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**Graphical Abstract**

**A novel approach for the synthesis of Crizotinib through the key chiral alcohol intermediate by asymmetric hydrogenation using highly active Ir-Spiro-PAP catalyst**

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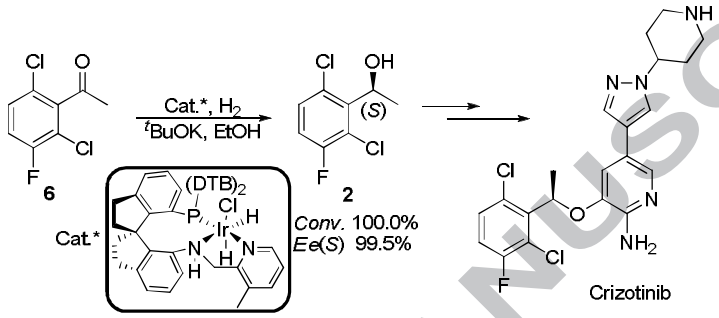

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# A novel approach for the synthesis of Crizotinib through the key chiral alcohol intermediate by asymmetric hydrogenation using highly active Ir-Spiro-PAP catalyst

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ABSTRACT

A novel approach for the synthesis of Crizotinib (**1**) is described. In addition, new efficient procedures have been developed for the preparation of (*S*)-1-(2,6-dichloro-3-fluorophenyl)ethanol (**2**) and *tert*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (**4**), the key intermediates required for the synthesis of Crizotinib.



## 1. Introduction

Crizotinib (**1**) (XALKORI®) is a potent and selective Mesenchymal epithelial factor/Anaplastic lymphoma kinase (c-Met/ALK) inhibitor[1,2], which has been developed by Pfizer and was approved by the US FDA in 2011 for the treatment of locally advanced or metastatic nonsmall-cell lung cancer (NSCLC). (**Figure 1**).[3]

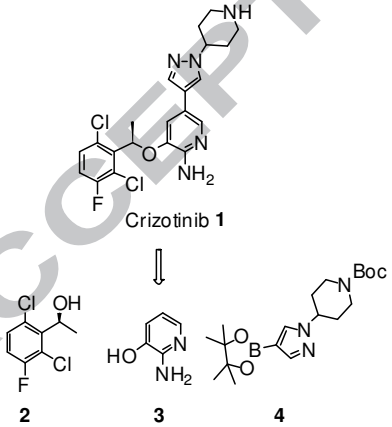



**Figure 1**

In the disclosed synthetic routes, (*S*)-1-(2,6-dichloro-3-fluorophenyl)ethanol (**2**) is a key intermediate, for which lots of efforts have been carried out to produce this chiral pure alcohol with high enantioselectivity. However, asymmetric reduction with well developed boran reagents such as $BH_3$·THF/(*R*)-methyl-CBS-oxazaborolidine (cat.)[4], (-)-DIPCl[5] and $NaBH_4$/TMSCl/(*S*)-α,α-diphenylpyrrolidinemethanol[6] etc. all gave low optical purity of the alcohol, and in most of the cases gave low conversion of the reaction. Kung et al developed a four-step biotransformation of 2,6-dichloro-5-fluoroacetophenone (**6**) to the chiral alcohol **2** via enzymatic hydrolysis of the racemic acetate with pig liver esterase, and the desired chiral alcohol **2** could be produced in 99.7% ee and 50% yield.[7] Codexis has developed an engineered ketoreductase enzyme, which was used in the asymmetric reduction of 2,6-dichlo-5-fluoroacetophenone (**6**) to provide **2** in high selectivity (>99% ee) and efficiency. Both enzymatic approaches were used in the manufacturing of **2** in multi-kilo scale.[8,9]

Catalytic asymmetric hydrogenation of ketones is one of the powerful methods to prepare chiral alcohols, and is considered as atom economic approach. However, chiral ligands which can be applied in the manufacturing are still rare, as in the manufacturing scale, not only high ee, but also a high turnover number (TON) and turnover frequency (TOF) are required, as the costs of catalysts are normally key issues in industry scale. As most of the reported catalysts have TONs lower than 1000 and cause the high cost of the catalysts which are unsuitable for the application in industry.[10] It is noteworthy that some of the synthetic chiral catalysts, which are much smaller and simpler than enzymes, exhibit activities and selectivities comparable to those of enzymes.[11, 12] Zhou et al has recently reported a new type of chiral iridium catalysts that bearing a spiro pyridine-aminophosphine ligand, which showed high selectivity and efficiency for the asymmetric reduction of phenylketone. Among those catalysts, Ir[(*R*)-DTB-SpiroPAP-3-Me] (**5**) can afford the corresponding chiral alcohol in up to 99.9% ee and with TONs as high as 4,550,000 in the reduction of acetophenone.[13]

On the other hand, the reported route to crizotinib still has room for improvement in the process perspectives, in which the nitro compound as intermediate cause safety issue, and using the iodo intermediate raise the cost concern of the whole process on manufacturing scale.[9,14] Therefore, an alternative synthetic route with lower cost and safer operation is still desired.

In this article, we report an asymmetric hydrogenation of 2,6-dichloro-5-fluoroacetophenone (**6**) to produce the key chiral alcohol **2** for Crizotinib, by applying highly efficient catalyst Ir[(*R*)-DTB-SpiroPAP-3-Me] (**5**) (**Figure 2**), and the complete

synthesis of an Crizotinib by an alternative approach, which is considered should be suitable for scaling up.

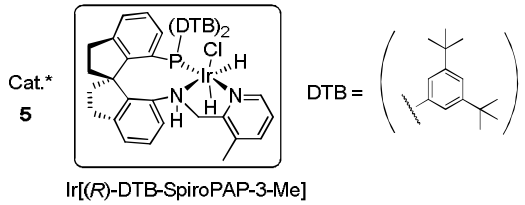
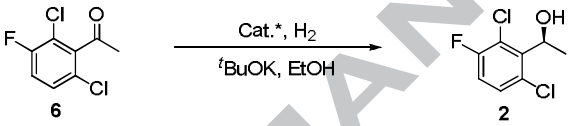



**Figure 2**

## 2. Results and discussions

The asymmetric catalytic hydrogenation of 2,6-dichloro-3-fluoroacetophenone (**6**) was carried out by using the extremely efficient catalyst Ir[(*R*)-DTB-SpiroPAP-3-Me] (**5**) (**Table 1**). The initial hydrogenation was performed under the conditions previously applied for the reduction of acetophenone (substrate/catalyst, S/C = 5000, 10 atm $H_2$, 30 °C) in the presence of potassium *tert*-butoxide (0.02 equiv. based on **6** as base (Table 1, entry 1). The reaction was completed in 2.5 h, and **2** was obtained in 99.6% ee with 100% conversion. When $^t$BuOK was increased to 0.04 equivalents, the conversion could be completed in 1.5 h (entry 2), and further increasing of $^t$BuOK to 0.08 equiv. did not result in obvious change (entry 3). When the reaction was carried out at room temperature (15 °C), full conversion was achieved within 4 h, giving the alcohol **2** in 99.9% ee (entry 4). When using 1 atm $H_2$, the hydrogenation reaction rate slowed down obviously, 62% conversion and 97.8% ee were obtained within 28 h (entry 5). While increasing the reaction temperature to 50 °C and 70 °C, the conversion rate was increased, and the reaction could be completed in 1 h (entries 6, 7). When the hydrogen pressure was increased from 10 atm to 30 and 50 atm at 50 °C with $^t$BuOK (0.04 equiv.), the reaction time could be reduced to 40 minutes (entries 8, 9). When the catalyst loading was lowered to 0.001 mol% (S/C = 100,000), the chiral alcohol **2** could be obtained in 99.5% ee in 100% conversion within 24 h at 50 °C under the initial hydrogen pressure of 30 atm (entry 10). This asymmetric hydrogenation condition was considered suitable for scaling up for manufacturing, as the low catalyst loading make the cost of the catalyst much lower than the solvent. The modified condition was carried out in the plant to produce **2** on 100 kg scale per batch and gave consistent results comparable to the lab scale.[15]

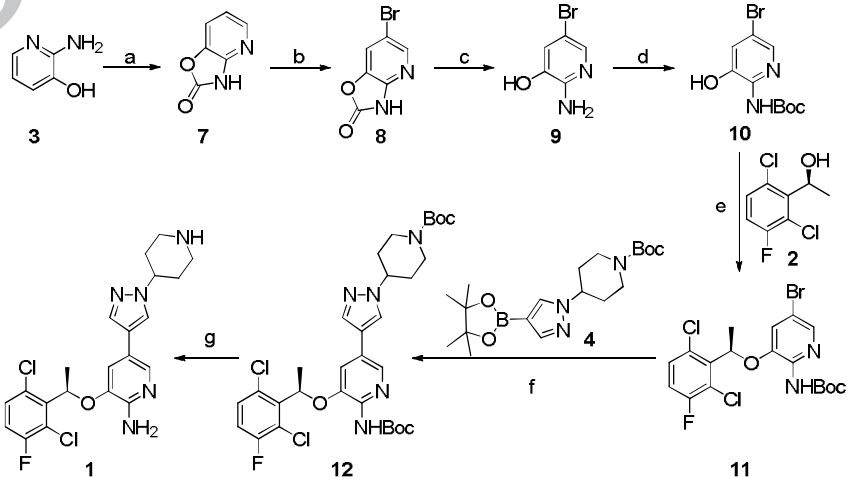
**Table 1.** Reaction screening for asymmetric hydrogenation of 1-(2,6-dichloro-3-fluorophenyl)ethanone[a]




6 2

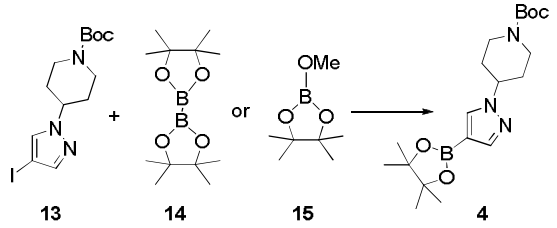
| Entry | S/C[b] | Base (B/S[c]) | $P_{H2}$ (atm) | Temp. (°C) | Time (h) | Conv. (%)[d] | Ee (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | 5000 | $^t$BuOK (0.02) | 10 | 30 | 2.5 | 100 | 99.6 (*S*) |
| 2 | 5000 | $^t$BuOK (0.04) | 10 | 30 | 1.5 | 100 | 99.7 (*S*) |
| 3 | 5000 | $^t$BuOK (0.08) | 10 | 30 | 1.5 | 100 | 99.6 (*S*) |
| 4 | 5000 | $^t$BuOK (0.04) | 10 | 15 | 4 | 100 | 99.9 (*S*) |
| 5 | 5000 | $^t$BuOK (0.04) | 1 | 30 | 28 | 62 | 97.8 (*S*) |
| 6 | 5000 | $^t$BuOK (0.04) | 10 | 50 | 1.0 | 100 | 99.6 (*S*) |
| 7 | 5000 | $^t$BuOK (0.04) | 10 | 70 | 1.0 | 100 | 99.4 (*S*) |
| 8 | 5000 | $^t$BuOK (0.04) | 30 | 50 | 40 min | 100 | 99.6 (*S*) |
| 9 | 5000 | $^t$BuOK (0.04) | 50 | 50 | 40 min | 100 | 99.6 (*S*) |
| 10 | 100000 | $^t$BuOK (0.04) | 30 | 50 | 24.0 | 100 | 99.5 (*S*) |

[a] Reaction: 1-(2,6-dichloro-3-fluorophenyl)ethanone **6** (0.1 mol), $^t$BuOK, anhydrous ethanol (25 mL), catalyst ([Ir((*R*)-DTB-SpiroPAP-3-Me)]) (**5**) and $H_2$ were used.
[b] the mole ratio of substrate to catalyst.
[c] the mole ratio of base to substrate.
[d] Determined by chiral HPLC.

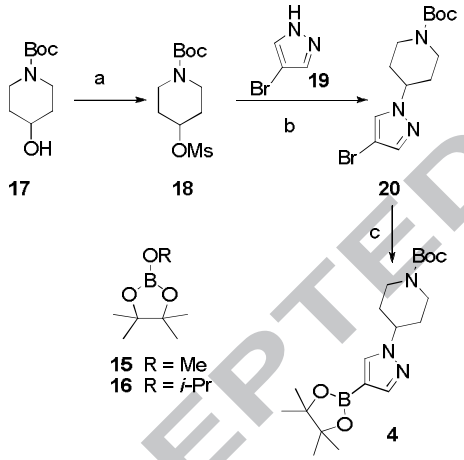



**Scheme 1.** Synthetic route of Crizotinib from chiral alcohol **2**. Reaction conditions: (a) bis(trichloromethyl)carbonate (BTC), DCE, pyridine, reflux, 3h, 86%; (b) $Br_2$, DMF, 0-30 °C, 2 h, 88%; (c) 10% NaOH (aq), 100 °C, 6 h, 90%; (d) $(Boc)_2O$, $Et_3N$, DCM, 20–30 °C, 12 h, 75%; (e) $Ph_3P$, DIAD, THF, 12 h, 20-30 °C, 50%; (f) $Pd(Ph_3P)_2Cl_2$, $Na_2CO_3$, DMF, $H_2O$, 60 °C, 3 h, 85%; (g) HCl/EtOH, DCM, 20–30 °C, 2 h, 87%.

With the enantio pure **2** in hand, the synthesis of crizotinib can be completed by the route shown in **Scheme 1**. The synthesis started with 2-aminopyridin-3-ol (**3**), which is commercial available. **3** reacted with bis(trichloromethyl)carbonate (BTC) to give oxazole compound **7** in 86% yield, in which both amino and hydroxy groups were protected. Bromination of **7** occurred regioselectively by reacting with bromine at 0-30 °C to give bromide **8** as the main product in 88% yield. Hydrolysis of **8** in 10% NaOH solution at 100 °C to give **9** in 90% yield, followed by the protection of amino group by Boc group to afford **10** in 75% yield. After coupling of **10** and **2** under Mitsunobu condition, intermediate **11** could be isolated in 50% yield. Suzuki coupling of intermediate **11** with boronate **4** by using $Pd(Ph_3P)_2Cl_2$ as catalyst in DMF at 60 °C for 3 h, to give Di-Boc protected compound **12** in 85% yield. Finally, removal of Boc groups of **12** with HCl in ethanol to produce crizotinib (**1**) in 87% yield with 99.5 % ee. It was noted that no racemization occurred during the above transformation.




**Scheme 2.** Original synthetic route of **4** from iodo compound **13**. Reaction conditions: (a) **14**, $Pd(Ph_3P)_2Cl_2$, KOAc, DMSO, 80 °C, 2 h; (b) **15**, 2 M *i*-PrMgCl in THF, 0-30 °C.




**Scheme 3.** Synthetic route of **4** through bromide **18**. Reaction conditions: (a) MsCl, $Et_3N$, MTBE, 0-30 °C, 1 h, 95 %; (b) **19**, NaH, DMF, 0 °C, 2 h; (ii) **18**, 100 °C, 12 h, 55 %; (c) (i) *i*-PrMgCl·LiCl in THF, 20–30 °C, 12 h; (ii) **15** (or **16**), THF, 20–30 °C, 6 h, 60–80 %.

In addition, another key intermediate boronate **4** was previously prepared from the corresponding iodide **13**. The general route can be divided in two classes: Pd-catalyzed boronation of **13** with pinacol boronate **14,**[14] or Knochel procedure of *i*-PrMgCl assisted coupling reaction of **13** with pinacol boronate **15** (**Scheme 2**).[9] However, the cost of iodo compound normally is considered much higher than its bromo derivatives in process perspective, and in most of the cases of using iodo compounds for the reaction, the color would be contained in the product, which needs extra cost for the purification. As shown in **Scheme 3**, synthesis of pinacol boronate intermediate **4** started from pipradrol (**17**), which was transformed to its mesylate **18** in 95% yield. Reaction of the mesylate **18** with 4-bromopyrazole (**19**), which was previously deprotonated by sodium hydride, and heating in DMF to give **20** in 55% yield. Reaction of **20** with *i*-PrMgCl·LiCl generated the expected Grignard reagent, which was quenched with 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**15**) to yield boronate intermediate **4** in 80% yield as the white solid. While using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**16**) for the coupling reaction, the target compound **4** could also be obtained in 60% yield. (**Scheme 3**)

In conclusion, we have demonstrated a new approach for the asymmetric synthesis of Crizotinib (**1**) with high enantioselectivity. The key step of this approach is the asymmetric synthesis of chiral alcohol (*S*)-1-(2,6-dichloro-3-fluorophenyl)ethanol **2** through asymmetric hydrogenation of ketone precursor **6** by using highly efficient and enantioselective Ir[(*R*)-DTB-SpiroPAP-3-Me] (**5**) as catalyst. The asymmetric hydrogenation was practiced in the pilot plant at 100 kg scale and **2** could be obtained in 99.5% ee with TON of 100,000,[15] which further proves highly efficiency of this type of the catalyst in producing chiral alcohols.[16]

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