

An efficient route to chiral *N*-heterocycles bearing a C–F stereogenic center *via* asymmetric hydrogenation of fluorinated isoquinolines†

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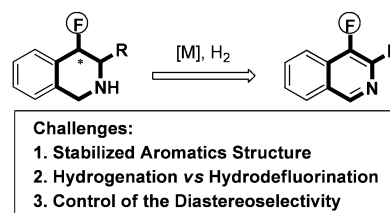
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An efficient iridium-catalyzed asymmetric hydrogenation of the fluorinated isoquinoline derivatives has been successfully developed for the synthesis of chiral fluorinated tetrahydroisoquinoline derivatives with up to 93% ee. This methodology features the use of a hydrochloride salt as well as a catalytic amount of halogenated hydantoin which were vital for the reactivity, enantioselectivity, and inhibition of the hydrodefluorination pathway.

Fluorine is consistently an integral part of pharmaceuticals, agrochemicals and materials due to its unique effects on properties of organic molecules.¹ As a fascinating and challenging topic in organofluorine chemistry, constructing enantioenriched fluorinated building blocks, especially with a fluorinated stereogenic carbon center has become increasingly important.² Besides direct asymmetric fluorination,³ asymmetric hydrogenation of fluorinated prochiral unsaturated compounds provides an alternative approach for construction of chiral carbon–fluorine centres. Given the great achievements in catalytic asymmetric hydrogenation and the utility of chiral fluorinated compounds, it is a surprise that the asymmetric hydrogenation of fluorinated unsaturated compounds was rarely explored. During the past decades, only a few pioneering works were reported by Saburi, Nelson, and Andersson⁴ on asymmetric reduction of fluorinated olefins. However, these works encountered limited substrate scope and some degrees of hydrodefluorination beyond prediction.

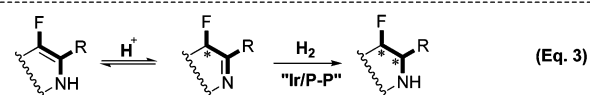
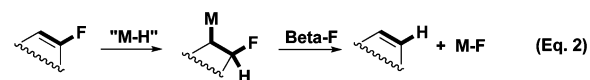
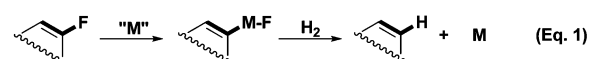
Asymmetric hydrogenation of heteroaromatic compounds has been intensively studied and considered as an efficient method for the synthesis of a variety of new chiral cyclic compounds.⁵ Fluorination of these products would provide other significantly modified structural motifs with desirable properties in pharmaceuticals or materials. However, as a straightforward and atom-economic route to the synthesis of the corresponding



Scheme 1 Challenges in asymmetric hydrogenation of fluorinated heteroaromatic compounds.

fluorinated compounds, the asymmetric hydrogenation of fluorinated heteroaromatics has been a “sleeping beauty” to date (Scheme 1). The inherent problems are apparent: the highly stabilized aromatic structure, unavoidable hydrodefluorination and the difficulty to control the stereoselectivity.

Considering the easy cleavage of the carbon–fluorine bond in transition metal catalyzed systems,⁶ two plausible hydrodefluorination pathways in asymmetric hydrogenation are proposed (Scheme 2). Path A: oxidative addition of C–F to a low-valent metal, followed by hydrogenolysis, causes hydrodefluorination^{4d,7} (eqn (1)). Path B: addition of a metal–hydride species to the C=C–F unit of aromatics, followed by β -fluorine elimination, causes hydrodefluorination^{4f,8} (eqn (2)). Based on the analysis above, we envisioned that the key factor for inhibiting hydrodefluorination is to regulate the catalytic elementary steps away from the hydrodefluorination pathways by carefully designing



Scheme 2 The plausible hydrodefluorination pathways in transition metal catalyzed asymmetric hydrogenation of fluorinated aromatic compounds.

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the substrate structure. Among the successful examples of asymmetric hydrogenation of heteroaromatics, a putative mechanism involving enamine–imine isomerization was proposed (eqn (3)),⁹ by which the C=C–NH unit was isomerized to CH=C=N and then reduced. This inspired us to synthesize 4-fluorinated isoquinolines,¹⁰ with similar catalytic elementary steps which would inhibit the hydrodefluorination pathways proposed above (eqn (1) and (2)). Herein, we described the first successful example of the asymmetric hydrogenation of fluorinated heteroaromatics with high chemo-, diastereo- and enantioselectivity.

Following the hypothesis, asymmetric hydrogenation of 4-fluorinated isoquinolines was carried out with the optimal system on 3,4-disubstituted isoquinolines: [Ir(cod)Cl]₂/(*R*)-SynPhos/BCDMH(1-bromo-3-chloro-5,5-dimethylhydantoin)/toluene/70 °C.^{9b} According to the catalyst activation strategy, the additive here was supposed to oxidize the low-valent metal to a more active species,¹¹ which was also coincident with the control experiment: >95% conversion and 74% ee were obtained with 10% BCDMH in contrast to 14% conversion with no additives.¹² In addition, the HCl generated *in situ* from reaction of the additive and [Ir(cod)Cl]₂ could accelerate isomerization between iminium and enamine.^{9b,d} Unfortunately, only moderate enantioselectivity was obtained albeit with high reactivity.

Considering that the extra Brønsted acid could accelerate iminium–enamine isomerization preferably as well as activate substrates to facilitate hydrogenation,^{9c,13} the asymmetric hydrogenation of the corresponding isoquinolinium chloride was examined.¹⁴ To our delight, a much better enantioselectivity was obtained with 26% conversion (86% ee, entry 1, Table 1). Next, the effect of the reaction medium was tested (entries 2–6). A dramatic solvent effect was revealed and a mixed solvent of dioxane and isopropanol with a ratio of 5/1 gave the best result in terms of both enantioselectivity and conversion (93% ee and >95% conversion, entry 6). Various halogen sources gave similar ee values between 89–93% (entries 5 and 7–9), and no deterioration of enantioselectivity was observed with half-amount of the additive employed (entry 10). A brief investigation on chiral ligands was conducted with some commercially available diphosphine ligands (entries 10–13). Most importantly, stoichiometric acid as well as 5% additives were vital to establish a final system on 3-butyl-4-fluoro-isoquinolinium chloride to give the best result of 93% ee: [Ir(cod)Cl]₂/(*R*)-SynPhos/DCDMH/H₂ (40 bar)/(dioxane–isopropanol 5:1)/30 °C.

Under the optimized conditions, the scope of enantioselective synthesis of **2** was explored (Table 2). In general, excellent yields (79–97%) and enantioselectivities (88–93% ee) were obtained regardless of the properties of the alkyl chain in 3-position of **1** (**1a–1h**). There is also only little fluctuation in enantioselectivity and yield no matter the electronic nature and position of substituents on aromatics (**1i–1m**). The initial substrate scope exploration demonstrated the potential application of the synthesis to access various chiral fluorinated tetrahydroisoquinolines, which represent modified structural motifs in many natural alkaloids and biologically active compounds.¹⁵

To further evaluate the practical utility of the current system, the asymmetric hydrogenation of fluorinated isoquinolines **1f**

Table 1 The evaluation of reaction parameters^a

Entry	Solvent	Additive	Ligand	ee ^b (%)	Conv. ^c (%)
1	Toluene	DCDMH	L1	86	28
2	Dioxane (D)	DCDMH	L1	89	88
3	i-PrOH (P)	DCDMH	L1	79	>95
4	D–P (1:1)	DCDMH	L1	91	>95
5	D–P (5:1)	DCDMH	L1	93	>95
6	D–P (1:5)	DCDMH	L1	87	>95
7	D–P (5:1)	I ₂	L1	89	>95
8	D–P (5:1)	BCDMH	L1	91	>95
9	D–P (5:1)	DBDMH	L1	91	>95
10 ^d	D–P (5:1)	DCDMH	L1	93	>95
11 ^d	D–P (5:1)	DCDMH	L2	93	>95
12 ^d	D–P (5:1)	DCDMH	L3	87	>95
13 ^d	D–P (5:1)	DCDMH	L4	91	>95

L1: (*R*)-SynPhos

L2: (*R*)-SegPhos

L3: (*R*)-Binap

L4: (*R*)-MeO-BiPhep

^a Reaction conditions: **1a**·HCl (0.20 mmol), (*R*)-SynPhos (2.2 mol%), [Ir(COD)Cl]₂ (1.0 mol%), H₂ (40 bar), solvent (3 mL), additive (10 mol%), 20 h, 30 °C. ^b Determined by HPLC analysis of the corresponding *N*-4-bromobenzoyl derivative. ^c Determined by ¹H NMR, with all reaction <5% hydrodefluorination by-product and >20:1 d.r. ^d DCDMH (5 mol%).

Table 2 Asymmetric hydrogenation of 4-fluoroisoquinolinium chlorides (**1**·HCl)^a

Entry	1·HCl (R ¹ /R ² /R ³)	Yield ^b (%)	ee ^c (%)
1	H/H/ <i>n</i> -Bu	92 (2a)	93 (–)
2	H/H/Me	92 (2b) ^d	93 (–)
3	H/H/Et	94 (2c) ^d	93 (–)
4	H/H/ <i>n</i> -Pr	93 (2d)	92 (<i>R,R</i>) ^e
5	H/H/cyclopropyl	79 (2e)	90 (–)
6	H/H/ <i>n</i> -pentyl	97 (2f)	90 (–)
7	H/H/Bn	88 (2f) ^f	88 (–)
8	H/H/phenethyl	95 (2g)	93 (–)
9	F/H/ <i>n</i> -Bu	88 (2h)	88 (–)
10	H/F/ <i>n</i> -Bu	91 (2i)	91 (–)
		93 (2j)	91 (–)
		91 (2j) ^f	89 (–)
11	Me/H/ <i>n</i> -Bu	97 (2k)	91 (–)
12	Cl/H/ <i>n</i> -Bu	93 (2l)	90 (–)
13	Me/H/ <i>n</i> -Pr	91 (2m)	91 (–)

^a Reaction conditions: **1**·HCl (0.20 mmol), (*R*)-SynPhos (2.2 mol%), [Ir(COD)Cl]₂ (1.0 mol%), H₂ (40 bar), dioxane–isopropanol (5:1, 3 mL), DCDMH (5 mol%), 20 h, 30 °C. ^b Isolated yields. ^c Determined by HPLC analysis of the corresponding *N*-4-bromobenzoyl derivative. ^d Determined by the corresponding *N*-4-bromobenzoyl derivatives due to their highly volatile characteristic. ^e The absolute configuration of **2d** was determined by single-crystal X-ray diffraction analysis of the corresponding *N*-4-bromobenzoyl derivative. ^f Gram scale.

and **1j** was carried out on a gram scale (entries 6 and 10, Table 2), and the desired products **2f** and **2j** were furnished with results of 88% ee, 88% yield and 89% ee, 91% yield.

In summary, we have successfully developed an efficient system to access the chiral fluorinated tetrahydroisoquinolines *via* asymmetric hydrogenation of the corresponding fluorinated isoquinoline derivatives with up to 93% ee. Stoichiometric acid as well as a catalytic amount of additive were vital for the reactivity, enantioselectivity and inhibition of the hydrodefluorination pathway. Further investigation on the application of the developed strategy and detailed mechanistic studies of the catalytic cycle are currently ongoing in our laboratory.

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