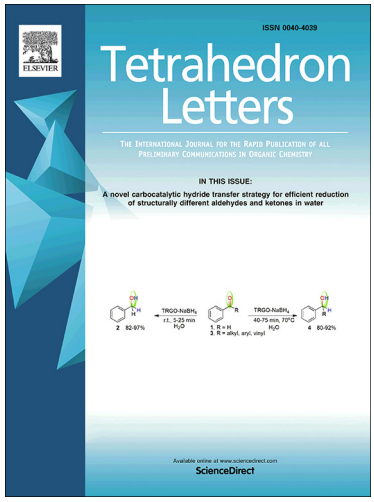

Enantioselective synthesis of GNE-6688, a potent and selective inhibitor of interleukin-2 inducible T-cell kinase (ITK)

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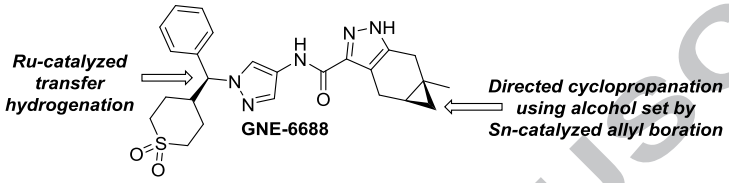

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Enantioselective synthesis of GNE-6688, a potent and selective inhibitor of interleukin-2 inducible T-cell kinase (ITK)

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ABSTRACT

An enantioselective synthesis of the previously-disclosed ITK inhibitor GNE-6688 is described. Synthesis of the nitropyrazole fragment is highlighted by a Ru-catalyzed transfer hydrogenation using the Wills tethered ligand system. Synthesis of the pyrazole carboxylic acid fragment features an allylboration catalyzed by a chiral diol-$SnCl_4$ complex, followed by a highly diastereoselective directed cyclopropanation.

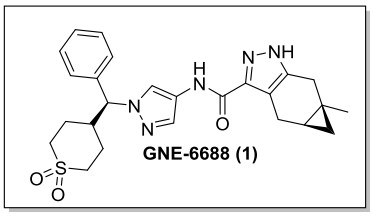
1. Introduction

Interleukin-2 inducible T-cell kinase (ITK) is a non-receptor tyrosine kinase of the Tec family which signals downstream from the T-cell receptor, and is implicated in T-cell development, differentiation and effector function.[1] Significant pre-clinical data supports the role of ITK in allergic asthmatic response, including the observation that $ITK^{-/-}$ mice are resistant to lung inflammation, eosinophil infiltration and mucous production following challenge by the antigen ovalbumin.[2] This promising pre-clinical data has prompted numerous pharmaceutical and academic laboratories to direct research efforts toward the development of selective inhibitors of ITK as potential treatments for allergic asthma.[3]

We have recently disclosed a tetrahydroindazole series of ITK inhibitors which demonstrate excellent potency, selectivity and ADME properties.[4] Compound **1** (GNE-6688; Figure 1) is a quintessential representative of this class that contains two stereogenic structural features important for ITK potency and selectivity: a benzylic pyrazole stereocenter that positions the phenyl ring to interact in an edge-to-face π-stack with Phe437 (Figure 1A), and a fused cyclopropane on the beta face of the ligand that fits into a lipophilic pocket adjacent to Phe435 (Figure 1B).

2. Retrosynthetic Analysis

Retrosynthetically, **1** can be disconnected via the amide bond to form two fragments of approximately equal complexity: aminopyrazole **2** and pyrazole carboxylic acid **3** (Scheme 1). In our original synthesis of inhibitor **1**,[4b, 5] these two fragments were synthesized as racemates, then resolved independently by supercritical fluid chromatography (SFC) on a chiral stationary phase prior to amide bond formation. In our second generation approach, we were interested in exploring the possibility of accessing **2** and **3** as single enantiomers through the use of chiral catalysis in the stereodifferentiating transformations.



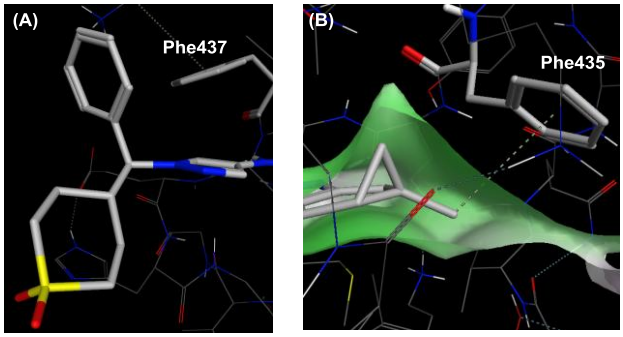
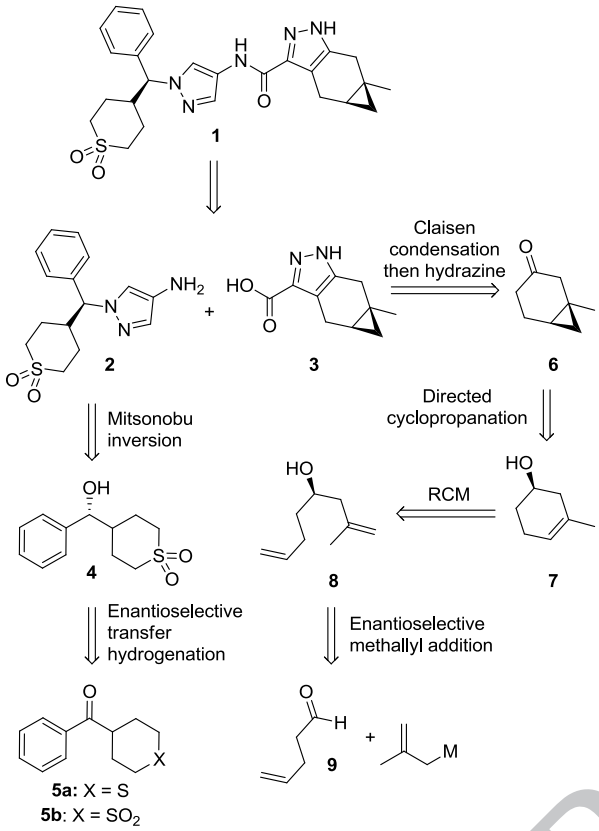


Figure 1. Structure of GNE-6688. (A) Edge-to-face π-stacking interaction with Phe437; (B) Cyclopropane occupying lipophilic pocket adjacent to Phe435. Structures are docking models

prepared using MOE (www.chemcomp.com) and crystal structures from related molecules. For further details see ref. 4b.

Scheme 1. Retrosynthetic analysis of GNE-6688

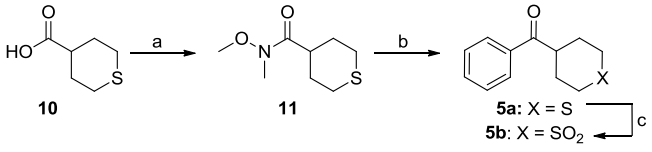


Our proposed synthesis of the nitropyrazole fragment **2**, mimicked the racemic synthesis disclosed previously,[4b,5] which utilized a Mitsunobu reaction[6] between 3-nitropyrazole (**14**) and (±)-**4** as the key step. We envisioned that preparation of **4** in an enantioselective fashion would be feasible through a transition-metal catalyzed transfer hydrogenation of ketone **5a** or **5b**. We had already shown that diethyl oxalate Claisen condensation of (±)-**6** followed by hydrazine addition is an effective method for the regioselective synthesis of pyrazole carboxylic acid (±)-**3**.[4b,5] Unfortunately, our previous racemic synthesis of **6** was not easily amenable to enantioselective variation, and thus we sought a distinct approach. Directed cyclopropanations of cyclohex-3-enols using Simmons-Smith conditions are well precedented,[7] therefore we envisioned that alcohol **7** would be a suitable precursor for cyclopropyl ketone **6**. Reterosynthetic ring-opening of **7** provides diene **8**, which contains an appropriate synthon for an enantioselective methallyl addition onto aldehyde **9**.

3. Results

The syntheses of ketones **5a** and **5b** were straightforward (Scheme 2). Weinreb amide **11** was accessible by HATU-mediated amide bond formation from acid **10**. Addition of phenylmagnesium bromide provided ketone **5a**, which could be oxidized to the sulfone **5b** with Oxone®.

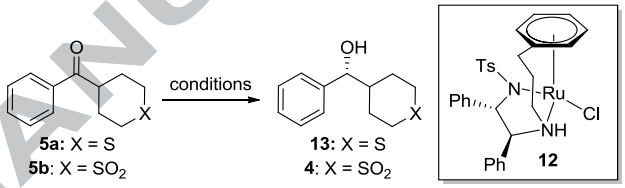
Scheme 2.[a] Synthesis of ketones **5a** and **5b**



[a]Reagents and Conditions: (a) MeONHMe·HCl, HATU, $^{i}Pr_2NEt$, DMF, 87%; (b) PhMgBr, THF, 60 °C, 90%; Oxone®, MeOH, H_2O, 82%.

For the enantioselective reduction of ketones **5**, we were drawn to a report by the Wills group, where a so-called "reverse-tethered" ruthenium complex (**12**) was shown to be an effective catalyst for the highly enantioselective transfer hydrogenation of aryl-alkyl ketones.[8] Reaction conditions determined by Wills to be optimal for the majority of substrates (cat. **12**, HCO_2H, Et_3N, 40 °C) proved unacceptable for sulfone **5b** (Table 1, entry 1). Gratifyingly, modified conditions also reported by Wills (cat. **12**, ^{i}PrOH, KOH, 40 °C, entry 2) provided the desired benzylic alcohol **4** in excellent yield and enantioselectivity. Sulfide **5a** also proved to be an acceptable substrate for this transformation (entry 3), albeit with reduced yield and enantioselectivity, presumably due to complications arising from coordination of the sulfide to ruthenium. Completion of fragment **2** was accomplished by a Mitsunobu reaction between alcohol **4** and 3-nitropyazole, followed by hydrogenative reduction of the nitro group (Scheme 3).

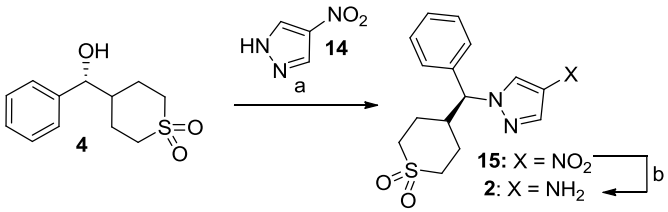
Table 1. Catalytic enantioselective transfer hydrogenation of ketones **5**



Entry	Substrate	Product	Conditions[a]	Yield	%ee[b]
1	**5b**	---	A	0%	---
2	**5b**	**4**	B	95%	>99%
3	**5a**	**13**	B	60%	95%

[a]Reagents and Conditions: (A) 0.5 mol% **12**, Et_3N, HCO_2H, 40 °C; (B) 0.5 mol% **12**, 2.5 mol% KOH, ^{i}PrOH, 40 °C. [b]See ref. 9 for details of chromatography conditions for ee determination.

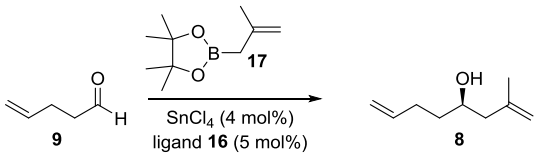
Scheme 3.[a] Completion of fragment **2**



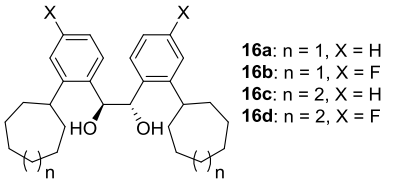
[a]Reagents and Conditions: (a) **14**, PPh_3, DIAD, THF, rt, 75%; (b) 0.1 equiv. Pd/C (10 wt%), H_2 (1 atm), MeOH, EtOAc, rt, quant.

Our attention then turned to optimization of the enantioselective methallyl addition to aldehyde **9**. Although aldehyde **9** had not previously been used as a substrate in enantioselective allyl additions, the related aldehyde dihydrocinnamaldehyde had shown to be an acceptable substrate for the enantioselective allylborations disclosed by Hall and co-workers.[10] Through variation of ligand **16** ("vivols"), we were able to determine that alcohol **8** could be obtained in good yields and good to excellent levels of enantioselectivity (Table 2).[11] Ligand **16b** ("F-vivol-7") proved optimal in this case, providing alcohol **8** in 88% ee on small scale (entry 2), which improved by a slight but reproducible margin when the scale was increased (entry 5), presumably due to limitation of background reactivity caused by adventitious water.

Table 2. Catalytic enantioselective methallyl addition to aldehyde **9**



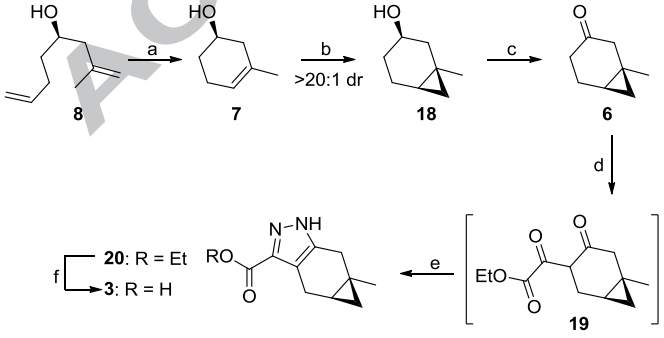
Entry	Ligand	Yield	%ee
1	*ent*-**16a**	42%	-84%
2	**16b**	69%	88%
3	*ent*-**16c**	41%	-78%
4	**16d**	76%	83%
5[b]	**16b**	55%	90%



[a]Reagents and Conditions: (i) 4 mol% $SnCl_4$, 5 mol% **16**, toluene, rt, 15 min; (ii) **17**, -78 °C, 30 min; 1.0 mmol **9**, -78 °C, 4 h; (iii) 2.0 equiv. DIBAL, -78 °C. [b]10.0 mmol scale.

With an acceptable enantioselective synthesis of **8** in hand, completion of fragment **3** proceeded as planned (Scheme 4).[12] Ring-closing metathesis was accomplished in good yield using the Grubbs Second Generation catalyst.[13] Directed cyclopropanation of alkene **7** was accomplished using modified Simmons-Smith conditions developed by Shi,[14] which provided cyclopropane **18** as a single diastereomer as judged by ^{1}H-NMR spectroscopy. Following Swern oxidation to ketone **6**, Claisen condensation with diethyl oxalate provided α-ketoester **19**, which was directly reacted with hydrazine to furnish pyrazole carboxylic ester **20**. Ester hydrolysis under basic conditions completed the synthesis of fragment **3**.

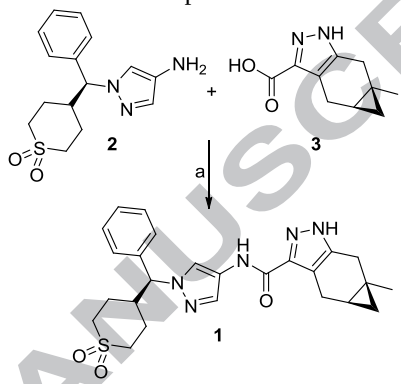
Scheme 4.[a] Completion of fragment **3**



[a]Reagents and Conditions: (a) 5 mol% [1,2-*Bis*-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine) ruthenium, CH_2Cl_2, rt, 79%; (b) Et_2Zn, CF_3COOH, CH_2I_2, CH_2Cl_2, 0 °C → rt, 92%; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C → rt, 94%; (d) sodium, diethyl oxalate, EtOH, 0 °C; (e) hydrazine, AcOH, 120 °C, 34% (2 steps); (f) LiOH, THF, MeOH, 50 °C, quant.

With fragments **2** and **3** available in high enantiomeric purity, all that remained to complete the stereoselective synthesis of inhibitor **1** was to merge the fragments via amide bond formation. Amidation using the peptide coupling reagent HATU proved successful for fragment coupling, providing **1** in good yield (Scheme 5). SFC on a chiral stationary phase (Whelk-1 (4.6x50 mm; 3 μm ID) column with 40% MeOH/0.1%NH_4OH as eluent) was successful in resolving all four diastereoisomers of **1**, and verified that material prepared via this route was enantio- and diastereomerically pure to the limit of detection (>20:1). Furthermore, comparison to an authentic standard of **1** confirmed that the material exhibited the relative and absolute stereochemistry as shown.

Scheme 5.[a] Completion of inhibitor **1**



[a]Reagents and Conditions: (a) 1.5 equiv. HATU, 2.5 equiv. ^{i}Pr$_2$NEt, DMF, rt, 84%.

In conclusion, we have developed a convergent, stereoselective synthesis of ITK inhibitor GNE-6688, highlighted by two highly enantioselective catalytic transformations. This synthesis should find utility for the synthesis of related molecules which contain either of these stereogenic fragments.

Acknowledgments

The authors are indebted to Prof. Dennis Hall for providing ligands *ent*-**16a**, **16b** and **16c** for use in the early phase of optimization of the allylboration reaction. Mengling Wong is gratefully acknowledged for the SFC analyses of enantioselectivity determination. Dr. Matthew Volgraf and Malcolm P. Huestis are acknowledged for their careful editing of this manuscript, and Daniel Shore is acknowledged for his assistance in final preparation.

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9. Enantioselectivity was determined by SFC analysis on a chiral stationary phase. For alcohol **4**, a Chiralpak ID column was used with 35% MeOH + 0.1% NH_4OH as the eluent. For alcohol **13**, a Chiralpak IA column was used with 15% MeOH + 0.1% NH_4OH as the eluent. Absolute stereochemistry was assigned by analogy (ref. 8), and verified by conversion to authentic **1**.
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11. Enantioselectivity was determined by conversion of **9** to its 3,5-dinitrobenzoate (3,5-dinitrobenzoylchloride, pyridine), and SFC analysis on a chiral stationary phase (Chiralpak AD; 5 to 50% MeOH + 0.1% NH_4OH). Absolute stereochemistry was assigned by analogy (ref. 10) and verified by conversion to authentic **1**.
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- A stereoselective synthesis of the ITK inhibitor GNE-6688 has been accomplished.
- An enantioselective transfer hydrogenation was used to prepare the Western fragment.
- An enantioselective allyl boration, and a directed cyclopropanation were key steps for the Eastern fragment.