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Nickel-catalyzed enantioselective α -heteroarylation of ketones *via* C-F bond activation to construct all-carbon quaternary stereocenters†

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Nickel-catalyzed asymmetric α -heteroarylation of ketones with fluorinated heteroarenes is reported *via* C-F bond activation. A series of ketones and 2-fluoropyridine derivatives with different functional groups proceed well to provide the corresponding products containing all-carbon quaternary stereocenters in good yields (up to 99% yield) and high ee values (up to 99% ee). In addition, drug molecule donepezil could also be compatible under the reaction conditions to afford late-stage diversification of pharmaceuticals.

a) The bond dissociation energy (kJ mol-1)

Over the past decade, transition metal-catalyzed organic fluorine chemistry including C–F bond formation and cleavage has become a popular topic to be explored by organic chemists. Compared with other carbon-halogen (C–I, C–Br, and C–Cl) bonds, catalytic C–F bond cleavage is a highly regioselective strategy to achieve late-stage functionalization of pharmaceuticals and construct diversified complex molecules. Although the C–F bond has high bond dissociation energy, transition metal-catalyzed C–F bond activation has still made some progress through the unremitting effort of organic chemists. The transition metal-catalyzed C–F bond cleavage proceeds primarily through direct oxidative addition of low-valence metal complex to the C–F bond, Ce-e, fluorine elimination of organic metal intermediates formed from fluorinated alkenes, Cf-5 or photocatalytic SET-type radical defluorinative functionalization.

 C_{Ar} –F bonds are arguably the strongest bonds that carbon can form. BDE (bond dissociation energy) of the C_{Ar} –F bond was calculated in the ESI† and is shown in Scheme 1a. Due to the high bond dissociation energy of the C_{Ar} –F bond (526 kJ mol $^{-1}$ for fluorobenzene), early examples of defluorinative functionalization of fluoroarenes mainly focused on extremely electron deficient fluorides. 7 Recently, transition metal-catalyzed C–F bond cleavage of (hetero)aryl fluoride has been widely developed to construct C–C and C–X (X = N, B, Si, etc) bonds with

Initially, 2-methyl-2,3-dihydro-1H-inden-1-one (1a) was chosen to explore the nickel-catalyzed enantioselective α -

c) Nickel-catalyzed asymmetric α -heteroarylation of ketones with heteroaryl fluorides (this work)

Scheme 1 Transition metal-catalyzed C-F bond activation.

organometallic reagents, alkynes, amines, borylation reagents or silylboranes as the coupling partner (Scheme 1b).⁸⁻¹² So far, there are rare examples of transition metal-catalyzed $C(sp^3)$ – H/C_{Ar} –F cross-coupling reactions,¹³ let alone asymmetric transformations with aryl or heteroaryl fluoride derivatives as coupling partners via C–F bond activation. Prompted by the nickel-catalyzed arylation of indanones with aryl triflates, chlorides, pivalates or pyrimidyl ether as arylation reagents,¹⁴ we develop herein the Nicatalyzed asymmetric α -heteroarylation of ketones via C–F bond activation to deliver all-carbon chiral quaternary carbon centers (Scheme 1c).

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Table 1 Optimization of reaction conditions^a

Entry	Ligand	Solvent	$Yield^{b}$ (%)	ee ^c (%)
1	L1	Toluene	39	68
2	L2	Toluene	21	65
3	L3	Toluene	NR	_
4	L4	Toluene	12	75
5	L5	Toluene	17	-74
6	L6	Toluene	67	-84
7	L7	Toluene	42	92
8	L8	Toluene	11	62
9	L7	1,4-Dioxane	84	90
10	L7	<i>m</i> -xylene	27	93
11	L7	Anisole	44	97
12^d	L7	Anisole	$78(77)^e$	97
13 ^d	L7	1,4-Dioxane	85	91

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Ni(cod)₂ (10 mol%), ligand (11 mol%), NaO t Bu (1.5 equiv.), dry solvent (1.0 mL), 120 °C, 24 h. ^b Yield of 3 was determined by t H NMR using dibromomethane as the internal standard. ^c Determined by chiral HPLC. ^d **1a** (0.2 mmol), **2a** (0.1 mmol), and NaO t Bu (1.1 equiv.). ^e Isolated yield.

heteroarylation with 2-fluoro-6-methoxypyridine (2a) including C–F and C–OMe bonds. To our delight, the single defluorinative product 3aa could be obtained in 39% yield and 68% ee in the presence of Ni(cod)₂, (S)-Binap (L1) and NaO^tBu (Table 1, entry 1). After the screening of a series of chiral phosphine ligands (Table 1, entries 2–8), (S)-Ph-GarPhos (L7) was found to afford the desired product in 42% yield and 92% ee. The reaction ee value could be improved to 97% with anisole as solvent, but the yield was just 44% (Table 1, entry 11). By adjusting the concentration ratio of substrates 1a and 2a, the reaction yield was improved to 77% yield (Table 1, entry 12). Finally, the defluorinative arylation product 3aa could be obtained in 77% yield and 97% ee in the presence of Ni(cod)₂ (10 mol%), L7 (11 mol%) and NaO^tBu (1.1 equiv.) in dry anisole.

Under the optimized reaction conditions, the scope of fluorinated heteroarene derivatives 2 with 2-methyl-2,3-dihydro-1*H*-inden-1-one 1a was examined (Scheme 2). A series of 2-fluoropyridines with an electron-donating group (*e.g.*, OMe, OBn, OCH₂R, OAr, PPh₂ and Me) on the 6-position of the pyridine ring proceeded well to provide arylated products in moderate to good yields and excellent ee values (3aa-3ai). The arylated product 3ac involving a chiral morpholine moiety could be obtained in 48% yield, >20:1 dr and 92% ee, which might be used as a potential dopamine receptor 4 (D₄R) antagonist.¹⁵

Interestingly, the 2-fluoro-6-aryloxypyridines just underwent defluorinative arylation to deliver the corresponding products in good enantioselectivities (3ad-3ag), in which CAr-O bond cleavage did not occur as reported by our group recently.14d The diphenyl phosphine group was also compatible with reaction conditions to give the desired product in 47% yield and a 90% ee value with the addition of MgBr₂ which probably assisted the coordination with pyridine or an indanone motif (3ah).16 2-Fluoro-6-aryl-pyridine derivatives involving a series of functional groups such as Me, OMe, OCF3, CF3 and CN all worked well to afford the corresponding products in good yields and excellent ee values (3aj-3ap). The absolute configuration of the major heteroarylation products was confirmed to be S-configuration by X-ray analysis of 3ap (CCDC 2156742).17 The 2-thienyl substituted 2-fluoropyridine derivative was also an effective coupling partner to deliver desired product 3aq in a good ee

Scheme 2 Substrate scope of fluorinated heteroarenes.^a Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), Ni(cod)₂ (10 mol%), L7 (11 mol%), NaO^tBu (0.11 mmol), anisole (1.0 mL), 120 °C, 24 h. Isolated yield. ee was determined by chiral HPLC.^b 1,4-dioxane was used instead of anisole.^c MgBr₂ (0.55 equiv.) was added as an additive.^d Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), Ni(cod)₂ (10 mol%), L7 (11 mol%), NaO^tBu (0.15 mmol), 1,4-dioxane (1 mL), 120 °C, 24 h.^e 96 h.

Scheme 3 Substrate scope of indanone derivatives. Reaction conditions: 1 (0.1 mmol), 2j (0.15 mmol), Ni(cod) $_2$ (10 mol%), L7 (11 mol%), NaO t Bu (0.15 mmol), 1,4-dioxane (1 mL), 120 °C, 24 h. Isolated yield. ee was determined by chiral HPLC.

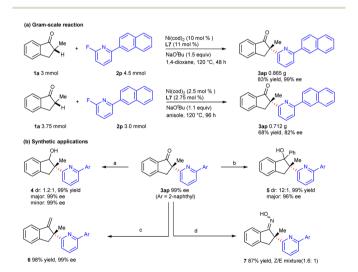
value. 2-Fluoropyridine derivatives without substituents on the 6-position could also couple well with 1a to provide the corresponding products (3ar). To our delight, the C-F bond activation is highly regioselective such that the cleavage only occurred at the 2-position of 2,4-difluorinated or 2,5-difluorinated pyridine, which is probably caused by the coordination-assistance of pyridine (3as-3at). 2-Fluoropyridine derivatives with functional groups such as CO₂Me, OMe, Me or Ph on the 5-position of the pyridine ring were compatible with the reaction conditions to deliver the corresponding products in medium yields and good ee values, but 6-fluoronicotinonitrile afforded the desired product in poor yield and enantioselectivity probably caused by the coordination of the cyano group with nickel (3au-3ay). Besides, 2-methyl-2,3-dihydro-1H-inden-1-one 1a could also effectively react with 2-fluoropyrazine to provide the desired product in good enantioselectivity (3az).

Next, we turn our attention to investigate the scope of ketones with 2-fluoro-6-phenylpyridine **2j**. Like described in Scheme 3, a series of 2-methyl-2,3-dihydro-1*H*-inden-1-one derivatives with electron-withdrawing or electron-donating groups (*e.g.*, F, OMe and Me) on the phenyl ring all proceeded smoothly to deliver the corresponding products in good yields and excellent ee values (**3bj-3gj**). Indanone derivatives with various substituents (*e.g.*, ethyl, *n*-pentyl, benzyl and allyl) at the α -position could well couple with 2-fluoro-6-phenylpyridine to afford the corresponding products in moderate to good yields and excellent ee values (**3hj-3lj**). In particular, acetylcholinesterase inhibitor donepezil **1m**, ¹⁸ for treating Alzheimer's and

vascular dementia, was also compatible with the reaction conditions to provide the chiral α-heteroaryl substituted derivative 3mj in 65% yield and 93% ee. This transformation provided an effective methodology for the late-stage functionalization of donepezils. Besides, six-member cyclic ketones such as 2-methyl-3,4-dihydronaphthalen-1(2*H*)-one 1n could also proceed well with 2-fluoro-6-phenylpyridine to afford desired product 3nj in 88% yield and 97% ee.

To evaluate the utility of this approach, a gram-scale reaction was carried out with 3 mmol of indanone 1a, and the coupling product 3ap could be obtained in 83% yield and 99% ee under the standard conditions. When the loading of the nickel catalyst decreased to 2.5 mol%, product 3ap could also be provided in medium yield and good enantioselectivity after the optimization of the reaction conditions (Scheme 4a). The chiral α -heteroarylation product could be further transformed via functionalization of the carbonyl group (Scheme 4b). Coupling product 3ap could be reduced by NaBH4 to deliver secondary alcohol 4 in excellent yield and enantioselectivity. Tertiary alcohol 5 was obtained in good diastereoselectivity via nucleophilic addition with phenylmagnesium bromide. Besides, the carbonyl group could be transformed into the C = X bond (X =C, N) by condensation with the Wittig reagent or hydroxylamine hydrochloride.

In order to explore the pathway of C-F bond cleavage, control experiments were explored (Table 2). When the reaction was carried out with 1a, 2a and NaO'Bu in dry anisole, almost no racemic 3aa and O-heteroarylation by-product 8 were obtained, but 1,4-dioxane could deliver 3aa and 8 in 13% yield and 14% yield, respectively (Table 2, entry 4–5). In addition, by-product 8 could not be further transformed into product 3aa in the presence of Ni(cod)₂ and L7 (Table S6†). Control experiments indicated that the excellent enantioselectivity of this methodology was probably derived from the faster reaction rate of oxidative addition of the chiral nickel complex to the C-F bond than that of



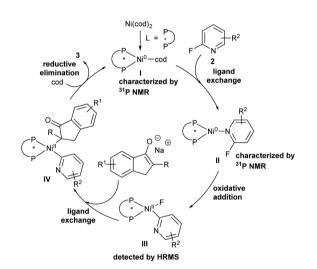
Scheme 4 Gram-scale reaction and synthetic applications. (a) NaBH₄ (2.0 equiv.), MeOH/THF = 1:1, 2 h, rt. (b) PhMgBr, -78 °C, 1 h, then rt, 2 h. (c) t-BuOK, PPh₃CH₃Br, rt, 5 min, THF, then rt, overnight. (d) NH₂OH·HCl, pyridine, EtOH, reflux.

Table 2 Exploring the influence of bases^a

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Entry	Additive (equiv.)	Solvent	3aa Yield b (%)	8 Yield ^b (%)
1	None	1,4-Dioxane	ND	ND
2	$Ni(cod)_2$ (0.1)	1,4-Dioxane	ND	ND
3	NaO^tBu (1.0)	1,4-Dioxane	14	17
4^c	NaO^tBu (1.1)	Anisole	Trace	Trace
5^c	NaO^tBu (1.1)	1,4-Dioxane	13	14
6^d	NaO^tBu (1.5)	1,4-Dioxane	15	19

 $[^]a$ Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), additive, dry solvent (1.0 mL), 120 °C, 24 h. b Yield was determined by 1 H NMR using dibromomethane as an internal standard. c **1a** (0.2 mmol). d **2a** (0.15 mmol).



Scheme 5 Proposed mechanism.

nucleophilic substitution. Besides, we also explored the existence of possible intermediates via ³¹P NMR and HRMS (ESI†). When 2-fluoropyridine was added to the mixture of Ni(cod)₂ and (*S*)-Ph-Garphos (L7), chiral complex Ni(L7)(cod) (³¹P NMR, $\delta = 33.32$) was absolutely transformed into intermediate Ni(L7)(2-fluoropyridine) (³¹P NMR, $\delta = 29.84$). HRMS indicated that oxidative addition of nickel(0) complex Ni(L7)(2-fluoropyridine) to the C–F bond was observed in the presence of Ni(cod)₂, L7 and 2-fluoropyridine at 120 °C for 4 h.

Based on the control experiments and related literature reported, ^{2h,8a,19} a plausible mechanism is described in Scheme 5. Initially, intermediate I formed by nickel(0) catalyst and chiral bidentate phosphine ligand undergoes ligand exchange with 2-fluoropyridine derivatives to provide intermediate II confirmed by ³¹P NMR, which provided nickel(II) intermediate III *via* oxidative addition of Ni(L7)(2-fluoropyridine) to the C–F bond detected by HRMS. Next, intermediate III is transformed into nickel(II) complex IV *via* ligand exchange. Finally, reductive

elimination of intermediate **IV** affords desired products, and the coordination of the resulting nickel complex with cycloocta-1,5-diene regenerates intermediate **I** to accomplish the catalytic cycle.

In summary, we have developed the nickel-catalyzed asymmetric α -heteroarylation of indanone derivatives with 2-fluoropyridines νia C–F bond activation. A series of ketones and 2-fluoropyridine derivatives proceed smoothly to deliver the corresponding products containing all-carbon quaternary stereocenters in good yields and high ee values. Drug molecule donepezil could also be compatible with the reaction conditions to afford the desired product in excellent enantioselectivity. Further research on asymmetric C–F activation of diverse compounds is still underway.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

X. Gu performed the experiments and prepared the ESI.† K. Liu repeated some experiments. L. Yang performed the DFT calculations. C. Xie ran some HRMS of intermediates. M. Li & J. W. conceived and directed the project, and wrote the paper.

Conflicts of interest

There are no conflicts to declare.

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