Tetrahedron 66 (2010) 1447–1457

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

N,*N*′-Dioxide–scandium(III) complex catalyzed highly enantioselective Friedel–Crafts alkylation of indole to alkylidene malonates

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ARTICLE INFO

Article history:
Received 1 October 2009
Received in revised form 9 December 2009
Accepted 11 December 2009
Available online 16 December 2009

Keywords:
Friedel–crafts alkylation
Alkylidene malonates
Indole derivatives
N,*N*′-Dioxide–scandium(III)

ABSTRACT

A highly efficient enantioselective Friedel–Crafts alkylation of indoles with alkylidene malonates has been developed using chiral *N*,*N*′-dioxide **L4**–scandium(III) complex as the catalyst, giving the corresponding products in high yields with excellent enantioselectivities (up to 99% yield and 95% ee). The product **3a** was facilely converted into several interesting compounds, such as tryptamines, indolepropionic acids and β-carbolines. It is noteworthy that the seven-membered β-carboline-like compound has been synthesized for the first time. Based on the crystal structure of the chiral *N*,*N*′-dioxide **L10**–scandium(III) complex, the proposed transition state and possible catalytic cycle were presented to elucidate the reaction mechanism.

1. Introduction

The Friedel–Crafts alkylation reaction is a powerful carbon–carbon bond-forming process in the organic synthesis. As a promising synthetic methodology for the synthesis of chiral indole derivatives, which has been identified as privileged structure or pharmacophore in medicinal chemistry,[1] the asymmetric Friedel–Crafts alkylation of indoles with electron-deficient olefins has recently attracted significant attentions.[2] However, to date, only a few highly enantioselective versions of indoles with alkylidene malonates have been reported. In 2001, Jørgensen et al. reported the reaction for the first time using chiral Cu(II)–bis(oxazolines) complex.[3] Subsequently, chiral Cu(II)–tris(oxazoline) complex was developed by Tang et al. and showed superior performance in the reaction.[4] Just recently, Reiser et al. disclosed that the mole ratio of the ligand to copper played a crucial role on the enantioselectivity of this reaction.[5] Despite these advanced achievement, the development of new and efficient asymmetric catalytic system is still challenging and interesting. Herein, we described our detailed effort on the enantioselective Friedel–Crafts alkylation of indoles with alkylidene malonates using chiral *N*,*N*′-dioxides–scandium(III) complex as the catalyst, giving the corresponding indole derivatives with high yields and enantioselectivities.[13]

2. Results and discussion

2.1. Preliminary experiment results

Since *N*,*N*′-dioxide–scandium(III) complexes have been proved to be effective chiral Lewis acid catalysts,[14] **L1**-Sc(OTf)$_3$ was first selected for the preliminary investigation on the Friedel–Crafts alkylation reaction. As shown in Table 1, the reaction proved to be highly solvent-dependent. Only racemic products were obtained in toluene, CH_2Cl_2 and PhOMe (Table 1, entries 1–3), while the indole derivative **3a** with 25% ee was isolated in Et_2O (Table 1, entry 4). Fortunately, better enantioselectivity could be achieved when the reaction was carried out in alcohols (Table 1, entries 5–12), and the best enantioselectivity was obtained in cyclopentanol (Table 1, entry 11).

2.2. Ligand effect

To further improve the enantioselectivity, various chiral *N*,*N*′-dioxides (Fig.1) were complexed with Sc(OTf)$_3$ in situ to catalyze the reaction. As far as the chiral backbone of *N*,*N*′-dioxide was concerned, **L4** derived from L-ramiprol acid was superior to L-proline derived **L2** and L-pipecolic acid derived **L3** for the reaction (Table 2, entries 1–3). The chiral *N*,*N*′-dioxide **L4** derived from L-ramiprol acid and diphenylmethyl amine provided the corresponding product with the highest enantiomeric excess (Table 2, entry 3). In contrast, ligands with smaller or bulkier amide moiety gave slightly lower enantioselectivities (Table 2, entries 4–6). Linker

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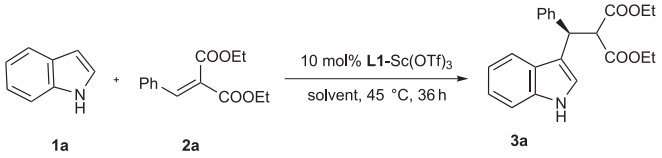
doi:10.1016/j.tet.2009.12.032

Table 1
Initial screening of solvents[a]



Entry	Solvent	Yield[b] (%)	Ee[c] (%)
1	Toluene	96	0
2	CH_2Cl_2	74	0
3	PhOMe	81	0
4	Et_2O	85	25(*R*)
5	MeOH	83	30(*R*)
6	EtOH	57	41(*R*)
7	^{i}PrOH	70	32(*R*)
8	*n*-butanol	39	33(*R*)
9	*n*-propanol	37	42(*R*)
10	*t*-butanol	85	34(*R*)
11	Cyclopentanol	64	45(*R*)
12	Cyclohexanol	48	34(*R*)

[a] Unless otherwise noted, reactions were carried out with **L1** (10 mol %), $Sc(OTf)_3$ (10 mol %), **2a** (0.125 mmol), and **1a** (0.15 mmol) in solvent (0.5 mL) at 45 °C for 36 h.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.

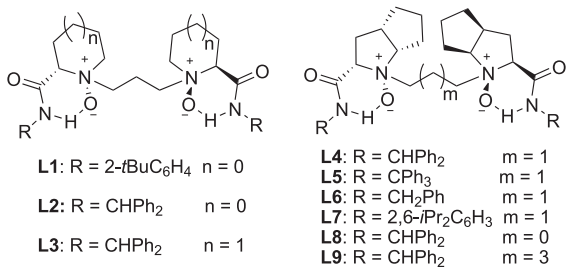
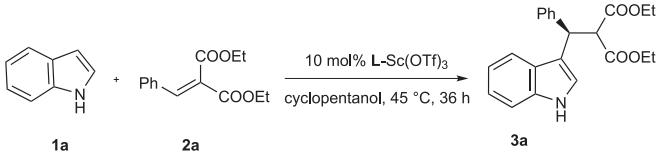


Figure 1. Chiral *N*,*N*′-dioxide ligands evaluated.

length of the *N*,*N*′-dioxide was also investigated. Unfortunately, shorting or increasing the linker all led to a significant decrease on enantioselectivity (Table 2, entries 7 and 8). The investigations on the relationship between the ligands and the enantioselectivities of the reaction obviously disclosed a cooperative effect of amino acid moiety, amide part and linker of *N*,*N*′-dioxide in creating a excellent chiral Lewis acid catalyst.

Table 2
Investigations on the ligand**s** effect[a]



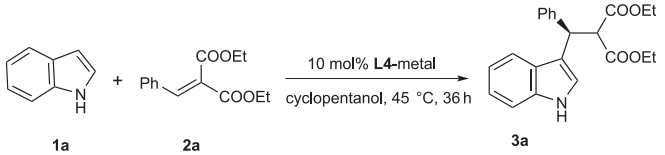
Entry	Ligand	Yield[b] (%)	Ee[c] (%)
1	**L2**	65	32(*R*)
2	**L3**	64	29(*R*)
3	**L4**	81	69(*R*)
4	**L5**	68	19(*R*)
5	**L6**	42	64(*R*)
6	**L7**	22	26(*R*)
7	**L8**	96	57(*R*)
8	**L9**	68	19(*R*)

[a] Unless otherwise noted, reactions were carried out with *Ligand* (10 mol %), $Sc(OTf)_3$ (10 mol %), **2a** (0.125 mmol), and **1a** (0.15 mmol) in cyclopentanol (0.2 mL) at 45 °C for 36 h.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.

2.3. Lewis acid effect

A variety of chiral Lewis acid catalysts generated in situ from metal salts and the **L4** were then evaluated, and the results were summarized in Table 3. When CuOTf, $Cu(OTf)_2$, $Zn(OTf)_2$, $Y(OTf)_3$ or $Sm(OTf)_3$ was employed as central metal, only negligible enantiomeric excess or even racemic product was obtained (Table 3, entries 1–5), while in the presence of $Sc(OTf)_3$, $La(OTf)_3$, $Yb(OTf)_3$ or $In(OTf)_3$, indole reacted well with alkylidene malonate **2a**, giving the desired product in poor to moderate enantioselectivity (Table 3, entries 6–9).

Table 3
Investigations on the metal sources[a]



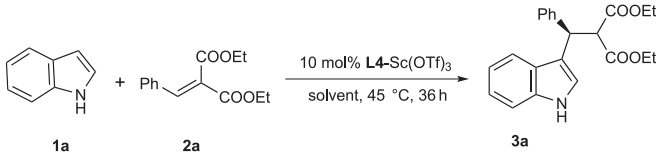
Entry	Metal	Yield[b] (%)	Ee[c] (%)
1	CuOTf	trace[d]	2
2	$Cu(OTf)_2$	4	0
3	$Zn(OTf)_2$	7	0
4	$Y(OTf)_3$	70	5(*S*)
5	$Sm(OTf)_3$	25	2
6	$Sc(OTf)_3$	81	69(*R*)
7	$La(OTf)_3$	62	13(*S*)
8	$Yb(OTf)_3$	85	15(*R*)
9	$In(OTf)_3$	13	14(*R*)

[a] Unless otherwise noted, reactions were carried out with **L4** (10 mol %), metal (10 mol %), **2a** (0.125 mmol), and **1a** (0.15 mmol) in cyclopentanol (0.2 mL) at 45 °C for 36 h.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.
[d] Not detected.

2.4. Solvent effect

Considering that different chiral Lewis acid catalysts may exhibit a distinct performance in solvent in some case, we reexamined the reaction solvents. In all cases, **L4**–$Sc(OTf)_3$ complex achieved better enantioselectivities compared with the catalyst **L1**-$Sc(OTf)_3$ (Table 4 vs Table 1). Furthermore, instead of cyclopentanol, the best

Table 4
Effect of solvents using chiral **L4**-$Sc(OTf)_3$ as the catalyst[a]



Entry	Solvent	Yield[b] (%)	Ee[c] (%)
1	Toluene	66	55(*R*)
2	CH_2Cl_2	85	64(*R*)
3	PhOMe	48	47(*R*)
4	Et_2O	99	63(*R*)
5	EtOH	57	64(*R*)
6	MeOH	77	40(*R*)
7	^{i}PrOH	81	68(*R*)
8	*n*-butanol	96	64(*R*)
9	*n*-propanol	90	57(*R*)
10	*t*-butanol	39	74(*R*)
11	Cyclopentanol	81	69(*R*)
12	Cyclohexanol	88	63(*R*)

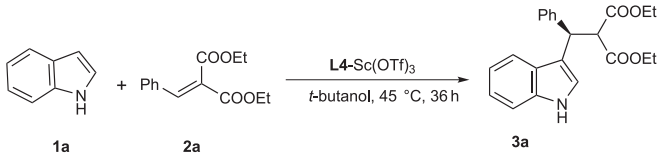
[a] Unless otherwise noted, reactions were carried out with **L4** (10 mol %), $Sc(OTf)_3$ (10 mol %), **2a** (0.125 mmol), and **1a** (0.15 mmol) in solvent (0.2 mL) at 45 °C for 36 h.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.

enantioselectivity was obtained using *tert*-butanol as the solvent albeit with lower yield (Table 1, entries 10 and 11 vs Table 4, entries 10 and 11).

2.5. Ratio of ligand/metal and catalyst loading effect

The ratio of ligand and $Sc(OTf)_3$ strongly influenced the enantioselectivity of the reaction. In the presence of equivalent or an excess of ligand, the yield and enantioselectivity were basically maintained (Table 5, entries 1–3). An excess of $Sc(OTf)_3$ led to improvement of the yield with some loss in enantioselectivity of the reaction (Table 5, entries 4 and 5). Moreover, changing the catalyst loading had no benefit effect on the enantioselectivity (Table 5, entries 6 and 7).

Table 5
Study on the ratio of Ligand/Metal and catalyst loading[a]



1a 2a 3a

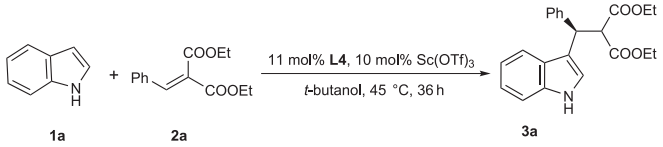
Entry	**L4** (mol %)	$Sc(OTf)_3$ (mol %)	Yield[b] (%)	Ee[c] (%)
1	10	10	39	74(*R*)
2	11	10	39	76(*R*)
3	13	10	39	76(*R*)
4	10	11	46	71(*R*)
5	10	13	90	0
6	5.5	5	37	72(*R*)
7	22	20	59	50(*R*)

[a] Unless otherwise noted, reactions were carried out with **L4**, $Sc(OTf)_3$, **2a** (0.125 mmol), and **1a** (0.15 mmol) in *t*-butanol (0.2 mL) at 45 °C for 36 h.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.

2.6. Substrate concentration effect

The substrate concentration was an important parameter for the reaction of indole **1a** and alkylidene malonate **2a**. High concentration was beneficial for the yield of the reaction (Table 6). The yield could be increased to 68% without considerable loss in enantioselectivity the substrate concentration of the reaction increased to 1.25 M (Table 6, entry 2). Furthermore, when the molar ratio of indole to alkylidene malonate **2a** was raised from 1.2:1 to 2:1, the yield of **3a** was remarkably improved from 68% to 94%, while the enantioselectivity was maintained (Table 6, entry 2 vs 8).[6]

Table 6
Effect of the substrate concentration [a]



1a 2a 3a

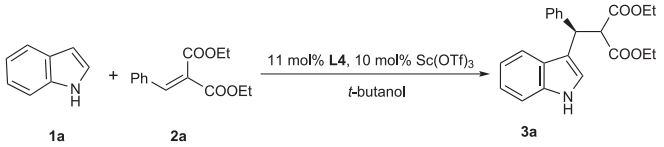
Entry	Concentration (mmol/mL)	Yield[b] (%)	Ee[c] (%)
1	2.50	68	72(*R*)
2	1.25	68	74(*R*)
3	0.63	41	75(*R*)
5	0.31	22	75(*R*)
7	0.21	13	76(*R*)
8[d]	1.25	94	73(*R*)

[a] Unless otherwise noted, reactions were carried out with **L4** (11 mol %), $Sc(OTf)_3$ (10 mol %), **2a** (0.125 mmol), and **1a** (0.15 mmol) in *t*-butanol at 45 °C for 36 h.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.
[d] 0.25 mmol indole was used.

2.7. Temperature effect

The reaction was extremely sensitive to the temperature. Lowering the reaction temperature, the enantioselectivity was further improved to 85% ee, which was accompanied with an obvious loss in reactivity (Table 7, entry 4). Considering the excellent reactivity and good enantioselectivity when the reaction proceeded in Et_2O and ^{t}BuOH, respectively (Table 4, entries 5 and 10), the reaction was then performed in Et_2O at −20 °C after the catalyst was prepared in ^{t}BuOH at 35 °C. It is delightful that both the yield and enantioselectivity were improved, giving the corresponding product **3a** in 94% yield with 90% ee (Table 7, entry 5). This finding clearly disclosed the decisive role of ^{t}BuOH in the generation of catalytically active species.

Table 7
Investigation of the reaction temperature[a]



1a 2a 3a

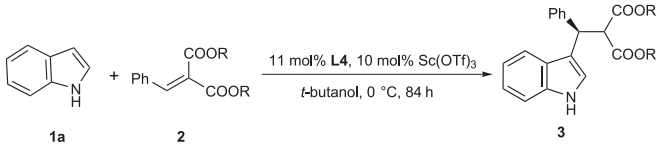
Entry	Temp (°C)	Yield[b] (%)	Ee[c] (%)
1	45	94	74(*R*)
2	25	68	77(*R*)
3	0	46	81(*R*)
4	−20	31	85(*R*)
5[d]	−20	94	90(*R*)

[a] Unless otherwise noted, reactions were carried out with **L4** (11 mol %), $Sc(OTf)_3$ (10 mol %), **2a** (0.125 mmol), and **1a** (0.25 mmol) in *t*-butanol (0.1 mL) at indicated temperature.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.
[d] Catalyst was prepared in ^{t}BuOH at 35 °C and the reaction was carried out in Et_2O.

2.8. Effect of ester group

Given alkylidene malonate coordinated with $Sc(OTf)_3$ in a bidentate manner,[4b,7] we envisioned that the size of the ester group of the alkylidene malonate might affect the enantioselectivity of the reaction. Thus, a number of benzylidene maonates with different ester groups were tested. A suitable steric hindrance of the ester groups played a crucial role on the reactivity and enantioselectivy (Table 8). Though diisopropyl benzylidenemalonate showed a slightly higher enantioselectivity, the yield was extremely poor compared with that of diethyl benzylidenemalonate (Table 8, entry 2 vs 4).

Table 8
Effect on ester moiety of benzylidene maonates[a]



1a 2 3

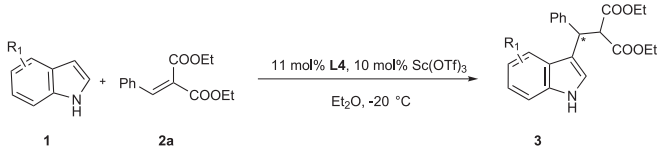
Entry	R	Yield[b] (%)	Ee[c] (%)
1	Me	12	64
2	Et	46	81(*R*)
3	^{n}Pr	20	80
4	^{i}Pr	6	83
5[d]	^{t}Bu	4	3[e]
6[d]	$PhCH_2$	59	71

[a] Unless otherwise noted, reactions were carried out with **L4** (11 mol %), $Sc(OTf)_3$ (10 mol %), **2** (0.125 mmol), and **1a** (0.25 mmol) in *t*-butanol (0.1 mL) at 0 °C for 84 h.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.
[d] The reaction was carried out at 45 °C.
[e] Reversed configuration of product was obtained.

2.9. Substrate scope

To study the generality of this reaction, a variety of indoles were examined (Table 9, entries 1–5) under the optimal reaction conditions (Table 7, entry 5). The reaction was found to be sensitive to the position of substituents on indoles. 4-MeO or 5-MeO indole gave good enantioselectivities and excellent yields (Table 9, entries 2 and 3). However, when the same substituent was introduced into indole ring at position 6, the yield was dramatically decreased (Table 9, entry 4). Furthermore, a C(5) bromine substituent facilitated the reaction to give the desired product **3af** with 84% ee (Table 9, entry 5).

Table 9
Catalytic enantioselective Friedel–Crafts reaction of indoles **1** with alkylidene malonate **2a**[a]



Entry	R_1	Product	Yield[b] (%)	Ee[c] (%)
1	**7**-CH_3	**3ab**	96	85
2	4-MeO	**3ac**	99	81
3	5-MeO	**3ad**	95	92(*R*)[e]
4	6-MeO	**3ae**	32	80
5	5-Br	**3af**	98	84[d]

[a] Unless otherwise noted, reactions were carried out with **L4** (11 mol %), $Sc(OTf)_3$ (10 mol %), **2a** (0.125 mmol), and **1** (0.25 mmol) in Et_2O (0.1 mL) at −20 °C. Catalyst was prepared in ^{t}BuOH at 35 °C.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.
[d] The reaction was carried out at 0 °C.
[e] The absolute configuration was determined by comparing with literature data.

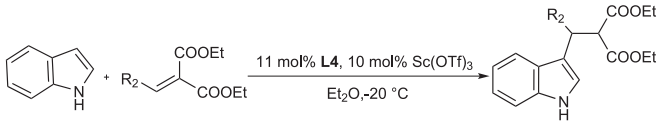
Alkylidene malonates with different structures were next evaluated, giving the corresponding products with good to excellent enantioselectivities (up to 92% ee). The enantioselectivity of the reaction was found to be insensitive to the steric and electronic properties of *meta*-substituents on the phenyl ring in arylidene malonate (Table 10, entries 2–8), which was different from the catalytic systems of chiral Cu(II)-oxazoline.[8] The *para*-substituted arylidene malonates were also efficient for the reaction with moderate to good enantioselectivities (Table 10, entries 9–15), albeit the *ortho*-substituted one showed a reduced enantioselectivity (Table 10, entry 16), which might be attributed to the steric hindrance effect of *ortho*-position. It was noteworthy that the reaction could also be extended to condensed-ring, heterocyclic and disubstituted arylidene malonates with good to excellent enantioselectivities (Table 10, entries 17–20). Unfortunately, only moderate yield and enantioslectivity were obtained for the cyclohexylidene malonate (Table 10, entry 21).

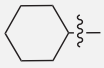
In addition, it was found that when 5-MeO indole reacted with different arylidene malonates, alkylation adducts were obtained with better enantioselectivities (Table 10, entries 2, 4, 6–8, 17 and 20 vs Table 11, entries 2–7 and 9). The enantioselectivity was increased to 92% ee when the reaction of 5-Br indole and *meta*-bromine substituted arylidene malonate were examined (Table 9, entry 9 vs Table 11, entry 1).

2.10. Product elaboration

In order to exploit the synthetic potential of the current catalyst system, the reaction was scaled up to 2.5 mmol of the starting material in the presence of **L4**–$Sc(OTf)_3$ complex. The corresponding product (*R*)-**3a** could be isolated in 72% yield with 86% ee. After a single recrystallization, optically pure product **3a** could be obtained (Scheme 1).

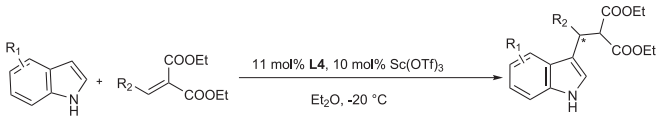
Table 10
Catalytic enantioselective Friedel–Crafts reaction of indole **1a** with alkylidene malonates **2**[a]



Entry	R_2	Product	Yield[b] (%)	Ee[c] (%)
1	Ph	**3a**	94	90(*R*)[f]
2	3-MeC_6H_4	**3b**	84	90
3	3-$MeOC_6H_4$	**3c**	59	92
4	3-$PhOC_6H_4$	**3d**	90	93
5	3-$CF_3C_6H_4$	**3e**	90	92
6	3-$NO_2C_6H_4$	**3f**	73	82
7	3-BrC_6H_4	**3g**	97	92
8[d]	3-ClC_6H_4	**3h**	84	87
9[d]	4-FC_6H_4	**3i**	98	83
10	4-BrC_6H_4	**3j**	97	80
11[e]	4-$NO_2C_6H_4$	**3k**	74	71
12[d]	4-ClC_6H_4	**3l**	92	80
13	4-CNC_6H_4	**3m**	55	75
14	4-$CF_3C_6H_4$	**3n**	87	82
15	4-$CH_3C_6H_4$	**3o**	97	80[e]
16	2-ClC_6H_4	**3p**	71	62
17	3-PhO-4-FC_6H_3	**3q**	77	88
18	3,4-$Cl_2C_6H_3$	**3r**	92	83
19[e]	2-naphthyl	**3s**	72	80
20	2-thienyl	**3t**	83	71
21		**3u**	57	43

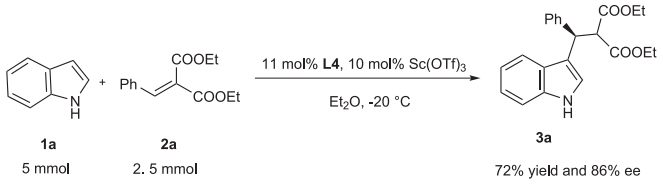
[a] Unless otherwise noted, reactions were carried out with **L4** (11 mol %), $Sc(OTf)_3$ (10 mol %), **2** (0.125 mmol), and **1a** (0.25 mmol) in Et_2O (0.1 mL) at −20 °C. Catalyst was prepared in ^{t}BuOH at 35 °C.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.
[d] 0.5 mmol indole was used.
[e] The reaction was carried out at 0 °C.
[f] The absolute configuration was determined by comparing with literature data.

Table 11
Catalytic enantioselective Friedel–Crafts reaction of indoles **1** with alkylidene malonates **2**[a]



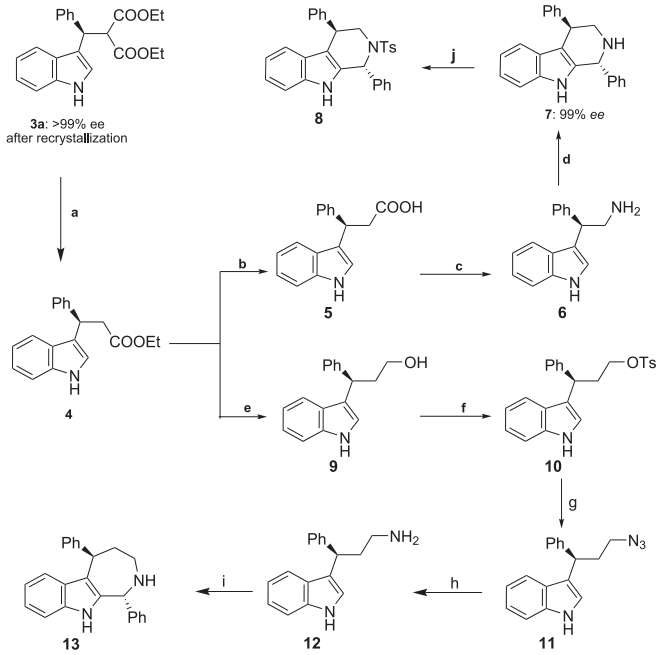
Entry	R_1	R_2	Product	Yield[b](%)	Ee[c](%)
1	5-Br	3-BrC_6H_4	**3jf**	77	92
2	5-MeO	3-$PhOC_6H_4$	**3cd**	75	95
3	5-MeO	3-ClC_6H_4	**3hd**	78	88
4	5-MeO	3-PhO-4-FC_6H_3	**3qd**	74	92
5	5-MeO	3-BrC_6H_4	**3jd**	89	92
6	5-MeO	3-$NO_2C_6H_4$	**3fd**	65	84
7	5-MeO	3-$CH_3C_6H_4$	**3bd**	99	92
8	5-MeO	4-PhC_6H_4	**3vd**	73	86
9	5-MeO	2-thienyl	**3td**	98	80

[a] Unless otherwise noted, reactions were carried out with **L4** (11 mol %), $Sc(OTf)_3$ (10 mol %), **1** (0.125 mmol), and **2** (0.25 mmol) in Et_2O (0.1 mL) at −20 °C. Catalyst was prepared in ^{t}BuOH at 35 °C.
[b] Isolated yield.
[c] Determined by HPLC using chiral OD-H column.



Scheme 1. Scaled up version of the Friedel–Crafts reaction.

Furthermore, the Friedel–Crafts alkylation product could be easily transformed to some useful intermediates for the synthesis of biologically active compounds, such as tryptamines,[1a] 3-indolepropionic acids[1k] and 1,2,3,4-tetrahydro-β-carbolines.[1e] As shown in Scheme 2, the adduct **3a** underwent decarboxylation smoothly to give the monoester **4** in good yield.[3,4c] Treatment of **4** with NaOH in the mixed solvent of THF and EtOH provided the potent neuroprotective agent **5** in high yield. The reaction of acid **5** with diphenylphosphoryl azide gave the corresponding acylazide, which was subjected to a Curtius rearrangement to give isocyanate.[1f,9] By the addition of *tert*-butyl alcohol, isocyanate was then transformed into carbamate ester, which was converted into the tryptamine **6** after removal of the Boc group. The crude product **6** then underwent Pictet–Spengler cyclization[10] with benzaldehyde to furnish the 1,2,3,4-tetrahydro-β-carboline[2e,11] **7** as a 92:8 mixture of diastereoisomers. On the other hand, reduction of ester **4** proceeded smoothly to give the corresponding alcohol **9** in quantitative yield, which then underwent the esterification, nucleophilic substitution and reduction to give the serotonin analogue **12**.[1j,15] The amine **12** has been embedded in numerous indole alkaloids. It is noteworthyl that the seven-membered β-carboline-like compound **13** was synthesized for the first time via a Pictet–Spengler reaction. The relative stereochemistry of **13** was tentatively assigned as 1,5-*trans* by means of NOE experiments. All the reactions proceeded well with no erosion in enantiomeric excess.



Scheme 2. Derivation of the Friedel–Crafts adduct **3a**. Conditions: (a) NaCl, DMSO, H_2O, reflux, 66%; (b) THF, EtOH, H_2O, 2 N NaOH, reflux, 97%; (c) Curtius rearrangement, Et_3N, DPPA, ^tBuOH, 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%. DPPA=diphenylphosphoryl azide; (j) TsCl, Et_3N, CH_2Cl_2, rt, 84%.

2.11. Reaction mechanism

Although the preparation of the single crystal of **L4**–$Sc(OTf)_3$ complex failed, the structure of the complex **L10**–$Sc(OTf)_3$, as its monohydrate **L10**-$Sc(OTf)_3\cdot(H_2O)$ was determined by X-ray crystallography (Fig. 2).[12] Not only the oxygens of *N*-oxide but also carbonyl oxygens coordinated with Sc(III) in a tetradentate manner. Based on this observation, a possible transition state was proposed (Fig. 3). In this transition state, Sc(III) coordinated in a hexadentate way with **L4** and alkylidene malonate. The *Re* face of the alkylidene malonate was blocked by the bulky diphenylmethyl group. Therefore, indole attacked from the *Si* face to give the corresponding product with *R* configuration. The transition state may help to explain the behaviour that only racemic product with moderate yield was afforded when the precursor of *N*,*N*′-dioxide **L4** was employed.[12]

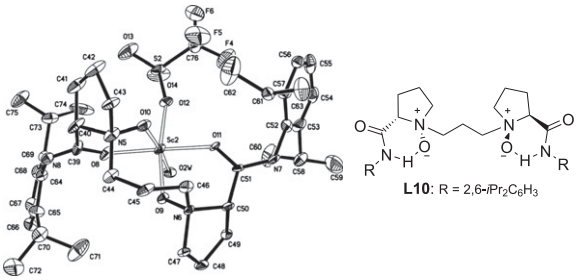


Figure 2. Crystal structure of **L10**–$Sc(OTf)_3\cdot(H_2O)$.

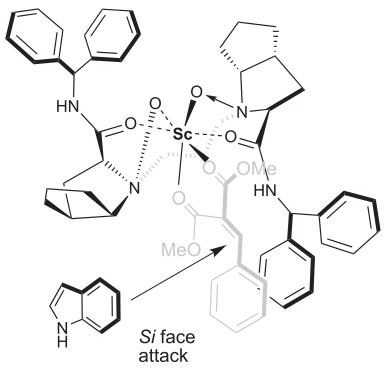


Figure 3. Proposed transition state.

As depicted in Figure 4, a catalytic cycle was also proposed to elucidate the reaction mechanism. First, the introduction of ^tBuOH to the mixture of **L4** and $Sc(OTf)_3$ generates the catalytically active species **T1**. After ligands exchange, the alkylidene malonate is introduce into the chiral environment to give the activated substrate–catalyst complex **T2**. Then, indole attack the *Si* face of the alkylidene malonate followed by the H-transfer and decomplexation of the desired product from the central metal to regenerate the intermediate **T2**. The catalytic cycle is thus completed.

3. Conclusions

In summary, we have developed an efficient catalytic enantioselective Friedel–Crafts alkylation of different indoles with a series of alkylidene malonates using chiral **L4**–$Sc(OTf)_3$ complex as catalyst. All of the condensed-ring, heterocyclic and different substituted arylidene malonates could be tolerated. Moreover, the products could be easily transformed into serotonin analogue **12** and seven-membered β-carboline-like **13**. Based on the X-ray structure of the $Sc(OTf)_3$ complex, a possible transition state was

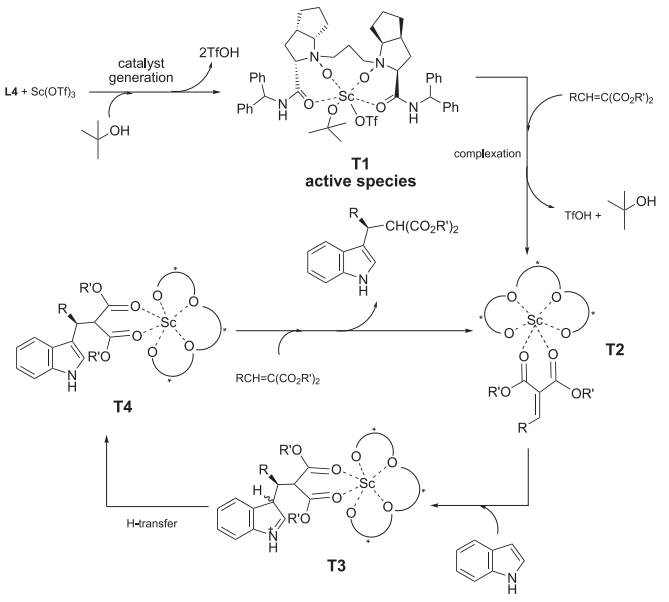


Figure 4. Proposed catalytic cycle.

proposed to explain the absolute configuration observed. The proposed catalytic cycle has also been introduced to demonstrate the mechanism of reaction.

4. Experimental

4.1. General information

^{1}H NMR spectra were recorded on commercial instruments (400 MHz). Chemical shifts were reported in part per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ=7.26). Spectra are reported as follows: chemical shift (δ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were collected on commercial instruments (100 MHz) with complete proton decoupling. Chemical shifts are reported in part per million from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ=77.0). The enantiomeric excesses were determined by HPLC analysis on chiral DAICEL CHIRALCEL AD-H, OJ-H, OD-H and AS-H column. Optical rotations were measured on a commercial polarimeter and reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, solvent). Reagents obtained from commercial sources were used without further purification. CH_2Cl_2 was distilled over CaH_2 before use. The other solvents were distilled over metal sodium before use. Melting points (mp) were measured on electrothermal digital melting point apparatus and were uncorrected.

4.2. Typical experimental procedure for the enantioselective Friedel–Crafts alkylation of indoles with alkylidene malonates

The mixture of ligand **L4** (9.8 mg, 0.0138 mmol), $Sc(OTf)_3$ (6.2 mg, 0.0125 mmol) and indole **1a** (29.3 mg, 0.25 mmol) in ^{t}BuOH (0.1 mL) was stirred at 35 °C for 1 h under nitrogen atmosphere. After the solvent was removed under vacuo, Et_2O (0.1 mL) was added. The reaction mixture was cooled to −20 °C and alkylidene malonate **2a** (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 **3a** in 94% yield with 90% ee.

4.2.1. (R)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-phenyl propanoate ***3a***[13]. White solid; HPLC analysis (Chiralcel OD-H, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=10.878 min, t_r (minor)=12.883 min) gave the isomeric composition of the product: 90% ee, mp 152–154 °C; $[\alpha]_D^{23}$ −51.4 (*c* 0.218, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07 (s, br s, 1H), 7.58 (d, *J*=8.0 Hz, 1H), 7.39 (d, *J*=6.8 Hz, 2H), 7.14–7.32 (m, 6H), 7.04–7.08 (m, 1H), 5.11 (d, *J*=11.6 Hz, 1H), 4.32 (d, *J*=12.0 Hz, 1H), 4.00–4.05 (m, 4H), 1.00–1.05 (m, 6H) ppm.

4.2.2. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(m-methylphenyl) propanoate ***3b***[13]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=10.907 min, t_r (major)=12.300 min) gave the isomeric composition of the product: 90% ee, mp 90–91 °C; $[\alpha]_D^{26}$ −60.5 (*c* 0.200, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.20 (s, br s, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.30 (d, *J*=8.4 Hz, 1H), 7.06–7.23 (m, 6H), 7.00 (d, *J*=7.2 Hz, 1H), 5.10 (d, *J*=12.0 Hz, 1H), 4.35 (d, *J*=11.6 Hz, 1H), 4.00–4.07 (m, 4H), 2.30 (s, 3H), 1.06 (t, *J*=7.2 Hz, 3H), 1.00 (t, *J*=7.2 Hz, 3H) ppm.

4.2.3. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(m-methoxylphenyl) propanoate ***3c***[13]. White solid; HPLC analysis (OD-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=14.939 min, t_r (minor)=19.784 min) gave the isomeric composition of the product: 92% ee, mp 97–99 °C; $[\alpha]_D^{27}$ −49.55 (*c* 0.222, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.13 (s, br s, 1H), 7.60 (d, *J*=7.6 Hz, 1H), 7.28–7.31 (m, 1H), 7.13–7.20 (m, 3H), 7.04–7.08 (m, 1H), 7.00 (d, *J*=8.0 Hz, 1H), 6.94 (t, *J*=2.0 Hz, 1H), 6.71 (dd, *J*=2.4, 8 Hz, 1H), 5.08 (d, *J*=11.6 Hz, 1H), 4.32 (d, *J*=12.0 Hz, 1H), 3.98–4.07 (m, 4H), 3.76 (s, 3H), 1.07 (t, *J*=7.2 Hz, 3H), 1.00 (t, *J*=7.2 Hz, 3H) ppm.

4.2.4. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(m-phenoxylphenyl) propanoate ***3d***[13]. White solid; HPLC analysis (OD-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=12.699 min, t_r (minor)=17.033 min) gave the isomeric composition of the product: 93% ee, mp 118–119 °C; $[\alpha]_D^{27}$ −39.92 (*c* 0.258, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12 (s, br s, 1H), 7.57 (d, *J*=8.0 Hz, 1H), 7.28–7.34 (m, 3H), 7.06–7.24 (m, 7H), 6.95 (dd, *J*=0.8, 7.6 Hz, 2H), 6.81 (dt, *J*=1.2, 8 Hz, 1H), 5.09 (d, *J*=12.0 Hz, 1H), 4.32 (dt, *J*=1.6, 12.0 Hz, 1H), 3.99–4.10 (m, 4H), 1.11 (t, *J*=7.2 Hz, 3H), 1.00 (t, *J*=7.2 Hz, 3H) ppm.

4.2.5. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(m-trifluoromethylphenyl) propanoate ***3e***[13]. White solid; HPLC analysis (OJ-H column, hexane/2-propanol 95:5, 1.0 mL/min, 254 nm; t_r (major)=37.180 min, t_r (minor)=46.858 min) gave the isomeric composition of the product: 92% ee, mp 85–86 °C; $[\alpha]_D^{23}$ −58.30 (*c* 0.204, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.17 (s, br s, 1H), 7.67 (s, 1H), 7.59 (d, *J*=7.6 Hz, 1H), 7.54 (d, *J*=7.6 Hz, 1H), 7.45 (d, *J*=7.6 Hz, 1H), 7.38 (d, *J*=7.6 Hz, 1H), 7.33–7.35 (m, 1H), 7.22 (d, *J*=2.4 Hz, 1H), 7.16–7.20 (m, 1H), 7.06–7.10 (m, 1H), 5.18 (d, *J*=11.6 Hz, 1H), 4.33 (d, *J*=12.0 Hz, 1H), 4.00–4.07 (m, 4H), 1.04 (t, *J*=7.2 Hz, 3H), 1.03 (t, *J*=7.2 Hz, 3H) ppm.

4.2.6. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(m-nitrophenyl) propanoate ***3f***[4b]. Yellow solid; HPLC analysis (AS-H column, hexane/2-propanol 80:20, 1.0 mL/min, 254 nm; t_r (minor)=10.269 min, t_r (major)=11.783 min) gave the isomeric composition of the product: 82% ee, mp 106–108 °C; $[\alpha]_D^{22}$ −28.82 (*c* 0.170, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.26 (t, *J*=2.0 Hz), 8.21 (s, br s, 1H), 8.04 (ddd, *J*=1.2, 2.4, 8.0 Hz, 1H), 7.76–7.78 (m, 1H), 7.51 (d, *J*=8.0 Hz, 1H), 7.44 (t, *J*=8.0 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 1H), 7.17–7.21 (m, 1H), 7.06–7.10 (m, 1H), 5.23 (d, *J*=11.6 Hz, 1H), 4.35 (d, *J*=11.6 Hz, 1H), 4.02–4.09 (m, 4H), 1.09 (t, *J*=7.2 Hz, 3H), 1.04 (t, *J*=7.2 Hz, 3H) ppm.

4.2.7. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(m-bromophenyl) propanoate ***3g***[13]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=27.957 min, t_r (major)=31.480 min) gave the isomeric composition of the product: 92% ee, mp 92–93 °C; $[\alpha]_D^{25}$ −57.21 (*c* 0.222, CH_2Cl_2); ^{1}H

NMR (400 MHz, $CDCl_3$): δ=8.25 (s, br s, 1H), 7.54–7.57 (m, 2H), 7.28–7.36 (m, 3H), 7.07–7.20 (m, 4H), 5.10 (d, J=11.6 Hz, 1H), 4.31 (d, J=11.6 Hz, 1H), 4.01–4.09 (m, 4H), 1.10 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H) ppm.

4.2.8. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(m-chlorophenyl) propanoate ***3h***[13]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=11.463 min, t_r (major)=12.648 min) gave the isomeric composition of the product: 87% ee, mp 82–94 °C; $[\alpha]_D^{26}$ −58.45 (c 0.284, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.20 (s, br s, 1H), 7.56 (d, J=7.6 Hz, 1H), 7.38 (t, J=1.6 Hz 1H), 7.28–7.33 (m, 2H), 7.14–7.21 (m, 4H), 7.06–7.10 (m, 1H), 5.10 (d, J=11.6 Hz, 1H), 4.30 (d, J=12.0 Hz, 1H), 4.00–4.08 (m, 4H), 1.09 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H) ppm.

4.2.9. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-fluorophenyl) propanoate ***3i***[13]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=12.492 min, t_r (major)=18.614 min) gave the isomeric composition of the product: 83% ee, mp 114–116 °C; $[\alpha]_D^{26}$ −77.32 (c 0.216, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15 (s, br s, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.28–7.38 (m, 3H), 7.15–7.18 (m, 2H), 7.04–7.08 (m, 1H), 6.92–6.70 (m, 2H), 5.11 (d, J=12.0 Hz, 1H), 4.28 (d, J=11.6 Hz, 1H), 4.03 (q, J=7.2 Hz, 2H), 4.04 (q, J=7.2 Hz, 2H), 1.07 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H) ppm.

4.2.10. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-bromophenyl) propanoate ***3j***[4b]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=11.100 min, t_r (major)=12.721 min) gave the isomeric composition of the product: 80% ee, mp 104–106 °C; $[\alpha]_D^{22}$ −23.26 (c 0.288, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.10 (s, br s, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.28 (t, J=2.0 Hz, 1H), 7.26 (t, J=2.0 Hz, 1H), 7.15–7.19 (m, 2H), 7.04–7.08 (m, 1H), 5.07 (d, J=12 Hz, 1H), 4.27 (d, J=11.6 Hz, 1H), 4.04 (q, J=7.2 Hz, 2H), 4.03 (q, J=7.2 Hz, 2H), 1.08 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H) ppm.

4.2.11. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-nitrophenyl) propanoate ***3k***[4b]. Yellow solid; HPLC analysis (AS-H column, hexane/2-propanol 80:20, 1.0 mL/min, 254 nm; t_r (minor)=11.460 min, t_r (major)=14.889 min) gave the isomeric composition of the product: 71% ee, ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12–8.15 (m, 3H), 7.56–7.58 (m, 2H), 7.49 (d, J=8.0 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H), 7.25 (d, J=2.4 Hz, 1H), 7.17–7.21 (m, 1H), 7.06–7.10 (m, 1H), 5.22 (d, J=11.6 Hz, 1H), 4.34 (d, J=11.6 Hz, 1H), 4.05 (q, J=7.2 Hz, 2H), 4.04 (q, J=7.2 Hz, 2H), 1.09 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H) ppm.

4.2.12. (R)-Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-chlorophenyl) propanoate ***3l***[4b]. White solid; HPLC analysis (OD-H column, hexane/2-propanol 95:5, 1.0 mL/min, 254 nm; t_r (major)=22.380 min, t_r (minor)=25.276 min) gave the isomeric composition of the product: 80% ee, mp 116–118 °C; $[\alpha]_D^{26}$ −46.15 (c 0.208, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.10 (s, br s, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.28–7.34 (m, 3H), 7.15–7.24 (m, 4H), 7.04–7.08 (m, 1H), 5.09 (d, J=11.6 Hz, 1H), 4.27 (d, J=11.6 Hz, 1H), 4.00–4.06 (m, 4H), 1.08 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H) ppm.

4.2.13. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-cyanophenyl) propanoate ***3m***. White solid; HPLC analysis (AD-H column, hexane/2-propanol 85:15, 1.0 mL/min, 254 nm; t_r (major)=26.424 min, t_r (minor)=32.077 min) gave the isomeric composition of the product: 75% ee, mp 119–121 °C; $[\alpha]_D^{25}$ −24.38 (c 0.320, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (s, br s, 1H), 7.48–7.56 (m, 5H), 7.34 (d, J=8.0 Hz, 1H), 7.16–7.20 (m, 2H), 7.05–7.09 (m, 1H), 5.17 (d, J=12 Hz, 1H), 4.32 (d, J=11.6 Hz, 1H), 4.05 (q, J=7.2 Hz, 2H), 4.04 (q, J=7.2 Hz, 2H), 1.08 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.53, 167.48, 147.19, 136.24, 132.22, 129.08, 126.29, 122.59, 121.25, 119.83, 118.91, 118.79, 115.43, 111.30, 110.58, 61.78, 61.75, 57.67, 42.74, 13.85, 13.74 ppm; ES-HRMS calcd for $[C_{23}H_{22}N_2O_4+Na^+]$ 413.1472, found: 413.1477.

4.2.14. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-trifluoromethylphenyl) propanoate ***3n***. White solid; HPLC analysis (OJ-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major) =17.064 min, t_r (minor)=21.494 min) gave the isomeric composition of the product: 82% ee, mp 111–112 °C; $[\alpha]_D^{25}$ −45.92 (c 0.294, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.27 (s, br s, 1H), 7.54 (d, J=11.2 Hz, 1H), 7.33 (d, J=8.0 Hz, 1H), 7.16–7.20 (m, 2H), 7.09–7.11 (m, 1H), 7.31 (t, J=8.8 Hz, 2H), 7.04 (t, J=7.6 Hz, 1H), 6.94 (t, J=7.6 Hz, 1H), 5.20 (d, J=11.6 Hz, 1H), 4.36 (d, J=11.6 Hz, 1H), 4.05 (q, J=7.2 Hz, 2H), 4.04 (q, J=7.2 Hz, 2H), 1.05 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.78, 167.67, 145.67, 136.26, 128.52 (J=32 Hz), 128.59, 126.42, 125.38 (J=4 Hz), 125.31 (J=4 Hz), 122.50, 121.16, 119.74, 115.96, 111.23, 61.71, 61.67, 57.96, 42.62, 13.73 ppm; ES-HRMS calcd for $[C_{23}H_{22}F_3NO_4+Na^+]$ 456.1393, found: 456.1366.

4.2.15. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-methylphenyl) propanoate ***3o***[5a]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 95:5, 1.0 mL/min, 254 nm; t_r (minor)=15.076 min, t_r (major)=17.795 min) gave the isomeric composition of the product: 80% ee, mp 100–102 °C; $[\alpha]_D^{25}$ −30.45 (c 0.220, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07 (s, br s, 1H), 7.58 (d, J=7.6 Hz, 1H), 7.26–7.31 (m, 2H), 7.13–7.17 (m, 2H), 7.03–7.07 (m, 3H), 5.07 (d, J=11.6 Hz, 1H), 4.31 (d, J=12 Hz, 1H), 4.00–4.05 (m, 4H), 2.24 (s, 3H), 1.06 (t, J=7.2 Hz, 3H), 1.00 (t, J=7.2 Hz, 3H) ppm.

4.2.16. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(2-chlorophenyl) propanoate ***3p***[13]. White solid; HPLC analysis (OD-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=11.163 min, t_r (minor)=16.864 min) gave the isomeric composition of the product: 62% ee, ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.25 (s, br s, 1H), 7.69–7.73 (m, 1H), 7.40–7.43 (m, 1H), 7.32–7.35 (m, 1H), 7.26–7.28 (m, 1H), 7.11–7.18 (m, 5H), 5.71 (d, J=12.0 Hz, 1H), 4.30 (d, J=11.6 Hz, 1H), 3.96–4.07 (m, 4H), 0.95–1.07 (m, 6H) ppm.

4.2.17. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(4-fluoro-3-phenoxyphenyl) propanoate ***3q***[13]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor) =14.765 min, t_r (major)=19.311 min) gave the isomeric composition of the product: 88% ee, mp 148–150 °C; $[\alpha]_D^{21}$ −49.60 (c 0.258, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.09 (s, br s, 1H), 7.48 (d, J=7.6 Hz, 1H), 7.28–7.33 (m, 3H), 7.04–7.20 (m, 7H), 6.89–6.92 (m, 2H), 5.05 (d, J=11.6 Hz, 1H), 4.22 (d, J=12.0 Hz, 1H), 4.00–4.09 (m, 4H), 1.12 (t, J=7.2 Hz, 3H), 1.01 (t, J=7.2 Hz, 3H) ppm.

4.2.18. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(3,4-dichlorophenyl) propanoate ***3r***[13]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 95:5, 1.0 mL/min, 254 nm; t_r (minor)=17.102 min, t_r (major)=19.594 min) gave the isomeric composition of the product: 83% ee, mp 107–108 °C; $[\alpha]_D^{26}$ −42.79 (c 0.208, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.21 (s, br s, 1H), 7.47–7.52 (m, 2H), 7.28–7.35 (m 2H), 7.17–7.26 (m, 3H), 7.07–7.11 (m, 1H), 5.08 (d, J=11.6 Hz, 1H), 4.27 (dd, J=1.6, 11.6 Hz, 1H), 4.02–4.11 (m, 4H), 1.12 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H) ppm.

4.2.19. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(2-naphthly) propanoate ***3s***[13]. White solid; HPLC analysis (Chiralcel AD-H, hexane/2-propanol 80:20, 1.0 mL/min, 254 nm; t_r (minor)=34.252 min, t_r (major)=36.852 min) gave the isomeric composition of the product: 80% ee, mp 173–174 °C; $[\alpha]_D^{24}$ −38.4 (c 0.320, CH_2Cl_2); ^{1}H

NMR (400 MHz, $CDCl_3$): δ=8.08 (s, br s, 1H), 7.88 (d, J=0.8 Hz, 1H), 7.80–7.81 (m, 1H), 7.75–7.77 (m, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.40–7.50 (m, 3H), 7.31 (d, J=8.0 Hz, 1H), 7.25 (d, J=2.4 Hz, 1H), 7.12–7.16 (m, 1H), 7.01–7.05 (m, 1H), 5.29 (d, J=11.6 Hz, 1H), 4.44 (d, J=11.6 Hz, 1H), 4.04 (q, J=7.2 Hz, 2H), 3.92–4.00 (m, 2H), 1.03(t, J=7.2 Hz, 3H), 0.94 (t, J=7.2 Hz, 3H) ppm.

4.2.20. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(2-thienyl) propanoate ***3t***. White solid; HPLC analysis (AS-H column, hexane/2-propanol 85:15, 1.0 mL/min, 254 nm; t_r (minor)=9.096 min, t_r (major)=12.284 min) gave the isomeric composition of the product: 71% ee, mp 88–90 °C; $[\alpha]_D^{29}$ −52.34 (*c* 0.214, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (s, br s, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.31 (d, J=8.0 Hz, 1H), 7.14–7.18 (m, 2H), 7.06–7.10 (m, 2H), 7.00 (d, J=3.6 Hz, 1H), 6.86 (dd, J=1.6, 3.6 Hz, 1H), 5.39 (d, J=11.2 Hz, 1H), 4.32 (dd, J=0.8, 10.4 Hz, 1H), 4.11 (q, J=7.2 Hz, 2H), 3.94 (q, J=7.2 Hz, 2H), 1.14 (t, J=7.2 Hz, 3H), 0.92 (t, J=7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.90, 167.64, 145.87, 136.26, 126.53, 125.18, 124.38, 122.44, 121.71, 119.76, 119.51, 116.63, 111.23, 61.77, 61.60, 59.46, 38.09, 14.02, 13.75 ppm; ES-HRMS calcd for [$C_{20}H_{21}NO_4S$+Na^+] 394.1083, found: 394.1084.

4.2.21. Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(cyclohexyl) propanoate ***3u***. White solid; HPLC analysis (AS-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=6.961 min, t_r (minor)=16.491 min) gave the isomeric composition of the product: 43% ee, ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.17 (s, br s, 1H), 7.69 (d, J=7.6 Hz, 1H), 7.33 (d, J=8.0 Hz, 1H), 7.10–7.20 (m, 2H), 7.02 (s, 1H), 4.23(t, J=7.2 Hz, 1H), 4.04 (d, J=11.2 Hz, 1H), 3.79–3.85 (m, 3H), 1.54–1.79 (m, 7H), 1.13–1.30 (m, 5H), 0.90–1.04 (m, 3H), 0.77 (t, J=7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.09, 168.44, 135.62, 128.54, 122.82, 121.70, 119.78, 119.22, 113.94, 110.82, 61.38, 60.95, 55.93, 41.89, 40.99, 32.28, 28.50, 26.60, 26.35, 26.21, 14.09, 13.45 ppm; ES-HRMS calcd for [$C_{22}H_{29}NO4_6$+Na^+] 394.1989, found: 394.2012.

4.2.22. Ethyl 2-ethoxycarbonyl-3-[3-(7-methylindolyl)]-3-phenyl propanoate ***3ab***[4c]. White solid; HPLC analysis (Chiralcel OD-H, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=9.897 min, t_r (minor)=11.959 min) gave the isomeric composition of the product: 85% ee, mp 91–93 °C; $[\alpha]_D^{22}$ −74.1 (*c* 0.348, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.93 (s, br s, 1H), 7.34–7.40 (m, 3H), 7.19–7.24 (m, 3H), 7.10–7.14 (m, 1H), 6.92–6.97 (m, 2H), 5.06 (d, J=11.6 Hz, 1H), 4.29 (d, J=11.6 Hz, 1H), 3.94–4.04 (m, 4H), 2.43 (s, 3H), 0.98–1.04 (m, 6H) ppm; ES-HRMS calcd for [$C_{23}H_{25}NO_4$+Na^+] 402.1676, found: 402.1683.

4.2.23. Ethyl 2-ethoxycarbonyl-3-[3-(4-methoxyindolyl)]-3-phenyl propanoate ***3ac***[4b]. White solid; HPLC analysis (Chiralcel OD-H, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=21.703 min, t_r (minor)=25.372 min) gave the isomeric composition of the product: 81% ee, mp 106–108 °C; $[\alpha]_D^{23}$ −50 (*c* 0.226, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.01 (s, br s, 1H), 7.36 (d, J=7.2 Hz, 2H), 7.22 (t, J=7.2 Hz, 2H), 7.11–7.13 (m, 2H), 7.04 (t, J=8.0 Hz, 1H), 6.90 (d, J=8.0 Hz, 1H), 6.43 (d, J=8.0, Hz, 1H), 5.52 (d, J=12.4 Hz, 1H), 4.30 (d, J=12 Hz, 1H), 3.95–4.07 (m, 4H), 3.87 (s, 3H), 0.99–1.03 (m, 6H) ppm; ES-HRMS calcd for [$C_{23}H_{25}NO_5$+Na^+] 418.1625, found: 418.1572.

4.2.24. (R)-Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-phenyl propanoate ***3ad***[13]. White solid; HPLC analysis (Chiralcel OD-H, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=13.173 min, t_r (minor)=16.208 min) gave the isomeric composition of the product: 92% ee, mp 120–122 °C; $[\alpha]_D^{22}$ −11.60 (*c* 0.328, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.97 (s, br s, 1H), 7.37–7.40 (m, 2H), 7.24–7.28 (m, 2H), 7.15–7.20 (m, 3H), 6.99 (d, J=2.4 Hz, 1H), 6.81 (dd, J=2.4, 6.4 Hz, 1H), 5.05 (d, J=11.6 Hz, 1H), 4.29 (d, J=12.0 Hz, 1H), 3.98–4.07 (m, 4H), 3.80 (s, 3H), 1.03 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H) ppm; ES-HRMS calcd for [$C_{23}H_{25}NO_5$+Na]$^+$ 418.1625, found: 418.1635.

4.2.25. Ethyl 2-ethoxycarbonyl-3-[3-(6-methoxyindolyl)]-3-phenyl propanoate ***3ae***. White solid; HPLC analysis (Chiralcel OD-H, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=17.037 min, t_r (minor)=21.476 min) gave the isomeric composition of the product: 80% ee, mp 126–128 °C; $[\alpha]_D^{23}$ −55.34 (*c* 0.206, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.96 (s, br s, 1H), 7.36–7.42 (m, 3H), 7.23–7.28 (m, 2H), 7.14–7.18 (m, 1H), 7.06 (d, J=2.4 Hz, 1H), 6.79 (d, J=2.0 Hz, 1H), 6.72 (dd, J=2.4, 6.4 Hz, 1H), 5.05 (d, J=12 Hz, 1H), 4.28 (d, J=12 Hz, 1H), 4.04 (q, J=7.2 Hz, 2H), 4.00 (q, J=7.2 Hz, 2H), 3.81 (s, 3H), 1.04 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.06, 167.86, 156.61, 141.43, 136.99, 128.32, 128.17, 126.73, 121.15, 119.98, 119.61, 117.03, 109.47, 94.51, 61.46, 61.38, 58.40, 55.60, 42.95, 13.78 ppm; ES-HRMS calcd for [$C_{23}H_{25}NO_5$+Na^+] 418.1625, found: 418.1621.

4.2.26. Ethyl 2-ethoxycarbonyl-3-[3-(5-bromoindolyl)]-3-phenyl propanoate ***3af***[13]. White solid; HPLC analysis (Chiralcel OD-H, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=10.460 min, t_r (minor)=12.545 min) gave the isomeric composition of the product: 84% ee, mp 154–156 °C; $[\alpha]_D^{25}$ +4.72 (*c* 0.212, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.13 (s, br s, 1H), 7.68 (d, J=2.0 Hz, 1H), 7.33–7.36 (m, 2H), 7.14–7.27 (m, 6H), 5.00 (d, J=11.6 Hz, 1H), 4.25 (d, J=12.0 Hz, 1H), 3.95–4.04 (m, 4H), 1.02 (t, J=7.2 Hz, 3H), 1.01 (t, J=7.2 Hz, 3H) ppm.

4.2.27. Ethyl 2-ethoxycarbonyl-3-[3-(5-bromoindolyl)]-3-(m-bromophenyl) propanoate ***3jf***[13]. White solid; HPLC analysis (Chiralcel OD-H, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=10.650 min, t_r (minor)=12.777 min) gave the isomeric composition of the product: 92% ee, mp 122–124 °C; $[\alpha]_D^{27}$ +32.59 (*c* 0.224, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.21 (s, br s, 1H), 7.68 (d, J=2.0 Hz, 1H), 7.48 (t, J=2.0 Hz, 1H), 7.33 (dd, J=2.0, 6.0 Hz, 2H), 7.26 (dd, J=2.0, 7.2 Hz, 1H), 7.17–7.21 (m, 2H), 7.14–7.16 (m, 1H), 5.00 (d, J=12.0 Hz, 1H), 4.23 (d, J=11.6 Hz, 1H), 4.00–4.08 (m, 4H), 1.09 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H) ppm.

4.2.28. Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-(p-phenylphenyl) propanoate ***3vd***[13]. White solid; HPLC analysis (AD-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=29.577 min, t_r (major)=36.887 min) gave the isomeric composition of the product: 86% ee, mp 146–147 °C; $[\alpha]_D^{25}$ +62.78 (*c* 0.266, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.00 (s, br s, 1H), 7.30–7.54 (m, 9H), 7.18–7.20 (m, 2H), 7.02 (d, J=2.4 Hz, 1H), 6.81 (dd, J=2.4, 6.4 Hz, 1H), 5.10 (d, J=12.0 Hz, 1H), 4.32 (d, J=11.6 Hz, 1H), 4.00–4.07 (m, 4H), 3.81 (s, 3H), 1.03 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H) ppm.

4.2.29. Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-(m-methylphenyl) propanoate ***3bd***[13]. White solid; HPLC analysis (OD-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=12.214 min, t_r (major)=14.926 min) gave the isomeric composition of the product: 92% ee, mp 60–62 °C; $[\alpha]_D^{25}$ +6.64 (*c* 0.226, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.98 (s, br s, 1H), 7.34 (s, 1H), 7.11–7.19 (m, 5H), 7.00 (d, J=2.0 Hz, 1H), 6.79 (dd, J=2.4, 6.4 Hz, 1H), 4.99 (d, J=12.0 Hz, 1H), 4.27 (d, J=12.0 Hz, 1H), 3.97–4.03 (m, 4H), 3.79 (s, 3H), 2.27 (s, 3H), 0.97–1.04 (m, 6H) ppm.

4.2.30. Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-(m-bromophenyl) propanoate ***3jd***[13]. White solid; HPLC analysis (OD-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r

(major)=12.806 min, t_r (minor)=16.073 min) gave the isomeric composition of the product: 92% ee, mp 91–92 °C; $[\alpha]_D^{27}$ +6.36 (*c* 0.472, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=8.02 (s, br s, 1H), 7.51 (t, *J*=1.6 Hz, 1H), 7.09–7.32 (m, 5H), 6.94 (d, *J*=2.4 Hz, 1H), 6.81 (dd, *J*=2.4, 6.4 Hz, 1H), 5.00 (d, *J*=11.6 Hz, 1H), 4.23 (d, *J*=11.6 Hz, 1H), 4.00–4.05 (m, 4H), 3.80 (s, 3H), 1.06 (t, *J*=7.2 Hz, 3H), 1.00 (t, *J*=7.2 Hz, 3H) ppm.

4.2.31. Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-(m-chlorophenyl) propanoate ***3hd***[13]. White solid; HPLC analysis (OD-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=14.123 min, t_r (major)=18.111 min) gave the isomeric composition of the product: 88% ee, mp 72–74 °C; $[\alpha]_D^{25}$ −1.55 (*c* 0.194, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=8.00 (s, br s, 1H), 7.34 (s, 1H), 7.11–7.27 (m, 5H), 6.93 (d, *J*=2.0 Hz, 1H), 6.80 (dd, *J*=2.4, 6.4 Hz, 1H), 5.00 (d, *J*=11.6 Hz, 1H), 4.22 (d, *J*=12.0 Hz, 1H), 4.02 (q, *J*=7.2 Hz, 2H), 4.01 (q, *J*=7.2 Hz, 2H), 3.79 (s, 3H), 1.05 (t, *J*=7.2 Hz, 3H), 1.00 (t, *J*=7.2 Hz, 3H) ppm.

4.2.32. Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-(4-fluoro-3-phenoxyphenyl) propanoate ***3qd***[13]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (minor)=16.500 min, t_r (major)=22.334 min) gave the isomeric composition of the product: 92% ee, mp 92–94 °C; $[\alpha]_D^{25}$ −10.39 (*c* 0.520, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.97 (s, br s, 1H), 7.02–7.29 (m, 9H), 6.88 (d, *J*=8.0 Hz, 3H), 6.80 (dd, *J*=2.4, 6.4 Hz, 1H), 4.96 (d, *J*=12 Hz, 1H), 4.16 (d, *J*=11.6 Hz, 1H), 4.03 (d, *J*=7.2 Hz, 2H), 4.00 (d, *J*=7.2 Hz, 2H), 3.76 (m, 1H), 1.09 (t, *J*=7.2 Hz, 3H), 0.99 (t, *J*=7.2 Hz 3H) ppm.

4.2.33. Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxy-indolyl)]-3-(m-phenoxylphenyl) propanoate ***3cd***[13]. White solid; HPLC analysis (OD-H column, hexane/2-propanol 90:10, 1.0 mL/min, 254 nm; t_r (major)=15.127 min, t_r (minor)=19.639 min) gave the isomeric composition of the product: 95% ee, mp 81–82 °C; $[\alpha]_D^{23}$ +13.3 (*c* 0.278, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.94 (s, br s, 1H), 7.26–7.31 (m, 2H), 7.17–7.22 (m, 2H), 7.05–7.13 (m, 4H), 6.90–6.95 (m, 3H), 6.78–6.82 (m, 2H), 5.00 (d, *J*=12.0 Hz, 1H), 4.23 (d, *J*=11.6 Hz, 1H), 4.04 (q, *J*=7.2 Hz, 2H), 4.00 (q, *J*=7.2 Hz, 2H), 3.78 (s, 3H), 1.08 (t, *J*=7.2 Hz, 3H), 0.99 (t, *J*=7.2 Hz, 3H) ppm.

4.2.34. Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-(2-thienyl) propanoate ***3td***[13]. White solid; HPLC analysis (AS-H column, hexane/2-propanol 85:15, 1.0 mL/min, 254 nm; t_r (minor)=10.430 min, t_r (major)=13.032 min) gave the isomeric composition of the product: 80% ee, mp 54–56 °C; $[\alpha]_D^{25}$ −24.28 (*c* 0.486, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=8.05 (s, br s, 1H), 7.18 (d, *J*=8.8 Hz, 1H), 7.15 (d, *J*=2.4 Hz, 1H), 7.10 (dd, *J*=1.2, 4.0 Hz, 1H), 7.03 (d, *J*=2.4 Hz, 1H), 6.99 (d, *J*=3.2 Hz, 1H), 6.86 (dd, *J*=1.6, 3.6 Hz, 1H), 6.81 (dd, *J*=2.4, 6.4 Hz, 1H), 5.34 (d, *J*=11.6 Hz, 1H), 4.28 (d, *J*=11.2 Hz, 1H), 4.11 (q, *J*=7.2 Hz, 2H), 3.96 (q, *J*=7.2 Hz, 2H), 3.81 (s, 3H), 1.14 (t, *J*=7.2 Hz, 3H), 0.93 (t, *J*=7.2 Hz, 3H) ppm.

4.2.35. Ethyl 2-ethoxycarbonyl-3-[3-(5-methoxyindolyl)]-3-(m-nitrophenyl) propanoate ***3fd***. Yellow solid; HPLC analysis (AS-H column, hexane/2-propanol 80:20, 1.0 mL/min, 254 nm; t_r (minor)=10.707 min, t_r (major)=12.550 min) gave the isomeric composition of the product: 84% ee, mp 118–119 °C; $[\alpha]_D^{26}$ +2.27 (*c* 0.220, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=8.24 (s, br s, 1H), 8.13 (s, 1H), 8.03 (dd, *J*=1.2, 6.8 Hz, 1H), 7.74 (d, *J*=7.6 Hz, 1H), 7.42 (t, *J*=8.0 Hz, 1H), 7.21 (t, *J*=2.4 Hz, 2H), 6.91 (d, *J*=2.4 Hz. 1H), 6.82 (dd, *J*=2.0, 6.4 Hz, 1H), 5.15 (d, *J*=11.6 Hz, 1H), 4.30 (d, *J*=11.6 Hz, 1H), 4.00–4.07 (m, 4H), 3.79 (s, 3H), 1.06 (t, *J*=7.2 Hz, 3H), 1.02 (t, *J*=7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.47, 154.18, 148.27, 143.83, 134.69, 131.37, 129.28, 126.71, 122.99, 121.95, 121.92, 115.20, 112.76, 112.00, 100.75, 61.79, 57.80, 55.87, 42.28, 13.85, 13.77 ppm; ES-HRMS calcd for [$C_{23}H_{24}N_2O_7-H^+$] 439.1511, found: 439.1497.

4.3. Data for alkylation derivatives

4.3.1. Ethyl-3-(1H-indol-3-yl)-3-phenylpropanoate ***4***[13]. To a suspension of NaCl (787 mg, 13.11 mmol) and **3a** (2.396 g, 6.56 mmol, >99% ee after recrystallization) in anhydrous DMSO (40 mL) was added H_2O (525 μL). The resulting mixture was refluxed for 26 h and then stirred at 80 °C for 12 h. After cooling to room temperature, to the reaction solution was added 100 mL of distilled water and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with saturated solution of NaCl, dried with anhydrous $MgSO_4$, filtered through cotton and concentrated under vacuo. The monoester **4** was obtained after purification by flash chromatography (CH_2Cl_2/petroleum ether, 1:1) as white solid (1.26 g, 66% yield); $[\alpha]_D^{26}$ −53.45 (*c* 0.290, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=7.99 (s, br s, 1H), 7.42 (d, *J*=7.6 Hz, 1H), 7.24–7.34 (m, 5H), 7.13–7.19 (m, 2H), 7.00–7.06 (m, 2H), 4.80 (t, *J*=7.6 Hz, 1H), 4.04 (q, *J*=7.6 Hz, 1H), 4.03 (q, *J*=7.6 Hz, 1H), 3.15 (dd, *J*=7.6, 15.2 Hz, 1H), 3.01 (dd, *J*=8.0, 15.2 Hz, 1H), 1.11 (t, *J*=7.2 Hz, 3H) ppm.

4.3.2. 3-(1H-indol-3-yl)-3-phenylpropionic acid ***5***[13]. To a solution of ethyl-3-(1*H*-indol-3-yl)-3-phenylpropanoate (548.6 mg, 1.87 mmol) in 19 mL of mixed solvent of THF and ethanol (1/1, v/v) was added a solution of 2 N NaOH (2.8 mL) and H_2O (3.7 mL). The resulting solution was refluxed for 3 h. After cooling to room temperature, to the reaction solution was added 0.5 N HCl till pH=1 and extracted with ethyl acetate (3×30 mL). The combined extracts were dried over anhydrous Na_2SO_4. After removal of solvent, the crude product **5** was obtained as a pale yellow solid (480 mg, 97%); $[\alpha]_D^{27}$ −39.58 (*c* 0.720, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ=7.98 (s, br s, 1H), 7.56 (d, *J*=8.0 Hz, 1H), 7.24–7.41 (m, 4H), 7.10–7.20 (m, 3H), 6.97–7.06 (m, 2H), 4.80 (t, *J*=8.0 Hz, 1H), 3.18 (dd, *J*=8.0, 15.2 Hz, 1H), 3.05 (dd, *J*=7.6, 15.6 Hz, 1H) ppm.

4.3.3. 2-(1H-indol-3-yl)-2-phenylethanamine ***6***[13]. To a suspension of **5** (264 mg, 1 mmol) in dry toluene was added Et_3N (153 μL, 1.1 mmol) and diphenylphosphoryl azide (DPPA) (237 μL, 1.1 mmol). The reaction mixture was stirred at 110 °C for 4 h under nitrogen atmosphere, then *tert*-butyl alcohol (141 μL, 1.5 mmol) was added and the heating was continued for 32 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (20 mL), and the solution was washed with 5% citric acid, brine and saturated K_2CO_3 solution, dried over $MgSO_4$. The organic phase was filtered and evaporated affording the *tert*-butyl 2-(1*H*-indol-3-yl)-2-phenylethylcarbamate as white solid. The crude product was dissolved in CH_2Cl_2 (10 mL), and TFA (1.0 mL) was added into the solution. Then the reaction mixture was stirred at room temperature for 12 h and concentrated in vacuo. After the addition of H_2O, the solution was added 2 N NaOH till pH=11–12 and extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with brine and dried over $MgSO_4$. After removal of solvent, the crude product **6** was obtained as pale yellow solid (61 mg, 28% yield); The crude product was used in the next steps without further purification. ^1H NMR (400 MHz, DMSO): δ=10.94 (s, br s, 1H), 7.13–7.37 (m, 9H), 7.02 (t, *J*=7.6 Hz, 1H), 6.88 (t, *J*=7.6 Hz, 1H), 4.20 (s, br s, 1H), 3.35 (s, br s, 3H) ppm.

4.3.4. 1,4-Diphenyl-1,2,3,4-tetrahydro-β-carboline ***7***[13]. To a stirred solution of crude product **6** (47 mg, 0.199 mmol) in dry CH_3CN (3 mL), were sequentially added TFA (30 μL, 0.398 mmol) and benzaldehyde (21 μL, 0.211 mmol). The resulting solution was refluxed for 32 h. After cooling to room temperature, the mixture was quenched by addition of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with

brine, dried over Na_2CO_3, filtered and concentrated giving crude product as a mixture of diastereoisomers. The crude product was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give the product in 68% yield and with *anti*/*syn*=92/8. The ee of the major diastreoisomer isolated by chromatography was determined on the corresponding sulfonamide derivative. $[\alpha]_D^{23}$ +59.3 (*c* 0.440, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=7.63 (s, br s, 1H), 7.17–7.44 (m, 11H), 7.08–7.12 (m, 1H), 6.84–6.93 (m, 2H), 5.32 (t, *J*=2.0 Hz, 1H), 4.41 (m, 1H), 3.58 (dd, *J*=5.2, 12.4 Hz, 1H), 3.07 (dd, *J*=8.8, 12.8 Hz, 1H), 1.96 (s, br s, 1H).

4.3.5. 1,4-Diphenyl-2-(p-tolylsulfonyl)-1,2,3,4-tetrahydro-β-carboline ***8***[10b]. To a stirred solution of 1,4-diphenyl-1,2,3,4-tetrahydro-β-carboline (36 mg, 0.111 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (23 μL, 0.166 mmol) and TsCl (32 mg, 0.166 mmol). The reaction mixture was then stirred for 17 h at room temperature, then directly purified by chromatography on silica gel (CH_2Cl_2/petroleum ether, 3:1) to give the title product in 84% yield with 99% ee as a white solid. The ee of the product was determined by chiral HPLC analysis on a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=70:30), Flow rate=1.0 mL/min, UV=254 nm, t_r (major)=8.949 min, t_r (minor)-=25.548 min. $[\alpha]_D^{27}$ −88.6 (*c* 0.720, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=7.73 (s, br s, 1H), 6.95–7.31 (m, 16H), 6.87 (d, *J*=8.4 Hz, 2H), 6.25 (s, 1H), 4.38 (d, *J*=2.0 Hz, 1H), 3.93 (ddd, *J*=1.6, 4.4, 13.2 Hz, 2H), 2.27 (s, 3H) ppm.

4.3.6. 3-(1H-indol-3-yl)-3-phenylpropan-1-ol ***9***[13]. To a stirred solution of $LiAlH_4$ (409 mg, 10.76 mmol) in THF (25 mL) was added the Ethyl-3-(1*H*-indol-3-yl)-3-phenylpropanoate (789 mg, 2.69 mmol in 15 mL THF) dropwise at 0 °C. In order to neutralize the residual hydride, after 18 h of stirring at 0 °C to room temperature, the reaction mixture was quenched by addition of H_2O (0.4 mL), NaOH (0.4 mL, 2 N) and H_2O (1.2 mL) orderly. The resulting suspension was filtered through a short pad of Celite, The pad washed several times with Et_2O. After drying ($MgSO_4$) of the combined organic fractions and filtration, the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give the title product **9** quantitatively. $[\alpha]_D^{27}$ −25.0 (*c* 0.364, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=8.05 (s, br s, 1H), 7.49 (d, *J*=8.0 Hz, 1H), 7.28–7.37 (m, 5H), 7.16–7.23 (m, 2H), 7.03–7.07 (m, 2H), 4.42 (t, *J*=8.0 Hz, 1H), 3.66–3.75 (m, 2H), 2.46–2.54 (m, 1H), 2.27–2.35 (m, 1H), 1.52 (s, br s, 1H). ppm.

4.3.7. 3-(1H-indol-3-yl)-3-phenylpropyl 4-methylbenzenesulfonate ***10***[13]. To a stirred solution of **9** (130.9 mg, 0.521 mmol) in CH_2Cl_2 (10 mL) was added pyridine (122 μL, 1.51 mmol) and TsCl (100 mg, 0.525 mmol) at 0 °C. The reaction mixture was then stirred at 50 °C for 23 h, then directly purified by chromatography on silica gel (CH_2Cl_2/petroleum ether, 2:1) to give the desired product **10** in 72% yield as a white solid. $[\alpha]_D^{27}$ −33.3 (*c* 0.720, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.97 (s, br s, 1H), 7.21 (d, *J*=8.4 Hz, 2H), 7.33 (t, *J*=7.6 Hz, 2H), 7.12–7.26 (m, 8H), 6.97–7.01 (m, 2H), 4.29 (t, *J*=7.6 Hz, 1H), 3.97–4.27 (m, 2H), 2.51–2.58 (m, 1H), 2.42 (s, 3H), 2.30–2.37 (m, 1H) ppm.

4.3.8. 3-(3-azido-1-phenylpropyl)-1H-indole ***11***[13]. Sodium azide (67 mg, 1.03 mmol) was added to a solution of the 3-(1*H*-indol-3-yl)-3-phenylpropyl 4-methylbenzenesulfonate **10** (207 mg, 0.511 mmol) in DMF (4 mL) at room temperature. The resulting mixture was warmed to 50 °C and maintained at that temperature for 10 h. The solution was then cooled, poured into water and extracted with ether (4×15 mL). The combined organic phases were washed successively with satd NaCl and water, dried over Na_2SO_4, and then concentrated. The crude product was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2, 2:1) to give the product as colourless thick oil in 98.6% yield. $[\alpha]_D^{28}$ −42.5 (*c* 1.12, CH_2Cl_2); ^1H NMR (400 MHz, DMSO): δ=10.95 (s, br s, 1H), 7.41 (d, *J*=8.0 Hz, 1H), 7.34–7.36 (m, 4H), 7.24–7.28 (m, 2H), 7.14 (t, *J*=7.6 Hz 1H), 7.02–7.06 (m, 1H), 6.88–6.92 (m, 1H), 4.28 (t, *J*=8.0 Hz, 1H), 3.24–3.31 (m, 2H), 2.38–2.47 (m, 1H), 2.20–2.30 (m, 1H) ppm.

4.3.9. 3-(1H-indol-3-yl)-3-phenylpropan-1-amine ***12***[13]. To a solution of 3-(3-azido-1-phenylpropyl)-1*H*-indole **11** (78 mg, 0.282 mmol) in MeOH (1 mL) was added activated Pd/C (10%, 10 mg) and the mixture was stirred under hydrogen atmosphere at room temperature for 41 h, and then filtered on a Celite pad. The pad was washed four times with CH_2Cl_2. After evaporation of the solvent, the crude product was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) in 64% yield as a white solid. $[\alpha]_D^{25}$ −20.63 (*c* 0.320, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=8.16 (s, br s, 1H), 7.43 (d, *J*=8.0 Hz, 1H), 7.22–7.32 (m, 3H), 6.98–7.17 (m, 6H), 4.26 (d, *J*=7.2 Hz, 1H), 2.76 (s, br s, 2H), 2.35 (s, br s, 1H), 2.18 (d, *J*=7.2 Hz, 1H), 1.80 (s, br, 2H) ppm.

4.3.10. β-carboline-like ***13***[13]. To a stirred solution of crude product **12** (40 mg, 0.163 mmol) in dry CH_3CN (2 mL), were sequentially added TFA (37 μL, 0.489 mmol) and benzaldehyde (26 μL, 0.261 mmol). The resulting solution was refluxed for three days. After cooling to room temperature, the mixture was quenched by addition of satd $NaHCO_3$ and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over Na_2CO_3, filtered and concentrated giving crude product as a mixture of diastereoisomers. The crude product was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give the product **7** in 44% yield; $[\alpha]_D^{29}$ +8.0 (*c* 0.100, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=7.76 (dd, *J*=7.6 Hz, 1H), 6.97–7.56 (m, 14H), 5.37 (s, 1H), 4.78 (t, *J*=4.4 Hz, 1H), 3.22 (dt, *J*=4.4, 14.4 Hz, 1H), 3.03–3.09 (m, 1H), 2.45–2.48 (m, 2H), 1.79(s, br s, 1H).

Acknowledgements

We appreciate the National Natural Science Foundation of China (No. 20732003), PCSIRT (No. IRT0 846) and the State Basic Research and Development Program (No.2010CB833302) for financial support. We also thank Sichuan University Analytical & Testing Centre for NMR analysis.

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