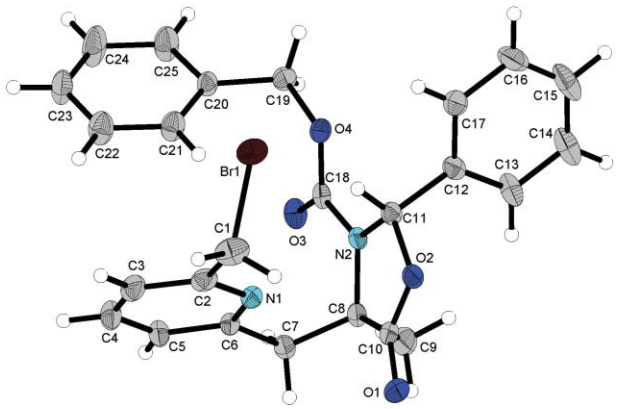


Fig. 5 X-Ray crystal structure of bromide **13**; thermal ellipsoids are drawn on the 25% probability level.

The aniline functionality was introduced to bromide **13** *via* a second nucleophilic substitution reaction. Thus, diphenylamine was deprotonated with *n*-BuLi at 0 °C in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU) and the lithium amide added to the bromide **13**, forming **14** in excellent yield (87%).

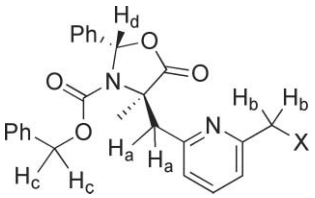
Finally, deprotection was effected in two steps to unmask the tetradentate ligand **5**. First the oxazolidinone moiety was cleaved hydrolytically, using an excess of lithium hydroxide in methanol to give the ring-opened product **15**. Then, removal of the *N*-Cbz group was achieved using catalytic transfer hydrogenation with ammonium formate as the hydrogen source.[35] Treatment with Pd/C and excess ammonium formate in refluxing methanol converted **15** to the triamine **5** smoothly and in excellent yield (95%). It is thought that the acidic ammonium counterion quenches the basicity of the pyridine nitrogen and the tertiary amine in the system, countering the capacity of the ligand to poison the palladium catalyst. This deprotection was initially attempted using hydrogen gas and Pd/C in methanol, but the *N*-Cbz group could not be removed under these conditions, and only starting material was recovered from the reaction. While Mutter and others have used catalytic hydrogenation to remove *N*-Cbz groups from similar oxazolidinone systems,[33,36] amines such as pyridine and triethylamine are known to retard hydrogenolysis of *O*-benzyl groups by catalyst poisoning.[37–39] Furthermore, bidentate amines like ethylenediamine and *o*-phenylenediamine further suppress rates of hydrogenolytic *O*-debenzylation,[39] with a two-carbon spacer between nitrogen atoms most effective at deactivating the Pd/C catalyst due to formation of a 5-membered cyclic complex with palladium.[40] It seems likely that compound **15** would bind to palladium in exactly this sort of bidentate arrangement, through its pyridyl and aniline nitrogen atoms (Fig. 4b), thereby poisoning the catalyst and stifling removal of the *N*-Cbz group under these conditions. The capacity of the ligand to poison the catalyst is counteracted when ammonium formate is present, as noted above.

NMR analysis

^{1}H NMR analysis reveals that compounds **11–14** all exist as mixtures of two stable conformers at room temperature. Each of these compounds displays two sets of signals for all protons, in a 3 : 1 ratio (Fig. 6). Most notable are the two methyl singlets at *ca.* 1.90 ppm in the spectra of all these compounds and two AB quartets between 3.30 and 4.00 ppm arising from the diastereotopic methylene protons. Furthermore, the spectrum of compound **13** shows that the protons of the bromomethyl (CH_2Br) group are non-equivalent and present as a pair of doublets between 4.40 and 4.60 ppm. This methylene group is four bonds away from the stereocentre; however, it is not unusual for diasterotopic effects to be observed several bonds distant from a chiral centre,[41] and the benzylic protons of the *N*-Cbz group also exhibit similar diastereotopy. The spectra of compounds **11–14** were fully assigned by detailed analysis of 1D (^{1}H and ^{13}C) and 2D-NMR experiments (COSY, HSQC, HMBC, NOESY, TOCSY, data not shown); key chemical shifts are summarised in Table 1.

Variable temperature NMR experiments were used to confirm that the two products observed are isomers that interconvert at higher temperatures (Fig. 7). Heating a solution of **11** in toluene-d_6 from 300 to 373 K causes each pair of signals to coalesce, confirming that the observed complication of these spectra is due to the occurrence of two isomers at room temperature that interconvert when additional energy is provided to the system. Similar dynamic behaviour has previously been described for other alkylated oxazolidinone systems.[42–44]

Table 1 ^{1}H NMR shifts of **major** and (minor) conformers of oxazolidinones **11–14**[a,b,c]



Compound	CH_3	H_a	H_b	H_c	H_d
11 (X = OTBDMS)	**1.92** (1.82)	**3.35, 3.98** (3.33, 3.59)	**4.77** (4.76)	**4.81, 4.85** (5.00, 5.17)	**5.73** (5.74)
12 (X = OH)	**1.94** (1.86)	**3.40, 4.02** (3.27, 3.65)	**4.72** (4.70)	**4.83, 4.95** (5.12, 5.26)	**5.79** (5.75)
13 (X = Br)	**1.92** (1.83)	**3.37, 4.04** (3.32, 3.62)	**4.44, 4.53** (4.48,4.56)	**4.82, 4.85** (5.01, 5.22)	**6.25** (6.04)
14 (X = NPh_2)	**1.94** (1.84)	**3.38, 4.01** (3.35, 3.64)	**4.85** (4.85)	**5.02–5.25** (4.99–5.17)	**5.70** (5.68)

[a] Spectra recorded at 600 MHz at 298 K in $CDCl_3$. [b] Chemical shifts in ppm referenced to TMS. [c] Signals coalesce at higher temperature—see Fig. 7.

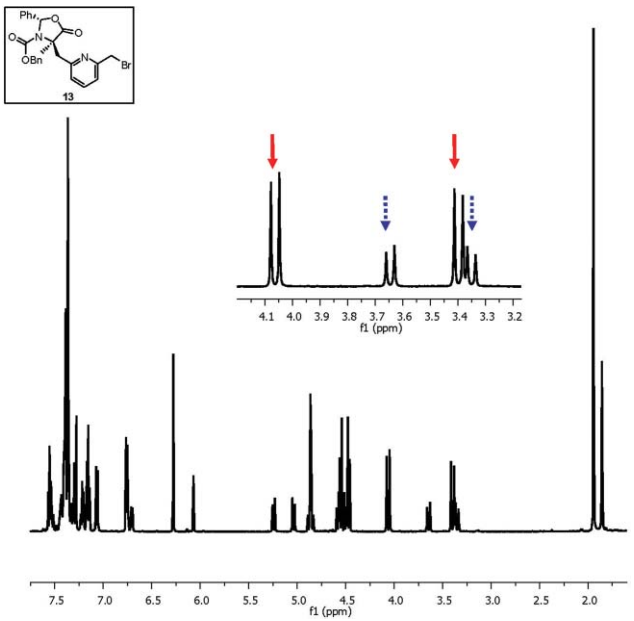


Fig. 6 ^{1}H NMR spectrum of bromide **13** in $CDCl_3$ with expansion of region 3.10–4.20 ppm showing the two sets of AB spin systems for the diastereotopic methylene protons in the major (solid arrows) and minor (dashed arrows) conformational isomers.

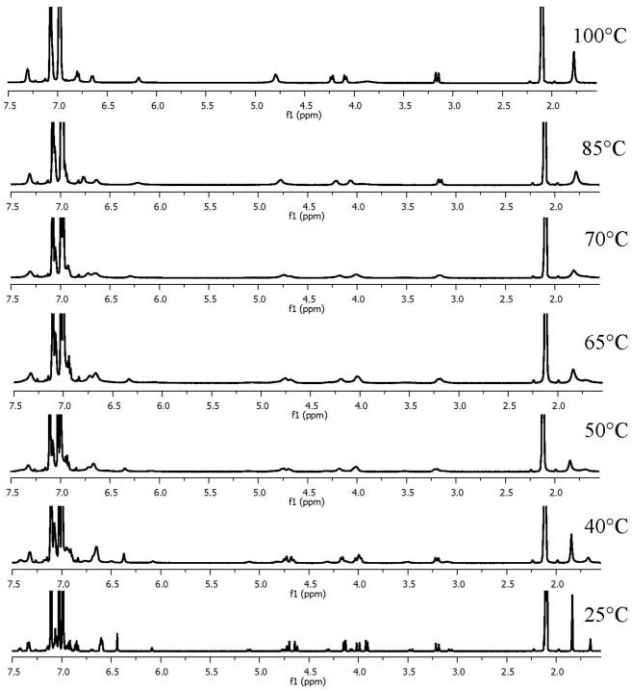
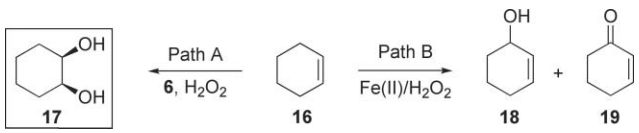


Fig. 7 ^{1}H NMR (500 MHz) spectra of the silyl ether **11** in toluene-d_6 at different temperatures.

Iron(II)-mediated oxidations

Ligand **5** was synthesised to determine its efficacy as a functional NHIO mimic—*i.e.* its potential as a ligand for the biomimetic iron-mediated oxidation of hydrocarbon substrates. Oxidative turnover experiments were carried out using both the target ligand **5** and the Cbz-protected precursor **15**, which also incorporates the 'three-nitrogen-one-oxygen' donor ligand set. The iron complexes **6a** and **6b** were prepared *in situ* by mixing equimolar amounts of **5** or **15** with iron(II) acetate in methanol, then used directly in oxidation reactions with cyclohexene **16** using hydrogen peroxide as oxidant.

Both complexes promote the *cis*-dihydroxylation of cyclohexene to give *cis*-cyclohexane-1,2-diol **17** at low levels, while also forming the allylic oxidation products alcohol **18** and ketone **19** (Scheme 2). Control experiments using iron(II) acetate and hydrogen peroxide in the absence of ligand show that no diol product is formed without **6a** or **6b**, and the allylic oxidation



Scheme 2 Potential products from the iron-mediated oxidation turnover of cyclohexene **16**: Path A is the desired biomimetic dihydroxylation reaction mediated by the iron complex **6** to give *cis*-cyclohexane-1,2-diol **17**, while Path B shows competing Fenton-type reactivity *via* an allylic radical to alcohol **18** and ketone **19**.

products **18** and **19** are formed in lower levels. However, the biomimetic dihydroxylation reaction is far from catalytic: complex **6b** promotes dihydroxylation with a turnover number (TN, amount of product in μmol per amount Fe complex in μmol) of 0.01. Allylic oxidation *via* radical mechanisms is the dominant pathway.

Conclusion

Towards the goal of biomimetic iron-mediated hydrocarbon oxidation, we have synthesised a new 'three-nitrogen-one-oxygen' ligand to mimic the metal binding environment at the NHIO active site. Ligand **5** has been prepared in 9 steps from pyridine-2,6-dimethanol **7** and *N*-Cbz-L-alanine **9**, using Seebach's oxazolidinone chemistry to transfer stereochemical information from the amino acid starting material to the final product. Compound **5** and the carbamate precursor **15** have been tested as ligands for iron-mediated alkene dihydroxylation. Both biomimetic ligands promote the dihydroxylation of cyclohexene, but yields and turnover numbers are very low and the reaction is far from catalytic. Competing pathways mediated by hydroxyl radicals divert much of the oxidizing power, giving rise to allylic C–H abstraction and forming allylic alcohol and enone products. These competing reactions presumably proceed either *via* a traditional Fenton pathway (in which the hydrogen peroxide oxidant reacts with uncomplexed iron(II) in solution to generate hydroxyl radicals) or a 'Fenton-type' mechanism (whereby an iron–ligand species mediates the formation of hydroxyl radicals). In either case it is evident that ligand **5** does not exert sufficient control over the chemistry of iron(II) and hydrogen peroxide to allow synthetically useful conversion of alkene substrates to diols. Work is under way to develop improved ligands which combine more effectively with iron(II) to suppress these competing allylic oxidation reactions.

Experimental

Synthesis

(2*S*,4*R*)-Benzyl 4-((6-(*t*-butyldimethylsilanyloxymethyl)pyridin-2-yl)methyl)-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylate 11. A solution of hexamethyldisilazane (HMDS, 1.86 mL, 9.2 mmol) in THF (30 mL) was cooled to 0 °C and *n*-BuLi (1.6 M solution in hexanes, 5.7 mL, 9.2 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 10 min and then cooled to −78 °C. This LHMDS solution was then transferred *via* cannula into a solution of **10** (2.2 g, 7.1 mmol) in THF (30 mL), which had been pre-cooled to −78 °C. The combined solution was stirred at −78 °C for 30 min, after which a solution of the bromide **8** (2.7 g, 8.5 mmol) in THF (30 mL) precooled to −78 °C, was added *via* cannula. The reaction mixture was stirred at −78 °C for an additional 3 h, then poured into saturated aqueous ammonium chloride (50 mL) and extracted with ether (4 × 50 mL). The combined organic phases were washed with saturated brine (60 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give an orange oil, which was purified by column chromatography (5 : 1 pentane : ether) to yield product **11** as an orange oil (3.29 g, 85%); R_f 0.60 (1 : 1 pentane : ether); $[\alpha]_D^{20} = -13.1$ (*c* 0.7, $CHCl_3$); ν_{max} (thin film): 3429 (s, C–H), 3053 (s, C–H), 2306 (s, C–H), 1801 (s, C=O), 1786 (s, C=O), 1594 (s, C=C); δ_H (500 MHz, $CDCl_3$): Major Conformer: 0.10 (6H, s, $Si(CH_3)_2$), 0.96 (9H, s, $SiC(CH_3)_3$), 1.92 (3H, s, CCH_3), 3.35 (1H, d, J = 14.5 Hz, one of CCH_2CN), 3.98 (1H, d, J = 14.5 Hz, one of CCH_2CN), 4.77 (2H, s, $CH_2OSi(CH_3)_2$), 4.81 (1H, d, J = 12.0 Hz, one of $CH_2(C_6H_5)$), 4.85 (1H, d, J = 12.0 Hz, one of $CH_2(C_6H_5)$), 5.73 (1H, s, $CH(C_6H_5)$), 6.70 (1H, d, J = 7.5 Hz, py-CH_β), 6.98 (1H, d, J = 7.5 Hz, py-CH_δ), 7.15–7.38 (10H, m, 2 × (C_6H_5)), 7.55 (1H, t, J = 7.5 Hz, py-CH_γ); Minor Conformer: 0.09 (9H, s, $SiC(CH_3)_3$), 0.98 (6H, s, $Si(CH_3)_2$), 1.82 (3H, s, CH_3), 3.33 (1H, d, J = 14.5 Hz, one of CH_2CN), 3.59 (1H, d, J = 14.5 Hz, one of CH_2CN), 4.76 (2H, s, CH_2OSi), 5.00 (1H, d, J = 12.0 Hz, one of $CH_2(C_6H_5)$), 5.17 (1H, d, J = 12.0 Hz, one of $CH_2(C_6H_5)$), 5.74 (1H, s, $CH(C_6H_5)$), 6.63 (1H, d, J = 7.5 Hz, py-CH_β), 7.13 (1H, d, J = 7.5 Hz, py-CH_δ), 7.15–7.38 (10H, m, 2 × (C_6H_5)), 7.52 (1H, t, J = 7.5 Hz, py-CH_γ); δ_C (125 MHz, $CDCl_3$): Major Conformer: 18.4 ($Si(CH_3)_2$), 24.8 (CCH_3), 26.0 ($SiC(CH_3)_3$), 42.2 (CH_2CN), 62.4 ($NCCH_3$), 65.8 (CH_2OSi), 66.9 ($OCH_2(C_6H_5)$), 89.7 ($CH(C_6H_5)$), 118.7 (py-CH_δ), 122.1 (py-CH_β), 127.1, 127.5, 127.9, 128.3, 128.6, 128.7, 129.7, 135.4, 137.1 (2 × (C_6H_5)), 137.2 (py-CH_γ), 151.8 ($NCOOBn$), 155.0 (py-C_α), 161.0 (py-C_ε), 174.6 ($NCCOOCHPh$); Minor Conformer: −3.3 ($Si(CH_3)_2$), 25.7 (CCH_3), 26.0 ($SiC(CH_3)_3$), 43.9 (CCH_2CN), 62.2 ($NCCOO$), 65.7 (CH_2OSi), 67.7 ($OCH_2(C_6H_5)$), 89.6 ($CH(C_6H_5)$), 118.2 (py-CH_δ), 121.5 (py-CH_β), 127.0, 127.5, 127.9, 128.3, 128.5, 128.7, 129.7, 135.6, 136.7 (2 × (C_6H_5)), 137.3 (py-CH_γ), 152.7 ($NCOOBn$), 154.3 (py-C_α), 161.5 (py-C_ε), 175.0 ($NCCOOCHPh$); m/z (ES+): 569 (40%, $[M + Na]^+$), 547 (100%, $[M + H]^+$); HRMS (ES+) m/z 547.2634 [$(M + H)^+$ calcd. for $C_{31}H_{39}N_2O_5Si$ 547.2628].

(2*S*,4*R*)-Benzyl 4-((6-(hydroxymethyl)pyridin-2-yl)methyl)-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylate 12. A solution of **11** (1.25 g, 2.3 mmol) in THF (30 mL) was cooled to 0 °C and a solution of tetra-*n*-butylammonium fluoride (TBAF, 1M solution in THF, 1.33 mL, 4.6 mmol) was added dropwise *via* syringe. The solution was stirred at room temperature for 90 min. The reaction was poured onto water (30 mL) and the aqueous phase was extracted with DCM (3 × 30 mL). The organic phases were combined, washed with saturated brine (30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography (1 : 1 pentane : ether) giving the product as a pale yellow oil (0.75 g, 77%); R_f 0.70 (1 : 1 pentane : ether); $[\alpha]_D^{20} = -15.1$ (*c* 1.8, $CHCl_3$); ν_{max} (thin film): 3681 (s, OH), 3621 (s, OH), 3446 (s, C–H), 3028 (s, C–H), 2401 (s, C–H), 1792 (s, C=O), 1704 (s, C=O), 1597 (s, C=C), 1523 (s, C=C); δ_H (600 MHz, $CDCl_3$); Major Conformer: 1.94 (3H, s, CH_3), 3.40 (1H, d, J = 14.5 Hz, one of CCH_2CN), 4.02 (1H, d, J = 14.5 Hz, one of CCH_2CN), 4.72 (2H, d, J = 8.0 Hz, CH_2OH), 4.83 (1H, d, J = 12.0 Hz, one of $CH_2C_6H_5$), 4.95 (1H, d, J = 12.0 Hz, one of $CH_2C_6H_5$) 5.79 (1H, s, $CH(C_6H_5)$), 6.72–7.37 (10H, m, 2 × (C_6H_5)), 7.04 (1H, d, J = 7.5 Hz, py-CH_β), 7.08 (1H, d, J = 7.5 Hz, py-CH_δ), 7.53 (1H, t, J = 7.5 Hz, py-CH_γ); Minor Conformer: 1.86 (3H, s, CH_3), 3.27 (1H, d, J = 14.0 Hz, one of CH_2CN), 3.65 (1H, d, J = 14.0 Hz, one of CH_2CN), 4.70 (2H, d, J = 14.5 Hz, CH_2OH), 5.12 (1H, d, J = 12.0 Hz, one of $CH_2C_6H_5$), 5.26 (1H, d, J = 12.0 Hz, one of $CH_2C_6H_5$), 5.75 (1H, s, $CH(C_6H_5)$, 6.79 (1H, d, J = 7.5 Hz, py-CH_β), 7.12 (1H, d, J = 8.0 Hz, py-CH_δ), 7.14–7.37 (10H, m, 2 × (C_6H_5), 7.53 (1H, t, J = 7.5 Hz, py-CH_γ); δ_C (150 MHz, $CDCl_3$): Major Conformer: 24.7 (CH_3), 42.5 (CH_2CN), 62.4 ($NCCOO$), 64.3 (CH_2OH), 67.0 ($CH_2(C_6H_5)$), 89.5 ($CH(C_6H_5)$), 118.8 (py-CH_δ), 122.8 (py-CH_β), 127.0, 127.7, 128.0, 128.3, 128.6, 128.7, 129.8, 135.3, 136.9 (2 × (C_6H_5)) 137.4 (py-CH_γ), 151.7 ($NCOOCH_2$), 155.3 (py-C_α), 158.8 (py-C_ε), 174.5 ($NCCOO$); Minor Conformer: 25.5 (CH_3), 43.5 (CH_2CN), 62.8 (CCH_2CN), 65.0 (CH_2OH), 68.0 ($CH_2(C_6H_5)$), 89.6 ($CH(C_6H_5)$), 119.5 (py-CH_δ), 122.6 (py-CH_β), 127.0, 127.7, 128.0, 128.3, 128.6, 128.7, 129.9, 135.4, 136.3 (2 × (C_6H_5)), 137.6

(py-CH_γ), 153.9 (NCO_2CH_2), 154.9 (py-C_α), 159.7 (py-C_ε), 174.6 (CCO_2CH); *m/z* (ES–): 431 (100%, [M – H]$^-$); HRMS (ES+) *m/z* 433.1773 [(M + H)$^+$ calcd. for $C_{25}H_{25}N_2O_5$ 433.1763].

(2*S*,4*R*)-Benzyl 4-((6-(bromomethyl)pyridin-2-yl)methyl)-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylate 13. To a solution of **12** (0.75 g, 1.74 mmol) in DCM (20 mL) cooled to 0 °C was added a solution of carbon tetrabromide (0.63 g, 1.90 mmol) in DCM (10 mL) *via* cannula. The resulting solution was stirred at 0 °C and to it was added a solution of triphenylphosphine (0.50 g, 1.91 mmol) in DCM (10 mL) *via* cannula. The resulting yellow solution was stirred at 0 °C for 5 min and then at room temperature for 2 h. The reaction mixture was poured onto ether (50 mL) to precipitate triphenylphosphine oxide as a white solid. The solution was filtered and reduced *in vacuo* to give an orange oil. The crude product was purified by column chromatography (3 : 2 ether : pentane), to afford the product as a white crystalline solid (0.66 g, 77%); R_f 0.3 (9 : 1, pentane : ether); $[\alpha]_D^{20} = -23.7$ (*c* 0.7, $CHCl_3$); ν_{max} (thin film): 3350 (s, C–H), 3019 (s, C–H), 2401 (s, C–H), 1796 (s, C=O), 1743 (s, C=O); δ_H (600 MHz, $CDCl_3$); Major Conformer: 1.92 (3H, s, CH_3), 3.37 (1H, d, *J* = 16.0 Hz, one of CCH_2CN), 4.04 (1H, d, *J* = 16.0 Hz, one of CCH_2CN), 4.44 (1H, d, *J* = 10.0 Hz, one of CH_2Br), 4.53 (1H, d, *J* = 10.0 Hz, one of CH_2Br), 4.82 (1H, d, *J* = 13.0 Hz, one of CH_2C$_6$H$_5$), 4.85 (1H, d, *J* = 13.0 Hz, one of CH_2C$_6$H$_5$), 6.25 (1H, s, CH(C$_6$H$_5$)), 6.74–7.50 (10H, m, 2 × (C$_6H_5$)), 7.04 (1H, d, *J* = 8.0 Hz, py-CH_β), 7.27 (1H, d, *J* = 8.0 Hz, py-CH_δ), 7.53 (1H, t, *J* = 8.0 Hz, py-CH_γ); Minor Conformer: 1.83 (3H, s, CH_3), 3.32 (1H, d, *J* = 14.5 Hz, one of CCH_2CN), 3.62 (1H, d, *J* = 14.5 Hz, one of CCH_2CN), 4.48 (1H, d, *J* = 10.0 Hz, one of CH_2Br), 4.56 (1H, d, *J* = 10.0 Hz, one of CH_2Br), 5.01 (1H, d, *J* = 12.0 Hz, one of CH_2C$_6$H$_5$), 5.22 (1H, d, *J* = 12.0 Hz, one of CH_2C$_6$H$_5$), 6.04 (1H, s, CH(C$_6$H$_5$)), 6.69 (1H, d, *J* = 7.5 Hz, py-CH_β), 6.74–7.5 (10H, m, 2 × (C$_6H_5$)), 7.30 (1H, d, *J* = 7.5 Hz, py-CH_δ), 7.51 (1H, t, *J* = 7.5 Hz, py-CH_γ); δ_C (150 MHz, $CDCl_3$): Major Conformer: 25.2 (*C*H$_3$), 34.0 (*C*H$_2$Br), 42.3 (*C*H$_2$CN), 62.2 (N*C*COO), 67.0 (*C*H$_2$(C$_6$H$_5$)), 89.9 (*C*H(C$_6$H$_5$)), 122.0 (py-*C*H$_\delta$), 123.6 (py-*C*H$_\beta$), 127.4, 127.7, 128.0, 128.4, 128.8, 129.0, 129.9, 135.8, 137.5 (2 × (*C*$_6$H$_5$)), 138.0 (py-*C*H$_\gamma$), 152.1 (py-C_α), 156.6 (py-C_ε), 175.0 (NC*C*OO); Minor Conformer: 26.0 (*C*H$_3$), 33.7 (*C*H$_2$Br), 43.9 (*C*H$_2$CN), 62.2 (N*C*COO), 67.9 (*C*H$_2$(C$_6$H$_5$)), 89.9 (*C*H(C$_6$H$_5$)), 122.1 (py-*C*H$_\delta$), 123.1 (py-*C*H$_\beta$), 122.1, 123.1, 127.3, 127.7, 128.0, 128.4, 128.8, 129.0, 129.9, 135.8, 136.9 (2 × (*C*$_6$H$_5$)), 138.0 (py-*C*H$_\gamma$), 152.9 (N*C*OOCH$_2$), 155.8 (py-C_α), 156.9 (py-C_ε), 175.1 (NC*C*OO); *m/z* (ES+): 497 (100%, [M + H]$^+$ for ^{81}Br), 495 (95%, [M + H]$^+$ for ^{79}Br); HRMS (ES+) *m/z* 495.0937 [(M + H)$^+$ calcd. for $C_{25}H_{24}N_2O_4{}^{79}Br$ 495.0919].

(2*S*,4*R*)-Benzyl 4-((6-((diphenylamino)methyl)-pyridin-2-yl)-methyl)-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylate 14. A solution of diphenylamine (81 mg, 0.48 mmol) in THF (5 mL) was cooled to 0 °C and *n*-BuLi (1.6 M solution in hexanes, 0.38 mL, 0.60 mmol) was added *via* syringe. The solution was stirred at 0 °C for 20 min before DMPU (0.07 mL, 0.60 mmol) was added and the solution stirred for a further 20 min. The solution was cooled to –15 °C and added *via* cannula to a solution of **13** (200 mg, 0.40 mmol) in THF (5 mL) also at –15 °C. The resulting solution was stirred at –15 °C for 5 h then allowed to warm to room temperature overnight with continued stirring. The mixture was poured onto saturated ammonium chloride solution (5 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a brown oil which was purified by column chromatography (5 : 1 pentane : ether) to afford **14** as a yellow oil (206 mg, 87%); R_f 0.38 (1 : 1, pentane : ether); $[\alpha]_D^{20} = -17.7$ (*c* 0.7, $CHCl_3$); ν_{max} (thin film): 3235 (br, C–H), 2940 (br, C–H), 2406 (s, C–H), 1770 (s, C=O), 1682 (s, C=O), 1566 (s, C=C), 1463 (br, C=C); δ_H (600 MHz, $CDCl_3$): Major Conformer: 1.94 (3H, s, CH_3), 3.38 (1H, d, *J* = 14.5 Hz, one of CCH_2CN), 4.01 (1H, d, *J* = 14.5 Hz, one of CCH_2CN), 4.85 (2H, br s, CH_2N(C$_6$H$_5$)$_2$), 5.02–5.25 (2H, m, CH_2C$_6$H$_5$), 5.70 (1H, s, CHC$_6$H$_5$), 6.67 (1H, d, *J* = 8.0 Hz, py-CH_β), 6.90–7.41 (20H, m, 4 × (C$_6H_5$)), 7.03 (1H, d, *J* = 8.0 Hz, py-CH_δ), 7.45–7.50 (1H, m, py-CH_γ); Minor Conformer: 1.84 (3H, s, CH_3), 3.35 (1H, d, *J* = 14.0 Hz, one of CCH_2CN), 3.64 (1H, d, *J* = 14.0 Hz, one of CCH_2CN), 4.85 (2H, br s, CH_2N(C$_6$H$_5$)$_2$), 4.99–5.17 (2H, m, CH_2C$_6$H$_5$), 5.68 (1H, s, CHC$_6$H$_5$), 6.67 (1H, d, *J* = 8.0 Hz, py-CH_β), 6.90–7.41 (20H, m, 4 × (C$_6H_5$)), 7.03 (1H, d, *J* = 8.0 Hz, py-CH_δ), 7.45–7.50 (1H, m, py-CH_γ); δ_C (150 MHz, $CDCl_3$): Major Conformer: 25.1 (*C*H$_3$), 42.4 (*C*CH$_2$CN), 58.3 (*C*H$_2$N(C$_6$H$_5$)$_2$), 62.6 (*C*H$_2$C$_6$H$_5$), 67.1 (N*C*COO), 89.8 (*C*HC$_6$H$_5$), 120.0 (py-*C*H$_\beta$), 122.1 (py-*C*H$_\delta$), 127.2, 127.3, 127.6, 127.8, 127.9, 128.1, 128.4, 128.7, 128.8, 129.5, 129.9 (4 × (*C*$_6$H$_5$)), 135.7 (py-*C*H$_\gamma$), 152.3 (N*C*OOCH$_2$), 156.3 (py-C_ε), 159.5 (py-C_α), 174.9 (NC*C*OO); Minor Conformer: 25.8 (*C*H$_3$), 44.0 (*C*H$_2$CN), 58.3 (*C*H$_2$N(C$_6$H$_5$)$_2$), 62.5 (N*C*COO) 67.8 (*C*H$_2$(C$_6$H$_5$)), 89.8 (*C*HC$_6$H$_5$), 119.9 (py-*C*H$_\beta$), 122.8 (py-*C*H$_\delta$), 127.2, 127.3, 127.6, 127.8, 127.9, 128.1, 128.4, 128.7, 128.8, 129.5, 129.9 (4 × (*C*$_6$H$_5$)), 136.0 (py-*C*H$_\gamma$), 153.3 (N*C*OOCH$_2$), 155.6 (py-C_α), 160.0 (py-C_ε), 175.3 (NC*C*OO); *m/z* (ES+): 606 (100%, [M + Na]$^+$), 584 (72%, [M + H]$^+$); HRMS (ES+) *m/z* 584.2574 [(M + H)$^+$ calcd. for $C_{37}H_{34}N_3O_4$ 584.2549].

(*R*)-2-(Benzyloxycarbonylamino)-3-(6-((diphenylamino)methyl)pyridin-2-yl)-2-methylpropanoic acid 15. Aqueous lithium hydroxide solution (2 M, 0.59 mL, 1.17 mmol) was added to a solution of **14** (340 mg, 0.59 mmol) in THF (3 mL). The resulting mixture was stirred at 45 °C for 2 h. The mixture was diluted with water (5 mL) and cooled to 0 °C, then adjusted to pH 3 by addition of dilute aqueous HCl (1 M) and extracted with ethyl acetate (5 × 10 mL). The combined extracts were washed with saturated brine (15 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a brown oil which was purified by column chromatography (1 : 1 pentane : ether) to yield **15** (95 mg, 32%); R_f 0.44 (1 : 1 pentane : ether); $[\alpha]_D^{20} = -21.1$ (*c* 0.7, $CHCl_3$); ν_{max} (thin film): 3401 (br, N–H), 3017 (br, O–H), 1707 (s, C=O), 1591 (s, C=O), 1512 (s, C=C), 1454 (s, C=C); δ_H (300 MHz, $CDCl_3$): 1.59 (3H, s, CH_3), 3.20 (1H, d, *J* = 13.5 Hz, one of CCH_2CN), 3.31 (1H, d, *J* = 13.5 Hz, one of CCH_2CN), 4.97 (2H, s, CH_2N(C$_6$H$_5$)$_2$), 4.91–5.04 (2H, m, CH_2(C$_6$H$_5$)), 6.61 (1H, br s, N*H*), 6.84 (1H, d, *J* = 7.5, py-CH_β), 6.90–7.29 (15H, m, 3 × (C$_6H_5$)), 7.20 (1H, d, *J* = 7.5 Hz, py-CH_δ), 7.42 (1H, t, *J* = 7.5 Hz, py-CH_γ); δ_C (75 MHz, $CDCl_3$): 22.5 (*C*H$_3$), 44.2 (*C*H$_2$CN), 52.3 (NH*C*CO$_2$H), 58.5 (*C*H$_2$N(C$_6$H$_5$)$_2$), 66.0 (*C*H$_2$C$_6$H$_5$), 120.5 (py-*C*H$_\beta$), 122.4 (py-*C*H$_\delta$), 121.6, 122.9, 124.2, 125.5, 128.7, 128.8, 129.2, 129.3, 130.1, 130.2 (3 × (*C*$_6$H$_5$)), 136.8 (py-*C*H$_\gamma$), 155.7 (NH*C*OOCH$_2$), 155.8 (py-C_ε), 158.9 (py-C_α), 179.0 (NC*C*OOH); *m/z* (ES+): 496 (100%, [M + H]$^+$); HRMS (ES+) *m/z* 496.2238 [(M + H)$^+$ calcd. for $C_{30}H_{29}N_3O_4$ 496.2231].

(*R*)-2-Amino-3-(6-((diphenylamino)methyl)pyridin-2-yl)-2-methylpropanoic acid 5. To a solution of **15** (26 mg, 52 mmol) in methanol (5 mL), 10% Pd/C (5 mg) was added, followed by ammonium formate (13.2 mg, 200 mmol). The resulting mixture was stirred at reflux for 2 h. After the reaction was adjudged complete by TLC analysis, the catalyst was removed by filtration through a Celite pad, which was washed with methanol (2 × 10 mL). The combined filtrates were evaporated under reduced pressure to afford the title compound **5** as a white solid (17.8 mg, 95%); R_f 0.15 (9 : 1 DCM–MeOH); $[\alpha]_D^{20} = +34.3$ (*c* 0.14, MeOH); ν_{max} (thin film): 3687 (s, N–H), 3618 (s, N–H), 3040 (br, O–H), 1685 (s, C=O); δ_H (300 MHz, CD_3OD): 1.43 (3H, s, CH_3), 3.07 (1H, d, $J = 15.5$ Hz, one of CCH_2CN), 3.32 (1H, d, $J = 15.5$ Hz, one of CCH_2CN), 5.07 (1H, d, $J = 18.0$ Hz, one of CH_2N), 5.14 (1H, d, $J = 18.0$ Hz one of CH_2N), 6.90–6.95 (2H, m, two of $2 \times (C_6H_5)$), 7.05–7.09 (4H, m, four of $2 \times (C_6H_5)$), 7.15 (1H, d, $J = 7.0$ Hz, py-CH_β), 7.21–7.27 (4H, m, four of $2 \times (C_6H_5)$), 7.30 (1H, d, $J = 8.0$ Hz, py-CH_δ), 7.67 (1H, t, $J = 7.5$ Hz, py-CH_γ); δ_C (75 MHz, CD_3OD): 23.6 (CH_3), 43.0 (CH_2CN), 58.4 (CCH_3NH_2), 62.5 (CH_2N), 121.4 (py-CH_β), 121.8, 122.7 (six of $2 \times (C_6H_5)$), 124.2 (py-CH_δ), 130.5 (four of $2 \times (C_6H_5)$), 139.3 (py-CH_γ), 149.2 (two of $2 \times (C_6H_5)$), 158.5 (py-C_ε), 159.7 (py-C_α), 175.8 (*C*OOH); *m*/*z* (ES+): 384 (33%, $[M + Na]^+$), 362 (100%, $[M + H]^+$); HRMS (ES+) *m*/*z* 362.1864 [$(M + H)^+$ calcd. for $C_{22}H_{23}N_3O_2$ 362.1863].

Iron-mediated oxidation reactions

Methanol was distilled anaerobically over calcium hydride and degassed in three freeze–thaw cycles before use. Substrates were distilled over calcium hydride and passed through activated alumina before use to remove peroxides. Reactions were carried out under an atmosphere of argon and performed in triplicate. Iron(II) acetate (12 mg, 0.07 mmol) was dissolved in degassed, dry methanol (1.2 mL) and a portion of this solution (0.2 mL) was added to a solution of ligand **5** or **15** (4 mg, 0.01 mmol) in methanol (0.2 mL) to give a yellow solution. This combined solution was stirred for 1 h at room temperature, after which time it was diluted with methanol (10.0 mL) and the alkene substrate (10 mmol) was added. Hydrogen peroxide (30% solution in water, 13 μL, 0.1 mmol) in methanol (1.0 mL) was added over 30 min *via* syringe pump. The reaction was stirred at room temperature for 16 h. The solution was concentrated *in vacuo* and diluted with ethyl acetate, then passed through a short silica column.

Decane was added as an internal standard and products were analysed by gas chromatography and identified unambiguously by comparison with authentic standards. Gas chromatography was performed using a Hewlett-Packard 5890 Series II gas chromatograph fitted with an HP-1ms column (30 m × 0.25 mm ID, 0.25 μm; S/N US2469051H), and (to distinguish *cis* and *trans* diols) a Hewlett-Packard 5890A gas chromatograph fitted with a BP-20 column (25 m × 0.22 mm ID, 0.25 μm) and ChemStation software. Both chromatographs were equipped with split/splitless capillary inlets and flame ionisation detectors (FID).

Crystallography

Crystal data were collected using a Bruker SMART APEX CCD area detector diffractometer. A full sphere of reciprocal space was scanned by phi-omega scans. Pseudo-empirical absorption correction based on redundant reflections was performed by the program SADABS.[45] The structures were solved by direct methods using SHELXS-97[46] and refined by full matrix least-squares on F^2 for all data using SHELXL-97.[46] Hydrogen atoms were added at calculated positions and refined using a riding model. Their isotropic temperature factors were fixed to 1.2 times (1.5 times for methyl groups) the equivalent isotropic displacement parameters of the carbon atom to which the H-atom is attached. Anisotropic thermal displacement parameters were used for all non-hydrogen atoms.

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