DOI: 10.1002/adsc.200600495

Asymmetric Friedel–Crafts Alkylations of Indoles with Ethyl Glyoxylate Catalyzed by (*S*)-BINOL-Titanium(IV) Complex: Direct Access to Enantiomerically Enriched 3-Indolyl-(hydroxy)acetates

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Received: September 29, 2006; Revised: March 31, 2007

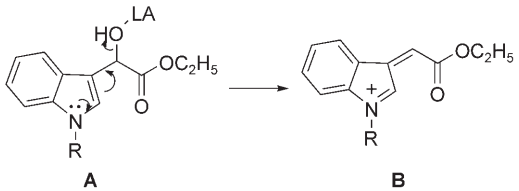
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Enantioselective Friedel–Crafts alkylation reactions of a variety of indoles with ethyl glyoxylate, catalyzed by a chiral (*S*)-BINOL-Ti(IV) complex (10 mol%), are reported. The corresponding ethyl 3-indolyl(hydroxy)acetates were formed in good yields and with high enantiomeric excess (up to 96%). When methyl pyruvate or *p*-chlorophenylglyoxal was used, the bisindole compound was obtained in excellent yield. A possible mechanism is proposed.

Keywords: asymmetric catalysis; (*S*)-BINOL-titanium(IV) complex; Friedel–Crafts alkylations; 3-indolyl(hydroxy)acetates

Friedel–Crafts alkylation reactions have been recognized as one of the most fundamental C–C bond-forming reactions in organic synthesis.[1] Among the aromatic systems suitable for Friedel–Crafts alkylations, indole has received much attention because of its widespread applications in material science,[2] agrochemicals,[3] and pharmaceuticals.[4] Since the pioneering study of Kerr and Harrington on the catalytic addition of indoles to electron-deficient C=C bonds with the use of $Yb(OTf)_3$,[5] mild and catalytic Friedel–Crafts alkylations of indoles have become a rapidly growing area of research. A large number of catalytic systems, which involve Lewis acids,[6] transition metal catalysts[7] or molecular iodine,[8] have been developed. However, the Friedel–Crafts chemistry has still not achieved its full potential. The research continues with the goal of increasing the diversity of possible substrates and reaction products.

More recently, the development of catalytic asymmetric Friedel–Crafts strategies has been the subject of intensive studies in order to access enantiomerically enriched aromatic compounds bearing benzylic stereocenters. Metal-based chiral complex catalysts[9] and MacMillan's imidazolidinone as well as other organocatalysts[10] proved to be highly effective for stereoselective Friedel–Crafts alkylations of indoles. In this context, various prochiral electrophiles, such as dicarbonyl compounds,[11] expoxides,[12] imines,[13] and electron-deficient olefins,[14] have been successfully employed in enantioselective Friedel–Crafts reactions of indoles. In contrast, the use of glyoxylate in the Friedel–Crafts reactions of indoles has been the subject of relatively few investigations, while there are numerous publications concerning the addition reactions of glyoxylate to electron-enriched benzenes.[15] It was found that dehydroxylation might arise from the high sensitivity of α-hydroxy(indolyl)acetate to acidic conditions at room temperature to form 3-alkylidene-*3H*-indolium cation **B** [Eq. (1)], which could react with indoles to afford bisindolylacetates.[16] Perhaps these facts have precluded intensive research in this reaction. Nevertheless, Mikami and co-workers reported in 2001 that biphenylphosphine-palladium(II) could successfully catalyze Friedel–Crafts reaction of indoles with glyoxylate to generate indolylacetates or bisindolylacetates as the main product, depending on

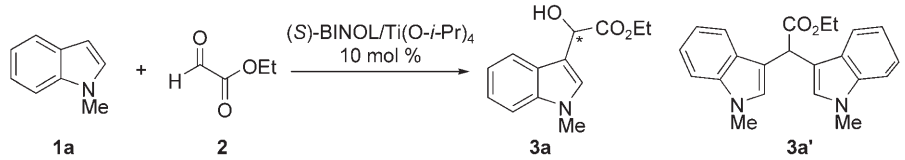


(1)

the reaction conditions.[17] In 2002, Jørgensen's group demonstrated that heteroaromatic compounds, including indoles, reacted with ethyl glyoxylate to give Friedel–Crafts addition adducts in good yields in various aqueous media.[18] During the preparation of this manuscript, Deng and co-workers reported enantioselective Friedel–Crafts reactions of indoles with carbonyl compounds catalyzed by bifunctional *Cinchona* alkaloids.[11c] To fully realize the potential of this strategy for generating enantiomerically enriched 3-indolyl(hydroxy)acetates,[19] herein we report an asymmetric Friedel–Crafts reactions of indoles with ethyl glyoxylate using an easily accessible chiral titanium complex as the catalyst.

The broad spectrum of asymmetric catalytic reactions in which titanium is engaged, together with its cheap and environmentally friendly character compared with other transition metals, make this metal especially unique.[20] Most significantly, as one of the most useful combinations, BINOL-Ti complexes were widely applied to various asymmetric reactions.[21,22] However, there are relatively few reports on the application of this versatile strategy for the Friedel–Crafts reactions, except for two impressive examples, in which a chiral 6,6′-dibromo-BINOL-Ti complex was employed as the catalyst.[15c,22b] Bearing all these facts in mind, we envisioned that BINOL-Ti complexes could also be good promoters for the Friedel–Crafts reactions of indoles with glyoxylates. Considering the availability of chiral ligands, we chose the simplest (*S*)-BINOL-Ti complex as the catalyst for optimization of the reaction conditions. Treatment of **1a** and **2** with 20 mol% of (*S*)-BINOL and 10 mol% $Ti(O\text{-}i\text{-}Pr)_4$ using toluene as the solvent at room temperature afforded the expected product ethyl 3-indolyl(hydroxy)acetate in 35% isolated yield with 60% *ee*, accompanied with some undesired bisindole side products after 2.5 h (Table 1, entry 1). Although the catalytic efficiency is somewhat low, the moderate enantiomeric excess obtained at room temperature prompted us for further exploration.

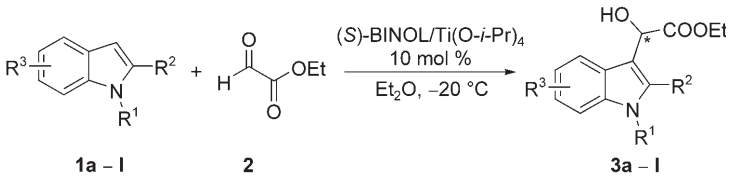
Table 1. Asymmetric Friedel–Crafts reaction of *N*-methylindole (**1a**) with ethyl glyoxylate (**2**) catalyzed by (*S*)-BINOL-Ti complex under various conditions.[a]



Entry	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1	toluene	2.5	35	60
2	CH_2Cl_2	2	15	59
3	$CHCl_3$	7	21	46
4	*n*-hexane	13	54	79
5	xylene	7	67	73
6	Et_2O	7	38	84
7	THF	2	(95)[d]	–
8	Et_2O	18	76	86[e]
9	**Et_2O**	**48**	**88**	**90**[f]
10	Et_2O	40	78	90 [g]
11	Et_2O	18	98	80[f,h]
12	Et_2O	72	80	76[f,i]
13	Et_2O	48	92	−87[f,j]
14	Et_2O	48	86	19[f,k]

[a] The reactions were carried out at room temperature with **1a** (0.5 mmol), **2** (1.5 equivs.), $Ti(O\text{-}i\text{-}Pr)_4$ (10 mol%) and (*S*)-BINOL (20 mol%) in 1 mL of solvent for 2–72 h.
[b] Isolated yield of **3a**
[c] Determined by chiral HPLC.
[d] Only **3a′** was obtained in 95% yield.
[e] Performed at 0 °C.
[f] Performed at −20 °C.
[g] Performed at −40 °C.
[h] 3.0 equivs. of **2** were used.
[i] 5 mol% of the catalyst was used.
[j] (*R*)-6,6′-Br_2-BINOL (20 mol%) was used instead of (*S*)-BINOL.
[k] (*S*)-H_8-BINOL (20 mol%) was used instead of (*S*)-BINOL.

Table 2. Asymmetric Friedel–Crafts reaction of indoles (**1a–l**) with ethyl glyoxylate (**2**) catalyzed by (*S*)-BINOL/Ti complex.[a]



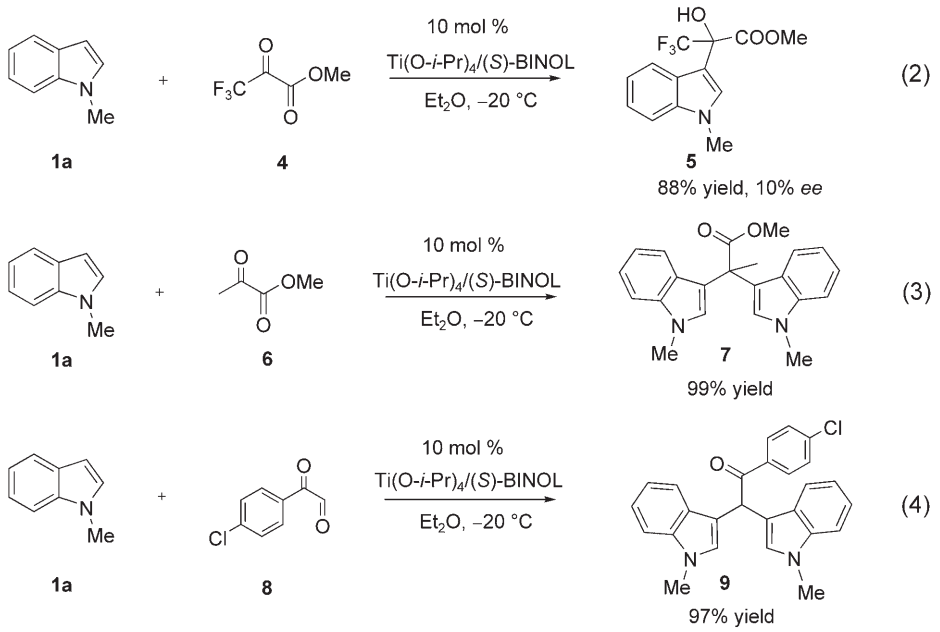
1a – l **2** **3a – l**

Entry	Product	R^1	R^2	R^3	Time [h]	Yield [%][b]	*ee* [%][c]
1	**3a**	Me	H	5-H	48	88	90
2	**3b**	Allyl	H	5-H	45	72	90
3	**3c**	Bn	H	5-H	64	86	91
4	**3d**	H	H	5-H	48	72	84
5	**3e**	Me	H	5-Br	72	71	90
6	**3f**	Me	H	5-F	54	80	89
7	**3g**	Allyl	H	6-Cl	60	70	92
8	**3h**	Me	H	5-CO_2Me	72	81	80
9	**3i**	Allyl	H	5-OMe	72	64	87
10	**3j**	Me	H	5-Me	60	75	66[d]
11	**3k**	Me	Me	H	65	70	62
12	**3l**	Bn	H	5-Br	96	64	96[e]

[a] Unless specified, the reactions were carried out at −20 °C with **1** (0.5 mmol), **2** (1.5 equivs.), Ti(O-*i*-Pr)$_4$ (10 mol %) and (*S*)-BINOL (20 mol %) in 1 mL of Et_2O for 45–72 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Performed at −40 °C.
[e] Absolute configuration determined to be *S* by single-crystal X-ray analysis, see Supporting Information.

As shown in Table 1, both solvent and temperature had dramatic effects on this asymmetric Friedel–Crafts reaction. Generally, the reactions at room temperature afforded a mixture of ethyl 3-indolyl-(hydroxy)acetate (**3a**) and bisindoles (**3a′**) (Table 1, entries 1–6), with the good selectivity for **3a** being obtained in low coordinating and non-polar solvents (such as hexane and xylene). When a more coordinating solvent, THF, was employed in the reaction, only the bisindole compound (**3a′**) was isolated (Table 1, entry 7). That is probably because THF can stabilize the 3-alkylidene-*3H*-indolium cation **B** [Eq. (1)] and results in the rapid formation of **3a′**. High yield (Table 1, entry 5, 67 % yield) and enantioselectivity (Table 1, entry 6, 84 % *ee*) were obtained by using xylene and diethyl ether as the solvent at room temperature, respectively. Further optimization revealed that, to our delight, the formation of **3a′** was not observed, and excellent enantioselectivities was obtained, when the reaction temperature was lowered to 0 °C or below (Table 1, entries 8–10). The best results were obtained when the reaction was carried out in Et_2O at −20 °C (Table 1, entry 9, 88 % yield with 90 % *ee*, 48 h), although the reaction took a longer time to go to completion. Further lowering the reaction temperature to −40 °C did not improve the enantioselectivity (Table 1, entry 10). Use of 3.0 equivs. of ethyl glyoxylate (**2**) can further increase the yield to 98 %, but decreases the enantioselectivity of the reaction (Table 1, entry 11). Lowering the catalyst loading resulted in longer reaction times and moderate *ee* (Table 1, entry 12). The catalytic activity and enantioselectivity of BINOL derivative-Ti catalysts have been also examined. Relatively low enantioselectivity was obtained with the presence of the electron-withdrawing group at the 6,6′-position of BINOL [(*R*)-6,6′-Br_2-BINOL-Ti system, Table 1, entry 13]. (*S*)-H_8-BINOL, an electron-rich BINOL derivative, was found to dramatically decrease the enantioselectivity of the reaction, although the chemical yield was good (Table 1, entry 14).

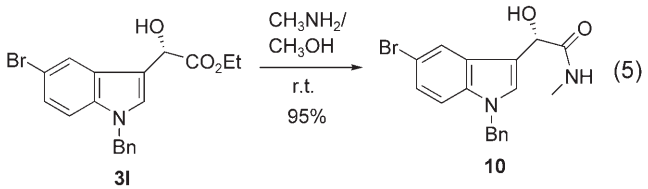
With the optimized conditions in hand, the catalytic enantioselective Friedel–Crafts reactions of readily available substituted indoles (**1a–l**) with ethyl glyoxylate (**2**) were then investigated (Table 2). As shown in Table 2, *N*-protected indole substrates proved to be superior to the free indole (Table 2, entries 1, 2, and 3 *vs.* entry 4). Both electron-withdrawing (Table 2, entries 5–8) and electron-donating substituents (Table 2, entry 9) on the aromatic ring could be tolerated and the corresponding products were isolated in good yields with high enantioselectivities. However, a methyl substituent at 5- or 2- position of the indole ring afforded moderate enantioselectivities (Table 2, entries 10 and 11), presumably due to the electronic and steric effects. Varying the substituent at the nitro-



gen atom does not affect the reaction efficiency (Table 2, entries 1–3). It is well documented that Lewis-acid catalyzed reactions of glyoxylates basically require that the substrate be freshly distilled before use. It is worthy to note that the commercially available solution of ethyl glyoxylate in toluene can be used directly in the present reaction without taking any precautions.

Next, we tried to expand our catalytic scaffold to other dicarbonyl electrophiles. Under our optimized conditions, methyl 3,3,3-trifluoropyruvate reacted with *N*-methylindole to give the corresponding trifluoro-2-hydroxy-2-indole-3-yl-propionate as the sole product in 88% yield with 10% *ee* [Eq. (2)]. In contrast, when methyl pyruvate and *p*-chlorophenylglyoxal were used, only bisindole derivatives were obtained in excellent yield [Eqs. (3) and (4)].

In order to determine the absolute configuration of the product, we have prepared the corresponding amide **10** from **3l** [Eq. (5)].



The absolute configuration of **3l** was determined by X-ray crystallography of **10** (Figure 1), while the others are tentatively assigned by assuming an analogous enantioinduction (Scheme 2).

A possible mechanism of the (*S*)-BINOL-Ti complex catalyzed asymmetric Friedel–Crafts reaction is

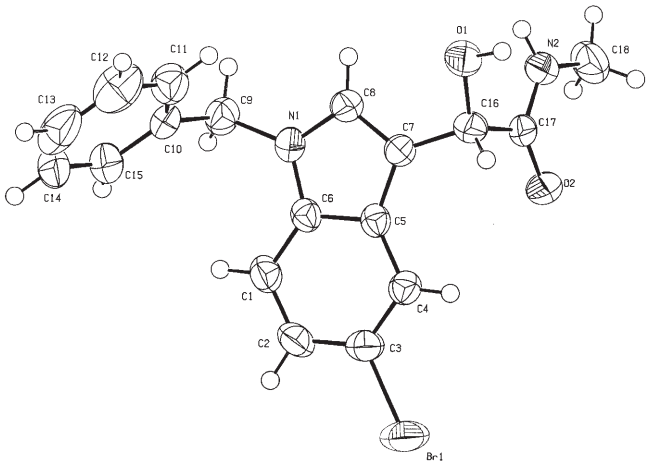
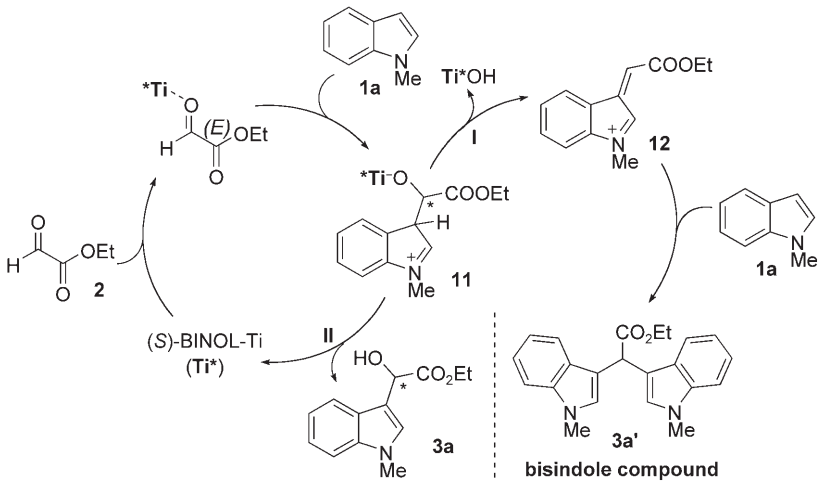


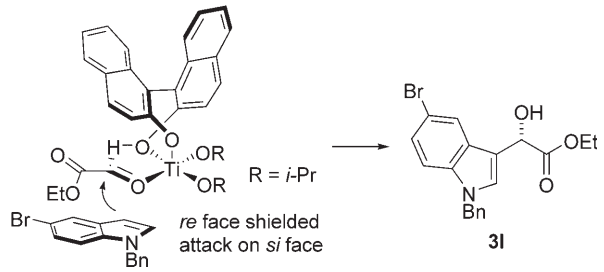
Figure 1. X-ray crystallographic structure of **10** (CCDC 645292).

outlined in Scheme 1, using the reaction of *N*-methylindole as a representative. In the first step, the chiral titanium catalyst might coordinate with ethyl glyoxylate (**2**) because of its high oxophilicity.[15c] Then *N*-methylindole (**1a**) could attack the activated carbonyl to form intermediate **11**. In the following steps, intermediate **11** may follow pathway **I**[17] to give the undesired bisindole product (**3a′**) or follow pathway **II** to provide the expected product (**3a**) and release the chiral catalyst for the catalytic cycles. Under our conditions, the pathway **I** may be suppressed at lower temperature.

Although the exact structure of the active catalyst species is unknown, the origin of the observed high enantioselectivity might be rationalized based on the previously reported transition state by Corey[23] and



Scheme 1. Proposed mechanism for the asymmetric Friedel–Crafts reaction.



Scheme 2. Proposed working model for the asymmetric Friedel–Crafts reaction.

Ding[15c]. As shown in Scheme 2, the formyl C–H···O hydrogen bonding may arise from the sterically favorable oxygen lone pair of the BINOL ligand. Thus, this five-member ring makes the coordination bond between Ti*–O less flexible. As a result, the *si* face of the formyl group is more prone to be attacked by indole derivatives than the *re* face since the latter is shielded by the nearby naphthyl subunit. This rationale is well consistent with our observed *S*-configuration of the product **3l**. In the reaction of methyl 3,3,3-trifluoropyruvate (**4**) with *N*-methylindole (**1a**), the rigid five-membered ring arising from the C–H···O hydrogen bonding did not exsist, because the H in the formyl group was replaced by a CF_3 group. Accordingly, this fact might explain why trifluoro-2-hydroxy-2-indole-3-yl-propionate (**5**) was obtained with lower enantioselectivity.

In summary, we have developed a successful and highly enantioselective Friedel–Crafts alkylaiton of various substituted indoles with ethyl glyoxylate catalyzed by an (*S*)-BINOL-Ti(IV) complex, which provided a direct access to enantiomerically enriched 3-indolyl(hydroxy)acetates in good yields and with up to 96% *ee*.

Experimental Section

General Remarks

The solvents were purified prior to use. Petroleum ether and ethyl acetate for flash column chromatography were distilled before use. Other commercially available materials were used as received. Flash column chromatography was performed using 200–300 mesh silica gel. Organic solutions were concentrated under reduced pressure on a rotary evaporator. ^{1}H NMR spectra were recorded on a Varian Mercury 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 100 MHz spectrometer with complete proton decoupling ($CDCl_3$: 77.0 ppm). Chiral HPLC was performed on an Agilent 1100 series with chiral (AS-H, AD-H and OD-H) columns.

General Procedure for Enantioselective Friedel–Crafts Reaction of Indoles with Ethyl Glyoxylate Catalyzed by (*S*)-BINOL-Ti Complex

To a 5-mL flask equipped with a magnetic stirrer, in which the air was replaced by nitrogen, was added (*S*)-BINOL (28.6 mg, 0.1 mmol), diethyl ether (1 mL), and Ti(O-*i*-Pr)$_4$ (14.9 μL, 0.05 mmol). The mixture was stirred at room temperature for 1 h. Then the resulting orange solution was cooled to the specified temperature, the indole (0.5 mmol) and ethyl glyoxylate (0.15 mL, 50% in toluene, 0.75 mmol) were introduced into the reaction system. After the completion of the reaction (monitored by TLC), H_2O (3 mL) and dichloromethane (5 mL) were added to the mixture. Insoluble material was filtered off through a pad of Celite, and the filtrate was extracted three times with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pres-

sure. The residue was submitted to flash chromatographic separation on silica gel using petroleum ether-ethyl acetate (3:1) as an eluent to give the corresponding Friedel–Crafts reaction product **3a–l**.

Supporting Information

Complete experimental procedures, absolute configuration determination of the products and characterization of **3a–l**, **5**, **7, 9** and **10** are given in the Supporting Information.

Acknowledgements

We are grateful to the National Science Foundation of China (20472021 and 20672040), the National Basic Research Program of China (2004CCA00100), the Program for New Century Excellent Talents in University (NCET-05–0672), and the Cultivation Fund of the Key Scientific and Technical Innovation Project (Ministry of Education of China, No 705039) for support of this research.

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