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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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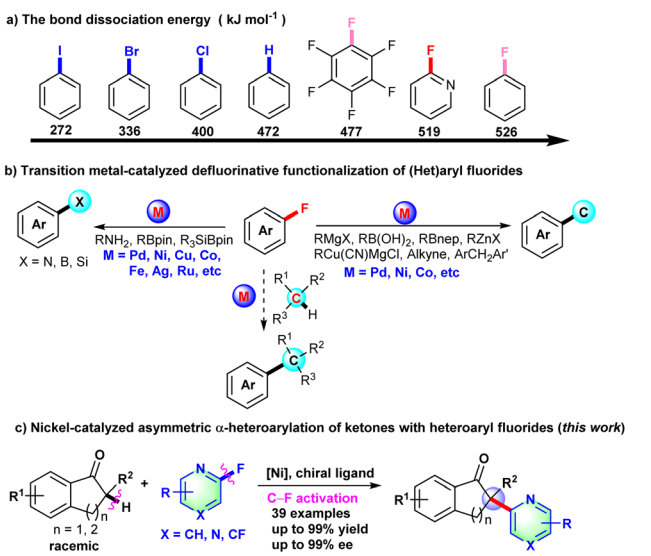
Nickel-catalyzed asymmetric α-heteroarylation of ketones with fluorinated heteroarenes is reported *via* C–F bond activation. A series of ketones and 2-fluoropyridine derivatives with different functional groups proceed well to provide the corresponding products containing all-carbon quaternary stereocenters 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.

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] fluorine 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(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 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.

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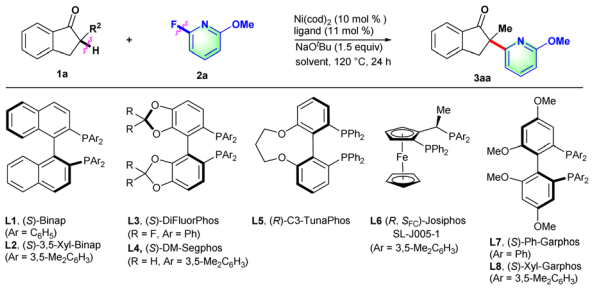
Table 1 Optimization of reaction conditions[a]



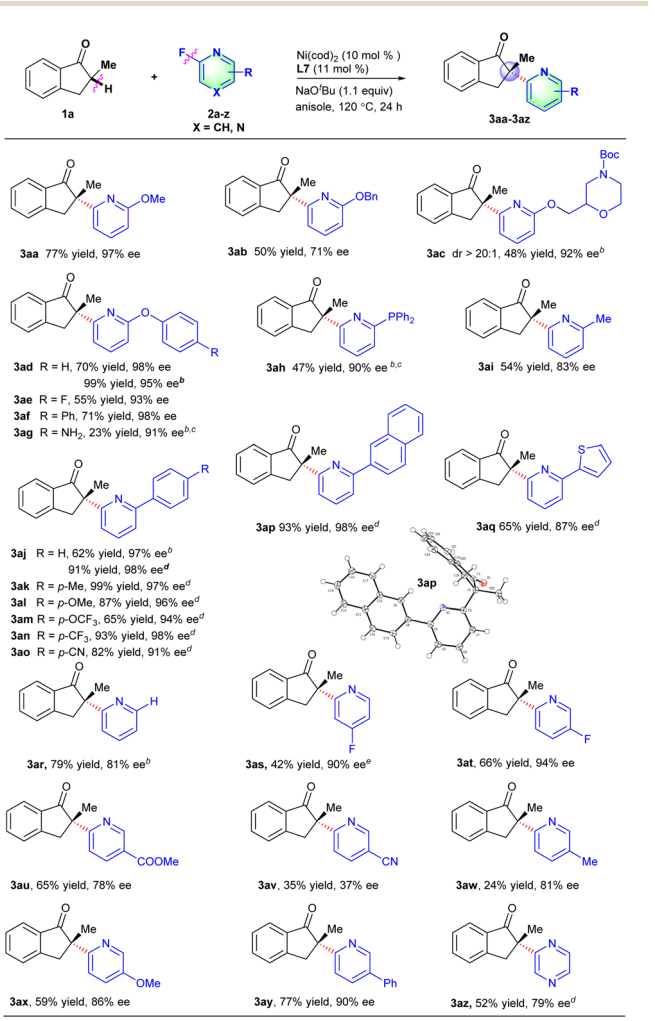
Entry	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	**L1**	Toluene	39	68
2	**L2**	Toluene	21	65
3	**L3**	Toluene	NR	—
4	**L4**	Toluene	12	75
5	**L5**	Toluene	17	−74
6	**L6**	Toluene	67	−84
7	**L7**	Toluene	42	92
8	**L8**	Toluene	11	62
9	**L7**	1,4-Dioxane	84	90
10	**L7**	*m*-xylene	27	93
11	**L7**	Anisole	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.

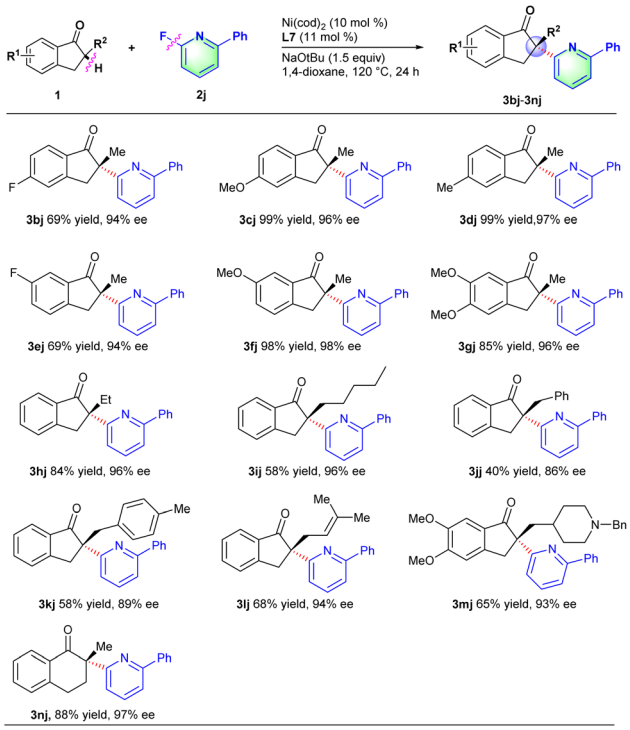
heteroarylation with 2-fluoro-6-methoxypyridine (**2a**) including C–F and C–OMe bonds. To our delight, the single defluorinative product **3aa** could be obtained in 39% yield and 68% ee in the presence of $Ni(cod)_2$, (*S*)-Binap (**L1**) and NaO^tBu (Table 1, entry 1). After the screening of a series 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, OCH_2R, OAr, PPh_2 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 (D_4R) antagonist.[15]

Interestingly, the 2-fluoro-6-aryloxypyridines 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 $MgBr_2$ 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, OCF_3, CF_3 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] $MgBr_2$ (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.



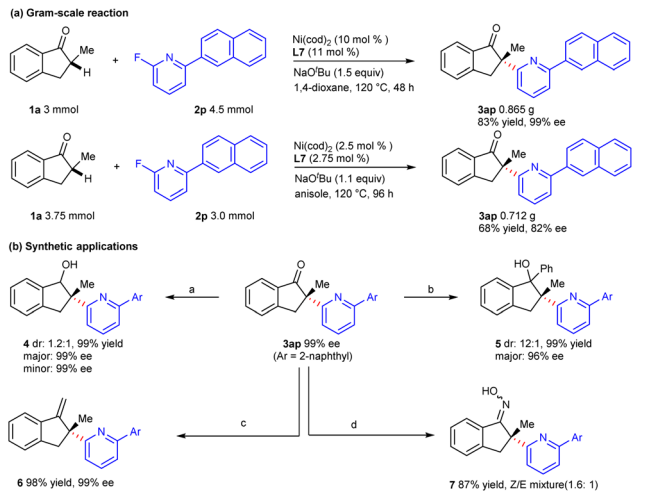
Scheme 3 Substrate scope of indanone derivatives. Reaction conditions: **1** (0.1 mmol), **2j** (0.15 mmol), $Ni(cod)_2$ (10 mol%), **L7** (11 mol%), NaO^tBu (0.15 mmol), 1,4-dioxane (1 mL), 120 °C, 24 h. Isolated yield. ee was determined by chiral HPLC.

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 CO_2Me, 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-1*H*-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.

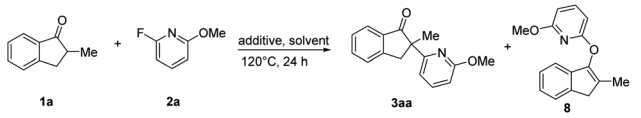
To evaluate the utility of this approach, a gram-scale reaction was carried out with 3 mmol of indanone **1a**, and the coupling product **3ap** could be obtained in 83% yield and 99% ee under the standard conditions. When the loading of the nickel catalyst decreased to 2.5 mol%, product **3ap** could 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 $NaBH_4$ 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^tBu 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



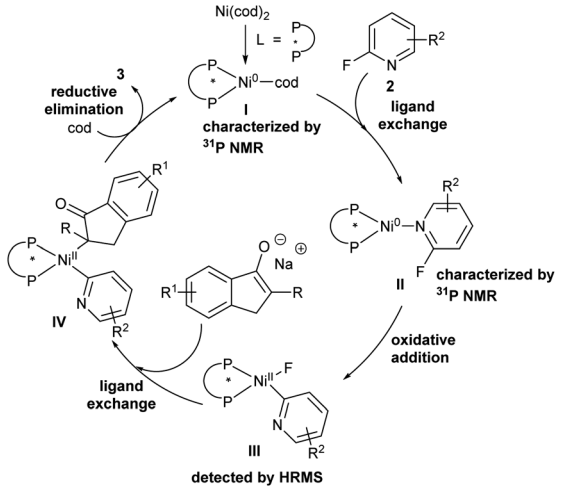
Scheme 4 Gram-scale reaction and synthetic applications. (a) $NaBH_4$ (2.0 equiv.), MeOH/THF = 1 : 1, 2 h, rt. (b) PhMgBr, −78 °C, 1 h, then rt, 2 h. (c) *t*-BuOK, PPh_3CH_3Br, rt, 5 min, THF, then rt, overnight. (d) $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux.

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^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 ^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* ^{31}P 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) (^{31}P NMR, $\delta = 33.32$) was absolutely transformed into intermediate Ni(**L7**)(2-fluoropyridine) (^{31}P 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 ^{31}P 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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17 CCDC 2156742 (**3ap**) contains the supplementary crystallographic data for this paper. These data can be obtained *via* the Cambridge Crystallographic Data Centre.

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