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$Dy(OTf)_3$/Pybox-catalyzed enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated trifluoromethyl ketones

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ABSTRACT

The first catalytic enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated trifluoromethyl ketones has been accomplished. The reaction was achieved in the presence of the $Dy(OTf)_3$/Pybox complex, producing the desired products in high yields (up to 99%) with good enantioselectivities (up to 86% ee). The absolute stereochemistry of the resulting adducts was determined by X-ray analysis.

Organic fluorine compounds often show unique bioactivities and behavior compared with their non-fluorinated parent compouds.[1] Currently, about 20–30% of agrochemicals and pharmaceuticals owe their effectiveness due to the presence of one or more fluorine atoms in their structure. Various organic fluorine compounds have been synthesized,[2] for example, α,β-unsaturated trifluoromethyl ketones have been prepared,[3] involving a directly linking electron-withdrawing trifluoromethyl group with a highly reactive π-system.

The Friedel–Crafts (F–C) alkylation of indoles[4] is of interest because a number of biologically active derivatives exist as natural compounds. However, there is yet no report on the F–C alkylation of indoles with α,β-unsaturated trifluoromethyl ketones. Here, we studied the role of such ketones as Michael acceptors yielding synthetic fluorine-containing indole derivatives.

The reactions of indole **1** with α,β-unsaturated trifluoromethyl ketones **2** were chosen as models for optimizing the reaction condition. To evaluate the behavior of acid catalysts (Table 1), **1** was reacted with 1.05 equiv of **2** and a catalytic amount of acids in dichloromethane (DCM) at room temperature to yield the product **3a**. Classical Brønsted (entries 2 and 3) and Lewis (entries 4 and 5) acid catalysis on F–C alkylation produced unsatisfactory results, but the one using $Sc(OTf)_3$ catalyst gave the desired adduct **3a** in good yield.

The above-mentioned result led us to investigate the complexes of lanthanide (Ln) and Pybox **4a**–**e** (Fig. 1), where the pyridine- and imine-building blocks support the ligand as a strong electron donor, and the isopropyl side chain of **4a** can be easily changed with other alkyl substituents.[5d] The use of the Ln/Pybox system in synthesis methodology has been reported.[5] In this work, various $Ln(OTf)_3$/Pybox **4a** systems were applied to the reaction of **1** with **2** (Table 2).

The reaction of **1** with **2** was attempted in the presence of 5 mol % $Sc(OTf)_3$ and **4** in DCM to give the corresponding adduct **3a** in good yield and with opposite enantioselectivity (entry 1). Based on the previous report, the formation of opposite enantio-

Table 1
Acid-catalyzed F–C alkylation of **1** with **2**

Entry	Catalyst	Conversion[a] (%)
1	None	5
2	*p*-TsOH	41
3	PPTS	No reaction
4	BF_3OEt_2	Trace
5	$Ti(Oi\text{-}Pr)_4$	18
6	$Sc(OTf)_3$	81

[a] Calculated by ^1H NMR spectra.

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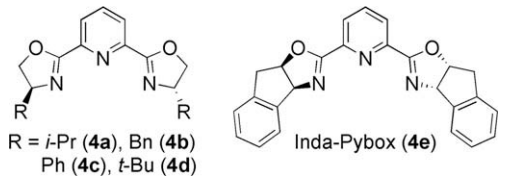


Figure 1. Pybox **4a–e**.

Table 2
Enantioselective F–C alkylation of **1** with **2**

Entry	Ln	Yield of **3a**[a] (%)	ee[b] (%)
1	Sc	85	−47
2	Y	>99	84
3	La	29	53
4	Sm	>99	76
5	Eu	>99	83
6	Gd	84	84
7	Tb	88	85
8	Dy	>99	87
9	Ho	93	83
10	Yb	60	74

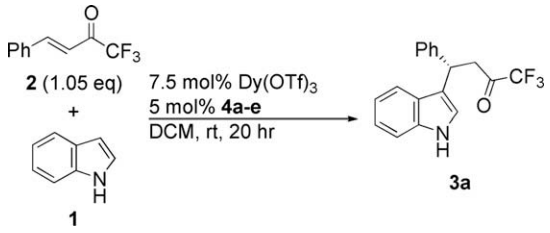
[a] Isolated yield.
[b] Determined by HPLC.

mers by changing the $Ln(OTf)_3$/Pybox catalyst has been already examined.[6] It was assumed that difference lanthanide ion radius gives different enantioselectivity due to the changing of their coordination with chiral ligand.[7] The reaction also proceeded smoothly in the presence of 5 mol % $Y(OTf)_3$ (entry 2). In contrast, $La(OTf)_3$ promoted no similar reactions (entry 3), although the other $Ln(OTf)_3$ compounds of f-blocks (except $Yb(OTf)_3$) were shown to be effective catalysts, yielding the adduct **3a** in good yields and enantioselectivities, and $Dy(OTf)_3$ was found to be the best (entries 4–10). Owing to the insufficient reproducibility of the $Dy(OTf)_3$ system, therefore, we examined the amount of $Dy(OTf)_3$ and Pybox to determine the optimum synthesis condition (7.5 mol % $Dy(OTf)_3$ and 5 mol % Pybox were used).[8]

We then turned our attention to the effect of ligand substitution on the F–C alkylation (Table 3). In terms of enantioselectivity, *i*-Pr-Pybox (**4a**) is clearly the most effective ligand in the $Dy(OTf)_3$-catalyzed F–C alkylation (entry 1). Rather surprisingly, *t*-Bu and indano-Pybox (**4d**, **e**) gave poor yield and enantioselectivity (entries 4 and 5). In this study we found that the optimum enantioselectivity was achieved with $Dy(OTf)_3$/*i*-Pr-Pybox catalyst.

Since the $Dy(OTf)_3$/Pybox **4a** system was found useful in the reaction of **1** with **2**, the enantioselective F–C alkylations of various indole derivatives **5** with **2** were attempted as shown in Table 4. In all cases, the reactions provided the desired adduct **3a–j** in good yields. However, N-alkylated indoles had a detrimental effect on enantioselectivity (R_1 = Me and Bn; entries 2 and 3). In contrast to the electron-donating groups, which have a beneficial effect (R_2 = MeO and Me; entries 4 and 5), the electron-withdrawing groups (R_2 = F, Cl, Br, CO_2Me, CN) in C-5 of the indole skeleton appear to result in low reactivities (entries 6–10) and enantioselectivities (entries 9 and 10). The low reactivities were overcome by

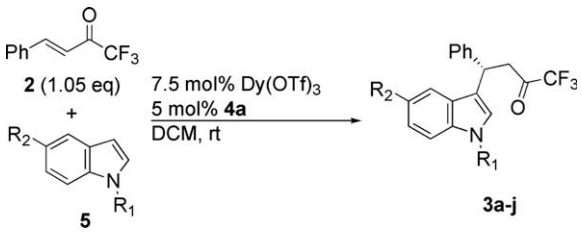
Table 3
Enantioselective F–C alkylation with $Dy(OTf)_3$/Pybox **4a–e**



Entry	Pybox	Yield of **3a**[a] (%)	ee[b] (%)
1	**4a**	95	84
2	**4b**	98	77
3	**4c**	62	64
4	**4d**	13	13
5	**4e**	55	70

[a] Isolated yield.
[b] Determined by HPLC.

Table 4
Enantioselective F–C alkylation of indoles **5** with **2**



Entry	R_1	R_2	Conc of **5** (mol/L)	Reaction time	Yield[a] (%)	ee[b] (%)
1	H	H	0.2	20 h	95 (**3a**)	84
2	Me	H	0.2	2 d	98 (**3b**)	16
3	Bn	H	0.2	2 d	77 (**3c**)	16
4	H	MeO	0.1	18 h	96 (**3d**)	77
5	H	Me	0.1	18 h	99 (**3e**)	85
6	H	F	0.4	4 d	91 (**3f**)	72
7	H	Cl	0.4	4 d	91 (**3g**)	78
8	H	Br	0.4	4 d	77 (**3h**)	77
9	H	CO_2Me	1	4 d	97 (**3i**)	19
10	H	CN	0.5	4 d	60 (**3j**)	7

[a] Isolated yield.
[b] Determined by HPLC.

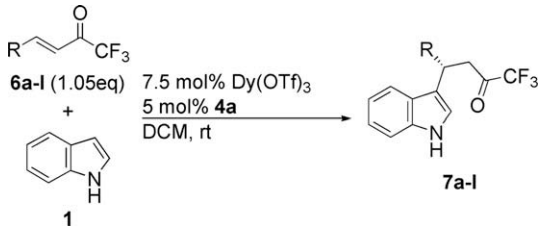
the use of high concentrations of indoles in a longer reaction time to obtain the products in good yields.

Next, the enantioselective F–C alkylations of various α,β-unsaturated trifluoromethyl ketones **6** were attempted in order to determine the reaction condition (Table 5). The presence of a range of electron-withdrawing substituents at the aromatic ring had little influence on enantioselectivity. However, replacing the aromatic ring with aliphatic groups such as *n*-C_6H_{13} (entry 12) resulted in lowering of the enantioselectivity.

The absolute configuration of **3a** was determined by X-ray analysis (see Supplementary data) of the bromo derivative **7k**. The hydrogenolysis of **7k** with $Pd(OH)_2/H_2$ afforded **3a**, and the absolute configuration proposed previously for **3a** was validated (Scheme 1).

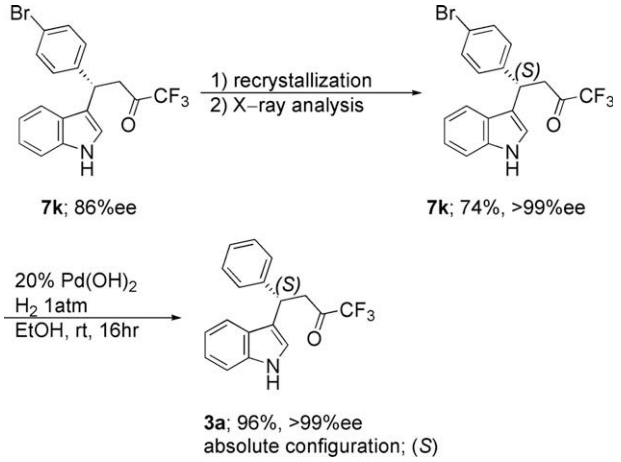
In summary, we devised $Dy(OTf)_3$/Pybox as an effective catalytic system for the enantioselective F–C alkylation of indoles with α,β-unsaturated trifluoromethyl ketones furnishing synthetic fluorine-containing indoles in good yields and enantioselectivities. The catalytic system can be easily obtained from a commercial source,

Table 5
Enantioselective F–C alkylation of **1** with **6a–l**



Entry	R	Reaction time	Yield[a] (%)	ee[b] (%)
1	*o*-MeO–Ph (**6a**)	4 d	98 (**7a**)	72
2	*m*-MeO–Ph (**6b**)	4 d	96 (**7b**)	84
3	*p*-MeO–Ph (**6c**)	4 d	78 (**7c**)	71
4	*o*-Me–Ph (**6d**)	3 d	90 (**7d**)	81
5	*m*-Me–Ph (**6e**)	3 d	95 (**7e**)	84
6	*p*-Me–Ph (**6f**)	3 d	95 (**7f**)	81
7	*p*-F–Ph (**6g**)	22 h	93 (**7g**)	79
8	*o*-Cl–Ph (**6h**)	22 h	99 (**7h**)	81
9	*m*-Cl–Ph (**6i**)	22 h	99 (**7i**)	83
10	*p*-Cl–Ph (**6j**)	22 h	94 (**7j**)	80
11	*p*-Br–Ph (**6k**)	22 h	99 (**7k**)	86
12	*n*-C_6H_{13} (**6l**)	36 h	95 (**7l**)	17

[a] Isolated yield.
[b] Determined by HPLC.



Scheme 1. Determination of absolute configuration of **7k** and **3a**.

and our simple procedure is particularly suitable for introducing a trifluoromethyl ketone unit into drug candidates having complex structures.

Acknowledgment

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Supplementary data

Experimental procedures, structural proofs, NMR spectra, HPLC profiles, and X-ray crystallography data are available. CCDC 730908 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.121.

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8. The reaction was performed with 2.5 mol % Dy(OTf)$_3$ and 5 mol % *i*-Pr-Pybox to give product **3a** in low yield and poor enantioselectivity (22%, 42%ee). Though 5 mol % dried Dy(OTf)$_3$ (60 °C, 30 min, under vacuum) was used, the F–C alkylation did not proceed. Therefore for providing the optimum condition we should use a little excess Dy(OTf)$_3$ (7.5 mol %) and 5 mol % of *i*-Pr-Pybox without purification.