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Enantioselective Friedel−Crafts Alkylation of Indoles with Trifluoroethylidene Malonates by Copper−Bis(oxazoline) Complexes: Construction of Trifluoromethyl-Substituted Stereogenic Tertiary Carbon Center

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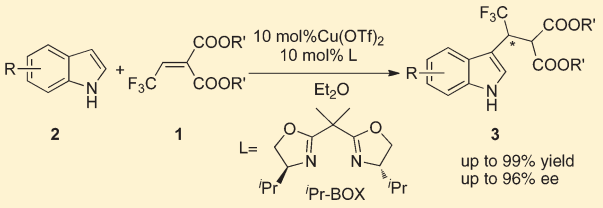
Supporting Information

ABSTRACT: An enantioselective alkylation of indoles with trifluoroethylidene malonates catalyzed by copper(II)−bis (oxazoline) complexes has been developed. The expected adducts with a stereogenic tertiary carbon center bearing a trifluoromethyl group were obtained in excellent yields (up to 99%) and ee values (up to 96% ee). The synthetic utility of this asymmetric catalytic reaction was demonstrated by the preparation of β-CF_3-tryptophan and 4-CF_3-β-carboline in high ee.



Recently, the stereospecific incorporation of the trifluoromethyl group into an organic compound has attracted considerable attention,[1] mainly due to the fact that the trifluoromethyl group often brings significant changes in the physical, chemical, and biological properties of the parent molecules,[2] such as enhanced binding selectivity, higher lipophilicity, and increased metabolic stability.[3] Up to now, although many methodologies for the preparation of optically active fluorinated compounds have been reported,[4−6] the development of general catalytic methods for the construction of stereogenic tertiary carbon centers bearing a trifluoromethyl group without any heteroatom substituent remains not only a demand for biochemists and medicinal chemists, but also a challenge for synthetic organic chemists.[7]

The Lewis acid-catalyzed enantioselective Friedel−Crafts reaction (FC reaction)[8] of prochiral trifluoromethylated building blocks is one of the most important and straightforward strategies to access structurally elaborated and optically pure trifluoromethylated molecules. However, most of these methods are limited to the use of trifluoromethyl ketones and trifluoropyruvates as the substrates,[4,5] whereas the use of simple trifluoromethyl-substituted α,β-unsaturated carbonyl compounds as electrophiles remains rare.[9,10] Very recently, during the preparation of this manuscript, Shibata[9] and Pedro[10] independently reported using β-trifluoromethylated acrylates and β-trifluoromethyl-α,β-unsaturated ketones in the enantioselective Friedel−Crafts alkylation with pyrroles or indoles, respectively. We envisioned that trifluoroethylidene malonate **1**,[11] a prochiral trifluoromethylated building block,[12] would be an excellent acceptor for the Lewis acid-catalyzed enantioselective Friedel−Crafts reaction. Herein, we report a copper(II)−bis(oxazoline) complex-catalyzed enantioselective Friedel−Crafts reaction of indoles with trifluoroethylidene malonates as a new method for efficient construction of a stereogenic tertiary carbon center bearing a trifluoromethyl group.

Initially, the catalytic enantioselective Friedel−Crafts alkylation was investigated with indole and ethyl trifluoroethylidene malonate **1a** in the presence of in situ generated cationic copper(II) catalyst using 10 mol % of $Cu(OTf)_2$ and 10 mol % of ^{i}Pr-BOX ligand in different solvents.[4,13−15] To our delight, the reaction occurred smoothly at room temperature to full conversion as determined by ^{19}F NMR spectroscopy and the desired adduct was obtained in 82% ee when diethyl ether was used as the solvent (Table 1, entry 7). Reactions in other solvents such as ^{i}PrOH, CH_2Cl_2, dioxane, ethanol, and ethylene glycol diethyl ether led to either slower reactions or lower selectivity. The use of $Cu(OTf)_2$/^{t}Bu-BOX (**4b**) or Ph-BOX (**4c**) resulted in low ee (Table 1, entries 8 and 17). This result indicates that the steric environment of the ligands was a key parameter to obtain high enantioselectivity. The effects of the reaction temperature were further evaluated. By lowering the reaction temperature from ambient temperature to −10 °C, the enantioselectivity of the product increased slightly to 86% (Table 1, entry 9).

We then further investigated the effects of the catalyst loading and the ratio of $Cu(OTf)_2$/^{i}Pr-BOX on the enantioselectivity of the reaction. It was found that lowering the catalyst loading from 10 mol % to 5 mol % did not cause a considerable loss in selectivity (Table 1, entry 10). However, the enantioselectivity of the reaction lowered significantly with 2 mol % of the catalyst loading (Table 1, entry 11). The ratio of metal/ligand also influenced the enantioselectivity of the reaction.[14] The best

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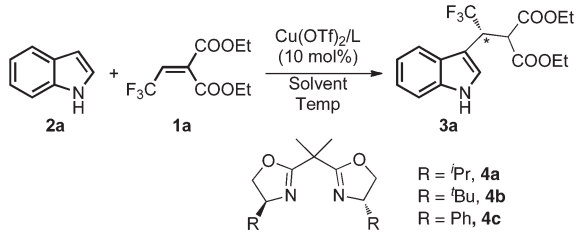
Table 1. Screening of Reaction Conditions for the Reaction of Indole 2a with Trifluoethylidene Malonate 1a[a]



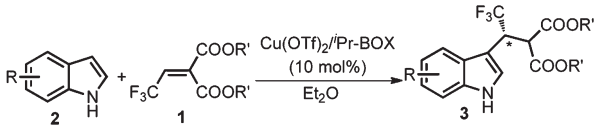
entry	catalyst	solvent	temp (°C)	conversion (%)[b]	ee (%)[c]
1	**4a**-Cu(OTf)$_2$	^{i}PrOH	RT	38	71
2	**4a**-Cu(OTf)$_2$	THF	RT	>99	65
3	**4a**-Cu(OTf)$_2$	DCM	RT	>99	68
4	**4a**-Cu(OTf)$_2$	Dioxane	RT	>99	64
5	**4a**-Cu(OTf)$_2$	EtOH	RT	43	59
6[d]	**4a**-Cu(OTf)$_2$	EGDE	RT	>99	60
7	**4a**-Cu(OTf)$_2$	Et$_2$O	RT	>99	82
8	**4b**-Cu(OTf)$_2$	Et$_2$O	RT	>99	52
9	**4a**-Cu(OTf)$_2$	Et$_2$O	−10	>99	86
10[e]	**4a**-Cu(OTf)$_2$	Et$_2$O	−10	>99	85
11[f]	**4a**-Cu(OTf)$_2$	Et$_2$O	−10	97	74
12[g]	**4a**-Cu(OTf)$_2$	Et$_2$O	−10	>99	85
13	**4a**-Cu(OTf)$_2$	Et$_2$O	−10	>99	88
14	**4a**-Cu(OTf)$_2$	Et$_2$O	−10	>99	87
15	**4a**-Cu(OTf)$_2$	Et$_2$O	−60	<10	
16[h]	**4a**-Cu(OTf)$_2$	Et$_2$O	−35	>99	90
17	**4c**-Cu(OTf)$_2$	Et$_2$O	−35	>99	−52

[a] The reaction was carried out with **1a** (0.125 mmol), **2a** (0.15 mmol, 1.2 equiv), Cu(OTf)$_2$ (10 mol %), and ligand **4** (10−11 mol %) in Et$_2$O (1 mL) at the indicated temperature for 10 h. [b] Determined by ^{19}F NMR. [c] The ee value was determined by chiral-phase HPLC analysis. [d] EGDE = ethylene glycol diethyl ether. [e] 5 mol % catalyst loading. [f] 2 mol % catalyst loading. [g] The ratio of metal/ligand: 1/1.3 for entry 12; 1.2/1 for entries 13, 15, and 16; 1.5/1 for entry 14. [h] 1.5 equiv of indole used.

result was observed with a 1.2/1 ratio of Cu(OTf)$_2$/^{i}Pr-BOX (Table 1, entry 16).

Under the optimized reaction conditions, we next explored the substrate scope for the asymmetric Friedel−Crafts reaction using a variety of indoles with trifluoroethylidene malonates, and the results are summarized in Table 2. Indoles with either electron-donating or electron- withdrawing substituents were all competent substrates, producing the desired CF$_3$-substituted indole derivatives in excellent yields and good enantioselectivities. Reactions of an electron-rich indole with methoxyl substituent proceeded rapidly even at −50 °C to give the desired products in high yields (up to 96% yield) and excellent optical purity (up to 92% ee) (Table 2, entries 4 and 6). Reaction with a weakly electron-withdrawing group such as a 6-bromo substituent reacted with slightly reduced reactivity and slightly lower enantioselectivities (Table 2, entries 10−12). Indoles with a strongly electron-withdrawing group such as a nitro group at the 5-position, however, reacted much slower. The reaction required warming to 0 °C for 23 h to give the desired products in excellent yields and good enantioselectivities (Table 2, entries 13 and 14, 75% and 79% ee). It was also found that the reaction was sensitive

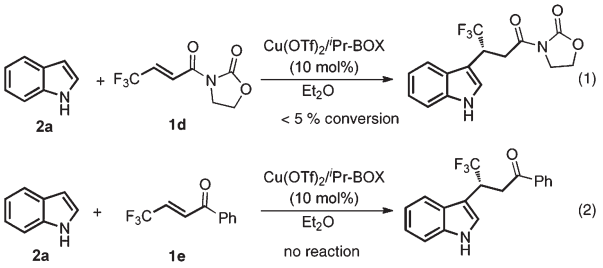
Table 2. Catalytic Enantioselective Friedel−Crafts Reactions of Indoles 2 with Trifluoethylidene Malonates 1[a]



entry	R	R′	product	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	H	Et	**3a**	−35	9	96	90
2	H	Bn	**3b**	−35	9	99	90
3	H	Me	**3c**	−35	9	99	90
4	5-OMe	Et	**3d**	−50	10	92	92
5	5-OMe	Bn	**3e**	−35	8	98	90
6	5-OMe	Me	**3f**	−50	10	96	90
7	7-Me	Et	**3g**	−35	11	97	91
8	7-Me	Bn	**3h**	−35	10	98	93
9	7-Me	Me	**3i**	−35	10	99	96
10	6-Br	Et	**3j**	−25	22	90	86
11	6-Br	Bn	**3k**	−25	22	84	84
12	6-Br	Me	**3l**	−25	20	95	86
13[d]	5-NO$_2$	Bn	**3m**	0	22	91	75
14[d]	5-NO$_2$	Me	**3n**	0	23	98	79
15[e]		Bn	**3o**	−50	20	70	16

[a] Reaction condition: malonate **1** (0.125 M), indoles **2** (1.5 equiv), Cu(OTf)$_2$/^{i}Pr-BOX (1.2/1, 10 mol %). [b] Isolated yield. [c] The ee value was determined by chiral-phase HPLC analysis. [d] 2.0 equiv of 5-nitroindole was used. [e] 5.0 equiv of pyrrole instead of indole was used.

Scheme 1. Reaction of Indole with β-Trifluoromethylated Acrylamide 1d and β-Trifluoromethyl-α,β-unsaturated Ketones 1e Using Cu(OTf)$_2$/^{i}Pr-BOX As Catalyst



to the steric properties of indoles. Reactions of methyl-substituted indole at the 7-position proceeded with good enantioselectivities (Table 2, entries 7−9, 91−96% ee). Reaction of pyrrole, however, occurred to give the coupled product in 70% yield with 16% ee after 20 h at −50 °C (Table 2, entry 15).

The effects of different prochiral trifluorimethyl-substituted Friedel−Crafts reaction acceptors were also evaluated. As shown in Scheme 1, using Cu(OTf)$_2$/^{i}Pr-BOX as the catalyst, reaction of indole with β-trifluoromethylated acrylamide **1d**, a good FC acceptor in Zn(NTf)$_2$/Ph-dbfox-catalyzed enantioselective Friedel−Crafts reaction,[9] occurred to less than 5% conversion. Likewise, no detectable FC product was observed for the reaction of indole with β-trifluoromethyl-α,β-unsaturated ketones **1e**, which was an effective substrate in the Zr(^{t}BuO)$_4$/BINOL-catalyzed

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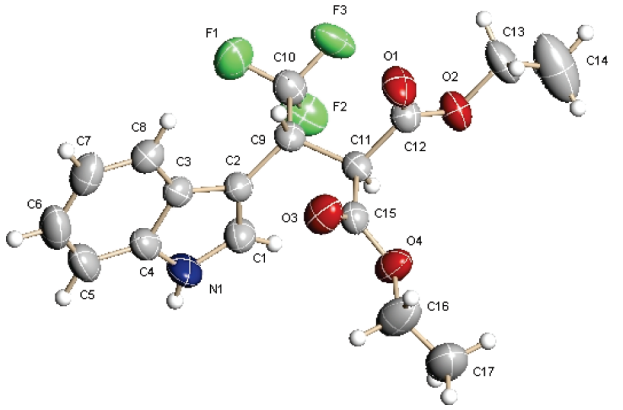
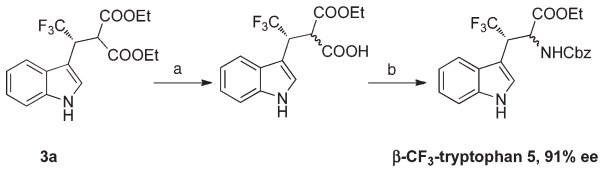


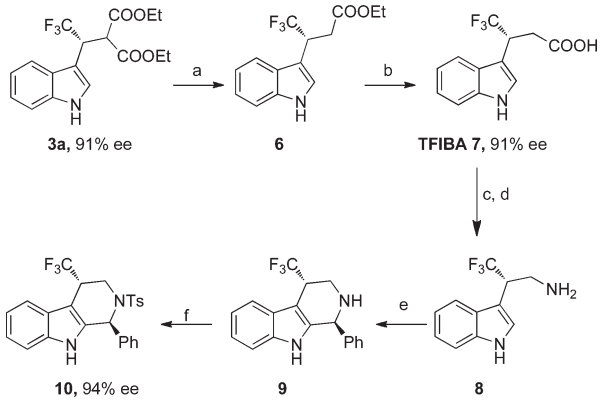
Figure 1. The ORTEP view of **3a**.

Scheme 2. Synthesis of of β-CF_3-tryptophan 5[a]



[a] Reaction conditions: (a) KOH, EtOH, RT, 95% yield, dr: 1.4:1; (b) (1) DPPA/Et_3N, toluene, 50 °C, (2) BnOH, DMAP, 80 °C, 25% yield.

Scheme 3. Synthesis of (*R*)-TFIBA 7 and 4-CF_3-β-carboline 9[a]



[a] Reaction conditions: (a) NaCl (wet), DMSO, 160 °C, 24 h, then 80 °C, 24 h, 72% yield; (b) NaOH (1 N), THF/EtOH, reflux, 94% yield; (c) NEt_3, DPPA, toluene, reflux, then DMAP, BnOH, reflux; (d) 10% Pd/C, MeOH, RT, 30% yield; (e) PhCHO, TFA, $MgSO_4$, CH_2Cl_2, RT, 68% yield; (f) TsCl, NEt_3, CH_2Cl_2, RT, 90% yield.

Friedel–Crafts alkylation with indoles.[10] These results clearly demonstrate that the current system catalysts generated from $Cu(OTf)_2$/^{i}Pr-BOX are particularly effective for the Friedel–Crafts alkylation of indoles with trifluoroethylidene malonates.

The absolute configuration of the stereogenic center (R) in compound **3** was determined by a combination of X-ray crystallographic analysis of a single crystal of **3a** (Figure 1) and comparison of its optical rotation with those reported in the literature.[16b] The configurations of the rest of the products were assigned on the assumption of a uniform mechanistic pathway.

As a demonstration of the synthetic utility of this catalytic approach, the adduct **3a** was further converted into a few trifluoromethyl-substituted indole derivatives. As shown in Scheme 2, the precursor of an enantiomerically enriched β-CF_3-tryptophan **5** was obtained from **3a** through diastereoselective monohydrolysis of **3a** in the presence of KOH in ethanol, followed by Curtius rearrangement.[16] Furthermore, **3a** could also be readily converted into (*R*)-4,4,4-trifluoro-3-(indol-3)butanoic acid (**7**, TFIBA),[17] a plant growth regulator, in two steps. TFIBA was previously prepared via enzymatic resolution.[17] In addition, through Curtius rearrangement and Pictet–Spengler cyclization, 4-trifluoromethyl tetrahydro-β-carboline (**9**), an analogue of a recently developed potential agent for treatment of human papillomaviruses (HPVs) infection,[15,18] was obtained (Scheme 3). The absolute configuration of the major diastereoisomer **9** was further confirmed by the X-ray crystallographic analysis of its derivative **10** (see the Supporting Information).

In summary, we have developed a catalytic enantioselective Friedel–Crafts alkylation of indoles with trifluoroethylidene malonates as a new method for the efficient construction of stereogenic tertiary carbon centers bearing a trifluoromethyl group. The reaction proceeded in high yields and excellent enantioselectivities (up to 99% yield and 96% ee). Moreover, with high synthetic versatility, the chiral products could be readily transformed into some optically pure trifluoromethyl-substituted alkylated indole derivatives with potentially interesting bioactivities. Further investigations of the reaction mechanism are in progress.

EXPERIMENTAL SECTION

Typical Procedure for the Friedel–Crafts Adducts 3a–n. To an oven-dried Schlenk tube were added $Cu(OTf)_2$ (4.6 mg, 0.013 mmol) and ligand **4a** (2.9 mg, 0.010 mmol) under Ar atmosphere. Diethyl ether (1 mL) was added and the mixture was stirred for 1 h at room temperature. Malonate (0.125 mmol) was added to the light-blue solution and the mixture was further stirred for an additional 20 min. The resulting mixture was then cooled to the indicated temperature, followed by the addition of indole (0.188 mmol, 1.50 equiv). After the reaction was completed as monitored by TLC, the reaction mixture was filtered through a plug of silica gel and washed with Et_2O. The solution was concentrated under vacuum. The product was obtained after purification by flash column chromatography on silica gel (performed with 7/1 petroleum/ethyl acetate).

Diethyl 2-(2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl)malonate, 3a: white solid, mp 76–78 °C; yield 43 mg (96%), 90% ee; $[\alpha]^{25}_D$ −4.1 (c = 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (br, 1 H), 7.69 (d, J = 8.4 Hz, 1 H), 7.34 (dd, J = 1.8, 6.3 Hz, 1 H), 7.17–7.23 (m, 3 H), 4.63 (q, J = 8.7 Hz, 1 H), 4.26 (q, J = 2.1 Hz, 2 H), 4.15 (d, J = 11.1 Hz, 1 H), 3.73 (q, J = 6.9 Hz, 2 H), 1.29 (t, J = 7.2 Hz, 3 H), 0.69 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CFCl_3$) δ −69.4 (d, J = 9.3 Hz, 3 F); IR (KBr, cm^{-1}) ν 3340, 1731, 1235, 1170, 1109; HRMS-ESI calcd for $C_{17}H_{18}NO_4F_3Na_{+1}$ 380.1080, found 380.1080; HPLC analysis (Phenomenex Cellulose-1, hexane/2-propanol 90/10, flow rate: 0.7 mL/min, 214 nm, t_r(major) = 11.018 min, t_r(minor) = 12.518 min

ASSOCIATED CONTENT

Supporting Information. Experimental details, spectra for new compounds, analysis of ee values of the all products, and CIF files for single crystal analysis of compounds **3a** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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