Article

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Development of a Scalable, Chromatography-Free Synthesis of *t*-Bu-SMS-Phos and Application to the Synthesis of an Important Chiral CF_3-Alcohol Derivative in High Enantioselectivity Using Rh-Catalyzed Asymmetric Hydrogenation

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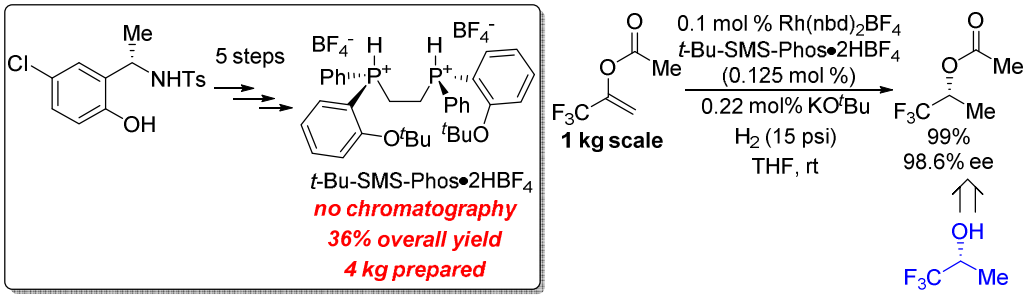
Abstract: A chromatography-free, asymmetric synthesis of the C2-symmetric *P*-chiral diphosphine *t*-Bu-SMS-Phos was developed using a chiral auxiliary based approach in 5 steps from the chiral auxiliary in 36% overall yield. Separtion and recovery of the auxiliary was acheived with good yield (97%) to enable recycling of the chiral auxiliary. An air-stable crystalline form of the final ligand was identified to enable isolation of the final ligand by crystallization to avoid chromatography. This synthetic route was applied to prepare up to 4 kg of the final ligand. The utility of this material was demonstrated in the asymmetric hydrogenation of trifluoromethyl vinyl acetate at 0.1 mol % Rh-loading to access a surrogate for the pharmaceutically relavent chiral trifluoroisopropanol fragment in excellent yield and enantiomeric excess (98.6% ee).



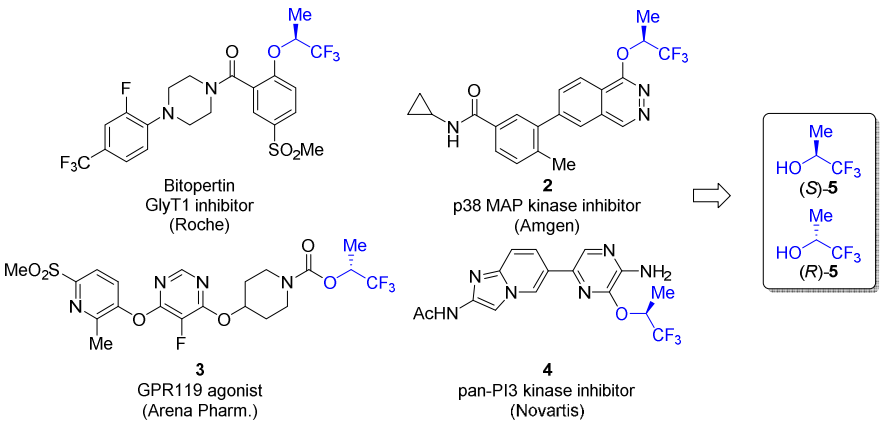
INTRODUCTION

Fluorinated organic compounds are of increasing importance for the identification of new therapeutics.[1] In particular, the CF_3-moiety has been demonstrated to increase lipophilicity and enhance metabolic stability. Recently, several new potential therapeutics containing a chiral trifluoroisopropanol motif have been described for a variety of different possible indications (Scheme 1).[2] This functionality is typically installed in the molecule using the chiral alcohol **5**. Therefore, there is a need for methods to prepare **5** in enantioenriched form. Furthermore, due to the fact that the active pharmaceutical ingredient (API) in new drugs must be prepared as single enantiomers (>99% ee), it is possible that **5** may need to be prepared in extremely high enantiopurities if enrichment by crystallization is not possible at some point in the synthetic route towards the API. Additionally, because **5** is a volatile, low molecular weight oil, enantioenrichment of **5** by direct crystallization is not possible.

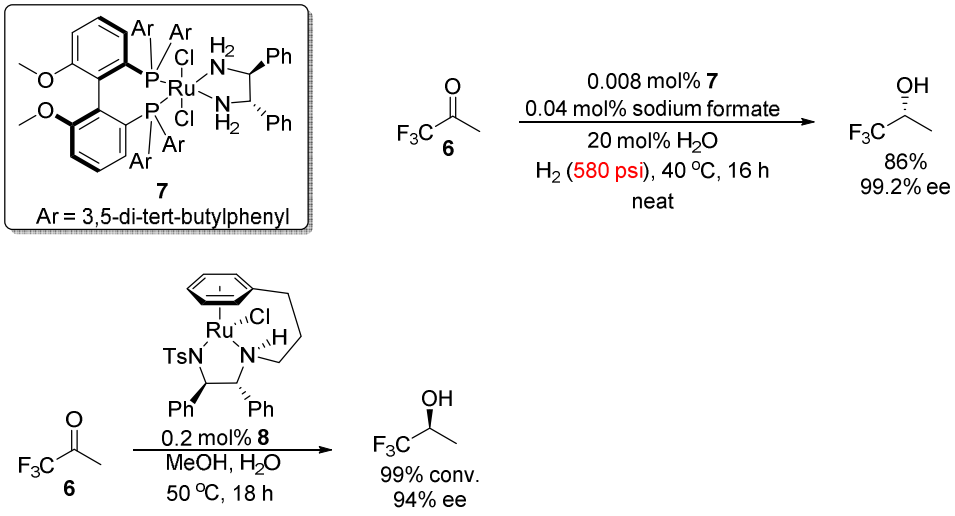
The first synthesis of enantiopure **5** was developed by Smith in 1968 using a resolution approach.[3] However, this is not desirable for scale-up from an overall yield perspective. Since that time, asymmetric methods for the preparation of **5** began to emerge.[4] One attractive strategy is to employ the asymmetric reduction of trifluoroacetone (Scheme 2, **6**). This was initially demonstrated using both Baker's yeast[4b] in only ~80% ee and using stoichiometric chiral reducing agents such as alpine-borane or DIP-chloride[4c] in 82% and 96% ee, respectively. In

terms of catalytic methods for the asymmetric reduction of ketone **6**, Noyori-type Ru-catalyzed ketone hydrogenation has been disclosed by Roche[4f,g] (Ru-catalyst **7**) and Johnson Matthey[4h] (Ru-catalyst **8**). Of these two methods, the Roche system allows for the preparation of **5** in excellent enantioselectivities (>99% ee). However, some drawbacks to this procedure are that it is run at relatively high hydrogen pressures (580 psi), and more significant is that trifluoroacetone (**6**) is known to undergo a thermal decomposition pathway that can lead to a runaway reaction scenario and possible explosion.[4g,5] This safety hazard is a significant concern for scale-up, especially considering that the reaction is run under neat conditions. Ketone **6** is also challenging to work with due to its low boiling point (22 °C, ~ rt).

Scheme 1: Importance of the Chiral Trifluoroisopropanol Fragment



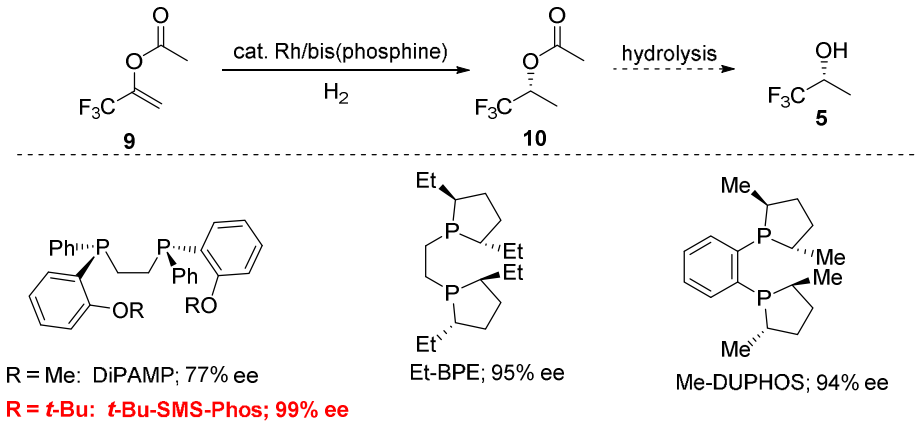
Scheme 2. Catalytic Asymmetric Synthesis of 5 by Hydrogenation of Ketone 6.



In an effort to avoid the safety and handling issues associated with ketone **6**, we sought a surrogate for alcohol **5** that could also be accessed through asymmetric hydrogenation with enantioselectivities of $\geq$ 97% ee but ideally at hydrogen pressures of < 500 psi. This search resulted in the switch from a ketone hydrogenation to a Rh-catalyzed olefin hydrogenation of (trifluoromethyl)vinyl acetate (**9**, Scheme 3) to afford the acetate-protected form of **5** (**10**). Several reports of this asymmetric hydrogenation have been disclosed in the literature using DiPAMP,[6] Et-BPE,[7] or Me-DUPHOS[7] as the chiral bis(phosphine) ligand; however, we were most interested in the recent report of the use of *t*-Bu-SMS-Phos[8] for this transformation since the highest enantioselectivities were reported using this ligand (99% ee). Unfortunately, *t*-Bu-SMS-Phos is not commercially available, and the synthesis of *P*-chiral phosphines is non-trivial. Furthermore, it is important to note that discovery of a "blockbuster" drug ultimately leads to the need for a multi-metric ton scale synthesis to supply this material to the market. If such a synthesis is to employ the power of asymmetric catalysis, then minimally, a kilogram-scale, chromatography-free method for preparation of the catalyst is just as critical as development of the catalyst itself. The challenges associated with the large-scale preparation of complex ligands and catalysts is often overlooked and can be equally or even more difficult than the design of a

total synthesis of a small natural product or new therapeutic. Herein, we disclose our work related to the development of a scalable, chromatography-free, kilogram-scale synthesis of *t*-Bu-SMS-Phos, and its application in the asymmetric hydrogenation of olefin **9** on kilogram scale.

Scheme 3. Rh-Catalyzed Asymmetric Olefin Hydrogenation to 5.



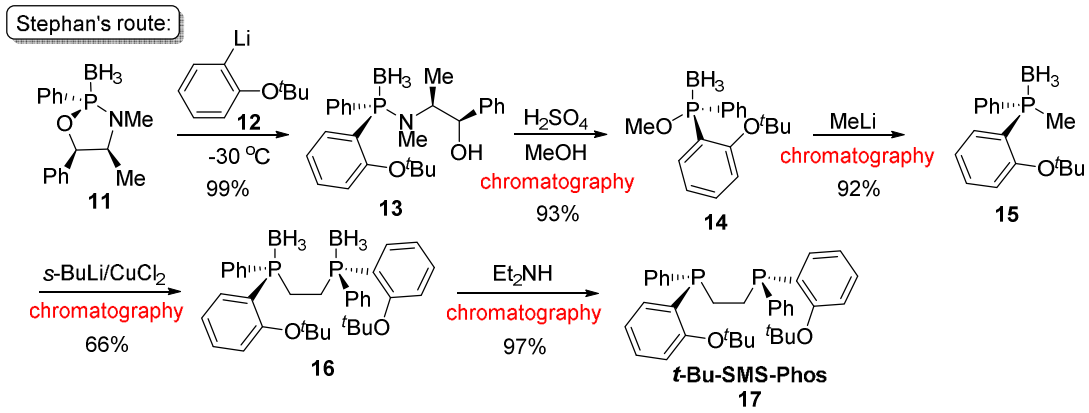
RESULTS AND DISCUSSION

Ligand Synthesis.

Tto further study the asymmetric hydrogenation of alkene **9** using *t*-Bu-SMS-Phos, a scalable and chromatography-free synthesis of this material was needed to supply the ligand. The published synthesis of **17** is shown in Scheme 4 as described by Stephan and coworkers.[8a] They employ the Jugé[9] method of *P*-chrial phosphine synthesis employing an ephedrine-derived chiral auxiliary using **11** as the starting material for the synthesis. Substitution of the *P*-*O* bond of **11** with aryllithium **12** proceeds with retention of configuration to provide intermediate **13** that is then converted to **14** by methonolysis of the *P*-*N* bond with inversion of configuration. The newly formed *P*-*O* bond in **14** is then substituted with inversion using MeLi to provide the *P*-chiral phosphine borane monomer **15**. Dimerization of **15**, followed by deblocking of the

phosphine borane generates the desired ligand **17**. While this procedure is a viable method to prepare ligand **17**, there were several issues with this procedure related to scale-up. First of all was the extensive use of column chromatography to purify intermediates, which is not desirable for scale-up. Furthermore, the ephedrine chiral auxiliary is a controlled substance, and therefore, can be troublesome to employ on scale because of the regulatory burden associated with its use.

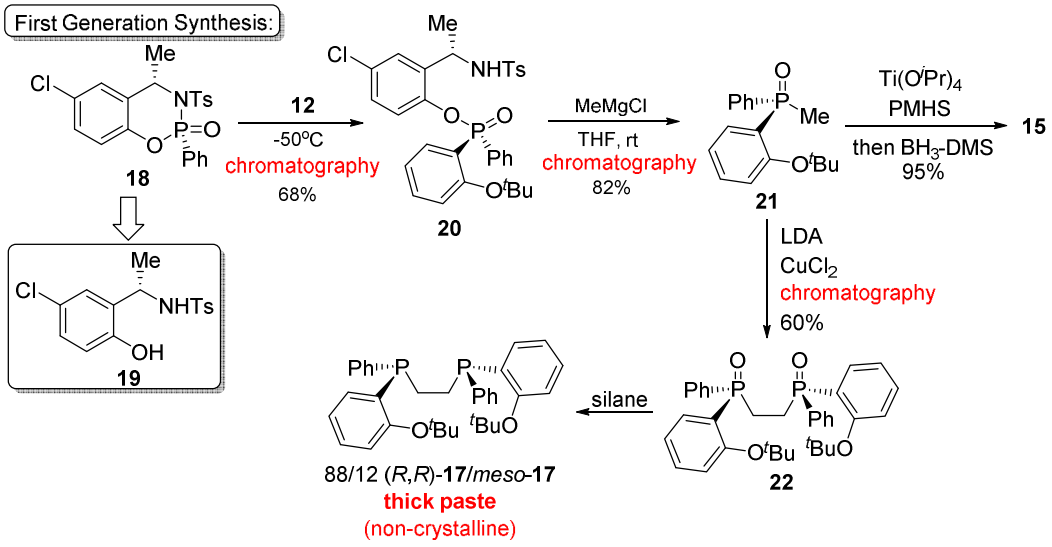
Scheme 4. Literature Synthesis of *t*-Bu-SMS-Phos.



Recently, we have disclosed a new chiral auxiliary for the efficient synthesis of *P*-chiral phosphines employing chiral auxiliary **19** (Scheme 5).[10] The advantages of this chiral auxiliary is that the *P*-*O* and the *P*-*N* bonds of the auxiliary can be cleaved chemoselectively with both Grignard or organolithium organometallic nucleophiles. Typically the use of Grignard reagents in the Jugé *P*-chiral phosphine synthesis is not possible, and Grignard's are much more desirable for handling on large scale due to their improved stability and higher safety margin compared with organolithium reagents. Furthermore, auxiliary **19**, and it's enantiomer, are available in kilogram quantities in four steps from 5'-chloro-2'-hydroxyacetophenone using a resolution approach.[10] Thus, application of our methodology for the synthesis of *P*-chiral phosphines was an obvious choice to investigate for the synthesis of **17** (Scheme 5). In our first generation

synthesis, **18** was treated with aryllithium **12** providing **20** with inversion of configuration. Treatment of **20** with MeMgCl then provided *P*-chiral phosphine oxide **21** in 99:1 er. From **21**, ligand **17** could be prepared either by conversion of **21** to borane **15** to intercept Stephan's synthesis,[8a] or one could envision dimerization of **21** to bis(oxide) **22** followed by reduction of **22** to give the desired ligand. Unfortunately, the latter method (**22** to **17**) was not completely stereoselective in the reduction step, and a mixture of the desired diasteromer of **17** and its *meso* isomer was obtained as an inseparable 88/12 mixture. Additionally, despite the fact that **17** is reported as a white solid in the literature,[8a] we were unable to isolate this material as a solid. It was always isolated as a thick oil/glass; therefore, we could not reject the *meso* isomer by crystallization. Furthermore, optimization of the silane reduction of **22** did not lead to a reduction in the amount of the *meso* isomer of **17**. As a result, we chose to further investigate the route employing conversion of **21** to borane **15**.

Scheme 5. First Generation Synthesis of *t*-Bu-SMS-Phos.

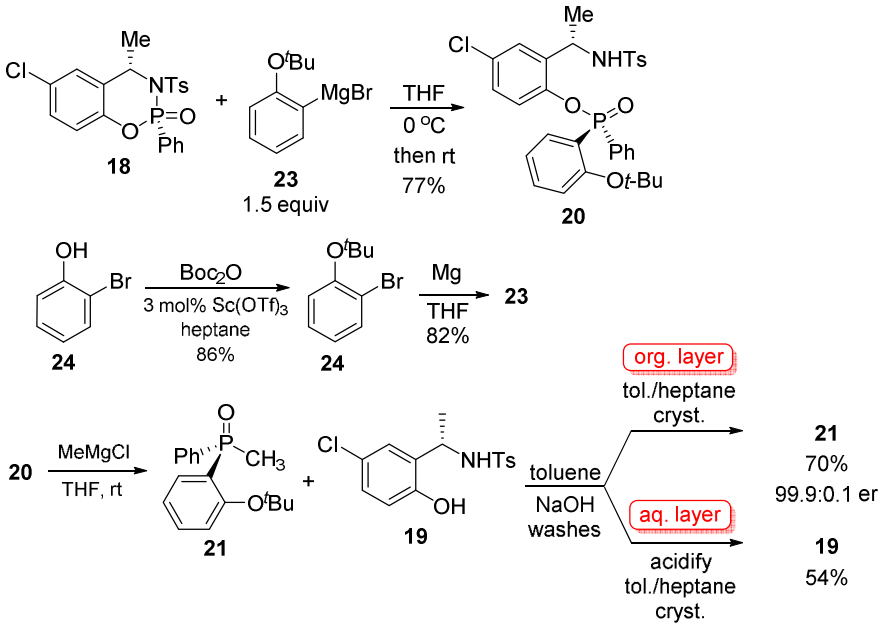


At this point, we had demonstrated the viability of using auxiliary **19** in the synthesis of ligand **17**; however, column chromatography was still required for purification of the

intermediates. The main issue was in the synthesis of oxide **21**. First, substitution of **18** by aryllithium **12** was not completely chemoselective for the substitiution of the *P-O* bond over the *P-N* bond. As a result, over-addition products were observed resulting from addition of **12** to the product **20**. This led to incomplete conversion of **18** along with the generation of free auxiliary **19**. This distribution of products could be easily separated by chromatography, but not using any extraction or crystallization procedures. Secondly, the conversion of **20** to **21** was a clean reaction; however, we resorted to chromatography in order to separate the chiral auxiliary **19** from oxide **20**. Ideally, we wanted to develop an extraction/crystallization procedure to separate auxiliary **19** from oxide **20** and allow for recycling of auxiliary **19**.

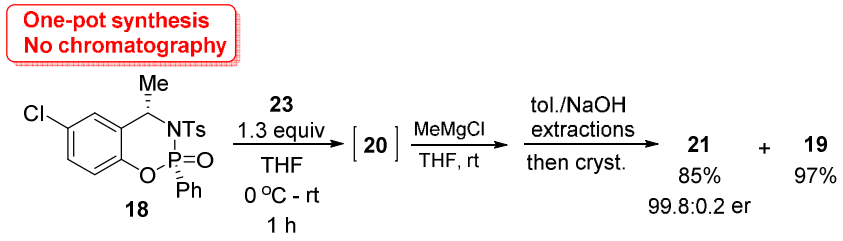
To address both of the issues mentioned for the synthesis of oxide **20**, we next examined the use of the Grignard reagent **23** in the substitution of **18** in an effort to reduce over-addition byproducts (Scheme 6). *Gratifyingly, clean conversion to **20** was obtained, and **20** could be isolated as a solid by direct precipitation from the reaction mixture in 77%.* Next, we investigated the separation of **21** from auxiliary **19** using extraction. After a survey of a variety of solvent combinations in conjunction with an aqueous base, it was determined that good partitioning of **21** from **19** could be achieved using toluene/2 M NaOH. In this procedure, oxide **21** remained in the toluene layer, and auxiliary **19** was washed into the 2 M NaOH layer. The oxide **21** could then be directly crystallized from the toluene layer to provide the material in good yield as a single enantiomer. The auxiliary was then recovered from the aqueous layer by acidification, extraction, and crystallization.

Scheme 6. Phosphine Oxide Synthesis.



Oxide **21** could now be prepared without chromatography; however, because the use of the Grignard reagent **23** led to such clean reaction profiles, we now could develop a one-pot synthesis of **21** without the need for isolation of **20** (Scheme 7). After the initial substitution of **18** with **23** was complete, MeMgCl was added to the reaction mixture. After complete consumption of **20** was observed (~4 h), the reaction was quenched, and the toluene/NaOH extraction process was performed to provide clean oxide **21**. *This process has been performed on up to 10 kg scale to furnish > 5 kg of oxide **21** as a single enantiomer in 85% yield along with 97% recovery of auxiliary **19** without the use of chromatography.*

Scheme 7. Development of Scalable One-Pot Phosphine Oxide Synthesis.

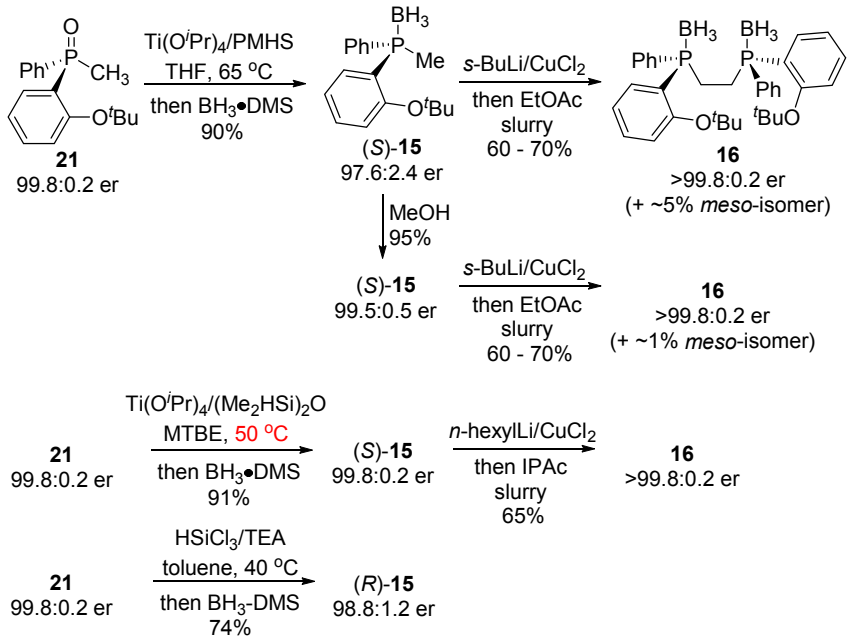


The remaining issue to be addressed in the synthesis of ligand **17** was the conversion of oxide **21** to the ligand without chromatography. First, reduction of the oxide and conversion to borane monomer **15** had to be performed with high chirality transfer (Scheme 8). Not surprisingly, we found that if the reduction of **21** proceeded with some loss of chiral purity, then when **15** was subsequently dimerized, some of the *meso* diastereomer of **16** was formed that was inseparable from the desired chiral diastereomer. Therefore, the reduction of **21** must occur with complete chirality transfer, or an enrichment method for **15** is required to ensure that >99% ee **15** is used in the dimerization step to avoid *meso* isomer formation. Fortunately, we were able to develop both. Reduction of **21** using $Ti(O\textit{i}\text{-}Pr)_4$ and tetramethyldisiloxane (TMDS, $(Me_2HSi)_2O$) at reduced temperature (50 ^oC *vs* 65 ^oC) lead to retention of stereochemistry[11] without any loss in chiral purity, and the material could be directly isolated from the reaction mixture by crystallization from heptane/IPA. PMHS was replaced by TMDS in this case to aid in the isolation of **15** from the reaction mixture. Borane **15** obtained with reduced enantiopurity (97.6:2.4 er) could also be enriched to 99% ee by rejecting the racemate by filtration in MeOH followed by recovery of the enriched product from the mothor liquor. Furthermore, if the opposite enantiomer of **15** is desired, (*R*)-**15** could also be obtained from **21** if $HSiCl_3$/TEA was employed in the reduction step through inversion of stereochemistry[12] at phosphorous with slight loss in enantiopurity (98.8:1.2 er).

Finally, dimerization of the anion of **15** generated from deprotonation with an alkyllithium base was further optimized to enable convenient isolation of product **16** with removal of stoichiometric Cu-salts. Complete deprotonation of **15** could be achieved at – 40 ^oC using either *s*-BuLi, *n*-BuLi, or *n*-hexylLi as determined by quenching studies with I_2. Ultimately, *n*-hexylLi was chosen as the base of choice since it is a safer alternative on large scale because

solutions in hexane are not pyrophoric. The main mass balance in the dimerization reaction was unreacted monomer **15** and alkylation of **15** with a hexyl group from radical coupling of the anion of **15** with hexyllithium. Separation of these compounds and removal of residual Cu-salts from **16** was achieved by first washing with aqueous solutions of NH_4OH followed by crystallization from EtOAc or IPAc.

Scheme 8. Conversion of Oxide 21 to Bis(BH_3) Adduct 16.

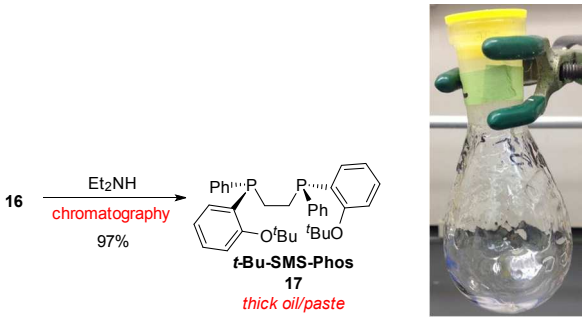


Lastly, the synthesis of the ligand from bis(borane) **16** was required. Use of the procedure published by Stephan[8a] on **16** prepared using our optimized synthesis still led to the formation of **17** as a thick oil/glass (Scheme 9a). Additionally, chromatography was still required to separate the $Et_2NH•BH_3$ byproduct from the desired free phosphine ligand. While this chromatography could be performed on the bench, and ligand **17** could be briefly handled in air, slow oxidation was observed on long-term storage outside of a glove-box. The free ligand could be stored for longer periods if left in a glove-box under a N_2 atmosphere. However, from a handling and

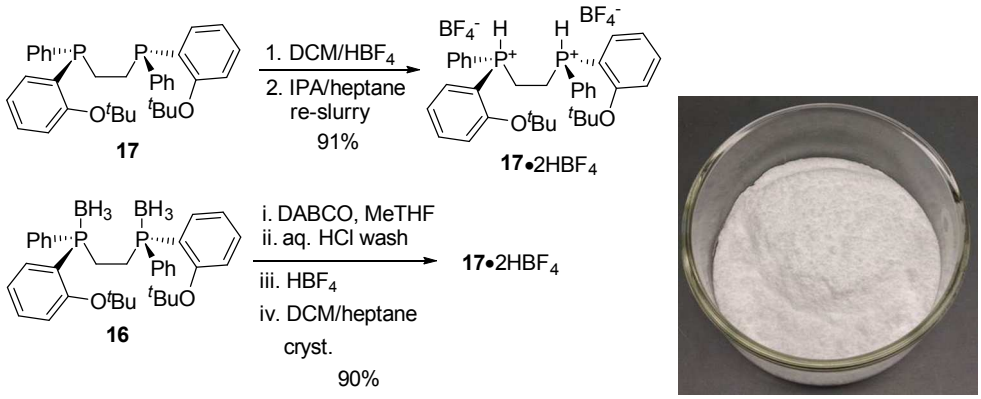
isolation perspective, these properties were not ideal. Therefore, we searched for a stable solid form of **17** that could be crystallized and stored on the bench-top. To do this, we first examined Fu's procedure[13] employing formation of the HBF_4 salt of the ligand (Scheme 9b). Gratifyingly, this material was a crystalline solid that was bench stable. Subsequently, a process was developed to remove the chromatographic separation of the amine-borane from the desired ligand. Et_2NH was replaced by dabco in the deblock step. This enables separation of the dabco•BH_3 byproduct by extraction using a dilute HCl wash. The bis(HBF_4) salt of the ligand was then generated, and the final salt was crystallized from the reaction mixture in good overall yield. Recrystallization of **17**•2HBF_4 from CH_2Cl_2/IPA/heptane afforded X-ray quality crystals to obtain the crystal structure given in Scheme 9c.

Scheme 9. Final Ligand Synthesis and Physical Characteristics.

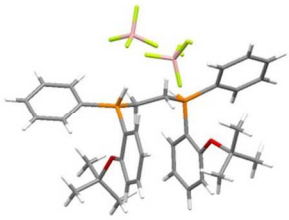
(a)



(b)



(c)



The stability of the ligand HBF_4 salt (**17**•2HBF_4) was monitored over time with storage of the material under an air atmosphere at ambient conditions. We saw no signs of phosphine oxidation by ^{31}P NMR spectroscopic analysis over a 24 month period. However, we did notice that some batches of ligand showed no change over this time period, but other batches showed the formation of two new species by ^{31}P NMR spectroscopy. The only differences in these different batches of ligand were related to the scale on which these materials had been prepared. In general, we found that **17**•2HBF_4 prepared on 100 g scale or less showed no degradation over 24 months, but materials prepared on > 100 g scale led to the slow formation of these two new compounds. It was determined that these new phosphorous compounds were the resulting *mono*-phenol and *bis*-phenol of **17** from *mono*-*t*-butyl ether and *bis*-*t*-butyl ether cleavage, respectively. We had previously observed this degradation pathway when trying to recrystallize **17**•2HBF_4 from polar protic solvents that the material had good solubility in such as MeOH or EtOH. Therefore, we hypothesized that residual excess acid was present in larger lots of **17**•2HBF_4 due

to the decreased efficiency of removing the excess HBF_4 when washing the filter cake on larger scale. To test this idea, various batches of **17**•2HBF_4 were assayed for BF_4 content by quantitative ^{19}FNMR spectroscopy using α,α,α-trifluoromethyltoluene as the standard. Indeed, ligand batches prepared on larger scale (>100 g) contained up to 2.5 equiv of BF_4 (2.0 equiv expected by theory). Stable batches of **17**•2HBF_4 contained < 2.2 equiv of BF_4 by quantitative ^{19}F NMR spectroscopic analysis.

Based on the ligand stability concerns outlined above, a re-work procedure to remove excess HBF_4 was required. It was determined that this could be achieved by slurrying the material in IPA followed by addition of heptane anti-solvent or by recrystallization of the material from CH_2Cl_2/IPA/heptane. With this new knowledge, the rework procedure was added directly to the ligand synthesis protocol. After the first isolation of **17**•2HBF_4 from the reaction by CH_2Cl_2/heptane crystallization (2 kg scale), the wet-cake was found to contain up to 2.5 equiv of BF_4 by quantitative ^{19}F NMR analysis. Placing a small sample of this wet cake in a vacuum oven at 45 ^{o}C led to ~50% bis(*t*-Bu) ether cleavage after 14 h. This first wet-cake was charged back to the reactor, slurried in IPA, and filtered to provide **17**•2HBF_4 in ~85% overall yield with < 2.2 equiv of BF_4 (^{19}FNMR). This material showed no degradation after 6 months under air at ambient conditions.

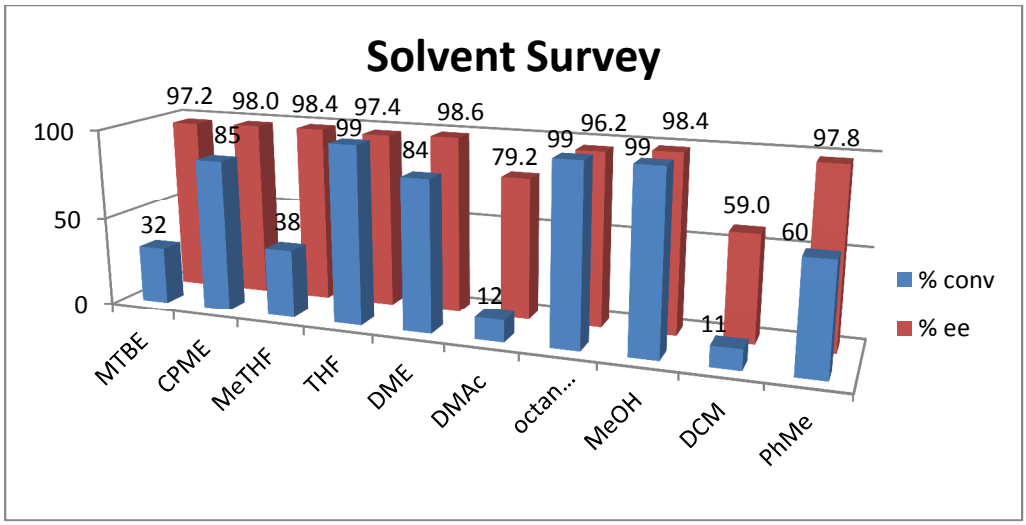
*Using the above procedures, we have successfully prepared 4 kg of **17**•2HBF_4 in 36% overall yield from auxiliary **19** without the use of chromatography.*

Asymmetric Hydrogenation of CF_3-vinyl acetate (9)

After having developed procedures to produce large quantities of ligand **17**, we next investigated the asymmetric hydrogenation of vinyl acetate **9** to access the chiral

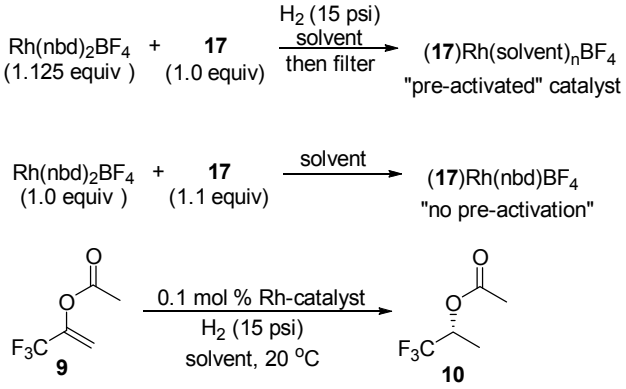
trifluoroisopropanol fragment. Our initial optimization studies employed use of the unprotected form of the phosphine ligand of (**17**). In Stephan's[8a] report for the application of **17** in Rh-catalyzed asymmetric hydrogenation of polar alkenes, the Rh-**17** complex is first generated from **17** in the presence of a slight excess of $Rh(nbd)_2BF_4$ in MeOH solvent. The resulting complex is then hydrogenated using 1 atm of H_2 to remove the olefin ligand (nbd) from the precatalyst and generate the active solvated Rh-species: (**17**)$Rh(MeOH)_n$. This solution of catalyst is subsequently filtered to remove elemental Rh (from the excess $Rh(nbd)_2BF_4$), and then charged into the reaction mixture containing alkene substrate in MeOH solvent followed by the introduction of H_2. We refer to this procedure as the "pre-activation" method. From a practical standpoint, it would be desirable to form the catalyst *in situ* without pre-activation and subsequent filtration. Additionally, because **10** is envisioned to be a surrogate for the chiral trifluoroisopropanol **5** that is often employed as a nucleophile for S_NAr chemistry, preparation of **10** in alcohol solvent (*i.e.* MeOH) is not practical since the solvent alcohol can be a competitive nucleophile in the subsequent S_NAr reaction. Furthermore, separation of MeOH from **10** or **5** will be difficult due to the similarity in boiling point and chemical properties. To address these concerns, we analyzed possible replacement solvents for MeOH (Scheme 10) in the asymmetric hydrogenation of **9** and studied generation of the catalyst *in situ* by using a slight excess of **17** relative to the $Rh(nbd)_2BF_4$ precatalyst without any pre-activation with H_2 (Scheme 11).

Scheme 10. Solvent Study.

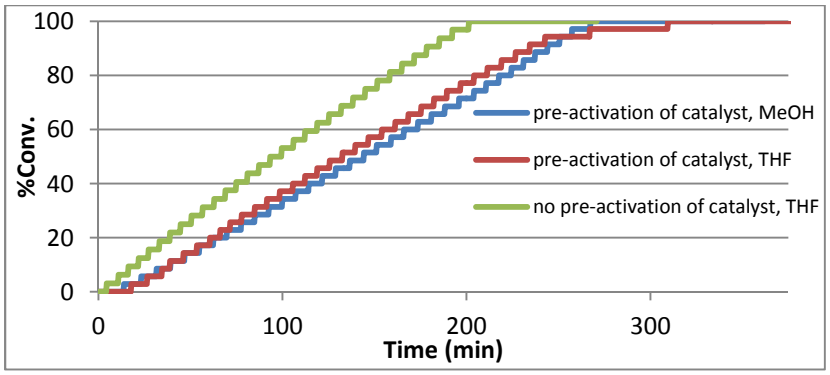


Conditions: 0.2 mol% (**17**)Rh(solvent)$_n$BF$_4$, 15 psi H_2, rt, 12 h, 0.5 M. Conversion was measured by quantitative ^{19}F NMR spectroscopy. Enantiomeric excess was determined by chiral GC (β-dex 225) analysis of alcohol **5** after *in situ* hydrolysis of **10** by treatment of an aliquot of the reaction mixture with a few drops of 2 M NaOH followed by dilution with MeOH.

Scheme 11. Effect of Catalyst Preparation

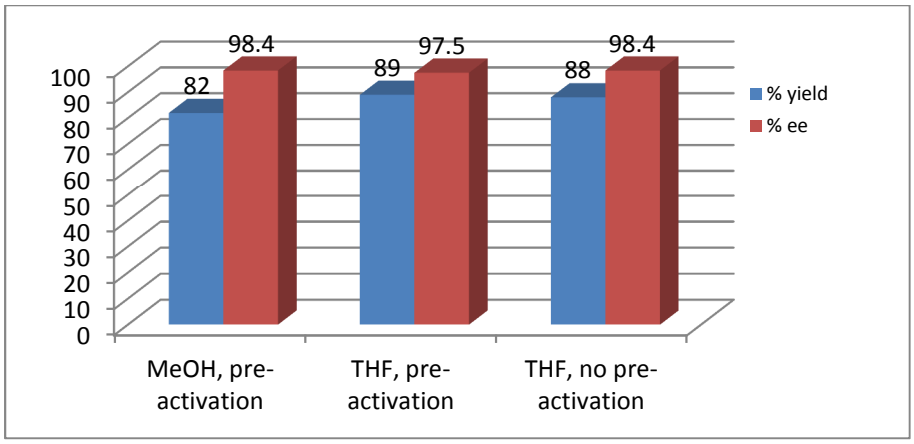


(a)



Pre-activation: $Rh(nbd)_2BF_4$ (6.0 mg, 0.016 mmol), **17** (6.9 mg, 0.013 mmol), solvent (1 mL), H_2 sparge (15 psi, 2 min, rt) followed by filtration through a syringe-frit (0.45 μM) directly into the reaction mixture with a 1 mL solvent rinse. No pre-activation: $Rh(nbd)_2BF_4$ (4.8 mg, 0.013 mmol), **17** (7.6 mg, 0.014 mmol), solvent (3 mL), rt, 15 min followed by direct addition to the reaction mixture. Reaction: Acetate **9** (1.97 g, 12.8 mmol), solvent (15 mL), H_2 (15 psi), 20 °C. Reaction conversion was measured by monitoring H_2 uptake. The plot 10b represents NMR assay yields determined using ^{19}F NMR spectroscopy with $PhCF_3$ as standard. Enantiomeric excess was measured by chiral GC (β-dex 225) analysis of alcohol **5** after *in situ* hydrolysis of **10** by treatment of an aliquot of the reaction mixture with a few drops of 2 M NaOH followed by dilution with MeOH

(b)

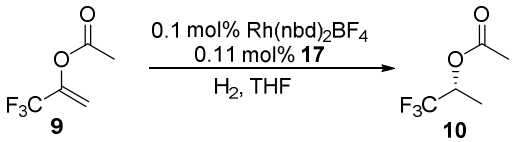


Analysis of ether based solvents where product **10** could be used in subsequent chemistries directly in the hydrogenation reaction solvent, or the use of high boiling solvents that

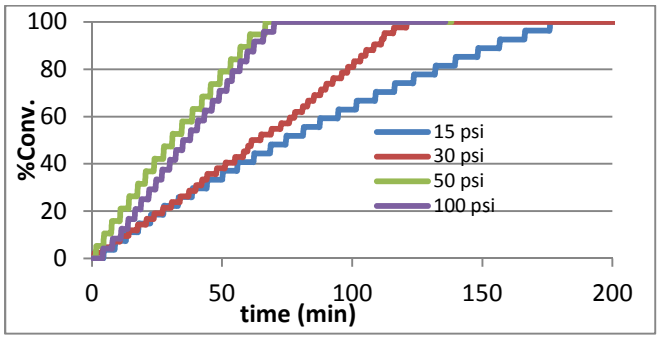
product **10** could be distilled out of led to the identification of THF as a better solvent choice to study further since good conversion was obtained with only a slight loss in enantiopurity (97.4% ee in THF *vs* 98.4% ee in MeOH). Comparison of generating the catalyst by the "pre-activation" method under the conditions reported by Stephan[8a] *vs* generation of the catalyst *in situ* without pre-activation were compared by monitoring reaction kinetics using "real-time" monitoring of H_2 uptake in the reaction (Scheme 11). Little difference was found between the two protocols in terms of reaction rate, yield, or enantioselectivity. As such, the user can decide which protocol is more practical to be run depending on the type of equipment available. Finally, it is important to note that the hydrogenation reaction of olefin **9** demonstrated zero-order kinetics in alkene as evident by the linear H_2 uptake plot.

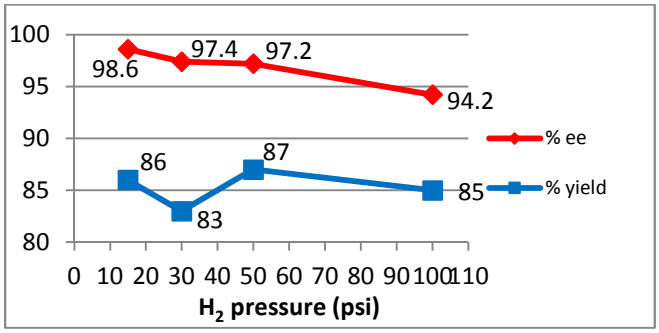
We next optimized the reaction parameters for the asymmetric hydrogenation of **9** (*i.e.* temperature, pressure, concentration, catalyst loading, and agitation rate). The kinetics of the reaction based on hydrogen uptake for each parameter studied is given in Scheme 12. In all cases, zero-order kinetics in alkene was observed as evident by the linear H_2 uptake plots. Additionally, it was determined that the hydrogenation reaction rate was dominated by the efficiency of the mass transfer of H_2 gas into the solution. This is evident by the strong positive effect on reaction rate with increased hydrogen pressure or increased agitation rate. However, it should be noted that while reaction rate improved with increased agitation rate, reaction efficiency in terms of yield was observed to decrease with increasing agitation rate. The reaction was also determined to be first-order in catalyst, and the reaction rate decreases significantly at low temperatures (0 ^{o}C). The enantioselectivity was also affected by reaction pressure and temperature. These effects in the Rh-catalyzed asymmetric hydrogenation of polar alkenes has been described previously.[14]

Scheme 12. Effect of Reaction Parameters

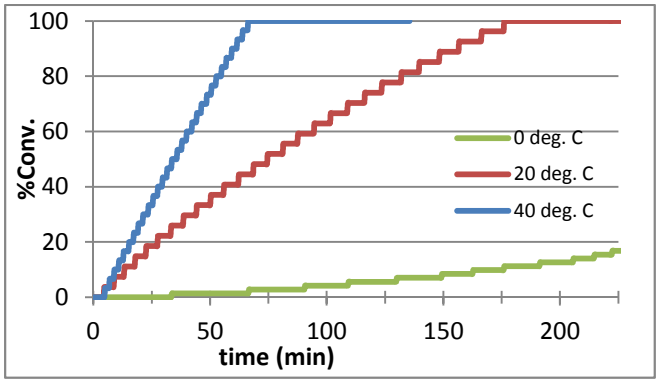


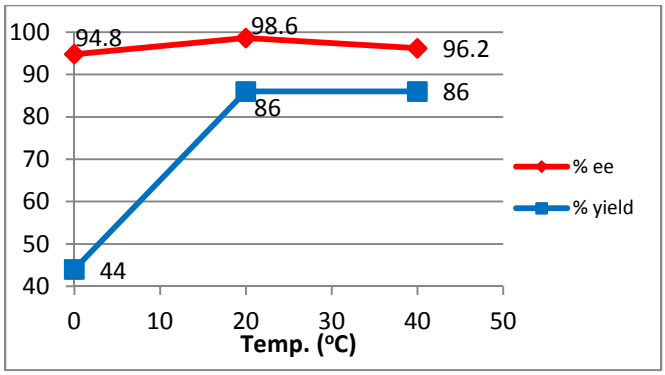
(a)



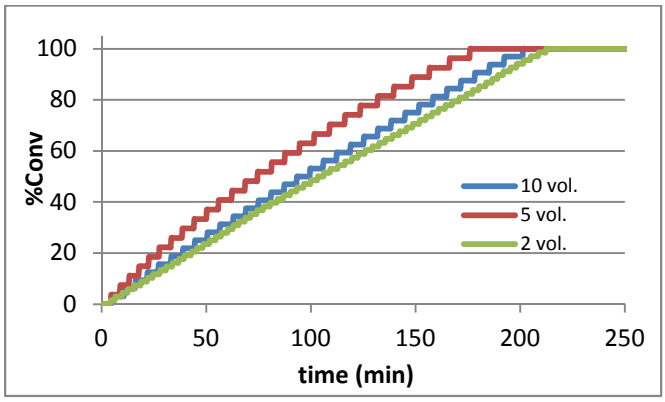


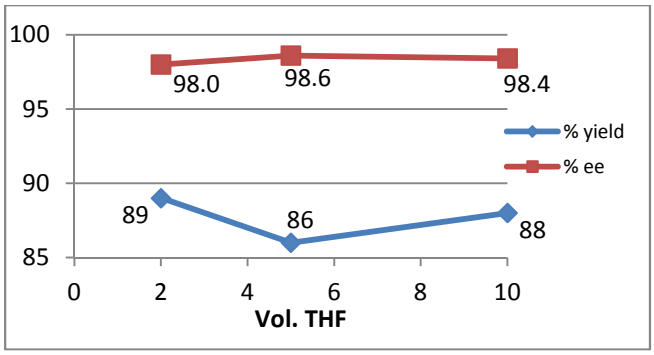
(b)



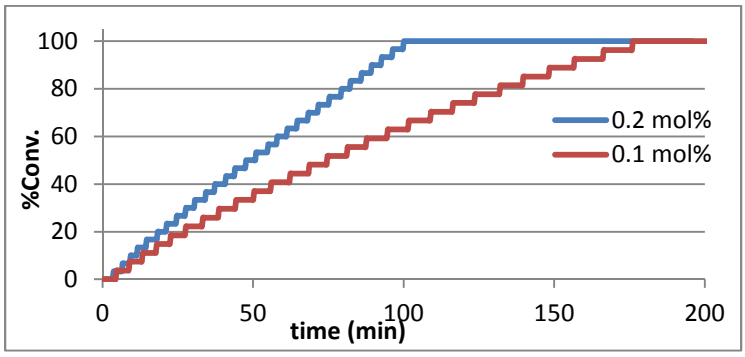

100
90
80
70
60
50
40
94.8
98.6
96.2
86
86
44
0
10
20
30
40
50
Temp. (°C)
% ee
% yield

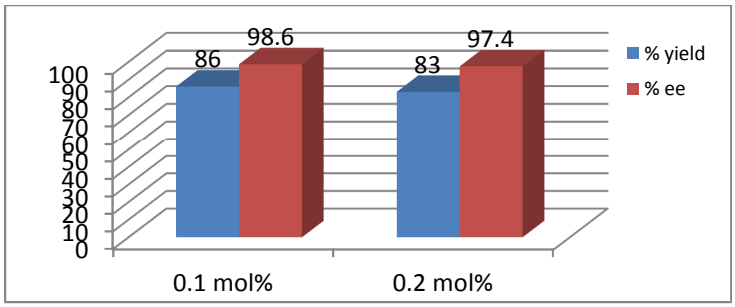
(c)


100
80
60
40
20
0
%Conv
0
50
100
150
200
250
time (min)
10 vol.
5 vol.
2 vol.

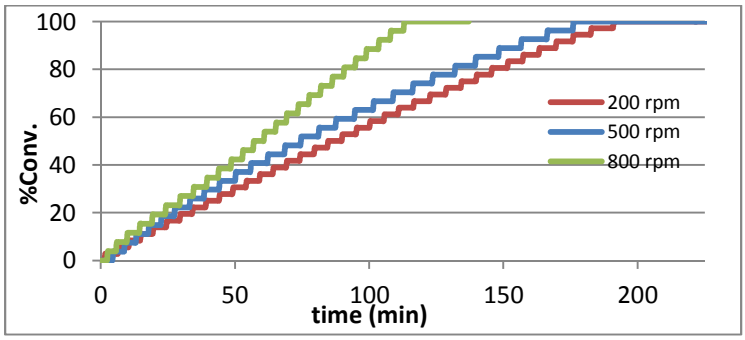

100
95
90
85
98.0
98.6
98.4
89
86
88
0
2
4
6
8
10
Vol. THF
% yield
% ee

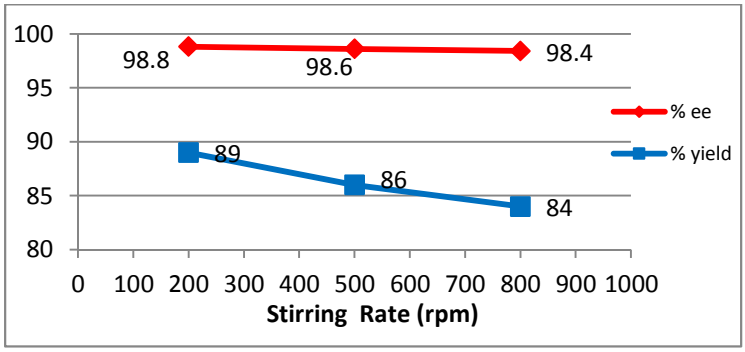
(d)


100
80
60
40
20
0
%Conv.
0
50
100
150
200
time (min)
0.2 mol%
0.1 mol%



(e)

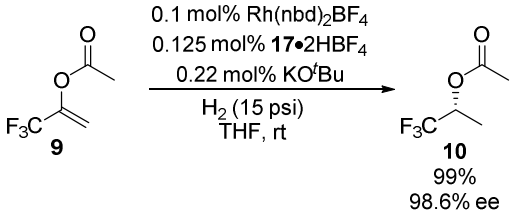




Acetate **9** (2.46 g, 15.9 mmol), $Rh(nbd)_2BF_4$ (6.0 mg, 0.016 mmol), **17** (9.5 mg, 0.018 mmol), THF (5 vol., 12.5 mL), H_2. Reaction conversion was measured by monitoring H_2 uptake. Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as standard. Enantiopurity was determined by chiral GC (β-dex 225) analysis of alcohol **5** after *in situ* hydrolysis of **10** by treatment of an aliquot of the reaction mixture with a few drops of 2 M NaOH followed by dilution with MeOH. (a) Effect of H_2 pressure at 20 °C, 5 vol. THF, and 500 rpm. (b) Effect of temperature at 15 psi H_2, 5 vol. THF, and 500 rpm. (c) Effect of concentration at 15 psi H_2, 20 °C, and 500 rpm. (d) Effect of catalyst loading at 20 °C, 15 psi H_2, 5 vol. THF, and 500 rpm. (e) Effect of agitation speed at 15 psi H_2, 20 °C, and 5 vol. THF.

After optimization of the reaction conditions employing the free ligand **17**, we next modified the hydrogenation procedure to employ **17**•2HBF$_4$ directly with *in situ* deprotonation to unmask the free-ligand (Scheme 13). This was possible by addition of a catalytic amount of KO^{t}Bu during the *in situ* generation of the Rh-catalyst for the hydrogenation. Using this process, 1.0 kg of **9** was hydrogenated in quantitative yield and 98.6% ee in a 10 L autoclave employing ambient temperature (20 ^{o}C) and pressure (15 psi).

Scheme 13. Kilo-Scale Asymmetric Hydrogenation Employing 17•2HBF$_4$

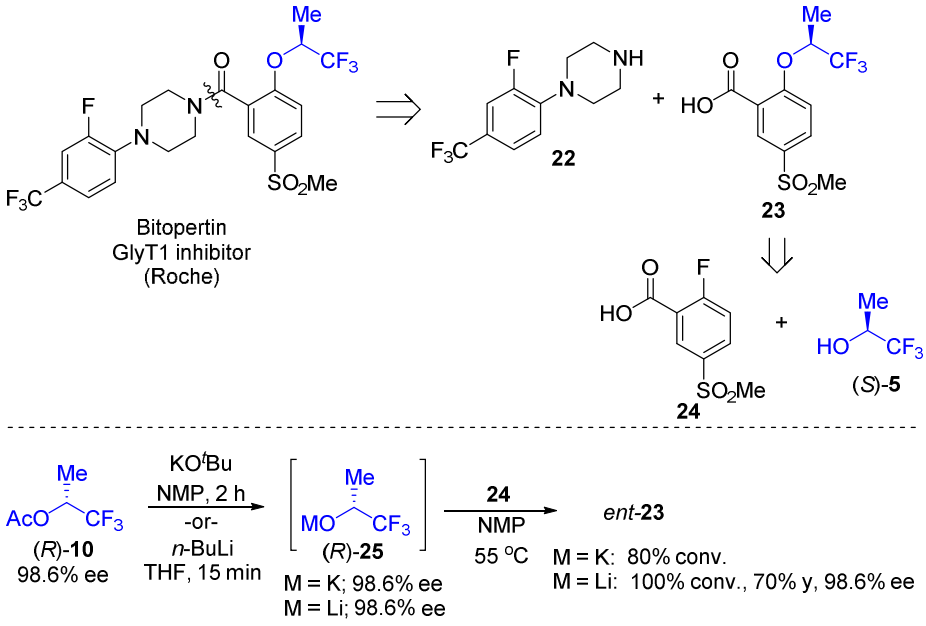


Acetate **9** (1.0 kg, 6.49 mol), Rh(nbd)$_2$BF$_4$ (2.40 g, 6.42 mmol), **17**•2HBF$_4$ (5.77 g, 8.03 mmol), KO^{t}Bu (1.0 M in THF, 14.1 mL, 14.1 mmol), THF (5 L), H_2 (15 psi), 20 ^{o}C, 12 h.

To demonstrate that **10** can be employed as a replacement for the chiral trifluoroisopropanol **5**, the enantiomer of acid **23** employed in the synthesis of Roche's Bitopertin was demonstrated using S_NAr chemistry (Scheme 14).[2a] Because alcohol **5** is a volatile oil that is soluble in both water and organic solvents, it is more practical to develop a protocol to hydrolyze acetate **10** to alcohol **5** and use the crude mixture directly rather than trying to isolate **5**. Acetate **10** was used as a solution in THF and can be used crude directly from the asymmetric hydrogenation reaction or distilled pot-to-pot to separate the product from Rh and **17**. Hydrolysis of **10** was effective using KO^{t}Bu in NMP or by the addition reaction of *n*-BuLi. In both cases, conversion is easily monitored by GC or ^{19}F NMR spectroscopy. Analysis of the resultant hydrolyzed material by chiral GC showed no loss in enantiopurity. The crude solutions

of alkoxide **25** were then investigated in the S_NAr reaction with aryl fluoride **24**. The S_NAr reaction employing the potassium alkoxide formed from hydrolysis of **10** with KO^{t}Bu stalled at ~80% conv. while the lithium alkoxide formed from the reaction of *n*-BuLi with **10** led to clean and full consumption of **24**. Pure *ent*-**23** could then be isolated by crystallization in good yield with high enantiopurity (98.6% ee).

Scheme 14. Application to the Synthesis of Bitopertin.



CONCLUSION

In conclusion, we have developed a scalable, chromatography-free synthesis of *t*-Bu-SMS-Phos•2HBF$_4$ employing chiral auxiliary **19** to access multi-kilograms of this useful ligand as an air-stable, white crystalline solid. Because of the efficiency of the Grignard addition reactions to prepare phosphine oxide **21**, the auxiliary can be easily separated from the oxide and recovered. Furthermore, both enantiomers of *t*-Bu-SMS-Phos can be prepared from oxide **21** depending on the choice of the phosphine oxide reduction method employed. Application of this

ligand to the hydrogenation of vinyl acetate **9** was performed on kilogram scale, and the hydrogenation was shown to be zero-order in olefin **9**, and the rate of reaction has a strong dependence on the mass-transfer of H_2 into the solution. This procedure represents an alternate method for the preparation of a surrogate of the chiral trifluoroisopropanol fragment **5** with high enantiopurity (98.6% ee) as demonstrated by the application of **10** in the S_NAr reaction with fluoroarene **24**.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all reactions were carried out using oven- or flame-dried glassware under an inert atmosphere of N_2 or Ar. ^{1}H NMR spectra were recorded on Bruker 400 MHz or 500 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as an internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR was recorded on a Bruker 500 MHz (125 MHz) or 400 MHz (100 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). ^{31}P NMR spectra were recorded on a Bruker 500 MHz (202 MHz) or 400 MHz (161 MHz) instrument and chemical shifts are reported relative to 85% H_3PO_4. High-resolution mass spectrometry (HRMS) was performed using a linear ion trap with a Fourier Transform Ion Cyclotron Resonance MS detector. Auxiliary **19** was prepared according to our previous procedures[10] and purchased from AstaTech.

(2*S*,4*S*)-6-chloro-4-methyl-2-phenyl-3-tosyl-3,4-dihydrobenzo[*e*][1,3,2]oxazaphosphine 2-oxide (18). To a mix tank was sequentially charged

15.0 kg (46.0 mol) of **19**, 100 kg (75 L) of CH_2Cl_2, and 12.7 kg (62.5 mol) of 96.0 wt% $PhP(O)Cl_2$. The resultant mixture was stirred until homogeneous (~30 min). To a 200 L glass-lined reactor under N_2 was charged 9.45 kg (115 mol) of 1-methylimidazole followed by 100 kg (75 L) of CH_2Cl_2, and the solution was cooled to – 10 ^oC. To the 1-methylimidazole solution was then charged the solution of **19**/$PhP(O)Cl_2$ while maintaining an internal batch temperature of < – 5 ^oC (~30 min). The mixture was then agitated at – 5 to – 10 ^oC for 1 h. Analysis of a reaction aliquot quenched into MeOH by HPLC showed < 1A% of **19** remaining. To the mixture was then charged 60 L of water over 30 min, and the mixture was subsequently warmed to rt and stirred an additional 1 h. The lower organic phase was then separated and subsequently washed with 5% $NaHCO_3$ (1 x 60 L) and water (1 x 60 L). The mixture was then distilled under vacuum (~400 torr) to ~45 L while maintaining an internal batch temperature of < 30 ^oC. EtOAc (108 kg, 120 L) was then charged, and the mixture was again distilled under vacuum (~78 torr) to ~60 L while maintaining an internal batch temperature of < 40 ^oC. At this point, a slurry was formed. The batch was then agitated for an additional 30 min at 30 ^oC with good agitation to remove any solids from the reactor walls into the main batch. Heptane (81 kg, 120 L) was then slowly charged to the slurry at 30 ^oC over 1 h. The batch was then cooled to rt within 1 h and agitated for an additional 3 h. The solid was isolated by filtration and subsequently washed with 22.5 L of 2/1 v/v heptane/EtOAc. The solid was then dried overnight in a vacuum oven at 45 ^oC. This afforded 18.5 kg of **18** (85%) in 95.2 wt% purity by quantitative ^{1}HNMR spectroscopy (dimethylfumarate as internal standard) as a white crystalline solid. Spectral data was in complete agreement with the published data.[10] Mp 207 – 210 ^oC; $[\alpha]_D^{22}$ = – 59.0 (*c* 0.94, $CHCl_3$).

4-chloro-2-((*S*)-1-((4-methylphenyl)sulfonamido)ethyl)phenyl (*R*)-(2-(*tert*-butyoxy)phenyl)(phenyl)phosphinate (20).

Synthesis employing aryllithium **12**:

Aryllithium **12**: To a dry flask under N_2 was charged 25.0 g (166 mmol) of *tert*-butoxybenzene and 125 mL of cyclohexane. To the batch was then charged 97.9 mL (166 mmol) of a 1.7 M solution of *t*-BuLi in pentane by canula. The batch was then warmed to 79 ^oC with removal of pentane by distillation. The mixture was then aged at this temperature for 20 h and then cooled to rt and used in the next step.

To a dry 3-neck flask with thermocouple was charged 64.4 g (144 mmol) of **18**, and the flask was inerted with N_2 using vacuum/purge cycles (3x). THF (520 mL) was then added, and the solution cooled to – 50 ^oC. The aryllithium solution of **12** prepared above was then charged by cannula. The reaction was stirred for 30 min at – 50 ^oC and then warmed to rt over 1 h. The batch was quenched with 150 mL of 10% NH_4Cl. Water (150 mL) was then added, and the layers were separated. The aqueous layer was extracted with EtOAc (1 x 300 mL). The combined organics were dried with anhydrous Na_2SO_4, and then concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (0 – 50% EtOAc in hexanes) to provide 56 g (65%) of oxide **20**.

Synthesis employing aryl Grignard **23**:

To a dry 3-neck flask with thermocouple was charge 2.1 g (4.69 mmol) of **18**, and the flask was inerted with N_2 using vacuum/purge cycles (3x). THF (8 mL) was then added, and the solution cooled to 0 ^oC. Grignard **23** (8.5 mL, 6.8 mmol, 0.8 M in MeTHF) was charged over 5 min with an internal batch temperature of < 5 ^oC. The reaction was stirred for 1 h at 0 ^oC and then warmed to rt over 30 min. The batch was held at rt until consumption of **18** was observed by HPLC analysis (typically 1 – 2 h, samples quenched with 10% NH_4Cl). The batch was then cooled back to 0 ^oC and quenched with 25 mL of 5% aqueous citric acid. The aqueous layer was

separated and extracted with MTBE (1 x 10 mL). The combined organics were washed with water (1 x 10 mL), 10 mL of 5% brine, dried with anhydrous Na_2SO_4, and then concentrated *in vacuo* to afford 3.35 g (93%) of **20** as a white solid in 77.6 wt% purity by quantitative ^{1}HNMR spectroscopy (dimethylfumarate as internal standard). A portion of crude **20** (3.03 g) was dissolved in 30 mL of MTBE. This solution was then transferred to an addition funnel and the residue transferred with an additional 5 mL of MTBE. This solution was then added dropwise to 105 mL of rapidly stirred heptane over ~5 min. The resultant slurry was agitated at 0 ^{o}C for 30 min, and the solid isolated by filtration and washed with 20 mL of heptane. This afforded 2.61 g (88% recovery) of the MTBE-solvate of **20** in 82.5 wt% purity by quantitative ^{1}HNMR spectroscopy (dimethylfumarate as internal standard). Mp 85 – 100 ^{o}C; $[\alpha]_D$ = + 12.6 (*c* 0.71, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (ddd, *J* = 13 Hz, *J* = 7.9 Hz, *J* = 2.0 Hz, 1H), 7.69 – 7.78 (m, 2H), 7.50 – 7.58 (m, 4H), 7.44 (td, *J* = 7.8 Hz, *J* = 3.8 Hz, 2H), 7.10 – 7.19 (m, 2H), 7.07 (dd, *J* = 8.8 Hz, *J* = 0.8 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.91 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1H), 6.78 (d, *J* = 2.8 Hz, 1H), 5.77 (d, *J* = 7.8 Hz, 1H), 4.65 (p, *J* = 7.4 Hz, 1H), 2.31 (s, 3H), 1.27 (s, 9H), 1.25 (d, *J* = 7.4 Hz, 3H); P{^{1}H}NMR (202 MHz, $CDCl_3$): δ 32.4 ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 159.1 (d, $J_{C\text{-}P}$ = 4.7 Hz), 146.5 (d, $J_{C\text{-}P}$ = 8.3 Hz), 142.9, 137.4, 135.0 (d, $J_{C\text{-}P}$ = 6.3 Hz), 134.7 (d, $J_{C\text{-}P}$ = 5.1 Hz), 134.5, 132.2 (d, $J_{C\text{-}P}$ = 142 Hz), 132.17 (d, $J_{C\text{-}P}$ = 2.9 Hz), 130.9 (d, $J_{C\text{-}P}$ = 11.4 Hz), 129.6, 129.1, 128.4, 128.2, 128.0, 126.9, 122.5 (d, $J_{C\text{-}P}$ = 3.0 Hz), 120.8 (d, $J_{C\text{-}P}$ = 12.6 Hz), 120.2 (d, $J_{C\text{-}P}$ = 138 Hz), 117.6 (d, $J_{C\text{-}P}$ = 7.9 Hz), 80.76, 49.26, 28.64, 22.30, 21.36; HRMS(DART) *m*/*z* calcd for $C_{31}H_{34}ClNO_5PS$ $[M + H]^+$: 598.1584; Found: 598.1581.

1-bromo-2-(*tert*-butoxy)benzene (25). To a mix tank was sequentially charged 37.8 kg (173 mol) of Boc_2O and 17 kg (25 L) of heptane. The resultant mixture was stirred until

homogeneous (~2 h). To a 200 L glass-lined reactor was charged 850 g (1.73 mol) of scandium triflate. The handhole was then sealed, and the reactor inerted with N_2 using vacuum-purge cycles (3x). To the reactor was then charged 10.0 kg (57.8 mol) of 2-bromophenol, and the charge was rinsed into the reactor using 7.0 kg (10 L) of heptane. To the reactor was then slowly charged the Boc_2O/heptane solution over 2.5 h (note: gas evolution, mild exotherm). The batch was then agitated at rt overnight. A sample of an aliquot of the reaction quenched into MeOH showed 11A% of 2-bromophenol remaining by HPLC analysis. An additional 7.0 kg (10 L) of heptane was then charged followed by 42.9 kg of 7.5 wt% aqueous NaOH solution. The batch was agitated for 30 min, and then the layers were separated. The organic layer was washed with water (2 x 40 L), and the batch was then distilled under vacuum (~150 torr) to ~24 L with an internal batch temperature of < 65 ^{o}C. MeTHF (69 kg, 80 L) was then charged, and the batch was again distilled under vacuum (~200 torr) to ~24 L with an internal batch temperature of < 65 ^{o}C. Analysis of the mixture by GC assay showed 7.8 wt% heptane present (note: residual *t*-BuOH was not detected by GC). An additional 34 kg (50 L) of MeTHF was charged, and the distillation was repeated under vacuum (~200 torr) to ~22 L with an internal batch temperature of < 65 ^{o}C to bring the batch to < 5 wt% heptane by GC assay (result: 1.9 wt%). The MeTHF solution of **25** was then drained from the reactor into a dry container. The residue in the reactor was rinsed out using 4.3 kg (6.3 L) of MeTHF and combined to the main batch. This afforded 22.2 kg (86%) of a MeTHF solution of **25** that was assayed to contain 50.9 wt% **25** by quantitative ^{1}HNMR spectroscopy (dimethylfumarate as internal standard). Neat **25** can be obtained as a colorless oil by concentration of a sample of this MeTHF solution *in vacuo* if desired; however, this MeTHF solution of **25** was used directly in the subsequent Grignard formation.

(2-(*tert*-butoxy)phenyl)magnesium bromide (23). To a dry 200 L glass-lined reactor was charged 2.54 kg (104 mol) of magnesium turnings. The handhole was then sealed, and the reactor inerted with N_2 using vacuum-purge cycles (3x). To the reactor was then charged 110 kg (128 L) of MeTHF, and the batch was distilled under vacuum (~128 torr) to ~50 L at < 35 ^oC to further dry the reactor. A portion of the MeTHF solution of **25** (3.87 kg, 51.6 wt% **25**, 8.72 mol) was then charged, and the batch was warmed to 60 ^oC. To the mixture was then charged 1.28 kg (1.75 L, 1.75 mol) of 1.0 M DIBAL in heptane, and the batch was held for initiation (initiation took ~5 min as evident by the increase in the internal temperature from 60 ^oC to 76 ^oC within this 5 min timeframe). The remainder of the MeTHF solution of **25** (34.86 kg, 51.6 wt% **25**, 78.51 mol) was then slowly charged while maintaining a gentle reflux (~40 min for complete addition). The batch was then held for an additional 1 h at ≥ 60 ^oC. The batch was then cooled to rt, and a sample of the mixture quenched into MeOH showed full consumption of **25** by HPLC analysis. The solution was transferred to a tared container and titrated against 2-hydroxybenzaldehyde phenylhydrazone.[15] This afforded 75.7 kg (82%) of a dark gold-yellow solution of **23** in MeTHF that was 24 wt% (0.92 M) by titration. The Grignard solution obtained was monitored for up to 1 month with storage at rt by titration and showed no loss in titre over this period.

(*R*)-(2-(*tert*-butoxy)phenyl)(methyl)(phenyl)phosphine oxide (21).

Synthesis from **20**: To a 3-neck round-bottom flask with magnetic stir-bar, N_2 inlet, and thermocouple was charged 2.50 g of **20**-MTBE (82.5 wt%, 3.45 mmol). The flask was sealed with a septa and inerted with N_2 using vacuum-purge cycles (3x). Anhydrous THF (12.5 mL) was then charged, and the solution was cooled to 0 ^oC. MeMgCl solution in THF (2.6M, 3.8 mL, 9.9 mmol) was charged over 10 min while maintaining an internal reaction temperature of < 5 ^oC. The mixture was then allowed to warm to rt and allowed to stir overnight. The reaction was then

cooled to 0 °C and quenched by the addition of 12 mL of 10% aqueous NH_4Cl while maintaining an internal batch temperature of < 10 °C (~10 min). After warming to rt, the layers were separated, and the aqueous layer was extracted 1x with EtOAc (15 mL). The combined organic layers were then concentrated *in vacuo*. The crude residue was then diluted with 18 mL of toluene and washed with 2M (7.5 wt%) NaOH (4x11mL). The organics were then dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to ~ 4 mL. This mixture was then immersed in an oil bath at 50 °C, and 8 mL of heptane was charged over ~5 min. The mixture was then allowed to cool to rt and seeded with a crystal of **21**. The mixture was allowed to stir at rt for 3 h, and then the solid was isolated by filtration, washed with 10 mL of heptane, and dried *in vacuo* at 40 °C to afford 701 mg (70%) of oxide **21** as a white solid. The combined NaOH layers were then washed with 15 mL of toluene (1x). The aqueous layer was then acidified to pH 1 using 5.5 mL of conc. HCl. The mixture was extracted 1x with 15 mL of EtOAc, and the organic layer dried with anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was dissolved in 2.7 mL of warm toluene and then placed in an oil bath at 35 °C. Heptane (1.2 mL) was charged followed by seeding with 13 mg of **19**. The mixture was aged at 35 °C for 1.5 h and then an additional 6.5 mL of heptane was charged over ~30 min. The resultant slurry was cooled to rt over ~30 min and then aged an additional 1 h. The solid was then isolated by filtration, washed with 15 mL of heptane, and dried *in vacuo* at 35 °C to afford 602 mg (54%) of recovered auxiliary **19**.

One-pot synthesis of **21**: To a dry 200 L glass-lined reactor was charged 10.5 kg (95.2 wt%, 22.3 mol) of **18**. The handhole was then sealed, and the reactor inerted with N_2 using vacuum-purge cycles (3x). To the reactor was then charged 43.6 kg (49 L) of THF, and the batch was cooled to 0 – 5 °C. Grignard **23** (30.7 kg, 24.0 wt% in MeTHF, 29.1 mol) was charged while

maintaining an internal batch temperature of < 5 °C (addition took ~40 min). The reaction was then agitated at 0 – 5 °C for 30 min and then warmed to rt over 30 min. The batch was agitated at rt until < 1A% of **18** was observed by HPLC analysis (typically 2 h, samples quenched in THF/10% aq. NH_4Cl). After 2 h at rt, the batch was cooled back to 0 – 5 °C, and MeMgCl (16.7 kg, 20.0 wt% in THF, 44.7 mol) was charged while maintaining an internal batch temperature of < 5 °C (addition took ~20 min). The reaction was then warmed to rt over 30 min and agitated at rt overnight. The batch was then recooled to 0 – 5 °C and carefully quenched by the slow addition of 39.4 kg of 9.5 wt% aq. HCl while maintaining an internal batch temperature of < 25 °C (quench took ~20 min, note significant foaming during the initial charging until excess MeMgCl was depleted). The batch was agitated at rt for ~15 min, and the lower aqueous layer was removed and extracted with MTBE (2 x 22 kg). The combined organic layers were then charged back to the reactor and washed with 20.0 kg of 5 wt% aq. $NaHCO_3$. The lower aqueous layer was removed from the reactor, and the batch was distilled to ~30 L at ~198 torr maintaining an internal batch temperature of < 40 °C. Toluene (35.0 kg) was then charged to the reactor, and the batch was again distilled to ~30 L at ~108 torr maintaining an internal batch temperature of < 60 °C. Toluene (35.0 kg) was then charged to the reactor, and the internal batch temperature was adjusted to 40 – 45 °C. Aqueous NaOH (7.5 wt%, 80.1 kg) was then charged while maintaining the batch temperature at 40 – 45 °C (~20 min). Agitation was continued for an additional ~5 min at 40 – 45 °C, and then agitation was stopped for ~15 min to allow for layer separation. The lower aqueous layer (pH 14) was then removed from the reactor. This aqueous NaOH wash procedure was repeated three more times employing 80.1 kg of 7.5 wt% NaOH (~2 M) for each wash. These four NaOH aqueous layers were then combined and held for recovery of auxiliary **19**. The organic layer containing oxide **21** remaining in the reactor was then distilled

to ~20 L at ~115 torr maintaining an internal batch temperature of < 75 ^{o}C. The batch temperature was then adjusted to 35 – 40 ^{o}C and seeded with 50 g of oxide **21** as a slurry in 500 mL of heptane. The batch was agitated at 35 – 40 ^{o}C for 30 min, and then, 19.0 kg of heptane was charged over 30 min. The batch was then aged an additional 30 min at 35 – 40 ^{o}C and then cooled to 20 – 25 ^{o}C over 30 min. The batch was agitated at 20 – 25 ^{o}C for 1 h, and then 28.0 kg of water was charged over ~15 min. The batch was agitated for 2 h at 20 – 25 ^{o}C and then cooled to 10 – 15 ^{o}C over 30 min. The mixture was aged at 10 – 15 ^{o}C for 4 h, and the solid product was isolated by filtration. Residues in the reactor were removed using the mothor liquor. The wet cake was then washed with water (20 kg) followed by heptane (14 kg). The solid was then dried *in vacuo* at 20 – 25 ^{o}C overnight and then at 40 – 45 ^{o}C overnight to afford 5.60 kg of oxide **21** (85%) in 98.4 wt% purity by quantitative ^{1}HNMR spectroscopy (dimethylfumarate as internal standard) as a white solid. The minor enantiomer was not detected by chiral HPLC analysis (Chiralpak AD-3, isocratic, 90:10 heptane:IPA, 1.2 mL/min), $t_{R\text{-}enantiomer}$ = 6.3 min, $t_{S\text{-}enantiomer}$ = 8.1 min. Mp 116 – 118 ^{o}C; $[\alpha]_D^{22}$ = + 12.4 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (ddd, *J* = 13 Hz, *J* = 7.5 Hz, *J* = 1.9 Hz, 1H), 7.60 – 7.68 (m, 2H), 7.37 – 7.51 (m, 4H), 7.02 – 7.12 (m, 2H), 2.10 (d, *J* = 14 Hz, 3H), 1.26 (s, 9H); P{^{1}H}NMR (202 MHz, $CDCl_3$): δ 30.5 ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 157.5 (d, $J_{C\text{-}P}$ = 3.7 Hz), 135.3 (d, $J_{C\text{-}P}$ = 104 Hz), 134.7 (d, $J_{C\text{-}P}$ = 6.4 Hz), 133.0 (d, $J_{C\text{-}P}$ = 1.8 Hz), 131.0 (d, $J_{C\text{-}P}$ = 2.7 Hz), 130.0 (d, $J_{C\text{-}P}$ = 10.2 Hz), 128.1 (d, $J_{C\text{-}P}$ = 12.1 Hz), 122.6 (d, $J_{C\text{-}P}$ = 101 Hz), 120.2 (d, $J_{C\text{-}P}$ = 11.3 Hz), 115.9 (d, $J_{C\text{-}P}$ = 6.3 Hz), 79.62, 28.53, 15.4 (d, $J_{C\text{-}P}$ = 75.4 Hz); HRMS (DART) *m*/*z* calcd for $C_{17}H_{22}O_2P$ $[M + H]^+$: 289.1357; Found: 289.1352.

Recovery of auxiliary 19: The four combined NaOH layers from the synthesis of **21** were separated into two equal portions (~160 kg each). One of the portions was charged to a 200

L glass-lined reactor. This solution was then washed with 19.0 kg of toluene. The layers were then separated, and the aqueous layer was charged back to the reactor. The batch was cooled to 0 – 5 ^{o}C and 10.4 kg of conc. HCl was slowly charged until a pH of 6 – 10 was reached as measured by a pH probe while maintaining an internal batch temperature of < 35 ^{o}C. Upon reaching this pH range, the conc. HCl addition was stopped, and 19.2 kg of IPAc was added. The remaining conc. HCl charge was then added to achieve a final pH of 1 – 2 for the aqueous layer. The layers were then separated, and the aqueous layer was extracted 1x with 19.2 kg of IPAc. The IPAc layers were combined and held, and the entire procedure outlined above was repeated on the second portion of the original NaOH layer. All of the IPAc layers were then combined and washed with 27.1 kg of 5% aqueous $NaHCO_3$ followed by 27.1 kg of water. The batch was then distilled at an internal batch temperature of < 47 ^{o}C under vacuum until a batch volume of ~32 L was reached. Toluene (44.3 kg) was then added, and the batch was distilled at an internal batch temperature of < 59 ^{o}C under vacuum back to a batch volume of ~32 L. The mixture was then cooled to an internal batch temperature of 30 – 35 ^{o}C, and subsequently seeded with 70 g of **19** as a slurry in 700 mL of heptane. The batch was then aged at 30 – 35 ^{o}C for 1.5 h. Heptane (34.8 kg) was then charged slowly over 1.5 h, and the batch was then cooled to 20 – 25 ^{o}C over 2 h. The resultant slurry was aged overnight, and the solid was isolated by filtration. Residual solids in the reactor were removed using the mothor liquor, and the final wet cake was then washed with 15 L of heptane. The wet cake was then dried *in vacuo* at 40 ^{o}C overnight to afford 7.20 kg (97% recovery) of **19** as an off-white solid in 98.3 wt% purity by quantitative ^{1}HNMR spectroscopic analysis (dimethylfumarate as standard). Mp 140 – 142 ^{o}C; $[\alpha]_D^{22}$ = – 80.2 (*c* 1, MeOH).

(*S*)-(2-*tert*-butoxyphenyl)(methyl)(phenyl)phosphine-*P*-borane (*S*-15). To a dry 50 L hastelloy reactor was charged 4.22 kg (98.4 wt%, 14.4 mol) of oxide **21**. The handhole was then sealed, and the reactor inerted with N_2 using vacuum-purge cycles (3x). To the reactor was then charged MTBE (21 L), 1,1,3,3-tetramethyl disiloxane (3.87 kg, 28.8 mol), and $Ti(O^iPr)_4$ (4.30 kg, 15.1 mol). The reaction mixture was then sparged with N_2 for 30 min. The batch was warmed to 45 – 50 ^oC and agitated at this temperature overnight (complete consumption of oxide **21** was typically observed after ~8 h by HPLC analysis (samples quenched onto solid sulfur), and the reaction turned a dark black-purple color upon completion). The batch was then cooled to 20 – 25 ^oC, and BH_3•DMS (1.24 kg, 15.1 mol) was charged while maintaining an internal batch temperature of < 35 ^oC (~10 min). The resultant mixture was agitated for an additional 1 h at rt, and then, 0.43 kg of *i*-PrOH was charged. Heptane (21 L) was then added, and the batch was distilled under vacuum with an internal reaction temperature of < 50 ^oC to ~20 L. Additional heptane (21 L) was then added, and the distillation was repeated to bring the batch volume to ~15 L. The batch temperature was then adjusted to 20 – 25 ^oC over 30 min, and the resultant slurry was agitated at rt for at least 2 h. The solid product was isolated by filtration. Residual solids in the reactor were removed using the mothor liquor, and the final wet cake was washed with 8 L of heptane. The wet cake was then dried *in vacuo* at 35 ^oC overnight to afford 3.86 kg (91%) of (*S*)-**15** as an off-white solid in 97.1 wt% purity by quantitative ^{1}HNMR spectroscopic analysis (dimethylfumarate as standard). Enantiopurity was >99.0% ee by chiral HPLC analysis (Chiralcel OD-H, isocratic 99:1 heptane:EtOH, 1.0 mL/min)), $t_{R\text{-}enantiomer}$ = 6.3 min, $t_{S\text{-}enantiomer}$ = 6.9 min. Spectral data was in complete agreement with that reported in the literature.[8a] Mp 85 – 87 ^oC (lit.[8a] mp 90 – 92 ^oC); $[\alpha]_D^{22}$ = + 21.2 (*c* 0.74, $CHCl_3$), lit.[8a] $[\alpha]_D^{25}$ = – 20.1 (*c* 1.0, $CHCl_3$, *R*-isomer).

(*R*)-(2-*tert*-butoxyphenyl)(methyl)(phenyl)phosphine-*P*-borane (*R*-15). To a 1 L jacketed reactor was charged 50.9 g (171 mmol) of oxide **21** and the reactor was sealed and inerted with N_2 using vacuum-purge cycles (3x). Toluene (400 mL) and trimethylamine (35.8 mL, 257 mmol) were then added, and the mixture was sparged with N_2 for 15 min. Trichlorosilane (25.9 mL, 34.8 g, 257 mmol) was then added over 5 min resulting in the formation of a white precipitate and an increase in the reaction temperature from rt to 40 ^{o}C. The mixture was then agitated at 40 ^{o}C for 17 h with monitoring by ^{31}PNMR spectroscopy or by HPLC (samples quenched onto solid sulfur with analysis of the P-sulfide, 99% conv. obtained after 17 h). The batch was then cooled to 0 ^{o}C and carefully quenched by the addition of 300 mL of 30% degassed (Ar sparge) aqueous NaOH while maintaining an internal batch temperature of < 45 ^{o}C (Caution: gas evolution, exothermic, quench took ~20 min). The resultant mixture was then allowed to agitate at rt for 1 h. The bottom aqueous layer was then removed, and the organic layer was then washed with 250 mL of degassed (Ar sparge) water. The batch was then distilled under vacuum to ~100 mL while maintaining an internal reaction temperature of < 40 ^{o}C. Additional degassed (Ar sparge) toluene (300 mL) was charged, and the distillation was repeated to bring the batch to ~100 mL volume. A sample was then analyzed by GC to verify that residual TEA was not present (note: TEA must be completely removed as TEA•BH_3 cannot be removed from the final product). BH_3•DMS (26.0 mL, 20.8 g, 260 mmol) was then charged over 5 min, and the batch was agitated for 1 h. IPA (30 mL) was then added, and the mixture was distilled under vacuum to ~50 mL with an internal batch temperature of < 40 ^{o}C. Heptane (400 mL) was then slowly added, and a slurry formed. The batch was distilled under vacuum at < 40 ^{o}C to ~100 mL, followed by addition of 200 mL of heptane. The batch was then agitated at rt for 1 h, and the solid product was collected by filtration. Solid residues in the reactor were removed using the

mothor liquor, and the wet cake was then washed with 100 mL of heptane. The wet cake was then dried *in vacuo* at 35 °C overnight to provide 39.0 g (74%) of (*R*)-**15** as an off-white solid in 92.9 wt% purity by quantitative ^{1}HNMR spectroscopic analysis (dimethylfumarate as standard). Enantiopurity was 98.8:1.2 er by chiral HPLC analysis (Chiralcel OD-H, isocratic 99:1 heptane:EtOH, 1.0 mL/min), $t_{R\text{-}enantiomer}$ = 6.3 min, $t_{S\text{-}enantiomer}$ = 6.9 min.

Enrichment of 15: The (*R*)-**15** isolated above (39.0 g, 98.8:1.2 er) was slurried in 780 mL of MeOH for 2 h. The mixture was then filtered through a pad of celite and washed with an additional 80 mL of MeOH. The filtrate was then concentrated *in vacuo* and then chased with 200 mL of heptane to afford a solid that was then dried *in vacuo* at 45 °C overnight to afford 37.3 g (96% recovery) of (*R*)-**15** in 99.5:0.5 er and 93.0 wt% purity by chiral HPLC and quantitative ^{1}HNMR spectroscopy, respectively.

(*S*, *S*)-1,2-Bis[(2-*tert*-butoxyphenyl)(methyl)(phenyl)phosphino-*P*-borane]ethane (16). To a dry 50 L hastelloy reactor was charged 4.02 kg (93.2 wt%, 13.1 mol) of (*S*)-**15**. The handhole was then sealed, and the reactor inerted with N_2 using vacuum-purge cycles (3x). To the reactor was then charged THF (26 L), and the resultant solution was sparged with N_2 for 30 min. The batch was then cooled to – 45 °C, and 2.3 M *n*-hexyl lithium in hexanes (30 wt%, 4.22 kg, 13.8 mol) was then charged while maintaining an internal batch temperature of < – 38 °C (~30 min). The batch was then aged at – 45 °C for 30 min. The batch was then cooled to – 55 °C, and $CuCl_2$ was charged in 4 portions (485 g per charge, 14.4 mol total) using an Ar sweep to keep the reactor inerted while maintaining an internal batch temperature of < – 35 °C (addition of all 4 charges took ~40 min). The batch was then agitated and slowly warmed to – 25 °C over 30 min – 1 h. To the reaction was then charged glacial acetic acid (390 g, 6.6 mol), and the batch was warmed to rt. The batch was then distilled under vacuum to ~12 L with an internal batch

temperature of < 30 °C. CH_2Cl_2 (26 L) was then charged and the distillation was repeated. Additional CH_2Cl_2 (38 L) was then charged, the batch temperature was adjusted to ~20 °C, and the batch was filtered through a pad of celite to remove precipitated Cu-salts. The celite pad was then washed with 6 L of CH_2Cl_2, and the combined filtrates were charged back to the reactor. Water (20 L), 10% Rochelle's salt solution (16 L), and 29 wt% NH_4OH solution (6.8 kg) was then charged. The mixture was agitated well for 2 h, and then the batch was allowed to stand without agitation overnight. The lower organic layer was then drained from the reactor, followed by removal of the upper blue aqueous layer from the reactor (note that a small emulsion layer is left with the organic layer). The organic layer was then charged back to the reactor and washed with 5% $NaHCO_3$ (1x20L) followed by water (2x20L). The organic layer was then charged back to the reactor and the distilled under vacuum to ~12 L with an internal batch temperature of < 40 °C. IPAc (26 L) was then charged, and the batch was distilled under vacuum to ~15 L with an internal batch temperature of < 45 °C. The internal batch temperature was then adjusted to 20 – 25 °C, and the resultant slurry was aged at rt for 2 h. The solid product was then isolated by filtration. Residual solids in the reactor were removed using the mothor liquor, and the wet cake was then washed with 6 L of IPAc followed by 6 L of heptane. The wet cake was then dried *in vacuo* overnight at 35 °C to provide 2.51 kg (63%) of **16** as an off-white solid in 94.1 wt% purity by quantitative ^{1}HNMR spectroscopic analysis (dimethylfumarate as standard). Spectral data was in agreement with that published in the literature.[3] The enantiopurity was >99.5% ee as determined by chiral HPLC analysis (Chiralpak AD-H, 90/10 heptane/IPA, 1.0 mL/min), $t_{R,R\text{-enantiomer}}$ = 5.0 min, $t_{S,S\text{-enantiomer}}$ = 5.7 min. Mp > 200 °C (dec.); $[\alpha]_D^{23}$ = – 82.0 (*c* 0.71, $CHCl_3$), lit.[3] $[\alpha]_D^{25}$ = + 78.2 (*c* 1.0, $CHCl_3$, *R,R*-isomer).

(*S*,*S*)-1,2-Bis[(2-*tert*-butoxyphenyl)(methyl)(phenyl)phosphino]ethane (17). The free phosphine was prepared according to the procedure of Stephan.[8a] To a 500 mL 3-neck round-bottom flask with magnetic stir-bar and reflux condensor was charged 25.0 g (94.6 wt%, 41.5 mmol) of bis(BH_3) adduct **16**. The remaining flask necks were then sealed with septa, and the mixture inerted with N_2 using vacuum-purge cycles (3x). Diethylamine (250 mL) was then added by canula, and the resultant mixture was allowed to stir in an oil bath at 65 ^oC until the reaction was judged complete by ^{31}PNMR spectroscopic analysis (~3 h). Volatile materials were then removed *in vacuo*, and the crude residue was purified by flash chromatography on 235 g of silica gel using degassed (Ar sparged) 10% EtOAc/hexanes and Ar pressure to elute the column. After concentration of the combined fractions *in vacuo*, a thick foamy paste was obtained that was further dried overnight under high vacuum (~1 torr) to afford 23.9 g of **17** (95%) in 89.5 wt% purity by quantitative ^{1}HNMR spectroscopic analysis (dimethylfumarate as standard, $CDCl_3$) as a thick waxy-glass.

(*S*,*S*)-ethane-1,2-diylbis[(2-*tert*-butoxyphenyl)(methyl)(phenyl)phosphonium] bis(tetrafluoroborate) (17•2HBF_4). To a dry 50 L hastelloy reactor was charged 2.25 kg (92.2 wt%, 3.64 mol) of **16** and 1.63 kg (14.6 mol) of DABCO. The handhole was then sealed, and the reactor inerted with N_2 using vacuum-purge cycles (3x). To the reactor was then charged MeTHF (10 L), and the resultant slurry was sparged with N_2 for 30 min. The batch was then warmed to 55 – 60 ^oC and agitated at this temperature for 1 h to reach full conversion (monitored by ^{31}PNMR spectroscopy). The batch was then cooled to rt and 15 L of degassed (Ar sparge) 2M HCl was charged over 30 min maintaining an internal batch temperature of < 30 ^oC. The batch was agitated an additional 10 min, and then the lower aqueous layer was removed. The batch was then distilled under vacuum to ~4 – 5 L with an internal batch temperature of < 35 ^oC. Degassed

(Ar sparge) heptane (12 L) was then charged, and the batch was again distilled as before to 4 – 5 L. Degassed (Ar sparge) CH_2Cl_2 (12 L) was then charged, and a sample of the mixture was analyzed by GC (residual MeTHF should be < 2wt% and the CH_2Cl_2/heptane ratio should be ≥89/11 wt/wt). Aqueous HBF_4 (50 wt%, 3.19 kg, 18.2 mol) was then charged, and the batch was agitated an additional 10 min. The lower aqueous layer was then removed from the reactor (*Caution: may contain conc. HF*). To the batch was then charged 2.5 L of heptane followed by 20 g of product seeds. Additional heptane (22.5 L) was then slowly charged over 1 h at rt to provide a slurry. The batch was then cooled to 0 – 5 ^{o}C over 30 min, and then aged at this temperature for 2 h. The solid product was isolated by filtration, and the solid residues in the reactor were removed using the mothor liquor. The wet cake was then washed with 3 L of 50/50 IPA/heptane followed by 4 L of heptane. The reactor was then rinsed with IPA, and the wet cake was charged back to the reactor. IPA (11 L) was then charged, and the slurry was agitated at 40 ^{o}C overnight. Heptane (12 L) was then charged over 30 min, and the batch was cooled to rt over ~30 min. The batch was aged an additional 1 h at rt, and the solid product was isolated by filtration and washed with the mothor liquor followed by 3 L of 50/50 IPA/heptane and 6 L of heptane. The wet cake was then dried *in vacuo* at 25 ^{o}C overnight to afford 2.47 kg (86%) of **17**•2HBF_4 as a white solid in 91.7 wt% purity by quantitative ^{1}HNMR spectroscopic analysis (dimethylfumarate as standard, $CDCl_3$). The amount of BF_4 present was quantitated at 2.19 equiv by ^{19}FNMR spectroscopy using $PhCF_3$ as the analytical standard in *d*6-DMSO. Mp 145 – 152 ^{o}C (decomp.); $[\alpha]_D^{24}$ = – 12.8 (*c* 1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (dm, $J_{P\text{-}H}$ = 550 Hz, 2H), 7.83 – 8.02 (m, 6H), 7.70 (p, *J* = 7.7 Hz, 4H), 7.60 (t, *J* = 7.2 Hz, 4H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.19 – 7.25 (m, 2H), 3.20 – 3.39 (m, 2H), 3.04 – 3.20 (m, 2H), 1.43 (s, 18H); P{^{1}H}NMR (202 MHz, $CDCl_3$): δ 1.9 ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 159.6, 137.4,

135.1, 134.7 (app. t, $J_{C\text{-}P}$ = 4.2 Hz), 133.2 (app. t, $J_{C\text{-}P}$ = 5.9 Hz), 130.2 (app. t, $J_{C\text{-}P}$ = 6.9 Hz), 122.7 (app. t, $J_{C\text{-}P}$ = 6.6 Hz), 116.9, 114.9 (m), 104.1 (m), 83.57, 28.45, 13.84 (m); HRMS(DART) *m*/*z* calcd for $C_{34}H_{41}O_2P_2$ [free base, M + H]$^+$: 543.2582; Found: 543.2578.

Recrystallization of 17•2HBF$_4$ from CH$_2$Cl$_2$/IPA/heptane: To a 20 L jacketed reactor was charged 1.0 kg (91.7 wt%, 1.28 mol) of **17•**2HBF$_4$. The reactor was sealed and inerted with N_2 using vacuum-purge cycles (3x). CH_2Cl_2 (2.5 L) was charged, and the batch was warmed to ~30 ^{o}C until a homogeneous solution was obtained (~15 min). The batch was then cooled to rt, and 5 L of IPA was added. Product seeds (10 g) were added, and the batch was aged at ~20 ^{o}C for 30 min. Heptane (10 L) was then charged slowly over 40 min. The batch was then cooled to 15 ^{o}C and held at this temperature for ~1 h. The solid product was isolated by filtration and then washed successively with 2 L of water, 1.5 L of 50/50 IPA/heptane, and 2 L of heptane. The wet cake was then dried *in vacuo* overnight at 25 ^{o}C to afford 919 g (86% recovery) of **17•**2HBF$_4$ as a white solid in 93.1 wt% purity by quantitative ^{1}HNMR spectroscopic analysis (dimethylfumarate as standard, $CDCl_3$). The amount of BF_4 present was quantitated at 2.11 equiv by ^{19}FNMR spectroscopy using $PhCF_3$ as the analytical standard in *d*6-DMSO. Crystals suitable for single-crystal Xray analysis were obtained.

Asymmetric Hydrogenation of enol acetate 9. To a 1 L Schlenk flask was charged 2.40 g (6.42 mmol) of Rh(nbd)$_2$BF$_4$ and 5.69 g (corrected for purity, 7.92 mmol) of **17•**2HBF$_4$, and the flask was sealed with a septum and inerted with N_2 using vacuum-purge cycles (3x). Degassed (Ar sparge) THF (500 mL) was charged followed by 14.1 mL (14.1 mmol) of a 1.0 M solution of KO^{t}Bu in THF, and the resultant mixture was stirred at ambient temperature for 1 h. To a 10 L autoclave was charged 1.00 kg (6.49 mol) of 1-(trifluoromethyl) vinyl acetate

followed by 4.5 L of THF, and the solution was cooled to 10 ^{o}C and degassed by N_2 sparge for 30 min. The catalyst solution prepared above was then charged to the autoclave using N_2 pressure, and the batch temperature was adjusted to 20 ^{o}C. The autoclave was then pressurized to 50 psi using N_2 followed by venting. After performing this pressure/vent cycle two more times using N_2, the process was repeated 3x using H_2 and pressurizing the autoclave to 15 psi. The autoclave was then pressurized to 15 psi using H_2 and was agitated at 500 rpm and 20 ^{o}C for 6 h. The autoclave was then vented followed by purging with N_2(3x). The THF solution of (*R*)-**10** was then drained from the reactor, and the residue transferred using an additional 600 mL of THF to afford 6.08 kg (quantitative) of a 16.5 wt% solution of (*R*)-**10** in THF as determined by quantitative ^{19}FNMR spectroscopic analysis ($PhCF_3$ as analytical standard, $CDCl_3$). This solution can be used crude or distilled pot-to-pot to remove the catalyst. The enantiomeric ratio was determined by chiral GC analysis (Supelco β-dex 225 column: 30 m x 0.25 mm x 0.25 μm, 70 ^{o}C hold for 7.5 min then 50 ^{o}C/min to 150 ^{o}C) of alcohol **5** prepared by hydrolysis of **10** by treating an aliquot of the reaction mixture with 1/3 (v/v) 2 M aq. NaOH/MeOH, $t_{R\text{-}isomer}$ = 4.8 min, $t_{S\text{-}isomer}$ = 5.4 min; 98.6% ee.

(*R*)-5-(methylsulfonyl)-2-((1,1,1-trifluoropropan-2-yl)oxy)benzoic acid (*ent*-23). To a dry 100 mL reactor with mechanical stirring was charged 12.3 g (11.2 mmol) of a 14.3 wt% solution of **10** in THF under N_2, and the solution was cooled to 0 ^{o}C. *n*-BuLi (2.4M in hexanes, 8.9 mL, 22 mmol) was then charged over ~15 min while maintaining the internal reaction temperature below 15 ^{o}C. The resultant mixture was then stirred at 0 – 10 ^{o}C for 15 min, and then a solution of 1.89 g (8.64 mmol) of aryl fluoride **24** in 6 mL of NMP was charged. The batch was warmed to 55 ^{o}C and aged for 1 h to consume the aryl fluoride (HPLC analysis). The batch was then concentrated to ~6 mL and 28 mL of water was then charged. The mixture was

warmed to 55 °C and 1.1 mL (30.1 mmol) of formic acid was then charged (pH ~4). The mixture was then seeded with ~20 mg of *ent*-**23** and cooled to rt over ~1 h. The resultant slurry was then aged at rt for 2 h, and the solid product was isolated by filtration and washed with water (3x10mL). The solid was then dried overnight *in vacuo* at 45 °C to afford 2.02 g (70%) of *ent*-**23** as a white solid in 93.3 wt% purity by quantitative ^{1}HNMR spectroscopic analysis (dimethylfumarate as standard, *d*6-DMSO). Enantiopurity was determined by chiral HPLC analysis (Chiralpak AD-3, 82/18 heptane/0.5% AcOH in IPA, 1.5 mL/min), $t_{\text{S-enantiomer}}$ = 4.3 min, $t_{\text{R-enantiomer}}$ = 5.6 min, 98.6% ee. Spectral data was consistent with that reported in the literature.[2a] Mp 170 – 173 °C. $[\alpha]_D^{22}$ = – 14.4 (*c* 1.08, MeOH), lit.[2a] $[\alpha]_D^{20}$ = + 16.9 (*c* 1.01, MeOH, *S*-isomer).

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of the compounds and X-ray crystallographic data for **17**•2HBF$_4$ are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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