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Enantioselective Friedel–Crafts Alkylation of Indoles with Alkylidene Malonates Catalyzed by *N,N′*-Dioxide–Scandium(III) Complexes: Asymmetric Synthesis of *β*-Carbolines

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Optically active indole derivatives have attracted significant attention in organic synthesis because they are important building blocks in a variety of interesting natural products and potential medicinal agents.[1,2] The asymmetric Friedel–Crafts alkylation of indoles[3–5] with alkylidene malonates has shown promise as a synthetic methodology towards functionalized indoles. In 2001, the Jørgensen's group[6] reported the first example of this reaction using a C_2-symmetric chiral bis(oxazoline)–Cu^{II} complex as catalyst. Subsequently, Tang and co-workers disclosed that the Friedel–Crafts alkylation of indoles with alkylidene malonates was further promoted by a pseudo-C_3-symmetric tris(oxazoline)–Cu^{II} complex.[7] Very recently, Reiser et al. described that the ratio of oxazoline/copper had a significant influence on the enantioselectivity.[8] Despite these impressive contributions, the catalysts were limited to chiral Cu^{II}–oxazoline complexes. Considering the high synthetic versatility of the products, the development of new and efficient catalysts is still an interesting demanding challenge.

As a bidentate substrate, alkylidene malonate can chelate a series of Lewis acids in many asymmetric reactions.[7b,9] On the other hand, *N,N′*-dioxide–scandium(III) complexes have proven to be effective chiral Lewis acid catalysts that exhibit good chelating potential.[10] Herein, we describe the highly enantioselective Friedel–Crafts alkylation of indoles with alkylidene malonates catalyzed by chiral *N,N′*-dioxide–scandium(III) triflate complexes.

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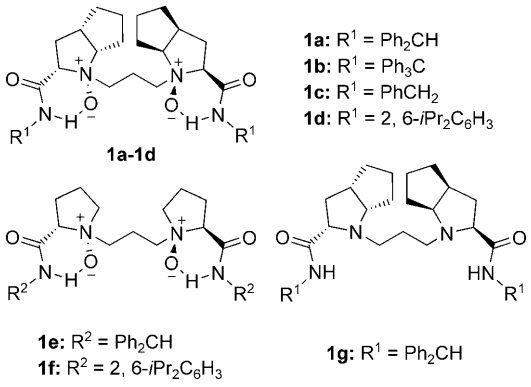
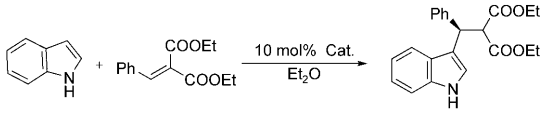
Some representative screening results[11] for the catalytic enantioselective alkylation of indole **2a** with alkylidene malonate **3a** in the presence of the chiral *N,N′*-dioxide–scandium(III) triflate complexes as catalysts are presented in Table 1. Initially, different chiral *N,N′*-dioxide ligands (**1a–1f**) complexed with $Sc(OTf)_3$ were investigated. As



shown in Table 1, ligand **1a** (derived from L-Ramiprol acid) containing a diphenylmethyl group emerged as a promising ligand to provide better yield and enantioselectivity, while ligands with smaller or bulkier groups such as benzyl, triphenylmethyl, and *ortho*-isopropylphenyl groups gave lower enantioselectivities (Table 1, entries 1–4). Further modifications to the ligand structure led to the observation that ligands **1e** and **1f** (derived from L-proline) afforded worse results compared with **1a** (Table 1, entries 5 and 6). All these studies indicated the cooperative role of both amino acid and amine in defining the enantioselectivity and reactivity of the reaction. Moreover, when ligand **1g**, which lacked a *N,N′*-dioxide, was employed, the reaction gave the racemic product **4a** in 79% yield, which revealed that the *N*-oxide group plays a crucial role in determining the enantioselectivity of the reaction (Table 1, entry 7). To our delight, the enantioselectivity was increased when the catalyst **1a**-Sc-

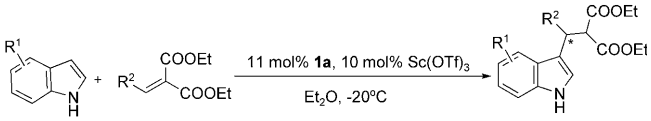
Table 1. Catalytic enantioselective Friedel–Crafts alkylation of indole **2a** with alkylidene malonate **3a**.[a]



Entry	Ligand	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	0	99	68
2	**1b**	0	90	39
3	**1c**	0	88	62
4	**1d**	0	13	33
5	**1e**	0	98	3
6	**1f**	0	24	51
7	**1g**	0	79	0
8[d]	**1a**	0	79	80
9[d]	**1a**	−20	35	90
10[d,e]	**1a**	−20	94	90

[a] Unless otherwise noted, reactions were carried out with ligand (11 mol%), $Sc(OTf)_3$ (10 mol%), **2a** (0.15 mmol), and **3a** (0.125 mmol) in Et_2O (0.1 mL) at indicated temperature for 84 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The catalyst **1a**-$Sc(OTf)_3$ was prepared in *t*BuOH. [e] The ratio of **2a**/**3a** was 2:1.

Table 2. Catalytic enantioselective Friedel–Crafts reaction of indoles **2** with alkylidene malonates **3.**[a]



Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	H	Ph	94 (**4a**)	90(*R*)[g]
2	H	3-MeC_6H_4	84 (**4b**)	90
3	H	3-$MeOC_6H_4$	59 (**4c**)	92
4	H	3-$PhOC_6H_4$	90 (**4d**)	93
5	H	3-BrC_6H_4	97 (**4e**)	92
6[d]	H	3-ClC_6H_4	84 (**4f**)	87
7	H	3-$CF_3C_6H_4$	90 (**4g**)	92
8[d]	H	4-FC_6H_4	98 (**4h**)	83
9	H	3-PhO-4-FC_6H_3	77 (**4i**)	88
10	H	3,4-$Cl_2C_6H_3$	92 (**4j**)	83
11[e]	H	2-naphthyl	72 (**4k**)	80
12	H	2-ClC_6H_4	71 (**4l**)	62
13[e]	5-Br	Ph	98 (**4m**)	84
14[f]	5-Br	3-BrC_6H_4	77 (**4n**)	92
15	5-OMe	Ph	95 (**4o**)	92(*R*)[g]
16	5-OMe	4-PhC_6H_4	73 (**4p**)	86
17	5-OMe	3-MeC_6H_4	99 (**4q**)	92
18	5-OMe	3-BrC_6H_4	89 (**4r**)	92
19	5-OMe	3-$PhOC_6H_4$	75 (**4s**)	95
20	5-OMe	3-ClC_6H_4	78 (**4t**)	88
21	5-OMe	3-PhO-4-FC_6H_3	74 (**4u**)	92
22	5-OMe	2-thienyl	98 (**4v**)	80

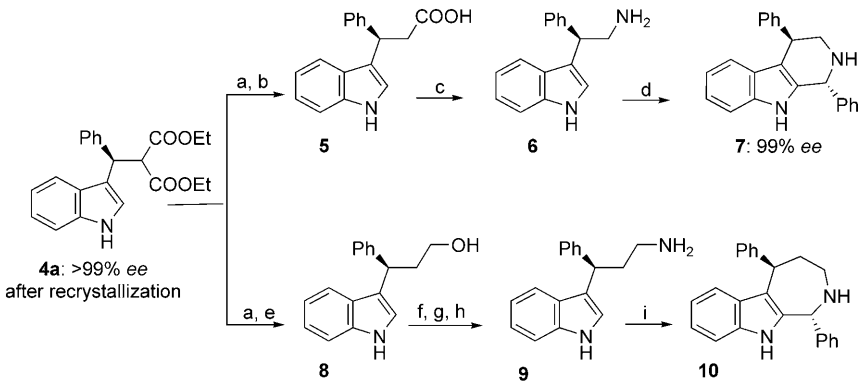
[a] Unless otherwise noted, reactions were carried out with **1a** (11 mol%), $Sc(OTf)_3$ (10 mol%), **2** (0. 25 mmol), and **3** (0.125 mmol) in Et_2O (0.1 mL) at −20°C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 0.5 mmol indole was used. [e] The reaction was carried out at 0°C. [f] 0.5 mmol 5-bromoindole was used. [g] The absolute configuration was determined by comparing with literature data.[7,8]

$(OTf)_3$ was prepared in *t*BuOH (Table 1, entry 8). Lowering the reaction temperature further enhanced the enantioselectivity to 90% *ee* but led to obvious loss in reactivity (Table 1, entry 9). Fortunately, the reactivity was dramatically improved by increasing the amount of indole,[12] while the enantioselectivity was maintained (Table 1, entry 10).

Under the optimal reaction conditions (Table 2, entry 1), various indoles and alkylidene malonates were evaluated, giving corresponding products with good to excellent enantioselectivities (up to 95% *ee*). As shown in Table 2, the enantioselectivity of the reaction was found to be insensitive to the steric and electronic properties of *meta*-substituents on the phenyl in arylidene malonate (Table 2, entries 2–7 and 17–20), which was different from the catalytic systems of chiral Cu^{II}–oxazoline.[13] The *para*-substituted arylidene malonates were also efficient for the reaction, albeit the *ortho*-substituted one showed a reduced enantioselectivity[14] (Table 2, entries 8, 12, and 16). It was noteworthy that the reaction could be extended to condensed-ring, heterocyclic, and disubstituted arylidene malonates with good to excellent enantioselectivities (Table 2, entries 9–11, 21, and 22).[15] In addition, indoles with either electron-withdrawing or electron-donating substituents were also competent substrates (Table 2, entries 13–22, up to 95% *ee*). Although a C(5) bromine substituent lowered yield, a good level of enantioselectivity was still observed (Table 2, entries 13 and 14).

To demonstrate the synthetic potential of this catalytic approach, the product **4a** was converted into some useful intermediates for the synthesis of biologically active compounds, such as tryptamines,[2a] indolepropionic acids,[2b] and β-carbolines.[2c] As shown in Scheme 1,[16] through the Curtius rearrangement[1h,17] and Pictet–Spengler cyclization,[5c,d] six-membered ring β-carboline **7**[2c,18] could be obtained from the potent neuroprotective agent **5**. Furthermore, adduct **4a** could also be transformed into serotonin analogue **9**.[2f] It was noteworthy that the seven-membered β-carboline-like **10** was furnished for the first time when product **9** was subjected to Pictet–Spengler reaction. The relative stereochemistry of **10** was tentatively assigned as 1,5-*trans* by means of NOE experiments. All reactions occurred in good to excellent yield with no drop in enantiomeric excess.

To understand the structure of the catalyst, we tried to grow a single crystal of **1a**-$Sc(OTf)_3$ but failed. However, we successfully determined by X-ray crystallography the structure of the complex **1f**-$Sc(OTf)_3$, which showed similar catalytic behavior to **1a**-$Sc(OTf)_3$ (Table 1, entry 6 vs. entry 1), as its monohydrate **1f**-$Sc(OTf)_3$·(H_2O).[19] As shown in Figure 1, both carbonyl oxygens and oxygens of *N*-oxide were coordinated with scandium in the complex. This may help to explain the behavior that only the racemic product with moderate yield was afforded when the ligand **1g** (the precursor of *N,N′*-dioxide **1a**) was employed (Table 1, entry 7). Moreover, the X-ray crystal structure of **1f**-$Sc(OTf)_3$·(H_2O) also indicated that both the amide moiety and the chiral backbone of the amino acid were essential for the generation of a good chiral environment in the reaction, which rationalized the observed phenomena (Table 1, entries 1–6) in the study to a certain extent.



Scheme 1. Derivatization of the Friedel–Crafts adduct. Conditions: a) NaCl, DMSO, H_2O, reflux, 66%; b) THF, EtOH, H_2O, 2N NaOH, reflux, 97%; c) Curtius rearrangement, Et_3N, DPPA, *t*BuOH, toluene, reflux; TFA, CH_2Cl_2, RT, 28%; d) Pictet–Spengler cyclization, TFA , benzaldehyde, CH_3CN, reflux, 88%; e) $LiAlH_4$, THF, RT, quantitative yield; f) TsCl, pyridine, CH_2Cl_2, 50°C, 72%; g) DMF, NaN_3, 50°C, 97%; h) Pd/C (10%), H_2, MeOH, 64%; i) Pictet–Spengler cyclization, TFA, benzaldehyde, CH_3CN, reflux, 44%. TFA = trifluoroacetic acid, DPPA = diphenylphosphoryl azide.

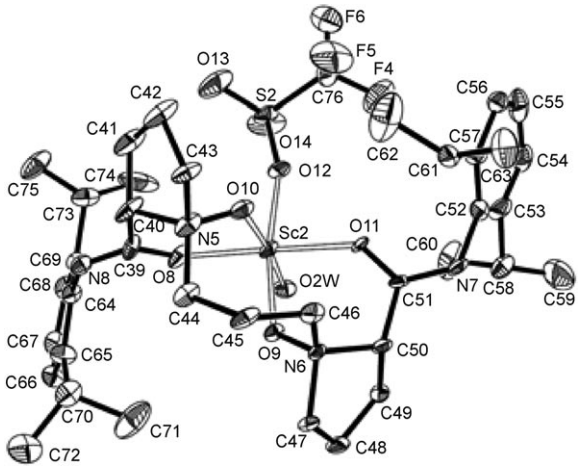


Figure 1. X-ray crystallographic structure of **1f**-$Sc(OTf)_3$·(H_2O).

In summary, we have developed an efficient catalytic enantioselective Friedel–Crafts alkylation of different indoles with a series of alkylidene malonates using the chiral **1a**-$Sc(OTf)_3$ complex as catalyst. The reaction could tolerate condensed-ring, heterocyclic, and different substituted arylidene malonates. Moreover, with high synthetic versatility, the products could be easily transformed into serotonin analogue **9** and the seven-membered β-carboline-like **10**. In particular, the X-ray crystal structure of the complex **1f**-$Sc(OTf)_3$·(H_2O) reveals the manner of the coordination between the chiral *N,N′*-dioxide and $Sc(OTf)_3$. Further investigations on the mechanism of this catalytic system are in progress.

Experimental Section

General experimental procedure: A mixture of ligand **1a** (9.8 mg, 0.0138 mmol), $Sc(OTf)_3$ (6.2 mg, 0.0125 mmol), and indole **2a** (29.3 mg, 0.25 mmol) in *t*BuOH (0.1 mL) was stirred at 35°C for 1 h under a nitrogen atmosphere. After the solvent was removed under vacuum, Et_2O (0.1 mL) was added. The reaction mixture was cooled to −20°C and alkylidene malonate **3a** (0.125 mmol) was added under stirring. The reaction mixture was stirred at −20°C for 84 h and directly purified by flash chromatography on silica gel to obtain the desired product **4a** in 94% yield with 90% *ee*.

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Keywords: alkylidene malonates · asymmetric synthesis · Friedel-Crafts alkylation · indole derivatives · scandium

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[11] Different standard reaction parameters (solvent, Lewis acid) were also evaluated during the optimization of the process (see Supporting Information for details).

[12] Excess indole could be recycled by flash chromatography on silica gel.

[13] In the catalytic systems of chiral Cu^{II}–oxazoline, *ortho*-substituted and *para*-substituted arylidene malonates gave very good results but *meta*-substituted arylidene malonates were not tolerated (see references [6–8] for details).

[14] It was probably attributed to the steric hindrance effect of the *ortho*-substituent on phenyl in arylidene malonate.

[15] Alkylidene malonates were also investigated, but only moderate results were obtained (propylidene malonate: 32% yield, 66% *ee*; cyclohexylmethylene malonate: 57% yield, 43% *ee*).

[16] See Supporting Information for details.

[17] K. Ninomiya, T. Shioiri, S. Yamada, *Tetrahedron* **1974**, *30*, 2151–2157.

[18] W. Q. Jiang, X. Q. Zhang, Z. H. Sui, *Org. Lett.* **2003**, *5*, 43–46.

[19] CCDC-704000 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

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