Synthesis of dipyrrins bearing chirality adjacent to the conjugated skeleton — Electron-poor pyrroles exhibit dramatically reduced nucleophilicity

Cory S. Beshara, Beth M. Pearce, and Alison Thompson

Abstract: With the aim of furthering our investigations into the asymmetric complexation of dipyrrinato ligands, a dipyrrin bearing a stereogenic centre directly adjacent to the conjugated skeleton was synthesized. The electron-withdrawing nature of the chiral 4-(2,2,2-trifluoro-1-hydroxyethyl)- substituent significantly reduced the nucleophilicity of corresponding pyrroles, such that 2,2′-symmetrically substituted bis(dipyrrin)s bearing this motif were inaccessible. Furthermore, solutions of mononuclear dipyrrinato complexes were found to be less stable to acid-catalyzed decomplexation than the corresponding dinuclear complexes.

Key words: dipyrrin, dipyrromethene, complexation, electron-poor pyrrole, chirality.

Résumé : Dans le cadre de nos travaux sur la complexation asymétrique des ligands dipyrrinato, on a effectué la synthèse d'une dipyrrine portant un centre stéréogène directement adjacent du squelette conjugué. La nature électro-affinitaire du substituant chiral 4-(2,2,2-trifluoro-1-hydroxyéthyle) réduit d'une façon significative le caractère nucléophile des pyrroles correspondants et, en conséquence, des bis(dipyrrines) substituées d'une façon symétrique dans les positions 2 et 2′ et portant ce motif ne sont pas accessibles. De plus, on a observé que les solutions de complexes dipyrrinato mononucléaires sont moins stables vis-à-vis les décomplexations catalysées par les acides que les complexes binucléaires correspondants.

Mots-clés : dipyrrine, complexation, pyrrole déficient en électron, chiralité.

[Traduit par la Rédaction]

Introduction

The asymmetric synthesis of dipyrrinato complexes is a field of current interest because dipyrrins (1) give mono-anionic, planar, bidentate ligands that complex to a wide variety of metal ions. For example, chiral fluorescent boron-dipyrrinato (BODIPY) (2) complexes have been synthesized through the use of chiral dipyrrins (3–5), and chiral metal-organic frameworks incorporating dipyrrinato ligands are also known (6). 2,2′-Bis(dipyrrin)s (Fig. 1) with methylene, ethylene, or propylene linkers joining the dipyrrinato units generate dinuclear (M_2L_2) double helicates with tetrahedrally coordinated metal ions, and mononuclear (ML) helicates are formed if the alkyl linker is four atoms or more in length (7). The incorporation of chiral auxiliaries within the ligand allows the diastereoselective synthesis of helicates. Indeed, excellent diastereoselectivity has been obtained in the synthesis of mononuclear bis(dipyrrinato) helicates bearing templating BINOL and tartrate moieties attached via ethanoate groups within the linker (8). However, the most successful asymmetric synthesis of dinuclear bis(dipyrrinato) helicates to date gives a diastereomeric ratio of only 69:31 (9–11). In all reported diastereoselective syntheses of dinuclear bis(dipyrrinato) helicates, the chiral auxiliary is attached through a pendent ester or amide linkage and thus the chiral centre itself is quite remote from the helical axis.

Cognizant that the degree of stereoselectivity depends upon the effectiveness of the chiral auxiliary in inducing asymmetric complexation and thus the distance between the site of the auxiliary and the helical axis, we explored the value of incorporating a chiral centre directly adjacent to the dipyrrin; such a motif is somewhat rare for pyrroles (12–17) and extremely rare for dipyrrins (16, 18, 19). β-Keto pyrroles are readily available through Knorr-type syntheses (20, 21) and asymmetric reduction would generate a chiral alcohol. Further derivitization would serve to incorporate the pyrrole into a dipyrrin and thus place a chiral centre directly adjacent to the dipyrrinato unit (Fig. 2). Previous studies involving haematoporphyrin have shown that such hydroxyl groups are labile under mildly acidic conditions thus introducing the possibility of racemization through reversible elimination and addition. The lability is caused by the electron-rich nature of the pyrrole ring facilitating racemization at the pseudobenzylic position. Kumadaki provided a viable solution to potential racemization of this nature through the use

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Fig. 1. Complexation of bis(dipyrrin)s with varying linker length.

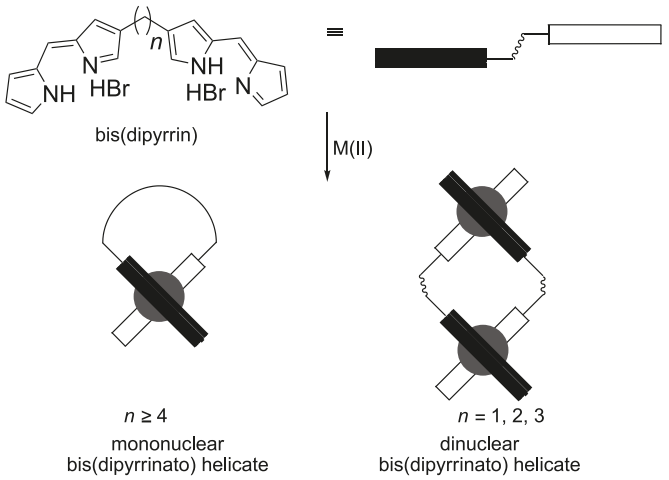
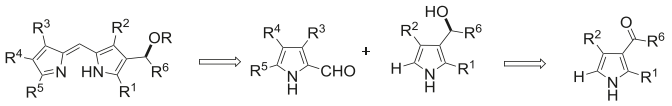


Fig. 2. Retrosynthetic incorporation of chirality adjacent to dipyrrin core.



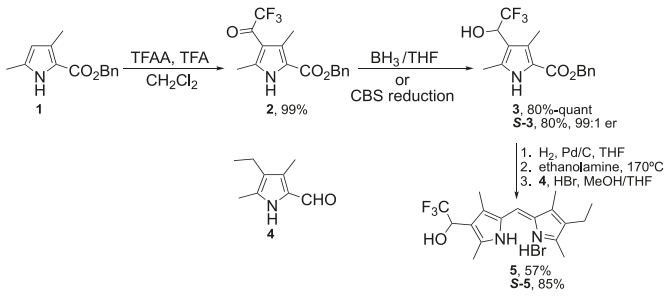
of 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituted pyrroles (18, 19) in the construction of homochiral haematoporphyrins (16). We herein report our work with 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituted dipyrrins. Our goals included the investigation of: the syntheses of dipyrrins and 2,2′-bis(dipyrrin)s incorporating 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituents; the stereochemical stability of 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituted dipyrrins; the ability of 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituted dipyrrinato units to undergo complexation; and the potential of the 4-(2,2,2-trifluoro-1-hydroxyethyl) group to influence diastereoselective complexation, either as an alcohol or as bulkier ether or ester derivatives.

Results and discussion

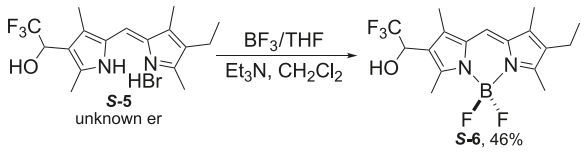
Synthesis of the first dipyrrin bearing a 4-(2,2,2-trifluoro-1-hydroxyethyl)-substitutent was achieved according to Scheme 1. Benzyl 3,5-dimethyl-pyrrole-2-carboxylate (**1**) (22) was converted to the corresponding trifluoroacetoxy-substituted pyrrole **2** using triflouroacetic acid (TFAA) under acidic conditions (23). Reduction of **2** with borane gave racemic alcohol **3**, and the use of the CBS protocol gave ***S*-3** with 99:1 enantiomeric ratio (er), akin to that reported by Kumadaki and co-workers (16). Hydrogenolysis of the benzyl ester, followed by thermolytic decarboxylation, gave the corresponding α-free pyrrole that was reacted directly with 4-ethyl-2-formyl-3,5-dimethylpyrrole (**4**) (24) under MacDonald-type coupling conditions (1) to afford the requisite racemic dipyrrin **5**, and the single enantiomer ***S*-5**.

The literature supports the stereochemical stability of the 2,2,2-trifluoro-1-hydroxyethyl moiety under acidic conditions (16, 18, 19), but we were concerned that the MacDonald-type coupling conditions (48% HBr, MeOH–THF) (1) might have afforded some racemization as exposure of enantiopure ***S*-3** to the same conditions resulted in loss of stereochemical integrity with the recovered material having only 76:24 er. To investigate its stereochemical purity a sample of the dipyrrin prepared from enantiopure ***S*-3** was converted into the corresponding BODIPY complex **6** (2) (Scheme 2). Because boron-dipyrrinato complexes are achiral at boron and amenable to chromatography, the enantiopurity of **6**, established by chiral HPLC, would reveal the enantiopurity of ***S*-5** by correlation.

Scheme 1. Synthesis of **5**.



Scheme 2. Synthesis of boron-dipyrrinato complex **6**.

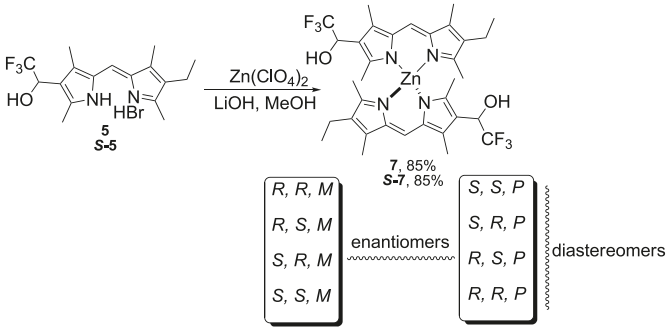


HPLC-analysis (Fig. S1) was used to determine that ***S*-6**, synthesized using ***S*-3**, had retained its enantiopurity during the MacDonald-type coupling step.[2] Thus, with a source of enantiopure ***S*-5** in hand, and having secured both the synthesis and the stereochemical stability of dipyrrins bearing the 4-(2,2,2-trifluoro-1-hydroxyethyl)-group, we progressed to investigating the stability of the corresponding complexes and assessing the influence of the electron-withdrawing substituent, essential for the stability of the chiral centre upon complexation. Racemic **5** was treated with zinc acetate under standard conditions (10) to give the homoleptic zinc complex **7** in 64% yield. The efficiency of complexation was then improved through the use of zinc perchlorate instead of the acetate salt and lithium hydroxide as base; complexation using enantiopure ***S*-5** was conducted in the same manner (Scheme 3). Although the zinc complex (**7**) was noticeably less stable under mildly acidic conditions (silica gel, aqueous extractions, wet solvents) than dipyrrinato complexes not bearing electron-withdrawing groups, isolation of **7** in good yield was achieved by rapid precipitation from the methanolic reaction mixture upon the addition of water. Mass spectrometry confirmed the formation of a mononuclear ML_2 complex.

Efforts turned to the investigation of the stereochemical outcome of the complexation reactions to determine whether **5** had undergone complexation with simple diastereo-

[2] Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 3784. For more information on obtaining material refer to cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Scheme 3. Complexation of **5** and possible stereochemical outcomes.

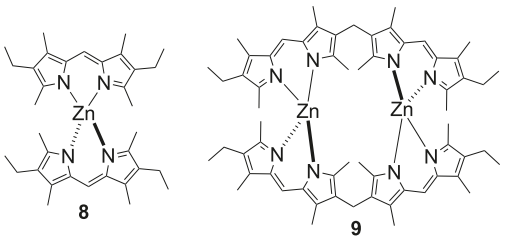


selectivity. Previously, NMR and circular dichroism (CD) spectroscopy, alongside chiral HPLC analysis, have been extremely useful for the evaluation of diastereoselective reactions involving dipyrrinato ligands. The neutral complexes are amenable to chromatography, and the helical nature of the chromophoric dipyrrinato units fixed in space through coordination to metal ions renders CD data very useful. As **5** constitutes an unsymmetrical A–B ligand architecture, the tetrahedrally coordinated metal ion in **7** gives rise to helicity. Thus, the complexation of racemic **5** allows for the possible production of eight ($2^3 = 8$) stereoisomers; *R* and *S* for the stereocentres on the ligands, and *M* and *P* for the metal centre (Scheme 3). Two species in each enantiomeric set (*R*,*S*,*P* – *S*,*R*,*P* and *R*,*S*,*M* – *S*,*R*,*M*) are identical, simplifying the possible outcomes to three (racemic) stereoisomers, with a 1:2:1 statistical ratio.

HPLC analysis of the crude product mixture obtained using racemic **5** showed one signal due to dipyrrinato complex(es) and two minor non-dipyrrinato impurities. The ChiralPak®-IA column used herein had previously proven to be superior for the resolution of dipyrrinato complexes and attempts to resolve the signals of **7** with other columns were unsuccessful. The ^{1}H NMR spectrum for the same product mixture was not useful for assigning stereoisomers but the ^{13}C nucleus allowed for improved resolution. The stereogenic carbon atom bearing the trifluoromethyl group normally appears as a quartet in the ^{13}C NMR spectrum with $J_{CF} \approx 33$ Hz. Indeed, **5** exhibits a quartet with $J_{CF} = 32$ Hz at a chemical shift of 65.8 ppm for this carbon atom. For the product mixture, the stereogenic carbon atom gave signals in the 64 ppm range that appeared as a pair of quartets of equal intensity ($J_{CF} = 33$ Hz), indicative either of a mixture of isomers or of two non-equivalent dipyrrinato units within a single ML_2 complex. Preparative HPLC served to separate the dipyrrinato complex(es) from the impurities, and ^{13}C NMR spectra of the isolated material retained the characteristic 1:1 pair of quartets. We identified that decomposition did not occur during HPLC, because NMR spectra of the initial product mixture and the material after preparative HPLC (and recombination of all fractions) were identical. Complex ***S*-7** was prepared from ***S*-5** (Scheme 3). With enantiopure ligand, the product mixture was found to exhibit identical HPLC and NMR characteristics to **7** (prepared from racemic dipyrrin **5**), thus suggesting that the chiral HPLC column was unable to resolve isomers of **7**.

Although the coordination abilities of dipyrrin ligands have been reported previously (25–27), a comparison of mononuclear and dinuclear analogues has not appeared. Using absorption spectroscopy, solutions of mononuclear **7**, bearing the 4-(2,2,2-trifluoro-1-hydroxyethyl)- substituent, were compared with solutions of the peralkyl mononuclear complex **8** (28) and the peralkyl dinuclear complex **9** (29) (Fig. 3). Studies at a variety of concentrations in technical-grade CH_2Cl_2 indicated that solutions of mononuclear complexes **7** and **8** are less stable to acid-catalyzed decomplexation than the dinuclear complex **9**; spectrophotometric-grade CH_2Cl_2 did not cause any decomplexation. These studies are important as dipyrrinato complexes are typically exposed to a range of solvents (including water) during work-up, purification, and analysis. As mentioned previously, the electron-deficient nature of **7** was a concern in terms of complex stability, and thus discovering that dinuclear dipyrrinato complexes are more stable than their mononuclear analogues suggested that the 4-(2,2,2-trifluoro-1-hydroxyethyl)- substituent might be more appropriate for use in bis(dipyrrinato) ligands. Furthermore, although ***S*-5** is unsymmetrical and thus gives an A–B dipyrrinato ligand that generates tetrahedrally coordinated Zn(II) helicates, formally the helicity is a consequence only of the two differently substituted pyrrolic units, that is, 4-ethyl versus 4-(2,2,2-trifluoro-1-hydroxyethyl).

Fig. 3. Mononuclear complex **8** and dinuclear complex **9**.

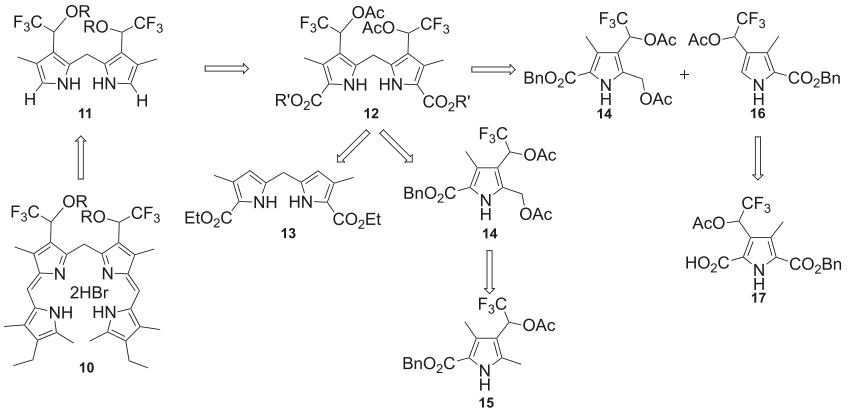


To increase the degree of asymmetry within the ligands, to thus improve both the stereoselectivity of complexation and the resolution by chiral HPLC, and to study the more stable dinuclear dipyrrinato complexes, we turned to the preparation of a bis(dipyrrin) bearing the chiral 4-(2,2,2-trifluoro-1-hydroxyethyl)- substituent directly adjacent to the conjugated skeleton. Retrosynthetic analysis (Fig. 4) of the symmetrical bis(dipyrrin) **10** reveals that the 2,2′-dipyrroles **11** and **12** are essential intermediates in the synthetic sequence, with successful condensation of **11** with **4** giving the required bis(dipyrrin). Three routes to **12** were envisaged, and each was investigated.

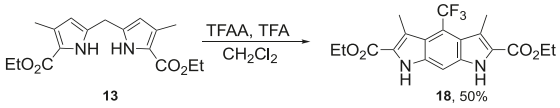
Trifluoroacylation of **13** (30), followed by reduction of the two trifluoromethyl ketones, was thought to be the most direct route to **12**. Unfortunately treatment of **13** with TFA and TFAA, under the conditions that had been successful for the synthesis of **2**, did not produce the required material and instead gave, tentatively, the pyrrolo-[3,2-*f*]-indole **18** where presumably mono-trifluoracylation had been followed by acid-catalyzed intramolecular condensation (Scheme 4) (31–33). Since indolic **18** does not feature the required prochiral signature, we sought an alternative route for the synthesis of **12**.

We thus investigated the synthesis of **12** through the homocoupling of **14** (34), itself prepared by mono-oxidation of **15** (16) using $Pb(OAc)_4$ (Scheme 5). Homocouplings of this type, using 2-methylene pyrroles, are commonplace for the synthesis of symmetrical dipyrromethanes and involve

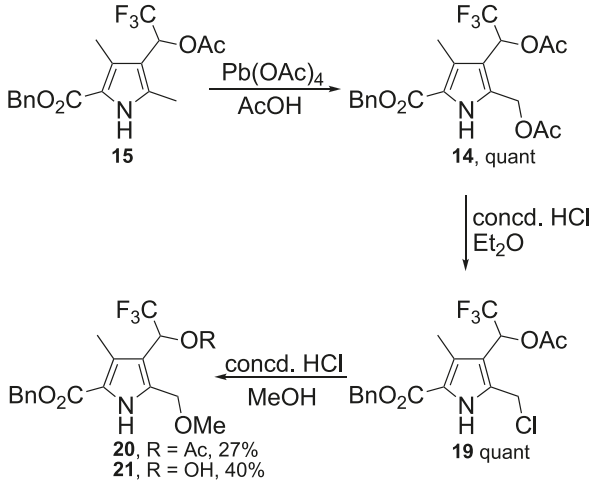
Fig. 4. Retrosynthetic analysis of bis(dipyrrin) **10**.



Scheme 4. Synthesis of **18**.



Scheme 5. Synthesis and attempted homocoupling of **14**.

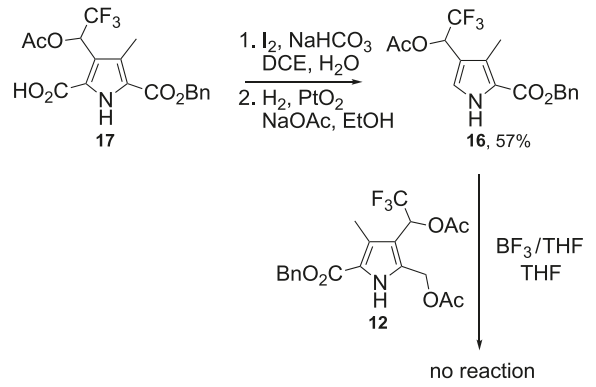


initial ring-protonation followed by the loss of an equivalent of formaldehyde to give in situ 5-unsubstituted pyrroles that then produce dipyrromethanes through condensation with remaining starting material (21, 35). However, treatment of **14** with HCl served only to effect substitution to give **19** and milder conditions (Montmorillonite K-10 clay (36)) gave no reaction at all. Presumably electron-poor **14** is resilient to ring-protonation and thus substitution dominates (12) under forcing conditions, preventing the typical nucleophilic chemistry of pyrroles from occurring; the presence of the electron-withdrawing ester and 2,2,2-trifluoro-1-acetoxyethyl substituents serves to inhibit the traditional nucleophilicity of the pyrrolic unit such that dipyrrins cannot be accessed using these intermediates.

Our final attempts to synthesize **12** required the condensation of a 5-unsubstituted pyrrole with **14**, in effect pre-preparing the same intermediate that was not formed in situ within the previous strategy; this strategy is often implemented for the synthesis of unsymmetrical dipyrromethanes (1). Thus, **16** was prepared via iodinative decarboxylation of **17** (16) followed by dehalogenation of the resulting iodopyrrole (Scheme 6). Attempted reaction of **16** with **14** met with failure and only starting materials were recovered. Once again, the classic nucleophilicity of pyrroles was absent for these electron-deficient pyrroles bearing both ester and (2,2,2-trifluoro-1-acetoxyethyl) substituents. In an attempt to reduce the electron-withdrawing nature of the 4-substituent in pyrrole **20**, the *O*-acyl protecting group was omitted from the synthesis and the free alcohol was exposed to the decarboxylation conditions. Unfortunately, these conditions resulted only in decomposition and the decarboxylated product could not be isolated.

Challenges associated with the low or unusual reactivity of electron-deficient pyrroles are not new. Indeed, Handy and co-workers have described problems associated with the *N*-protection of poly-halogenated pyrroles (37) and Clezy has made observations concerning problems in constructing dipyrromethanes using electron-deficient pyrroles (30). The

Scheme 6. Synthesis and attempted coupling of **16**.



poor reactivity of pyrroles substituted with the 4-(2,2,2-trifluoro-1-hydroxyethyl)- substituent have prevented our synthesis of a bis(dipyrrin) bearing this chiral moiety adjacent to the conjugated skeleton. The conflicting requirements of (i) electron-withdrawing groups to stabilize the stereocentre adjacent to the pyrrolic core and (ii) adequate nucleophilicy of the pyrrolic heterocycle render the (2,2,2-trifluoro-1-hydroxyethyl)- substituent an inappropriate group with which to introduce chirality directly adjacent to the pyrrolic core.

In summary, a dipyrrin containing a chiral 4-(2,2,2-trifluoro-1-acetoxyethyl)- substituent directly adjacent to the pyrrolic core was prepared and complexed with Zn(II). Although the corresponding mononuclear helicate was isolated in good yield, complexation occurred with poor selectivity. Attempts to prepare an analogous bis(dipyrrin), a skeleton that was found to be generally more stable in solution than the monomeric homologue, were thwarted by the low reactivity of electron-deficient pyrroles. These results again demonstrate that the balance between the reactivity and stability of pyrroles is a fine balance indeed (38, 39): the search continues for moieties that facilitate the introduction of chirality directly adjacent to the pyrrolic core without concurrent inhibition of pyrrolic reactivity.

General experimental

All reagents were purchased from Sigma-Aldrich and used as received, except phosphoric acid that was purchased from Fischer Scientific and reagent grade acetonitrile that was purchased from Caledon. Dry THF and CH_2Cl_2 were obtained from a solvent purification system and stored under nitrogen unless otherwise indicated. Dry ether was obtained via distillation from benzophenone sodium ketal. Unless otherwise indicated all glassware was flame-dried under vacuum prior to use, followed by a nitrogen fill. Column flash chromatography was performed using Silicycle Ultra Pure Silica Gel 60, 230–400 mesh. TLC was performed using Silicycle Ultra Pure Silica Gel 60 aluminum-backed plates, visualized under UV light, and stained using an ethanolic vanillin dip. Absorption spectroscopy was performed with samples in quartz cuvettes with a standard path-length of 1 cm. HPLC separations were performed using a Chiralpak®-IA column composed of amylose tris(3,5-dimethylphenylcarbamate) with particle size of 5 μm; the analytical column had an ID of 0.46 cm and the preparatory column an ID of 2 cm with both columns having a length of 25 cm. The chiral analytical column used for the determination of er in compound ***S*-3** was the Chiralpak® AD-RH, also composed of amylose tris(3,5-dimethylphynylcarbamate) but with a silica support (ID 0.46 cm; length 15 cm). NMR spectroscopy utilized 500 MHz, 400 MHz, and 250 MHz spectrometers at 300 K, as indicated. All ^1H and ^{13}C chemical shifts (δ) are referenced to TMS at 0 ppm in the solvents indicated and are reported on the ppm scale. All coupling constants (*J*) are reported in Hz. ^{19}F NMR spectra were referenced to $CFCl_3$ as an external standard at 0 ppm. Mass spectra were obtained using double focusing magnetic sector (EI) and TOF (ESI) spectrometers. Compounds **1** (22), **2** (3), **3** (16), **4** (24), **8** (28), **9** (29), **13** (30), **15** (16), and **17** (16) were prepared according to known procedures. WARNING: Perchlorate salts are powerful oxidants and care should be taken to avoid exothermic or explosive conditions.

2,3-Dimethyl-4-(2,2-2-trifluoroethyl-1-hydroxy-)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrole hydrobromide (5)

Pd–C catalyst (10% on C, 0.306 g, 10 mol%) was added to a solution of pyrrole **3** (1.00 g, 3.06 mmol) in THF (40 mL) through a stream of nitrogen and the reaction mixture was then stirred under a hydrogen (1.0 atm) atmosphere. After three days the mixture was filtered through celite and concentrated to facilitate the precipitation of the carboxylic acid (87%), which was then suspended in ethanolamine (25 mL), and the mixture was heated to 170 °C for 45 min, after which the mixture was poured into ice water and extracted with CH_2CH_2 (3 × 20 mL). The combined organic layers were washed with water (50 mL) and then brine (50 mL), followed by drying over sodium sulfate and concentratation. The residue was dissolved in $CHCl_3$ and reconcentrated to yield the α-free intermediate as a yellow crystalline solid (72%). This pyrrole (0.384 g, 1.99 mmol) and **4** (0.190 g, 2.00 mmol) were dissolved in 1:1 MeOH–THF (25 mL) and 48% aq hydrogen bromide (0.300 mL) was added to the solution. After stirring overnight at room temperature, the mixture was concentrated until very little solvent remained. Ether, pre-treated with sodium borohydride, was then added until a copious precipitate was present. Filtration and drying in air gave the title compound as a red solid (0.399 g, 57%); mp 190–230 °C. ^1H NMR (500 MHz, DMSO-d_6) δ_H: 1.04 (t, J_{HH} = 8 Hz, 3H), 2.34 (s, 3H), 2.42–2.45 (m, 5H), 2.58 (s, 3H), 2.60 (s, 3H), 5.27 (q, J_{HF} = 8 Hz, 1H), 6.83 (bs, 1H), 7.45 (s, 1H), 12.52 (bs, 1H), 12.69 (bs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 10.7, 11.1, 13.6, 14.2, 15.0, 17.4, 65.8 (q, J_{CF} = 32 Hz), 121.9, 122.3, 126.2, 126.4 (q, J_{CF} = 281 Hz), 128.5, 132.6, 143.9, 145.2, 151.7, 158.1. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F: -78.2 (d, J_{HF} = 8 Hz). MS-ESI *m/z*: 327.1 $(M + 1 - Br)^-$.

N,N′-Difluoroboryl-[2,3-dimethyl-4-(1-hydroxy-2,2-2-trifluoroethyl)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrolato-kN] (6)

To a suspension of **5** (1.00 g, 2.4 mmol) in CH_2Cl_2 (15 mL) under a nitrogen atmosphere was added, first, NEt_3 (6.37 mL, 45 mmol) and, second, $BF_3{\cdot}OEt_2$ (6.33 mL, 51.3 mmol) giving a colour change from brown-orange to dark orange-pink. After stirring the solution (the suspension becomes a solution after the addition of $BF_3{\cdot}OEt_2$) for one hour at room temperature the reaction mixture was concentrated. The residue was taken up in Et_2O and run through a plug of silica to remove baseline material and then further purified using chromatography and 1:50 to 1:10 ethyl acetate – hexanes as eluent to yield the title compound as a pink-red solid (0.395 g, 46%); mp 175–178 °C. R_f (1:5 ethyl acetate – hexanes): 0.19. UV (nm) λ_{max}: 514. ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.07 (t, J_{HH} = 7.5 Hz, 3H), 2.17 (s, 3H), 2.27 (s, 3H), 2.39 (q, J_{HH} = 7.5 Hz, 2H), 2.52 (s, 3H), 2.54 (s, 3H), 2.55 (d, J_{HH} = 3 Hz, 1H), 5.04 (qd, J_{HF} = 7 Hz, J_{HH} = 3 Hz, 1H), 7.03 (s, 1H). ^{13}C NMR (125 MHz, $CDC1_3$) δ_C: 9.7, 10.3, 13.2 (2C), 14.6, 17.6, 67.7 (q, J_{CF} = 33 Hz), 119.9, 120.2, 125.3 (q, J_{CF} = 280 Hz), 131.7, 134.1, 134.5, 138.0, 139.4, 152.6, 159.8. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F: –78.77 (d, J_{FH} = 7 Hz), –146.16 to –146.85 (m). MS-ESI *m/z*: 354.3 (28%), 355.3 [$(M - F)^+$, 100%)], 356.3 (26%), 374.1 (20%).

Zinc bis[2,3-dimethyl-4-(2,2-2-trifluoroethyl-1-hydroxy-)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrolato-kN] (7)

Dipyrromethene salt **5** (1.00 g, 2.5 mmol) was dissolved in methanol (80 mL) and lithium hydroxide monohydrate (0.932 g, 9 mmol) was added directly to the solution causing a dramatic shift in colour from orange-red to yellow.

Zinc(II) perchlorate (CAUTION, 1.30 g, 5.0 mmol) was then added and the yellow solution turned orange immediately. The mixture was stirred for one hour followed by dilution with water to precipitate the desired product, which was isolated by filtration as a very fine orange powder after drying overnight in a vacuum oven at room temperature (0.763 g, 85%); mp 197–198 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H:1.01 (t, J_{HH} = 7.5 Hz, 3H), 1.02 (t, J_{HH} = 7.5 Hz, 3H), 1.89–1.94 (m, 3H), 1.95–2.20 (m, 3H), 2.20 (bs, 1H), 2.22 (d, J_{HH} = 1.5 Hz, 3H), 2.35–2.40 (m, 5H), 5.00–5.05 (m, 1H), 7.04 (s, 1H). ^{13}C NMR (125 MHz, $CDC1_3$) δ_C: 10.6, 10.7, 15.1, 15.5, 15.6, 18.2, 68.1 (q, J_{CF} = 33 Hz), 68.1 (q, J_{CF} = 33 Hz), 117.9, 121.8, 125.6 (q, J = 280 Hz), 132.3, 134.8, 134.9, 137.8, 139.6, 153.3, 161.5. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F: –78.9 (d, J = 7.5 Hz). MS-ESI *m/z*: 327.2 (ligand), 715.1 $(M + 1)^+$, 737.1 $(M + Na)^+$.

Benzyl 5-acetoxymethyl-4-(1-acetoxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate (14)

According to a published procedure (18), to a solution of benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-3,5-methylpyrrole-2-carboxylate (381.5 mg, 1.03 mmol) in acetic acid (9 mL) under N_2 at room temperature was added $Pb(OAc)_4$ (490.7 mg, 1.107 mmol) as a solid with stirring. The resulting mixture was stirred at 50 °C and monitored using TLC. After full conversion was apparent (4 h), the reaction mixture was cooled to room temperature and then diluted with ethylene glycol (1.0 mL). Distilled water (20 mL) was added to the solution, and the product was extracted using dichloromethane (3 × 50 mL). The organic layer was washed with 5% sodium bicarbonate (3 × 50 mL) and dried over sodium sulfate, and the solvent removed in vacuo to give the product (34) as a white solid (435.6 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.06 (3H, s), 2.17 (3H, s), 2.39 (3H, s), 5.16 (2H, q, J = 13.5 Hz), 5.31 (2H, d, J = 12.5 Hz), 5.33 (1H, d, J = 12.5 Hz), 6.23 (1H, q, J = 7.0 Hz), 7.33–7.42 (5H, m), 9.45 (1H, bs). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 10.5, 20.6, 20.9, 57.2, 66.3, 66.3 (q, J = 139 Hz), 114.2, 119.7, 123.7 (q, J = 1114 Hz), 127.7, 128.3, 128.4, 128.7, 130.3, 136.1. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F: –76.62. MS-ESI *m/z* for $C_{20}H_{20}F_3NNaO_6$ calcd.: 450.1140; found: 450.1130.

Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate (16)

Water (2 mL) and dichloroethane (DCE, 4 mL) were added to a flask containing pyrrole **17** (0.16 g, 0.40 mmol) and sodium bicarbonate (0.11 g, 1.3 mmol). Sodium iodide (0.16 g, 1.1 mmol) and iodine (0.48 g, 1.9 mmol) were added to the biphasic reaction mixture, which was heated at reflux temperature for an hour. After the mixture cooled to room temperature, sodium bisulfite was added very slowly as a solid, to quench the excess iodine (quenching was complete with loss of colour and cessation of effervescence). The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with magnesium sulfate followed by concentration to give the iodopyrrole as an off-white solid. The crude product was suspended in ethanol (4 mL) followed by the addition of sodium acetate (0.045 g, 0.55 mmol) and platinum(IV) oxide (0.014 g, 0.06 mmol) through a stream of nitrogen. A hydrogen atmosphere was maintained utilizing a balloon and needle through a septum and the reaction was stirred for 0.5 h. The product was partially purified using flash column chromatography and 1:5 EtOAc–hexanes as eluent to yield the title compound as a white solid which was used without further purification (0.080 g, 57%). ^{1}H NMR (500 MHz, acetone-d_6) δ_H: 2.12 (s, 3H), 2.40 (s, 3H), 5.31 (s, 2H), 6.20 (q, J_{HF} = 7 Hz, 1H), 7.00 (d, J_{HH} = 3 Hz, 1H), 7.32–7.42 (m, 5H), 9.50 (bs, 1H).

Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-5-chloromethyl-3-methylpyrrole-2-carboxylate (19)

To a solution of benzyl 5-acetoxymethyl-4-(1-acetoxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate (278.6 mg, 0.652 mmol) in dichloromethane (DCM, 20 mL) under nitrogen was added HCl (1 mol/L in ether, 3.129 mL) and the solution was stirred at room temperature overnight. The solution was washed with 5% aqueous sodium bicarbonate (3 × 10 mL) and the aqueous layer extracted using DCM (3 × 20 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo to give the product as a light pink solid (111 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.20 (3H, s), 2.39 (3H, s), 4.63 (1H, d, J = 13.0 Hz), 4.79 (1H, d, J = 13.0 Hz), 5.33 (2H, d, J = 12.5 Hz), 5.36 (1H, d, J = 12.5 Hz), 6.24 (1H, q), 7.35–7.43 (5H, m), 9.52 (1H, bs). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 10.5, 20.7, 36.5, 66.1 (q, J = 139 Hz), 66.5, 113.8, 120.1, 123.7 (q, J = 1114 Hz), 127.9, 128.4, 128.5, 128.8, 131.0, 135.9, 161.1, 168.6. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F: –7.06. MS-ESI *m/z* for $C_{18}H_{17}ClF_3NO_4$ calcd.: 403.0798; found: 402.0717.

Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-5-methoxymethyl-3-methylpyrrole-2-carboxylate (20)

To a solution of benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-5-chloromethyl-3-methylpyrrole-2-carboxylate (50 mg, 0.124 mmol) in methanol (2 mL) at room temperature was added concd. HCl (12 mol/L, 0.07 mL), and the mixture was then stirred at room temperature for 4 h. The solvent was removed in vacuo, and the crude mixture was purified using preparative TLC and 70:30 hexane–ethyl acetate as the eluent to give the product as a colourless oil (16.2 mg, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.15 (3H, s), 2.41 (3H, s), 3.40 (3H, s), 4.52 (1H, d, J = 13.5 Hz), 4.55 (1H, d, J = 13.5 Hz), 5.31 (2H, s), 6.20 (1H, q, J = 7.5 Hz), 7.34–7.43 (5H, m), 9.20 (1H, bs). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 10.7, 20.6, 58.8, 66.1, 66.2, 66.2 (q, J = 138.5 Hz), 111.7, 118.7, 123.9 (q, J = 1114 Hz), 128.4, 128.6, 133.5, 136.3, 161.0, 168.6. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F: –76.93. MS-ESI *m/z* for $C_{19}H_{20}F_3NO_5Na$ calcd.: 422.1191; found: 422.1175.

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