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ORIGINAL PAPER

# Ir C–H Activation and Other Catalysis Applied to a Complex Drug Candidate

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**Abstract** Transition metal catalysis by Cu ($CF_3Cu$), Ir (C–H activation), and Ru (ring-closing metathesis) were applied to prepare a complicated tetra substituted pyrazolopyridine drug candidate at GlaxoSmithKline. CuI/$FSO_2CF_2CO_2Me$ was utilized to install a $CF_3$ group in a position otherwise difficult to access. IrOMe(COD)/bipyridine was utilized to activate the remote $C_5$ position of a pyrazolopyridine, and Ru (Hoveyda–Grubbs catalyst) was utilized to prepare a chiral aminocyclopentenone for oxysulfonium cyclopropanation. These methods were employed to synthesize a drug candidate, where previous syntheses were considered insufficiently safe by process safety to scale. The synthesis is presented in three parts: $CF_3$ installation in a complicated heterocycle; C–H activation at a remote site; enantioselective cyclopropanation and aminoketone reduction.

**Keywords** Catalytic $CF_3$ · C–H activation · Ring-closing metathesis · Ylides · Cyclopropanation

## 1 Introduction

GSK2585337A, Fig. 1 is a drug candidate antiviral. The complex poly-substituted pyrazolopyridine core (GSK2531339A) is required to achieve the best balancing of the attributes sought in development candidates, such as potency, selectivity, pharmacokinetics and stability. The substitution pattern could be accessed initially only through high-energy intermediates and reactions. Meanwhile, the specific amino-alcohol "tail" imparts an order of magnitude activity compared to its monocyclic equivalents. The remit of the early development team, as always, was two-fold: supply the wider project team with active pharmaceutical ingredient (API, drug substance) to keep the project moving along in formulations development, early toxicology, metabolism, pharmokinetics and stability of API and finished product; and focus on how the team would supply larger quantities of API for such activities as 1-month toxicology and first-time clinical studies.

Herein, the team describes the uses of various catalytic methods to achieve a safe and effective preparation of the very complex API: preparation of the pyrazolopyridine CORE through $C_7$ manipulation of simpler commercial pyrazolopyridine intermediates; C–H activation at $C_5$ for HEAD installation; and enantioselective preparation of a 4-chiral center amino alcohol TAIL from a single chiral center amino acid through ring closing metathesis, ylide addition, and ketone reduction.

## 2 Discussion

The original route to prepare this intermediate is shown in Scheme 1. The synthesis involved a problematic *N*-amination step, which was not amenable to scale up due to its low yield and in particular the thermal instability of the reagent, *O*-mesitylsulfonylhydroxylamine (MSH) [1, 2][1,2]. The more

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[1] MSH onset reported to be 41.5 °C, see [1].

[2] Storage incident, see [2].

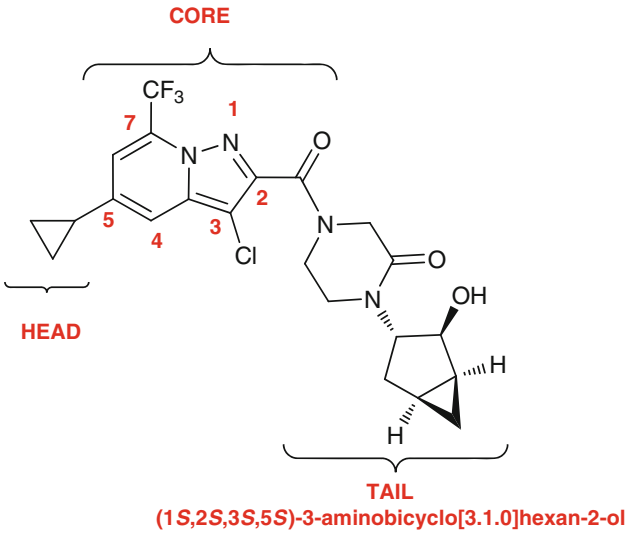



**Fig. 1** Drug candidate GSK2585337A

thermally stable hydroxylamine *O*-sulfonic acid (HOSA) did not provide the desired *N*-aminopyridinium. Therefore, significant improvements were needed in the safety of the synthetic approaches to the 7-trifluoromethylpyrazolo[1,5-*a*]pyridine that would facilitate the delivery of multi-kilogram quantities of material to support the drug development programs. There was also an expense factor, in that 2,4-disubstituted pyridine were not easily obtained and were expensive to purchase.

### 2.1 A Tale of Trifluoromethyl Daring-Do

After evaluating a number of different possibilities, two approaches, as shown in Fig. 2, were successful: the *N*-ylide and the 7-zincate approaches. Both approaches sought to introduce a trifluoromethyl group into the starting materials with the N–N bond already incorporated, thus obviating the need to use highly energetic MSH. These approaches were completely dependent on a later C–H activation at the 5-position of the pyrazolopyridine, which successful application is described later.

The *N*-ylide approach, demonstrated in Scheme 2, depended on installing $CF_3$ in the 2-position of a commercially available, stable *N*-aminopyridinium salt.

This was achieved through the use of trimethylsilyltrifluoromethane in the presence of cesium fluoride (Rupert's Reagent) [3][3] and cyclization [4]. Although somewhat lengthy, each intermediate of the synthesis was easily isolated as a solid, with very little work-up required.

[3] For reviews on $CF_3SiR_3$ as nucleophilic trifluoromethylating reagents, see [3].

The 7-zincate chemistry, demonstrated in Scheme 3, depended on selective deprotonation of commercially available unsubstituted pyrazolopyridine-2,3-dicarboxylate.

Initially, metallation of the pyrazolopyridine gave complex mixtures, in which attack of the formed organometallic on its own ester was detected. This very fast attack was avoided through the use of tetramethylpiperidide (TMP) as the Mg–Zn–Li salt, which is commercially available in bulk. The ensuing zincate could be trapped with iodine, but the methyl esters were not stable under the resulting $ZnI_2$ conditions. The dealkalation instability was handled by using the diethyl esters, at −10 °C. The 7-iodopyrazolopyridine was then further elaborated to the required 7-$CF_3$ by the methods described by Johnson [5], using $FSO_2CF_2CO_2Me$ and catalytic CuI. Eventually, these two steps were telescoped into a single isolation: the 7-iodo intermediate was not isolated; instead, the solution was turned over from methyltetrahydrofuran to DMF solvent, and treated under the trifluoromethyling conditions.

The two routes were compared against development issues, and numeric values assigned in Table 1. Either route could be scaled, but the shorter zincate route was selected for progress into plant (two batches, 10 kg each).

### 2.2 A Tale of Activation

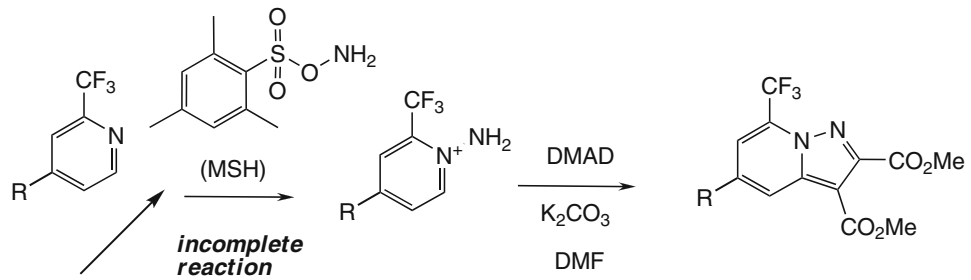
Previous research on pyrazolopyridines had indicated promiscuous C–H activation, with the $C_7$, $C_5$ and $C_3$ positions all active to some degree, as shown in Fig. 3. For the purposes of the key molecule, $C_7$ was blocked by the $CF_3$ group. The $C_3$ ester was kept for time being.

The 5-position was elaborated through Ir-catalyzed C–H activation, using the methoxy-Ir-COD catalyst and a dipyridine ligand [6]. The resulting boronate was not isolated, but was onward oxidized to the phenol. Direct halogenation was not successful. While cyclohexane was an effective solvent for Ir activation, due to its 80 °C boiling point, the oxidation with aq. hydrogen peroxide left an unstirrable gel. The boronate could be isolated from cyclohexane and treated with peroxide in a separate reactor, but methyl cyclopentyl ether was found to be appropriate for both boronation and oxidation. Again, the phenol was not isolated, but rather saponified and decarboxylated at $C_3$, as shown in Scheme 4.

After decarboxylation, the phenol was converted to its triflate (as ester), and a surfactant-enhanced Suzuki-Miyura C–C bond formation [7] with cyclpropylboronic acid gave the CORE group, as shown in Scheme 5.

### 2.3 The Case of the Tricyclic Tail

The specific tricyclic "TAIL" 1-((1S,2S,3S,5S)-2-hydroxybicyclo[3.1.0]hexan-3-yl)piperazin-2-one, Fig. 4, was selected




MSH = mesitylenesulfonylhydroxylamine

DMAD = dimethyl acetylenedicarboxylate

DMF = dimethylformamide

**Scheme 1** Initial synthesis of substituted pyrazolopyridines. *MSH* mesitylenesulfonylhydroxylamine, *DMAD* dimethyl acetylenedicarboxylate, *DMF* dimethylformamide

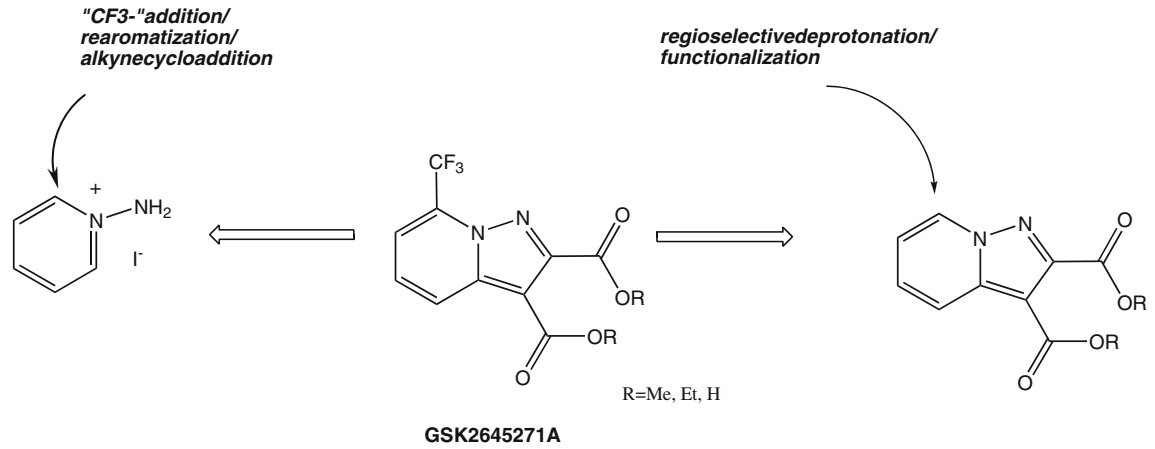
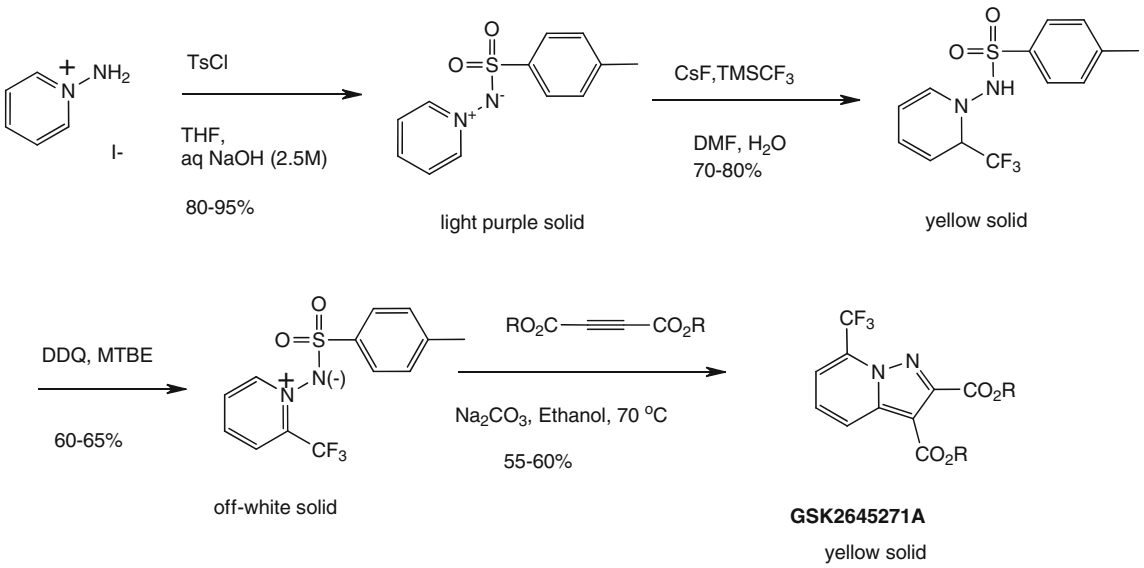



**Fig. 2** Two successful approaches

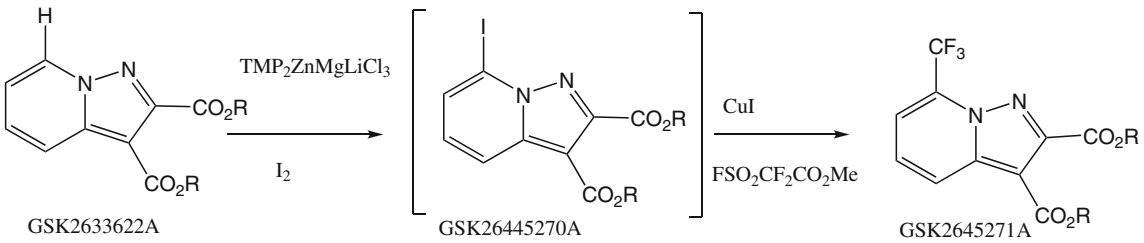
over simpler hydroxycyclohexylpiperazines, due to its unique and enhanced potency. The initial synthesis, shown in Scheme 6, presented major challenges which would have been difficult to implement on larger scale. Specifically, the diastereoselective Simmons–Smith cyclopropanation and the Curtius rearrangement to install the amino group proceed through highly energetic intermediates. Although Simmons–Smith reactions are conducted on very large industrial scale, the reactors and equipment are dedicated to this reaction. Our multi-purpose pilot plant was not equipped to handle such an energetic reaction. Additional difficulties were identified. The synthesis requires a chiral auxiliary, which is not easily recovered. But perhaps the most difficult complication was oils, oils, oils everywhere, and the resulting chromatographic purification required.

Retrosynthetic analysis, Fig. 5, presented the team with an opportunity to avoid the Curtius rearrangement, through purchase of a protected amine, and to avoid the Simmons–Smith, through a sulfur ylide cyclopropanation. No chiral auxiliary would be required: one chiral center purchased, and the others set through diastereoselective reactions. The number of steps was expected to be the same as the initial synthesis, and the end-game identical.

Going forward, Scheme 7, the cyclopentenone was accessed in three steps from commercially available allylglycine (>70 % yield) [8]. Cyclopropanation resulted in several byproducts and <20 % yield of desired cyclopropane. A cyclopropane-epoxide and undesired diastereomer of the cyclopropane were identified as byproducts,




**Scheme 2** *N*-ylide synthesis of substituted pyrazolopyridines




**Scheme 3** Zincate synthesis of substituted pyrazolopyridines

**Table 1** Comparison of two routes against development criteria

| | Ylide route | | Zincate route | |
|---|---|---|---|---|
| Availability of SMs | High | 10 | Good | 8 |
| Cost of SMs | Inexpensive | 10 | Mid | 8 |
| Reagents (time, temp) | F ion | 6 | Good | 8 |
| Process safety findings | At dihydropyridine | 5 | Good | 8 |
| Volumes | Low | 10 | Good | 8 |
| Isolated steps | 4 | 6 | 2 (1?) | 10 |
| Complication of work-ups | 1 Of 4 | 8 | 1 | 8 |
| Direct crystallizations | 3 Of 4 | 8 | No | 7 |
| Waste streams | F ion | 6 | Mg, Zn, Cu, MeI | 7 |
| Yields | Decent | 8 | Good | 10 |
| Total | | 77 | | 82 |

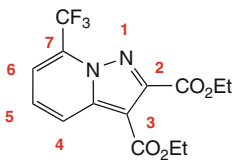
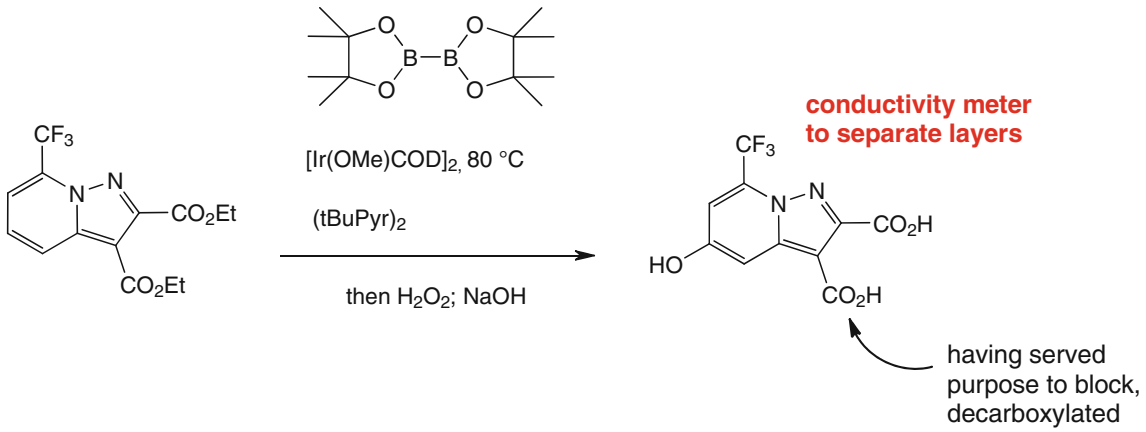


**Fig. 3** Pyrazolopyridine diester

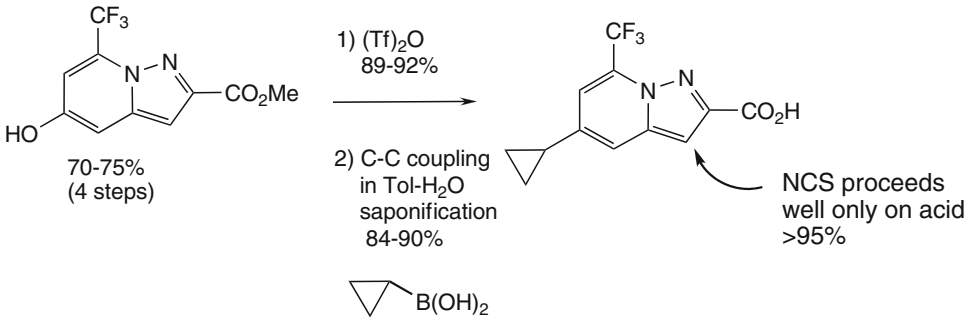
together with decomposition products likely formed from the epoxide.

When the N–H in the aminocyclopentenone was blocked, however, the reaction proceeded with no undesired diastereomer and no unwanted byproducts, as demonstrated in Scheme 8.




**Scheme 4** C–H activation

**Scheme 5** Completion of the CORE



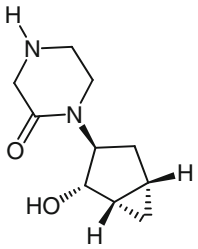



**Fig. 4** Tricyclic tail

Reduction of the bis-protected (1S,3S,5S)-3-aminobicyclo[3.1.0]hexan-2-one gave exclusively the undesired diastereomer. One of the two Boc-groups was removed (89 % yield, $CeCl_3$/NaI) and reduction of the mono-Boc aminobicyclo[3.1.0]hexan-2-one gave exclusively the desired diastereomer (94 % yield). The alcohol could be further elaborated to the desired tail, as shown in Scheme 9.

**Scheme 6** Initial synthesis of tricyclic tail.
*NS* = nosylate = 4-nitrophenylsulfonate

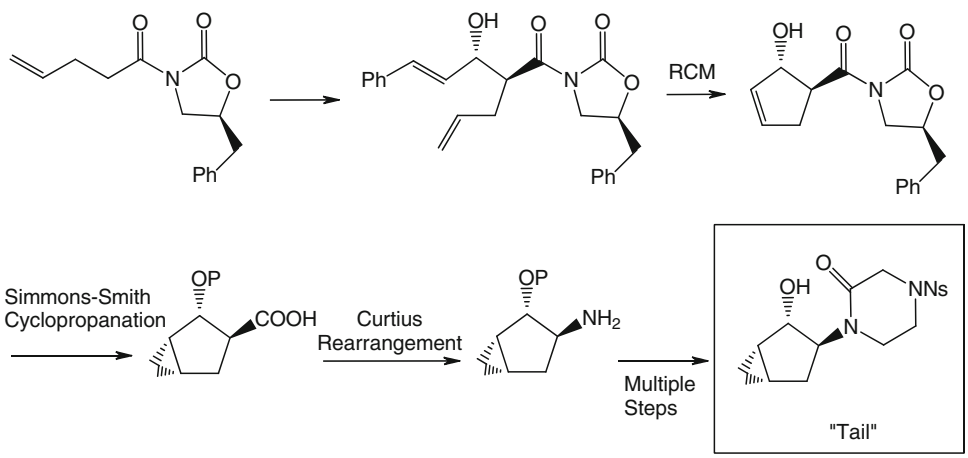
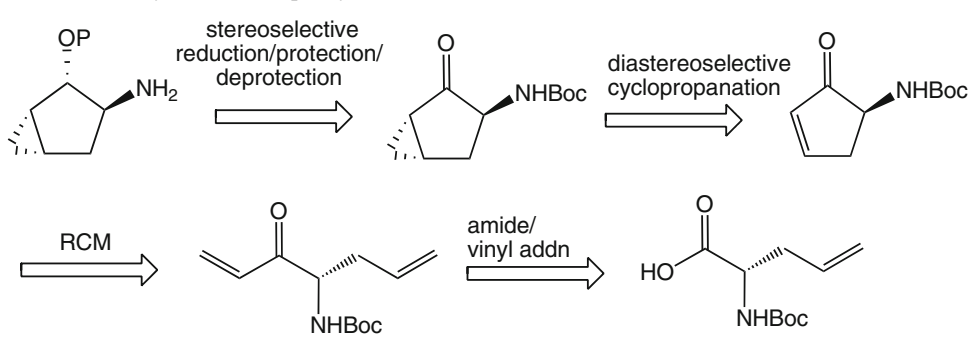
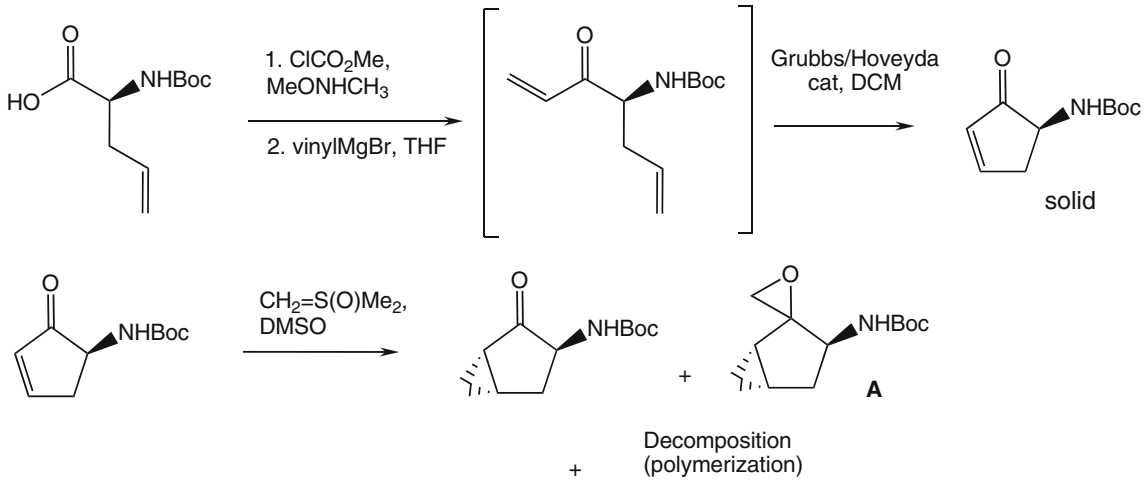
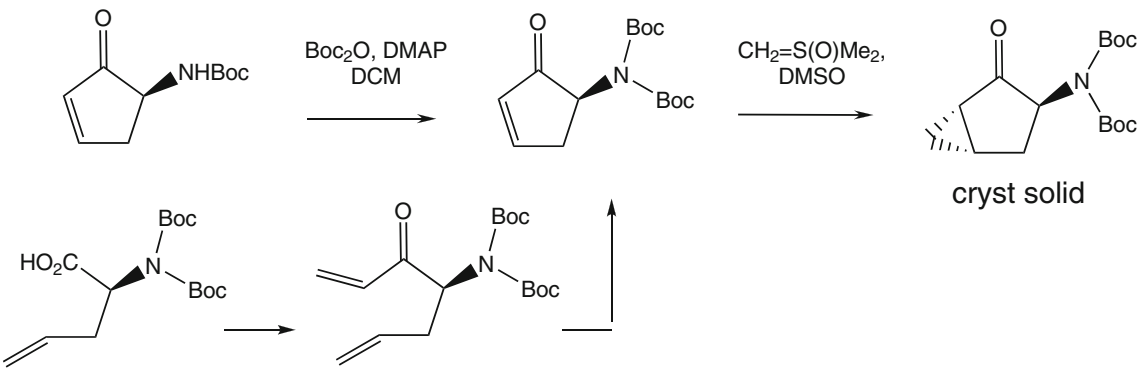


**Fig. 5** Retrosynthetic analysis




**Scheme 7** Forward from allyl glycine



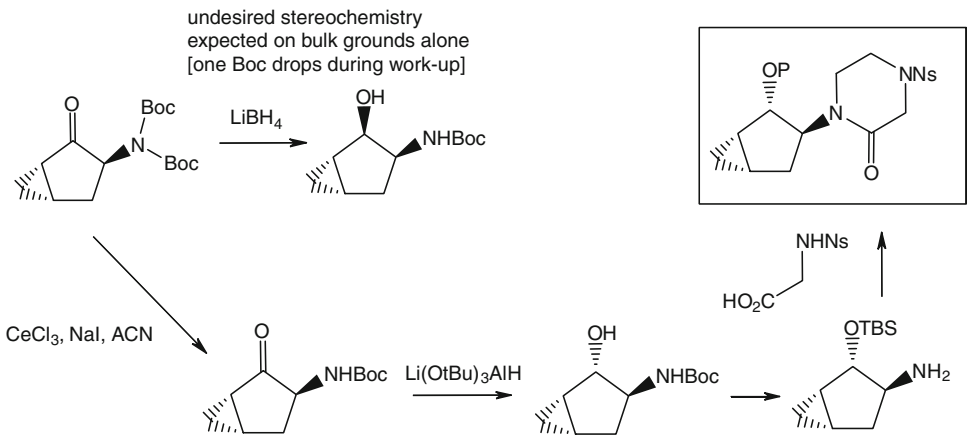

**Scheme 8** Blocked N–H

## 3 Conclusions

New distinct routes to the $CF_3$ substituted pyrazolopyridine core were developed, which improved the scalability of the processes. Both routes relied on starting materials that incorporate the problematic N–N bond. One route was demonstrated in fixed equipment. C–H activation at $C_5$ with Ir catalyst provided the hook on which to hang the cyclopropyl head of the molecule.

For the tail portion of the molecule, the team demonstrated a diasteroselective sulfur ylide cyclopropanation and diastereoselective reduction. This route circumvents

**Scheme 9** Completion of tricyclic tail




problematic Simmons–Smith cyclopropanation and Curtius rearrangement. The key to diastereocontrol is choice of protecting groups on the amine.

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