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Efforts towards a Noyori reduction of a 3-fluorpiperidin-4-one with dynamic kinetic resolution

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ABSTRACT

A Noyori reduction of racemic 1-Boc-3-fluoropiperidin-4-one has been achieved under dynamic kinetic resolution conditions that results in a single cis enantiomer being obtained with both diastereo- and enantioselectivity > 90%. This medicinal chemistry building block can be generated on multi-gram scale using the developed conditions to a single enantiomer in a 60% yield after employing a crystallisation procedure.

Piperidines are a common building block in medicinal chemistry. They are found in both natural product and synthetic drugs, where medicinal chemists prize their ability to act as pharmacophores and the basic amine can be used to improve pharmacokinetic properties including the aqueous solubility of the molecule through lowering the lipophilicity. In addition the conformational rigidity allows the piperidine to play a role as a scaffold for displaying substituents with defined vectors [1]. Marketed agents include the anti-cancer alkaloid vinblastine (Veblan®) isolated from the Madagascar Periwinkle, the stimulant methylphenidate (Ritalin®) and the Janus kinase inhibitor (Xeljanz®) tofacitinib (Fig. 1). Indeed, an analysis by Njardarson in 2014 found the piperidine to be the most commonly found nitrogen-containing heterocycle in FDA-approved pharmaceuticals [2], while 25% of all kinase inhibitors licensed by the FDA in the United States as of April 2020 contain a piperidine [3].

Although the basicity of the piperidine has benefits, it can also lead to off-target liabilities. For example, it has been implicated in the inhibition of the hERG potassium ion channel [1], which can lead to cardiac arrhythmias that can be fatal. Modulation of the basicity of the piperidine has been demonstrated to reduce the hERG liabilities and an increasingly common tactic has been the introduction of a 3-fluoro-group [4]. The addition of a fluoro group can improve both the off-target liabilities and on-target potency as well as improving the pharmacokinetic properties of the molecule by improving permeability and adsorption [4–7]. The orientation of the fluorine group has a significant influence on the piperidine basicity with the equatorial fluoro-group reducing the pKa by approximately 2 units, while a smaller reduction of about 1 unit is observed with an axial fluoro-group [4–7]. These properties continue to be exploited in medicinal chemistry programs [8,9]. In one of our own drug discovery programs we were keen to probe 3-fluoropiperidines for their effects on hERG and PK. These compounds are usually synthesised in a racemic fashion followed by a chiral separation. Thus, MacMillan's reported chiral fluorination of 1-Boc-piperidin-4-one **1** using a modified Cinchona alkaloid catalyst appeared to be very useful [10]. We were able to use this chemistry to generate either enantiomer of cis-1-Boc-3-fluoropiperidin-4-ol **2** through use of the catalyst derived from either quinine or the pseudoenantiomer quinidine followed by reduction of the ketone **3** with enantiopurities of 95% [11]. A recrystallization procedure was employed to obtain enantiopure material in an overall yield of 44%. We further showed that similar enantioselective fluorination could be obtained by employing simple benzylamines (for example α-methylbenzylamine) as catalyst albeit with lower enantioselectivities.

As part of our evaluation of alternative routes to enantiopure (3*S*, 4*R*)-1-Boc-3-fluoropiperidin-4-ol **(+)-2** we were intrigued by the possibility of carrying out a dynamic kinetic resolution (DKR) of racemic 1-Boc-3-fluoropiperidinone **rac-3** under reducing conditions. The Noyori dynamic kinetic resolution is a powerful

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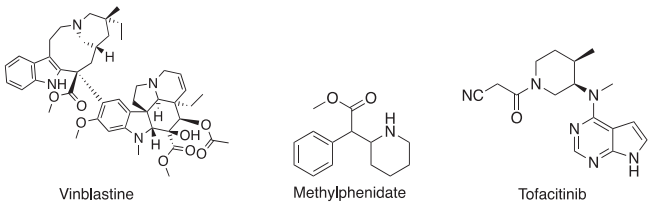
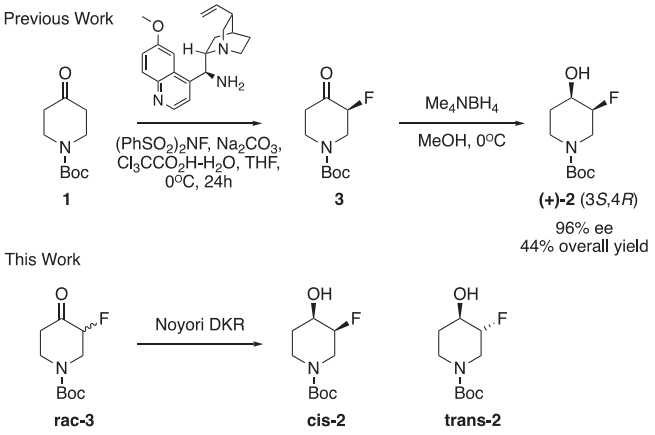


Fig. 1. Piperidine-containing pharmaceuticals.

method for setting stereochemistry and relies on establishing an equilibrium between the two enantiomers that can be differentiated by the catalyst system to effect reduction of the ketone [12–14]. In this way racemic material can be converted to a single enantiomer. Since our previous experience suggested that if we could obtain >90% ee of (3*S*, 4*R*)-1-Boc-3-fluoropiperidin-4-ol **(+)-2**, we would be able to recrystallize to enantiopurity, we proceeded to investigate the potential for such a DKR (Scheme 1).

To our knowledge the dynamic kinetic resolution of an α-fluoropiperidinone has not been reported although a enzymatic transanimation strategy has recently been published [15]. Given the small difference in size between hydrogen and fluorine we considered enantioselective reduction to be challenging but wondered whether the rigidity of the piperidinone ring may be beneficial. Notably, cis-diastereoselective reduction of 2-methylcyclohexanone has been reported along with dynamic kinetic resolution of 2-isopropylcyclohexanone [16]. Further, we noted that there have been successful examples of substituted piperidinones as



Scheme 1. Comparison of previous enantioselective fluorination with the dynamic kinetic resolution.

substrates for the DKR reduction with Noyori showing that a 3-phenylpiperidin-4-one could be reduced enantioselectively [17]. In addition workers at Hoffmann-La Roche were able to use the methodology to effect reduction of 4-benzyl-3-piperidinone [18]. In each of these examples the cis diastereomer was obtained, the desired diastereomer in our situation.

In our studies we focused on attempting to obtain the (3*S*, 4*R*)-1-Boc-3-fluoropiperidinol **(+)-2** and began by developing a chiral hplc method to separate the two cis enantiomers from the trans diastereomers (the two trans enantiomers did not separate under the column conditions) and starting ketone (see Supplementary Material for details). A series of ruthenium pre-catalysts containing a chiral diphosphine ligand and a chiral diamine, which are known to be effective in such reactions, were screened [12,19]. The reactions were carried out with a substoichiometric amount of potassium tert-butoxide as base under a high pressure of hydrogen at elevated temperature. Under the conditions screened many catalyst combinations resulted in almost complete consumption of the ketone with the cis diastereomer being favoured in moderate ee's (Table 1). The S,S catalyst system gave the desired enantiomer **(+)-2** with encouraging enantioselectivity of up to 71%, while the enantiomeric catalysts resulted in the undesired 3*R*, 4*S* enantiomer **(−)-2** being preferred (Entry 9 vs 10). The mis-matched catalysts resulted in poor enantioselectivity and often low diastereoselectivity (Entries 2 vs 12 and 5 vs 13).

Having identified the (S,S) catalyst system as leading to the desired enantiomer we investigated a smaller set of catalyst combinations looking to improve the catalyst loading (Table 2). At a five-fold lower loading the diastereoselectivity was retained but the enantioselectivity was improved and we were able to reach 84%ee using the [(S)Xyl-PPhos $RuCl_2$ (S)DAIPEN] catalyst (entry 2). Reducing the amount of potassium tert-butoxide under these catalyst conditions did not change the product ratio but reducing the catalyst loading to 1:500 resulted in a 91%ee of the desired enantiomer **(+)-2** in improved diastereoselectivity. There are several interesting observations from the screen. The BINAP ligand does not perform to the same level as the Chan dipyridylphosphine ligand (entries 6 vs 2, 3 vs 4). Also, using the bulkier Xyl-PPhos ligand with the DIAPEN diamine improves the enantioselectivity (84 vs 73%ee, entries 2 vs 4) while with the DPEN diamine the smaller PPhos ligand is clearly superior (entries 1 vs 5).

Doubling the concentration from [0.17 M] to [0.34 M] while halving the catalyst ratio to 1000:1 (0.1 mol%) and using only 10 mol% potassium tert-butoxide resulted in good cis diastereoselectivity (86%de) but a reduction in enantioselectivity to 85%ee. Interestingly using the enantiomeric catalyst [(R)Xyl-PPhos $RuCl_2$ (R)DAIPEN] under these same 1000:1 conditions resulted in 80% de in favour of the cis diastereomer with the (3*R*, 4*S*)-enantiomer

Table 1
Initial screen of catalysts for the reduction of **rac-3**.

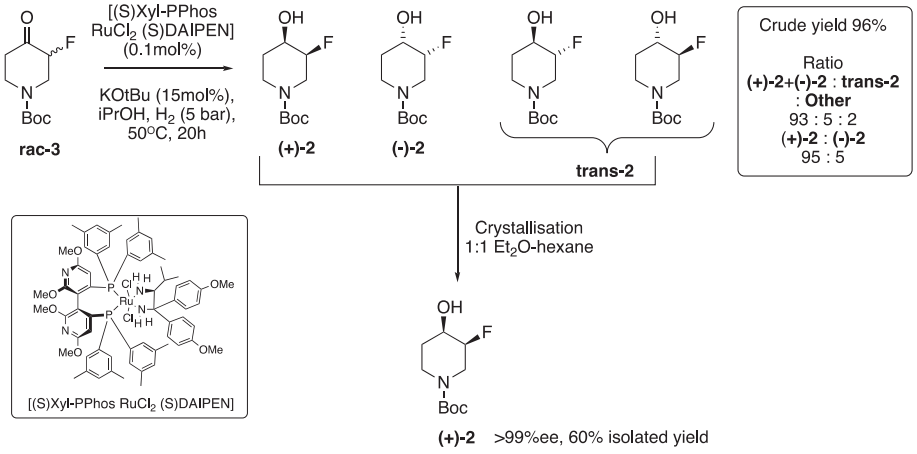
Entry	Catalyst	Conversion (%)	trans-**2** (%)	cis-**2** (%)	ee (cis) (%)	de (%)	Other (%)
1	[(S)Xyl-PPhos $RuCl_2$ (S)DAIPEN]	100	8	91	71	84	1
2	[(S)PPhos $RuCl_2$ (S)DAIPEN]	100	11	89	64	78	0
3	[(S)Xyl-BINAP $RuCl_2$ (S)DAIPEN]	100	13	86	30	74	1
4	[(S)dm-SegPhos $RuCl_2$ (S)DAIPEN]	100	15	83	25	69	2
5	[(S)BINAP $RuCl_2$ (S)DAIPEN]	100	10	88	25	80	2
6	[(S)Tol-BINAP $RuCl_2$ (S,S)DPEN]	100	1	99	58	98	0
7	[(S)PPhos $RuCl_2$ (S,S)DPEN]	86	4	81	48	91	1
8	[(S,S)ChiraPhos $RuCl_2$ (S,S)DPEN]	100	48	51	25	3	1
9	[(S)Xyl-PPhos $RuCl_2$ (S,S)DPEN]	96	4	87	6	91	5
10	[(R)Xyl-PPhos $RuCl_2$ (R,R)DPEN]	84	7	76	−42	83	1
11	[(R)PPhos $RuCl_2$ (R,R)DACH]	85	15	70	−14	65	0
12	[(R)PPhos $RuCl_2$ (S)DAIPEN]	83	9	73	−18	78	1
13	[(S)BINAP $RuCl_2$ (R)DAIPEN]	100	10	89	−24	80	1

Conditions: Substrate/catalyst ratio 50:1, 20 mol% KOtBu in iPrOH [0.17 M], H_2 (30 bar), 50 °C, 18 h.

Table 2
Reduced catalyst loading for the reduction of **rac-3**.

Entry	Catalyst	Conversion (%)	trans-**2** (%)	cis-**2** (%)	ee (cis) (%)	de (%)	Other (%)
1	[(S)Xyl-PPhos $RuCl_2$ (S,S)DPEN]	100	29	70	54	41	1
2	[(S)Xyl-PPhos $RuCl_2$ (S)DAIPEN]	100	9	90	84	82	1
3	[(S)BINAP $RuCl_2$ (S)DAIPEN]	100	1	92	56	97	7
4	[(S)PPhos $RuCl_2$ (S)DAIPEN]	100	4	95	73	92	1
5	[(S)PPhos $RuCl_2$ (S,S)DPEN]	100	5	94	68	90	1
6	[(S)Xyl-BINAP $RuCl_2$ (S)DAIPEN]	100	6	92	50	88	2
7	[(S)Xyl-PPhos $RuCl_2$ (S)DAIPEN]*	100	9	90	82	82	1
8	[(S)Xyl-PPhos $RuCl_2$ (S)DAIPEN]**	100	4	95	91	92	1

Conditions: Substrate/catalyst ratio 250:1, 20 mol% KOtBu in iPrOH [0.17 M], H_2 (30 bar), 50 °C, 18 h; * 10 mol% KOtBu; ** Substrate/catalyst ration 500:1.



Scheme 2. Large scale formation of **(+)-2** from **rac-3** by Noyori reduction followed by crystallisation.

(−)-2 being the major product but with a lower enantioselectivity of 61%ee. By reducing the concentration back to [0.2 M] allowed us to match our best conditions to date achieving 94%de and 91%ee with catalyst ratio of 1000:1 and 10 mol% potassium tert-butoxide.

Reduction could also be achieved under transfer hydrogenation conditions without the need for high pressure. However, using triethylamine as base, the reductions showed little diastereoselectivity with low enantioselectivity of the cis product being observed. We assume that under these conditions there is little epimerization of the α-fluoro stereocenter occurring. Using potassium tert-butoxide in these reactions did increase the ratio of the cis diastereomer; however, there was considerable decomposition in these reactions and further studies were not carried out.

The reactions discussed above were carried out using a parallel multi-reactor synthesizer on a 0.5–1 mmol scale [20]. Attempts to lower the pressure of the reaction at catalyst loading of 0.1 mol% had resulted in incomplete conversion after 18 h but did go to completion with similar product ratios at higher catalyst concentrations. To make the reaction more useful we turned to a high-pressure reaction vessel to carry out multi-gram reactions, where it was hoped that the increase in scale would allow for lower hydrogen pressures. In a series of studies with the [(S)Xyl-PPhos $RuCl_2$ (S)DAIPEN] catalyst on an increased scale it was shown that the hydrogen pressure could be reduced down to 5 bar without effecting the diastereo- or enantioselectivity. Indeed, we were able to achieve complete conversion on a 16 g scale with only 5 bar of hydrogen (Scheme 2). On completion of the reaction, the mixture was filtered through a pad of silica and recrystallised using the conditions developed previously [11]. The crystallization removed the trans impurity and the undesired enantiomer to obtain **(+)-2** with >99%ee, albeit in three crops, in an overall yield of 60%, which compares well with the previously reported enantioselective fluorination method (see Supplementary Material for experimental details).

In summary, we have been able to develop a Noyori reduction under dynamic kinetic resolution conditions of 1-Boc-3-fluoropiperidin-4-one which is both diastereoselective and enantioselective, a reaction that to our knowledge has not been reported despite the significance of the resulting fluoropiperidinol to the medicinal chemistry community. The reaction can be carried out on a multi gram scale without impact to the selectivity with catalyst loadings of 0.1 mol%. By carrying out a crystallisation protocol the fluoropiperidinol can be obtained in >99%ee in a yield that competes well with our previous enantioselective fluorination procedure.

Declaration of Competing Interest

The authors are or were shareholders of either Johnson-Matthey or Rigel Pharmaceuticals

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152764.

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