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Palladium-Catalyzed, Enantioselective α-Arylation of α-Fluorooxindoles

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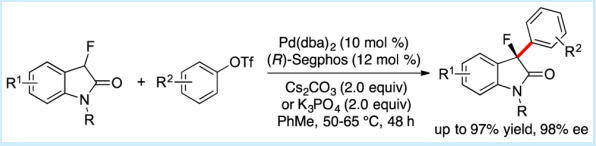
Supporting Information

ABSTRACT: Transition-metal-catalyzed asymmetric α-arylation of carbonyl compounds is a widely studied method for C−C bond formation. Recently, the α-arylation of α-fluoro ketones has been reported, including enantioselective α-arylation of α-fluoro ketones. However, the asymmetric α-arylation of α-fluoro carbonyl compounds in the carboxylic acid oxidation state has not been reported. We report the enantioselective α-arylation of α-fluorooxindoles with aryl triflates. The reaction occurs in high yield and with high enantioselectivity when catalyzed by a Pd−Segphos complex. This general class of product serves as an enantioenriched, nonenolizable version of α-aryl oxindoles.



Fluorinated organic compounds are ubiquitous in pharmaceuticals, agrochemicals, materials, and radio-chemicals.[1] Because of their unique chemical and biological properties, many methods have been developed for the syntheses of fluorine-containing compounds.[2] Chiral, nonracemic molecules that contain a stereogenic center bearing a fluorine atom are of particular importance in the pharmaceutical industry.[1] However, methods for enantioselective syntheses of these optically active, fluorinated compounds, particularly enantioenriched tertiary alkyl fluorides, are limited.[3] Few methods have been developed that generate chiral, nonracemic tertiary alkyl fluorides,[4,5] and the majority of these methods rely on α-fluorination of carbonyl compounds or 1,3-dicarbonyl compounds with electrophilic fluorinating agents. A complementary route would generate the stereogenic center by formation of a C−C bond.

Enantioenriched oxindoles that contain a tertiary fluorinated stereogenic center at the 3-position[6] are biologically important and can be found in many medicinally relevant compounds and drug candidates (Figure 1). For example, compound **A**, a potassium channel opener[7] known as MaxiPost (BMS 204352), contains an enantioenriched 3-aryl-3-fluorooxindole fragment. Oxindole **B** has been an antipsychotic drug candidate,[8] and oxindole **C** was reported to be a corticotropin-releasing factor receptor.[9]

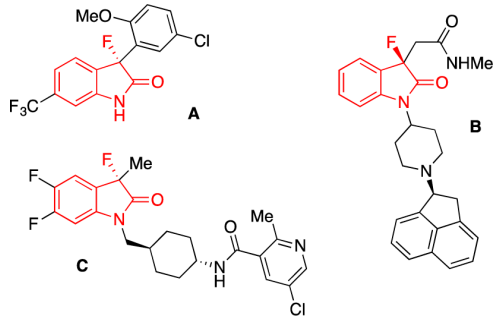
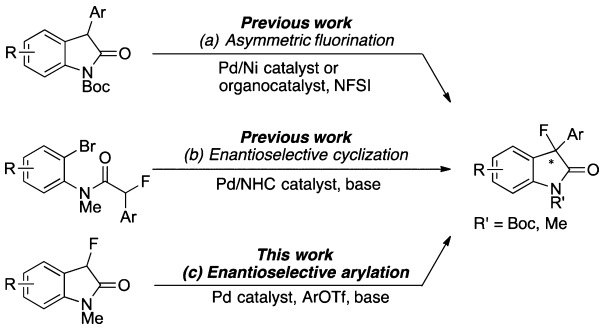


Figure 1. Optically active, bioactive compounds containing a 3-fluorooxindole unit.

Strategies for the syntheses of enantioenriched 3-aryl-3-fluorooxindoles are outlined in Scheme 1. To date, most of the methods that have been developed for the synthesis of this class of molecules rely on the enantioselective fluorination of 3-aryloxindoles (route a). For example, Sodeoka and co-workers reported a palladium-catalyzed fluorination of 3-aryloxindoles with an electrophilic fluorinating agent, NFSI, that gave 3-fluorooxindoles in high enantiomeric excess.[6a] This approach has been adopted by several other groups to synthesize enantioenriched fluorooxindoles by varying the catalyst or fluorinating reagent.[6b−d] A second approach involving an intramolecular, palladium-catalyzed cyclization was disclosed by Dorta and co-workers (route b).[6e] However, the substituent

Scheme 1. Enantioselective Syntheses of 3-Aryl-3-fluorooxindoles



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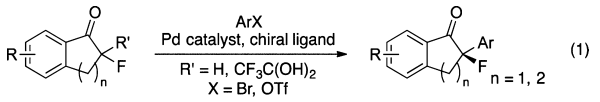
on the nitrogen atom in the amide starting material was limited to a methyl group. Here, we report an enantioselective, palladium-catalyzed, intermolecular α-arylation of 3-fluorooxindoles with aryl triflates that forms highly enantioenriched 3-aryl-3-fluorooxindoles (route c).

Recently, we developed an asymmetric α-arylation and heteroarylation of 2-fluoroindanones and tetralones (eq 1).[10]



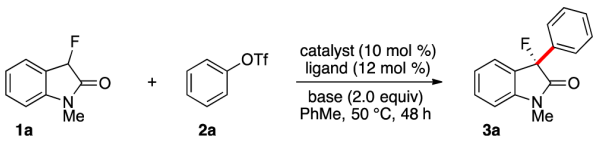
(1)

The reactions were catalyzed by palladium complexes of chiral, nonracemic mono- and bisphosphine ligands to provide the products in high yields and enantioselectivities with a wide range of aryl electrophiles. We sought to extend this class of reaction to the enantioselective, intermolecular coupling of aryl electrophiles with α-fluoro carboxylic acid derivatives. Because of the medicinal relevance of 3-fluorooxindoles, as well as the easy availability of the 3-fluorinated oxindole substrates,[6f−i] we initiated these studies by seeking systems for the enantioselective syntheses of 3-aryl-3-fluorooxindoles by asymmetric α-arylation.

We initiated our studies on the α-arylation of 3-fluorooxindole (see the SI for the syntheses of 3-fluorooxindoles **1a**−**f**) under the reaction conditions we developed for the enantioselective α-arylation of α-fluoroketones.[10] However, the reaction of *N*-methyl-3-fluorooxindole (**1a**) and bromobenzene catalyzed by the combination of $Pd(dba)_2$ and (*S*)-Segphos with K_3PO_4 as the base (2 equiv) did not form any detectable product **3a** from arylation (Table 1, entry 1).

Aryl triflates are generally more reactive than aryl bromides toward oxidative addition to palladium catalysts bound with a bidentate phosphine ligand,[11] the metal center is more electrophilic, and the leaving group is more labile in an arylpalladium triflate complex than in an arylpalladium halide complex. Therefore, reactions with an aryl triflate as the coupling partner were examined. As shown in Table 1, the reaction of oxindole **1a** and phenyl triflate (**2a**) with K_3PO_4 as the base at 50 °C in toluene provided product **3a** in 52% yield (entry 2). The reaction with NaO^{t}Bu as the base under otherwise identical reaction conditions did not give any detectable product **3a** (entry 3). However, the reaction with Cs_2CO_3 (2 equiv) as the base led to product **3a** in 66% isolated yield with 90% ee (entry 4).

Table 1. Development of Conditions for the Asymmetric α-Arylation of α-Fluorooxindoles[a]



entry	[Pd]	ligand	base	yield[b] (%)	ee[c] (%)
1[d]	A	(*S*)-Segphos	K_3PO_4	0	
2	A	(*S*)-Segphos	K_3PO_4	52[e]	ND
3	A	(*S*)-Segphos	NaO^{t}Bu	0	
4	A	(*S*)-Segphos	Cs_2CO_3	66	90
5	B	(*S*)-Segphos	Cs_2CO_3	82	86
6	C	(*S*)-Segphos	Cs_2CO_3	90	82
7	A	(*S*)-BINAP	Cs_2CO_3	38[e]	ND
8[f]	A	(*S*)-Segphos	Cs_2CO_3	5[e]	ND
9[g]	A	(*S*)-Segphos	Cs_2CO_3	82	91
10[h]	A	(*S*)-Segphos	Cs_2CO_3	63	ND
11[i]	A	(*S*)-Segphos	Cs_2CO_3	81	88

[a]Reactions were conducted on a 0.2 mmol scale in toluene (1.0 mL) at 50 °C for 48 h unless otherwise noted. The ratio of **1a**/**2a**/catalyst/ligand/base was 2/1/0.1/0.12/2. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC or SFC analysis. [d]Bromobenzene was used instead of **2a**. [e]NMR yield. [f]The reaction was conducted in CyH (1.0 mL). [g]The reaction was conducted at 65 °C. [h]The reaction was conducted at 80 °C. [i]The reaction was conducted with 3 Å molecular sieves (15 mg): A, $Pd(dba)_2$; B, $Pd(OAc)_2$; C, $[Pd(cinnamyl)Cl]_2$.

Reactions with alternative Pd precatalysts and ligands were also examined. Although the reactions with $Pd(OAc)_2$ (entry 5) or $[Pd(cinnamyl)Cl]_2$ (entry 6) with (*S*)-Segphos as the ligand provided product **3a** in higher yields than did that with $Pd(dba)_2$, the enantiomeric excess of **3a** formed from these reactions was lower (86% ee and 82% ee, respectively). The reaction with the simpler biarylphosphine (*S*)-BINAP as the ligand gave product **3a** in only 38% yield (entry 7).

Studies on additional reaction parameters showed the effect of solvent and temperature on this α-arylation. The asymmetric α-arylation of 2-fluoroindanones occurred in the highest yield and ee in cyclohexane,[10] but only a trace amount of **3a** was detected when the reaction of oxindole **1a** was conducted in cyclohexane in place of toluene (entry 8). The reaction temperature significantly affected the yield, but not the enantioselectivity. At 65 °C in the presence of 10 mol % of $Pd(dba)_2$, 12 mol % of (*S*)-Segphos, and 2 equiv of Cs_2CO_3, product **3a** formed in 82% yield (entry 9), versus 66% yield at 50 °C, but at 80 °C under otherwise identical reaction conditions **3a** formed in only 63% yield (entry 10). The addition of 3 Å molecular sieves to the reaction mixture did not improve the yield and ee of product **3a** (entry 11).

Scheme 2 summarizes the scope of aryl triflates that undergo asymmetric α-arylation with oxindole **1a** under the conditions of entry 9 in Table 1 with (*R*)-Segphos as the ligand. In general, asymmetric arylation of oxindole **1a** with a variety of aryl triflates gave products in high yields and enantioselectivities. Arylation of **1a** with electron-poor aryl triflates, including phenyl and those containing cyano, methoxycarbonyl, and nitro groups in the *para* position, gave arylated products **3a**−**d** in 58−82% yield with 86−96% ee (entries 1−4, Scheme 2), and *meta*-cyanophenyl triflate gave **3e** in 52% yield with 95% ee (entry 5, Scheme 2). The reaction of **1a** with the more electron-rich 3,5-dimethoxyphenyl triflate also occurred to give arylated oxindole **3f** in 95% ee, albeit in a moderate yield (52%). Finally, halogen-substituted aryl triflates were suitable electrophiles for arylation at the triflate position. The reaction of **1a** with *p*-chlorophenyl triflate proceeded to provide product **3g** in 71% yield with moderate enantioselectivity (78% ee). Reactions with *o*-substituted aryl triflates, however, occurred in low yields and enantioselectivities. The absolute configuration of one of the products (**3b**) was determined by single-crystal X-ray diffraction.

Although reactions with Cs_2CO_3 generally occurred in higher yields than those with other bases, the reactions with K_3PO_4 did occur in higher yields in a few cases. The reactions of **1a** with *p*-nitrophenyl triflate, *p*- and *m*-cyanophenyl triflates occurred in low yields when the reactions were conducted with Cs_2CO_3 as the base but occurred smoothly at 50 °C with K_3PO_4 as the base to give arylated products in 52−82% yield with 86−96% ee (entries 2, 4, and 5, Scheme 2).

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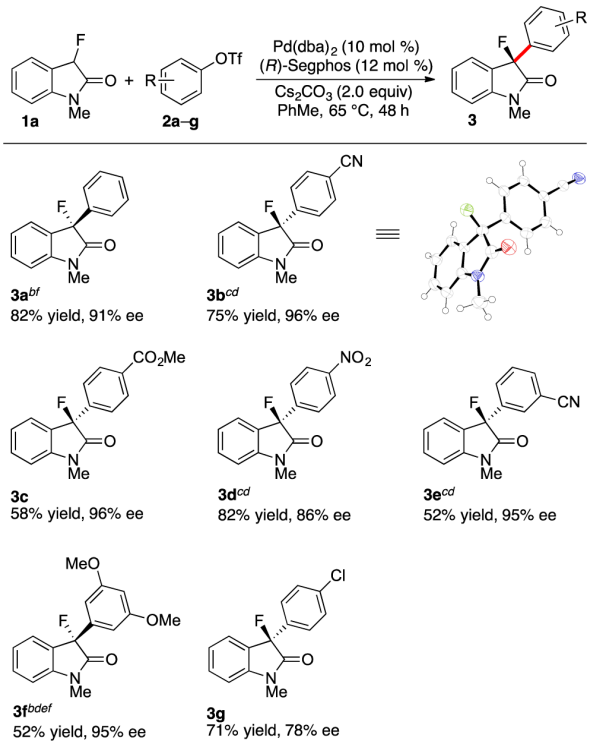
Org. Lett. 2017, 19, 1390−1393

Scheme 2. Scope of Aryl Triflates 2 That Couple with Oxindole 1a[a]

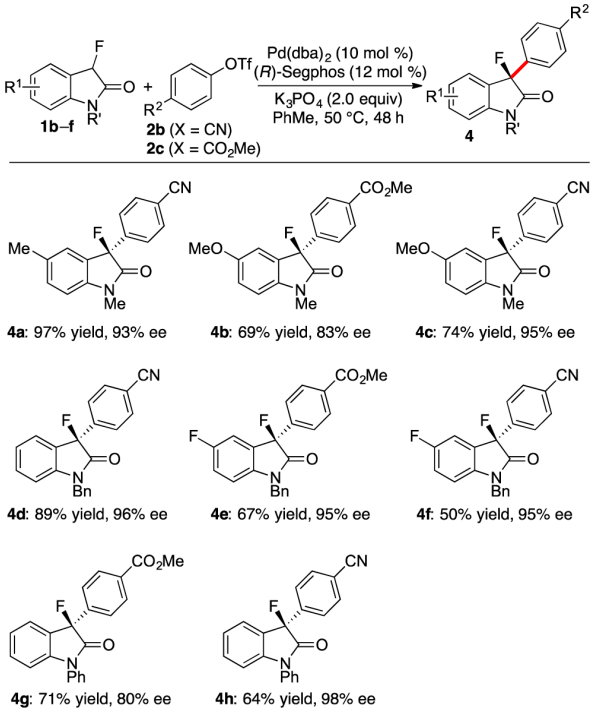


[a]Reactions were conducted on 0.1 mmol scale in toluene (0.5 mL) at 65 °C for 48 h unless otherwise noted. The ratio of **1a**/**2**/Pd(dba)$_2$/Segphos/base was 2/1/0.1/0.12/2. All yields were isolated yields. All enantiomeric excesses were determined by HPLC or SFC analysis. [b]The reaction was conducted with (*S*)-Segphos. [c]The reaction was conducted with K_3PO_4 as base. [d]The reaction was conducted at 50 °C. [e]The reaction was conducted with 3 Å molecular sieves (7.5 mg). [f]The reaction was conducted on a 0.2 mmol scale.

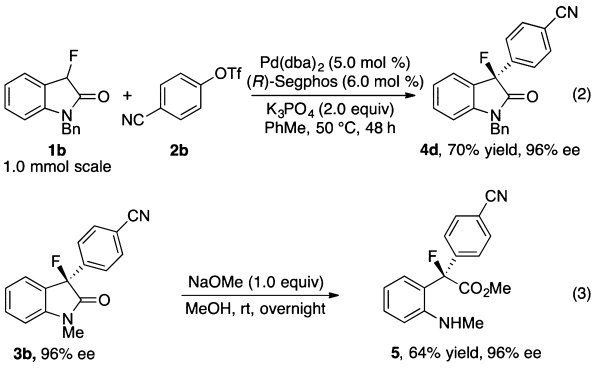
Scheme 3 summarizes the scope of substituted 3-fluorooxindoles that underwent the asymmetric α-arylation reaction with aryl triflates **2b** and **2c**. Again, we found that the identity of the base was important to obtain products in high yields with various *N*-methyl-, benzyl-, and phenyl-substituted 3-fluorooxindoles. In these cases, reactions with K_3PO_4 as the base gave arylated products in much higher yields than did the reactions with Cs_2CO_3. Therefore, K_3PO_4 was used as the base for the arylations of 3-fluorooxindoles **1b–f**. Under the modified conditions, the complex generated from (*R*)-Segphos and Pd(dba)$_2$ catalyzed the reactions of 5-methyl- or 5-methoxy-substituted *N*-methyl-3-fluorooxindoles with aryl triflates **2b** and **2c** to give products **4a–c** in 69–97% yield with 83–95% ee. 3-Fluorooxindoles substituted with *N*-benzyl and *N*-phenyl groups also reacted with aryl triflates **2b** and **2c** to provide products **4d–h** in 50–89% yield with 80–98% ee.

The asymmetric α-arylation reaction was also conducted on a larger scale and with a lower catalyst loading than the reactions shown in Schemes 2 and 3. Specifically, the α-arylation reaction of oxindole **1b** (1.0 mmol) and aryl triflate **2b** (0.5 mmol) in the presence of 5.0 mol % of Pd(dba)$_2$ and 6.0 mol % of (*R*)-Segphos with K_3PO_4 as the base formed the α-arylated product **4d** in 70% yield with the same enantioselectivity (96% ee) (eq 2) as the reactions on a smaller scale with higher loadings of the palladium catalyst and ligand.

Scheme 3. Scope of Substituted 3-Fluorooxindoles That Couple with Aryl Triflates 2b and 2c[a]



[a]Reactions were conducted on a 0.1 mmol scale in toluene (0.5 mL) at 50 °C for 48 h. The ratio of **1**/**2**/Pd(dba)$_2$/(*R*)-Segphos/K_3PO_4 was 2/1/0.1/0.12/2. All yields were isolated yields. All enantiomeric excesses were determined by SFC analysis.



Although oxindoles have a wide range of biological activities, they are also suitable for ring-opening reactions to form carboxylic acids and esters. For example, treatment of the enantioenriched α-fluoro-α-aryl product **3b** with 1.0 equiv of NaOMe in methanol afforded the corresponding α,α-diaryl-α-fluoroester product **5** in 64% yield with the same ee as the starting oxindole (96% ee) (eq 3).[6a] This procedure would be useful for the synthesis of optically active acyclic α,α-diaryl-α-fluoro carbonyl compounds, which are generally difficult to obtain without resorting to kinetic resolution or separation by chiral HPLC.[7]

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In conclusion, we have demonstrated that reactions between 3-fluorooxindoles and aryl triflates catalyzed by the combination of $Pd(dba)_2$ and Segphos occur to give enantioenriched 3-aryl-3-fluorooxindoles. Under the developed conditions, most of the arylated products were obtained in high yields with high enantioselectivities. Further studies to expand the scope of α-fluoro carbonyl compounds that undergo enantioselective reactions, as well as mechanistic studies that could reveal the structure and reactivity of the arylpalladium fluoroenolate complexes, are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00294.

Experimental procedures; spectra for all new compounds (PDF)

X-ray data for compound **3b** (CIF)

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Notes

The authors declare no competing financial interest.

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