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Practical Asymmetric Synthesis of a Potent PDE4 Inhibitor via Stereoselective Enolate Alkylation of a Chiral Aryl−Heteroaryl Secondary Tosylate

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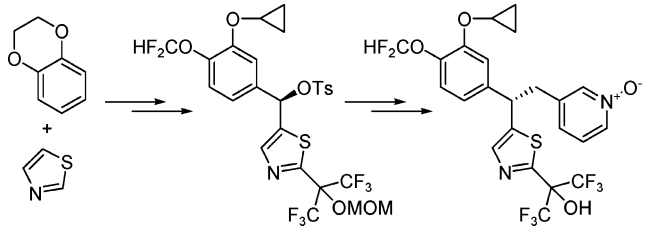

A practical, chromatography-free catalytic asymmetric synthesis of a potent and selective PDE4 inhibitor (L-869,298, **1**) is described. Catalytic asymmetric hydrogenation of thiazole ketone **5a** afforded the corresponding alcohol **3b** in excellent enantioselectivity (up to 99.4% ee). Activation of alcohol **3b** via formation of the corresponding *p*-toluenesulfonate followed by an unprecedented displacement with the lithium enolate of ethyl 3-pyridylacetate *N*-oxide **4a** generated the required chiral trisubstituted methane. The displacement reaction proceeded with inversion of configuration and without loss of optical purity. Conversion of esters **2b** to **1** was accomplished via a one-pot deprotection, saponification, and decarboxylation sequence in excellent overall yield.

Introduction

Phosphodiesterase-4 (PDE4) is a member of a broad family of cyclic nucleotide phosphodiesterases, enzymes responsible for the hydrolysis of cyclic adenosine 3′,5′-monophosphate (cAMP) and cyclic guanosine 3′,5′-monophosphate (cGMP).[1] PDE4 enzymes are specific to the hydrolysis of cAMP and are abundant in inflammatory, immune, and airway smooth muscle cells.[2] It has been demonstrated that inhibition of PDE4 leads to a reduction in inflammatory cell activity and results in a general antiinflammatory and bronchodilatory response.[3] Therefore, selective PDE4 inhibitors have received considerable attention as potential therapeutic agents for the treatment of diseases such as asthma and chronic obstructive pulmonary disease (COPD), and a number have entered clinical trials.[4]

As part of an ongoing drug discovery program at our laboratories compound **1** has been identified as a potent and selective inhibitor of PDE4.[5] Herein we wish to report a chromatography-free, catalytic asymmetric synthesis that is suitable for the preparation of kilogram quantities of **1**.

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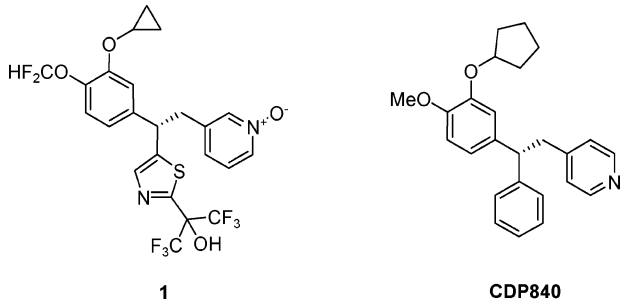
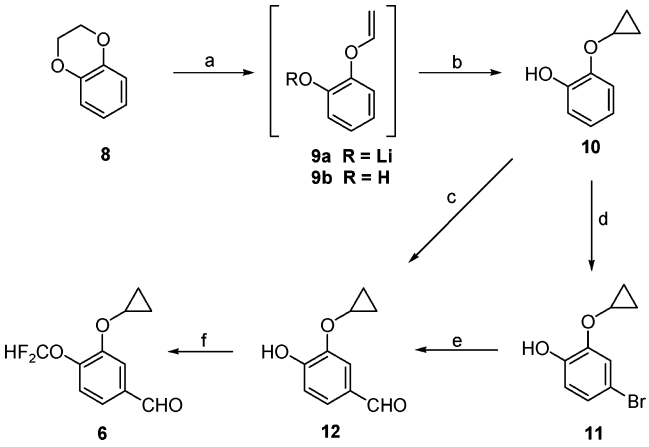


FIGURE 1. PDE4 inhibitors.

Compound **1** has structural similarities to CDP840,[6] the asymmetric synthesis of which has received considerable attention in the literature (Figure 1). The reported syntheses of CDP840 include methods based on asymmetric epoxidation,[7] Michael addition to an unsaturated chiral sultam[8] or chiral vinyl sulfoxide,[9] and asymmetric C−H insertion of rhodium carbenoids derived from aryl diazoacetates.[10] However, upon comparing CDP840 to **1** it is clear that the introduction of the cyclopropyl and difluoromethyl ether substituents on the aryl ring, the replacement of the unsubstituted phenyl with a substituted thiazole, and the different positional substitution on the pyridine ring dramatically increases the complexity of the synthesis of **1**. The retrosynthetic analysis we proposed for the construction of **1** is outlined in Figure 2. Establishment of the benzylic stereocenter in an asymmetric manner presents a difficult synthetic challenge. Our retrosynthetic analysis for **1** was based on the activation of enantiomerically enriched alcohol **3** and displacement with an enolate derived from pyridine acetate **4**. Such an approach is unprecedented in the literature. The viability of this approach is dependent on the introduction of chirality via a highly enantioselective reduction of ketone **5**, the success of which is not obvious from the literature. Deprotection followed by decarboxylation would afford **1** in a straightforward manner. Also key to this strategy is the requirement for an efficient synthesis of the functionalized aldehyde **6** and thiazole **7** fragments.

SCHEME 1[a]



[a] Reagents and conditions: (a) *s*-BuLi, THF, <−20 °C; (b) TFA, Et_2Zn, CH_2I_2, 80 °C, 72% (two steps); (c) $HCCl_2OCH_3$, $AlCl_3$, CH_2Cl_2, −78 °C, 40%; (d) NBS, MeOH, −70 °C, 80%; (e) MeLi, *s*-BuLi, DMF, THF, −40 °C, 91%; (f) $ClCF_2CO_2Na$, K_2CO_3, DMF, H_2O, 100 °C, 92%.

Results and Discussion

Synthesis of Aldehyde 6. There are few reported syntheses of hydroxy vinyl ethers[11] or arylcyclopropyl ethers.[12] Installation of the preformed cyclopropyl group is an attractive strategy; however, commercially available cyclopropyl bromide is a poor alkylating agent and no reaction was observed with catechol derivatives. Other possible methods for introducing the intact cyclopropyl group require multiple steps for reagent preparation.[13] Therefore, we decided to adopt a two-step strategy toward the synthesis of **6** requiring initial preparation of vinyl ether **9** followed by cyclopropanation as outlined in Scheme 1.

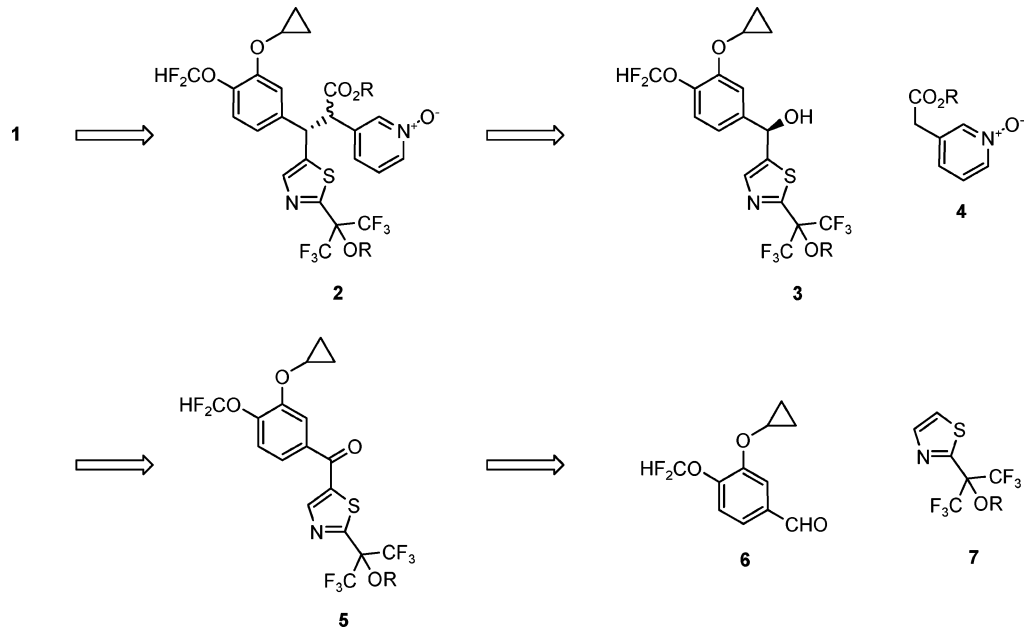
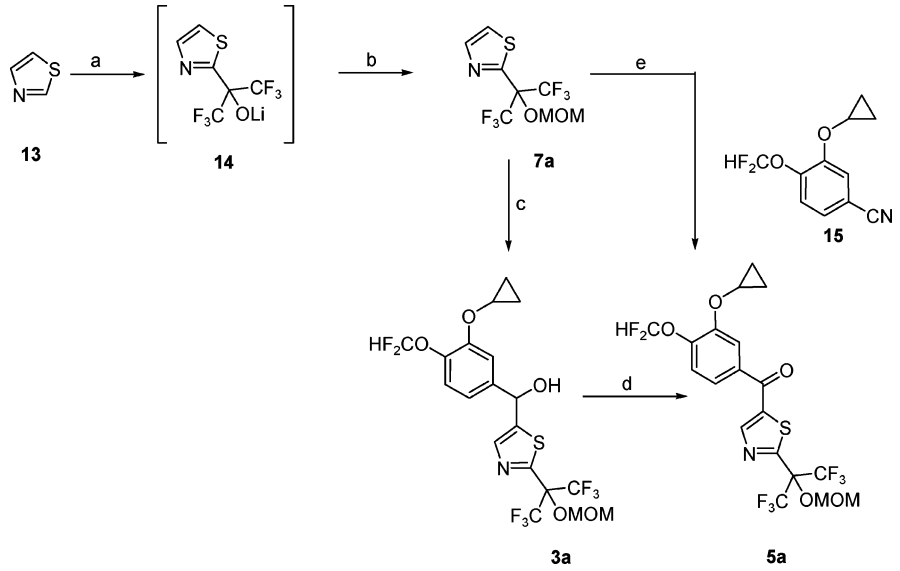


FIGURE 2. Retrosynthetic analysis.

SCHEME 2[a]



[a] Reagents and conditions: (a) LiHMDS, CF_3COCF_3, MTBE, −40 °C; (b) MOMCl, *i*-Pr_2NEt, THF, 40 °C, 89% (two steps); (c) *n*-BuLi, MTBE, −50 °C, **6**, 91%; (d) MnO_2, MTBE, 60 °C, 96%; (e) *n*-BuLi, MTBE, −50 °C, **15**, 87%.

We began the synthesis of aldehyde **6** with a base-induced ring opening of commercially available 1,4-benzodioxane **8** to give 2-vinyloxyphenoxide **9a**.[14] When this transformation was carried out using *n*-BuLi in THF at −40 to −30 °C incomplete conversion was observed. Additives such as TMEDA or *t*-BuOK did not improve the conversion. However, switching to *sec*-BuLi improved the conversion to 98% and **9b** was obtained in 90−93% assay yield. Cyclopropanation of **9b** was achieved using Furukawa's modification[15] of the Simmons−Smith reaction[16] to give **10** in 80% yield. While the isolation of **9b** was possible, the workup proved tedious and irreproducible results were obtained in the cyclopropanation reaction upon scale-up. To overcome these issues we were interested in developing a one-pot ring-opening cyclopropanation procedure. Shi has reported a dramatic rate acceleration in the cyclopropanation reaction for a range of substrates upon treatment of a Et_2Zn/CH_2I_2 mixture with an acidic additive such as trifluoroacetic acid.[17] Treatment of **9a** under these conditions in solvents such as MTBE, Bu_2O, DME, or toluene gave poor conversion; however, when THF was used as solvent the desired cyclopropanation was observed. Thus, a solution of **8** in THF was treated with *s*-BuLi at <−20 °C and the resulting vinyl phenoxide treated directly with trifluoroacetic acid, Et_2Zn, and CH_2I_2. The mixture was heated at 80 °C for 2 h to give cyclopropyl ether **10** in 72% yield. Following an extensive screen of reaction conditions the direct formylation of phenol **10** to aldehyde **12** was achieved in ∼40% yield but only under conditions using 1,1-dichloromethyl methyl ether with $AlCl_3$.[18] To avoid using 1,1-dichloromethyl methyl ether on large scale we investigated a two-step procedure to aldehyde **12**. Treatment of **10** in MeOH with *N*-bromosuccinimide at −70 °C gave the desired bromide **11** in 80% isolated yield. Low levels of ortho- and dibromination byproducts were easily removed via crystallization of **11** directly from the reaction mixture by addition of water. Addition of MeLi followed by *s*-BuLi to bromide **11** in THF at −40 °C generated the corresponding aryllithium, and quenching with DMF gave the desired aldehyde **12** in 91% yield. Installation of the difluoromethoxy group was achieved in 92% yield by heating **12** with sodium chlorodifluoroacetate and K_2CO_3 in aqueous DMF at 100 °C.

Synthesis of Ketone 5a. Functionalization of the thiazole ring relied on regioselective deprotonation at C-2,[19] and the synthetic procedure is shown in Scheme 2. A screen of bases indicated that treatment of thiazole **13** with LiHMDS gave clean formation of the C-2 anion. Thus, addition of LiHMDS to a mixture of thiazole and hexafluoroacetone in MTBE at −40 °C yielded lithium alkoxide **14**. The mixture was concentrated to remove MTBE and HMDS. The removal of HMDS is required to avoid competitive formation of the TMS protected thi-

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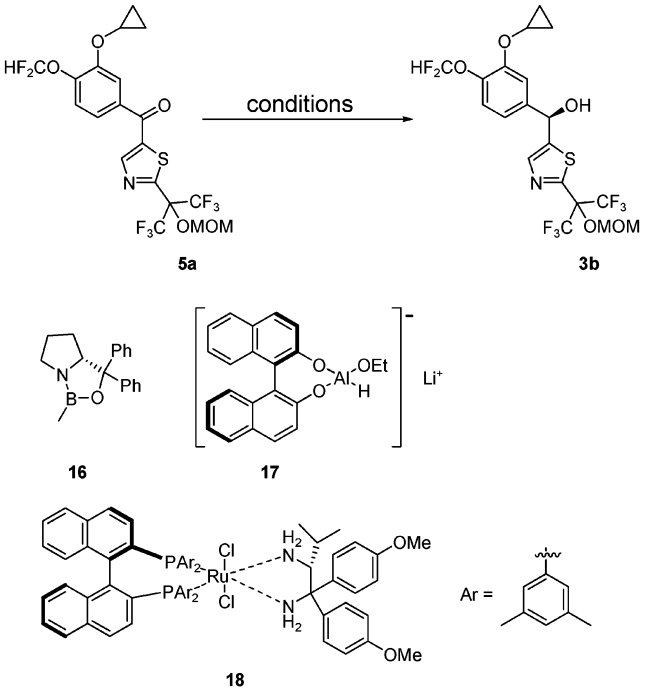
azole. The residue was dissolved in THF and after addition of Hünig's base and MOM-Cl the protected thiazole **7a** was obtained in 89% yield after workup. Deprotonation of **7a** in MTBE with *n*-BuLi at −50 °C followed by addition of aldehyde **6** yielded the secondary carbinol **3a** in 91% yield. Oxidation of the benzylic alcohol was readily achieved by treatment of **3a** with activated MnO_2 in MTBE at 60 °C and provided ketone **5a** in 96% yield. A direct synthesis of ketone **5a** via addition of C-5 thiazole anion to nitrile **15** was also developed yielding **5a** in 87% yield. This methodology has been expanded to prepare a number of thiazole ketones.[20]

Asymmetric Reduction of Ketone 5a. The asymmetric reduction of alkyl aryl ketones has received considerable attention and many excellent general methods are available.[21] However, the enantioselective reduction of diaryl ketones poses a considerable synthetic challenge and a general methodology remains elusive. High enantioselectivities have been obtained with ortho-substituted benzophenones using a variety of catalysts; however, with meta or para substitutions the enantioselectivity is eroded considerably.[22] Benzophenones with a large electronic bias between phenyl rings have also been reduced with high enantioselectivity.[23] Reports of asymmetric reduction of phenyl heteroaryl ketones are scarce[24] so we began a screen of methodologies to determine if **5a** was a good substrate for reduction (Table 1).

Our initial efforts were focused on the chiral oxazaborolidine (OAB) catalyzed reduction of ketone **5a**.[25] Preliminary experiments showed some promise with enantiomeric excesses in the 50−60% range as measured by chiral HPLC. After an extensive screen of conditions the best results (80% ee, >95% yield) were obtained using 10 mol % of Me-OAB **16** with toluene as solvent and BH_3·Me_2S as reducing agent at 10 °C (Table 1). Unfortunately, all attempts to upgrade the optical purity of the alcohol were unsuccessful. A thorough investigation of transfer hydrogenation conditions[26] did not improve on the OAB results.

Next we turned our attention to the reduction using BINAL-H **17**,[27] with initial experiments giving enantiomeric excesses in the 75−80% range. However, in the presence of TMEDA[28] the ee improved to ∼88%. The optimum alcohol additive was determined to be EtOH. While use of MeOH or *n*-PrOH did give similar results

TABLE 1. Asymmetric Reduction of Ketone 5a



entry	catalyst (mol %)	conditions	yield (%)	ee (%)
1	**16** (10)	BH_3·Me_2S, 10 °C	95	80
2	**17** (300)	THF, −70 °C	99	77
3	**17** (300)	TMEDA, THF, −60 °C	99	93−96
4	**17** (250)	TMEDA, THF, −60 °C	76	82
5	**18** (0.2)	*t*-BuOK, H_2 (40 psi), *i*-PrOH/THF	95	94.5
6	**18** (0.2)	TMG,[a] H_2 (40 psi), *i*-PrOH/THF	54	99.5
7	**18** (0.1)	K_2CO_3, H_2 (40 psi), *i*-PrOH/THF	95	99

[a] Tetramethylguanidine.

to EtOH we observed that the BINAL-H prepared using these alcohols generally performed less reproducibly in the reduction step. Lower enantioselectivities were obtained when benzyl alcohol, 2-methoxyethanol, or 2-propanol was used. Interestingly, use of 2,2,2-trifluoroethanol resulted in the formation of the undesired (*S*) enantiomer in ∼20% ee. Following further optimization with regard to alcohol additive, solvent, temperature, addition rate and stoichiometry the reduction consistently delivered 92−96% ee in >95% yield. Reduction of ketone **5a** was effected by addition to **17** at −60 °C and was generally complete within 30 min.

The reduction with BINAL-H was completed on a multikilogram scale. However, it has a major disadvantage in that it is not efficient in the use of BINAL-H reagent. The reaction required 3 eq. of BINAL-H to ensure high conversion and ee. For example, when 2.5 equiv was used the reaction only reached 76% conversion (Table 1, entries 3 and 4). We were therefore interested in developing a catalytic asymmetric reduction of **5a**. The catalytic, asymmetric hydrogenation of ketones is one of the most efficient and cost-effective methods for the production of chiral secondary alcohols.[29] Since their introduction by Noyori and co-workers, chiral $RuCl_2$(diphosphine)(diamine) complexes[30] have been demonstrated as highly efficient catalysts for the asymmetric hydrogenation of a wide array of ketones.[31] Remarkably,

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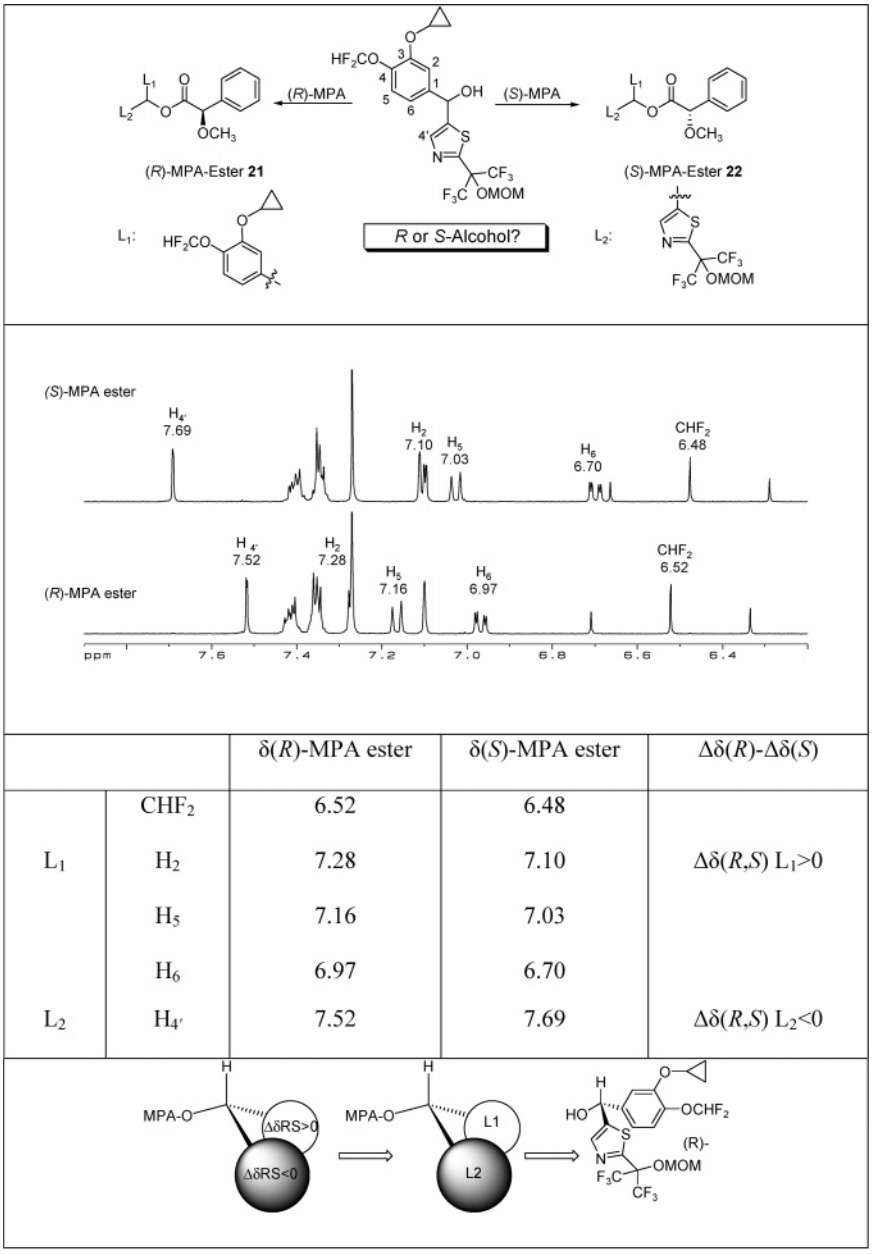

		δ(*R*)-MPA ester	δ(*S*)-MPA ester	Δδ(*R*)-Δδ(*S*)
	CHF_2	6.52	6.48	
L_1	H_2	7.28	7.10	Δδ(*R*,*S*) L_1>0
	H_5	7.16	7.03	
	H_6	6.97	6.70	
L_2	$H_{4'}$	7.52	7.69	Δδ(*R*,*S*) L_2<0

FIGURE 3. ^{1}H NMR analysis of MPA esters **21** and **22**.

asymmetric hydrogenation of ketone **5a** using chiral $RuCl_2$(*R*-xylBINAP)(*R*,*R*-DAIPEN) complex **18** gave alcohol **3b** in exceedingly high enantioselectivity (99.4% ee) on the first attempt under standard conditions (40 psi H_2, K_2CO_3/Ru = 25/1, S/C = 50/1 in *i*-PrOH). Using other ligands such as BINAP, however, led to lower enatioselectivity (66% ee). An investigation of different bases at S/C 500:1 indicated that K_2CO_3 performed best (100% conv, 99.4% ee). *t*-BuOK afforded complete conversion and 94.5% ee and tetramethylguanidine gave high ee (>99.5%) but low conversion (54%) (Table 1, entries 5, 6). Following optimization, we found that the reaction was best carried out under the following conditions: 40 psi H_2, K_2CO_3/Ru = 25/1, S/C = 1000/1, in 4:1 *i*-PrOH−THF at 20−25 °C reproducibly afforded alcohol **3b** in >99% ee (Table 1, entry 7). At S/C greater than 1000/1 both conversion and enantioselectivity were considerably lower. However, we felt that at S/C 1000/1, the process is viable for the preparation of an advanced pharmaceutical intermediate such as **3b**. Extension of this hydrogenation protocol to other aromatic-heteroaromatic ketones has shown that high ee's are obtained from a range of aryl thiazole and other aryl heteroaryl ketones.[32]

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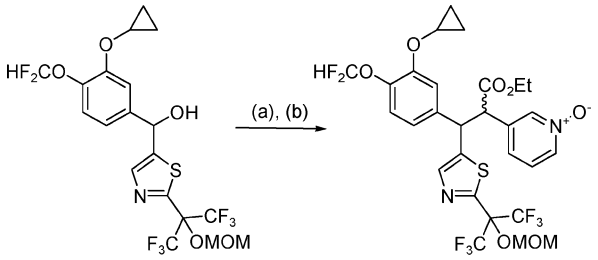
The similarity of the aryl and heteroaryl substituents of ketone **5a** did not allow us to assign the absolute configuration of alcohol **3b** by analogy to reported ketone reductions. We were therefore interested in determining the absolute configuration of alcohol **3b**. All attempts to grow crystals of **3b** or a considerable number of derivatives thereof were unsuccessful. Therefore, we sought to assign the absolute configuration using ^{1}H NMR methodology. It has been reported that the absolute configuration of secondary alcohols can be deduced by ^{1}H NMR studies of alcohol enantiomers as either (*R*) or (*S*) methoxyphenylacetic acid esters (MPA).[33] However, the application of this methodology to bis-aromatic alcohols such as **3b** has not been reported. Thus **3b** was converted to its corresponding (*R*)- and (*S*)-MPA esters **21** and **22** via EDC mediated coupling. The diastereoisomers were isolated by preparative TLC and their ^{1}H NMR spectra recorded. We were delighted to observe measurable chemical shift differences between diastereoisomers, which allowed us to assign the absolute configuration of **3b** as (*R*) (Figure 3). This observed stereochemical outcome of (*R*)-alcohol **3b** from (*R*)-catalyst **16** and (*R*,*R*)-catalyst **18** indicates that the thiazole ring behaves as the small group by analogy to the simple alkyl aryl ketone model. In the case of the reduction using (*R*)-BINAL-H **17** and again assuming that the thiazole behaves as the small group, the opposite sense of induction to the simple ketone model was observed.[27a]

Displacement of Alcohol 3b. The chiral diaryl methane structural element of **1** is a recurring motif found in a number of pharmacologically active compounds, most notably sertraline[34] and tolterodine,[35] and a number of synthetic approaches to this framework have been reported.[36] However, we reasoned that the most straightforward and direct assembly would be via the displacement of a suitably activated chiral secondary alcohol with a carbon nucleophile. Despite the apparent simplicity of this approach a number of important issues such as the choice of activating group, the stability of the activated intermediate, and the reaction stereoselectivity (given the possibility of competing S_N1 and S_N2 pathways) needed to be addressed. While in a general sense the activation of an alcohol and subsequent displacement with a nucleophile is a fundamental chemical reaction,[37] there are very few examples of the stereoselective displacement of chiral secondary alcohols with carbon nucleophiles. The S_N2 displacement of activated chiral nonbenzylic secondary alcohols with carbon nucleophiles such as organo cuprates[38] and malonate[39] has been reported to proceed with high stereoselectivity. The displacement of a chiral benzylic mesylate with a phenyl cuprate has been demonstrated to proceed in good yield but with moderate loss of optical purity.[40] Recently the displacement of chiral secondary benzylic alcohols with malonate under Mitsunobu[41] conditions has been reported in good yield with no erosion of enantiomeric purity but when chiral diaryl methanols were used significant erosion of enantiomeric purity was observed.[42] To our knowledge, the activation of substrates such as **3** and displacement with carbon nucleophiles has not been reported in the literature. Despite the lack of precedent we reasoned that given the wide range of potential activating groups the reactivity of the electrophile could be modulated to enable a stereospecific displacement to take place with a suitable pyridine nucleophile and generate the required trisubstituted methane.

Thus, we began with a careful investigation of possible activating groups using racemic alcohol **3a**. Treatment of **3a** with $SOCl_2$ or $SOBr_2$ gave the corresponding chloride and bromide, respectively.[43] Displacement of the bromide with the lithium anion of 3-picoline gave poor results whereas the lithium enolate of ethyl-3-pyridyl acetate *N*-oxide **4a** gave adduct **2a** in good yield (Table 2).

TABLE 2. Activation and Displacement of Alcohol 3a[a]



3a **2a**

entry	activation	yield (%)
1	$SOCl_2$	50
2	$SOBr_2$	80
3	$ClP(O)(EtO)_2$	0
4	$ClP(O)(i\text{-}PrO)_2$	0
5	(1) *n*-BuLi, (2) MsCl	50−70
6	(1) *n*-BuLi, (2) TsCl	0
7	(1) *n*-BuLi, (2) Ms_2O	0
8	(1) *n*-BuLi, (2) Ts_2O	92

[a] Reagents and conditions: (a) activation; (b) LiHMDS, THF/DMPU, **4a**, −40 °C.

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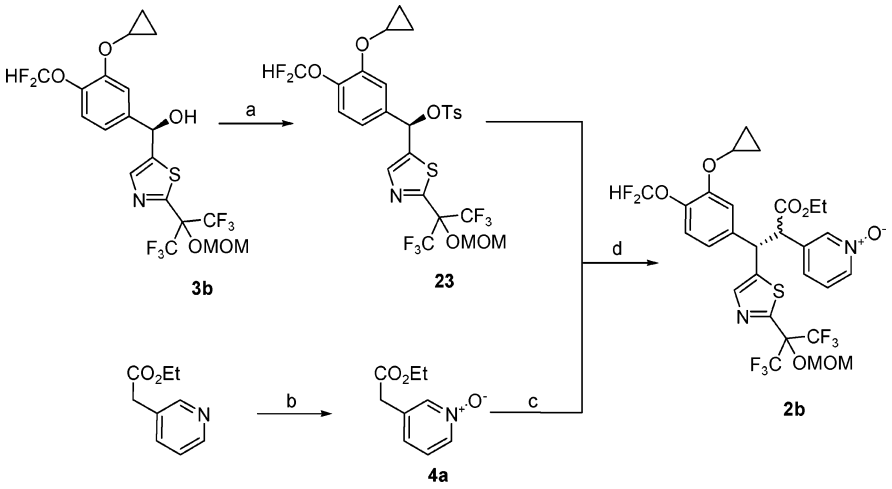
SCHEME 3[a]

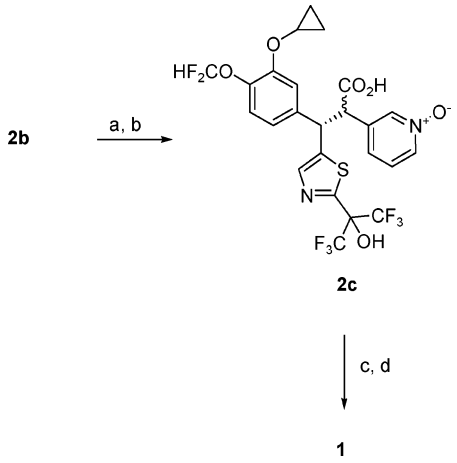


[a] Reagents and conditions: (a) *n*-BuLi, Ts_2O, THF, −65 °C; (b) $MeReO_3$, H_2O_2, CH_2Cl_2, 20 °C, 87%; (c) LiHMDS, DMPU, THF, −40 °C; (d) <−50 °C, 24 h, 92% from **3b**.

Pyridine *N*-oxide **4a** was conveniently prepared in high yield via H_2O_2 oxidation of the corresponding pyridyl acetate in the presence of catalytic $MeReO_3$.[44] Attempts to extend the halide displacement reaction to enantiomerically enriched alcohol **3b** were unsuccessful with the corresponding chloride and bromide obtained in low ee under various reaction conditions. Dialkyl phosphates were prepared however they did not undergo displacement with the lithium enolate of **4a** under conditions where the enolate was stable. Preparation of the mesylate using methane sulfonyl chloride led exclusively to the chloride, whereas methane sulfonyl anhydride or *p*-toluenesulfonyl chloride led to decomposition of the starting alcohol. Therefore, we were delighted to find that treatment of the lithium alkoxide of **3a** with *p*-toluenesulfonyl anhydride at <−60 °C followed by addition of the lithium enolate of **4a** led to formation of adduct **2a** in high yield (Table 2, entry 8). It was essential to use the tosylate **23** in situ as decomposition was observed in solution at temperatures above −20 °C and all attempts to isolate **23** were unsuccessful. Having demonstrated that the chemistry was viable with racemic alcohol we switched our attention to optically enriched alcohol to assess the stereochemical outcome (Scheme 3).

At temperatures above −40 °C considerable erosion of optical purity at the benzylic center was observed during the displacement reaction by chiral HPLC. However, when the reaction was conducted at <−50 °C no loss of stereochemical integrity was observed. Thus treatment of optically enriched alcohol **3b** in THF with *n*-BuLi at <−60 °C followed by the addition of *p*-toluenesulfonyl anhydride generated tosylate **23**. In a separate flask, ethyl-3-pyridyl acetate *N*-oxide **4a** in THF/DMPU at −40 °C was treated with LiHMDS to form the corresponding lithium enolate. Addition of the enolate to the tosylate mixture followed by a 24 h age at <−50 °C completed the reaction. When the reaction was run with alcohol **3b** of 96% ee the expected esters (1.6:1 dr) **2b** were obtained with 96% ee (at the benzylic center) in 92% yield (Scheme 3). Single-crystal X-ray analysis of **1** determined the absolute configuration as (*S*) and in conjunction with the ^{1}H NMR determination of **3b** as (*R*) confirmed inversion at the benzylic stereocenter during the displacement reaction. This displacement methodology has been extended to a number of benzhydryl derivatives, and a preliminary investigation into the scope of the reaction has recently been reported.[45]

SCHEME 4[a]



[a] Reagents and conditions: (a) HCl, MeOH, reflux; (b) $LiOH·H_2O$, H_2O, 25 °C, 94% over two steps; (c) DCHA, *i*-PrOH, heptane, 81%; (d) *n*-BuOAc, 128 °C, 85%.

Conversion of Esters 2b to 1. Removal of the MOM ether protecting group was effected by heating a methanol solution of **2b** with HCl at reflux for 3 h (Scheme 4). The solution was cooled and diluted with water and $LiOH·H_2O$ was added. Saponification was complete within 3 h to give acids **2c** in 94% yield.

Preparation of various salts of **2c** revealed that the optical purity (at the benzylic center) could be upgraded by formation of a *N*,*N*-dicyclohexylamine (DCHA) salt. Thus, **2c** was dissolved in *i*-PrOH and DCHA added. The solution was diluted with heptane and seeded with a

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racemic diastereomeric (1:1) mixture. The mixture was aged for 16 h during which time lower optical purity DCHA salt crystallized (typically 40−70% ee), upgrading the material in the mother liquors. Filtration of the mixture gave **2c** of >98% ee at the benzylic center. Thermally induced decarboxylation to **1** was effected by heating a solution of **2c** as its DCHA salt in *n*-butyl acetate at 128 °C for 3 h. Crystallization by addition of heptane gave **1** in 65% yield over four steps.

In summary, we have developed a practical asymmetric synthesis of **1** in high yield and purity suitable for large scale preparation. The key steps include a highly enantioselective catalytic reduction of an aryl heteroaryl ketone **5a** to give alcohol **3b** in >99% ee. Activation of **3b** as its corresponding tosylate **23** and subsequent displacement with the lithium enolate of **4a** was completed with inversion of configuration and no loss of optical purity at the benzylic center. An efficient one-pot deprotection/decarboxylation sequence afforded **1** in high yield and purity.

Experimental Section

2-Cyclopropyloxyphenol (10). A solution of 1,4-benzodioxane (2.93 kg, 21.5 mol) in THF (6 L) was cooled to −25 to −30 °C. *s*-BuLi (1.3 M in cyclohexane, 18.2 L, 23.6 mol) was added maintaining the temperature at <−20 °C. Diethylzinc (1.1 M in toluene, 40.0 L, 44.0 mol) was added over 1.5 h maintaining the temperature less than −20 °C. Trifluoroacetic acid (3.3 L, 42.8 mol) was added over 2 h maintaining the temperature less than −5 °C. The reaction mixture was warmed to 5 °C over 1 h, and diiodomethane (3.70 L, 45.8 mol) was added over 20 min. The resulting white milky mixture was heated to 70−80 °C at a rate of ∼0.5 °C/min. The reaction mixture was aged at 80 °C for 2.5 h, cooled to 0 °C, and quenched by addition of aqueous HCl (2 N, 16 L) maintaining the temperature at <10 °C and a final pH of 2−3. The aqueous layer was separated, and the organic layer was washed with water (15 L). The organic layer was extracted with cold (5 °C) degassed aqueous NaOH (2 N, 14.4 L). The aqueous layer was added to a mixture of toluene (30 L) and degassed HCl (2 N, 15 L) at 5 °C. The layers were separated, and the aqueous layer was extracted with toluene (20 L). The combined toluene layers were washed with water (12 L) and filtered through a pad of silica gel (2.0 kg). The silica gel pad was washed with toluene (4 L), and the wash was combined with the filtrate. The batch was concentrated under vacuum to ∼8 L. The remaining toluene was azeotropically removed by switching solvent to methanol (∼53 L) to yield **10** (2.3 kg, 72% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (dd, 1H, J = 2.0, 7.2 Hz), 6.90 (m, 3H), 5.50 (s, 1H), 3.82 (m, 1H), 0.83 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 145.6, 121.8, 120.3, 114.9, 113.0, 51.6, 6.2. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.95; H, 6.71. HPLC: YMC ODS-AQ, 4.6 × 250 mm column. Eluents: A, 10 mM K_2HPO_4 pH = 4.5; B acetonitrile; 1 mL/min. Gradient: A/B from 65:35 to 30:70 in 15 min, then to 5:95 in 5 min, λ = 220 nm, temperature 35 °C. t_R: **10** = 9.6 min.

4-Bromo-2-(cyclopropyloxy)phenol (11). A solution of 2-cyclopropyloxyphenol (2.2 kg, 14.6 mmol) in MeOH (14 L) was cooled to −70 °C. *N*-Bromosuccinimide (2.63 kg, 14.8 mol) was added portionwise over 1 h maintaining the reaction temperature at <−68 °C. The reaction mixture was warmed to 10 °C, and water (9.0 L) was added over 30 min during which time precipitation began. Additional water (13.5 L) was added over 1 h, and the slurry was cooled to ∼0 °C and aged for 1 h. The mixture was filtered, and the cake was washed with MeOH/water (20% v/v, 5 L) and dried under vacuum at 20−25 °C to give bromophenol **11** (3.13 kg, 80% yield) as a crystalline solid: mp 78−79.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, 1H, J = 2.4 Hz), 7.00 (dd, 1H, J = 8.6, 2.4 Hz), 6.79 (d, 1H, J = 8.6 Hz), 5.42 (s, 1H), 3.79 (m, 1H), 0.83 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 144.7, 124.4, 115.9, 115.8, 111.5, 51.9, 6.2. Anal. Calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.96. Found: C, 47.26; H, 3.85. HPLC: YMC ODS-AQ, 4.6 × 250 mm column. Eluents: A, 10 mM K_2HPO_4 pH = 4.5; B acetonitrile; 1 mL/min. Gradient: A/B from 65:35 to 30:70 in 15 min, then to 5:95 in 5 min, λ = 220 nm, temperature 35 °C. t_R: **11** = 13.8 min.

3-(Cyclopropyloxy)-4-hydroxybenzaldehyde (12). 4-Bromo-2-(cyclopropyloxy)phenol (2.3 kg, 10.1 mol) was dissolved in THF (23.1 L), and the mixture was cooled to −40 °C. MeLi (1.4 M in Et_2O, 8.2 L, 11.5 mol) was added maintaining the reaction temperature at <−30 °C. The mixture was cooled to −40 °C and charged with *s*-BuLi (1.3 M in cyclohexane, 15.5 L, 20.1 mol) maintaining the reaction temperature at <−30 °C. The reaction mixture was cooled to −60 °C, and anhydrous DMF (2.34 L, 30.2 mol) was added maintaining the temperature <−30 °C. The batch was warmed to 0 °C, diluted with toluene (13 L), and quenched with aqueous HCl (2 N, 21 L). The layers were separated, and the organic layer was washed with water (13 L) and brine (13 L). The organic layer was concentrated under vacuum at ∼45−50 °C to ∼2 mL of toluene/g of product to give a slurry. Heptane (15 L) was added over 1 h, and the slurry was cooled to 0 °C. The mixture was filtered, and the cake was washed with toluene/heptane (15% v/v, 3 × 1.3 L) and dried under vacuum at 20−25 °C to give hydroxyaldehyde **12** (1.7 kg, 91% yield): mp 87.5−88.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.72 (d, 1H, J = 1.8 Hz), 7.44 (dd, 1H, J = 8.1, 1.8 Hz), 7.00 (d, 1H, J = 8.1 Hz), 6.13 (s, 1H), 3.89 (m, 1H), 0.85 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 151.5, 146.6, 129.9, 127.5, 114.6, 111.2, 52.1, 6.3. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.08; H, 5.51. HPLC: YMC ODS-AQ, 4.6 × 250 mm column. Eluents: A, 10 mM K_2HPO_4 pH = 4.5; B acetonitrile; 1 mL/min. Gradient: A/B from 65:35 to 30:70 in 15 min, then to 5:95 in 5 min, λ = 220 nm, temperature 35 °C. t_R: **12** = 14.5 min.

3-(Cyclopropyloxy)-4-(difluoromethoxy)benzaldehyde (6). A mixture of DMF (17.9 L), water (2.1 L), 3-cyclopropyloxy-4-hydroxybenzaldehyde (1.8 kg, 10.1 mol), K_2CO_3 (1.68 kg, 12.1 mol), and sodium chlorodifluoroacetate (3.08 kg, 20.2 mol) was degassed for 15 min using a subsurface nitrogen sparge and heated to 100 °C. After 2 h, the reaction mixture was cooled to 20−25 °C. Aqueous HCl (12 N, 2.9 L) and water (4.2L) were added, and the mixture was aged for 16 h. The pH was adjusted to 10.5 by addition of aqueous NaOH (5 N, 6.65L) maintaining the temperature at 5−10 °C. The batch was diluted with MTBE (28.8 L) and water (9.9 L). The layers were separated, and the organic layer was washed successively with water (21.5 L), buffer (20 mM K_3PO_4, pH = 7, 21.5 L), and water (16 L). The organic layer was concentrated under vacuum and the solvent replaced with toluene to give difluoromethoxyaldehyde **6** (2.1 kg, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.7 (s, 1H), 7.83 (d, 1H, J = 1.8 Hz), 7.47 (dd, 1H, J = 8.1, 1.8 Hz), 7.29 (d, 1H, J = 8.1 Hz), 6.62 (t, 1H, J = 74.2 Hz), 3.88 (m, 1H), 0.87 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 151.0, 144.8, 134.6, 124.7, 121.7, 115.6 (t, J = 262 Hz), 113.5, 52.1, 6.4. Anal. Calcd for $C_{11}H_{10}F_2O_3$: C, 57.90; H, 4.42. Found: C, 58.05; H, 4.51. HPLC: Phenomenex Luna C18 5 μm, 4.6 × 250 mm column. Eluents: A, 0.2% aqueous H_3PO_4; B acetonitrile; 1 mL/min. Gradient: A/B hold 40:60 for 5 min to 5:95 in 20 min, hold 5 min, λ = 220 nm, temperature 30 °C. t_R: **6** = 7.5 min.

2-[2,2,2-Trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl)-1,3-thiazole (7a). A solution of thiazole **13** (2.26 kg, 26.5 mol) in anhydrous MTBE (44.8 L) was cooled to −40 °C, and hexafluoroacetone (5.1 kg, 29.9 mol) was condensed into the mixture. LiHMDS (1.0 M in THF, 27.1 L, 27.1 mol) was added over ∼0.5 h while maintaining the temperature <−40 °C. The mixture was warmed to 20−25 °C and concentrated under vacuum to remove THF and $(Me_3Si)_2NH$.

The residue was dissolved in MTBE (30 L), and 2-chloromethyl methyl ether (2.6 L, 34.2 mol) and *i*-Pr_2NEt (0.92 L, 5.3 mol) were added at 20−25 °C. The reaction mixture was heated at 40 °C for 2 h. After the mixture was cooled to 0 °C MTBE (66 L) and water (6.6 L) were added. The layers were separated, and the organic layer was washed with aqueous NaOH (1.0 N, 16.5 L) and water (3 × 16.5 L). The organic layer was concentrated and flushed with MTBE under vacuum to give MOM-thiazole **7a** (6.92 kg, 89% yield) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 3.2 Hz), 7.60 (d, 1H, J = 3.2 Hz), 5.07 (s, 2H), 3.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 143.6, 122.7, 121.6 (q, J = 290.3 Hz), 94.9, 80.7 (m), 57.0. Anal. Calcd for $C_8H_7F_6NO_2S$: C 32.55; H 2.39; N 4.74. Found C 32.19; H 2.23; N 4.52. HPLC: YMC ODS-AQ, 4.6 × 250 mm column. Eluents: A, 0.1% aqueous H_3PO_4; B acetonitrile; 1 mL/min. Gradient: A/B from 65:35 to 30:70 in 15 min, then to 5:95 in 5 min, λ = 220 nm, temperature 35 °C. t_R: **7a** = 17.1 min.

[3-(Cyclopropoxy)-4-(difluoromethoxy)phenyl]{2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]-1,3-thiazol-5-yl}methanol (3a). Thiazole **7a** (3.10 kg, 10.5 mol) was diluted with MTBE (28 L), and the mixture was cooled to −50 °C. *n*-BuLi (1.6 M in hexanes, 6.6 L, 10.5 mol) was added maintaining the temperature at <−45 °C. A 50 wt % toluene solution of aldehyde **6** (2.0 kg, 8.76 mol) was added to the thiazole anion while maintaining the temperature <−45 °C. The reaction mixture was transferred into water (10 L) and the mixture warmed to 20−25 °C. The layers were separated, and the organic layer was washed with aqueous NaCl solution (10 wt %, 2 × 10 L). The toluene layer was concentrated and dried by azeotropic removal of water to yield carbinol **3a** (4.1 kg, 91% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.39 (d, 1H, J = 2.0 Hz), 7.17 (d, 1H, J = 8.2 Hz), 7.00 (dd, 1H, J = 8.2, 2.0 Hz), 6.52 (t, 1H, J = 74.9 Hz), 6.12 (d, 1H, J = 3.6 Hz), 5.06 (s, 2H), 3.79 (m, 1H), 3.53 (s, 3H), 2.62 (br s, 1H), 0.80 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 150.8, 146.6, 140.4, 140.3, 139.7, 122.4, 121.3 (q, J = 291 Hz), 118.9, 115.9 (t, J = 261 Hz), 112.5, 94.8, 80.5 (app quintet, J = 30 Hz), 69.8, 57.0, 51.7, 6.2, 6.1; HRMS calcd for $C_{19}H_{17}F_8NO_5S$ (M + H^+) 524.0778, found 524.0778. HPLC: Phenomenex Luna C18 5 μm, 4.6 × 250 mm column. Eluents: A, 0.2% aqueous H_3PO_4; B acetonitrile; 1 mL/min. Gradient: A/B 40:60 hold 5 min to 5:95 in 20 min, hold 5 min, λ = 220 nm, temperature 30 °C. t_R: **3a** = 14.7 min.

[3-(Cyclopropoxy)-4-(difluoromethoxy)phenyl]{2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]-1,3-thiazol-5-yl}methanone (5a). A toluene solution of alcohol **3a** (8.4 kg, 16.0 mol) was concentrated to <20 L and diluted to 30 L with MTBE. MnO_2 (7.0 kg, 80.2 mol) was charged, and the batch was heated at 60 °C for 2 h. The mixture was cooled to 20−25 °C and filtered over solka floc, and the cake was washed with MTBE (7 × 4 L). The batch was concentrated and the MTBE replaced with heptane to a final volume of 32 L. The slurry was filtered, and the cake was washed with heptane (6 L) and dried under vacuum to yield ketone **5a** (8.4 kg, 96% yield): mp 69−70 °C; ^{1}H (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.86 (d, 1H, J = 1.99 Hz), 7.53 (dd, 1H, J = 2.0, 8.3 Hz), 7.28 (d, 1H, J = 8.1 Hz), 6.64 (t, 1H, J = 74.2 Hz), 5.16 (s, 2H), 3.89 (m, 1H), 3.57 (s, 3H), 0.88 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3, 164.7, 150.9, 147.8, 144.1, (t, J = 2.9 Hz), 141.8, 134.8, 123.0, 121.6, 121.3 (q, 2C, J = 291.2 Hz), 115.6 (t, J = 262.1 Hz), 115.2, 95.4, 80.8 (q, J = 30.3 Hz), 57.3, 52.1, 6.4 (2C). Anal. Calcd for $C_{19}H_{15}F_8NO_5S$: C, 43.77; H, 2.90; N, 2.69. Found: C, 43.39; H, 2.67; N, 2.62. HPLC: Phenomenex Luna C18 5 μm, 4.6 × 250 mm column. Eluents: A, 0.2% aqueous H_3PO_4; B acetonitrile; 1 mL/min. Gradient: A/B 40:60 hold 5 min to 5:95 in 20 min, hold 5 min, λ = 220 nm, temperature 30 °C. t_R: **5a** = 20.1 min.

Ethyl (1-Oxidopyridin-3-yl)acetate (4a). A mixture of ethyl 3-pyridyl acetate (2.9 kg, 17.5 mol), CH_2Cl_2 (7 L), and methyltrioxorhenium (21.9 g, 0.05 mol) was cooled to ∼16 °C. Aqueous hydrogen peroxide (30 wt %, 1.9 L, 19.3 mol) was added dropwise over 1.5 h maintaining the temperature at 16−21 °C. The mixture was aged for 4.5 h at 20−25 °C and cooled to 5 °C, and a solution of sodium sulfite (221.4 g, 1.75 mol) in water (885 mL) was added over 1 h maintaining the temperature <20 °C. The organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (3 × 2 L). The combined CH_2Cl_2 layers were concentrated under reduced pressure to yield a solid. The solid was flushed with toluene (3 × 2 L) and the volume adjusted to 15 L of toluene. The mixture was heated to 82 °C to dissolve the solids, and was cooled to 20−25 °C over 16 h during which time the product crystallized. The mixture was cooled to 5 °C, filtered, and washed with cold (5 °C) toluene (2 × 3 L) and dried to yield pyridine *N*-oxide **4a** (2.8 kg, 87% yield). Analytical data for a sample recrystallized from ethyl acetate/hexanes: mp 104.5−105.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.13 (d, 1H, J = 5.4 Hz), 7.25 (m, 2H, 4.18 (q, 2H, J = 7.1 Hz), 3.57 (s, 2H), 1.27 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 139.7, 137.8, 133.3, 126.9, 125.5, 61.5, 37.9, 14.0. Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.57; H, 6.03; N, 7.76. HPLC: YMC ODS-AQ, 4.6 × 250 mm column. Eluents: A, 10 mM K_2HPO_4 pH = 4.5; B, acetonitrile; 1 mL/min. Gradient: A/B 65:35 to 30:70 in 15 min, λ = 220 nm, temperature 35 °C. t_R: **4a** = 3.7 min.

***(R)*-[3-(Cyclopropoxy)-4-(difluoromethoxy)phenyl]{2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)-ethyl]-1,3-thiazol-5-yl}methanol (3b) via BINAL-H Reduction.** To a solution of $LiAlH_4$ (1.0 M in THF, 11.3 kg, 12.6 mol) was added a solution of EtOH (726 mL, 12.6 mol) in THF (2.2 L) over ∼0.5 h. A solution of (*R*)-(+)-1,1′-bi-2-naphthol (3.6 kg, 12.6 mol) in THF (10.1 L) was added to the clear reaction mixture over ∼1 h maintaining the temperature at <55 °C. The pale yellow slurry was stirred for 0.5 h while maintaining the temperature at 50−55 °C. TMEDA (1.90 L, 12.6 mol) was added, and the mixture was stirred for an additional 45 min at 50−55 °C and cooled to −60 °C. A solution of ketone **5a** (2.2 kg, 4.2 mol) in THF (4.4 L) was cooled to −40 °C and added to the cooled (−62 °C) BINAL-H slurry over ∼5 min. After stirring for 30 min at −40 °C, the reaction was quenched by addition of satd aqueous NH_4Cl (8.8 L) and Celite 545 (2.2 kg). The mixture was warmed to 20−25 °C, aged for 1 h, and filtered through a pad of Celite 545. The cake was washed with THF (3 × 4 L). The combined filtrate and washes were diluted with MTBE (30 L). Saturated aqueous NH_4Cl (20 L) and water (20 L) were added, and after mixing for 10 min the aqueous layer was separated. Heptane (40 L) was added, and the organic layer was successively washed with aqueous NaOH (2.5 N, 4 × 20 L), water (1 × 20 L), aqueous HCl (0.01 N, 20 L), satd aqueous $NaHCO_3$ (10 L), and H_2O (20 L). The organic layer was concentrated and water removed by azeotropic distillation with toluene to yield alcohol **3b** (2.2 kg, 99% yield, 96% ee). For NMR data see **3a** above: $[\alpha]^{20}_D$ −22.7 (MeOH, *c* = 7.0). Chiral HPLC: Chiralpak AS, 4.6 × 250 mm column. Eluents: A, hexanes; B *i*-PrOH; A/B 98.5:1.5; 1.5 mL/min, λ= 220 nm, temperature 30 °C. t_R: (*R*) **3b** = 48.5 min, t_R: (*S*) = 58.6 min (96% ee).

***(R)*-[3-(Cyclopropoxy)-4-(difluoromethoxy)phenyl]{2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)-ethyl]-1,3-thiazol-5-yl}methanol (3b) via Ru Catalyzed Reduction.** A mixture of ketone **5a** (10.4 g, 20 mmol), K_2CO_3 (0.69 g, 5 mmol), 2-propanol (37.5 mL), and THF (7.5 mL) was degassed via nitrogen/vacuum and followed by the addition of the catalyst (*R*,*R*)-xylBINAPRuCl$_2$(*R*)-DAIPEN (24.4 mg, 0.02 mmol). The mixture was hydrogenated under 40 psi for 3 days to complete the reaction. The mixture was concentrated to a residue that was partitioned between toluene (200 mL) and water (100 mL). The toluene layer was washed with water (2 × 100 mL) and concentrated under reduced pressure to yield alcohol **3b** (10.6 g, 100%, 99.2% ee).

(3-Cyclopropoxy-4-difluoromethoxyphenyl)-2-(1-oxypyridin-3-yl)-3-[2-(2,2,2-trifluoro-1-methoxymethoxy-1-

trifluoromethylethyl)thiazol-5-yl]propionic Acid Ethyl Ester (2b). A mixture of alcohol **3b** (2.2 kg, 4.2 mol), THF (11.0 L), and triphenylmethane (10.3 g, 0.042 mol) was cooled to −68 °C. *n*-BuLi (1.6 M in hexanes, 2.9 L, 4.6 mol) was added over 2 h while maintaining the temperature at <−60 °C until a color change was observed. The alkoxide solution was agitated at −65 °C for 10 min, followed by addition of a solution of *p*-toluenesulfonic anhydride (1.6 kg, 5.0 mol) in THF (10 L) over 2 h, maintaining the temperature at <−60 °C. The toluenesulfonate solution was agitated at −65 °C for 20 min following the addition.

Enolate Formation. A separate flask was charged with THF (13.6 L), DMPU (4.5 L),and ethyl 3-pyridylacetate *N*-oxide **4a** (2.3 kg, 12.5 mol). The suspension was cooled to −60 °C, and LiHMDS (1.0 M in THF, 12.1 L, 12.1 mol) was added over 2 h while maintaining the temperature at <−40 °C. The dark reaction mixture was stirred for 1 h at −40 °C.

The lithium enolate was added to the toluenesulfonate solution at a rate such that the temperature of the reaction mixture was maintained at <−55 °C. The reaction mixture was aged at −60 to −52 °C for 23 h to complete the reaction. The reaction mixture was quenched at −52 °C by addition of aqueous HCl (1 N, 17.0 L, 17.0 mol). The temperature was adjusted to ∼0 °C, toluene (40 L) was added, and the aqueous layer was separated. The organic layer was washed with water (5 × 30 L) and concentrated under vacuum and flushed with toluene (20 L) to yield esters **2b** (2.6 kg, 92% yield, 96% ee) as a toluene solution. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (1H, s), 8.04 (1H, m), 7.84 (1H, s), 7.18−7.11 (3H, m), 7.02 (1H, d, J = 2.1 Hz), 6.71 (1H, dd, J = 8.2, 2.1 Hz), 6.43 (1H, t, J = 74.7 Hz), 5.04 (2H, s), 4.92 (1H, 12.0 Hz), 4.16 (1H, d, J = 11.9 Hz), 4.14−3.94 (2H, m), 3.69 (1H, m), 3.52 (3H, s), 1.12 (1H, t, J = 7.1 Hz), 0.89−0.76 (3H, m), 0.65−0.62 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 157.7, 150.7, 143.2, 140.9, 139.2, 139.1, 138.5, 136.3, 135.3, 125.5, 122.6, 121.2 (q, J = 291 Hz), 120.4, 115.6 (t, J = 260 Hz), 114.2, 94.9, 80.1 (app m), 62.2, 57.0, 55.4, 51.6, 47.2, 6.21. Minor diastereomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (1H, s), 8.11 (1H, m), 7.45 (1H, s), 7.32 (1H, d, J = 2.1 Hz), 7.18−7.11 (2H, m), 7.00 (2H, m), 6.51 (1H, t, J = 74.8 Hz), 4.94 (2H, s), 4.87 (1H, 12.0 Hz), 4.17 (1H, d, J = 8.9 Hz), 4.06−3.94 (2H, m), 3.83 (1H, m), 3.48 (3H, s), 1.00 (1H, t, J = 7.1 Hz), 0.89−0.76 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 157.6, 150.8, 142.4, 141.3, 140.9, 139.3, 139.2, 138.8, 138.7, 137.5, 135.5, 125.7, 125.6, 122.7, 121.1 (q, J = 291 Hz), 115.7 (t, J = 260 Hz), 94.8, 80.1 (app m), 61.9, 56.9, 55.6, 51.6, 47.5, 13.6, 13.5; HRMS calcd for $C_{28}H_{26}F_8N_2O_7S$ ($M + H^+$) 687.1411, found 687.1410. HPLC: Zorbax Rx-C8 4.6 × 250 mm column. Eluent: A, 0.1% aqueous H_3PO_4; B, acetonitrile; 2 mL/min. Gradient: A/B 60:40 to 40:60 over 16 min, hold 1 min, then to 20:80 over 3 min, hold 5 min, λ = 220 nm, temperature 35 °C. t_R: **2b** (minor) = 15.1 min, (major) = 15.7 min. Chiral HPLC: Chiralpak AD 4.6 × 250 mm column. Eluent: A, hexanes; B *i*-PrOH; A/B 88:12; 1 mL/min, λ = 254 nm, temperature 40 °C. t_R: $\mathbf{2b}_{minor}$ = 13.1 min and 17.2 min; t_R: $\mathbf{2b}_{major}$ = 25.1 min and 28.9 min (96% ee).

2-{5-[(1*S*)-1-[3-(Cyclopropyloxy)-4-(difluoromethoxy)-phenyl]-2-(1-oxidopyridin-3-yl)ethyl]-1,3-thiazol-2-yl}-1,1,1,3,3,3-hexafluoropropan-2-ol (1). A mixture of diastereomeric esters **2b** (4.6 kg, 6.7 mol), methanol (17.7 L), and concd HCl (12 N, 580 mL, 6.7 mol) was heated at reflux for 3 h. The mixture was cooled to 5 °C, and water (17.7 L) and $LiOH·H_2O$ (1.1 kg, 26.2 mol) were added maintaining the temperature <20 °C. The batch was aged at 18−20 °C for 3.5 h. MTBE (20 L) was added and the aqueous layer separated. The aqueous layer was washed with MTBE (20 L) and transferred to a mixture of aqueous HCl (2 N, 12.8 L, 25.6 mol) and *i*-PrOAc (45 L). The aqueous layer was separated, and the organic layer was washed with water (2 × 10 L) to yield **2c** (3.9 kg, 94% HPLC assay yield, 96% ee). HPLC: Phenomenex Luna C-18 (2) 4.6 × 250 mm column. Eluents: A, 0.2% aqueous H_3PO_4; B, acetonitrile; 1 mL/min. Gradient A/B 60:40 for 5 min to 5:95 over 25 min, hold 5 min, 220 nm, temperature 30 °C. t_R: $\mathbf{2c}_{major\ diast}$ = 13.0 min, t_R: $\mathbf{2c}_{minor\ diast}$ = 13.4 min. The solvent was removed under reduced pressure and the residue dissolved in *i*-PrOH (40 L). *N*,*N*-Dicyclohexylamine (1.28 L, 6.3 mol) was added in one portion followed by heptane (12 L). The mixture was seeded and aged for 16 h at 20−25 °C. The batch was filtered and the cake was washed with *i*-PrOH/heptane (2:1 v/v, 3 × 4 L). The HPLC assay yield of **2c** in the filtrate was 3.2 kg (81%, 98.2% ee). Chiral HPLC: Chiralpak AS 4.6 × 250 mm column. Eluents: A, 0.1% TFA in hexanes; B, 0.1% TFA in EtOH; A/B 85:15, 1 mL/min, λ = 215 nm, temperature 30 °C. t_R: $\mathbf{2c}_{diast\ 1}$ = 9.7 min and 19.8 min, t_R $\mathbf{2c}_{diast\ 2}$ = 15.0 min and 36.3 min. The solvent was removed under reduced pressure and the residue dissolved in *n*-BuOAc (12 L). The solution was heated at 130 °C for 3 h. The mixture was cooled to 20−25 °C, heptane (12 L) was added over 1 h, and the slurry was aged for 16 h. The slurry was filtered, washed with heptane/*n*-BuOAc (1:1 v/v, 5 L), and dried under vacuum to yield **1** as a white solid (2.5 kg, 85% yield): mp 158−160 °C; $[\alpha]^{25}_D$ +60.56 (*c* =1, $CHCl_3$); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.42 (br s, 1H), 8.10 (s, 1H), 7.95 (d, 1H), 7.87 (s, 1H), 7.49 (s, 1H), 7.23 (t, 1H), 7.13 (m, 2H), 7.01 (dd, 1H), 6.79 (t, 1H), 4.90 (dd, 1H), 3.90 (m,1H), 3.57 (dd, 1H), 3.48 (dd, 1H), 0.71−0.85 (m, 3H), 0.63 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 160.5, 151.4, 147.0, 141.5, 141.2, 140.2, 140.0, 139.4, 137.9, 127.5, 126.6, 122.84 (q), 122.83, 121.3, 117.6 (t), 115.6, 52.3, 45.3, 39.8, 6.6, 6.5. Anal. Calcd for $C_{23}H_{18}F_8N_2O_4S$: C, 48.43; H, 3.18; N, 4.91. Found: C, 48.27; H, 3.13; N, 5.01. HPLC: Phenomenex Luna C18 5 μm, 4.6 × 250 mm column. Eluents: A, 0.2% aqueous H_3PO_4; B: acetonitrile; 1 mL/min. Gradient: 60:40 for 5 min to 5:95 over 20 min, hold 5 min, λ = 220 nm, temperature 30 °C. t_R: **1** = 14.4 min. Chiral HPLC: Chiracel OD-H, 4.6 × 250 mm column. Eluents: A, hexanes; B EtOH; A/B 75:25, 0.6 mL/min, λ= 215 nm, temperature 35 °C. t_R: (*S*) **1** = 12.5 min, t_R: (*R*) **1** = 18.1 min (98.2% ee).

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