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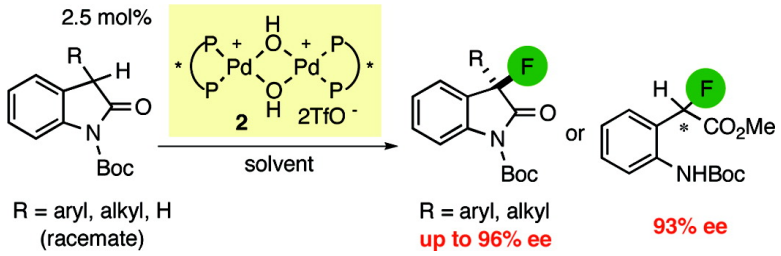

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Catalytic Enantioselective Fluorination of Oxindoles

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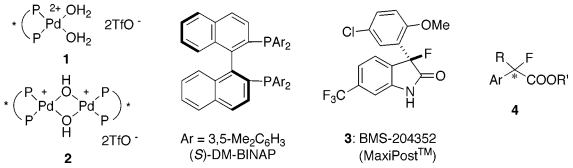
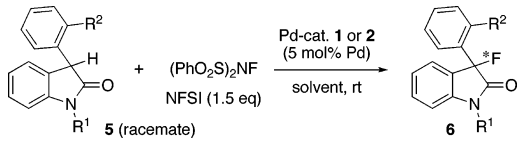
Introduction of fluorine atoms into bioactive compounds is a common approach to improve the biological activity profile.[1] Therefore, catalytic enantioselective fluorination has attracted growing interest.[2] We recently reported efficient fluorination reactions of β-ketoesters and β-ketophosphonates.[3] Several chiral catalysts for enantioselective fluorination have been developed,[4] but in most cases, they were applied only to β-ketoesters, and other nucleophiles were rarely examined. Therefore, development of novel reactions applicable to other carbonyl compounds is still required.

BMS 204352 (MaxiPost) **3** developed by Bristol-Myers Squibb is a promising agent for the treatment of stroke and is undergoing clinical phase III trial.[5] It was reported that replacement of a hydroxyl group at the 3-position of the oxindole ring by a fluorine atom played a key role in enhancing its pharmaceutical efficiency. Because the oxindole ring is widely found among natural products, its optically active fluorinated derivatives could have many applications in the field of medicinal chemistry.[6,7] Moreover, further conversion of fluorinated oxindoles would provide access to the chiral α-fluorophenylacetic acid derivatives **4**, which are fluorinated analogues of important structural components of various drug candidates. Herein, we wish to report the first example of catalytic enantioselective fluorination of oxindoles using chiral Pd complexes **1** and **2**.



Initially, we examined the reaction of the phenyl-substituted oxindole **5a** (Table 1). (*S*)-DM-BINAP was chosen as a chiral ligand based on our previous results.[3,8] In the presence of **1**, the reaction of **5a** with *N*-fluorobenzenesulfonimide (NFSI) was sluggish, and negligible asymmetric induction was observed (entry 1). Thus, we planned to protect the nitrogen moiety of **5a** with a *t*-butoxycarbonyl (Boc) group, expecting that the *N*-Boc-protected oxindoles would be activated effectively to form a configurationally stable Pd enolate. Gratifyingly, the reaction of **5b** in THF afforded the desired product **6b** in 53% yield with 81% ee (entry 2). Further optimization revealed that 2-propanol (IPA) and acetone gave better selectivity (entries 3 and 4).[8] However, the chemical yield was still unsatisfactory (<66%), which was attributed to deprotection of the Boc group due to the acidic nature of **1**. This problem was overcome by using the less acidic Pd complex **2**, and **6b** was isolated in 90% yield without any loss of enantioselectivity (entry 5).[9] Next, we assessed the influence of a methoxy group at the R^2 position. Despite the possible steric interaction, the reaction of **5c** proceeded smoothly

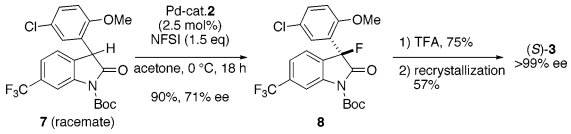
Table 1. Optimization of the Reaction Conditions



entry	Pd catalyst	5	R^1/R^2	solvent	time (h)	yield (%)	ee[a] (%)
1	**1**	**5a**	H/H	THF	60	20	5
2	**1**	**5b**	Boc/H	THF	12	53	81
3	**1**	**5b**	Boc/H	IPA	3	66	88
4	**1**	**5b**	Boc/H	acetone	3	58	89
5	**2**	**5b**	Boc/H	IPA	5	90	88
6	**2**	**5c**	Boc/OMe	acetone	18	89	76
7	**2**	**5d**	OC(O)$CHPh_2$/OMe	acetone	12	93	73
8[b]	**2**	**5e**	OC(O)-9-Fl/OMe	acetone	5	95	81

[a] Determined by chiral HPLC analysis. [b] 9-Fl = 9-fluorenyl.

Scheme 1. Catalytic Asymmetric Synthesis of BMS 204352



to give **6c** in 89% yield with 76% ee (entry 6). Although several bulkier protecting groups were tested, the observed enantiomeric excesses were comparable (up to 81% ee) to that in the case of **5c** (entries 7 and 8).

With these results in hand, we applied our reaction to the catalytic asymmetric synthesis of **3** (Scheme 1).[8,10] A starting material **7** was subjected to the fluorination reaction, and the desired product **8** was isolated in 90% yield with 71% ee. After treatment with TFA, recrystallization furnished optically pure **3** (>99% ee).

Encouraged by these results, we next examined the generality of this reaction (Table 2).[8] The enantiomeric excess of **6b** was slightly improved (90% ee) when the reaction was conducted at 0 °C (entry 1, see also entries 3 and 7). Regardless of the electronic nature of the substituents on the aromatic rings, other aryl-substituted oxindoles (**5f**−**h**) were also good substrates (entries 2−5). In addition, the reaction of alkyl-substituted substrates (**5i**−**m**) proceeded well in good yield with high to excellent enantioselectivities (75−96% ee) (entries 6−11). Thus, we have developed an efficient enantioselective fluorination of oxindoles with broad generality. It should be noted that these reactions are operationally convenient and can be performed without exclusion of air and moisture.

As shown in Scheme 2, the optically active α-fluoro-α-aryl acetate **9** was readily obtained by treatment with MeONa in MeOH.[8] In view of the versatility of the amine moiety for further functionalization, this procedure would be useful for the synthesis of various α-fluorophenylacetate derivatives.

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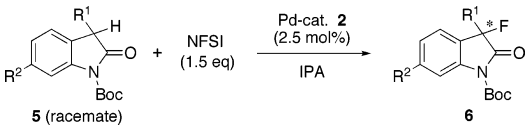
Table 2. Catalytic Enantioselective Fluorination of Oxindoles



5 (racemate) 6

entry	5	R^1/R^2	temp[a]	time (h)	yield (%)	ee (%)
1	**5b**	Ph/H	0 °C	18	96	90
2	**5f**	*p*-MeC_6H_4/H	rt	3	97	86
3	**5f**	*p*-MeC_6H_4/H	0 °C	18	92	88
4	**5g**	*p*-FC_6H_4/H	rt	3	94	84
5[c]	**5h**	*o*-$MeOC_6H_4/CF_3$	rt	3	80	75
6	**5i**	Me/H	rt	5	86	95
7	**5i**	Me/H	0 °C	18	85	96
8	**5j**	Et/H	rt	10	85	92
9	**5k**	$CH_2C(O)CH_3$/H	rt	2	85	86
10	**5l**	Bn/H	rt	4	72	80
11	**5m**	*i*-Bu/H	rt	2	85	75

[a] rt = 20−23 °C. [b] Determined by chiral HPLC analysis. [c] Acetone was used as a solvent.

Scheme 2. Conversion of **6i**

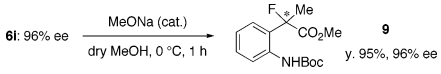
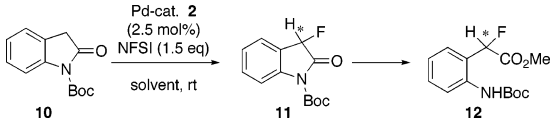


Table 3. Catalytic Enantioselective Monofluorination of **10**



10 11 12

entry	solvent	product	time (h)	yield (%)	ee[a] (%)
1	THF	**11**	43	29	21
2	THF/MeOH (5:1)	**12**	60	55	60
3	THF/MeOH (1:1)	**12**	18	51	84
4	$ClCH_2CH_2Cl$/MeOH (1:1)	**12**	18	53	93

[a] Determined by chiral HPLC analysis.

Although we could not observe a key intermediate by spectroscopic analysis, the high enantioselectivity obtained in this reaction can be explained by postulating involvement of a chiral Pd enolate (see Supporting Information).[11] The stereochemistry predicted on the basis of this model was in accord with the absolute stereochemistry observed in the case of BMS compound **3**.

In contrast to the fluorination of active methine compounds to give chiral quaternary carbon centers, there has been, to our knowledge, no successful example of the catalytic asymmetric synthesis of fluorinated compounds with a tertiary chiral center having a hydrogen atom.[12,13] This fact prompted us to attempt the enantioselective monofluorination of **10**.[8] Since the fluorinated product **11** would be more susceptible to enolization than **10**, racemization of the product was considered unavoidable. Indeed, an attempt at obtaining **11** resulted in low selectivity (Table 3, entry 1). We envisaged that solvolysis of **11** with alcohol before racemization would be possible. Racemization of **11** was indeed significantly suppressed, and the monofluorinated product **12** was obtained with reasonably high enantioselectivity (entries 2 and 3). After examining several solvents, we found that the use of halogenated solvent mixed with MeOH (1:1) afforded **12** with an excellent enantioselectivity of 93% (entry 4). Although competitive solvolysis of **10** should be suppressed to increase the chemical yield, catalytic asymmetric monofluorination, which is considered to be difficult under basic conditions, was achieved at a synthetically useful level.

In conclusion, we have developed a highly efficient catalytic enantioselective fluorination of oxindoles. This method can provide various fluorinated compounds, including oxindoles and phenylacetate derivatives, in a highly enantioselective manner. We believe that the availability of these compounds will be valuable in the field of medicinal chemistry. Further examination of the scope of the reaction and mechanistic studies are underway in our laboratory.

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Supporting Information Available: Details of optimization of the reaction conditions, experimental details of the fluorination reaction, and the spectroscopic characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For details, see Supporting Information.

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