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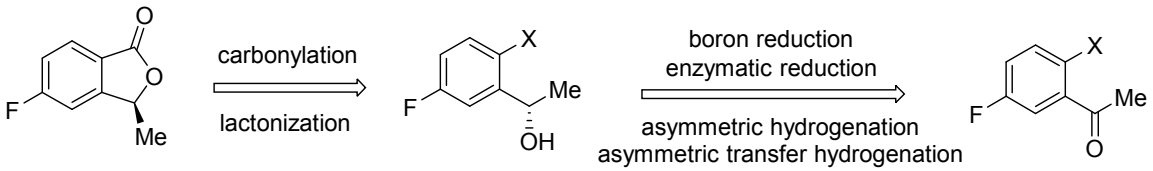
TOC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Abstract

Synthesis of (S)-5-fluoro-3-methylisobenzofuran-1(3*H*)-one (**6**), a key intermediate to lorlatinib, is described. A few synthetic methodologies, i. e. boron reduction, enzymatic reduction, asymmetric hydrogenation, and asymmetric transfer hydrogenation, were evaluated for the chiral reduction of the substituted acetophenone intermediate (**8**). A manufacturing process based on the asymmetric transfer hydrogenation, was developed. This process was successfully scaled up to prepare 400 kg of **6**.

Keywords

Asymmetric Transfer Hydrogenation, Asymmetric Hydrogenation, Enzymatic Reduction, Boron Reduction, Substituted Acetophenone, Lorlatinib

1. Introduction

Lorlatinib (**1**) (Figure 1) is an investigational medicine that inhibits the anaplastic lymphoma kinase (ALK) and ROS1 proto-oncogene.[1a, b] Due to tumor complexity and development of resistance to treatment, disease progression is a challenge in patients with ALK-positive metastatic non-small cell lung cancer (NSCLC). A common site for progression in metastatic NSCLC is in the brain, where the current standard of care and recent experimental agents have only limited effectiveness. Lorlatinib was specifically designed to inhibit tumor mutations that drive resistance to other ALK inhibitors and to penetrate the blood-brain barrier. Lorlatinib is being studied in ongoing clinical trials.

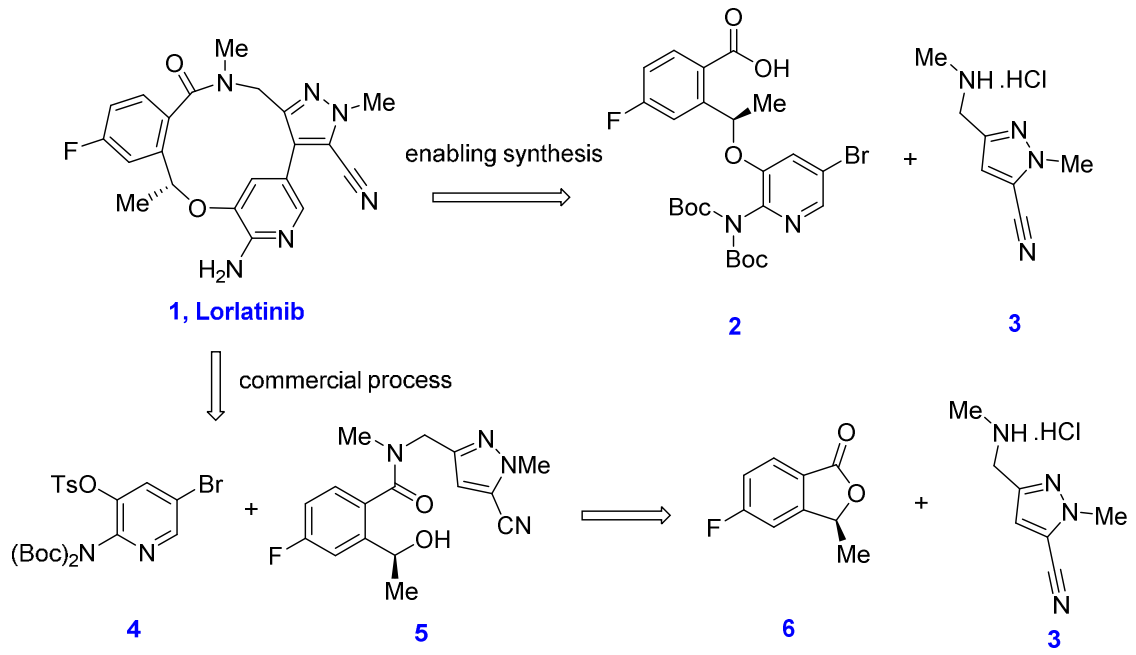


Figure 1. Retrosynthesis of Lorlatinib (1)

In the enabling synthesis of lorlatinib,[2a] **1** was prepared through an amide coupling between carboxylic acid **2**, and the pryazole methyl amine **3**, followed by a palladium catalyzed macrocyclization (Figure 1). While this route was amenable to provide the clinical supply at kilogram scale, synthesis of **2** was lengthy and linear. A more

convergent synthesis [2b] was developed for the commercial manufacturing, in which the key transformation is to prepare the macrocyclization precursor through a sequential *in-situ* tosyl transfer between **4** and **5,** and a subsequent S_N2 substitution. The intermediate **5** can be obtained through an aluminum chloride facilitated lactone opening of **6** with **3**.[3] Control strategy for the chiral purity of lorlatinib is to control the undesired enantiomer at NMT 0.15% in API. [4a, b] It is found that the enantiomeric purity of lorlatinib is solely depended on the enantiomeric purity of **6**, as the proposed commercial manufacturing route has no impact on the API chiral purity. Thus, synthesis of (S)-5-fluoro-3-methylisobenzofuran-1(3*H*)-one (compound **6**) with high optical purity, has become an important objective for the commercial process development. This paper summarizes the evolution of the synthesis of this key intermediate, focusing on the chiral reduction of the substituted acetophenone to make the chiral benzyl alcohol precursor to lactone **6**.

2. Results and Discussion

It is envisioned that the lactone **6** can be accessed via either a carbonylation reaction (via **7a-c**) or a lactonization reaction (via **7d-h**), with a variety of possible functional groups at the *para* position to the fluoro group (Figure 2). The flexibility at this step allows us to assess different chiral reduction methods for the substituted acetophenone compound **8**.

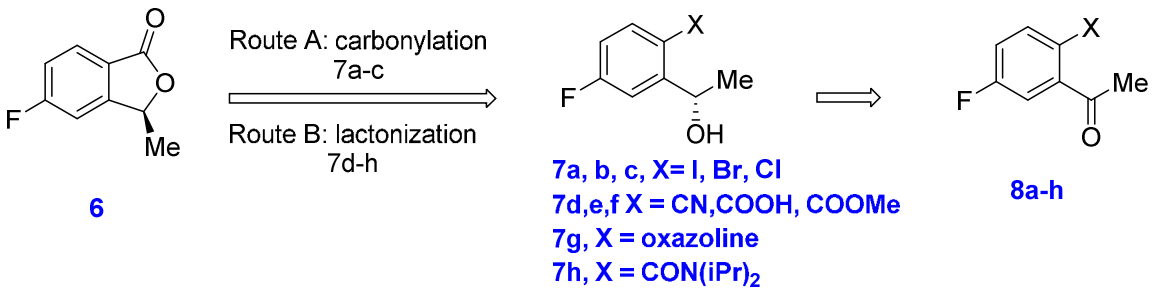


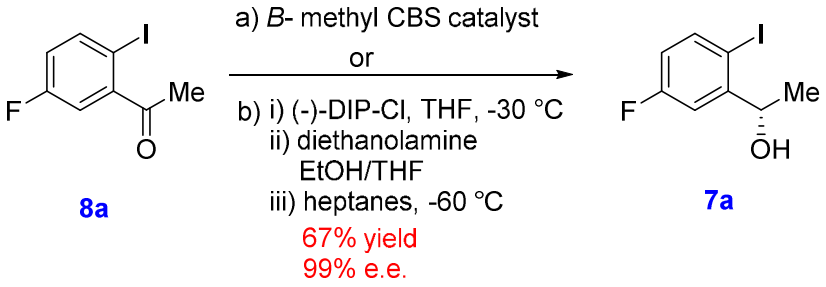
Figure 2. Proposed Synthesis of 6

2.1. Preparation of 6 via Carbonylation

2.1.1 Boron Reduction of 1-(5-fluoro-2-iodophenyl)ethan-1-one (8a)

In the enabling synthesis, intermediate **2** was synthesized from the fluoroiodobenzyl alcohol **7a.** As the acetophenone compound **8a** is commercially available and the asymmetric reduction of prochiral ketones by boron reducing agent is well documented in the literature, [5] reduction of **8a** with chiral boron reagent was first studied (Scheme 1). CBS catalyst [6] was successfully used at lab scale and provided **7a** with good yield and e.e. However, use of CBS catalyst at industrial scale was not cost efficient. (-)-DIP-Cl (B-chlorodiisopinocampheylborane, Figure 3) [7a, b] was then evaluated to be used on scale.

Scheme 1. Reduction of 8a Using Chiral Boron Reagents



The reduction of **8a** using (-)-DIP-Cl gave excellent enantioselectivity (>97% ee). [8] However, the isolation of the product **7a** posed great challenge on scale, in order to avoid purification by chromatography. First, diethanolamine is required to break the borate intermediate in the reaction mixture. A complete break of the borate is important as any incomplete cleavage will impact the downstream reaction. The resulting diethanolamine borate is removed by filtration, but the filtration of the side product is extremely slow, even when the filter aid is used to help the filtration. Second, a recrystallization is needed to purge the α-pinene from the crude product. As compound **7a** is a low melting point

solid, this recrystallization has to be carried out under cryogenic conditions (-60 °C in heptanes) due to the low purity of the crude mixture. This resulted in significant yield loss (yield 67%) although the reaction always proceeded to complete conversion. During production, it was also found that the diethanolamine borate side product is a potential sensitizer. These challenges prompted us to find an alternative reduction condition for this transformation.

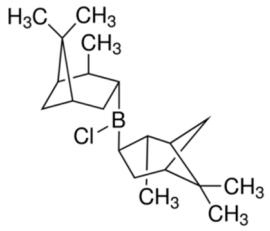


Figure 3. (-)-DIP-Cl

2.1.2 Enzymatic Reduction of 8a

With the challenge associated with the DIP-Cl reduction of **8a**, we shifted our focus to enzymatic reduction (Scheme 2). Over the past decade, bioreduction of substituted acetophenones has been well developed, many ketoreductase enzymes are known with high activity and selectivity on the substituted acetophenone substrates. [9, 10] A quick screening of in-house and commercially available enzyme libraries identified multiple enzyme hits with high selectivity for either isomer of alcohol (see ESI). The desired S-alcohol **7a** was obtained in high chemical purity (>98%) and high enantiomeric purity (>99 % ee) using 2,4-diketo gluconic acid (DkgA) enzyme and using NADPH as a cofactor. Cofactor recycling was performed using isopropanol as a co-substrate and *Lactobacillus Brevis* alcohol dehydrogenase as a recycling enzyme. Further study of the reaction parameters identified the optimal conditions for this transformation as follows:

enzyme/substrate 0.06 – 0.07 w/w, pH 6.5 – 7.0, temperature 35 – 40 °C, and isopropanol/substrate 1.0 – 1.2 w/w (Table 1).

Scheme 2. Enzymatic Ketone Reduction of 8a

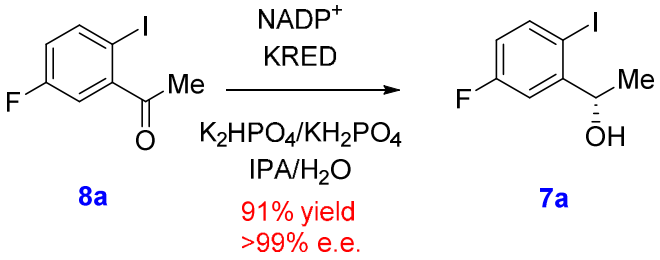


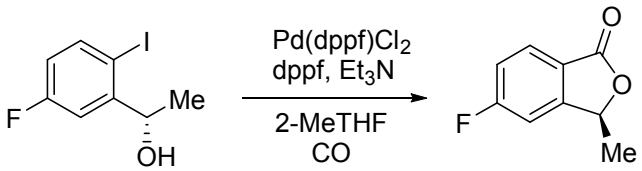
Table 1. Study on Process Parameters of Enzymatic Reduction of 8a

Reaction Parameters	Ranges Evaluated	Optimal Conditions
Enzyme/ Substrate	0.05 – 0.10 w/w	0.06 – 0.07 w/w
pH	6.5 – 8.0	6.5 – 7.0
Temperature (°C)	25 - 45	35 - 40
Isopropanol/ Substrate	0.5 – 4.0 w/w	1.0 – 1.2 w/w

The identified optimal conditions were successfully implemented on scale up to 350 kg. IPA is used here as hydrogen donor and acetone is the side product. It was found that the reaction can reach >99% conversion without the need to remove acetone from the system. Compared to the boron reduction, the product isolation in the enzymatic process is trivial. The crude product precipitates out from the IPA/water upon the completion of the reaction, and it is easily purified by a recrystallization from MTBE/*n*-heptane. No cryogenic conditions were required as there was no interference from the borate/ pinene side product. Instead, compound **7a** was isolated at ambient temperature at high yield (91%) and nearly 100% e.e. The enzymatic process is a significant upgrade on the boron reduction process, in terms of ease to scale up and the simple operation.

2.1.3 Carbonylation Reaction

Scheme 3 Preparation of 6 through Carbonylation Reaction



7a **6**

Compound **7a** is then converted to **6** through a CO insertion reaction. Palladium catalyzed carobonylation of haloarene is a very powerful method to synthesize carbonyl derivatives and is well documented in the literature. [11a, b] It was found that the carbonylation/lactone formation proceeded smoothly when $Pd(dppf)Cl_2$ was used as catalyst, under 50 psi CO and at 80 °C. Pre-formed catalyst with $Pd(OAc)_2$ and dppf is equally effective towards this transformation. It was found that the reaction rate was too fast at the high catalyst loading and high reaction temperature. The fast reaction resulted in hydrogen starvation due to fast hydrogen uptake. It was also challenging to control the exotherm when the reaction was too fast. A more controllable process can be achieved by lowering the catalyst charge. The reaction can reach complete conversion in 6 – 7 hours with as low as 0.05 mol% catalyst. Lowering the reaction temperature to 60 °C and below significantly slows down the reaction and incomplete conversion was observed after overnight. It was also found that addition of small quantity of dppf (0.025 mol%) is beneficial to prevent formation of palladium black.

Surprisingly, it was found that the selection of solvent has an impact on the product chiral purity (see ESI). Chirality erosion of the product was observed in alcoholic solvents, with up to 10% (R)-isomer formed in methanol. No stereochemistry inversion was detected in the non- alcohol solvents, i. e. THF and 2-MeTHF. It is believed that this racemization is not due to the deprotonation by triethylamine as the pKa of the benzylic proton is around

30. Instead, the formation of the (R)-isomer is resulted from a Pd mediated β-hydride elimination/ reduction. Kinetics study indicated that the reaction was initially faster in MeOH and then slowed down significantly, while the reaction in THF/2-MeTHF was faster after the initial induction period. It is speculated that the kinetics might play a role in the stereochemistry outcome as the slow kinetics of major reaction pathway allows the side reaction to compete. Although the undesired isomer can be readily purged by crystallization, it was decided to avoid using of alcoholic solvents. 2-MeTHF was chosen as the reaction solvent as it eases the work-up due to its immiscibility with water.

The enzymatic reduction/carbonylation process was successfully implemented on scale and up to 1070 kg of desired **6** was manufactured, with high yield (90%) and high purity (>99.8% HPLC and >99.9% e.e.).

2.2 Preparation of 6 via Lactonization

While the carbonylation approach provided compound **6** in required quantity and quality, there are a few issues associated with this process that are not ideal in the long run. First, it is not cost efficient. Compound **8a,** though commercially available, is synthesized in 4-6 steps from commodity chemicals, and the room for further cost reduction is limited. Replacement of **8a** with its bromo- or chloro- analog **8b/8c** is feasible but still not optimal. In addition, the cost of enzyme and the co-factor in the bioreduction step also contributes to the overall cost for **6**. Second, use of the poisonous CO gas in the carbonylation step is a concern on scale as special handling is required for worker safety, which limits the supplier pool. Thus it is desirable to develop an alternative synthetic strategy during commercial process development. The target would be using a cheap

commercially available starting material, with the carbonyl group already in place. The acetyl group is then installed through a directed ortho-metallation and the subsequent chiral reduction/ cyclization furnishes the synthesis of **6**. In first approach, we replaced halogens ortho to the acyl group with nitrile (**8d**), carboxylic acid (**8e**) and carboxylic acid methyl ester (**8f**), with a goal to perform enzymatic reduction to obtain corresponding alcohols. However, enzymatic ketone reduction of these substrates turned out to be problematic, and was not clean from process perspective, and was not pursued further. In second approach we focused our attention on **8g** and **8h**, these were synthesized starting with 4-fluorobenzoyl chloride as a suitable starting material as it is readily available and widely used in the polymer, pesticide, and dye industry. [12a, b] Various directing groups had been used in the literature [13a, b, c] for ortho-metallation. A proper choice of the directing group is important not only for the selectivity of the metalation but also for the downstream transformations. We chose to work on two of the directing groups, 2-oxazoline and N,N-diisopropyl amide.

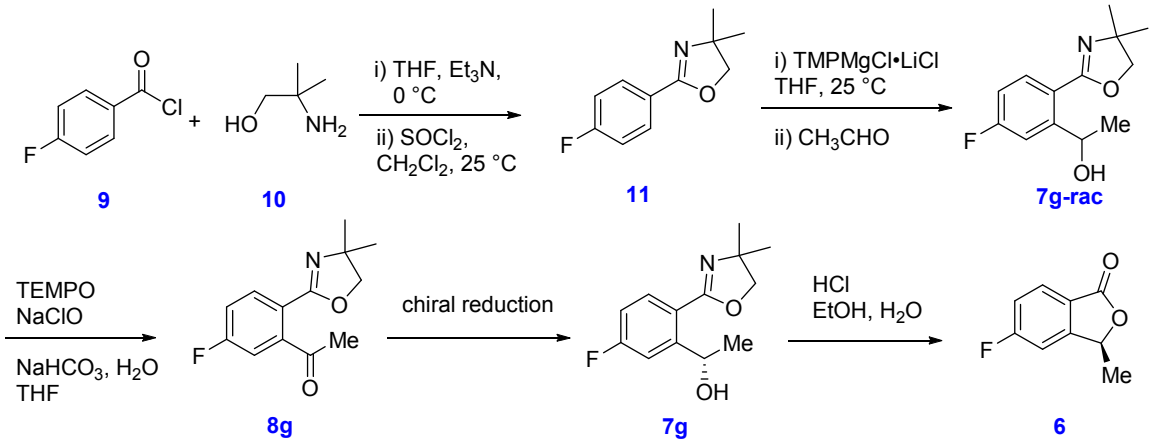
2.2.1 2-Oxazoline as Directing Group

Research from Clososki, et al. [14] suggested that the 2-oxazoline group has powerful ortho-directing effect and 4-halophenyl-2-oxazoline can be metalated selectively at the ortho- position. In addition, the mixed Li-Mg amide TMPMgCl•LiCl is highly reactive and the magnesiation can be achieved at ambient temperature. [15]

To this end, compound **8g** is prepared by treating the fluorobenzoyl chloride **9** with 2-amino-2-methylpropanol (**10**) followed by a $SOCl_2$ mediated cyclization (Scheme 4). Ortho-metallation was successful when **11** was treated with TMPMgCl•LiCl in THF.

The anion generated from the ortho-magnesiation was trapped with acetaldehyde and it provided **7g** as a racemic alcohol, and the subsequent oxidation afforded the acetophenone compound **8g**.

Scheme 4 Attempt to Synthesize 6 via Oxazoline Intermediate



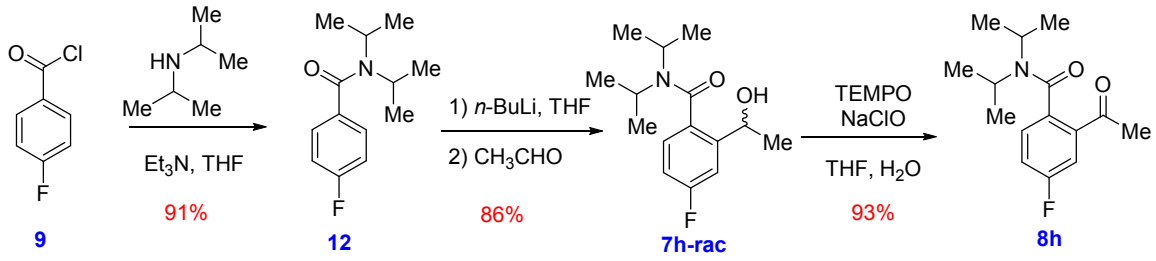
While some success was met in this synthesis, this approach was not further pursued due to a few limitations. First, incomplete magnesiation was observed and no improvement was realized at different temperature, concentration, and stoichiometry. Second, the oxidation of the benzyl alcohol was problematic. Low yield was obtained under a variety of conditions. Third, all of the intermediates are either oil or low melting point solid and that is foreseen as a problem for manufacturing. On the contrast, better results were obtained when the diisopropyl amide was used as the directing group (*vide infra*).

2.2.2 Chiral Reduction of Diisopropylamide Intermediate 8h

An alternative approach is to direct the ortho- metalation using diisopropylamide group. Beak et al. first demonstrated that the N,N-diisopropylbenzamide could be ortho-lithiated using n-BuLi/TMEDA. [16] Volk et al. then developed a process that simply used *n*-BuLi only to lithiate the N,N-diisopropyl 4-fluorobenzamide. [17] To this end, compound **8h** was

synthesized following literature procedure [17] staring from the 4-fluorobenzoyl chloride (Scheme 5).

Scheme 5 Preparation of 8h



N,N-diisopropylbenzamide **12** was synthesized by coupling of the fluorobenzoyl chloride with diisopropylamine in the presence of trimethylamine. Ortho- lithiation of the benzamide was carried out with *n*-BuLi in THF. It was found that the reaction temperature has impact on the regio- selectivity. Control of the temperature to lower than -70 °C is critical to minimize the *meta*-lithiation. Local hot spot due to fast addition of *n*-butyllithium could result in formation of up to 20% *meta*-isomer. To our happiness it was found that a reverse addition of the amide to *n*-butyllithium can suppress the regioisomer formation.

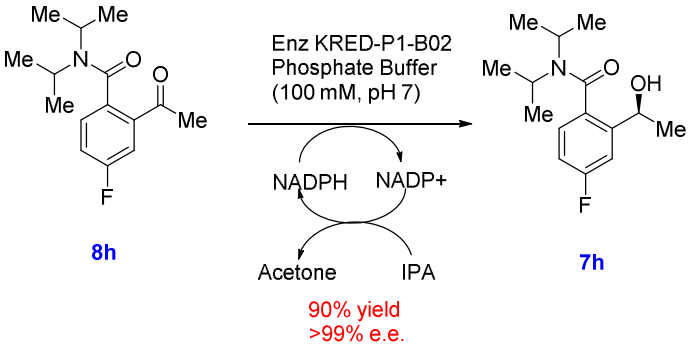
A one-step direct synthesis of **8h** from **12** was attempted. However, quenching the lithiated anion with acetic anhydride or acetyl chloride resulted in a complicated mixture. Analysis of the impurities suggested that the acidic methyl proton in the product allowed further deprotonation under the strong basic conditions, which caused side reactions. Use of Weinreb amide was successful but the high cost of this reagent cannot be justified. To this end, a two-step sequence – quenching with acetaldehyde followed by TEMPO mediated oxidation, was developed. These two steps can either be telescoped in one-pot, or with the intermediate **7h-rac** isolated. Note that no formation of the lactone **6** was

observed under the strong basic conditions. For the conversion of **12** to **7h-rac**, use of acetaldehyde as a solution in THF is more desirable due to the volatility of acetaldehyde and better dosing control. The facile synthesis of **8h** allows for favorable cost reduction compared to the originally used **8a**.

2.2.2.1 Enzymatic Reduction of 8h

With **8h** in hand, asymmetric reduction of this compound is studied. First, the enzymatic reduction using ketoreductase (KRED) was explored (Scheme 6). Screening of in-house and commercially available KRED enzyme libraries resulted in identification of several enzyme hits (see ESI). However, it was found that the enzyme used for **8a** reduction was not effective for this substrate. Instead, two new enzymes KRED-P1-B02 (from Codexis) and evo 1.1.440 (from Evocatal) from commercial sources were identified as best hits. Both of these enzymes gave high selectivity (>98% ee) and high conversion. With KRED-P1-B02, efficient cofactor recycling was achieved using isopropanol as a co-substrate. For efficient cofactor recycling with isopropanol as a co-substrate, purge of the side product acetone by a combination of N_2 stream and vacuum is required in order to achieve complete conversion. These conditions were successfully demonstrated at lab scale and the desired chiral alcohol was isolated in high yield (>95% conversion, 90% isolated yield) and high purity (>99% e.e.). It is expected that the developed conditions are amenable to scale based on our experience on the bioreduciton of **8a**. The enzymatic reduction of **8h** was not selected for eventual manufacturing after the cost analysis showed that the asymmetric hydrogenation approach was advantageous (*vide infra*).

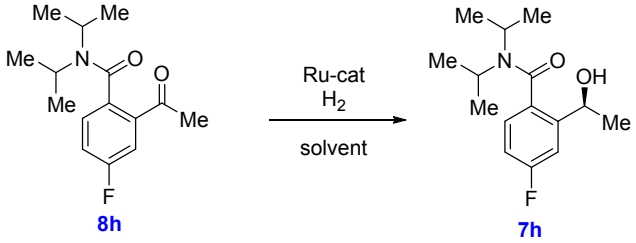
Scheme 6 Enzymatic Reduction of 8h



2.2.2.2 Asymmetric Hydrogenation Study

In parallel, asymmetric hydrogenation of **8h** was also studied (Scheme 7). Since the pioneering work [18a, b, c] of Noyori and coworkers, the ruthenium (Ru)-catalyzed asymmetric hydrogenation of acetophenone and other ketones has become a powerful tool for preparing chiral secondary alcohols with high optical purities. Our work thus focused on using the Ru catalyst for this transformation.

Scheme 7 Asymmetric Hydrogenation of 8h



10 commercially available catalysts (see ESI for structure of the catalysts) were screened. The screening experiments were run at 4.6 mg of **8h** and the results are summarized in Table 2. It was found that the sulfonyl diphenylethylenediamine (DPEN) type ligand is highly active for this hydrogenation (entries 1-6, Table 2). In contrast, the binap type ligand and the segphos type ligand (entries 7-10, Table 2) showed no to low reactivity, with most conversion lower than 10%. Interestingly, the (R)-alcohol was obtained instead of the desired (S)-alcohol when C4-[(S,S)-teth-MsDPEN RuCl] was used (entry 5,

Table 2). The solvents had some impact on the conversion, with higher conversion observed in iPrOH than MeOH. While this could be due to that IPA is facilitating the transfer hydrogenation, control experiment with no hydrogen showed very low conversion and low e.e. Based on the screening results, RuCl[(S,S)-TsDPEN] (p-cymene) was selected as catalyst and IPA was selected as reaction solvent. These conditions were confirmed at 1 g scale. Complete conversion and >98% e.e. was obtained. It is believed that the bulky diisopropylamide group contributed to the high enantiomeric selectivity of this reduction.

Table 2. Catalyst Screening Results for Asymmetric Hydrogenation of 8h

Entry	Catalyst	Catalyst loading mol %	Solvent	Conversion %	e.e %	Config.
1	RuCl[(S,S)-TsDPEN] (p-cymene)	5	MeOH	100	95.8	S
		5	iPrOH	100	98.5	S
2	C4-[(S,S)-teth-TrisDPEN RuCl]	5	MeOH	100	95.0	S
		5	iPrOH	100	99.0	S
3	C4-[(S,S)-teth-TsDPEN RuCl]	5	MeOH	92	93.2	S
		5	iPrOH	99.9	99.7	S
4	C3-[(S,S)-teth-MtsDPEN RuCl]	5	MeOH	83	90.1	S
		5	iPrOH	100	96.4	S
5	C4-[(S,S)-teth-MsDPEN RuCl]	5	MeOH	99.7	84.2	R
		5	iPrOH	100	86.5	R
6	RuCl[(S,S)-TsDPEN] (mesitylene)	5	MeOH	100	79.8	S
		5	iPrOH	100	92.7	S
7	$RuCl_2$[(S)-XylBinap](S-Daipen)	5	MeOH	5.4	59.6	S
		5	iPrOH	8.9	9.1	R
8	$RuCl_2$[(S)-XylBinap](S,S-Dpen)	5	MeOH	1.0	NA	NA
		5	iPrOH	4.8	NA	NA
9	$RuCl_2$[(R)-XylSegphos](R,R-Dpen)	5	MeOH	5.1	NA	NA
		5	iPrOH	57	34	S
10	$RuCl_2$[(S)-XylSegphos](S-Daipen)	5	MeOH	4.5	NA	NA
		5	iPrOH	29.3	50.4	R

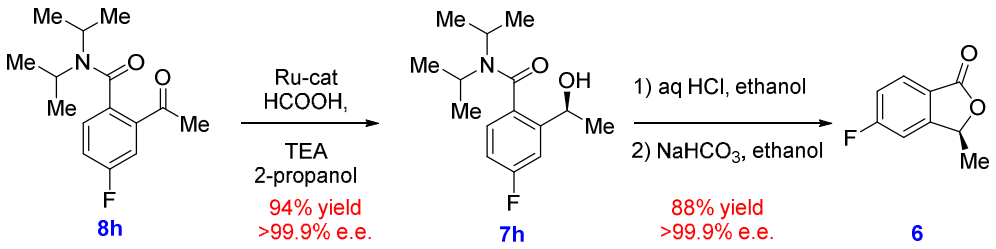
Screening conditions: substrate/catalyst ratio 20:1; 0.1 equiv. KO*t*-Bu, 90 psi H_2, 50 °C, reaction time 64 – 72 h

2.2.2.3 Asymmetric Transfer Hydrogenation

When the asymmetric hydrogenation process was transferred to the supplier for industrial campaign, it was found that this step became a bottle neck for the process throughput due to the limited reactor size of the hydrogenator. 15 batches of hydrogenation would be required to complete a 300 kg campaign and this would greatly limit the throughput. This limitation prompted us to consider asymmetric transfer hydrogenation, [19, 20] as its operation is simple, safe and environmentally friendly (Scheme 8).

The asymmetric transfer hydrogenation was developed on the basis of the asymmetric hydrogenation conditions. The same catalyst, RuCl[(S,S)-TsDPEN] (p-cymene) and the same solvent (iPrOH), were used, and the mixture of formic acid/trimethylamine was used as hydrogen source. It was found that the catalyst was even more effective under the transfer hydrogen conditions. The catalyst loading can be further reduced to 0.25 mol% for complete conversion. Since the optical purity of **6** can be further upgraded in the crystallization and isolation, the desired (S)-alcohol was isolated in high e.e. (>99.9%). Switch to the transfer hydrogenation thus became obvious as only 4 batches were needed to make the 300 kg delivery. These conditions were successfully scaled up to 125 kg. The reaction reached completion at 50 - 55 °C within 2 hours and the product **7h** was isolated in 94% yield and >99.9% e.e.

Scheme 8 Asymmetric Transfer Hydrogenation/ Lactonization



Ru-cat = RuCl[(S,S)-TsDPEN] (p-cymene)

The subsequent lactonization is straightforward (Scheme 8), when **7h** is treated with hydrochloric acid. Conversion of **7h** to **6** is through a tetrahedron intermediate (Figure 4). This intermediate can be detected by LC/MS under acidic conditions, but it reverts back to the starting material under basic conditions. The kinetics of the lactonization reaction is directly related to the reaction temperature so heating (45 – 55 °C) is preferred. The reaction became sluggish towards the end and it eventually achieved equilibrium between the intermediate and product. It was found that using higher boiling point alcohol (i.e. *n*-BuOH) and reacting at higher temperature did not improve the conversion nor the reaction rate, possibly due to the evaporation of HCl into headspace at higher temperature. Usually the reaction was worked up after 18 hrs before complete conversion was attained (up to 6% residual starting material left after base quench), in order to shorten the process time. The penultimate is readily purged in the final isolation.

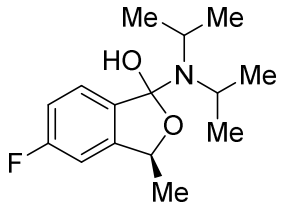


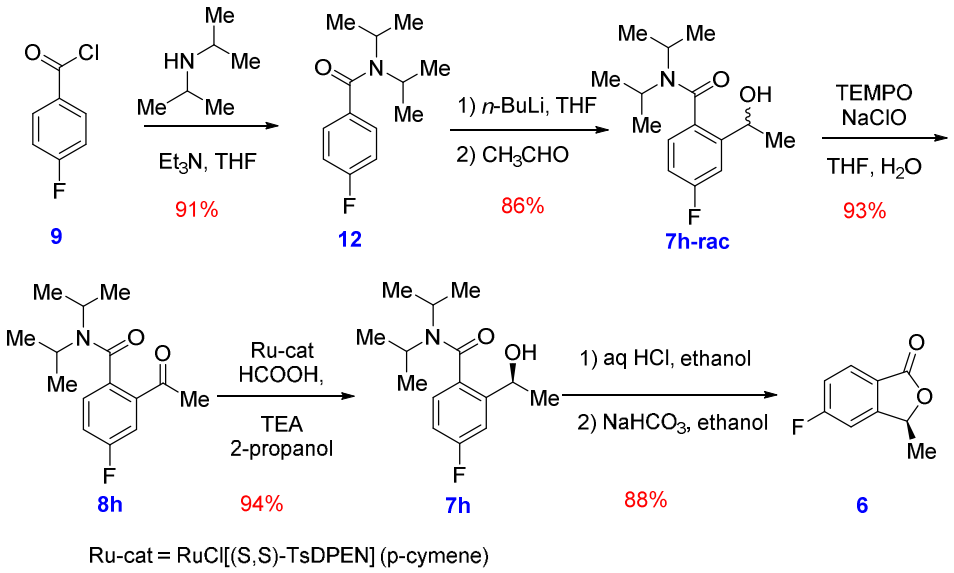
Figure 4. Tetrahedron Intermediate in the Lactonization

The isolation of **6** is fairly simple. The crude product directly precipitates out from the reaction mixture upon cooling to 0 -5 °C and reslurry in a mixture of ethanol and 3% aqueous $NaHCO_3$ further upgrades the purity of the product to 99.9%.

The final manufacturing process to compound **6** is illustrated in Scheme 9. This five-step sequence allows for quick access to lactone **6** from an economically, commercially available 4-fluorobenzoyl chloride. Throughout the process, the readily available commodity chemicals were used. The reaction and work-up in each step is simple and

straightforward. It is worthy to note that the presence of diisopropylamide group renders each intermediate as highly crystalline solid, which greatly facilitates the isolation. The impurity purge capability of this process is highly powerful so **6** is always isolated with high purity (>99.9% by HPLC, >99.9% e.e.).

Scheme 9 Manufacturing Route to Compound 6



3. Conclusion

In summary, a robust, cost-efficient manufacturing process has been developed for preparation of (S)-5-fluoro-3-methylisobenzofuran-1(3*H*)-one, a key intermediate to lorlatinib. Asymmetric transfer hydrogenation is the key strategy to obtain the chiral benzyl alcohol intermediate. This process has been successfully implemented on scale and 400 kg of **6** was manufactured.

4. EXPERIMENTAL SECTION

All reactions were performed under a nitrogen atmosphere. All reagents purchased from vendors were used as received. NMR data was collected using a Bruker AV III 400MHz spectrometer with TCI cryoprobe. HRMS data was obtained using a Thermo Orbitrap XL using Electrospray Ionization in positive mode. Reactions were monitored by reverse phase UPLC. UPLC conditions: Waters XSelect T3, 3.0 × 100 mm, 2.5 μm, 30 °C, flow 0.5 mL/min; λ = 230 nm, 5 μL injection volume; A: 0.1% phosphoric acid in water; B: 0.1% phosphoric acid in acetonitrile. Gradient 5% B to 90% B in 18 minutes, re-equilibrate to 5% B in 0.1 min. Diluent: 100% acetonitrile. The enantiomeric purity of PF-06811569 was monitored by chiral HPLC. Chiral HPLC conditions: Chiralpak AD-RH, 4.6 × 150 mm, 5 μm, 30 °C, flow 0.7 mL/min; λ = 230 nm, 10 μL injection volume; A: 0.05% trifluoroacetic acid in water; B: 100% acetonitrile. Gradient isocratic 60% A and 40% B. Diluent: 60:40 water : acetonitrile. The enantiomeric purity of PF-06845648 was monitored by chiral HPLC. Chiral HPLC conditions: Chiralpak IC, 4.6 × 250 mm, 5 μm, 30 °C, flow 1.0 mL/min; λ = 214 nm, 10 μL injection volume; A: 0.1% diethylamine in isopropanol; B: 100% n-heptane. Gradient isocratic 10% A and 90% B. Diluent: 100% methanol.

4.1 Preparation of 4-fluoro-N,N-diisopropylbenzamide (12)

To a solution of K_2CO_3 (1.2 equiv.) in water (3 volumes) was charged toluene (5 volumes) and N, N-diisopropylamine (1.2 equiv.). 4-Fluorobenzoyl chloride (100 kg) was added to the reaction and the resulting mixture was held at 20 – 25 °C for 2 hrs. Upon reaction completion, the phase was separated and the organic phase was washed with water (2 volumes). Removal of solvent *in vacuo*, followed by addition of *n*-heptane, resulted in

precipitation of the product. **12** was isolated by filtration, wash with *n*-heptane and drying. Yield 127.5 kg, 90.6%. Purity 99.2%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.29 – 7.34 (m, 2 H), 7.04 – 7.10 (m, 2 H), 3.67 (bs, 2 H), 1.33 (bs, 12 H) ppm; **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ 170.2, 162.8 (d, J_{CF} =248.5 Hz), 134.5, 127.8 (d, J_{CF}=8.0 Hz), 115.5 (d, J_{CF} = 22 Hz), 77.2, 20.7 ppm; **^{19}F NMR (376.5 MHz, $CDCl_3$)**: δ –112 ppm. **HRMS:** Calcd for $C_{13}H_{19}FNO$ $(M+H)^+$: 224.1445. Found: 224.1437.

4.2 Preparation of 4-fluoro-2-(1-hydroxyethyl)-N,N-diisopropylbenzamide (7h-rac)

n-BuLi (2.5 M in THF) solution was diluted with THF (3 volumes) and cooled to -85 - -65 °C. A solution of **12** (111.6 kg) in THF (4.2 volumes) was dosed into the reactor over 3 hrs and the mixture was held for an additional 1.5 hrs. Acetaldehyde in THF solution (1.5 equiv.) was then added over 3 hrs. Once the reaction was complete, the reaction was quenched with aqueous NH_4Cl solution. After work-up, the product was precipitated by addition of *n*-heptane into the concentrated organic phase. The racemic alcohol was isolated after filtration, wash with *n*-heptane and drying. Yield 115 kg, 86%, purity 99.8%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.12-7.24 (m, 1 H), 7.02-7.08 (m, 1 H), 6.88 – 6.96 (m, 1 H), 4.75 – 4.86 (m, 1 H), 4.24 (s, 1H), 3.67-3.77 (m, 1H), 3.48 – 3.54 (m, 1 H), 1.41-1.56 (m, 9 H), 1.08 - 1.15 (m, 6 H) ppm; **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ 170.6, 170.1, 162.9 (d, J_{CF} = 246 Hz), 162.7 (d, J_{CF} = 245 Hz), 145.4, 145.4, 132.4, 131.8, 126.8 (d, J_{CF} = 8.0 Hz), 126.5 (d, J_{CF} = 8.0 Hz), 114.2 (d, J_{CF} = 22 Hz), 113.9 (d, J_{CF} = 22 Hz), 113.8(d, J_{CF} = 22 Hz), 113.2 (d, J_{CF} = 22 Hz), 68.2, 65.7, 51.2, 51.1, 46.2, 45.9, 24.9, 21.6, 20.7, 20.4, 20.4, 20.3, 20.2 ppm; **^{19}F NMR (376.5 MHz, $CDCl_3$)**: δ –111.1, –111.9 ppm. **HRMS:** Calcd for $C_{15}H_{23}FNO_2$ $(M+H)^+$: 268.1707. Found: 268.1699.

4.3 Preparation of 2-acetyl-4-fluoro-N,N-diisopropylbenzamide (8h)

To a solution of $NaHCO_3$ (1 equiv.) in water (3 volumes) was added step 2 product **7h-rac** (150 kg) and TEMPO (0.04 equiv.). Ethyl acetate (5 volumes) was added and the mixture was cooled to 0 – 10 °C. Aqueous NaClO (2.3 equiv.) was then added over 2 - 3 hrs and the mixture was allowed to warm to ambient temperature. Upon reaction completion, the batch was quenched with sodium sulfite. After aqueous work-up, the organic phase was concentrated and *n*-heptane was added to precipitate the product. The product **8h** was isolated by filtration, wash with *n*-heptane and drying. Yield 138 kg, 93%. Purity 99.8%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48 (dd, J = 2.4, 9.0 Hz, 1 H), 7.22 (ddd, J = 2.4, 8.4, 16.0 Hz, 1 H), 7.21 (dd, J = 9.0, 16.0 Hz, 1 H), 3.46 – 3.60 (m, 2 H), 2.59 (s, 3 H), 1.58 (d, J = 7.2 Hz, 6 H), 1.13 (d, J = 7.2 Hz, 6 H) ppm; **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ 197.5 (d, J_{CF} = 2.0 Hz), 170.2, 162.1 (d, J_{CF} = 249.5 Hz), 137.2 (d, J_{CF} = 6.0 Hz), 133.5, 128.3 (d, J_{CF} = 8.0 Hz), 119.3 (d, J_{CF} = 22 Hz), 116.6 (d, J_{CF} = 22 Hz), 115.4, 51.7, 46.4, 27.7, 20.1 ppm; **^{19}F NMR (376.5 MHz, $CDCl_3$)**: δ −112 ppm. **HRMS:** Calcd for $C_{15}H_{21}FNO_2$ $(M+H)^+$: 266.1551. Found: 266.1543.

4.4 Preparation of (S)-4-fluoro-2-(1-hydroxyethyl)-N,N-diisopropylbenzamide (7h)

To a solution of formic acid (0.75 weight equiv.) in isopropanol (10 volumes) was added trimethylamine (0.95 weight equiv.) at 10 - 30 °C. **8h** (125 kg) was added to obtain a solution. The catalyst RuCl[(S,S-TsDpen)](p-cymene) (0.0033 equiv.) was added into the reactor under nitrogen atmosphere, and the batch was heated to 50 – 55 °C for 2 h to complete the reaction (99.6% conversion, 99.5% e.e.). Upon reaction completion the

batch was filtered and the filtrate was concentrated *in vacuo*. The product **7h** was crystallized from *n*-heptane/ ethyl acetate, filtered, washed with *n*-heptane and dried. Yield 118 kg, 93.7%. Purity 99.8%, e.e. >99.9%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.21 (dd, J = 2.8, 10.0 Hz, 0.6 H), 7.15 (dd, J = 2.8, 10.0 Hz, 0.6 H), 7.07 (dd, J = 6.0, 8.0 Hz, 0.4 H), 7.04 (dd, J = 6.0, 6.8 Hz, 0.6 H), 6.94 (ddd, J = 1.8, 8.0, 8.4 Hz, 0.4 H), 6.91 (ddd, J = 1.8, 8.0, 10.4 Hz, 0.6 H), 4.85 (ddd, J = 1.8, 6.8, 12.4 Hz, 0.6 H), 4.78 (dd, J = 6.8, 12.4 Hz, 0.4 H), 4.13 (s, 1H), 3.73 (m, 1H), 3.51 (sept, J = 6.8 Hz, 1H), 1.55-1.43 (m, 9H), 1.15 (d, J = 6.8 Hz, 2.4H), 1.09 (dd, J = 2.0, 6.8 Hz, 3.6 H) ppm; **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ 170.7, 170.3, 162.9 (d, J_{CF} = 248.5 Hz), 162.8 (d, J_{CF} = 248.5 Hz), 145.5, 145.5, 132.5, 131.9, 127.0 (d, J_{CF} = 8.0 Hz), 126.6 (d, J_{CF} = 8.0 Hz), 114.3 (d, J_{CF} = 22 Hz), 114.1 (d, J_{CF} = 22 Hz), 113.9 (d, J_{CF} = 22 Hz), 113.3 (d, J_{CF} = 22 Hz), 68.3, 65.8, 51.3, 51.2, 46.3, 46.0, 25.0, 21.6, 20.8, 20.6, 20.5, 20.4, 20.3 ppm; **^{19}F NMR (376.5 MHz, $CDCl_3$)**: δ –111.1, –111.9 ppm. **HRMS:** Calcd for $C_{15}H_{23}FNO_2$ $(M+H)^+$: 268.1707. Found: 268.1698.

4.5 Preparation of (S)-5-fluoro-3-methylisobenzofuran-1(3*H*)-one (6)

To a solution of **7h** (125 kg) in ethanol (5 volumes) was added 13.5% hydrochloric acid (3 wt. equiv.). The mixture was heated to 50 – 55 °C and stirred at this temperature for 24 – 36 hrs. Upon the reaction completion, the batch was cooled to 0 – 5 °C to obtain a slurry. After filtration, the crude product was reslurried in a mixture of ethanol and 3% aqueous $NaHCO_3$. The desired product **6** was isolated by filtration, wash with water and drying. Yield 68.4 kg, 88%. Purity 99.9%, e.e. >99.9%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88 (dd, J = 4.8, 8.4 Hz, 1 H), 7.21 (ddd, J = 2.0, 8.4, 8.8 Hz, 1 H), 7.12 (dd, J = 2.0,

8.8 Hz, 1 H), 5.53 (q, J = 6.4 Hz, 1 H), 1.63 (d, J = 6.4 Hz, 3 H) ppm; **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ 169.1, 166.5 (d, J_{CF} = 256.6 Hz), 153.8 (d, J_{CF} = 9.1 Hz), 128.0 (d, J_{CF} = 10 Hz), 121.8, 117.2 (d, J_{CF} = 24.1 Hz), 108.9 (d, J_{CF} = 25.2 Hz), 77.0, 20.2 ppm; **^{19}F NMR (376.5 MHz, $CDCl_3$)**: δ –102.8 ppm. **HRMS:** Calcd for $C_9H_8O_2F$ $(M+H)^+$: 167.0503. Found: 167.0497.

4.6 Preparation of (S)-1-(5-fluoro-2-iodophenyl)ethan-1-ol (7a) by Enzymatic Reduction

To a solution of KH_2PO_4 (0.13 equiv.) and K_2HPO_4 (0.2 equiv.) in water (14 volumes vs. **8a**) was added NADP (0.01 w/w) and KRED (0.6 w/w) solution. A solution of **8a** (267 kg) in IPA (1.0 w/w) was transferred to the enzyme solution. The batch was heated to 35 – 40 °C for 10 - 12 h till the reaction reached completion. The batch was cooled to 20 – 30 °C and the crude product was filtered. The crude product was dissolved in MTBE (4 volumes) and washed with water (3 volumes). The organic layer was concentrated and *n*-heptane (8 volumes) was added to precipitate the product. **7a** was isolated after filtration, wash with *n*-heptane, and drying. Yield 245.95 kg, 91%. Purity 100%, e.e. >99.9%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71 (dd, J = 5.6, 8.8 Hz, 1 H), 7.30 (dd, J = 3.2, 10.0 Hz, 1 H), 6.73 (ddd, J = 3.2, 8.0, 10.0 Hz, 1 H), 4.99 (dq, J = 0.8, 6.4 Hz, 1 H), 2.39 (s, 1 H), 1.43 (d, J = 6.4 Hz, 3 H) ppm; **^{13}C NMR (100.6 MHz, $CDCl_3$):** δ 163.5 (d, J_{CF} =247.5 Hz), 150.0 (d, J_{CF} = 7.0 Hz), 140.3 (d, J_{CF} = 7.0 Hz), 116.5 (d, J_{CF} = 22 Hz), 113.8 (d, J_{CF} = 22 Hz), 89.2 (d, J_{CF} = 3 Hz), 73.4 (d, J_{CF} = 1 Hz), 23.6 ppm. **^{19}F NMR (376.5 MHz, $CDCl_3$)**: δ –112 ppm.

4.7 Preparation of (S)-5-fluoro-3-methylisobenzofuran-1(3*H*)-one (6) by Carbonylation via 7a

To a solution of **7a** (287.8 kg) in 2-MeTHF (4.5 volumes), was added palladium acetate (0.001 equiv.), 1,1'-bis(diphenylphosphino)ferrocene (0.0015 equiv.) and trimethylamine (2 equiv.). The system was purged with nitrogen, followed by carbon monoxide. The reaction was heated to 80 °C under 50 psi of carbon monoxide, and agitated at this temperature for 12 hrs. Upon the reaction completion, the reaction mixture is diluted with EtOAc (2 volumes) and water (5 volumes). The layers were separated and the organic layer was concentrated to 2 volumes. Heptane (5 volumes) was added and the solvent was further removed to obtain a slurry. The slurry was filtered, washed and the wet cake was dried to obtain compound **6**. Yield 164 kg, 90.5%. Purity 99.9%. e.e. >99.9%.

4.8 Preparation of (S)-1-(5-fluoro-2-iodophenyl)ethan-1-ol (7a) by (-)-DIP-Cl Reduction

A solution of (-)-DIP-Cl (6.1 kg) in THF (4 L) was cooled to -30 °C. A solution of compound **8a** (2 kg) in THF (4 L) was then added dropwise over 2 hr at -30 °C. Upon reaction completion, the reaction was allowed to warm up to RT. The solvents were removed *in vacuo* and the residue re-dissolved in MTBE (7 L). The solution was cooled to 10 °C and a solution of diethanolamine (2.18 kg) in EtOH/THF (1.1 L/2.2 L) was added dropwise over 2 h; formation of a white precipitate was observed. The suspension was heated to reflux for 2 h then cooled to RT. The slurry was filtered and the mother liquor was concentrated *in vacuo*, which was purified by re-crystallization from heptanes

at -60 °C several times to give product **7a** as white solid. Yield 1.35 kg, 67%. Purity 97.4%. 99.1% e.e.

ASSOCIATED CONTENT

Supporting Information The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx. Enzymatic screening results for reduction of **8a** and **8h**; solvent and catalyst study results for carbonylation reaction; the structure of the catalysts for asymmetric hydrogenation screening; ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS spectrum of compounds **12, 7h-rac, 8h**, **7a** and product **6** (PDF).

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Notes

The authors declare no competing financial interest.

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