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Catalytic and asymmetric Friedel–Crafts alkylation of indoles with nitroacrylates. Application to the synthesis of tryptophan analogues

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Abstract—An asymmetric Friedel–Crafts alkylation of indoles with nitroacrylates catalyzed by chiral (4*R*,5*S*)-DiPh-BOX (**L1**)–$Cu(OTf)_2$ complex (10 mol %) has been developed. The reactions provide tryptophan nitro-precursors in moderate diastereoselectivities (*anti*/*syn* up to 72:28) and good to excellent enantioselectivities (up to 99% ee). The alkylation products could be easily reduced to optically active tryptophan analogues with Zn/H^+.

1. Introduction

Tryptophan as an essential amino acid with an indole moiety has received considerable attention because of its biological activities,[1] such as inhibition of indoleamine 2,3-dioxygenase (IDO)[2] and the growth of bacterium coli.[3] Tryptophan analogues are also important building blocks for synthesizing many bioactive compounds and natural products such as cyclomarines,[4] trypostatin A,[5] fumitremorgin C,[6] and many other alkaloids. Many synthetic methods to access substituted tryptophans have been developed, including resolution of racemic compounds,[7] asymmetric reduction of dehydrotryptophan,[8] Fischer-indole cyclization,[9] palladium-catalyzed heteroannulation,[10] and asymmetric ene reaction.[11] However, the demands for more convenient and efficient method to chiral tryptophan, in particular, multi-substituted tryptophan analogues still remain.

The Friedel–Crafts alkylation of aromatic C-nucleophile with electron-deficient olefins is not only an important carbon–carbon bond-forming reaction, but also able to provide versatile synthetic intermediate in organic synthesis.[12] Recently, the asymmetric Friedel–Crafts alkylation of indoles has attracted much attention.[13] The product of Friedel–Crafts alkylation of indoles with alkylidene malonate derivatives[14] could be employed in the synthesis of tryptophans, but it required multi-synthetic steps.[15] Meanwhile, the catalytic asymmetric reactions of indoles with β-nitrostyrenes[16] have been reported. Since nitro group can be easily converted to an amino group, it was suggested that nitroacrylate was an efficient Michael acceptor in the catalytic asymmetric Friedel–Crafts alkylation of indoles to directly afford a nitro-precursor of chiral tryptophans. Herein, we wish to report the first asymmetric Friedel–Crafts alkylation of indoles with nitroacrylates catalyzed by chiral (4*R*,5*S*)-DiPh-BOX (**L1**)–$Cu(OTf)_2$ complex. The alkylation products are transformed to tryptophan analogues via reduction.

2. Results and discussion

2.1. Catalytic asymmetric Friedel–Crafts alkylation of indoles with nitroacrylates

Initially, the chiral Lewis acid catalysts prepared from bisoxazoline-type ligands (**L1**–**L5**, Fig. 1) and metal salts were employed in the asymmetric catalytic Friedel–Crafts reaction of indole **1a** with nitroacrylate (*Z*)-**2a**. The results are summarized in Table 1. Although **L1**–$Yb(OTf)_3$ and **L1**–$Zn(OTf)_2$ could catalyze the reaction and afford the product ethyl 3-(1*H*-indol-3-yl)-2-nitro-3-*p*-tolylpropanoate **3aa** in good yield, the dr and ee values of **3aa** were negligible or moderate (entries 1 and 3). Among the bisoxazoline ligands employed in the reaction, (4*R*,5*S*)-DiPh-BOX (**L1**) was found to be the best one (entries 5–8). By using **L1**–$Cu(OTf)_2$ complex, it was found that indole **1a** reacted with nitroacrylate (*Z*)-**2a** in dichloromethane smoothly, giving a mixture of *anti*- and *syn*-**3aa** (*anti*/*syn*=72:28) in 85% yield with 94% ee of *anti*-**3aa** and 58% ee of *syn*-**3aa**

Keywords: Catalytic and asymmetric Friedel–Crafts alkylation; Chiral DiPhBOX–Cu(II) complex; Indole; Nitroacrylate; Tryptophan.
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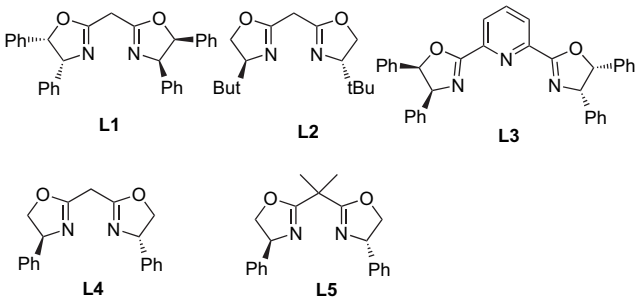
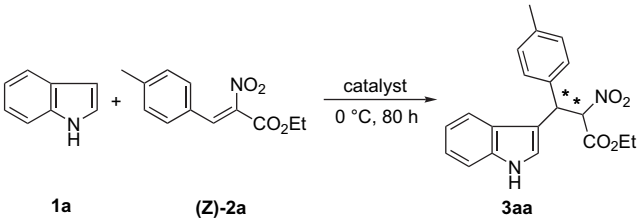


Figure 1.

Table 1. Catalytic asymmetric Friedel–Crafts reaction of **1a** with (*Z*)-**2a**[a]



Entry	Ligand	MX_n	Solvent	Yield[b] (%) (*anti*/*syn*)[c]	ee[d] (%) *anti*/*syn*-**3aa**
1	**L1**	$Yb(OTf)_3$	CH_2Cl_2	86 (46/54)	6/5
2	**L3**	$Yb(OTf)_3$	CH_2Cl_2	91 (41/59)	45/41
3	**L1**	$Zn(OTf)_2$	CH_2Cl_2	86 (46/54)	72/43
4	**L5**	$Zn(OTf)_2$	Toluene	75 (40/60)	6/61
5	**L1**	$Cu(OTf)_2$	CH_2Cl_2	85 (72/28)	94/58
6	**L2**	$Cu(OTf)_2$	CH_2Cl_2	28 (41/59)	6/1
7	**L3**	$Cu(OTf)_2$	CH_2Cl_2	<10 (n.d.)[e]	n.d.[e]
8	**L4**	$Cu(OTf)_2$	CH_2Cl_2	15 (45/55)	n.d.
9	**L1**	$Cu(OTf)_2$	Toluene	88 (70/30)	96/9
10	**L1**	$Cu(OTf)_2$	THF	Trace	n.d.[e]
11	**L1**	$Cu(OTf)_2$	*i*-PrOH	<10 (n.d.)[e]	n.d.[e]

[a] Reaction temperature: 0 °C for 80 h; MX_n/ligand/**1a**/(*Z*)-**2a**=0.1:0.11:1.2:1.0.
[b] Yield of isolated product.
[c] Determined by ^1H NMR of crude reaction mixture.
[d] Determined by chiral HPLC.
[e] Not determined.

(entry 5). *syn* or *anti* described the relative position of indole moiety with nitro group. The significant solvent effect was also observed. The reaction in toluene catalyzed by **L1**–$Cu(OTf)_2$ could give high yield and diastereoselectivity, but the ee value of *syn*-**3aa** was very poor (entry 9). The yields of the product **3aa** decreased when the reaction was carried out in THF or *i*-PrOH (Table 1, entries 10 and 11). It was noteworthy that **L5**–$Zn(OTf)_2$ complex was not suitable for the reaction of indole **1a** with nitroacrylate (*Z*)-**2a**, only giving moderate dr and ee (Table 1, entry 4), though, it was reported to be an excellent catalyst in the reaction of indoles with β-nitrostyrenes.[16c]

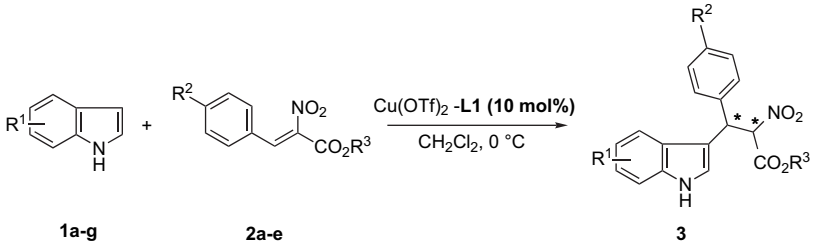
Based on the above experimental results, various indoles (**1a**–**g**) and nitroacrylates [(*Z*)-**2a**–**e**] were employed in the asymmetric Friedel–Crafts alkylation in CH_2Cl_2 catalyzed by chiral complex **L1**–$Cu(OTf)_2$ (10 mol %) (Scheme 1). As shown in Table 2, the indoles bearing the substituents, either electron-withdrawing or electron-donating group, at 5-position could react with *Z*-nitroacrylates smoothly to afford corresponding products (**3**) in good yields with excellent enantioselectivities of *anti*-isomers (82–99% ee), but moderate diastereoselectivities and enantioselectivities of *syn*-isomers in general. It was interesting to note that the reaction of 5-bromoindole **1e** with (*Z*)-3-(4′-chlorophenyl)-acrylate [(*Z*)-**2c**] afforded both *anti*- and *syn*-**3ec** with excellent enantioselectivities (99% and 95% ee) (Table 2, entry 11), while for 4-bromoindole **1f**, the enantioselectivities of the products, both *anti*- and *syn*-**3fc**, decreased noticeably (Table 2, entry 12). The use of nitroacrylate with bulky ester group [(*Z*)-**2e**] did not further improve the diastereoselectivity of the reaction at all (Table 2, entry 15). 2-Substituted indole, for example, 2-methylindole **1b**, was not a good substrate to achieve high stereoselectivities, though, the Friedel–Crafts alkylation proceeded smoothly (entry 5). Optical purities of the products were improved through recrystallization. For instance, *anti*-**3ab** with 99% ee was obtained through recrystallization of the same compound with 92% ee in a co-solvent of CH_2Cl_2 and *n*-hexane.

2.2. The synthesis of tryptophan analogues

There are several methods to transfer nitro group to amino group. The alkylation product *anti*-**3aa** (99% ee after recrystallization) can be easily transformed to the corresponding tryptophan analogue *anti*-**4aa** through hydrogenation of nitro group by Zn/H^+[17] and acylation in 61% yield without decrease of enantiomeric purity of the starting material (Scheme 2). According to the same procedure, *syn*-**3ec** (99% ee after recrystallization) was converted to the corresponding reduced product *syn*-**4ec** in 85% yield.

2.3. On stereochemistry of the reaction

The absolute configuration of the alkylation product *syn*-**3ec** was supported by X-ray crystallography data of its reduced product *syn*-**4ec**. The newly formed chiral centers were (2*S*,3*R*) (Fig. 2). To determine the absolute stereochemistry of *anti*-products, ethyl 3-(1*H*-indol-3-yl)-2-nitro-3-phenylpropionate (**3af**) was synthesized and *anti*-**3af** with 70% ee was treated with 2,2′-azobis(2-methylpropionitrile) (AIBN)



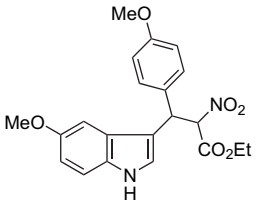
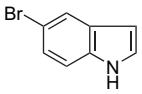
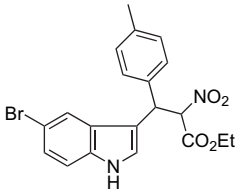
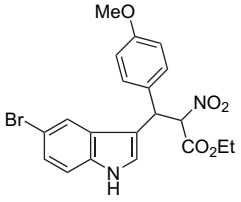
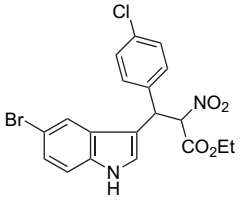
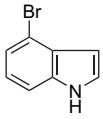
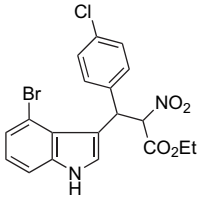
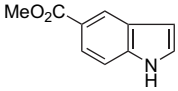
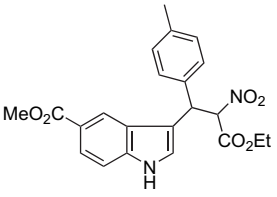
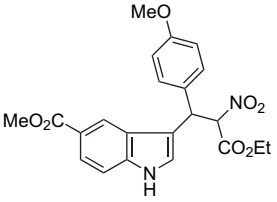
Scheme 1.

Table 2. Catalytic asymmetric reaction of **1a–g** with **2a–e**[a]

Entry	Indole	Nitroacrylate	Time (h)	Product	Yield[b] (%) (*anti*/*syn*)[c]	ee[d] (%) (*anti*/*syn*)
1	**1a**	(*Z*)-**2a**	80	**3aa**	85 (72:28)	94/58
2	**1a**	(*Z*)-**2b**	100	**3ab**	90 (62:38)	92/48
3	**1a**	(*Z*)-**2c**	70	**3ac**	70 (58:42)	96/53
4	**1a**	(*Z*)-**2d**	120	**3ad**	84 (65:35)	97/46
5	**1b**	(*Z*)-**2a**	60	**3ba**	80 (55:45)	69/47
6	**1c**	(*Z*)-**2a**	100	**3ca**	60 (45:55)	74/46
7	**1d**	(*Z*)-**2a**	70	**3da**	82 (62:38)	90/55

(*continued*)

Table 2. (*continued*)

Entry	Indole	Nitroacrylate	Time (h)	Product	Yield[b] (%) (*anti*/*syn*)[c]	ee[d] (%) (*anti*/*syn*)
8	**1d**	(*Z*)-**2b**	96	**3db** 	79 (55:45)	82/47
9	**1e** 	(*Z*)-**2a**	80	**3ea** 	78 (72:28)	98/41
10	**1e**	(*Z*)-**2b**	88	**3eb** 	81 (71:29)	85/54
11	**1e**	(*Z*)-**2c**	96	**3ec** 	78 (72:28)	99/95
12	**1f** 	(*Z*)-**2c**	100	**3fc** 	80 (n.d.)[e]	78/89
13	**1g** 	(*Z*)-**2a**	100	**3ga** 	85 (71:29)	96/44
14	**1g**	(*Z*)-**2b**	100	**3gb** 	80 (67:33)	93/40

(*continued*)

Table 2. (*continued*)

Entry	Indole	Nitroacrylate	Time (h)	Product	Yield[b] (%) (*anti*/*syn*)[c]	ee[d] (%) (*anti*/*syn*)
15	**1a**	(*Z*)-**2e**	130	**3ae**	15 (55:45)	n.d.[e]

[a] Reaction temperature: 0 °C; $Cu(OTf)_2$/**L1**/indoles/nitroacrylate=0.1:0.11:1.2:1.0; catalyst loading: 10 mol %.
[b] Isolated yield.
[c] Determined by ^1H NMR of crude reaction mixture.
[d] Determined by chiral HPLC.
[e] Not determined.

and Bu_3SnH in benzene, the known compound **5** was obtained in 67% yield (Scheme 3). On comparison of the optical rotation of **5** ($[\alpha]_D^{20}$ −26.0 (*c* 0.9, $CHCl_3$)) with that of known compound ($[\alpha]_D^{20}$ +25.5 (*c* 1.3, $CHCl_3$)),[14d] the configuration of C-3 of the product **5** was assigned to be (*R*), while the absolute configuration of *anti*-**3af** was assigned as (2*R*,3*R*) accordingly.

We observed that (*Z*)-**2a** was converted to (*E*)-**2a** partially during the course of the reaction, while the bisoxazoline-type ligand as a base promoted the conversion. For example, a solution of (*Z*)-**2a** in CH_2Cl_2 in the presence of 10 mol % **L1** was stirred at 0 °C for 96 h to generate a mixture of (*Z*)- and (*E*)-**2a** (62:38) (Scheme 4). Then, a mixture of (*Z*)- and (*E*)-**2a** (or **2b**) with different ratios was employed in the reaction with indoles (Table 3). Along with increasing the part of (*E*)-**2a** (or **2b**) in the mixture, the diastereoselectivity and enantioselectivity of the reaction dropped markedly (entry 1 vs entry 2, entry 3 vs entry 4), but the configuration of the major products remained unchanged.

The stereochemistry outcome can be explained by Figure 3. In general, a four-coordinated Cu(II) complex prefers a square planar geometry. However, when nitroacrylate coordinates with the complex of (4*R*,5*S*)-DiPh-BOX–Cu(II), a tetrahedral transition state is formed, driven by the stacking interaction of the two phenyl groups of the ligand and nitroacrylate, leading to *Si* face attack of the double bond of nitroacrylate. Another phenyl group may also play a role in the stereochemical control. Although the transition

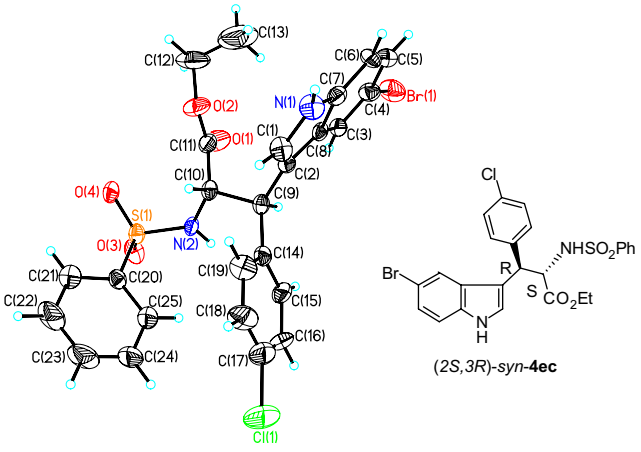
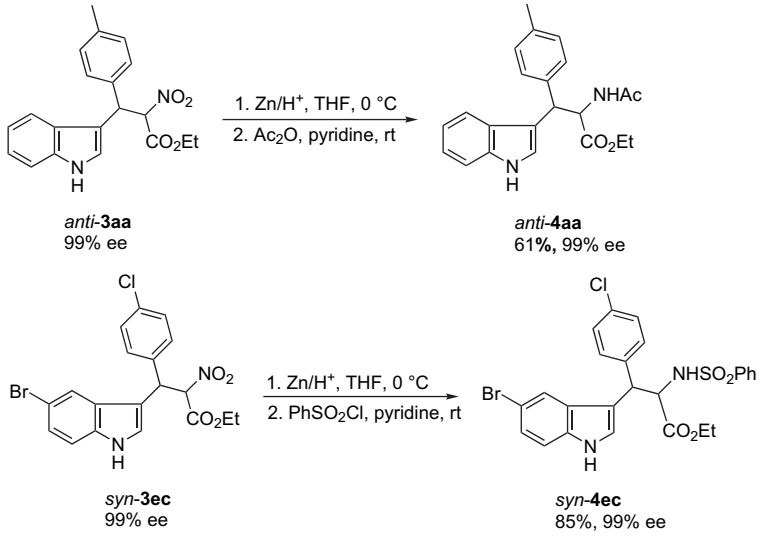
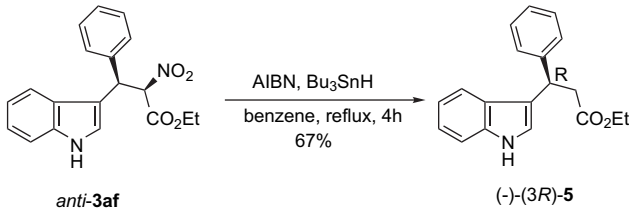


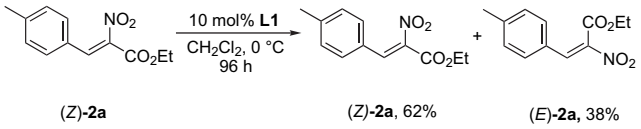
Figure 2. ORTEP of (2*S*,3*R*)-*syn*-**4ec**.



Scheme 2.



Scheme 3.



Scheme 4.

Table 3. Asymmetric reaction of indoles with a mixture of *Z*- and *E*-**2**[a]

Entry	Indole	Nitroacrylate (*Z*/*E*)[b]	Time (h)	Yield[c] (%) (*anti*/*syn*)[d]	ee[e] (%) (*anti*/*syn*)
1	**1a**	**2b** (100/0)	100	90 (62:38)	92/48
2	**1a**	**2b** (16/84)	100	87 (51:49)	76/29
3	**1e**	**2a** (100/0)	80	78 (72:28)	98/41
4	**1e**	**2a** (52/48)	80	79 (56:44)	50/40

[a] Reaction temperature: 0 °C; catalyst **L1**–$Cu(OTf)_2$ (10 mol %).
[b] Molar ratio.
[c] Isolated yield.
[d] Determined by ^1H NMR of crude reaction mixture.
[e] Determined by chiral HPLC.

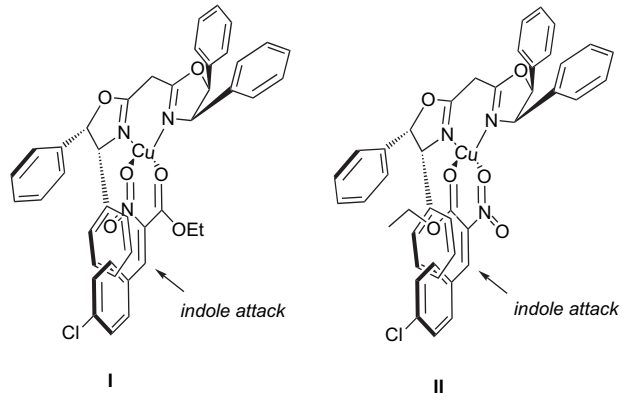


Figure 3. Transition state of the reaction.

states would adopt two coordination modes **I** and **II** (Fig. 3), which correspond to *Z*- and *E*-nitroacrylate, respectively, both modes **I** and **II** form the same configuration (3*R*) at 3-position of product **3**. It can be found from the investigations that the transition state **I** may be more favorable to high stereoselectivity.

3. Conclusion

An asymmetric Friedel–Crafts alkylation of indoles with nitroacrylates catalyzed by (4*R*,5*S*)-DiPh-BOX (**L1**)–$Cu(OTf)_2$ complex has been developed. The alkylation products were obtained in good yields with high enantioselectivities (up to 99% ee) of *anti*-isomers. The transformation from *Z*- to *E*-nitroacrylates during the reaction was observed. Subsequent reduction of the nitro group with Zn/H^+ afforded the optically active tryptophan analogues.

4. Experimental

4.1. General

IR spectra were recorded with a Perkin–Elmer 782 IR spectrometer. ^1H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ at room temperature with a Bruker DMX-300 (300 MHz) spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane (TMS). Mass spectra were recorded with a Bruker APEX-2 spectrometer. Elemental analyses were performed with a Carlo Erba 1102 Element Analysis instrument. Optical rotations were measured with a Perkin–Elmer 241 instrument (589 nm). HPLC analysis was performed with a Shimadzu CTO_10ASVP instrument equipped with the stated chiral columns. Melting points were measured with a Beijing-Taike X-4 apparatus and are uncorrected. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification.

4.2. Typical experimental procedure for the catalytic asymmetric Friedel–Crafts reaction of indoles and nitroacrylates

$Cu(OTf)_2$ (5.4 mg, 0.015 mmol) and ligand **L1** (7.6 mg, 0.0165 mmol) were charged in a dried 5 mL tube under argon, followed by addition of CH_2Cl_2 (0.9 mL). The solution was stirred at room temperature for 30 min and nitroacrylate **2a** (35 mg, 0.15 mmol) was added. The mixture was stirred for 10 min at room temperature, then for 15 min at 0 °C. Indole **1a** (21 mg, 0.18 mmol) was added. After stirring for indicated time, water (6 mL) was added, followed by extraction with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=4:1) to afford product **3aa** (45 mg, yield 85%).

4.2.1. Ethyl 3-(1*H*-indol-3-yl)-2-nitro-3-*p*-tolylpropanoate 3aa. The dr value (*anti*:*syn*=72:28) was determined by ^1H NMR signals at δ: 1.02 and 0.91. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=4:1); *anti*-**3aa**: a white solid, mp: 146–148 °C. $[\alpha]_D^{25}$ −58.2 (*c* 0.55, $CHCl_3$); ee value (99% after recrystallization) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=90:10, 0.5 mL/min, *T*=25 °C): t_R(major)=58.1 min and t_R(minor)=77.2 min. FTIR (KBr): ν 3420, 2924, 1745, 1561, 1358, 1097, 1013, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.48 (d, *J*=7.9 Hz, 1H), 7.32 (d, *J*=9.2 Hz, 1H), 7.28–7.22 (m, 2H), 7.18–7.13 (m, 2H), 7.09–7.03 (m, 3H), 5.89 (d, *J*=11.4 Hz, 1H), 5.34 (d, *J*=11.4 Hz, 1H), 4.07–4.01 (m, 2H), 2.27 (s, 3H), 1.02 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 137.5, 136.3, 134.4, 129.5, 128.4, 126.3, 122.7, 120.5, 119.9, 118.9, 114.0, 111.3, 91.8, 62.9, 44.2, 21.1, 13.6.

HRMS (FAB) *m/z* calcd for $C_{20}H_{20}N_2O_4$ (M^+): 352.1417, found: 352.1414; *syn*-**3aa**: a white solid, mp: 145–146 °C; ee value (58%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=90:10, 0.5 mL/min, T=25 °C): t_R(major)=46.3 min and t_R(minor)=77.7 min. FTIR (KBr): ν 3419, 2984, 1744, 1561, 1457, 1182, 1031, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (br s, 1H), 7.59 (d, J=7.9 Hz, 1H), 7.33–7.26 (m, 4H), 7.18–7.08 (m, 4H), 5.89 (d, J=11.6 Hz, 1H), 5.32 (d, J=11.6 Hz, 1H), 4.03–3.94 (m, 2H), 2.27 (s, 3H), 0.91 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 137.3, 136.0, 135.6, 129.5, 127.5, 126.2, 122.7, 121.7, 120.0, 119.0, 113.2, 111.6, 91.9, 62.9, 43.5, 21.0, 13.4. HRMS (EI) *m/z* calcd for $C_{20}H_{20}N_2O_4$ (M^+): 352.1423, found: 352.1425.

4.2.2. Ethyl 3-(1*H*-indol-3-yl)-3-(4-methoxyphenyl)-2-nitropropanoate 3ab. The dr value (*anti*/*syn*=62:38) was determined by ^1H NMR signals at δ: 1.03 and 0.92. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=4:1); *anti*-**3ab**: a white solid, mp: 172–174 °C. $[\alpha]_D^{25}$ −42.1 (*c* 0.57, $CHCl_3$); ee value (>99% after recrystallization) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(minor)=23.5 min and t_R(major)=28.3 min. FTIR (KBr): ν 3346, 3008, 1736, 1609, 1556, 1458, 1304, 1247, 1177, 1003, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.14 (br s, 1H), 7.44 (d, J=7.9 Hz, 1H), 7.34–7.16 (m, 6H), 6.81, 6.78 (dd, J=2.1, 6.7 Hz, 2H), 5.84 (d, J=11.4 Hz, 1H), 5.33 (d, J=11.4 Hz, 1H), 4.10–4.01 (m, 2H), 3.74 (s, 3H), 1.03 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 159.1, 136.3, 129.7, 129.3, 126.3, 122.7, 120.2, 119.9, 119.1, 114.4, 114.1, 111.2, 91.7, 62.9, 55.3, 43.8, 13.6. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 64.85; H, 5.49; N, 7.33; *syn*-**3ab**: a white solid, mp: 129–131 °C; ee value (48%) was determined by HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=20.3 min and t_R(minor)=25.7 min. FTIR (KBr): ν 3416, 2985, 1743, 1560, 1512, 1459, 1367, 1308, 1251, 1180, 1030, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.13 (br s, 1H), 7.57 (d, J=7.8 Hz, 1H), 7.32–7.28 (m, 3H), 7.18–7.09 (m, 3H), 6.80 (d, J=8.7 Hz, 2H), 5.86 (d, J=11.6 Hz, 1H), 5.31 (d, J=11.6 Hz, 1H), 4.02–3.94 (m, 2H), 3.73 (s, 3H), 0.92 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 158.9, 136.0, 130.6, 128.8, 126.2, 122.7, 121.6, 120.0, 119.0, 114.2, 113.3, 111.2, 92.1, 63.0, 55.2, 43.2, 13.4. HRMS (EI) *m/z* calcd for $C_{20}H_{20}N_2O_5$ (M^+): 368.1372, found: 368.1375.

4.2.3. Ethyl 3-(4-chlorophenyl)-3-(1*H*-indol-3-yl)-2-nitropropanoate 3ac. The dr value (*anti*/*syn*=58:42) was determined by ^1H NMR signals at δ: 1.05 and 0.93. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=3:1); *anti*-**3ac**: a white solid, mp: 77–79 °C; ee value (96%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=19.8 min and t_R(minor)=24.1 min. FTIR (KBr): ν 3421, 2986, 1745, 1563, 1490, 1372, 1308, 1098, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.41 (d, J=8.0 Hz, 1H), 7.34–7.22 (m, 6H), 7.20–7.15 (m, 1H), 7.08–7.03 (m, 1H), 5.86 (d, J=11.3 Hz, 1H), 5.36 (d, J=11.3 Hz, 1H), 4.11–4.02 (m, 2H), 1.05 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 135.2, 134.9, 132.6, 128.8, 127.8, 124.9, 121.8, 119.4, 119.0, 117.7, 112.4, 110.2, 90.2, 62.0, 42.7, 12.5. HRMS (EI): *m/z* calcd for $C_{19}H_{17}N_2O_4Cl$ (M^+): 372.0877, found: 372.0875; *syn*-**3ac**: a white solid, mp: 85–91 °C; ee value (53%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=14.6 min and t_R(minor)=22.3 min. FTIR (KBr): ν 3403, 1725, 1556, 1372, 1311, 1012, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (br s, 1H), 7.53 (d, J=7.9 Hz, 1H), 7.34–7.17 (m, 6H), 7.13–7.09 (m, 2H), 5.87 (d, J=11.5 Hz, 1H), 5.34 (d, J=11.5 Hz, 1H), 4.05–3.95 (m, 2H), 0.93 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 137.2, 136.1, 133.6, 129.1, 126.0, 122.9, 121.8, 120.2, 118.9, 112.6, 111.3, 91.6, 63.1, 43.3, 13.4. HRMS (EI): *m/z* calcd for $C_{19}H_{17}N_2O_4Cl$ (M^+): 372.0877, found: 372.0881.

4.2.4. Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-3-(1*H*-indol-3-yl)-2-nitropropanoate 3ad. The dr value (*anti*/*syn*=65:35) was determined by ^1H NMR signals at δ: 1.02 and 0.95. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=3:1); *anti*-**3ad**: a white solid, mp: 109–111 °C. $[\alpha]_D^{25}$ −51.7 (*c* 1.08, $CHCl_3$); ee value (97%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(minor)=19.6 min and t_R(major)=26.9 min. FTIR (KBr): ν 3418, 2986, 1742, 1562, 1493, 1449, 1246, 1037, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.56 (d, J=7.7 Hz, 1H), 7.38 (d, J=8.9 Hz, 1H), 7.19–7.14 (m, 2H), 7.08–7.03 (m, 1H), 6.88–6.83 (m, 1H), 6.77 (d, J=1.6 Hz, 1H), 6.70 (d, J=8.0 Hz, 1H), 5.89, 5.86 (dd, J=1.0, 9.3 Hz, 2H), 5.81 (d, J=11.3 Hz, 1H), 5.29 (d, J=11.3 Hz, 1H), 4.13–4.03 (m, 2H), 1.02 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 147.9, 147.2, 136.3, 131.1, 126.2, 122.8, 122.0, 120.2, 119.7, 119.0, 114.1, 111.3, 108.9, 108.3, 101.2, 91.7, 62.9, 44.2, 13.7. HRMS (EI): *m/z* calcd for $C_{20}H_{18}N_2O_6$ (M^+): 382.1165, found: 382.1162; *syn*-**3ad**: a colorless solid, mp: 170–172 °C; ee value (46%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=19.5 min and t_R(minor)=23.5 min. FTIR (KBr): ν 3420, 1742, 1560, 1496, 1366, 1242, 1036, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.57 (d, J=7.9 Hz, 1H), 7.32 (d, J=8.1 Hz, 1H), 7.21–7.08 (m, 3H), 6.89–6.82 (m, 2H), 6.71 (d, J=8.0 Hz, 1H), 5.90 (d, J=1.4 Hz, 2H), 5.82 (d, J=11.6 Hz, 1H), 5.27 (d, J=11.6 Hz, 1H), 4.04–3.97 (m, 2H), 0.95 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 148.0, 147.1, 136.1, 132.3, 126.2, 122.9, 121.4, 121.1, 120.1, 119.1, 113.3, 111.2, 108.5, 101.2, 92.1, 63.0, 43.7, 13.4. HRMS (EI): *m/z* calcd for $C_{20}H_{18}N_2O_6$ (M^+): 382.1165, found: 382.1168.

4.2.5. Ethyl 3-(2-methyl-1*H*-indol-3-yl)-2-nitro-3-*p*-tolylpropanoate 3ba. The dr value (*anti*/*syn*=55:45) was determined by ^1H NMR signals at δ: 1.11 and 0.69. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=5:1); *anti*-**3ba**: a yellow oil. $[\alpha]_D^{25}$ +8.4 (*c* 0.48, $CHCl_3$); ee value (69%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(minor)=11.8 min and t_R(major)=13.9 min. FTIR (neat): ν 3409, 2923, 1747, 1562, 1459, 1303, 1183, 1016,

740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (br s, 1H), 7.67–7.64 (m, 1H), 7.29–7.19 (m, 3H), 7.10–7.05 (m, 4H), 6.29 (d, J=12.0 Hz, 1H), 5.24 (d, J=12.0 Hz, 1H), 4.17–4.09 (m, 2H), 2.45 (s, 3H), 2.25 (s, 3H), 1.11 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 137.0, 135.3, 135.2, 133.0, 129.4, 127.8, 126.5, 121.2, 119.9, 118.6, 110.8, 108.5, 90.3, 63.0, 44.2, 21.0, 13.6, 12.1. HRMS (FAB) m/z calcd for $C_{21}H_{22}N_2O_4$ (M^+): 366.1580, found: 366.1571; *syn*-**3ba**: a yellow oil. $[\alpha]_D^{25}$ +58.1 (c 0.59, $CHCl_3$); ee value (47%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(minor)=12.0 min and t_R(major)=26.2 min. FTIR (neat): ν 3407, 2923, 1745, 1561, 1460, 1311, 1183, 1019, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (br s, 1H), 7.56–7.53 (m, 1H), 7.24 (d, J=8.1 Hz, 2H), 7.18–7.15 (m, 1H), 7.08–7.04 (m, 4H), 6.27 (d, J=11.9 Hz, 1H), 5.31 (d, J=11.9 Hz, 1H), 3.86–3.79 (m, 2H), 2.37 (s, 3H), 2.23 (s, 3H), 0.69 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 136.9, 135.9, 135.2, 132.9, 129.6, 127.0, 126.9, 121.3, 119.8, 118.7, 110.6, 107.8, 89.8, 62.6, 43.2, 21.0, 13.1, 12.2. HRMS (EI) m/z calcd for $C_{21}H_{22}N_2O_4$ (M^+): 366.1580, found: 366.1582.

4.2.6. Ethyl 3-(5-(benzyloxy)-1*H*-indol-3-yl)-2-nitro-3-*p*-tolylpropanoate 3ca. The dr value (*anti*/*syn*=45:55) was determined by ^1H NMR signals at δ: 1.01 and 0.91. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=4:1); *anti*-**3ca**: a white solid, mp: 164–166 °C. $[\alpha]_D^{25}$ +11.1 (c 0.36, $CHCl_3$); ee value (89% after recrystallization) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=19.7 min and t_R(minor)=27.4 min. FTIR (KBr): ν 3426, 2984, 1746, 1562, 1482, 1308, 1188, 1021, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (br s, 1H), 7.44–7.33 (m, 5H), 7.21–7.18 (m, 4H), 7.06 (d, J=8.0 Hz, 2H), 6.96 (d, J=2.3 Hz, 1H), 6.90, 6.87 (dd, J=2.3, 8.8 Hz, 1H), 5.83 (d, J=11.4 Hz, 1H), 5.25 (d, J=11.4 Hz, 1H), 5.01 (d, J=2.1 Hz, 2H), 4.08–3.99 (m, 2H), 2.27 (s, 3H), 1.01 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 153.4, 137.5, 137.4, 134.3, 131.6, 129.5, 128.5, 128.3, 127.8, 127.6, 126.7, 121.1, 113.9, 113.6, 111.9, 102.6, 91.7, 70.9, 62.9, 44.1, 21.0, 13.5. HRMS (FAB): m/z calcd for $C_{27}H_{26}N_2O_5$ (M^+): 458.1842, found: 458.1831; *syn*-**3ca**: a colorless solid, mp: 141–146 °C; ee value (46%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=14.7 min and t_R(minor)=19.7 min. FTIR (KBr): ν 3426, 2984, 1746, 1562, 1482, 1455, 1308, 1187, 1021, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (br s, 1H), 7.46 (d, J=6.5 Hz, 2H), 7.45–7.34 (m, 3H), 7.25–7.17 (m, 3H), 7.09–7.07 (m, 4H), 6.93 (dd, J=2.4, 8.7 Hz, 1H), 5.85 (d, J=11.6 Hz, 1H), 5.24 (d, J=11.6 Hz, 1H), 5.07 (s, 2H), 4.00–3.92 (m, 2H), 2.27 (s, 3H), 0.91 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 153.5, 137.5, 137.3, 135.6, 131.4, 129.6, 128.5, 127.8, 127.6, 127.5, 126.7, 122.5, 113.8, 113.0, 111.9, 102.6, 91.8, 70.9, 62.9, 43.6, 21.0, 13.4. HRMS (EI): m/z calcd for $C_{27}H_{26}N_2O_5$ (M^+): 458.1842, found: 458.1847.

4.2.7. Ethyl 3-(5-methoxy-1*H*-indol-3-yl)-2-nitro-3-*p*-tolylpropanoate 3da. The dr value (*anti*/*syn*=62:38) was determined by ^1H NMR signals at δ: 1.02 and 0.93. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=4:1); *anti*-**3da**: a white solid, mp: 132–134 °C. $[\alpha]_D^{25}$ +51.9 (c 0.30, $CHCl_3$); ee value (90%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=15.7 min and t_R(minor)=22.5 min. FTIR (KBr): ν 3421, 2937, 1745, 1561, 1485, 1359, 1309, 1212, 1035, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (br s, 1H), 7.24–7.18 (m, 4H), 7.07 (d, J=7.8 Hz, 2H), 6.88–6.79 (m, 2H), 5.84 (d, J=11.4 Hz, 1H), 5.27 (d, J=11.4 Hz, 1H), 4.09–3.99 (m, 2H), 3.77 (s, 3H), 2.27 (s, 3H), 1.02 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5, 152.4, 135.6, 132.6, 129.6, 127.6, 126.5, 125.0, 119.3, 112.1, 111.0, 110.0, 99.2, 90.0, 61.0, 54.0, 42.3, 19.2, 11.7. HRMS (EI): m/z calcd for $C_{21}H_{22}N_2O_5$ (M^+): 382.1529, found: 382.1527; *syn*-**3da**: a white solid, mp: 128–129 °C. $[\alpha]_D^{25}$ +133.3 (c 0.61, $CHCl_3$); ee value (55%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, λ=254 nm, T=25 °C): t_R(major)=14.2 min and t_R(minor)=20.8 min. FTIR (KBr): 3421, 2938, 1744, 1561, 1485, 1456, 1358, 1213, 1176, 1024, 917, 801, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (br s, 1H), 7.29–7.17 (m, 3H), 7.11–7.06 (m, 3H), 7.00 (d, J=2.3 Hz, 1H), 6.85, 6.82 (dd, J=2.4, 8.8 Hz, 1H), 5.87 (d, J=11.6 Hz, 1H), 5.27 (d, J=11.6 Hz, 1H), 4.04–3.92 (m, 2H), 3.83 (s, 3H), 2.28 (s, 3H), 0.93 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 154.3, 137.3, 135.6, 131.2, 129.6, 127.5, 126.7, 122.5, 113.0, 112.9, 111.9, 100.8, 91.9, 62.9, 55.9, 43.5, 21.0, 13.4. HRMS (EI): m/z calcd for $C_{21}H_{22}N_2O_5$ (M^+): 382.1529, found: 382.1532.

4.2.8. Ethyl 3-(5-methoxy-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-2-nitropropanoate 3db. The dr value (*anti*/*syn*=55:45) was determined by ^1H NMR signals at δ: 1.03 and 0.86. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=4:1); *anti*-**3db**: a white solid, mp: 105–108 °C; ee value (82%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=15.4 min and t_R(minor)=20.9 min. FTIR (KBr): ν 3421, 2928, 1746, 1611, 1562, 1511, 1460, 1373, 1305, 1251, 1211, 1177, 1033, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (br s, 1H), 7.27–7.24 (m, 2H), 7.20–7.17 (m, 2H), 6.86–6.78 (m, 4H), 5.81 (d, J=11.3 Hz, 1H), 5.27 (d, J=11.3 Hz, 1H), 4.10–3.99 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 1.03 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 159.1, 154.2, 131.4, 129.7, 129.3, 126.8, 121.0, 114.2, 114.0, 112.8, 111.9, 101.0, 91.8, 62.9, 55.8, 55.3, 43.7, 13.6. HRMS (EI): m/z calcd for $C_{21}H_{22}N_2O_6$ (M^+): 398.1478, found: 398.1480; *syn*-**3db**: a white solid, mp: 95–99 °C; ee value (47%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=15.1 min and t_R(minor)=17.5 min. FTIR (KBr): ν 3418, 2935, 1744, 1611, 1560, 1512, 1461, 1372, 1303, 1252, 1211, 1178, 1114, 1028, 801 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (br s, 1H), 7.24–7.18 (m, 2H), 7.11 (d, J=8.8 Hz, 1H), 6.99 (d, J=2.2 Hz, 1H), 6.90 (d, J=1.6 Hz, 1H), 6.77–6.73 (m, 3H), 5.76 (d, J=11.6 Hz, 1H), 5.18 (d, J=11.6 Hz, 1H), 4.00–3.89 (m, 2H), 3.74 (s, 3H), 3.67 (s, 3H), 0.86 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 159.0, 154.3, 131.2, 130.5, 128.8, 126.7, 122.3, 114.3,

112.9, 111.9, 100.8, 92.1, 62.9, 55.9, 55.2, 43.2, 13.4. HRMS (EI): *m/z* calcd for $C_{21}H_{22}N_2O_6$ (M^+): 398.1478, found: 398.1482.

4.2.9. Ethyl 3-(5-bromo-1*H*-indol-3-yl)-2-nitro-3-*p*-tolylpropanoate 3ea. The dr value (*anti*/*syn*=72:28) was determined by ^{1}H NMR signals at δ: 1.03 and 0.97. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=3:1); *anti*-**3ea**: a white solid, mp: 156–158 °C. $[\alpha]_D^{25}$ −6.7 (*c* 0.60, $CHCl_3$); ee value (99% after recrystallization) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, *T*=25 °C): t_R(major)=13.0 min and t_R(minor)=16.0 min. FTIR (KBr): ν 3425, 2985, 1744, 1562, 1512, 1460, 1373, 1251, 1186, 1108, 1040, 885, 799 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (br s, 1H), 7.59 (d, *J*=1.7 Hz, 1H), 7.25–7.14 (m, 5H), 7.08 (d, *J*=8.0 Hz, 2H), 5.83 (d, *J*=11.4 Hz, 1H), 5.25 (d, *J*=11.4 Hz, 1H), 4.07–4.01 (m, 2H), 2.28 (s, 3H), 1.03 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 137.7, 134.8, 133.9, 129.6, 128.3, 128.0, 125.7, 121.6, 121.5, 113.9, 113.3, 112.7, 91.6, 63.0, 43.9, 21.1, 13.6. HRMS (EI): *m/z* calcd for $C_{20}H_{19}N_2O_4Br$ (M^+): 430.0528, found: 430.0532; *syn*-**3ea**: a white solid, mp: 153–154 °C; ee value (41%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, *T*=25 °C): t_R(major)=10.9 min and t_R(minor)=14.1 min. FTIR (KBr): ν 3423, 2984, 1743, 1561, 1512, 1459, 1360, 1314, 1182, 1106, 883, 798 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (br s, 1H), 7.72 (d, *J*=1.7 Hz, 1H), 7.28–7.24 (m, 4H), 7.19–7.09 (m, 3H), 5.85 (d, *J*=11.6 Hz, 1H), 5.25 (d, *J*=11.6 Hz, 1H), 4.04–3.97 (m, 2H), 2.28 (s, 3H), 0.97 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 137.6, 135.2, 134.6, 129.7, 127.9, 127.4, 125.7, 123.0, 121.5, 113.4, 112.9, 112.7, 91.8, 63.1, 43.2, 21.0, 13.5. HRMS (EI): *m/z* calcd for $C_{20}H_{19}N_2O_4Br$ (M^+): 430.0528, found: 430.0531.

4.2.10. Ethyl 3-(5-bromo-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-2-nitropropanoate 3eb. The dr value (*anti*/*syn*=71:29) was determined by ^{1}H NMR signals at δ: 1.05 and 0.99. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=3:1); *anti*-**3eb**: a colorless solid, mp: 162–164 °C; ee value (85%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, *T*=25 °C): t_R(major)=14.2 min and t_R(minor)=18.0 min. FTIR (KBr): ν 3424, 2987, 1745, 1560, 1511, 1459, 1253, 1180, 1030, 799 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (br s, 1H), 7.57 (d, *J*=1.4 Hz, 1H), 7.26–7.17 (m, 5H), 6.81 (dd, *J*=2.0, 6.7 Hz, 2H), 5.79 (d, *J*=11.3 Hz, 1H), 5.25 (d, *J*=11.3 Hz, 1H), 4.09–4.01 (m, 2H), 3.76 (s, 3H), 1.05 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 159.2, 134.9, 129.6, 128.8, 128.0, 125.7, 121.6, 121.5, 114.3, 114.0, 113.3, 112.7, 91.6, 63.0, 55.3, 43.5, 13.6. Anal. Calcd for $C_{20}H_{19}N_2O_5Br$: C, 53.71; H, 4.28; N, 6.26. Found: C, 53.66; H, 4.37; N, 6.01; *syn*-**3eb**: a white solid, mp: 151–153 °C; ee value (54%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, λ=254 nm, *T*=25 °C): t_R(major)=13.2 min and t_R(minor)=16.1 min. FTIR (KBr): ν 3424, 2933, 1744, 1561, 1511, 1460, 1251, 1180, 1028, 798 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (br s, 1H), 7.69 (d, *J*=1.6 Hz, 1H), 7.29–7.17 (m, 5H), 6.82 (d, *J*=6.7 Hz, 2H), 5.81 (d, *J*=11.5 Hz, 1H), 5.24 (d, *J*=11.5 Hz, 1H), 4.02 (q, *J*=7.1 Hz, 2H), 3.75 (s, 3H), 0.99 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 159.1, 134.7, 130.1, 128.8, 128.0, 125.7, 122.9, 121.6, 114.4, 113.4, 113.1, 112.7, 92.0, 63.1, 55.2, 42.9, 13.5. HRMS (EI): *m/z* calcd for $C_{20}H_{19}N_2O_5Br$ (M^+): 446.0477, found: 446.0481.

4.2.11. Ethyl 3-(5-bromo-1*H*-indol-3-yl)-3-(4-chlorophenyl)-2-nitropropanoate 3ec. The dr value (*anti*/*syn*=72:28) was determined by ^{1}H NMR signals at δ: 1.05 and 0.99. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=2:1); *anti*-**3ec**: a white solid, mp: 56–59 °C; ee value (99%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, *T*=25 °C): t_R(major)=12.3 min and t_R(minor)=15.1 min. FTIR (KBr): ν 3427, 2923, 1743, 1562, 1460, 1370, 1312, 1252, 1187, 1093, 1014, 797 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (br s, 1H), 7.55 (s, 1H), 7.29–7.22 (m, 6H), 7.18 (d, *J*=8.6 Hz, 1H), 5.81 (d, *J*=11.2 Hz, 1H), 5.28 (d, *J*=11.2 Hz, 1H), 4.09–4.04 (m, 2H), 1.05 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0, 135.6, 134.9, 133.9, 129.8, 129.1, 127.8, 125.9, 121.8, 121.3, 113.5, 113.1, 112.9, 91.3, 63.3, 43.5, 13.6. HRMS (FAB): *m/z* calcd for $C_{19}H_{16}N_2O_4BrCl$ (M^+): 449.9976, found: 449.9977; *syn*-**3ec**: a white solid, mp: 161–165 °C. $[\alpha]_D^{25}$ +116.9 (*c* 0.77, $CHCl_3$); ee value (99% after recrystallization) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, *T*=25 °C): t_R(major)=11.1 min and t_R(minor)=15.2 min. FTIR (KBr): ν 3428, 2984, 1743, 1561, 1491, 1460, 1359, 1251, 1182, 1093, 1013, 797 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (br s, 1H), 7.67 (t, *J*=0.99 Hz, 1H), 7.32–7.26 (m, 5H), 7.22–7.19 (m, 1H), 7.13 (d, *J*=2.6 Hz, 1H), 5.82 (d, *J*=11.5 Hz, 1H), 5.27 (d, *J*=11.5 Hz, 1H), 4.07–3.99 (m, 2H), 0.99 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 136.7, 134.6, 133.8, 129.2, 129.0, 127.8, 125.9, 123.0, 121.4, 113.6, 112.8, 112.3, 91.5, 63.3, 43.0, 13.5. HRMS (EI): *m/z* calcd for $C_{19}H_{16}N_2O_4BrCl$ (M^+): 449.9982, found: 449.9978.

4.2.12. Ethyl 3-(4-bromo-1*H*-indol-3-yl)-3-(4-chlorophenyl)-2-nitropropanoate 3fc. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=2:1); *anti*-**3fc**: a yellow solid, mp: 62–65 °C; ee value (78%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, *T*=25 °C): t_R(major)=11.7 min and t_R(minor)=14.3 min. FTIR (KBr): ν 420, 2923, 1743, 1562, 1487, 1372, 1310, 1187, 1092, 1015, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (br s, 1H), 7.38 (s, 1H), 7.31–7.22 (m, 6H), 7.02–6.96 (m, 1H), 6.28 (d, *J*=11.4 Hz, 1H), 5.77 (d, *J*=11.4 Hz, 1H), 4.10–4.00 (m, 2H), 1.04 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0, 137.2, 135.8, 133.2, 130.3, 128.4, 124.6, 123.7, 121.7, 113.7, 113.4, 110.4, 91.6, 62.7, 42.0, 13.1. HRMS (EI): *m/z* calcd for $C_{19}H_{16}N_2O_4BrCl$ (M^+): 449.9982, found: 449.9987; *syn*-**3fc**: a white crystal, mp: 153–155 °C; ee value (89%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, *T*=25 °C): t_R(major)=10.7 min and t_R(minor)=13.0 min. FTIR (KBr): ν 415, 2984, 1741, 1562, 1488, 1367, 1249, 1186, 1093,

1012, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 7.36 (d, J=8.4 Hz, 1H), 7.30–7.20 (m, 5H), 7.02 (t, J=7.8 Hz, 1H), 6.37 (d, J=11.2 Hz, 1H), 5.81 (d, J=11.2 Hz, 1H), 4.06 (q, J=7.1 Hz, 2H), 1.01 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 137.1, 136.8, 133.1, 129.4, 128.5, 124.9, 123.5, 123.4, 123.0, 113.4, 113.2, 110.4, 92.4, 62.7, 40.9, 13.0. HRMS (EI): m/z calcd for $C_{19}H_{16}N_2O_4BrCl$ (M^+): 449.9982, found: 449.9988.

4.2.13. Methyl 3-(3-ethoxy-2-nitro-3-oxo-1-*p*-tolylpropyl)-1*H*-indole-5-carboxylate 3ga. The dr value (*anti*/*syn*=71:29) was determined by ^1H NMR signals at δ: 1.04 and 0.93. The diastereomers were separated by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=3:1); *anti*-**3ga**: a yellow solid, mp: 134–136 °C; ee value (96%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=11.9 min and t_R(minor)=14.3 min. FTIR (KBr): ν 3412, 2989, 1745, 1705, 1620, 1561, 1438, 1366, 1314, 1247, 1112, 1028, 820, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (br s, 1H), 8.29 (d, J=0.6 Hz, 1H), 7.87 (dd, J=1.4, 8.6 Hz, 1H), 7.32–7.24 (m, 4H), 7.08 (d, J=7.9 Hz, 2H), 5.87 (d, J=11.4 Hz, 1H), 5.38 (d, J=11.4 Hz, 1H), 4.10–4.00 (m, 2H), 3.91 (s, 3H), 2.27 (s, 3H), 1.04 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 163.1, 138.8, 137.7, 133.9, 129.6, 128.3, 126.0, 124.2, 122.2, 121.9, 121.8, 115.6, 111.0, 91.7, 63.0, 51.9, 43.8, 21.0, 13.6. HRMS (FAB): m/z calcd for $C_{22}H_{22}N_2O_6$ (M^+): 410.1478, found: 410.1474; *syn*-**3ga**: a colorless solid, mp: 180–183 °C; ee value (44%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=10.5 min and t_R(minor)=12.4 min. FTIR (KBr): ν 3412, 2987, 1745, 1701, 1619, 1561, 1437, 1359, 1246, 1184, 1015, 908, 851, 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 8.40 (s, 1H), 7.90, 7.87 (dd, J=1.5, 8.6 Hz, 1H), 7.32–7.29 (m, 3H), 7.19 (d, J=2.4 Hz, 1H), 7.09 (d, J=7.9 Hz, 2H), 5.91 (d, J=11.6 Hz, 1H), 5.37 (d, J=11.6 Hz, 1H), 4.01–3.94 (m, 2H), 3.94 (s, 3H), 2.27 (s, 3H), 0.93 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 163.2, 138.6, 137.6, 135.3, 129.7, 127.4, 125.9, 124.1, 123.3, 122.2, 121.8, 114.6, 111.1, 91.8, 63.1, 52.0, 43.2, 21.0, 13.4. HRMS (EI): m/z calcd for $C_{22}H_{22}N_2O_6$ (M^+): 410.1478, found: 410.1482.

4.2.14. Methyl 3-(3-ethoxy-1-(4-methoxyphenyl)-2-nitro-3-oxopropyl)-1*H*-indole-5-carboxylate 3gb. The dr value (*anti*/*syn*=67:33) was determined by ^1H NMR signals at δ: 1.05 and 0.95. A white solid was obtained as a mixture of *syn* and *anti*. FTIR (KBr): ν 3408, 2952, 1702, 1564, 1619, 1512, 1434, 1249, 1029, 909, 824, 732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.37_{syn}, 8.27_{anti} (s, 1H), 8.31_{syn}, 8.30_{anti} (br s, 1H), 7.91–7.86 (m, 2H), 7.34–7.20 (m, 8H), 6.87–6.78 (m, 4H), 5.86_{syn}, 5.84_{anti} (d, J=11.4 Hz, 1H), 5.38_{anti}, 5.37_{syn} (d, J=11.4 Hz, 1H), 4.09–4.01_{anti}, 4.01–3.93_{syn} (m, 2H), 3.94_{syn}, 3.91_{anti} (s, 3H), 3.74 (s, 6H), 1.05_{anti}, 0.95_{syn} (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 163.4 (163.3), 159.2 (159.0), 138.9 (138.7), 130.3 (129.0), 129.6 (128.8), 126.0 (125.9), 124.0, 123.4, 122.0 (121.9), 121.8 (121.7), 115.5 (114.6), 114.4 (114.3), 111.2, 92.1 (91.8), 63.1, 55.2 (55.2), 52.0 (51.9), 43.5 (43.0), 13.6 (13.4) (the data in parentheses are diastereomeric peaks). HRMS (EI): m/z calcd for $C_{22}H_{22}N_2O_7$ (M^+): 426.1427, found: 426.1424; *anti*-**3gb**: ee value (93%) was determined by chiral HPLC (Chiralcel OD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=13.7 min and t_R(minor)=19.6 min; *syn*-**3gb**: ee value (40%) was determined by chiral HPLC: t_R(major)=13.6 min and t_R(minor)=18.0 min.

4.2.15. *tert*-Butyl 3-(4-chlorophenyl)-3-(1*H*-indol-3-yl)-2-nitropropanoate 3ae. *anti*-**3ae**: a white solid, mp: 147–149 °C. FTIR (KBr): ν 3402, 2979, 1734, 1560, 1490, 1316, 1149, 1093, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.34–7.29 (m, 3H), 7.26–7.23 (m, 3H), 7.21–7.14 (m, 1H), 7.08–7.03 (m, 1H), 5.79 (d, J=11.1 Hz, 1H), 5.30 (d, J=11.1 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=162.0, 136.3, 133.5, 130.1, 129.0, 128.8, 126.2, 122.9, 120.5, 120.1, 118.8, 113.9, 111.3, 92.1, 84.8, 43.8, 27.4. HRMS (EI): m/z calcd for $C_{21}H_{21}N_2O_4Cl$ (M^+): 400.1190, found: 400.1193.

4.3. Typical experimental procedure for the synthesis of tryptophan analogues

To a solution of *anti*-**3aa** (39 mg, 0.11 mmol) in a mixture of THF (9 mL), concd HCl (0.37 mL), AcOH (2 mL), and water (3.7 mL) was added at 0 °C Zn dust (190 mg, 2.9 mmol), followed by stirring for 3 h at 0 °C. The Zn dust was filtrated out, and the reaction mixture was diluted with CH_2Cl_2 and washed with water and satd aq $NaHCO_3$. The combined organic layer was dried over Na_2SO_4. After evaporation, conventional acetylation (by Ac_2O in pyridine) of the residue was carried out, followed by concentration and purification by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=1:1) to afford the tryptophan analogue *anti*-**4aa** (24 mg, 61% yield).

4.3.1. Ethyl 2-acetamido-3-(1*H*-indol-3-yl)-3-*p*-tolylpropanoate, *anti*-4aa. A white solid, mp: 70–73 °C. $[\alpha]_D^{25}$ −58.7 (c 0.4, $CHCl_3$); ee (99%) was determined by chiral HPLC (Chiralpak AD-H, hexane/isopropanol=70:30, 0.5 mL/min, T=25 °C): t_R(major)=10.0 min and t_R(minor)=21.4 min. FTIR (KBr): ν 3305, 2926, 1733, 1659, 1516, 1455, 1373, 1233, 1106, 1025, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.34 (d, J=8.6 Hz, 2H), 7.20–7.12 (m, 3H), 7.06–7.01 (m, 4H), 5.98 (d, J=8.6 Hz, 1H), 5.31 (t, J=8.6 Hz, 1H), 4.65 (d, J=8.6 Hz, 1H), 3.96–3.87 (m, 2H), 2.27 (s, 3H), 1.89 (s, 3H), 0.95 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 169.9, 136.9, 136.6, 136.4, 129.1, 128.2, 127.1, 122.3, 121.9, 119.7, 119.1, 114.7, 111.3, 61.2, 56.3, 45.6, 23.2, 21.0, 13.7. HRMS (EI): calcd for $C_{22}H_{24}N_2O_3$ (M^+): 364.1787, found: 364.1790.

4.3.2. (2*S*,3*R*)-Ethyl 3-(5-bromo-1*H*-indol-3-yl)-3-(4-chlorophenyl)-2-(phenylsulfonamido)propanoate (2*S*,3*R*)-4ec. A colorless crystal, mp: 182–184 °C. FTIR (KBr): ν 3382, 3272, 2983, 1730, 1452, 1336, 1249, 1162, 1044, 924, 798, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.25 (br s, 1H), 7.76–7.74 (m, 3H), 7.55–7.52 (m, 1H), 7.47–7.42 (m, 2H), 7.23–7.18 (m, 5H), 7.07–7.04 (m, 2H), 4.90 (d, J=10.8 Hz, 1H), 4.74, 4.71 (dd, J=4.6, 10.8 Hz, 1H), 4.60 (d, J=4.6 Hz, 1H), 3.78–3.65 (m, 2H), 0.93 (t,

J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 139.1, 136.2, 134.6, 133.7, 133.0, 130.1, 129.0, 128.9, 128.4, 127.4, 125.3, 124.1, 121.2, 114.0, 112.9, 112.7, 61.8, 59.4, 44.6, 13.8. HRMS (EI) calcd for $C_{25}H_{22}N_2O_4SClBr$ (M^+): 560.0172, found: 560.0179. The crystal used for the X-ray study had the dimensions 0.65×0.40×0.20 mm. Crystal data: $C_{25}H_{22}N_2O_4SClBr$, M=561.87, orthorhombic, space group $P2$, a=25.926(5), b=9.861(2), c=10.282(2) Å, β=105.9490(19)°, V=2628.5(9) Å^3, Z=4, D_{calcd}=1.420 g/cm^3, F_0=1144, reflections collected: 24,439, λ=0.7176 Å. CCDC 640616.

4.4. Typical procedure for the removal of nitro group

To a solution of *anti*-**3af** (51 mg, 0.145 mmol) in benzene (5 mL) were added AIBN (6 mg, 0.037 mmol) and Bu_3SnH (55 mg, 0.189 mmol). The mixture was refluxed for 4 h, and concentrated. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=5:1) to give the product, ethyl 3-(1*H*-indol-3-yl)-3-phenylpropanoate **5**[14d] (28 mg, 67% yield). $[\alpha]_D^{20}$ −26.0 (*c* 0.9, $CHCl_3$).

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