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Highly Efficient Asymmetric Synthesis of 3-Indolyl(hydroxy)acetates via Friedel−Crafts Alkylation of Indoles

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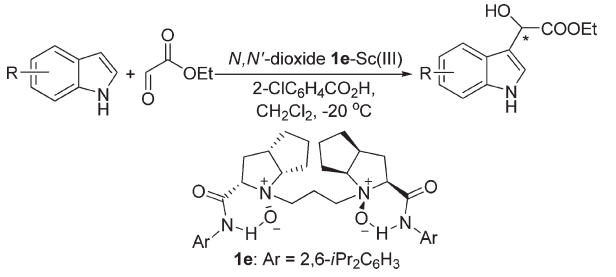
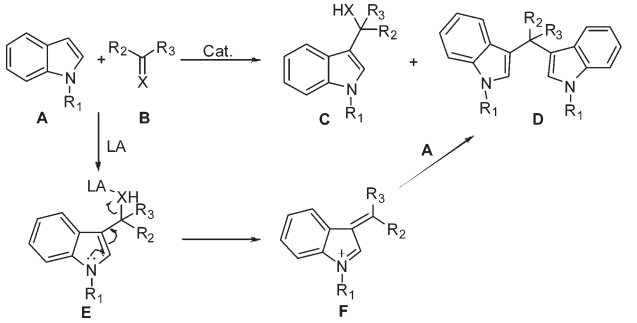


An efficient enantioselective Friedel−Crafts alkylation of indoles to ethyl glyoxylate catalyzed by chiral *N*,*N*′-dioxide−Sc(III) complex was developed. The corresponding 3-indolyl(hydroxy)acetates compounds were afforded in good yields with high enantioselectivities (up to 95% ee).

Chiral functionalized indole derivatives have attracted significant attention due to the frequent appearance of indoles in biologically interesting natural and unnatural compounds.[1] Thus the asymmetric synthesis of chiral indole derivatives becomes a fascinating subject in organic synthesis.[1−5] The enantioselective Friedel−Crafts reactions of indoles with readily available prochiral electrophilic compounds provide a strategically important approach to access enantiomerically enriched indole derivatives.[3,4] Contrasted to the well-developed enantioselective conjugate additions of indoles, the catalytic enantioselective 1,2-nucleophilic additions were still limited.[5] Perhaps the instability of the adducts **E** as well as the tendency of forming bisindoly derivatives **D** precluded the intensive research (Scheme 1).[5a,6] Such a phenomenon was extremely noticeable for the reaction of glyoxylate, a large amount of bisindolylacetate was formed even in the absence of catalyst. Though the enantioselective Friedel−Crafts reactions of indoles with glyoxylate provide potentially important biologically active 3-indolyl(hydroxy)acetates, such a reaction was rarely investgated. Nevertheless, Jørgensen in 2005 was the first to report this reaction utilizing chiral Brønsted acid catalysts with indoles and glyoxylate to generate indolylacetates as the main product.[5i] Deng's group later demonstrated the Friedel−Crafts reaction of indoles

SCHEME 1. Proposed Pathways for the Catalyzed Reaction Leading to Bisindoles



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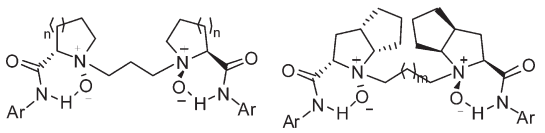


1a: n = 1, Ar = 2,6-*i*Pr$_2$C$_6$H$_3$
1b: n = 1, Ar = Ph
1c: n = 1, Ar = 2,6-Me$_2$C$_6$H$_3$
1d: n = 2, Ar = 2,6-*i*Pr$_2$C$_6$H$_3$
1e: m = 1, Ar = 2,6-*i*Pr$_2$C$_6$H$_3$
1f: m = 3, Ar = 2,6-*i*Pr$_2$C$_6$H$_3$

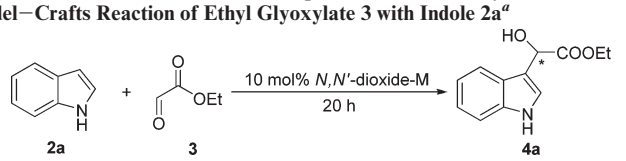
FIGURE 1. *N*,*N*′-Dioxide ligands evaluated.

with ethyl glyoxylate by bifunctional *cinchona* alkaloids.[5h] In 2007, Xiao and co-workers reported that the BINOL−Ti(IV) complex could successfully catalyze Friedel−Crafts reaction of indoles with ethyl glyoxylate.[7] Considering the high synthetic versatility of the products, the remaining challenge lies in the selection of a more efficient and practical catalyst system. As excellent chiral scaffolds, the chiral *N*,*N*′-dioxide−metal complexes have exhibited excellent abilities for the activation of various electrophiles and showed strong asymmetry-inducing capability for many reactions.[8,9] In light of these, herein, we presented our intensive studies on the asymmetric Friedel−Crafts reaction of indoles with glyoxylate using *N*,*N*′-dioxide−Sc(III) complex, providing chiral 3-indolyl(hydroxy)acetates in good yield and enantioselectivities.

To obtain the effective ligand (Figure 1), various *N*,*N*′-dioxides complexed with Sc(OTf)$_3$ were investigated to catalyze the reaction. It was found that both the steric hindrance of aniline and the chiral backbone had much influence on enantioselectivity. In terms of the amide groups, a bulkier group at the ortho position of aniline, such as isopropyl, could achieve higher enantioselectivities than smaller ones (Table 1, entries 6−8). As for the amino acid backbone, L-ramipril-derived *N*,*N*′-dioxide **1e** was obviously superior to the L-proline derived **1c** and L-pipecolic acid-based **1d**: the enantioselectivity was dramatically increased to 70% ee (Table 1, entry 10 vs. entries 6 and 9). Moreover, by further increasing the length of the carbon chain, only racemic product was obtained (Table 1, entry 11). Accordingly, **1e** was chosen as the ligand for the next investigation.

To further improve the enantioselectivity of the reaction, other reaction conditions such as solvent, temperature, and additives were investigated (Table 1, entries 12−20). Adjusting the molar ratio of *N*,*N*′-dioxide/Sc(OTf)$_3$ led to a slight improvement on the enantioselectivity of the reaction.

TABLE 1. Reaction Condition Optimization on the Asymmetric Friedel−Crafts Reaction of Ethyl Glyoxylate 3 with Indole 2a[a]



2a **3** **4a**

entry	ligand	metal	solvent	yield [%][b]	ee [%][c]
1	**1a**	$Ni(ClO_4)_2$	toluene	89	4
2	**1a**	$FeSO_4$	toluene	77	2
3	**1a**	$In(OTf)_3$	toluene	80	7
4	**1a**	$La(OTf)_3$	toluene	75	2
5	**1a**	$Cu(OTf)_2$	toluene	76	0
6	**1a**	$Sc(OTf)_3$	toluene	85	29
7	**1b**	$Sc(OTf)_3$	toluene	77	0
8	**1c**	$Sc(OTf)_3$	toluene	87	11
9	**1d**	$Sc(OTf)_3$	toluene	89	57
10	**1e**	$Sc(OTf)_3$	toluene	81	70
11	**1f**	$Sc(OTf)_3$	toluene	87	0
12[d]	**1e**	$Sc(OTf)_3$	toluene	90	77
13[d]	**1e**	$Sc(OTf)_3$	CH_3OH	33	5
14[d]	**1e**	$Sc(OTf)_3$	THF	79	14
15[d]	**1e**	$Sc(OTf)_3$	Et_2O	81	21
16[d]	**1e**	$Sc(OTf)_3$	CH_2Cl_2	90	80
17[d]	**1e**	$Sc(OTf)_3$	$CHCl_3$	44	73
18[d]	**1e**	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	77	66
19[d,e]	**1e**	$Sc(OTf)_3$	CH_2Cl_2	87	85
20[d,e,f]	**1e**	$Sc(OTf)_3$	CH_2Cl_2	89	95

[a]Unless otherwise noted, reactions were carried out with 0.1 mmol of indole **2a** and 0.15 mmol of ethyl glyoxylate **3**, 0.01 mmol of *N*,*N*′-dioxide, and 0.01 mmol of metal under N_2 atmosphere at 0 °C for 20 h. [b]Isolated yield of **4a**. [c]Determined by HPLC analysis (see the Supporting Information). [d]Ligand:metal =1.1:1. [e]Performed at −20 °C. [f]0.01 mmol of *o*-chlorobenzoic acid was added to the reaction mixture.

Furthermore, the solvents played an important role on the enantioselectivity of the reaction. Low coordinating and nonpolar solvents generally provided the expected product with higher yield and enantioselectivity compared with more coordinating solvents. CH_2Cl_2 was shown to be the best solvent for the reaction, giving the corresponding products with 90% yield and 80% ee (Table 1, entry 16). The enantioselectivity of the reaction could be further improved to 85% ee under −20 °C (Table 1, entry 19). To further improve the reactivity and enantioselectivity of the reaction, some achiral additives were employed.[10] The investigations revealed that *o*-chlorobenzoic acid had a beneficial effect on the enantioselectivity of the reaction and the desired product was obtained in high yield with 95% ee (Table 1, entry 20).

Under the optimized reaction conditions, the substrate scope of the enantioselective Friedel−Crafts reaction of glyoxylate was investigated. As shown in Table 2, indoles tolerated substitutions at any position of the aromatic ring, and both electron-donating and electron-withdrawing

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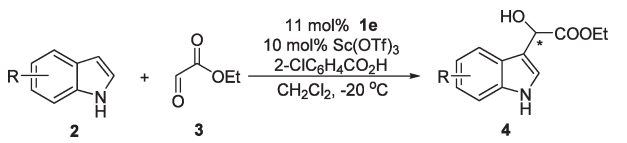
TABLE 2. Asymmetric Friedel−Crafts Reaction of Indoles (2a−k) with Ethyl Glyoxylate (3) Catalyzed by *N*,*N*′-Dioxide−Sc(III) Complex[a]



entry	R	product	time [h]	yield [%][b]	ee [%][c]
1	H	**4a**	20	89	95
2	5-Me	**4b**	24	86	86
3	7-Me	**4c**	12	90	94
4	7-Et	**4d**	12	95	92
5	4-MeO	**4e**	20	91	83
6	5-MeO	**4f**	12	90	88
7	6-MeO	**4g**	24	91	91
8	5-F	**4h**	12	87	90
9	5-Cl	**4i**	12	83	87
10	5-Br	**4j**	24	89	88
11	5-NO_2	**4k**	148	61	76

[a]Unless otherwise noted, reactions were carried out with 0.1 mmol of indole **2**, 0.15 mmol of ethyl glyoxylate **3**, 0.011 mmol of *N*,*N*′-dioxide **1e**, 0.01 mmol of $Sc(OTf)_3$, 0.01 mmol of *o*-chlorobenzoic acid, and CH_2Cl_2 (0.5 mL) under N_2 atmosphere at −20 °C. [b]Isolated yield. [c]Determined by HPLC analysis (see the Supporting Information).

groups were comparable. Indoles containing electron-donating groups on the aromatic ring had a slightly higher reaction activity than those with electron-withdrawing groups (Table 2, entries 2−7 vs. 8−11). The electron-rich substrate **2c** gave the best results, and the corresponding product **4c** was obtained in 90% yield with 94% ee (Table 2, entry 3). In the case of the 7-ethyl indole **2d**, excellent yield and enantioselectivity were achieved as well: 95% yield with 92% ee (Table 2, entry 4). For various positions of MeO on the indole ring from position 4, 5, to 6, the enantioselectivity was slightly increased from 83% ee, 88% ee, to 91% ee (Table 2, entries 5−7). Notably, both the electron-donating groups CH_3 and OCH_3 and the electron-withdrawing group halogen at the 5-position of indole got good results (Table 2, entries 2, 6, and 8−10). It was delightful to find that the reaction could be extended to 5-nitroindole, although a longer reaction time was needed. The Friedel−Crafts alkylation product 3-(5-nitro)indolyl(hydroxy) acetate (**4k**) was isolated in 61% yield with 76% ee (Table 2, entry 11).

In conclusion, we have developed an efficient enantioselective Friedel−Crafts alkylation of indoles with ethyl glyoxylate leading to optically active α-hydroxy esters. A chiral *N*,*N*′-dioxide−Sc(III) complex was shown to be an efficient catalyst for this reaction, and *o*-chlorobenzoic acid as an additive could have a beneficial effect on the enantioselectivity: the corresponding α-hydroxy(indolyl)esters compounds were afforded in excellent yields and up to 95% ee. The mechanism studies of the reaction and the application of this catalyst are under investigation.

Experimental Section

Typical Procedure for the Enantioselective Friedel−Crafts Reaction of Indole 2a. To a test tube were added *N*,*N*′-dioxide **1e** (7.7 mg, 0.011 mmol), $Sc(OTf)_3$ (4.9 mg, 0.01 mmol), indole **2a** (11.7 mg, 0.1 mmol), and *o*-chlorobenzoic acid (1.6 mg, 0.01 mmol) under nitrogen. Then 0.5 mL of CH_2Cl_2 was added and the solution was stirred at 30 °C for 1 h. Subsequently, ethyl glyoxylate **3** (0.15 mmol) was added under −20 °C, and the reaction mixture was stirred for an additional 20 h. The 3-indolyl(hydroxy)acetate was directly purified by column chromatography on silica gel with petroleum ether and EtOAc, 89% yield, 95% ee, $[\alpha]^{20}_D$ +77.5 (*c* 3.02 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.26−7.12 (m, 3H), 5.47 (d, J = 6.0 Hz, 1H), 4.33−4.25 (m, 1H), 4.21−4.13 (m, 1H), 3.38 (s, 1H), 1.34−1.20 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 136.5, 123.2, 122.6, 120.2, 119.5, 114.0, 111.3, 67.3, 62.8, 14.1; HPLC analysis [Chiralpak AS-H, 80:20 *n*-hexane/*i*PrOH, 1.0 mL/min; t_r(major) = 11.33 min, t_r(minor) = 16.33 min].

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Supporting Information Available: Experimental procedures and spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.