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Asymmetric Friedel–Crafts Alkylation of Indoles with Methyl (*E*)-2-Oxo-4-aryl-3-butenoates Catalyzed by $Sc(OTf)_3$/pybox**

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Abstract: The asymmetric Friedel–Crafts reaction between a series of substituted indoles **2a–l** and methyl (*E*)-2-oxo-4-aryl-3-butenoates **3a–c** has been efficiently catalyzed by the scandium(III) triflate complex of (4′*S*,5′*S*)-2,6-bis[4′-(triisopropylsilyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (pybox; **1**). Substituted 4-(indol-3-yl)-2-oxo-4-arylbutyric acid methyl esters **4a–n** were usually formed in excellent yields and the enantioselectivity was up to 99% *ee*, irrespective of the electronic character of the substituent and its location on the indole ring, albeit with the exclusion of position 2. The adducts could be obtained as stable enol tautomers and the equilibrium with the keto structure is discussed. The X-ray crystal structure determination of **4m** indicated the 4*R* absolute configuration, thus confirming the proposal of Jørgensen for **4i**. The sense of the stereoinduction can be rationalized by the same octahedral complex **5** between **3**, pybox **1**, and scandium triflate already proposed for the Diels–Alder/hetero-Diels–Alder and the Mukaiyama–aldol reactions of pyruvates.

Keywords: asymmetric catalysis · enantioselectivity · Friedel–Crafts reaction · indoles · N ligands

Introduction

Catalytic enantioselective Friedel–Crafts reactions have attracted the interest of many groups because of the synthetic relevance of the molecules obtainable with this approach and for the flexibility of these reactions. A successful catalytic asymmetric addition of aromatic C–H bonds to alkenes requires the synergistic concurrence of three elements:

1) An electron-rich aromatic or heteroaromatic ring and indoles are by far preferred for the biologic relevance of these molecules.[1–13]
2) An electron-poor alkene, which is usually an activated α,β-unsaturated carbonyl compound, such as an aryliden pyruvate,[1–3] ethane di- or tri-carboxylate,[4–7] α,β-unsaturated acyl phosphonate,[8,9] or a nitroalkene.[10–12]
3) A suitably designed catalyst based on a Lewis acid and a chiral ligand, among which Cu^{II}/bis(oxazoline) complexes are by far preferred,[1,4–7,11,12,13] whereas pyridine bis(oxazoline) (pybox) complexes are less frequently used.[8,14,15]

Our previous investigations focused on the Diels–Alder reaction of cyclopentadiene with either 3-alkenoyl-2-oxazolidinone or methyl (*E*)-2-oxo-4-aryl-3-butenoates. The cycloadditions were found to be catalyzed by the scandium(III) triflate complex of (4′*S*,5′*S*)-2,6-bis[4′-(triisopropylsilyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**1**) in excellent yields and enantiomeric excess,[16,17] and the chiral induction was strongly related to the structure of the reactive intermediate involved in the catalytic cycle. If these α,β-unsaturated carbonyl compounds, when coordinated to the complex [Sc^{III}(**1**)], undergo an enantioselective reaction with cyclopentadiene, it should be expected that indoles could be used instead of cyclopentadiene, thus giving rise to catalytic enantioselective Friedel–Crafts reactions. This specific reaction between indoles and β,γ-unsaturated α-keto esters has been carried out in excellent yields and enantiomeric excess by Jørgensen and co-workers, who used a chiral copper(II) triflate/*tert*-butylbis(oxazoline) complex as the catalyst.[1,2] Hence, both from a synthetic and a mechanistic viewpoint, **1**

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[**] pybox = pyridine bis(oxazoline).

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is worth investigating as a chiral ligand in the asymmetric catalysis of this reaction.

Results and Discussion

Initially, the catalytic activity of the scandium(III) ion in the absence of any chiral ligand was tested in the reaction of indole **2a** with methyl (*E*)-2-oxo-4-phenyl-3-butenoate (**3a**) in CH_2Cl_2 at −70 °C (Scheme 1). The reaction was observed to be very fast (a few minutes), but the crude product, isolated as a white solid, was not the expected, and already described, 4-(1*H*-indol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (**4a**).[1] The IR and ^{1}H NMR spectra are in agreement with the structure of the enol tautomer **4a′**; the product can be crystallized from methanol and is stable in $CDCl_3$, but it slowly transforms into **4a** in solution with dimethyl sulfoxide (DMSO), as evidenced by the ^{1}H NMR spectrum in this solvent. The same results were obtained by using the copper(II) ion as the catalyst, the Lewis acid most frequently used in the reaction.

The reaction between **2a** and **3a** catalyzed by the scandium(III) triflate complex of **1** (Scheme 2) was carried out at different temperatures with different solvents and in the presence of 3-Å molecular sieves (MS) to optimize the asymmetric reaction conditions.

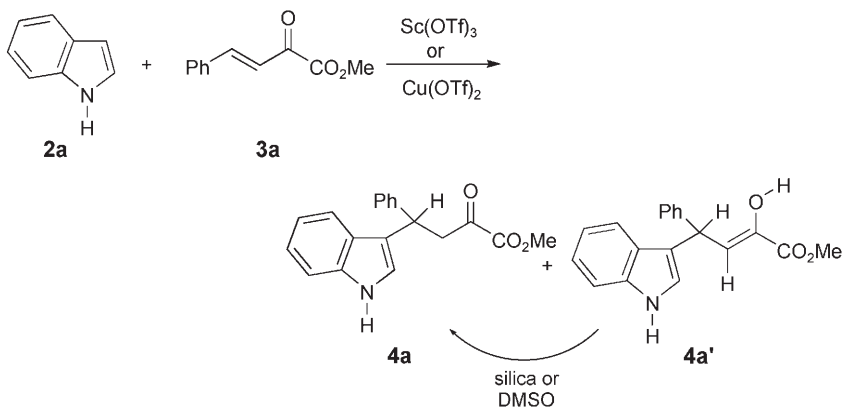
The ^{1}H NMR and IR spectroscopic analysis of the product isolated after separation from **1** by column chromatography of the reaction product shows that the reaction product corresponds to the ketonic tautomer **4a** under all the investigated conditions. The best results were obtained by using diethyl ether or dichloromethane as the solvent at −50/−70 °C, since **4a** was obtained in excellent yield with 96–98 % *ee* (Table 1).

The origin of the tautomeric preference (i.e., the keto tautomer **4a** from the optically active catalyzed reaction, which always requires purification of the product from the pybox ligand by chromatography, and the enol tautomer **4a′** in the absence of chiral catalytic conditions) can be rationalized if a sample of **4a′** is isolated by chromatography under the same conditions used for the separation of optically enriched **4a** from **1**. After elution on silica, the ketonic tautomer **4a** is separated, and the experiment simply suggests that the chromatographic support is the responsible for the tautomerization. The same isomerization occurs when racemic **4a′** is separated by chiral HPLC since the enantiomer peaks correspond to those obtained from enantioenriched **4a**. Therefore, the keto–enol equilibration is induced by the chromatographic support. A deci-

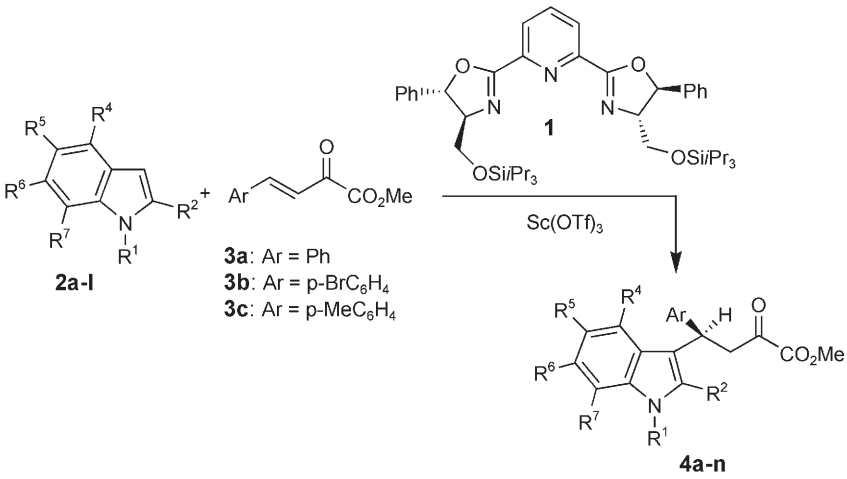
Table 1. Catalytic enantioselective Friedel–Crafts reaction of indole **2a** with **3a** catalyzed by $Sc(OTf)_3$/**1**.[a]

Entry	Solvent	*T* [°C]	Time	Yield [%][b]	*ee* [%]
1	CH_2Cl_2	ambient	10 min	90	5
2	CH_2Cl_2	−50	20 min	90	96
3	CH_2Cl_2	−70	20 min	quant.	96
4	toluene	−70	2 h	75	75
5	THF	−70	2 h	85	60
6	Et_2O	−50	10 min	95	97
7	Et_2O	−70	10 min	quant.	98

[a] Reaction was performed in the presence of 3-Å MS. [b] Yield of the isolated product of **4a** after column chromatography.



Scheme 1. The catalyzed Friedel–Crafts reaction between **2a** and **3a** that gives the adduct in the keto **4a** or enol **4a′** forms.



Scheme 2. The scandium triflate complex of **1** as a chiral catalyst in the Friedel–Crafts reactions between **2a–l** and **3a–c**, which give **4a–n** after chromatographic purification.

sive further experiment was carried out. The ^{1}H and ^{13}C NMR spectra of the optically active catalyzed reaction mixture, recorded before any preventive separation of the product by chromatography, demonstrate that **4a′** is always the primary reaction product. In any case, this keto–enol equilibrium has no relevance on the detected selectivity of the reaction since it does not involve the stereogenic center of the adduct.

Usually the asymmetric alkylation of the indole is carried out using a variety of alkylating agents and a few selected indoles.[10,11] To test the flexibility of the catalyst and evaluate the effect of the substituent in different positions on the indole ring, the Friedel–Crafts reaction with methyl (*E*)-2-oxo-4-phenyl-butenoate (**3a**) was tested on a large family of different indoles **2a–l** (Table 2).

Table 2. Catalytic enantioselective Friedel–Crafts reaction of indoles **2a–l** with methyl (*E*)-2-oxo-4-phenylbutenoate (**3a**) in diethyl ether at −70 °C catalyzed by $Sc(OTf)_3$/**1**.[a]

Entry	2	R^1	R^2	R^4	R^5	R^6	R^7	4	Time	Yield [%][b]	*ee* [%]
1	**2a**	H	H	H	H	H	H	**4a**	10 min	quant.	98
2	**2b**	Me	H	H	H	H	H	**4b**	15 min	85	97
3	**2c**	H	Me	H	H	H	H	**4c**	15 min	95	67
4	**2d**	H	Ph	H	H	H	H	**4d**	24 h	quant.	52
5	**2e**	H	H	OMe	H	H	H	**4e**	2 h	92	98
6	**2f**	H	H	H	OMe	H	H	**4f**	30 min	90	88
7	**2g**	H	H	Cl	H	H	H	**4g**	24 h	89	99
8	**2h**	H	H	H	Cl	H	H	**4h**	45 min	97	95
9	**2i**	H	H	H	H	Cl	H	**4i**	15 min	81	98 (*R*)[c]
10	**2j**	H	H	H	H	H	Cl	**4j**	2 days	89	94
11	**2k**	H	H	H	H	CO_2Me	H	**4k**	3 days	quant.	99
12	**2l**	H	H	H	NO_2	H	H	**4l**	10 days	35[d]	90

[a] Reaction was performed in the presence of 3-Å MS. [b] Yield of the isolated product. [c] The absolute configuration was determined by comparing the optical rotation with that reported in ref. [1]. [d] Significant amounts of starting material were isolated.

The nucleophilicity of the indole, which is a key factor in the Friedel–Crafts reaction, was reported to increase with increasing electron-donating character of the substituent in the 1, 2, and 5 positions.[18,19] The group of indoles **2a–l**, chosen as a cluster of reagents, allowed us to compare the effect of the electronic character of the substituents and their positions on the heterocyclic ring on the indole nucleophilicity.

Several factors may determine the reactivity of **2**, for example, nucleophilicity, reagent, and product solubility. As expected, the time required to accomplish the reaction increases with decreasing nucleophilicity of the indole induced by electron-attracting substituents and ranges from 10 min to 3 days at −70 °C (Table 2, entries 1 and 11). In the case of the indole bearing the strongest electron-withdrawing substituent (**2l**), poor reaction yields of **4l** were obtained after 10 days (Table 2, entry 12).

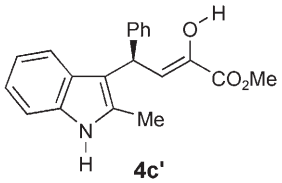
On the contrary, the nucleophilicity of **2** does not influence the enantioselectivity of the reaction since excellent results were obtained for all the 2-unsubstituted indoles, independent of the electron-donating or -attracting character of the substituents.

The absolute configuration of **4i** was compared to that determined by Jørgensen and co-workers by X-ray analysis.[1] Furthermore, the negative $[\alpha]_D$ value of the adduct obtained from the experiment reported in Table 2, entry 8 led to an assignment of the stereocenter formed in the reaction catalyzed by the scandium(III) triflate complex of **1** as the *R* configuration. By analogy, the same absolute 4*R* configuration can be proposed for all the other Friedel–Crafts alkylation products **4a–h,j–l**.

By using the data in Table 2, the effect induced by the substituent at different positions of the indole moiety can be discussed:

1) An alkyl substituent on the nitrogen atom changes neither reactivity nor selectivity (Table 2, entry 2).
2) Whereas a substituent at positions 5 or 6 does not change the reactivity and selectivity (Table 2, entries 8 and 9), the same substituent at position 7 strongly decreases the reactivity but not the selectivity (Table 2, entry 10).
3) Positions 2 and 4 are close to the reactive C3 position and could cause significant steric hindrance in the reaction. Electron-donating and -attracting substituents at position 4 (Table 2, entries 5 and 7) give results comparable or even better than those obtained with the corresponding 5- or 6-substituted indoles.
4) When the substituent at position 2 is a methyl group (indole **2c** is a strong nucleophile),[18] the yield and reaction time are comparable to those of **2a** and **2b**. If the substituent is a phenyl group (i.e., **2d**), the yield is again excellent, but the reactivity is significantly decreased (Table 2, entry 3 versus 4). In both cases, the substituent at position 2 has a negative influence on the enantioselectivity, and the *ee* values of **4c** and **4d** are the lowest obtained in the entire cluster of the tested indoles.

The determination of the enantiomeric excess for **4c** required interpretation of its anomalous HPLC chromatogram (see the Supporting Information). Pure samples of racemic and chiral **4c** have, in addition to the peaks of the enantiomers at 44 and 56 min, a second couple of peaks at 20 and 23 min, whose ratio is the same as the first couple of peaks. Following the method used for the synthesis of **4a′**, racemic **4c′** (Scheme 3) was prepared from **2c**, and its HPLC chromatogram confirmed the equilibrium **4c**/**4c′** as the origin of the phantom peaks. The keto–enol equilibration occurs also with the enantiomerically enriched product obtained after



4c'

Scheme 3. The enol tautomer of **4c**.

purification by column chromatography without any loss of the product enantiopurity, and the tautomers are stable enough to be detected under chiral-HPLC conditions.

Having examined a large number of indoles with several groups in different positions, we treated **2a** with **3b** and **3c**, with the substituent on the electrophilic reagent. The result shows that the influence of a substituent on the phenyl group of **3** is limited since both the reactivities and enantioselectivities observed for **4m** and **4n** are analogous to those obtained for **4a** (Table 3).

Table 3. Catalytic enantioselective Friedel–Crafts reaction at −70 °C of indole **2a** with **3a–c** in diethyl ether catalyzed by $Sc(OTf)_3$/**1**.[a]

Entry	2	3	4	Time	Yield [%][b]	*ee* [%] (conf.)
1	**2a**	**3a**	**4a**	10 min	quant.	98
2	**2a**	**3b**	**4m**	1 h	62	96 (*R*)
3	**2a**	**3c**	**4n**	15 min	85	90

[a] Reaction performed in the presence of 3-Å MS. [b] Yield of the isolated products.

To confirm the enantioselectivity induced by $Sc(OTf)_3$/**1** as the catalyst, the absolute configuration of **4m** was determined by X-ray analysis and its structure (Figure 1) allowed us to confirm the previously assumed *R* configuration of the stereocenter.

In the solid state, the molecular crystal is characterized by bifurcated hydrogen bonds, in which the N–H group of each molecule acts as a proton donor towards the two C=O groups of an adjacent molecule. In particular, the hydrogen bonds show a major component towards the O(2) atom (H(1N)···O(2): 2.17(4) Å) and a minor component towards the O(1) atom (H(1N)···O(1): 2.53(3) Å). These intramolecular hydrogen bonds form infinite molecular chains along the *a* axis in the crystal (Figure 2) and give rise to the unusual *cisoid* α-dicarbonyl conformation.

Conclusion

The *R* configuration for the products of the Friedel–Crafts reaction is consistent with an octahedral reactive intermediate **5**, obtained by bidentate coordination of **3b** to the scandium(III) complex of **1** with the ketonic C=O group in the equatorial position and the ester carbonyl group and triflate ion in axial positions, which undergoes the sterically less demanding attack to the *Re* face of the indole **2a** (Figure 3).

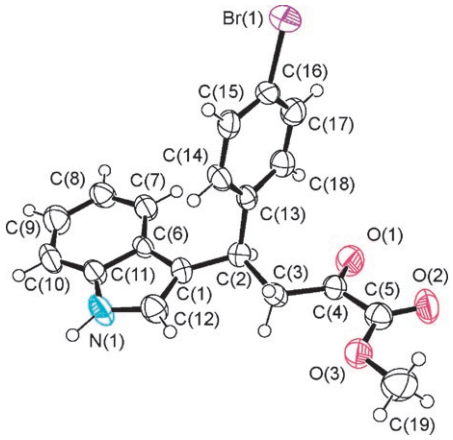


Figure 1. An ORTEP view of the crystal structure of **4m** (ellipsoids are drawn at the 50% probability level) labeled with crystallographic atom names, thus confirming the absolute *R* configuration.

This intermediate **5** has already been used to rationalize the sense of the stereoinduction of the Diels–Alder/hetero-Diels–Alder reactions of cyclopentadiene on **3**,[16,17] and the Mukaiyama–aldol reaction of pyruvates.[20] The consistency of the model of the reactive intermediate in so many different reactions is not only a good indicator of the flexibility of the catalyst, but offers promising insight into predicting the sense of the stereoinduction in new reactions involving dicarbonylic substrates.

Experimental Section

General: The melting points were determined by the capillary method and are uncorrected; ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively; the IR spectra were recorded on a Perkin–Elmer

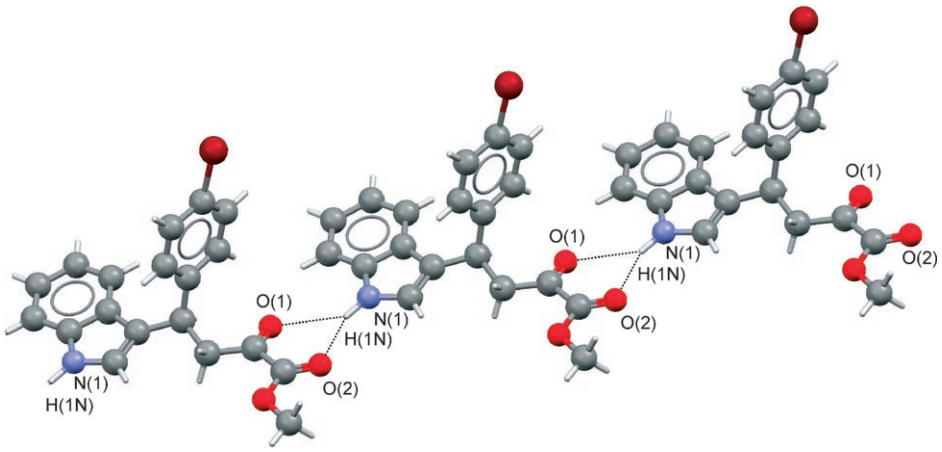


Figure 2. The infinite molecular chain adopted in the solid state by (*R*)-**4m** as determined by X-ray structure studies. Features of the N–H···O interactions are: N(1)···O(1) 3.31(1) Å, H(1N)···O(1) 2.53(3) Å, N(1)–H(1N)···O(1) 139(2)°, N(1)···O(2) 3.03(1) Å, H(1N)···O(2) 2.17(4) Å, N(1)–H(1N)···O(2) 150(2)°.

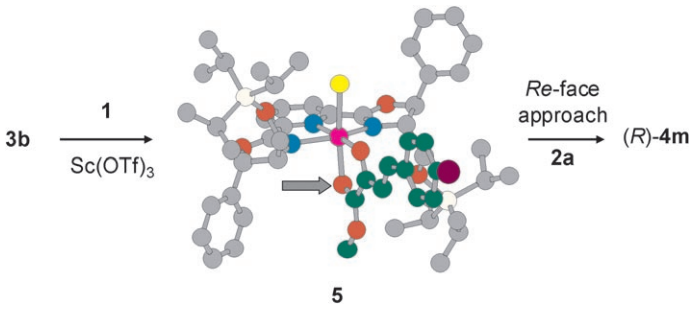


Figure 3. The assumed reactive intermediate **5** of the Friedel–Crafts alkylation reaction between **3b** and indole **2a** catalyzed by the $Sc(OTf)_3$ complex of pybox **1**, which gives (*R*)-**4m**.

RX I spectrophotometer; optical rotations were measured on a Perkin–Elmer 241 polarimeter. The separation and purification of the products was carried out by column chromatography on silica gel 60 (230–400 mesh; Merck). The enantiomeric excess (*ee*) of the products was determined by HPLC using Daicel columns, small differences in the eluant composition may give reasonably different retention times.

Materials: Hydrocarbon-stabilized ACS grade dichloromethane (Aldrich) was distilled from calcium hydride and used immediately. The other solvents were dried according to standard procedures. ACS reagent grade scandium triflate was used (Aldrich). The powdered 3-Å MS (Aldrich) were heated under vacuum at 300 °C for 5 h and kept in sealed vials in a dryer. (4′*S*,5′*S*)-2,6-Bis[4′-(triisopropylsilyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**1**) was prepared as previously described.[21] (*E*)-2-Oxo-4-phenylbut-3-enoic acid methyl ester (**3a**) was prepared following a previously reported method[22,23] from its potassium salt, which was obtained from benzaldehyde and pyruvic acid in the presence of KOH. The potassium salt was esterified with methanol to give yellow needles from diisopropyl ether (m.p. 69–70 °C; m.p. 70–71 °C in ref. [23]). Following the same procedure and starting from a suitable aldehyde, the following products were prepared: (*E*)-2-oxo-4-(4-bromophenyl)but-3-enoic acid methyl ester (**3b**) in 35% yield as yellow needles from methanol (m.p. 120 °C; m.p. 122 °C in ref. [24]); (*E*)-2-oxo-4-(4-methylphenyl)but-3-enoic acid methyl ester (**3c**) in 45% yield as yellow needles from diisopropyl ether (m.p. 80–81 °C; m.p. 81 °C in ref. [25]).

General procedure for the reaction between indoles 2a–k and methyl (*E*)-2-oxo-4-aryl-3-butenoates 3a–c

Reactions between 2a and 3a catalyzed by scandium (or copper) triflates: Solid $Sc(OTf)_3$ or $Cu(OTf)_2$ (14.8 and 10.9 mg, respectively, 0.03 mmol) was added to a solution of indole **2a** (35.1 mg, 0.30 mmol) and methyl (*E*)-2-oxo-4-phenyl-3-butenoate (**3a**) (57.0 mg, 0.30 mmol) in anhydrous CH_2Cl_2 (0.3 mL) at −70 °C in a vial sealed with a rubber septum. The reaction mixture was stirred for a few minutes until the yellow solution solidified. The white solid was filtered and washed with water. The almost pure product **4a′** was crystallized from methanol to give a pure sample of 4-(1*H*-indol-3-yl)-2-hydroxy-4-phenyl-2-butenoic acid methyl ester (**4a′**) as a white solid. M.p. 156–157 °C (methanol); ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, trimethylsilane (TMS)): $\delta = 10.91$ (s, 1H; OH), 8.80 (s, 1H; NH), 7.35–6.85 (m, 10H; aromatic and indole protons), 6.16 (d, ^3J(H,H) = 10.3 Hz, 1H; vinylic proton), 5.41 (d, ^3J(H,H) = 10.3 Hz, 1H; benzylic proton), 3.72 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 164.4$, 143.5, 139.4, 136.1, 127.9, 127.3, 125.7, 125.6, 122.2, 120.6, 118.4, 117.9, 116.4, 116.1, 111.1, 51.7, 37.5 ppm; IR (nujol): $\tilde{\nu} = 3448$ (NH), 1700 (C=O), 1672 cm^{-1} (C=C).

A sample of pure **4a′**, with the above spectroscopic characteristics was isolated by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate 75:25) to give pure 4-(1*H*-indol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (**4a**) as a white solid. M.p. 137–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.04$ (bs, 1H; NH), 7.45–7.05 (m, 10H; aromatic and indole protons), 4.95 (t, ^3J(H,H) = 7.5 Hz, 1H; CH), 3.79 (s, 3H; OCH_3), 3.69 (dd, ^2J(H,H) = 16.8, ^3J(H,H) = 7.5 Hz, 1H; C*H*H), 3.60 ppm (dd, ^2J(H,H) = 16.8, ^3J(H,H) = 7.5 Hz, 1H; CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 192.1$, 160.8, 142.7, 136.1, 128.0, 127.3, 126.1, 125.9, 121.8, 121.0, 119.0, 118.9, 117.8, 110.6, 52.4, 45.2, 37.2 ppm (see the ^{1}H and ^{13}C NMR spectra in ref. [1]); IR (nujol): $\tilde{\nu} = 3357$ (NH), 1744 cm^{-1} (C=O).

General procedure for the reaction of 2a–k and 3a–c catalyzed by Sc(OTf)$_3$/1: (*E*)-2-Oxo-4-arylbut-3-enoic acid methyl esters **3a–c** (0.30 mmol), pybox (**1**) (22.2 mg, 0.03 mmol), scandium triflate (14.8 mg, 0.03 mmol), and MS (0.020–0.025 g) were added to anhydrous diethyl ether or CH_2Cl_2 (0.3 mL) at ambient temperature in a vial sealed with a rubber septum. The reaction mixture was stirred for 15 min and cooled at the temperatures reported in Tables 1–3. The solid indole **2a–f** (0.30 mmol) was added in one portion and the reaction mixture was stirred until all the starting material had been consumed. The reaction times are indicated in Tables 1–3. The reaction mixture was quenched with water, extracted with CH_2Cl_2, and dried. The crude-product mixture was separated by column chromatography on silica gel (length: 30 cm, diameter: 1.5 cm; the eluant is given for each specific product). HPLC analysis, column, eluant, experimental conditions, and retention times are given for **4a–k**. The melting-point and spectroscopic data refer to racemates **4** purified by column chromatography.

(−)-4-(1*H*-Indol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4a): The product from Table 2, entry 1 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 80:20) as a white solid with 98% *ee*. $[\alpha]_D^{20} = -23.3$ ($c = 1.1$ in $CHCl_3$) ($[\alpha]_D^{20} = -23.9$ ($c = 0.01$ in $CHCl_3$) for 99.5% *ee* in ref. [1]); chiralpak AD column (hexane/*i*PrOH 80:20, flow rate = 1.0 mL min^{-1}) $t_R = 14$ min (major), $t_R = 16$ min (minor). The ^{1}H and ^{13}C NMR spectra of the reaction mixture, quenched in water, dried, and without any column chromatography, correspond to those of **4a′** previously described (see the Supporting Information).

(−)-4-(1-Methylindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4b): The racemate was obtained as a white solid from methanol. M.p. 98–99 °C (m.p. 100 °C in ref. [1]); the ^{1}H and ^{13}C NMR spectra are identical to those reported in ref. [1]; IR (nujol): $\tilde{\nu} = 1729$ cm^{-1} (C=O). The product from Table 2, entry 2 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 90:10) as a white solid with 97% *ee*. $[\alpha]_D^{20} = -24.1$ ($c = 1.0$ in $CHCl_3$) ($[\alpha]_D^{20} = -26.6$ ($c = 0.01$ in $CHCl_3$) for 96% *ee* in ref. [1]); chiralpak IA column (hexane/ethyl acetate 90:10, flow rate = 0.5 mL min^{-1}) $t_R = 22$ min (major), $t_R = 24$ min (minor).

(+)-4-(2-Methylindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4c): The racemate was obtained as a light yellow oil, which was only stable for a few days in the refrigerator. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.84$ (s, 1H; NH), 7.5–7.0 (m, 9H; aromatic and indole protons), 4.95 (dd, ^3J(H,H) = 6.1 and 9.1 Hz, 1H; CH), 3.95 (dd, ^2J(H,H) = 17.0, ^3J(H,H) = 9.1 Hz, 1H; C*H*H), 3.75 (dd, ^2J(H,H) = 17.0, ^3J(H,H) = 6.1 Hz, 1H; C*H*H), 3.67 (s, 3H; OCH_3), 2.44 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 192.5$, 160.5, 142.6, 134.9, 131.6, 127.9, 126.8, 126.6, 125.7, 120.5, 118.8, 118.6, 111.8, 109.9, 52.3, 43.5, 35.7, 11.6 ppm; IR (film): $\tilde{\nu} = 3404$ (NH), 1731 cm^{-1} (C=O); elemental analysis (%) calcd for $C_{20}H_{19}NO_3$ (321.4): C 74.75, H 5.96, N 4.36; found: C 74.65, H 6.03, N 4.41.

The product from Table 2, entry 3 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 90:10) as an oil with 67% *ee*. $[\alpha]_D^{20} = +6.64$ ($c = 1.5$ in $CHCl_3$); chiralcel OJ column (hexane/*i*PrOH 70:30, flow rate = 0.75 mL min^{-1}) $t_R = 44$ min (major), $t_R = 56$ min (minor) (a further couple of peaks were observed at 20 min (major) and 23 min (minor)).

4-(1*H*-2-Methylindol-3-yl)-2-hydroxy-4-phenyl-2-butenoic acid methyl ester (4c′): Solid $Sc(OTf)_3$ (0.02 mmol) was added to a solution of 2-methylindole (**2c**; 0.20 mmol) and methyl (*E*)-2-oxo-4-phenyl-3-butenoate (**3a**; 0.20 mmol) in anhydrous diethyl ether (0.3 mL) at −70 °C in a vial sealed with a rubber septum. The reaction mixture was stirred for a few minutes until a clear solution was obtained. The reaction mixture was washed with water, and the organic layer was dried with anhydrous sodium sulfate and evaporated to give almost pure **4c′**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.85$ (s, 1H; NH), 7.3–7.0 (m, 9H; aromatic and indole protons), 6.41 (d, ^3J(H,H) = 10.1 Hz, 1H; vinylic proton), 5.78 (s, 1H; OH) 5.59 (d, ^3J(H,H) = 10.1 Hz, 1H; benzylic

proton), 3.83 (s, 3H; OCH_3), 2.44 ppm (s, 3H; CH_3); ^{13}C NMR, (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 165.7, 142.1, 138.6, 135.0, 131.5, 128.6, 127.8, 127.2, 125.6, 120.5, 118.9, 118.7, 115.1, 111.8, 109.9, 52.4, 36.6, 11.6 ppm; IR (nujol): $\tilde{\nu}$ = 3401 (NH), 1700 cm^{-1} (C=O); chiralcel OJ column (hexane/*i*PrOH 70:30, flow rate = 0.75 mL min^{-1}) t_R = 19 min and t_R = 22 min.

(+)-4-(2-Phenylindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4d): The racemate was obtained as a light-yellow solid from benzene/hexane. M.p. 98–99 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.12 (s, 1H; NH), 7.6–7.1 (m, 14H; aromatic and indole protons), 5.13 (dd, ^3J(H,H) = 6.5 and 8.7 Hz, 1H; CH), 3.90 (dd, ^2J(H,H) = 16.9, ^3J(H,H) = 8.7 Hz, 1H; C*H*H), 3.75 (dd, ^2J(H,H) = 16.9, ^3J(H,H) = 6.5 Hz, 1H; C*H*H), 3.59 ppm (s, 3H; OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 192.1, 160.5, 142.9, 135.7, 135.5, 132.2, 128.3, 128.0, 127.8, 126.9, 126.8, 125.8, 121.7, 120.1, 119.4, 112.4, 110.6, 52.2, 44.4, 36.1 ppm; IR (nujol): $\tilde{\nu}$ = 3381 (NH), 1744 cm^{-1} (C=O); elemental analysis (%) calcd for $C_{25}H_{21}NO_3$ (383.4): C 78.31, H 5.52, N 3.65; found: C 78.37, H 5.48, N 3.62.

The product from Table 2, entry 4 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 85:15) as a yellow solid with 52% *ee*. $[\alpha]_D^{20}$ = +11.2 (*c* = 0.9 in $CHCl_3$); chiralpak AD column (hexane/*i*PrOH 80:20, flow rate = 1.0 mL min^{-1}) t_R = 23 min (minor), t_R = 27 min (major).

(+)-4-(1*H*-4-Methoxyindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4e): The racemate was obtained as light-yellow crystals from ethyl acetate/hexane. M.p. 150–151 °C; ^1H NMR ($CDCl_3$): δ = 7.95 (s, 1H; NH), 7.8–7.15 (m, 5H; aromatic protons), 7.09 (t, ^3J(H,H) = 8.0 Hz, 1H; 6-H indole), 6.94 (d, ^3J(H,H) = 8.1 Hz, 1H; 7-H indole), 6.73 (d, ^4J(H,H) = 2.2 Hz, 1H; 2-H indole), 6.48 (d, ^3J(H,H) = 7.8 Hz, 1H; 5-H indole), 5.28 (dd, ^3J(H,H) = 6.6 and 8.4 Hz, 1H; CH), 3.84 (s, 3H; OCH_3), 3.78 (s, 3H; OCH_3), 3.73 (dd, ^2J(H,H) = 17.2, ^3J(H,H) = 6.6 Hz, 1H; C*H*H), 3.64 ppm (dd, ^2J(H,H) = 17.2, ^3J(H,H) = 8.4 Hz, 1H; C*H*H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 192.6, 161.1, 154.0, 143.3, 137.7, 127.7, 127.5, 125.7, 122.7, 120.1, 119.1, 116.1, 103.9, 99.3, 54.4, 52.3, 46.1, 37.9 ppm; IR (nujol): $\tilde{\nu}$ = 3365 (NH), 1747 cm^{-1} (C=O); elemental analysis (%) calcd for $C_{20}H_{19}NO_4$ (337.4): C 71.20, H 5.68, N 4.15; found: C 71.25, H 5.77, N 4.08.

The product from Table 2, entry 5 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 80:20) as a yellow solid with 98% *ee*. $[\alpha]_D^{20}$ = +47.1 (*c* = 0.7 in $CHCl_3$); chiralcel OJ column (hexane/*i*PrOH 70:30, flow rate = 0.9 mL min^{-1}) t_R = 65 min (major), t_R = 198 min (minor).

(+)-4-(1*H*-5-Methoxyindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4f): The racemate was obtained as a light-yellow solid from methanol. M.p. 135–136 °C (obtained as a yellow semicrystalline oil in ref. [1]); the ^1H and ^{13}C NMR spectra are identical to those reported in ref. [1]; IR (nujol): $\tilde{\nu}$ = 3364 (NH), 1745 and 1734 cm^{-1} (C=O). The product from Table 2, entry 6 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 80:20) as a light-yellow solid with 88% *ee*. $[\alpha]_D^{20}$ = +8.2 (*c* = 0.7 in $CHCl_3$) ($[\alpha]_D^{20}$ = +5.2 (*c* = 0.01 in $CHCl_3$) for 99.5% *ee* in ref. [1]); chiralpak AD column (hexane/*i*PrOH 80:20, flow rate = 1.0 mL min^{-1}) t_R = 14 min (major), t_R = 20 min (minor).

(+)-4-(1*H*-4-Chloroindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4g): The racemate was obtained as white crystals from ethyl acetate/hexane. M.p. 140–141 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.17 (s, 1H; NH), 7.4–7.0 (m, 9H; aromatic and indole protons), 5.57 (t, ^3J(H,H) = 7.6 Hz, 1H; CH), 3.80 (s, 3H; OCH_3), 3.68 and 3.65 ppm (two pseudo-singlets, 2H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 191.9, 160.9, 142.9, 137.4, 127.9, 127.5, 126.0, 125.8, 122.9, 122.7, 122.4, 120.5, 118.5, 109.5, 52.4, 46.5, 36.7 ppm; IR (nujol): $\tilde{\nu}$ = 3354 (NH), 1743 cm^{-1} (C=O); elemental analysis (%)calcd for $C_{19}H_{16}ClNO_3$ (341.8): C 66.77, H 4.72, N 4.10; found: C 66.52, H 4.63, N 4.21.

The product from Table 2, entry 7 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 80:20) as a white solid with 99% *ee*. $[\alpha]_D^{20}$ = +13.3 (*c* = 0.9 in $CHCl_3$); chiralcel OJ column (hexane/*i*PrOH 70:30, flow rate = 0.9 mL min^{-1}) t_R = 84 min (minor), t_R = 119 min (major).

(+)-4-(1*H*-5-Chloroindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4h): The racemate was obtained as a light-cream solid from hexane/ethyl acetate. M.p. 162 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.06 (s, 1H; NH), 7.4–7.1 (m, 9H; aromatic and indole protons), 4.88 (t, ^3J(H,H) = 7.5 Hz, 1H; CH), 3.82 (s, 3H; OCH_3), 3.68 (dd, ^2J(H,H) = 17.1, ^3J(H,H) = 7.2 Hz, 1H; C*H*H), 3.60 ppm (dd, ^2J(H,H) = 17.1, ^3J(H,H) = 7.5 Hz, 1H; C*H*H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 191.8, 160.7, 142.2, 134.4, 128.2, 127.1, 127.0, 126.3, 124.8, 122.3, 122.2, 118.3, 117.6, 111.7, 52.5, 45.1, 37.0 ppm; IR (nujol): $\tilde{\nu}$ = 3347 (NH), 1740 cm^{-1} (C=O); elemental analysis (%) calcd for $C_{19}H_{16}ClNO_3$ (341.8): C 66.77, H 4.72, N 4.10; found: C 66.63, H 4.78, N 4.03.

The product from Table 2, entry 8 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 80:20) as a white solid with 95% *ee*. $[\alpha]_D^{20}$ = +15.4 (*c* = 0.5 in $CHCl_3$); chiralpak IA column (hexane/ethyl acetate 85:15, flow rate = 0.5 mL min^{-1}) t_R = 27 min (major), t_R = 30.5 min (minor).

(−)-(4R)-4-(1*H*-6-Chloroindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4i): The racemate was obtained as a white solid. M.p. 157–158 °C (m.p. 158 °C in ref. [1]); the ^1H and ^{13}C NMR spectra are identical to those reported in ref. [1]; IR (nujol): $\tilde{\nu}$ = 3335 (NH), 1732 cm^{-1} (C=O). The product from Table 2, entry 9 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 80:20) as a white solid with 98% *ee*. $[\alpha]_D^{20}$ = −18.8 (*c* = 0.9 in $CHCl_3$) ($[\alpha]_D^{20}$ = −18.5 (*c* = 0.01 in $CHCl_3$) for 97% *ee* in ref. [1]) chiralpak IA column (hexane/ethyl acetate 85:15, flow rate = 0.5 mL min^{-1}) t_R = 31 min (major), t_R = 35 min (minor).

(−)-4-(1*H*-7-Chloroindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4j): The racemate was obtained as white needles from ethyl acetate/hexane. M.p. 105–107 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.27 (s, 1H; NH), 7.4–7.0 (m, 9H; aromatic and indole protons), 4.93 (t, ^3J(H,H) = 7.5 Hz, 1H; CH), 3.81 (s, 3H; OCH_3), 3.72 (dd, ^2J(H,H) = 17.1, ^3J(H,H) = 7.4 Hz, 1H; C*H*H), 3.62 ppm (dd, ^2J(H,H) = 17.1, ^3J(H,H) = 7.6 Hz, 1H; C*H*H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 191.8, 160.8, 142.3, 133.3, 128.1, 127.4, 127.2, 126.3, 121.5, 121.2, 119.9, 119.0, 117.6, 116.1, 52.5, 45.0, 37.2 ppm; IR (nujol): $\tilde{\nu}$ = 3392 (NH), 1743 cm^{-1} (C=O); elemental analysis (%) calcd for $C_{19}H_{16}ClNO_3$ (341.8): C 66.77, H 4.72, N 4.10; found: C 66.89, H 4.77, N 3.99.

The product from Table 2, entry 10 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 80:20) as a white solid with 94% *ee*. $[\alpha]_D^{20}$ = −43.5 (*c* = 1.4 in $CHCl_3$); chiralpak IA column (hexane/ethyl acetate 85:15, flow rate = 0.5 mL min^{-1}) t_R = 21 min (major), t_R = 23 min (minor).

(−)-3-(3-Methoxycarbonyl-3-oxo-4-phenylpropyl)-1*H*-indole-6-carboxylic acid methyl ester (4k): The racemate was obtained as a white solid from ethyl acetate/hexane. M.p. 178–179 °C (obtained as pale-yellow solid, m.p. 180 °C in ref. [1]); the ^1H and ^{13}C NMR spectra are identical to those reported in ref. [1]; IR (nujol): $\tilde{\nu}$ = 3354 (NH), 1740 and 1702 cm^{-1} (C=O). The product from Table 2, entry 11 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 70:30) as a white solid with 99% *ee*. $[\alpha]_D^{20}$ = −4.6 (*c* = in 0.7 $CHCl_3$) ($[\alpha]_D^{20}$ = −2.9 (*c* = 0.01 in $CHCl_3$) for 94% *ee* in ref. [1]); Chiralpak AD column (hexane/*i*PrOH 80:20, flow rate = 1.0 mL min^{-1}) t_r = 42 min (major), t_r = 49 min (minor).

(+)-4-(1*H*-5-Nitroindol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (4l): The racemate was obtained as a light-yellow solid from ethyl acetate/hexane. M.p. 150–151 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.52 (s, 1H; NH), 8.41 (d, ^3J(H,H) = 2.0 Hz, 1H; 4-H indole), 8.08 (dd, ^3J(H,H) = 9.0 and 2.0 Hz, 1H; 6-H indole), 7.4–7.2 (m, 7H; aromatic and indole protons), 4.97 (t, ^3J(H,H) = 7.5 Hz, 1H; CH), 3.84 (s, 3H; OCH_3), 3.73 (dd, ^2J(H,H) = 17.4, ^3J(H,H) = 7.4 Hz, 1H; C*H*H), 3.64 ppm (dd, ^2J(H,H) = 17.4, ^3J(H,H) = 7.4 Hz, 1H; C*H*H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 191.5, 160.7, 141.7, 141.2, 139.0, 128.3, 127.1, 126.6, 125.4, 123.9, 120.4, 117.6, 116.2, 110.7, 52.6, 45.0, 36.8 ppm; IR (nujol): $\tilde{\nu}$ = 3357 (NH), 1739 cm^{-1} (C=O); elemental analysis calcd (%) for $C_{19}H_{16}N_2O_5$ (352.3): C 64.77, H 4.58, N 7.95; found: C 64.89, H 4.47, N 8.01.

The product from Table 2, entry 12 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 75:25) as a yellowish solid with 90% *ee*. $[\alpha]_D^{20}$ = +59.1 (*c* = 0.4 in $CHCl_3$); Chiralpak IA column (hexane/ethyl acetate 85:15, flow rate = 0.75 mL min^{-1}) t_r = 49 min (major), t_r = 56 min (minor).

(−)-(4*R*)-4-(1*H*-Indol-3-yl)-2-oxo-4-(4-bromophenyl)butyric acid methyl ester (4m): The racemate was obtained as a white solid from methanol/water. M.p. 166–167 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.9 (s, 1H; NH), 7.4–7.3 (m, 7H; aromatic and indole protons), 7.04 (t, ^3J(H,H) = 7.5 Hz, 1H; indole proton), 6.90 (t, ^3J(H,H) = 7.4 Hz, 1H; indole proton), 4.70 (t, ^3J(H,H) = 7.4 Hz, 1H; CH), 3.75 (s, 3H; OCH$_3$), 3.73 (dd, ^2J(H,H) = 18.0, ^3J(H,H) = 7.2 Hz, 1H; C*H*H), 3.59 (dd, ^2J(H,H) = 18.0, ^3J(H,H) = 7.7 Hz, 1H; C*H*H), 2.31 ppm (s, 3H; CH$_3$); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 192.0, 160.8, 143.9, 136.3, 131.0, 129.9, 126.0, 122.1, 121.1, 119.0, 118.5, 118.4, 116.7, 111.4, 52.6, 44.7, 36.2 ppm; IR (nujol): $\tilde{\nu}$ = 3341 (NH), 1735 cm^{-1} (C=O); elemental analysis calcd (%) for $C_{19}H_{16}BrNO_3$ (386.2): C 59.08, H 4.18, N 3.63; found: C 59.25, H 4.22, N 3.52.

The product from Table 3, entry 2 was isolated by column chromatography (eluant cyclohexane/ethyl acetate 85:15) as a white solid with 96% *ee*. $[\alpha]_D^{20} = -3.6$ (c = 0.9 in CHCl$_3$); Chiralcel AD column (hexane/*i*PrOH 80:20, flow rate = 1.0 mL min^{-1}) t_r = 13 min (major), t_r = 20 min (minor).

(−)-4-(1*H*-Indol-3-yl)-2-oxo-4-(4-methylphenyl)butyric acid methyl ester (4n): The racemate was obtained as a white solid from methanol. M.p. 138 °C; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 8.03 (s, 1H; NH), 7.5–7.0 (m, 9H; aromatic and indole protons), 4.92 (t, ^3J(H,H) = 7.6 Hz, 1H; CH), 3.80 (s, 3H; OCH$_3$), 3.72 (dd, ^2J(H,H) = 16.9, ^3J(H,H) = 7.3 Hz, 1H; C*H*H), 3.61 (dd, ^2J(H,H) = 16.9, ^3J(H,H) = 7.9 Hz, 1H; C*H*H), 2.31 ppm (s, 3H; CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C, TMS): δ = 192.2, 160.8, 139.6, 136.1, 135.6, 128.7, 127.1, 125.9, 121.8, 121.0, 119.0, 118.9, 118.0, 110.6, 52.4, 45.2, 36.8, 20.5 ppm; IR (nujol): $\tilde{\nu}$ = 3360 (NH), 1747 (C=O), 1738 cm^{-1} (C=O); elemental analysis calcd (%) for $C_{20}H_{19}NO_3$ (321.4): C 74.75, H 5.96, N 4.36; found: C 74.89, H 5.99, N 4.48.

The product from Table 3, entry 3 was isolated by column chromatography (eluant: cyclohexane/ethyl acetate 80:20) as a white solid with 90% *ee*. $[\alpha]_D^{20} = -11.3$ (c = 1.6 in CHCl$_3$); Chiralcel AD column (hexane/*i*PrOH 80:20, flow rate = 1.0 mL min^{-1}) t_r = 14 min (major), t_r = 18 min (minor).

X-ray crystallographic study: Diffraction data for a crystal of **4m** were collected at ambient temperature by means of an Enraf–Nonius CAD4 four-circle diffractometer with graphite-monochromatized Mo$_{K\alpha}$ X-ray radiation (λ = 0.71073 Å). Crystal data for **4m**: $C_{19}H_{16}BrNO_3$; M_r = 386.23; T = 293 K; crystal dimensions = 0.45 × 0.14 × 0.09 mm^3; orthorhombic; $P2_12_12_1$ (No. 19); a = 9.6759(13), b = 12.6207(11), c = 14.0733(9) Å; V = 1718.6(3) Å^3; Z = 4; ρ_{calcd} = 1.493; $F(000)$ = 784; μ = 2.407 mm^{-1}; 2θmax = 50°; 3828 measured reflections, 3066 independent reflections (R_{int} = 0.026), 1832 strong reflections ($Io > 2\sigma(Io)$), 221 refined parameters, $R1$ = 0.0526 (strong data) and 0.1168 (all data), w$R2$ = 0.0704 (strong data) and 0.0844 (all data), GOF = 1.002, 0.27, and −0.36 maximum (max.) and minimum (min.) residual electron density. Data reductions (including intensity integration, background, Lorentz, and polarization corrections) were performed with the WinGX package.[26] Absorption effects were evaluated with the psi-scan method[27] and absorption correction was applied to the data (min./max. transmission factors were 0.654/0.807). Crystal structures were solved by direct methods (SIR 97)[28] and refined by full-matrix least-square procedures on F^2 using all reflections (SHELXL 97).[29] Anisotropic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms bonded to carbon atoms were placed at calculated positions with the appropriate AFIX instructions and refined using a riding model; hydrogen-bonding interactions with the N(1) atom were located in the ΔF map and refined restraining the N−H distance to be 0.89 ± 0.02 Å.

CCDC–668902 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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