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Enantioselective synthesis of a chiral fluoropiperidine via asymmetric hydrogenation of a vinyl fluoride

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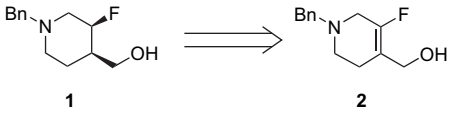
ABSTRACT

Asymmetric hydrogenation of a vinyl fluoride derivative gives efficient access to enantioenriched 1,3,4-trisubstituted piperidine **1** with a stereogenic alkyl fluoride center. Extensive catalyst screening across transition metals and chiral ligands identified only one catalyst, a Rh/Walphos complex, that gives high conversion, enantioselectivity and chemoselectivity for olefin reduction over defluorination. The presence of acid additives in the hydrogenation exerts a profound effect on reaction outcome. The results of deuterium labeling studies demonstrate that significant olefin isomerization accompanies the undesired defluorination side-reaction.

1. Introduction

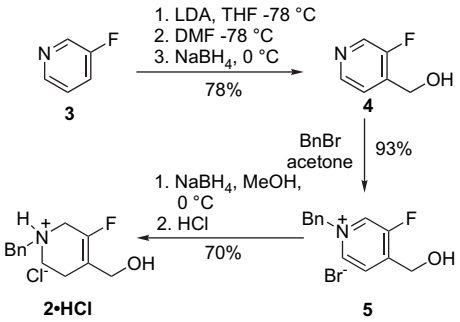
The asymmetric synthesis of chiral organofluorine compounds with stereogenic fluorine-bearing carbon atoms remains an active area of research.[1] By far the most commonly studied methods involve asymmetric fluorinations of carbonyl derivatives, often catalyzed by chiral transition metal complexes or Lewis bases.[1a–c] The products of such transformations provide ready synthetic access to a number of useful enantioenriched fluorinated building blocks, among them 1,2-fluorohydrins. As part of a recent drug development program, we required a means to synthesize kilogram quantities of enantiopure **1**, a chiral 1,3-fluorohydrin (Scheme 1). Since the standard methodologies discussed above did not give efficient access to **1**, we envisioned a complementary approach involving the asymmetric hydrogenation of a fluorinated allylic alcohol **2**. This report describes the successful identification of a chiral catalyst and conditions that give high chemo- and enantioselectivity in the asymmetric hydrogenation of **2**, as well as the results of mechanistic experiments that shed light on the divergent pathways that comprise the catalytic reaction network.



Scheme 1. Retrosynthesis of enantioenriched fluoropiperidine.

2. Results

The tetrahydropyridine substrate for the asymmetric hydrogenation was obtained in a three step process from 3-fluoropyridine **3** (Scheme 2). Directed metallation of **3** and quench with DMF gave 3-fluoro-4-formylpyridine,[2] which was reduced in situ with sodium borohydride to the corresponding hydroxymethyl pyridine **4**, isolated as a white crystalline solid in 79% yield. Alkylation of **4** with benzyl bromide gave crystalline pyridinium bromide **5**, which was isolated in 93% yield. Reduction of **5** with sodium borohydride gave tetrahydropyridine **2**, which was purified by column chromatography and used as the free base for catalyst screening studies. Compound **2** could also be crystallized in 70% yield as the hydrochloride salt.



Scheme 2. Synthesis of vinyl fluoride.

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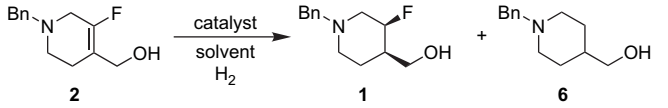
Table 1
Initial catalyst screen for the asymmetric hydrogenation of vinyl fluoride **2**[a]



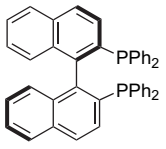
2 **1** **6**

Entry	Metal[b]	S/C[c]	Ligand[d]	Solvent	% Conv[e]	**1**:**6**[e]	er[f]
1	Ir	4	**7**	CH_2Cl_2	14	7:93	—
2	Ir	4	**8**	CH_2Cl_2	32	9:91	—
3	Ir	4	**9**	CH_2Cl_2	25	11:89	—
4	Ir	4	**10**	CH_2Cl_2	18	19:81	—
5	Ir	4	**11**	CH_2Cl_2	38	3:97	—
6	Ir	4	**12a**	CH_2Cl_2	26	5:95	—
7	Ru[g,h]	5	**7**	MeOH	48	91:9	2:98
8	Rh[h]	4	**7**	MeOH	5	33:67	—
9	Rh[h]	4	**8**	MeOH	6	44:56	—
10	Rh[h]	3	**9**	MeOH	38	33:67	—
11	Rh[h,i]	4	**13**	MeOH	1	—	—
12	Rh[h]	4	**11**	MeOH	4	44:56	—
13	Rh[h]	4	**12a**	MeOH	85	98:2	19:81

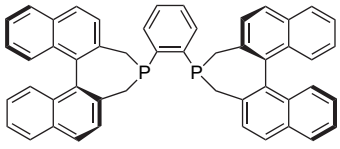
[a] Reaction conditions: 4 mg/mL **2**, 90 psi g H_2, 50 °C, 15–16 h.
[b] Ir catalysts prepared in situ by ageing [(1,5-cyclooctadiene)$_2$Ir]BF_4 and chiral ligand (1.1–1.2 equiv relative to Ir) in CH_2Cl_2 for 2 h at 50 °C prior to hydrogenation reaction. Rh catalysts prepared in a similar manner from [(norbornadiene)$_2$Rh]BF_4 at room temperature.
[c] Substrate to catalyst ratio.
[d] See Figure 1 for ligand structures.
[e] Determined by HPLC (compounds **1**, **2** and **6** have approximately equal UV response factors).
[f] Enantiomeric ratio of (3*S*,4*R*)- to (3*R*,4*S*)-**1** determined by HPLC.
[g] Preformed (*R*-BINAP)Ru(*p*-cymene)Cl_2 catalyst used.
[h] Reaction conducted at room temperature.
[i] Ligand/Rh ratio of 2:1 was used.

With vinyl fluoride **2** in hand, we began screening reaction conditions to effect the asymmetric hydrogenation. At the initiation of this work, the published literature contained only limited examples of asymmetric hydrogenations of vinyl fluorides, namely the reduction of fluorinated α,β-unsaturated carboxylic acids catalyzed by Ru-BINAP complexes.[1d,3] More recently, Andersson and co-workers have described Ir-phosphino-oxazoline catalysts that are tuned to give high chemo- and enantioselectivity in the asymmetric hydrogenations of vinyl fluorides, including simple fluorinated allylic alcohols.[4] For asymmetric hydrogenations of non-fluorinated allylic alcohols, most literature examples have utilized either Ru[5] or Ir[5a,5c,6] catalysts. Thus, our initial catalyst screens incorporated both Ir and Ru catalysts, utilizing chiral ligands that could be obtained commercially on a bulk scale (Table 1, entries 1–7; Fig. 1).

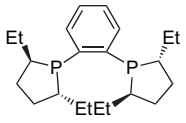
As shown in Table 1, cationic Ir catalysts exhibited poor reactivity and chemoselectivity, resulting in the formation of defluorinated piperidine **6** as the major product (entries 1–6). In contrast, BINAP-Ru showed promising chemo- and enantioselectivity (entry 7). However, further optimization studies in which the reaction solvent, temperature and pressure were varied failed to raise the activity of this catalyst system to useful levels. At this point, our attention turned to cationic Rh catalysts. Although such catalysts have found scant use in the literature for asymmetric reductions of allylic alcohols,[7] we reasoned that the advent of newer classes of chiral bis(phosphine) ligands might increase the odds of finding a useful catalyst. Entries 8–13 of Table 1 show results of initial screens. In general, Rh catalysts provided higher chemoselectivity of the desired product over defluorination versus Ir, but in most cases this did not reach useful levels. One particular catalyst stood out in the screen, Josiphos **12a** (entry 13), which exhibited high conversion to product, moderate enantioselectivity, and an impressive 49:1 ratio of **1**:**6**. This was an extremely promising lead result since Josiphos and related ferrocenyl-phosphine



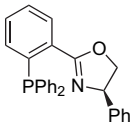
7: (R)-BINAP



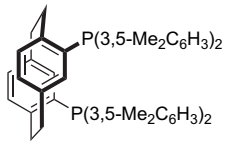
8: (S)-Binaphane



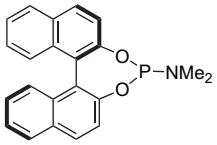
9: (R,R)-Et-DuPHOS



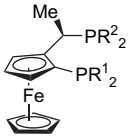
10: (R)-PHOX



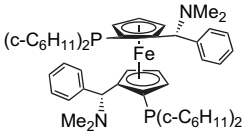
11: (R)-Xyl-PHANEPHOS



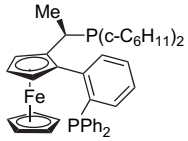
13: (R)-MonoPhos



(R)-(S)-Josiphos



14: (R)-(S)-Mandyphos



15: (R)-(R)-Walphos

12a: R^1 = Ph; R^2 = t-Bu
12b: R^1 = p-$CF_3C_6H_4$; R^2 = t-Bu
12c: R^1 = Ph; R^2 = c-C_6H_{11}
12d: R^1 = c-C_6H_{11}; R^2 = t-Bu
12e: R^1 = Ph; R^2 = 3,5-$Me_2C_6H_3$
12f: R^1 = t-Bu; R^2 = 2-MeC_6H_4
12g: R^1 = t-Bu; R^2 = 3,5-$Me_2C_6H_3$

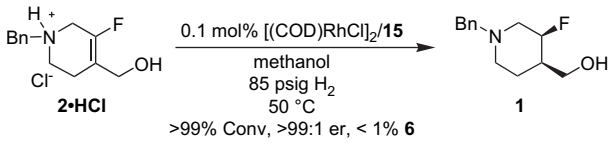
Figure 1. Representative chiral ligands screened for the asymmetric hydrogenation of **2**.

ligands are highly tunable, with many commercially available derivatives bearing various substitution patterns on the phosphorus atoms.[8]

Following up on the Rh-Josiphos lead, subsequent experiments examined 14 differentially substituted Josiphos ligands in a variety of solvents. Representative results are shown in Table 2. In general, methanol was found to give the highest activities and selectivities across all solvents examined. Josiphos derivatives similar to the initial lead, **12a**, with a diarylphosphino group attached directly to the ferrocene ring and a dialkylphosphino group attached to the chiral alkyl bridge, also gave high selectivity for product **1** over defluorinated **6**, but with only moderate enantioselectivity (entries 1,2). Replacing the diphenylphosphino group in **12a** with a dicyclohexylphosphino group also gave good chemoselectivity, but with nearly complete loss in enantioselectivity (entry 3). Josiphos ligands with two diarylphosphino groups gave poor chemo- and enantioselectivity (entry 4). However, Josiphos ligands in which the substitution pattern of **12a** was reversed, with the di-*tert*-butylphosphino moiety attached directly to the ferrocene ring and a diarylphosphino substituent on the chiral alkyl bridge, gave good **1**/**6** selectivity and enhanced enantioselectivity versus **12a**, albeit with low conversion (entries 5, 6). Unfortunately, further optimization experiments with these two ligands demonstrated that the inherent activities were too low to be useful. However, further screening with 11 examples of chiral ferrocenyl-phosphines from the Walphos[9] and Mandyphos[10] ligand families turned up two additional leads (Table 2, entries 7,8). Although the activity of the Mandyphos ligand **14** was not at a useful level, the Walphos ligand **15** gave excellent enantioselectivity, good **1**/**6** selectivity, and high catalytic activity. Other derivatives of these ligands tested exhibited low catalytic activities.

inhibited the hydrogenation reaction. Somewhat surprisingly, using the isolated HCl salt gave the best combination of reactivity and selectivity.[11] Since this salt was readily isolable as a crystalline solid, it was utilized for further development of the catalytic reaction.

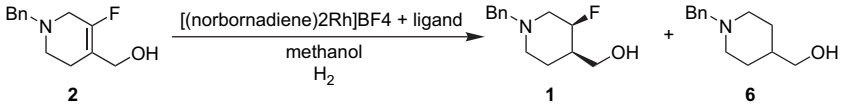
Final reaction optimization involved varying substrate concentration, hydrogen pressure, temperature and catalyst loading. As is commonly the case, improvements in the crystallization process for isolating **2**·**HCl** removed trace amounts of unidentified catalyst poisons and led to a dramatic reduction in the amount of catalyst required for the reaction to reach full conversion, as little as 0.1 mol % in the final optimized conditions. It was also found that the catalyst derived from $[(1,5\text{-cyclooctadiene})RhCl]_2$ performed as well as, or better than, that formed from the cationic $[(norbornadiene)_2Rh]BF_4$. The final optimized conditions shown in Eq. 1 were demonstrated on 15 g scale to give enantiomerically pure fluorohydrin **1** in >99% conversion, 99% assay yield, >99% ee, <1% **6**.[12] These conditions were repeated successfully on multi-kg scale with only slight modifications to accommodate vessel pressure limitations.



(1)

Intrigued by the strong effect of acid additive on the rate, product/defluorination ratio and enantioselectivity, we conducted some simple deuterium labeling experiments to better characterize the reaction pathways operative during the asymmetric hydrogenation reaction. As shown in Eq. 2, running the asymmetric hydrogenation of the hydrochloride salt of **2** under a D_2 atmosphere resulted in *syn* addition across the olefin, with nearly complete deuterium incorporation at the two formerly olefinic carbon atoms and essentially no deuterium incorporation on adjacent carbon atoms. Reduction of the freebase of **2** under the same conditions gave a ~1:1 mixture of desired product **1-*d*$_2$** and defluorinated **6-*d*$_4$**, which were separated by semi-preparative SFC and analyzed by multinuclear NMR spectroscopy (Eq. 3). The pattern of deuterium incorporation in the desired reduced product **1-*d*$_2$** was identical to that obtained from the hydrochloride salt, with no deuterium incorporation outside of the two formerly olefinic carbons. For the defluorinated by-product **6-*d*$_4$**, however, the picture was much more complex. The isotopically labeled mixture obtained from the

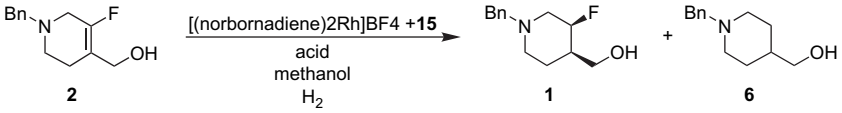
Table 2
Selected results from screening of rhodium ferrocenyl-phosphine catalysts for the asymmetric hydrogenation of **1**[a]



Entry	Substrate	S/C[b]	Ligand[c]	% Conv[d]	**1**:**6**[d]	er[e]
1	**2**	5	**12b**	39	96:4	25:75
2	**2**	5	**12c**	32	88:12	27:73
3	**2**	5	**12d**	42	96:4	41:59
4	**2**	5	**12e**	15	50:50	44:56
5	**2**	5	**12f**	47	92:8	8:92
6	**2**·**HCl**	5	**12g**	73	86:14	6:94
7	**2**·**HCl**	5	**14**	17	93:7	9:91
8	**2**·**HCl**	5	**15**	100	90:10	>99:1

[a] Reaction conditions: 4 mg/mL **2** or 5 mg/mL **2**·**HCl** in methanol, 90 psig H_2, 20 °C, 15–16 h. Catalysts prepared in situ by ageing $[(norbornadiene)_2Rh]BF_4$ and chiral ligand (1.1–1.4 equiv relative to Rh) in MeOH for 1 h at ambient temperature prior to hydrogenation reaction.
[b] Substrate to catalyst ratio.
[c] See Figure 1 for ligand structures.
[d] Determined by HPLC (compounds **1**, **2** and **6** have approximately equal UV response factors).
[e] Enantiomeric ratio of (3*S*,4*R*)- to (3*R*,4*S*)-**1** determined by HPLC.

Table 3
Effect of acid additives on the asymmetric hydrogenation of **1** catalyzed by Rh/Walphos **15**[a]

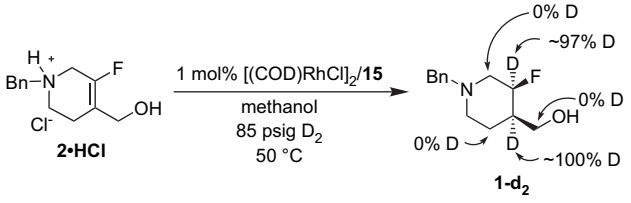


2 **1** **6**

Entry	Additive (equiv)	% Conv[d]	**1**:**6**[b]	er[c]
1	none	60	74:26	95:5
2	HBF_4 (1.5)	99	91:9	98:2
3	HPF_6 (4)	96	88:12	97:3
4	p-$CH_3C_6H_4SO_3H$ (1.3)	99	93:7	97:3
5	CF_3CO_2H (2.5)	50	77:23	99:1
6	CH_3SO_3H (3)	99	93:7	>99:1
7	HBr (3)	7	—	—
8	HCl (1)[d]	99	96:4	>99:1

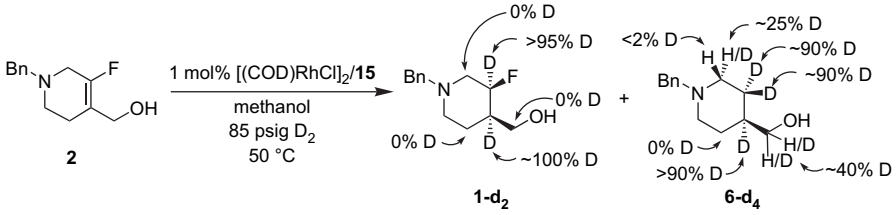
[a] Reaction conditions: 8 mg/mL **2** in methanol, 90 psi g H_2, 20 °C, 15–16 h, S/C=20. Catalyst prepared in situ by ageing [(norbornadiene)$_2$Rh]BF_4 and **15** (1.2 equiv relative to Rh) in MeOH for 1 h at ambient temperature prior to hydrogenation reaction.
[b] Determined by HPLC (compounds **1**, **2** and **6** have approximately equal UV response factors).
[c] Enantiomeric ratio of (3*S*,4*R*)- to (3*R*,4*S*)-**1** determined by HPLC.
[d] Preformed HCl salt used.

hydrogenation incorporated the equivalent of two molecules of D_2. As in the desired product, one molecule of D_2 formally added across the olefin in a *syn* fashion. As for the second molecule of D_2, one deuteron replaced the fluorine atom in **2**, whereas the other was distributed across the axial proton on the adjacent ring carbon atom at the 2-position (~25%) and the exocyclic methylene protons (~40% of two protons, or 0.8 proton equivalent). This pattern of deuterium incorporation traces the path of Rh migration across the ring via successive insertions and β-hydride elimination steps.



(2)

desired olefin reduction over defluorination as well as the enantioselectivity varied strongly with small variations in chiral ligand structure, and selectivity trends for one class of substrate did not necessarily translate to other classes.[4] In the present case, examination of catalysts derived from different transition metals and numerous chiral ligands revealed in most cases poor reactivity and high levels of defluorination (Tables 1 and 2). Only a small subset of chiral catalysts, including BINAP/Ru and ferrocenyl-phosphine complexes of Rh, favored simple olefin reduction over defluorination. Amongst the latter, variations in ligand structure away from the original Josiphos **12a** lead produced profound changes in the enantioselectivity and amount of defluorination (Table 2). In the end, among the catalysts that gave high chemoselectivity and enantioselectivity in the reduction of **2**, only one, Rh/Walphos **15**, gave acceptable conversion with reasonable catalyst loading. This catalyst seems uniquely tuned to fit the structure of the prochiral vinyl fluoride, allowing for exquisite enantioselectivity (>99:1 er), chemoselectivity (>99:1 **1**:**6**) and activity (full conversion with 0.1 mol % catalyst). Of the other five Walphos derivatives screened under identical reaction conditions, all were essentially catalytically inactive (maximum 10% conversion). Even in the case of **15**,



(3)

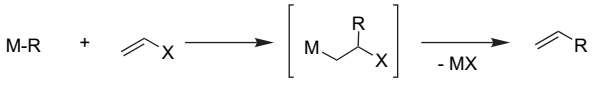
3. Discussion

Achieving high enantioselectivity and reactivity in the asymmetric hydrogenation of structurally complex olefins requires identifying a catalyst that presents a chiral environment closely matching the inherent structural and conformational bias of the substrate to maximize energy differences in the diastereomeric transition states leading to desired over undesired enantiomers of the product.[13] Finding such a catalyst is typically accomplished through iterative alterations of a catalyst core structure, or more efficiently though screening of a wide variety of catalysts in parallel.[14] Taking the literature reports of enantioselective hydrogenation of vinyl fluorides as a case in point, the chemoselectivity for the reaction performance was profoundly altered by the presence of added acid (Table 3), whereas the selectivity of other catalysts screened (e.g., Rh/**12a**) varied only slightly in the hydrogenation of **2** versus **2**·**HCl**.

The origins of the acid effect in the hydrogenation with Rh/**15** were examined through deuterium labeling studies (Eqs. 2 and 3). There are at least three possiblities for how the addition of strong acid may alter the course of the present asymmetric hydrogenation reaction, leading to higher enantioselectivity and lower levels of defluorination: (1) through altering the catalyst structure, most likely through binding of the conjugate base anion to the metal; (2) through direct participation in an elementary step of the catalytic cycle such as product release through protonolysis of

a metal–carbon bond; or (3) through altering the substrate conformational bias or dynamics through protonation of the basic nitrogen. In the case of hypothesis (1), the similar positive effects of a variety of strong acids with weakly coordinating counterions on chemo-and enantioselectivity argues against coordination of the conjugate base anion to Rh being a primary cause of the observed acid effect (Table 3). As for hypothesis (2), the high levels of deuterium incorporation at both olefinic carbons of **1-*d*$_2$** formed both in the absence and presence of added HCl suggests a simple mechanism for olefin reduction involving olefin insertion into the Rh–D bond followed by reductive C–D elimination, without significant protolytic cleavage of the Rh–C bond of the incipient olefin insertion intermediate (Eqs. 2 and 3). On the other hand, there are no obvious experimental observations to discount hypothesis (3), and this explanation seems reasonable in light of the discussion in the previous paragraph that slight alterations in the conformational bias and/or dynamics of the substrate, such as might be expected to occur upon protonation of the basic nitrogen, could facilitate the desired olefin hydrogenation reaction over defluorination, at the same time enhancing substrate-catalyst interactions that increase the enantioselectivity of the reaction.

A number of transition metal mediated dehalogenations of vinyl halides have been reported in the literature.[15–18] Although in the case of some perhalogenated olefins mechanistic evidence supports direct metal insertion into a vinylic C–X (X=halogen) bond,[15,17] for most vinyl halides dehalogenation is believed to proceed via insertion of the vinyl halide into a metal hydride or alkyl complex to give a metal 2-haloalkyl intermediate that then undergoes facile β-halogen elimination to give the dehalogenated olefin and metal halide as products (Eq. 4).[16,18] For early metals, mechanistic and computational studies point to a concerted, four-center *syn* elimination process involving an interaction between the metal and the β-halogen.[16] However, stereochemical analysis of products of Pd-catalyzed cycloisomerizations of tethered alkyne–allylic halides suggest an *anti* β-elimination process is operative in this late metal system.[18a]



(4)

R = H, alkyl
X = F, Cl, ...

In the present case, it seems likely that a β-fluoride elimination process similar to the one depicted in Eq. 4 should be operative, but it is difficult to predict based on what is known in the literature as to whether this reaction would be expected to proceed with *syn* or *anti* stereochemistry, thus requiring a *syn*- or *anti*-periplanar arrangement of the coordinated Rh atom and fluoride leaving group in the olefin insertion intermediate. Nevertheless, analysis of the deuterium distribution patterns in the desired product **1-*d*$_2$** and the defluorinated product **6-*d*$_4$** arising from deuteration of the freebase **2** (Eq. 3) provides some insight into the divergence of reaction pathways that lead ultimately to defluorination over simple olefin hydrogenation (Scheme 3). The fact that the desired reduction product **1-*d*$_2$** only contains deuterium at the formerly olefinic carbons, while the des-fluoro product **6-*d*$_4$** shows additional deuterium incorporation at the 2-position and *exo*-methylene carbon suggests that olefin isomerization, most likely via successive β-hydrogen elimination/insertion sequences, at least accompanies defluorination and may very well be on the mechanistic path to defluorination. A number of possible scenarios are discussed below.

As depicted in Scheme 3, initial insertion of the olefin **2** into the Rh dideuteride complex leads to one of two regioisomeric Rh-alkyl complexes **16** or **18** that could either undergo reductive elimination to give **1-*d*$_2$** or a series β-hydride elimination/insertion sequences to migrate the Rh center around the ring with concomitant washing of the deuterium label into adjacent positions (e.g., **17** and **19**). In accord with published observations of the dynamics of Pd cycloalkyl complexes,[19] in all likelihood the postulated olefin intermediates formed by β-hydride elimination remain bound to Rh throughout the olefin isomerization/Rh migration process, thus restricting the Rh center to one diastereotopic face of the substrate.[20] Consistent with this, the 2-position in **6-*d*$_4$** only contains deuterium (25%) in the axial position according to ^{1}H NMR spectroscopy, i.e., on the proton *anti* to the hydroxymethyl substituent (cf. **17** in Scheme 3).

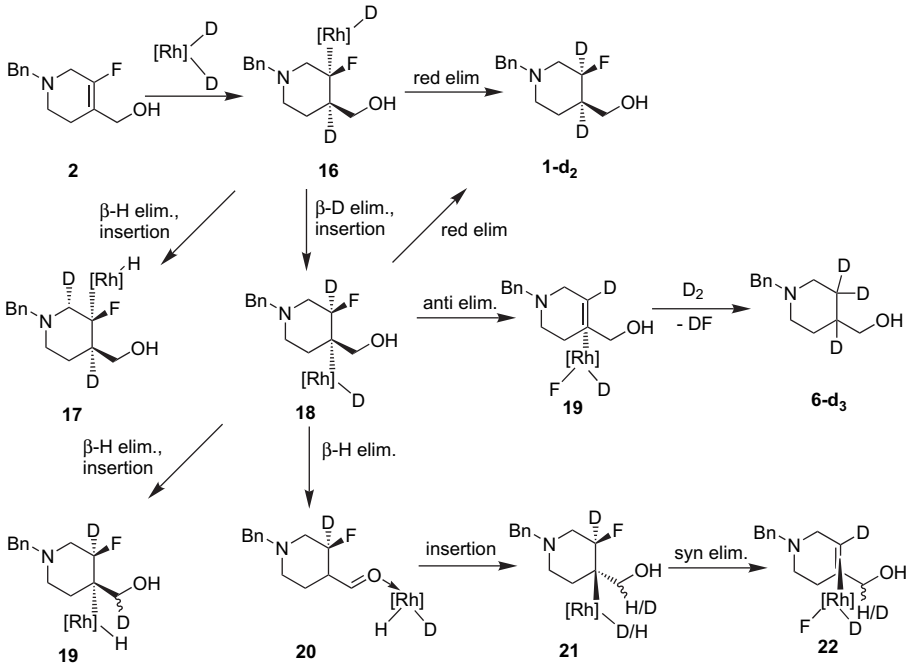
As stated above, β-fluoride elimination conceivably could occur either via a *syn* or *anti* elimination process. Thus, Rh-alkyl complex **18**, which exhibits an *anti* 1,2-disposition of the Rh and F atoms, could potentially eliminate to form des-fluoro olefin complex **19**. Base-induced reductive elimination of (deutero)hydrofluoric acid would generate the Rh(I) olefin complex,[21] which could then activate another mole of deuterium gas and reduce the bound olefin to give the defluorinated product **6-*d*$_3$** containing three out of the four experimentally observed incorporated deuterons. The other observed deuteron, statistically distributed across the ring 2-position and *exo*-methylene carbon, could arise via the Rh-migration processes outlined in the previous paragraph (i.e., via intermediates like **17** and **19**). This putative sequence to **6** correctly predicts the relative *anti* stereochemistry of the partial deuterium label at C2 and the hydroxymethyl substituent.

In order for β-fluoride elimination to occur via a *syn* process, the Rh atom would have to migrate to the same face of the ring as the fluoride substituent. One sequence of steps that could lead to this arrangement is shown in Scheme 3 wherein olefin insertion isomer **18** undergoes β-hydrogen elimination onto the *exo*-methylene substituent, forming an aldehyde complex **20** (either in the keto or enol tautomeric form), which allows the Rh to migrate to the top face of the substrate while washing the deuterium label into the *exo* methylene position. So-formed Rh alkyl intermediate **21** is set up to eliminate in *syn* fashion, giving des-fluoro olefin complex **22**, which could lead to defluorinated product **6-*d*$_4$** analogously to the sequence from **19**. However, in complex **22** the Rh complex is coordinated to the top face of the cyclic olefin, and reduction would lead to the opposite (*syn*) stereochemistry of the hydroxymethyl substituent relative to the partial deuterium label at C2 as would be predicted from the sequence passing through **19** and was observed experimentally.

In either case, olefin insertion intermediates **16** and **18** are the postulated mechanistic branch points between formation of desired product versus eventual defluorination, and their relative rates of C-H/D reductive elimination versus β-hydride (or fluoride) elimination ought to govern the product distribution of the reaction. Consistent with this proposal, the **1**:**6** product ratio from freebase **2** decreases from 2:1 with H_2 as reductant to 1:1 using D_2, consistent with a deuterium isotope effect slowing the rate of C-D reductive elimination relative to β-hydride or fluoride elimination.

4. Conclusion

Broad catalyst screening across multiple metals and classes of chiral ligands identified a Rh-Walphos complex uniquely suited for the asymmetric hydrogenation of vinyl fluoride **2**, giving exquisite control over enantioselectivity and the ratio of olefin hydrogenation to hydrodefluorination. This reaction represents a rare example of a Rh-catalyzed asymmetric hydrogenation of an allylic



Scheme 3. Possible reaction pathways in the asymmetric hydrogenation/defluorination of vinyl fluoride **2**.

alcohol, and one of the few examples in the literature of a successful asymmetric hydrogenation of a vinyl fluoride. The discovery of this unique transformation allowed efficient access to enantioenriched 1,3,4-trisubstituted piperidine **1** with a stereogenic alkyl fluoride center, enabling the synthesis of **1** on multi-kg scale. The reaction performance showed an unsual dependence on the presence of acid additives. Further exploration of this unusual observation through deuterium labeling studies revealed the presence of significant olefin isomerization accompanying the undesired defluorination side-reaction.

5. Experimental

5.1. General

Unless otherwise noted all reactions were run under an inert atmosphere, and solvents and reagents were transferred by syringe. *N*,*N*-Dimethylformamide (DMF), tetrahydrofuran (THF), isopropyl acetate, ethyl acetate, heptane, hexanes, acetone, dioxane, methanol, chloroform-*d* ($CDCl_3$), methanol-d_4 (CD_3OD), diisopropylamine, *n*-butyllithium (10 M in hexanes), 3-fluoropyridine, benzyl bromide, sodium borohydride and defluorinated product **6** were purchased from commercial sources and used as received without further purification. (*R*)-(−)-1-[(*R*)-2-(2′-(Diphenylphosphino)-phenyl)ferrocenyl]ethyldicyclohexylphosphine (Walphos SL-W003-1) was purchased from Solvias, AG, Fort Lee, NJ 07024. ^1H and ^{13}C NMR spectra were referenced to residual solvent; ^{19}F NMR spectra were referenced to added benzotrifluoride (δ −67.73 ppm). Coupling constants are reported in hertz (Hz). Multiplicities are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad signal. Reverse phase and chiral normal phase HPLC were run on an Agilent 1100 series system. Optical rotations were obtained on a Perkin Elmer 241 polarimeter. Melting points were obtained on a Buchi B-545 melting point apparatus and are uncorrected. Electrospray ionization mass spectrometry was performed on an Agilent 1100 HPLC-MSD. Elemental analysis was performed by QTI, Whitehouse, NJ 08888.

5.2. Synthetic procedures

*5.2.1. 3-Fluoro-4-hydroxymethyl-pyridine (**4**)*

A solution of *n*-BuLi (123 mL, 10 M in hexanes, 1.23 mol) was added over 15 min to THF (1.87 L) in a 5 L round bottom flask, keeping the internal temperature below −10 °C. After the addition was complete, the resulting solution was further cooled to -35 °C, and diisopropylamine (197 mL, 142 g, 1.41 mol) was added over 15 min. The solution was then further cooled until it reached −75 °C. 3-Fluoropyridine (125 g, 1.29 mol) was then added slowly to this solution while maintaining the temperature below −70 °C. Neat DMF (168 mL, 159 g, 2.17 mol) was then added to the reaction mixture over 1 h maintaining the temperature ≤−70 °C. After confirming complete formation of the aldehyde, the reaction was warmed to 0 °C, and H_2O (230 mL) was added, followed by $NaBH_4$ (48.4 g, 1.28 mol) in two portions over 5 min. Concentrated HCl (1.17 L) was then added over the course of 1 h, keeping the internal temperature of the reaction mixture ≤25 °C. The resulting mixture was then heated to 40 °C and kept at this temperature for 1 h. After cooling to 0–15 °C, 6 M NaOH (747 mL) was slowly added to adjust the pH of the aqueous layer to 12. Approximately 700 mL of H_2O was added to dissolve any precipitate in the aqueous layer. The aqueous layer was then extracted with isopropyl acetate (1×1.275 L, 2×800 mL). The combined organic layers were treated with 20 wt.% of Darco-G60 carbon and the solution was heated to 40 °C for 1 h followed by filtration over solka floc. After filtration the organic layer was concentrated in vacuo and the solvent composition adjusted to a mixture of 15–20% (v/v) isopropyl acetate in heptane. The product **4** crystallized as a white solid. The resulting slurry was then cooled to 0 °C for 30 min and filtered, using 250 mL of heptane cooled to 0 °C to wash the crystals. Yield=128.5 g (79%). Mp=83–84 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J*=5, 1H), 8.31 (br s, 1H), 7.48 (t, *J*=6, 1H), 4.81 (s, 2H), 3.46 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.2 (d, *J*=255), 146.0 (d, *J*=6), 137.6 (d, *J*=12), 137.3 (d, *J*=24), 122.7 (d, *J*=2), 57.7 (d, *J*=4); ^{19}F NMR (376 MHz, $CDCl_3$) δ -138.39 (s). Anal. Calcd for C_6H_6FNO: C, 56.69; H, 4.76. Found: C, 56.64; H, 4.62.

*5.2.2. 1-Benzyl-3-fluoro-4-(hydroxymethyl)pyridinium bromide (**5**)*

A solution of **4** (50.0 g, 0.39 mol) and benzyl bromide (50.0 mL, 71.5 g, 0.42 mol) in acetone (524 mL) was heated to reflux for ~12 h. The reaction mixture was cooled to room temperature, diluted with heptane (550 mL), and the pyridinium salt was collected by filtration. The crystals were washed at ambient temperature with 25% (v/v) acetone/heptane (200 mL), filtered and dried, affording **5** as a light pink solid. Yield=109.5 g (93%). mp=154–156 °C (dec); ^{1}H NMR (500 MHz, CD_3OD) δ 9.20 (d, J=4, 1H), 8.97 (d, J=6, 1H), 8.28 (t, J=7, 1H), 7.55 (m, 2H), 7.48 (m, 3H), 5.85 (s, 2H), 4.96 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, CD_3OD) δ 159.1 (d, J=255), 152.8 (d, J=12), 143.1 (d, J=3), 134.4, 134.3 (d, J=38), 131.3, 130.9, 130.4, 127.8 (d, J=6), 65.8, 58.0 (d, J=3); ^{19}F NMR (376 MHz, CD_3OD) δ -126.82 (d, J=98). Anal. Calcd for $C_{13}H_{13}BrFNO$: C, 52.37; H, 4.39. Found: C, 52.40; H, 4.18.

*5.2.3. 1-Benzyl-3-fluoro-4-hydroxymethyl-1,2,5,6-tetrahydropyridine hydrochloride (**2**·**HCl**)*

A solution of compound **3** (100.3 g, 0.336 mol) in methanol (960 mL) was cooled to −10 °C, and $NaBH_4$ (19.10 g, 0.504 mol) was added portion-wise while keeping the temperature ≤0 °C. The reaction mixture was held at −10 °C for approx. 30 min and then diluted with isopropyl acetate (1.0 L), followed by addition of 11.25% (w/w) NaCl (aq) (1.0 L). The resulting mixture was aged 15 min, then the organic layer was further washed with 15% (w/w) NaCl (aq) (500 mL). The reaction mixture was concentrated in vacuo and the solvent composition adjusted to roughly 1:1 methanol:isopropyl acetate (c=100 g/L) by addition of methanol. The resulting solution was treated with 25 wt % of Ecosorb C-941 at 50 °C for approx. 2 h and then filtered through a plug of Celite, rinsing with 1:1 methanol:isopropyl acetate (250 mL). The filtrate was then concentrated to a residue and redissolved in 5% methanol in isopropyl acetate (636 mL). The resulting solution was warmed to 50 °C, and a solution of 4 M HCl in dioxane (1.10 equiv) was added slowly over ~1 h. At this point, the solution was seeded with a small amount of crystalline **2**·**HCl** and the mixture allowed to cool to room temperature slowly overnight. The solids were isolated by filtration, washed with 5% (v/v) methanol in isopropyl acetate (200 mL) and dried, giving **2**·**HCl** as a white solid, mass 66.1 g (77% yield). This material was further purified by dissolving in 1:1 methanol:isopropyl acetate (900 mL) and treating with 25 wt % of Ecosorb C-941 at 50 °C for 2 h. After filtration and washing with 500 mL of 25% (v/v) methanol in isopropyl acetate, the mixture was concentrated and the solvent composition adjusted to roughly 10% (v/v) methanol in isopropyl acetate (c=100 g/L). The resulting solution was seeded with a small amount of crystalline **2**·**HCl** resulting in instantaneous crystallization. The mixture was further concentrated (final c=189 g/L) and filtered, washing with 200 mL of 5% (v/v) methanol in isopropyl acetate. The resulting crystalline product was dried, giving 60.2 g of **2**·**HCl** (70% yield). Mp=164–167 °C (dec); ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (br m, 2H), 7.51 (br m, 3H), 4.50 (br s, 2H), 4.21 (br s, 2H), 3.85 (br s, 2H), 3.38 (br s, 2H), 2.59 (br s, 2H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 146.6 (d, J=251), 132.5 (s), 131.6 (s), 130.6 (s), 130.2 (s), 115.3 (d, J=8), 60.88 (s), 56.86 (d, J=7), 50.0 (s), 48.9 (d, J=42), 22.4 (d, J=4); ^{19}F NMR (376 MHz, CD_3OD) δ −124.18 (s). Anal. Calcd for $C_{13}H_{17}ClFNO$: C, 60.58; H, 6.65. Found: C, 60.28; H, 6.88.

*5.2.4. (3S,4R)-1-Benzyl-3-fluoro-4-(hydroxymethyl)piperidine (**1**)*

In a nitrogen atmosphere glovebox, (*R*)-(−)-1-[(*R*)-2-(2′-(Diphenylphosphino)phenyl)ferrocenyl]ethyldicyclohexylphosphine (60.1 mg) and $[(COD)RhCl]_2$ (20.3 mg) were dissolved in anhydrous dichloromethane (3 mL) and aged for 45 min at room temperature. Compound **2**·**HCl** (15.0 g) was charged to a 6 oz. glass pressure vessel (Andrews Glass Co., Vineland, NJ) containing a magnetic stir bar. Anhydrous methanol (69 mL) was added, followed by the catalyst solution and a dichloromethane (3 mL) rinse. The reactor was degassed with H_2 (40 psi g) and immersed in a pre-heated 50 °C oil bath. After a few minutes, the vessel was further pressurized with H_2 to 85 psi g and allowed to age for 18.75 h. After this time, the vessel was vented and cooled to room temperature. HPLC analysis indicated >99% conversion of the vinyl fluoride, less than 1% of the des-F impurity **6**, and an assay yield of 99% compared to a previously prepared analytical standard of **1**. Chiral HPLC analysis indicated 99.3% ee. The reaction mixture was concentrated in vacuo to a dark brown oil, which was then diluted with 50 mL of ethyl acetate, to which was added 50 mL of saturated $NaHCO_3$ (aq). This biphasic mixture was stirred at room temperature for 30 min. The organic layer was separated, and the aqueous layer extracted with 3×10 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to an oil, which was purified by column chromatography (1:1 ethyl acetate:hexanes) to afford 9.45 g of free base compound **1** (74.4% isolated yield) as a pale yellow oil. Reversed phase HPLC: Waters Symmetry Shield® RP_{18}, 25 cm×4.6 mm, 5 μm; 40 °C; 210 nm; 1.0 mL/min; mobile phase A=0.1% (v/v) $HClO_4$ (aq), B=acetonitrile; 10% B for 5 min, then ramp to 75% B over 5 min, hold 2.5 min, then ramp back to 10% B over 2.5 min, 5 min post time; retention times (min): **1,** 5.7; **6**, 6.5; **2**, 7.0; toluene, 14.3. 98.9 A% **1**, 1.1 A% **6**. Chiral normal phase HPLC[22]: Samples treated with ethyl acetate/satd $NaHCO_3$(a) prior to analysis. Chiralcel Chiralpak OJ-H, 25 cm×4.6 mm, 5 μm; 20 °C; 210 nm; 0.5 mL/min; isocratic 90/10 heptane/2-propanol; retention times (min): **2,** 17.8; **6**, ~17 (br); (3*R*,4*S*)-**1**, 20.0; (3*S*,4*R*)-**1**, 23.2. (3*R*,4*S*)-**1**, 0.33 A%; (3*S*,4*R*)-**1**, 99.67 A%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 4H), 7.26 (m, 1H), 4.83 (d, J=48.4, 1H), 3.73 (m, 1H), 3.61 (m, 3H), 3.22 (tt, J=1.5, 12, 1H), 2.96 (br d, J=9.8, 1H), 2.10 (m, 4H), 1.70 (br m, 2H), 1.54 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.7 (s), 129.4 (s), 128.4 (s), 127.3 (s), 87.7 (d, J=175), 63.5 (d, J=4), 62.9 (s), 56.6 (d, J=9), 52.5 (s), 41.6 (d, J=20), 23.4 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −204.50 (s); ESI-MS m/z calcd for $C_{13}H_{19}FNO^+$ ($M+H^+$) 224.1, found 224.0. Anal. Calcd for $C_{13}H_{18}FNO$: C, 69.93; H, 8.13. Found: C, 69.19; H, 8.38. $[\alpha]_D^{25}$ −51 (c 0.05 M, MeOH).

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