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Note

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Stereoselective Synthesis of a Dipyridyl Transient Receptor Potential Vanilloid-3 (TRPV3) Antagonist

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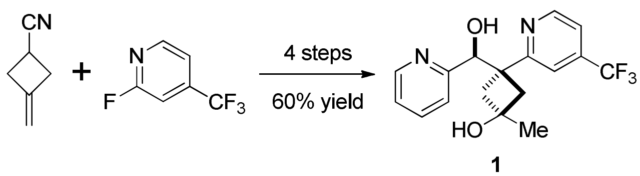


An efficient asymmetric synthesis of dipyridyl TRPV3 antagonist **1** is reported. The 4-step route involves two C-C bond forming steps, a highly diastereoselective alkene hydration, and asymmetric ketone hydrosilylation in 97% ee.

The identification of effective and safe small molecule analgesic agents is still a largely unmet medical need.[1] Transient receptor potential vanilloid-3 (TRPV3) is one of the members of the TRP family of non-selective cation channels implicated in the perception of pain.[2] Pyridinols such as **1** (Figure 1) are potent TRPV3 antagonists and demonstrate analgesic efficacy in preclinical models of neuropathic pain.[3] Following extensive lead optimization efforts, an efficient synthesis of pyridinol **1** was required to allow advanced preclinical characterization of the compound as a potential drug candidate.

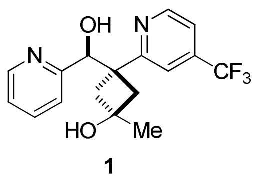
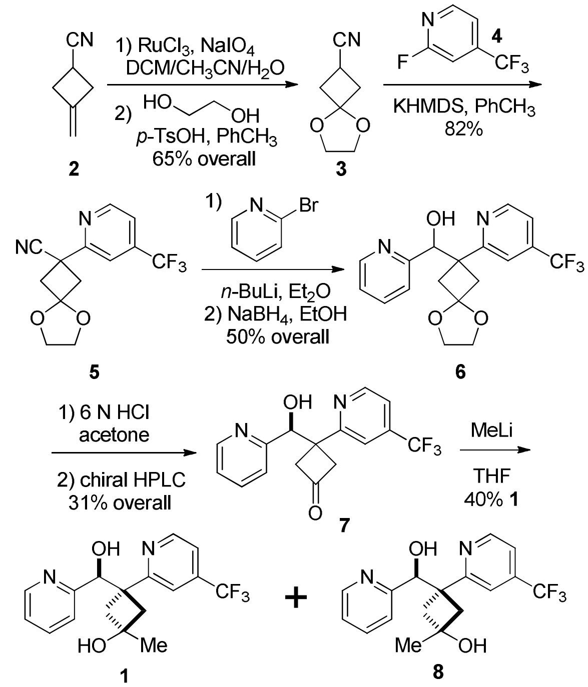


Figure 1. Structure of dipyridyl TRPV3 antagonist **1**

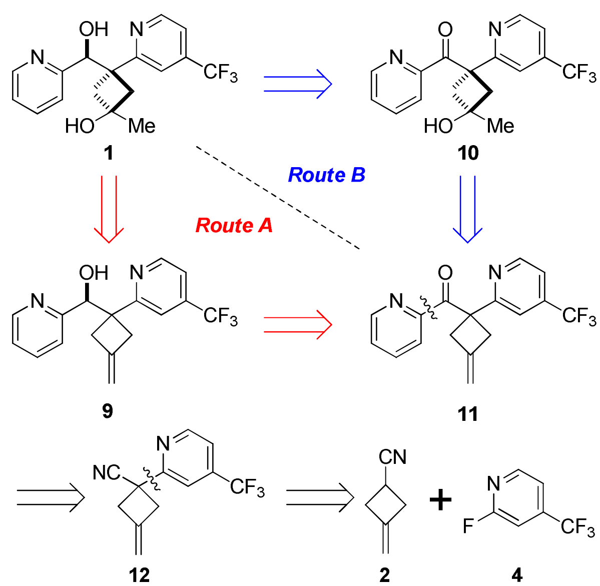
The original synthesis of **1** began with commercially available methylenecyclobutane **2** (Scheme 1).[3] Oxidative cleavage of the olefin and ketone protection provided cyanoketal **3**, which was deprotonated with KHMDS and added to fluoropyridine **4** to furnish pyridylnitrile **5**. Addition of 2-pyridyllithium to **5** and reduction with sodium borohydride gave racemic secondary alcohol **6**. Ketal deprotection facilitated chiral HPLC separation of enantiomers to provide enantiopure alcohol **7**. Finally, methyllithium addition generated a mixture of diols **1** and **8**, which could be separated by silica gel chromatography to give TRPV3 antagonist **1** in 8 steps and 3% overall yield from **2**.

Scheme 1. Original synthesis of TRPV3 antagonist **1**



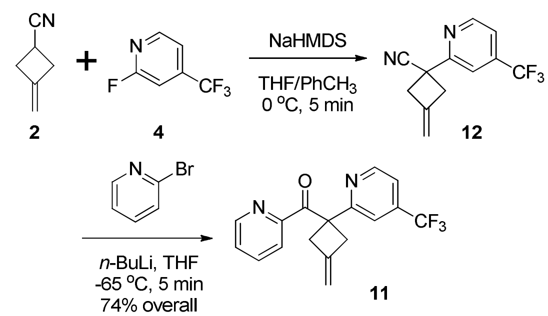
The original route to TRPV3 antagonist **1** was sufficient to provide gram quantities of material. However, several route improvements would be needed to access larger quantities of material. Oxidative cleavage of the starting material olefin **2** caused a need for ketone protection/deprotection steps and a non-selective late-stage reintroduction of the carbon atom that was cleaved. Furthermore, sodium borohydride reduction gave racemic **6**, requiring enantiomer separation via chiral HPLC. Despite efforts to find stereoselective ketone reduction and methyl addition conditions to increase the efficiency of the original route, little progress was made. Clearly, an alternative route was required.

Scheme 2. Retrosynthetic analysis



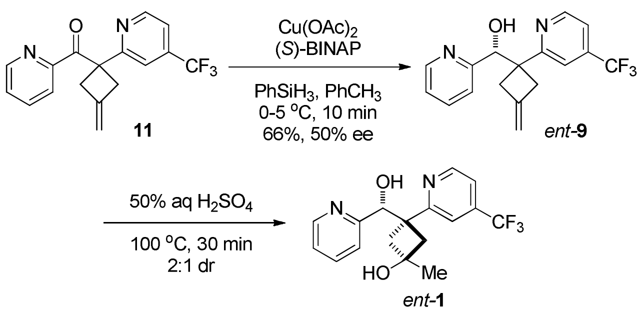
Towards a new route to TRPV3 antagonist **1**, we envisioned a retrosynthesis involving late-stage diastereoselective olefin functionalization of alkene **9**, which would arise from an asymmetric ketone reduction of bispyridylketone **11** (Route A, Scheme 2). Alternatively, the order of steps could be switched, with asymmetric reduction of ketone **10** preceded by olefin functionalization (Route B, Scheme 2). Each route would utilize **11** as a key intermediate, which could arise via two C-C bond forming steps: S_nAr addition of the anion of nitrile **2** to fluoropyridine **4** and 2-pyridyl anion addition to pyridylnitrile **12** to furnish key intermediate **11**. A further advantage of these routes was the use of readily available starting materials **2** and **4**, which were the same starting materials utilized in the original route. Finally, ketones **10** and **11** provided new opportunities for identification of asymmetric reduction conditions that could lead to efficient pathways to diol **1**.

Scheme 3. Preparation of key intermediate **11**



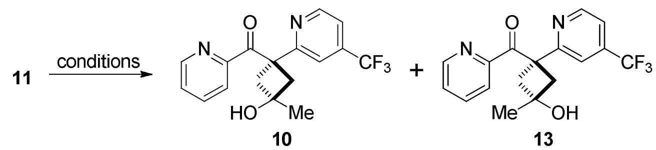
The preparation of key intermediate **11** began with the union of nitrile **2** with fluoropyridine **4** (Scheme 3). Addition of a NaHMDS solution to a solution of nitrile **2** and fluoropyridine **4** was key to efficient nitrile anion S_nAr, which was complete after only 5 min.[4] The reaction was more rapid and generated less byproducts than the comparable reaction between ketal **3** and fluoropyridine **4** in the original route (Scheme 1), providing pyridylnitrile **12** in sufficient purity for the next reaction without the need for purification. From crude nitrile **12**, a solution of 2-pyridyllithium was prepared by addition of *n*-butyllithium to 2-bromopyridine. Nitrile **12** was added to the 2-pyridyllithium solution, providing key intermediate **11** in 74% overall yield from nitrile **2** after acidic hydrolysis.

Scheme 4. Route A to dipyridyl TRPV3 antagonist **1**



With dipyridyl ketone **11** in hand, routes A and B (Scheme 2) were investigated simultaneously. Route A required enantioselective reduction of **11** (Scheme 4). Unfortunately, as with asymmetric reduction attempts in the original route, all initial transfer hydrogenation,[5] CBS reduction,[6] or DIP-Cl reduction[7] attempts failed. As an alternative reduction approach, copper-catalyzed asymmetric hydrosilylation was considered.[7] This recently developed method, pioneered by Lipshutz,[7a,b] was successfully applied to cyclohexyl 2-pyridylketone by Wu and coworkers,[7f] albeit with moderate enantioselectivity (63% ee) and extended reaction times (48 h) at -50 °C. When these conditions were applied to pyridylketone **11**, using (*S*)-BINAP as ligand, complete hydrosilylation was observed in only 10 min at 0 °C, giving pyridinol ***ent*-9** in 66% yield (50% ee).[8] With this encouraging preliminary result, alkene functionalization was investigated. Initial attempts at directed epoxidation, dihydroxylation, and halohydrin formation failed. Much to our delight, a Markovnikov hydration of the methylenecyclobutane of ***ent*-9** could be achieved with 50% aq sulfuric acid,[9] giving an improved 2:1 dr (by LCMS) in favor of the desired diol ***ent*-1** compared to the original MeLi addition approach (Scheme 1). Further optimization of Route A was not pursued since preliminary Route B results appeared more promising (Scheme 5).[10]

Table 1. Markovnikov hydration of **11**



entry	acid (% aq)	temp (°C)	time	dr (**10**:**13**)	Yield of **10** (%)
1	H_2SO_4 (50)	100	5 min	2:1	56
2	H_2SO_4 (50)	23	15 hr	2:1	61
3	H_3PO_4 (85)	40	22 hr	50:1	71
4	HBF_4 (48)	50	2.5 hr	9:1	90

An alternative route was also considered, involving olefin functionalization of key intermediate **11** followed by asymmetric hydrosilylation (Route B, Scheme 2). The Route A Markovnikov hydration conditions gave similar selectivity with a shorter reaction time (Table 1, entry 1). Optimization of the hydration of alkene **11** began with investigation of lower temperature in an attempt to improve selectivity (entry 2). Unfortunately, reaction at ambient temperature only resulted in a longer reaction time (15 h) with no selectivity improvement. While weak or dilute acids led to decomposition, other concentrated acid solutions also led to olefin hydration as shown in Table 1. Concentrated phosphoric acid (entry 3) gave remarkably high selectivity (50:1). However, tertiary phosphate was a major byproduct that could not be avoided or converted to desired product. While the phosphate could be washed away with aqueous $NaHCO_3$, the yield was limited to 71%. Tetrafluoroboric acid proved to be optimal (entry 4), giving a 9:1 dr after 2.5 hr at 50 °C with no other byproducts. Desired tertiary alcohol **10** could be isolated in 90% yield after chromatography. The mechanistic rationale for the selectivity observed in this hydration has not been investigated, but intramolecular delivery of water to a tertiary carbocation via a hydrated ketone may be involved in the selective formation of **10** (Figure 2).[11]

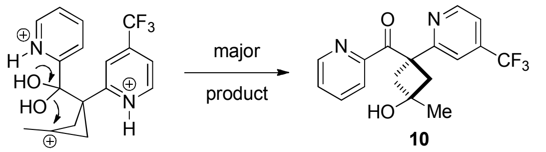
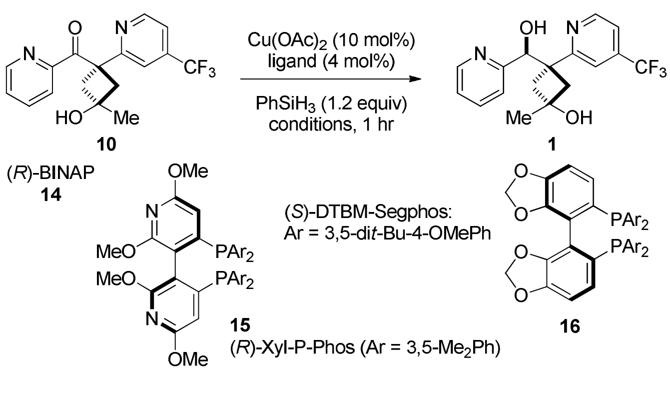


Figure 2. Possible mechanism for selective formation of **10**

After securing efficient access to cyclobutanol **10**, optimization of the asymmetric hydrosilylation was pursued (Table 2). The preliminary conditions employed for route A using (*S*)-BINAP as ligand gave the product pyridinol ***ent*-1** in moderate yield and poor enantioselectivity (Table 2, entry 1).[8] Switching to THF with (*R*)-BINAP improved the selectivity slightly (entry 2). Moving to more electron rich and/or sterically hindered BINAP derivatives, P-Phos and Segphos ligands were considered.[7] Indeed, (*R*)-xyl-P-Phos gave desired diol with a higher ee of 82% when the reaction was carried out at -70 °C (entry 4). Switching to (*R*)-DTBM-Segphos, we were surprised to find that the opposite enantiomer was produced, although with an excellent degree of enantioinduction (93% ee, entry 5).[12] Finally, using (*S*)-DTBM-Segphos at -30 °C, with a 1:1 Cu/ligand ratio and a low temperature AcOH quench, desired product **1** was produced in 90% isolated yield with 97% ee. The spectroscopic data for TRPV3 antagonist **1** generated via the new route were indistinguishable from material prepared via the original route.

Table 2. Asymmetric hydrosilylation of **10**

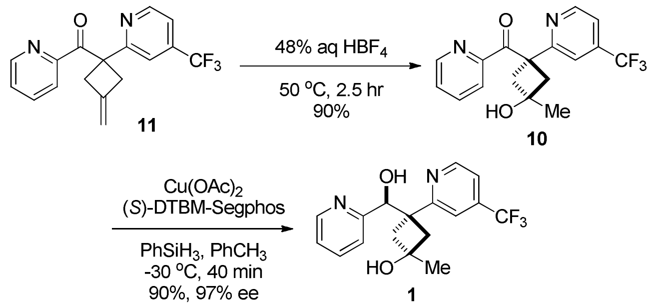


entry	ligand	temp (°C)	solvent	ee (%)	yield (%)
1	***ent*-14**	0	$PhCH_3$	31 (***ent*-1**)	49
2	**14**	0	THF	50	52
3	**15**	0	THF	67	52
4	**15**	-70	THF	82	89
5	***ent*-16**	0	THF	93 (***ent*-1**)	62
6[a]	**16**	-30	$PhCH_3$	97	90

[a]4 mol% $Cu(OAc)_2$ was used instead of 10 mol%

In conclusion, an efficient route to dipyridyl TRPV3 antagonist **1** was identified, improving the synthesis from 8 steps, 3% overall to 4 steps, 60% overall yield. The route involved two C-C bond forming steps, a surprisingly diastereoselective Markovnikov hydration of a methylenecyclobutane, and a highly enantioselective ketone asymmetric hydrosilylation. This route was used to rapidly produce 125 g of TRPV3 antagonist **1**,[13] enabling advanced preclinical studies.

Scheme 5. Route B to dipyridyl TRPV3 antagonist **1**



Experimental Section

General Procedures. All solvents and reagents were purchased at the highest commercial quality and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded at the specified temperature using 300 or 400 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane standard on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), coupling constants (Hz), and integration. All IR spectra were collected using a FT-MIR spectrometer with a Germanium (Ge) single bounce internal reflecting element.

Pyridylnitrile 12. A solution of 3-methylenecyclobutanecarbonitrile **2** (2.00 g, 21.5 mmol), 2-fluoro-4-(trifluoromethyl)pyridine **4** (3.55 g, 21.5 mmol), and toluene (20 mL) was cooled to < 5 °C and sodium bis(trimethylsilyl)amide (1 M in toluene, 23.6 mL, 23.6 mmol) was added dropwise at < 5 °C. After 5 min, 3.6 M aq NH_4Cl solution (20 mL) was added, the layers were separated, and the organic layer was washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), concentrated, and crude 3-methylene-1-(4-(trifluoromethyl)pyridin-2-yl)cyclobutanecarbonitrile **12** (5.12 g, 21.5 mmol, >99%) was used without further purification.

Dipyridylketone 11. A solution of 2-bromopyridine (3.13 ml, 32.2 mmol) in THF (10 mL) was cooled to < -70 °C and *n*-BuLi (12.9 ml, 32.2 mmol) was added dropwise at < -70 °C. After 5 min, 3-methylene-1-(4-(trifluoromethyl)pyridin-2-yl)cyclobutanecarbonitrile **12** (5.12 g, 21.5 mmol) was added as a solution in THF (5 + 2 + 2 mL THF rinse) dropwise at < -

65 ^{o}C. After 5 min, 2 N HCl (51 mL) was added and the solution was heated to 50 ^{o}C for 15 min. The biphasic solution was cooled to ambient temperature, diluted with MTBE (50 mL), and the layers were separated. The organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (0-20% EtOAc/heptanes, gradient elution) giving (3-methylene-1-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)(pyridin-2-yl)methanone **11** (5.08 g, 16.0 mmol, 74 % over 2 steps) as a light yellow oil that solidified on standing. On larger scale (>10 g), ketone **11** was isolated in 57% yield using *i*-PrOH crystallization. MP = 112-114 ^{o}C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 (d, *J* = 5.1 Hz, 1H), 8.37 (dt, *J* = 4.9, 1.2 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.82 (s, 1H), 7.78 (td, *J* = 7.8, 1.8 Hz, 1H), 7.30 – 7.25 (m, 2H), 4.96 (p, *J* = 2.4 Hz, 2H), 3.74 – 3.65 (m, 2H), 3.39 – 3.31 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 198.4, 165.5, 151.3, 150.5, 148.8, 142.9, 138.0, 137.9, 127.5, 123.8, 123.4, 117.3, 115.5, 108.5, 54.3, 41.5. HRMS (ESI+) *m/e* calcd for $[M + H]^+$ $C_{17}H_{13}N_2OF_3$ 318.0980, found 318.0991.

Dipyridyl alcohol 10. A solution of (3-methylene-1-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)(pyridin-2-yl)methanone **11** (510 mg, 1.60 mmol) and aq tetrafluoroboric acid (48%, 2.5 mL) was heated to 50 ^{o}C. After 2.5 hr, the yellow solution was poured into saturated aq $NaHCO_3$ (20 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated to a yellow oil. The residue was purified via column chromatography (0-40% ethyl acetate/heptanes gradient elution) to give ((1*s*,3*s*)-3-hydroxy-3-methyl-1-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)(pyridin-2-yl)methanone **10** (486 mg, 1.45 mmol, 90 %) as the major diastereomer. On larger scale (>10 g), tertiary alcohol **10** was isolated using heptanes trituration in 75% yield (upgrading dr from 9:1 to 24:1) and the minor diastereomer was completely rejected during isolation of **1**. MP = 85-87 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, *J* = 5.1 Hz, 1H), 8.41 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 7.96 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.93 – 7.88 (m, 2H), 7.50 – 7.47 (m, 1H), 7.44 (ddd, *J* = 7.5, 4.7, 1.4 Hz, 1H), 4.99 (s, 1H), 2.95 – 2.89 (m, 2H), 2.84 – 2.77 (m, 2H), 1.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 198.4, 164.7, 151.4, 150.7, 148.7, 138.0, 137.3, 127.5, 124.0, 123.4, 117.3, 117.0, 67.7, 50.7, 46.7, 29.3. HRMS (ESI+) *m/e* calcd for $[M + H]^+$ $C_{17}H_{15}N_2O_2F_3$ 336.1086, found 336.1087.

TRPV3 antagonist 1. A mixture of copper(II) acetate monohydrate (5.94 mg, 0.030 mmol), (*S*)-(+)-5,5'-bis[du(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole [(*S*)-(+)-DTBM-Segphos 35.1 mg, 0.030 mmol] and toluene (2 ml) was stirred at ambient temperature for 10 min, then heated to 50 °C for 15 min. Phenylsilane (0.2 equiv, 0.019 ml, 0.15 mmol) was added and the solution was stirred for 10 min at 50 °C. The mixture was cooled to -35 °C and ((1*s*,3*s*)-3-hydroxy-3-methyl-1-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)(pyridin-2-yl)methanone **10** (250 mg, 0.743 mmol) in toluene (2 mL) was added over 15 min, keeping the internal temperature < -30 °C. Phenylsilane (1 equiv, 0.0925 mL, 1.49 mmol) was then added at < -30 °C. After 40min, acetic acid (0.085 ml, 1.5 mmol) was added and the mixture was warmed to ambient temperature. The layers were separated, and the organic layer was washed with 2 N HCl (2 x 10 mL), water (10 mL), and saturated aq $NaHCO_3$ (10 mL). The combined aq layers were back extracted with MTBE (3 x 10 mL), then the combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (0-50% EtOAc/heptanes gradient elution) to give (1*R*,3*s*)-3-((*S*)-hydroxy(pyridin-2-yl)methyl)-1-methyl-3-(4-(trifluoromethyl)pyridin-2-yl)cyclobutanol **1** (227 mg, 0.671 mmol, 90 %). On larger scale (>10 g), TRPV3 antagonist **1** was isolated in >99% ee and >99% HPLC purity via initial HCl salt isolation (1 equiv 12 N HCl, 5:1 EtOAc/IPA) in 91% yield, followed by free-base (aq NaHCO3) isolation (83% yield) and 5% i-PrOH/heptanes crystallization (x 2) in 76% yield. MP 119-121 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, *J* = 5.1 Hz, 1H), 8.28 – 8.23 (m, 1H), 7.47 (td, *J* = 7.7, 1.8 Hz, 1H), 7.41 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.19 (d, *J* = 1.5 Hz, 1H), 7.08 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 5.77 (d, *J* = 3.3 Hz, 1H), 4.95 (brs, *J* = 2.7 Hz, 2H), 2.91 (d, *J* = 12.1 Hz, 1H), 2.84 (d, *J* = 12.1 Hz, 1H), 2.59 (dd, *J* = 12.0, 3.7 Hz, 1H), 2.50 (dd, *J* = 12.0, 3.7 Hz, 1H) 0.83 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.0, 161.8, 149.5, 147.8, 136.1, 136.0, 123.5, 122.4, 121.3, 118.9, 116.4, 80.2, 67.1, 46.0, 45.7, 45.2, 29.2. HRMS (ESI+) *m/e* calcd for $[M + H]^+$ $C_{17}H_{17}N_2O_2F_3$ 338.1242, found 338.1243. $[\alpha]_D$ = -42.5 (c 1.0, MeOH). Chiral SFC analysis revealed 97.0% ee.

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Supporting Information Available. NMR spectra of all new compounds and chiral SFC data for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Moderate isolated yields reported for asymmetric hydrosilylation in Scheme 4 and Table 2 were a consequence of employing unoptimized workup/isolation techniques which led to complex mixtures. Low temperature AcOH quench proved critical for efficient product isolation. See the experimental section preparation of final product **1** for details.
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(10) When optimized Table 2 asymmetric hydrosilylation conditions were applied to pyridylketone **11**, decomposition was observed, perhaps due to competing olefin hydrosilylation.
(11) For an experimental study on the formation of pyridinium ketone hydrates in aqueous solution, see: Huang, S.; Miller, A. K.; Wu, W. *Tetrahedron Lett.* **2009**, *50*, 6584.
(12) The effect of temperature on reversal of the sense of enantio-induction in hydrosilylation of pyridyl ketones was studied by Wu and coworkers,[7e,f] although in their studies, 2-pyridylketones did not display this behavior. Detailed investigations of temperature effects were not carried out in our studies, although these subtle effects on selectivity may explain the reversal we observed with different BINAP derivatives.
(13) Yields and experimental details described herein are for small scale optimization experiments using silica gel chromatography for isolation. Larger scale (>10 g) isolation procedures are included in the experimental section. These isolation procedures were unoptimized, favoring purity over recovery. Therefore, chromatography procedures and yields were used for the purpose of this study since they more accurately reflect reaction efficiency.