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

Xiaodong Gu,^a Kexin Liu,^a Limin Yang,^b Chengyi Xie,^a Mingliang Li^{*b} and Jun (Joelle) Wang^{†*ab}

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.

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.^{1,2} 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.^{2,3} The transition metal-catalyzed C–F bond cleavage proceeds primarily through direct oxidative addition of low-valence metal complex to the C–F bond,^{2c–e,4} fluoride elimination of organic metal intermediates formed from fluorinated alkenes,^{2f,5} or photocatalytic SET-type radical defluorinative functionalization.^{2a,b,6}

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

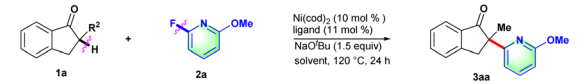
organometallic reagents, alkynes, amines, borylation reagents or silylboranes as the coupling partner (Scheme 1b).^{8–12} So far, there are rare examples of transition metal-catalyzed C(sp³)–H/C_{Ar}–F cross-coupling reactions,¹³ let alone asymmetric transformations with aryl or heteroaryl fluoride derivatives 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 Ni-catalyzed asymmetric α -heteroarylation of ketones *via* C–F bond activation to deliver all-carbon chiral quaternary carbon centers (Scheme 1c).

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



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

^aDepartment of Chemistry, Hong Kong Baptist University, Kowloon, Hong Kong, China. E-mail: junwang@hkbu.edu.hk^bDepartment of Chemistry, Southern University of Science and Technology (SUSTech), Shenzhen, 518055, China. E-mail: liml@mail.sustech.edu.cn^cCollege of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China† Electronic supplementary information (ESI) available. CCDC 2156742. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2sc03409c>

Table 1 Optimization of reaction conditions^a


L1, (S)-Binap (Ar = C₆H₅)
L2, (S)-3,5-Xyl-Binap (Ar = 3,5-Me₂C₆H₃)
L3, (S)-DiFluorPhos (R = F, Ar = Ph)
L4, (S)-DM-Segphos (R = H, Ar = 3,5-Me₂C₆H₃)
L5, (R)-C3-TunaPhos
L6 (R, S_{rac})-Josiphos SL-J005-1 (Ar = 3,5-Me₂C₆H₃)
L7, (S)-Ph-GarPhos (Ar = Ph)
L8, (S)-Xyl-GarPhos (Ar = 3,5-Me₂C₆H₃)

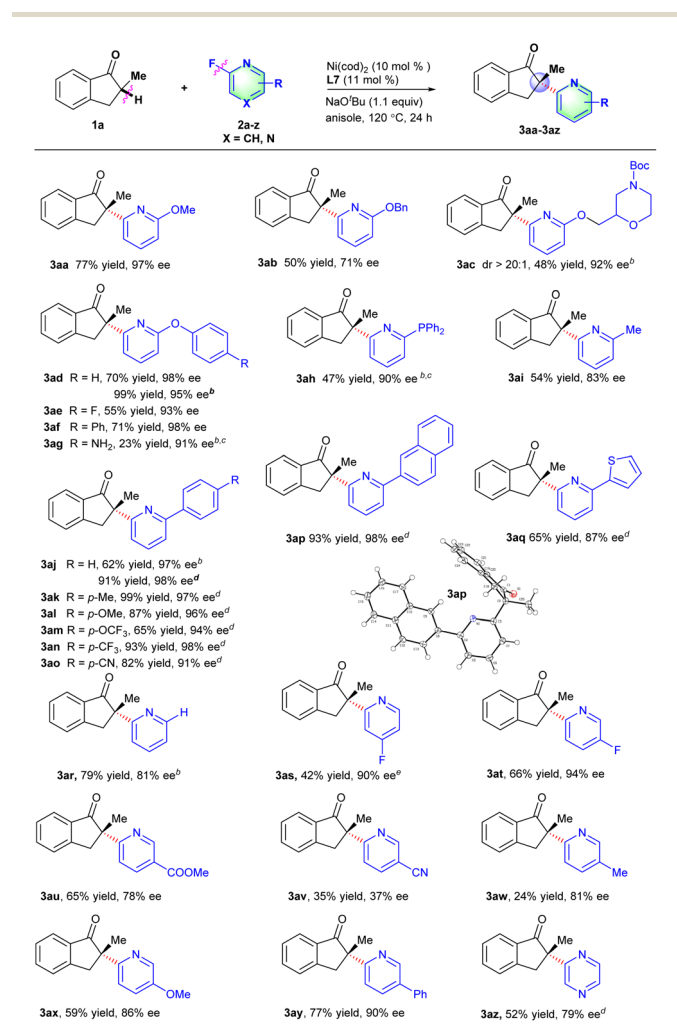
Entry	Ligand	Solvent	Yield ^b (%)	ee ^c (%)
1	L1	Toluene	39	68
2	L2	Toluene	21	65
3	L3	Toluene	NR	—
4	L4	Toluene	12	75
5	L5	Toluene	17	-74
6	L6	Toluene	67	-84
7	L7	Toluene	42	92
8	L8	Toluene	11	62
9	L7	1,4-Dioxane	84	90
10	L7	<i>m</i> -xylene	27	93
11	L7	Anisole	44	97
12 ^d	L7	Anisole	78(77) ^e	97
13 ^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^tBu (1.5 equiv.), dry solvent (1.0 mL), 120 °C, 24 h. ^b Yield of **3** was determined by ¹H NMR using dibromomethane as the internal standard. ^c Determined by chiral HPLC. ^d **1a** (0.2 mmol), **2a** (0.1 mmol), and NaO^tBu (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-aryloxy pyridines just underwent defluorinative arylation to deliver the corresponding products in good enantioselectivities (**3ad–3ag**), in which C_{Ar}–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.



Table 2 Exploring the influence of bases^a


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 ^t Bu (1.0)	1,4-Dioxane	14	17
4 ^c	NaO ^t Bu (1.1)	Anisole	Trace	Trace
5 ^c	NaO ^t Bu (1.1)	1,4-Dioxane	13	14
6 ^d	NaO ^t Bu (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 ¹H 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 *via* 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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