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Highly enantioselective yttrium(III)-catalyzed Friedel–Crafts alkylation of β-trichloro(trifluoro)methyl aryl enones with indoles†

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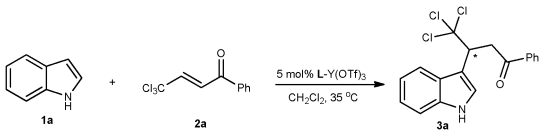
An efficient yttrium(III)-catalyzed highly enantioselective Friedel–Crafts alkylation of β-trichloro(trifluoro)methyl aryl enones is described. The reaction delivered a series of functionalized indoles with a chiral tertiary carbon center bearing a trichloro(trifluoro)methyl group in excellent results (up to 96% ee and 99% yield) under mild conditions.

Enantiomerically pure trichloro(trifluoro)methylated compounds are fascinating in the field of biological and medicinal chemistry, and are also utilized as versatile building blocks in modern organic synthesis.[1] Among them, especially those featuring a trichloro(trifluoro)methyl group at an all-C tertiary chiral carbon center remain challenging synthetic targets.[2] On the other hand, the indole framework is considered to be one of the "privileged" structures in pharmaceutical chemistry.[3] In this context, to introduce these simple structures to complex molecules would not only have potential biological applications but also represent a significant contribution to synthetic methodologies. The Friedel–Crafts alkylation[4,5] of indoles with trichloro(trifluoro)methyl olefins represents a direct and promising route to this class of compounds, and the development of asymmetric catalysts for such processes has been the focus of recent research effort. In 2010, Shibata and co-workers reported the first enantioselective Friedel–Crafts reaction of β-trifluoromethylated acrylates with pyrroles and indoles promoted by 20 mol% of bis(oxazoline)–$Zn(NTf_2)_2$ complex at −75 °C.[6a] Very recently, Pedro *et al.* described a highly enantioselective Friedel–Crafts alkylation of β-trifluoromethyl-α,β-unsaturated ketones with indoles using 20 mol% of zirconium(IV) complex.[6b] Although the impressive advances have been made in this area,[6c] searching for efficient catalysts that could achieve high reactivity and enantioselectivity under mild reaction conditions and extending the substrate scope are still desirable and challenging. Furthermore, to our knowledge to date, there is no report in which trichloromethyl olefins are employed. Nevertheless trichlorinated molecules exhibit a wide range of biological activities, including antitumor, anti-HIV and analgesic activities.[7] Herein, we wish to report an efficient yttrium(III) complex-catalyzed highly enantioselective Friedel–Crafts alkylation of β-trichloro(trifluoro)methyl aryl enones with indoles to address these issues.

Initially, we selected the Friedel–Crafts alkylation of indole **1a** with β-trichloromethyl-α,β-enone **2a** as the model reaction, which would readily give access to many bioactive indole derivatives. Using 5 mol% of *N*,*N*′-dioxide **L1**–$Y(OTf)_3$ as the catalyst,[8] the reaction proceeded sluggishly to afford the corresponding (*R*)-adduct **3a** with 9% yield and 80% ee (Table 1, entry 1). The outcome of each asymmetric reaction may be different depending on the relative steric hindrance and electronic property of the ligand. Therefore, further optimization of the reaction conditions was then aimed at exploring the efficacy of $Y(OTf)_3$ with other *N*,*N*′-dioxide ligands (Table 1, entries 2–8). It was found that the steric effect of the amide moiety (Fig. 1) played a crucial role in the activity and enantioselectivity of the reaction. For example, when the ligand **L5** having a bulkier isopropyl group at the *ortho* position of aniline was employed, the product **3a** was obtained

Table 1 Evaluation of reaction parameters



Entry[a]	Ligand	Metal	Time/h	Yield[b] (%)	ee[c] (%)
1	**L1**	$Y(OTf)_3$	30	9	80 (*R*)
2	**L2**	$Y(OTf)_3$	30	8	65 (*R*)
3	**L3**	$Y(OTf)_3$	26	55	90 (*S*)
4	**L4**	$Y(OTf)_3$	45	67	93 (*S*)
5	**L5**	$Y(OTf)_3$	45	75	94 (*S*)
6	**L6**	$Y(OTf)_3$	30	16	0
7	**L7**	$Y(OTf)_3$	49	31	85 (*S*)
8	**L8**	$Y(OTf)_3$	45	76	91 (*S*)
9	**L5**	$Sc(OTf)_3$	30	82	76 (*S*)
10	**L5**	$La(OTf)_3$	36	NR[d]	—
11	**L5**	$Sm(OTf)_3$	36	NR[d]	—
12[e]	**L5**	$Y(OTf)_3$	52	89	94 (*S*)

[a] Unless otherwise noted, reactions were carried out with 5 mol% of L–metal (1 : 1), **1a** (0.12 mmol) and **2a** (0.10 mmol) in CH_2Cl_2 (0.25 mL) at 35 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] NR = No reaction. [e] CH_2Cl_2 (0.15 mL) was used.

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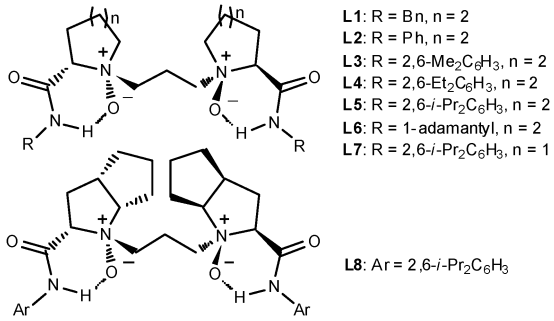


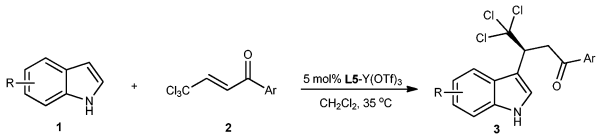
Fig. 1 Screened ligands in this study.

with opposite configuration in 75% yield and 94% ee (Table 1, entry 5). Decreasing the steric hindrance of the amide moiety led to poor results (Table 1, entry 2). However, a racemic product was obtained when 1-adamantylamine-derived *N*,*N*′-dioxide **L6** was used as the chiral ligand (Table 1, entry 6). As for the chiral backbone moiety, L-pipecolic acid-derived *N*,*N*′-dioxide **L5** was superior to both **L7** (derived from L-proline) and **L8** (derived from L-ramipril acid) (Table 1, entry 5 *vs.* entries 7 and 8). Subsequently, we surveyed other rare earth metal salts and found that $Sc(OTf)_3$ exhibited higher activity, whereas the enantioselectivity of the reaction was lower than $Y(OTf)_3$ (Table 1, entries 9–11). To our delight, the moderate yield of **3a** could be overcome to some extent by prolonging the reaction time and increasing the concentration, and the enantiomeric excess remained the same (Table 1, entry 12, 89% yield, 94% ee). Therefore, the optimal reaction conditions were as follows: 5 mol% of **L5**–$Y(OTf)_3$ (1 : 1), **1** (0.12 mmol) and **2** (0.10 mmol) in CH_2Cl_2 at 35 °C.

Under the optimal reaction conditions (Table 1, entry 12), various β-trichloromethyl aryl enones **2** and indoles **1** were screened, giving the desired products with high to excellent enantioselectivities (up to 96% ee).[9] It was noteworthy that either the electronic nature or the position of the substituents at the phenyl ring of enones had little influence on the enantioselectivity and activity of the reaction (Table 2, entries 1–11, 88–96% ee, 71–99% yield). Moreover, heteroaromatic and fused ring substrates were also applicable, giving the desired products with good results (Table 2, entries 12–14). With regard to the indole ring containing electron-donating groups (CH_3 or CH_3O), the reaction also proceeded smoothly to afford trichloroalkylated indoles in excellent yields with up to 93% ee (Table 2, entries 15–20). However, in the case of halogen-substituted indoles, moderate reactivities and enantioselectivities were obtained (Table 2, entries 21 and 22). Notably, by treatment of 1.0 mmol of starting materials under the optimal reaction conditions, the reaction still worked well to afford **3a** in 85% yield with 93% ee (Table 2, entry 23). The absolute configuration of the product **3a** was determined to be *S* by X-ray crystallography analysis.

Encouraged by the above good performance of the current catalyst system, its general applicability in the Friedel–Crafts reaction of indoles with β-trifluoromethyl-enones was also examined under the same reaction conditions.[9] As shown in Table 3, usually, the β-trifluoromethyl aryl enones **4** exhibited higher activity than β-trichloromethyl aryl enones **2**. It seems that the CF_3 group favors the Friedel–Crafts reaction due to

Table 2 Catalytic enantioselective Friedel–Crafts alkylation of indoles **1** with β-trichloromethyl aryl enones **2**

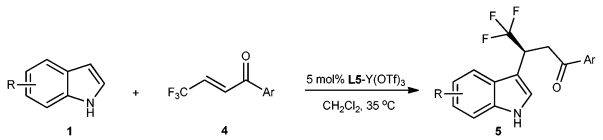


1 2 3

Entry[a]	R	Ar	Product	Yield[b] (%)	ee[c] (%)
1	H	Ph	**3a**	89	94 (*S*)
2	H	4-FC_6H_4	**3b**	87	91
3	H	4-ClC_6H_4	**3c**	95	92
4	H	4-BrC_6H_4	**3d**	77	88
5	H	4-$NO_2C_6H_4$	**3e**	92	95
6	H	4-MeC_6H_4	**3f**	71	90
7	H	3-ClC_6H_4	**3g**	97	92
8	H	3-$NO_2C_6H_4$	**3h**	95	93
9	H	2-ClC_6H_4	**3i**	96	91
10	H	2-FC_6H_4	**3j**	96	96
11	H	3,4-$Cl_2C_6H_3$	**3k**	99	90
12[d]	H	2-Naphthyl	**3l**	95	94
13[d]	H	1-Naphthyl	**3m**	65	91
14	H	2-Thienyl	**3n**	84	85
15	5-Me	Ph	**3o**	94	90
16	6-Me	Ph	**3p**	95	90
17	7-Me	Ph	**3q**	94	86
18	5-MeO	Ph	**3r**	99	93
19	7-Et	Ph	**3s**	98	83
20	6-MeO	Ph	**3t**	78	90
21	5-Cl	Ph	**3u**	68	72
22	5-F	Ph	**3v**	40	82
23[e]	H	Ph	**3a**	85	93 (*S*)

[a] Unless otherwise noted, reactions were carried out with 5 mol% of **L5**–$Y(OTf)_3$ (1 : 1), **1** (0.12 mmol) and **2** (0.10 mmol) in CH_2Cl_2 (0.15 mL) at 35 °C for 26–74 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis; the absolute configuration of **3a** was determined to be *S* by X-ray crystallographic analysis. [d] Indole (0.2 mmol) was used. [e] The reaction was conducted on a 1.0 mmol scale, for details see ESI.†

Table 3 Catalytic enantioselective Friedel–Crafts alkylation of indoles **1** with β-trifluoromethyl aryl enones **4**



1 4 5

Entry[a]	R	Ar	Product	Yield[b] (%)	ee[c] (%)
1	H	Ph	**5a**	96	94 (*S*)
2	H	4-$NO_2C_6H_4$	**5b**	99	96
3	H	4-MeC_6H_4	**5c**	95	93
4	H	3-$NO_2C_6H_4$	**5d**	99	96
5	H	2-FC_6H_4	**5e**	96	92
6	H	4-ClC_6H_4	**5f**	96	80
7	H	2-Naphthyl	**5g**	88	86
8	5-Me	Ph	**5h**	99	81
9	6-Me	Ph	**5i**	87	90
10	5-MeO	Ph	**5j**	99	96
11	6-MeO	Ph	**5k**	99	96
12	5-F	Ph	**5l**	60	79
13[d]	H	Ph	**5a**	99	94 (*S*)

[a] Unless otherwise noted, reactions were carried out with 5 mol% of **L5**–$Y(OTf)_3$ (1 : 1), **1** (0.12 mmol) and **4** (0.10 mmol) in CH_2Cl_2 (0.25 mL) at 35 °C for 17–30 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis; the absolute configuration of **5a** was determined to be *S* by comparison with the reported value of optical rotation.[6b,d] The reaction was conducted on a 1.0 mmol scale, for details see ESI.†

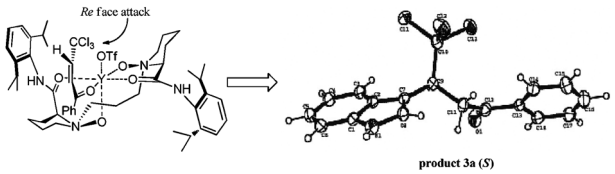


Fig. 2 Proposed working model and X-ray crystallographic structure of **3a**.

its higher electron-withdrawing character. And the corresponding trifluoromethylated indoles were obtained in high to excellent yields and enantioselectivities (Table 3, entries 1–12, 60–99% yield, 79–96% ee). In addition, when the reaction was scaled up tenfold with 5 mol% of **L5**–$Y(OTf)_3$ complex, excellent results (99% yield and 94% ee) were still maintained (Table 3, entry 13), which highlighted the synthetic usefulness of the protocol. Furthermore, compounds **3**/**5** could be transformed into several $CCl_3(CF_3)$-containing building blocks by reduction of the carbonyl group.[6b]

Based on the absolute configuration of the product **3a** and our previous studies on *N*,*N*′-dioxide–metal complexes,[8e,f] a possible working model was proposed (Fig. 2). As shown in Fig. 2, the oxygens of *N*,*N*′-dioxide, amide oxygens coordinated to Y(III) in a tetradentate manner to form two six-membered chelate rings, and the enone **2a** can coordinate to Y(III) from the more accessible side. The incoming indole prefers to attack the *Re* face rather than the *Si* face of the enone **2a** because the latter is strongly shielded by the nearby 2,6-diisopropylphenyl group of *N*,*N*′-dioxide **L5**, which results in the *S*-configured product.

In conclusion, we have developed a highly enantioselective Friedel–Crafts alkylation of β-trichloro(trifluoro)methyl aryl enones with indoles promoted by 5 mol% of *N*,*N*′-dioxide **L5**–$Y(OTf)_3$ complex under mild conditions. The reaction not only provides a wide variety of biologically interesting indoles with high to excellent yields (up to 99%) and excellent enantioselectivities (up to 96% ee), but also opens a new entry to construct tertiary carbon stereogenic centers bearing a CCl_3 group. Further applications of the methodology are currently underway in our laboratory.

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9 For the results of sub-optimal substrates, see ESI† (page 20–22).