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To be cited as: *Chem. Asian J.* 10.1002/asia.201601306

Link to VoR: http://dx.doi.org/10.1002/asia.201601306

A Journal of

ACES
Asian Chemical Editorial Society

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10.1002/asia.201601306

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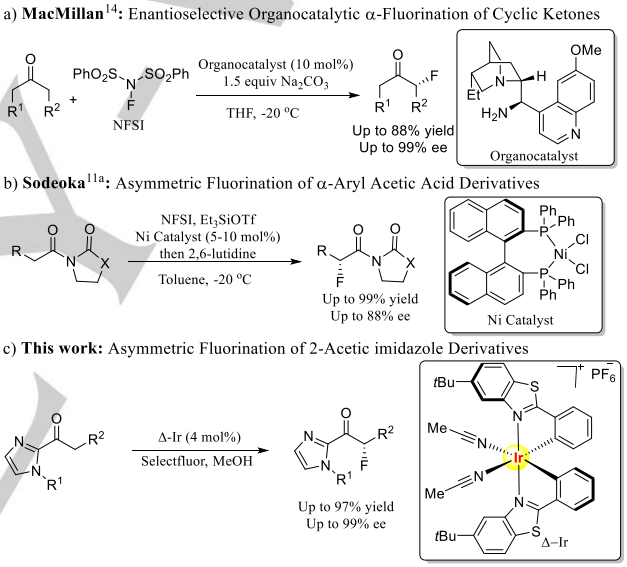
Catalytic Enantioselective *α*-fluorination of 2-acyl imidazoles via Iridium Complexes

Guo-Qiang Xu, Hui Liang, Jie Fang, Zhi-Long Jia, Jian-Qiang Chen and Peng-Fei Xu*[a]

Abstract: The first highly enantioselective *α*-fluorination of 2-acyl imidazoles utilizing iridium catalysis has been accomplished. This transformation features mild conditions and a remarkably broad substrate scope, providing an efficient and highly enantioselective approach to obtain a wide range of fluorine-containing 2-acyl imidazoles which are found in a variety of bioactive compounds and prodrugs. A large scale synthesis has also been tested to demonstrate the potential utility of this fluorination method.

Fluorine plays a conspicuous and increasingly important role in pharmaceuticals[1, 2], agrochemicals[3], materials[4] and tracers for positron emission tomography[5], due to its unique effect on the properties of organic molecules[6]. Regrettably, to date only a few organic compounds possessing this special atom have been found in nature.[7] Therefore, the preparation of various organofluorine compounds is one of the most significant tasks of synthetic organic chemistry, and the mono-fluorination is a simple and direct way to introduce fluorine atom into various useful and bioactive compounds. Recently, major advances have been made in the field of the fluorination chemistry.[8] Hintermann and Togni developed the first enantioselective catalytic fluorination of *α*-branched *β*-ketoesters via titanium catalysis.[9] Later, several laboratories have established a variety of elegant systems for the catalytic asymmetric fluorination reactions of carbonyl compounds via palladium catalysis,[10] nickel catalysis,[11] copper catalysis[12] and other transition-metal catalysis[13]. Notably, MacMillan,[14] Barbas[15] and Jørgensen[16] group developed the highly enantioselective *α*-fluorination of aldehydes and ketones using organocatalysis(**see scheme 1-a**). However, the enantioselective introduction of mono-fluorine atom into highly activated carbonyl compounds which have no branched chain in the *α*-position of carbonyl, such as 2-phenylacyl imidazole, unbranched β-ketoesters, *α*-aryl acetic acid derivatives, is still a big challenge, because the enolate form of corresponding fluorination compounds is relatively stable[17]. Sodeoka and co-workers reported the enantioselective fluorination of *α*-aryl acetic acid derivatives catalyzed by a chiral nickel complex,[11a] but the enantioselectivity of this reaction is still not very ideal, and the best enantiomer excess value is only up to 88% (**see scheme 1-b**). In view of this limitation, the design and development of new mono-fluorination reaction with higher enantioselectivity and better efficiency is one of the major goals for fluorine chemists.

2-Acyl imidazole is one of useful molecular scaffolds, which is found in a variety of bioactive compounds and prodrugs[18]. Meggers and co-workers[19] have accomplished a series of valuable transformations and significant modifications upon this biologically active skeleton. However, to the best of our knowledge, there is still no effective method to enantioselectively introduce fluorine atom into this valuable 2-acyl imidazole so far, the biggest obstacle of which is that the corresponding chiral fluorine products are very easy to racemize due to their enolization[17]. Based on the development of asymmetric catalytic method for the construction of drug molecules containing trifluoromethyl[20] and diverse complex chiral scaffolds[21], herein, we report the first example of highly enantioselective mono-fluorination of 2-acyl imidazole derivatives utilizing a chiral iridium complex (**see scheme 1-c**).



Scheme 1. Asymmetric Fluorination of activated carbonyl compounds

Initially, we investigated the reaction of 2-phenylacetyl-1-methylimidazole **1a** with commercially available 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2] octanebis (tetrafluoroborate) (Selectfluor)[22] in the presence of the enantiomerically pure iridium complex Δ-Ir (2 mol%) under nitrogen atmosphere. Excitingly, when MeOH/THF (4:1) was used as the reaction solvent, the expected fluorinated product **2a** was obtained in 87 yield and 57% enantioselectivity (Table 1, entry 1). In an attempt to improve the reaction efficiency and enantioselectivity, various solvents were tested in the reaction, and the results showed that the pure methanol was the best solvent, compared with THF, MeCN, DMF, DCM, EtOH and *i*-PrOH in yield and enantioselectivity (Table 1, entries 2-8). Although the fluorination yield was close to be quantitative, the enantioselectivity of this reaction was still unsatisfactory. Therefore, based on using methanol as the optimal solvent, other factors which could affect the reaction yield and enantiocontrol were evaluated. First, the concentration of substrate **1a** was gradually decreased from 0.2 mol/L to 0.025 mol/L (Table 1, entries 9-11), to our delight, the

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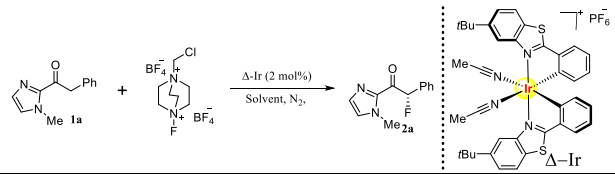
10.1002/asia.201601306

results showed that the yield of fluorination was decreasing, but the enantioselectivity was increasing at first and then started to decrease. Considering both of the reaction yield and enantiocontrol, the optimal concentration of **1a** was 0.05mol/L for this fluorination methodology. Next, the reaction temperature was also evaluated from 40 ^{o}C to -20 ^{o}C (Table 1, entries 12-15), the results indicated that the room temperature (20 ^{o}C) was the optimal temperature for the best enantiocontrol of this reaction. To further optimize the reaction conditions, 4Å MS was added to reaction system to examine the effect of water (Table 1, entries 16). Unfortunately, the enantioselectivity of the fluorinated product was still unsatisfactory even though the quantitative yield was obtained. When the amount of catalyst Δ-Ir was increased to 4 mol%, to our delight, the fluorinated product **2a** was obtained in 96% yield with 92% enantioselectivity (Table 1, entries 17).

Table 1. Optimization of the reaction conditions[a]



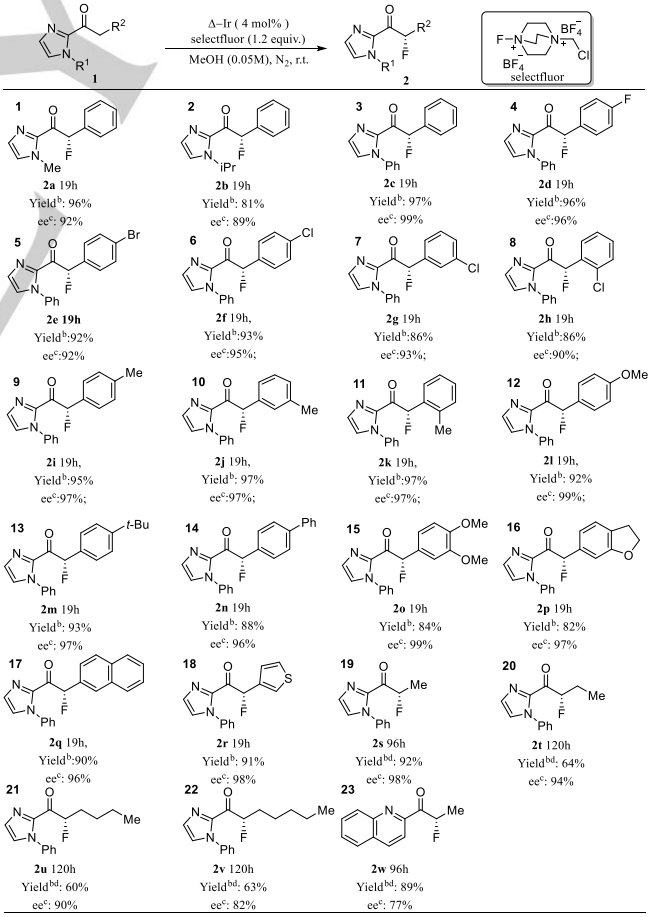
Entry	Solvent	Con. (M)	Δ-Ir (mol%)	T (^{o}C)	Yield (%)[b]	ee (%)[c]
1	MeOH/THF	0.2	2.0	20	87	57
2	MeOH	0.2	2.0	20	Quant.	60
3	THF	0.2	2.0	20	18	11
4	MeCN	0.2	2.0	20	55	Trace
5	DMF	0.2	2.0	20	64	13
6	DCM	0.2	2.0	20	23	10
7	EtOH	0.2	2.0	20	37	46
8	iPrOH	0.2	2.0	20	41	50
9	MeOH	0.1	2.0	20	87	66
10	MeOH	0.05	2.0	20	69	75
11	MeOH	0.025	2.0	20	60	72
12	MeOH	0.05	2.0	40	Quant.	65
13	MeOH	0.05	2.0	30	83	59
14	MeOH	0.05	2.0	0	32	50
15	MeOH	0.05	2.0	-20	Trace	/
16[d]	MeOH	0.05	2.0	20	Quant.	46
17	MeOH	0.05	4.0	20	96	92
18	MeOH	0.05	8.0	20	78	88
19	MeOH	0.05	15.0	20	73	90
20[e]	MeOH	0.05	4.0	20	41	8
21[f]	MeOH	0.05	4.0	20	64	77

[a] Unless otherwise noted, the reaction was carried out with 1 (0.1 mmol), Selectfluor (0.12 mmol, 1.2equiv.) and Δ-Ir (0.004 mmol, 4 mol%) in MeOH (2 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC. [d] 50mg 4A MS. [e] 1.2 equiv. Na_2HPO_4 was added. [f] 1a:Selectfluor=1:1.

However, both of the yields and enantioselectivities of the reaction rapidly decreased when the amount of the catalyst was increasing to 8 mol% and 15 mol% for this reaction (Table 1, entries 18, 19). Additionally, adding Na_2HPO_4 or decreasing Selectfluor's amount had a negative effect on both of the yield and enantioselectivity (Table 1, entries 20, 21). As a summary, using the iridium complex Δ-Ir as the chiral catalyst at 20 ^{o}C with methanol as the solvent provided α-fluoro-1-(1-methyl-1H-imidazol-2-yl)-2-phenylethan-1-one **2a** in 96% yield and 92% ee (Table 2, entry 1), which was established as the optimal protocol for this α-fluorination methodology.

The substrate scope of this novel fluorination reaction was extensively investigated with the catalyst Δ-Ir. Table 2 showed that the reactions of a series of 2-acyl imidazoles with Selecfluor (1.2 equiv.) in the presence of Δ-Ir (4 mol%) at room temperature (20 ^{o}C) provided the expected fluorination products **2** in good yields with excellent enantioselectivities. Interestingly, the substituents on the imidazole ring had a significant influence on the yield and enantioselectivity of this fluorination reaction. For example, the product **2b** was obtained in 81% yield with only 89% ee (entry 2), whereas, the substrate of N-phenyl substituent on the imidazole ring could provide the corresponding product **2c** in 97% yield and 99% excellent enantioselectivity (entry 3).

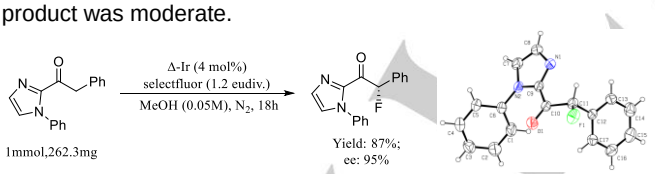
Table 2. Substrate scope of the asymmetric fluorination.



Unless otherwise noted, the reaction was carried out with 1 (0.1 mmol), Selectfluor (0.12 mmol, 1.2euiv.) and Δ-Ir (0.004mmol, 4 mol%) in MeOH (2

mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC. [d] 1.2 euqiv Na_2HPO_4 was added.

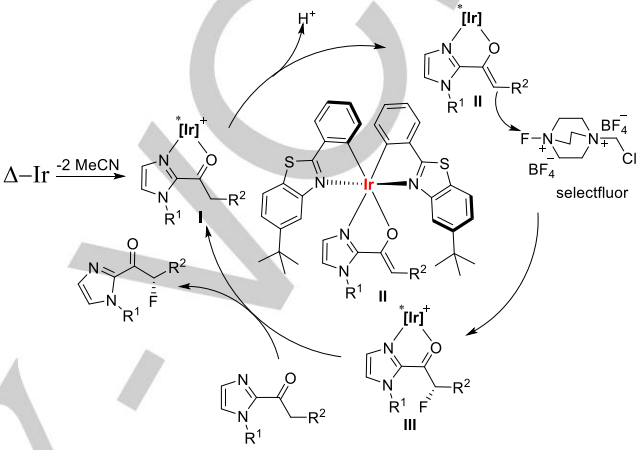
Various substrates with bulky, electron-donating, and electron-withdrawing groups on the phenyl ring could be smoothly converted into the corresponding *α*-fluorination product in good yields and excellent enantioselectivities. For instance, the substrate with fluoro-substituent on *para*-position of phenyl ring was smoothly converted into the corresponding fluorination product **2d** with 96% yield and 96% ee (entry 4), which contains two fluorine atoms at different positions of 2-phenylacyl imidazole. Similarly, other halo-substituent products, such as **2e** and **2f**, also could be acquired in 92% yield with 92% ee and in 93% yield with 96% ee, respectively (entries 5, 6). In addition, phenyl groups with *meta*- or *ortho*-chloro substituents had a negative effect on the yields and enantioselectivities (entry 7: **2g**, 86%, 93% ee, entry 8: **2h**, 86%, 90% ee). Remarkably, the introduction of electron-donating substituents on the 4-position of phenyl ring enabled highly efficient fluorination with excellent enantiocontrol (entry 9, **2i**, 95%, 97% ee, entry 12, **2l**, 92%, 99% ee, entry 13, **2m**, 93%, 97% ee,). Interestingly, the position of electron-donating groups on the phenyl ring seemingly had no influence on this asymmetric fluorination (entry 10, **2j**, 97%, 97% ee, entry 11, **2k**, 97%, 97% ee). The conjugated substrate which had two phenyl rings could also be efficiently converted to the corresponding product (entry 14, **2n,** 88%, 94% ee). Substrates with di-substituents on the phenyl ring could also participate in this transformation with excellent enantioselectivities (entry 15: **2o**, 84%, 96% ee, entry 16: **2p**, 82%, 99% ee). Moreover, 2-acyl imidazole substrates with a naphthyl (**2q**) or thiophenyl (**2r**) moiety were successfully fluorinated (entry 17: **2q**, 90%, 96% ee, entry 18: **2r**, 91%, 98% ee). More surprisingly, this enantioselective fluorination method also worked with aliphatic group (entry 19: **2s**, 92%, 98% ee; entry 20: **2t**, 64%, 94% ee; entry 21: **2u**, 60%, 90% ee; entry 22: **2v**, 63%, 82% ee), however, the enantioselectivity of products was decreased with the growth of the carbon chain. Importantly, this methodology also was applicable to the asymmetric fluoration of 2-acyl quinoline(entry 23: **2w**, 89%, 77% ee), but the ee value of product was moderate.



Scheme 2 Large scale synthesis and the X-ray crystal structure of compound **2c**

To demonstrate the potential utility of this enantioselective fluorination methodology, we also tested a large scale synthesis of **2c** (Scheme 2). The reaction proceeded smoothly to afford the fluorinated product **2c** with a slight decrease in yield and ee value (87%, 95% ee). The absolute configuration of the product **2c** was determined to be *S* configuration by using X-ray crystallographic analysis.[23]

A plausible catalytic cycle for this enantioselective fluorination reaction was outlined in Scheme 3. Generally, the catalytic cycle was initiated by bidentate coordination of the 2-acyl imidazole with the iridium catalyst (intermediate **I**), followed by deprotonation to generate an electron-rich *Z*- iridium enolate complex (intermediate **II**), in which the *re*-face of *Z*-enolate was shielded by chiral iridium complex. Whereafter, the electrophilic Selectfluor attacked on the *si*-face of *Z*-enolate to afford an iridium-coordinated complex (intermediate **III**). Finally, the iridium catalyst was regenerated and participated in the next catalytic cycle, and the corresponding chiral product **2** was obtained simultaneously.



Scheme 3. Proposed mechanism for the enantioselective fluorination reaction

In summary, a highly enantioselective *α*-fluorination of 2-acyl imidozales utilizing an electrophilic fluorine reagent (Selectfluor) and the chiral iridium catalyst has been established. Various 2-acyl imidozales could be smoothly fluorinated to provide the corresponding fluorine-containing compounds in high yields with excellent enantioselectivities under mild conditions. A large scale synthesis was also tested to demonstrate the potential utility of this fluorination method. This methodology can serve as an efficient tool for the direct introduction of valuable carbon-fluorine stereocenter into highly activated carbonyl compounds. The bioactivity tests of these organofluorine compounds are ongoing in our laboratory.

Acknowledgements

We are grateful to the NSFC (21202070, 21302075, 21372105 and 21572087), the International S&T Cooperation Program of China (2013DFR70580), and the “111” program from MOE of P. R. China.

Keywords: asymmetric catalysis• fluorination • iridium catalysis • 2-acyl imidazoles

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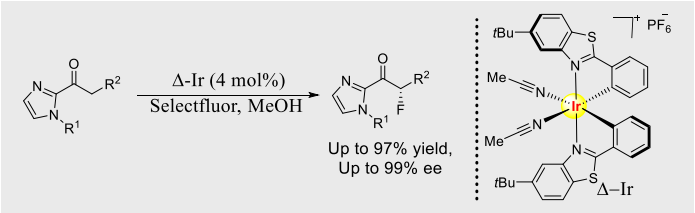
[23] CCDC 1480082 (**2c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

10.1002/asia.201601306

COMMUNICATION



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