Thiourea-Catalyzed Addition of Indole to Aliphatic β,γ -Unsaturated α -Ketoesters

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Abstract: The first thiourea-catalyzed addition reaction of indoles to aliphatic β,γ -unsaturated α -ketoesters has been developed. The easily accessible thiourea aminoindanol derivative makes this approach an interesting alternative for these aliphatic substrates, very scarcely employed in previously reported procedures, highlighting the complementarity of the strategy presented here. Final adducts, which are valuable intermediates for the obtainment of the corresponding α -amino acid or α -hydroxy acid derivatives, are obtained in good results under mild reaction conditions.

Since the first work reported in 1877 by Friedel and Crafts, the Friedel–Crafts (F–C) reaction has become undoubtedly one of the most important carbon–carbon bond forming protocol in organic synthesis.^[1] Consistently, many research groups have focused their efforts in the development of new catalytic and asymmetric versions of this process especially in the area of metal catalysis^[2] and organocatalysis.^[3] In this field, the indole skeleton has been center of many appealing works due to the great importance of natural products or medicinal agents containing this privileged moiety.^[4]

The catalytic asymmetric F–C reactions can be mainly categorized into two different classes of alkylations attending to the electrophile used: (1) with activated alkenes and (2) with carbonyl or imine compounds. In the frame of the first case, we have previously studied the thiourea^[5] catalyzed Friedel–Crafts alkylation reaction using nitroalkenes,^[6] an interesting class of activated Michael acceptors.^[7] In this work, we want to focus on β,γ -unsaturated α -ketoesters,^[8] which are also interesting Michael acceptors because they exhibit a high and rich reactivity and they are intermediates of the corresponding α -amino^[9] or α -hydroxy acid derivatives.^[10] In this context, few efforts have been devoted in the Friedel–Crafts alkylation reaction of indole with β,γ -unsaturated α -ketoesters.^[8] It is worth noting that the catalysts previously used in this process have been mainly metals^[2a,11] and only scarce organocatalytic examples using chiral phosphoric acid derivatives have been described (Figure 1).^[9,12,13]

Figure 1. Organocatalysts employed in the Friedel–Crafts alkylation reaction of indole with β,γ -unsaturated α -ketoesters: **1**,^[9] **2**^[12] and **3**.^[13]

Remarkably, merely aromatic β,γ -unsaturated α -ketoester derivatives have been employed in the already described cases.^[2a,9,11,12,13] However, the aliphatic ones have been overlooked in the literature so far. In the frame of our research program about the study of new thiourea-catalyzed reactions, we focused our attention in the possibility of performing this process in the presence of thiourea catalysts. Herein, we report the preliminary results obtained concerning this idea, highlighting the extension of the study to aliphatic substrates, in order to expand and to contribute to the development of this field (Scheme 1).

Scheme 1.

We decided to explore the efficiency of (thio)urea catalysts **4a–j** in the reaction of β,γ -unsaturated α -ketoesters with indole (Figure 2), since to the best of our knowledge, this kind of catalysts has not been previously considered for the development of this particular reaction. Moreover, their easy preparation in one synthetic step, compared with the abovementioned chiral phosphoric acids used in this process, adds value to the current work.

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Figure 2. (Thio)ureas **4a-j** tested.

Two kind of catalytic structures were considered for this study: a) simple chiral thioureas (**4c**, **4d** and **4g**) and b) those with an additional functional group in their structure (OH-, -SO₂NH-), such as **4a**, **4b**, **4e-f**, **4h-j**, able to act in a bifunctional way, as previously invoked for catalyst **4a**.^[6b,c,d,14] With this wide range of chiral thioureas we moved on to explore the viability of our idea testing the potential of these catalysts in the model reaction depicted in table 1, using β,γ -unsaturated α -ketoester **5a**. We firstly explored aromatic derivative **5a** in order to test the efficiency of thiourea catalysts compared with those catalysts previously reported.

Table 1. Screening of the viability of the process using catalysts **4a-j**.

entry	cat.	time (day)	yield (%) ^a	ee (%) ^b
1	4a	1	69	20
2 ^c	4b	1	75	rac. ^d
3	4c	1	63	7

4	4d	1	63	rac. ^d
5	4e	1	80	6
6	4f	1	80	rac. ^d
7	4g	2	85	rac. ^d
8	4h	1	65	10
9	4i	1.5	77	8

[a] Isolated yields after column chromatography. [b] Determined by chiral HPLC analysis (Daicel Chiralpak IA, 90:10 Hex: iPrOH, 1 mL/min). [c] Reaction performed in CHCl₃. [d] Racemic mixture.

We explored the activity and efficiency of all catalysts at room temperature (r.t.) in toluene (except urea **4b**, carried out in CHCl₃ due to its less solubility in toluene, entry 4) with β,γ -unsaturated α -ketoester **5a**, and in all cases the desired product **7a** was obtained with good yields. In contrast, only catalyst **4a** provided a promising value of enantioselectivity (20% ee, entry 1). Unfortunately, no other catalyst afforded enantioselectivities good enough to be considered in further explorations. Then, we continued testing different key parameters of this model reactions using catalyst **4a** (Table 2). In this study, the temperature of the process was decreased for a variety of solvents with the main aim of improving the enantioselectivity.

Table 2. Study of solvents and temperature using catalyst **4a** (20 mol%) and β,γ -unsaturated α -ketoester **5a**.

entry	T (°C)	solvent	time (day)	yield (%) ^a	ee (%) ^b
1	12	toluene	2	76	17
2	r.t.	CHCl ₃	1	98	18
3	12	CHCl ₃	2	78	40
4	-26	CHCl ₃	6	74	41
5	-40	CHCl ₃	10	32	rac. ^c
6	-26	ClCH ₂ CH ₂ Cl	6	74	36
7	-26	CH ₃ CN	6	62	rac. ^c
8	-26	CH ₂ Cl ₂	6	82	26
9	-26	xileno	6	90	rac. ^c
10	-26	EtOAc	6	88	rac. ^c
11	-26	1,4-dioxane	6	86	rac. ^c
12	-26	CCl ₄	6	85	14

[a] Isolated yields after column chromatography. [b] Determined by chiral HPLC analysis (Chiralpak Daicel IA, Hex: iPrOH 90:10, 1 mL/min). [c] Racemic mixture.

Thus, we made slight changes in the reaction conditions, lowering first the temperature to 12 °C (entry 1), getting values very close to those at r.t. (Table 1, entry 1). In parallel, CHCl₃ was tested as solvent at both temperatures: r.t. and 12 °C (entries 2 and 3, respectively). The enantioselectivity doubled its value and the yield was slightly increased when the experiment was carried out at 12 °C in CHCl₃ (entry 3 vs Table 1, entry 1). Then, we continued lowering the temperature using this solvent: -26 and -40 °C (entries 4 and 5, respectively). Unfortunately, the reaction rate was extremely slow at -40 °C and the ee of the process drastically decreased to racemic mixture. The results obtained at -26 °C were similar to those obtained at 12 °C (compare, entries 3 and 4). Additionally to this study of the temperature, a number of different solvents were tested at -26 °C (entries 6-12), and remarkably, only chlorinated solvents were appropriated to induce enantioselectivity (entries 6, 8 and 12).

Interestingly, exploring the efficiency of the catalyst **4a** with the aliphatic derivative **5b**, a higher enantioselectivity was reached in comparison with that obtained with aromatic derivative **5a**,

under the better conditions found for it: 71% ee vs 40% ee (Table 3, entry 1 vs Table 2, entry 3, respectively).

Table 3. Study of solvent and temperature using catalyst **4a** and aliphatic β,γ -unsaturated α -ketoester **5b**.

entry	T (°C)	solvent	time (day)	yield (%) ^a	ee (%) ^b
1	12	CHCl ₃	4	71	71
2	0	CHCl ₃	5	70	60
3	12	CH ₂ Cl ₂	4	51	71
4 ^c	12	CH ₂ Cl ₂	4	n.r. ^d	n.d. ^e
5 ^f	12	CH ₂ Cl ₂	6	11	22
6	0	CH ₂ Cl ₂	5	70	66
7	0	toluene	5	63	60

[a] Isolated yields after column chromatography. [b] Determined by chiral HPLC analysis (Daicel Chiralpak IA, 95:5 Hex: iPrOH, 1 mL/min). [c] Catalyst **4e** was used. [d] No reaction observed. [e] No determined. [f] Catalyst **4j** was used.

Then, we made additional tests with this aliphatic substrate (**5b**), but unfortunately, no improvement was obtained. A decreasing in the ee values was found lowering the temperature from 12 to 0 °C (compare, entries 1 and 2), and the yield dropped changing the solvent to CH₂Cl₂ (compare, entries 1 and 3). Additional experiments were carried out at 0 °C in different solvents: CH₂Cl₂ and toluene (entries 6 and 7, respectively) which led to similar results to those obtained at this temperature in CHCl₃. Furthermore, catalysts **4e** and **4j**, structurally related to catalyst **4a**, were tested with this substrate (entries 4-5), but they did not provide good results. The best conditions were finally obtained at 12 °C and with CHCl₃, as the solvent of choice, using catalyst **4a** and aliphatic substrate **5b** (Table 3, entry 1). Although the best ee% value with the aromatic substrate **5a** was only 40%, to our delight, aliphatic derivatives were found to be a better option to develop this process. Thus, we examined other aliphatic substrates **5c-g** and different indoles **6a-e** to extend the scope of this catalytic approach (Scheme 2).

Scheme 2. Scope of the reaction for aliphatic β,γ -unsaturated α -ketoester **5b-g**. (n.d. No determined)

As shown in Scheme 2, the enantioselectivity of the reaction was found to be independent to steric effects of the substituents on the conjugated system and to the electronic environment in the indole. In contrast, the data suggest a clear correlation between the electronic properties of the indole ring and the reactivity of the process, being higher with electron-donating substituents. Thus, different γ,γ -disubstituted α -ketoesters **7b-k** were isolated by the first time, in good yields (up to 90%) and good enantiomeric excesses (up to 76%).

The activation of different substrates through thiourea based catalysts has been previously invoked in other many examples.^[5] In the current system, it can be assumed that the catalyst plays a dual role, on the basis of previous works for the Michael addition of indole to nitroalkenes (**TSI**)^[6b,c,d] or the addition of *N,N*-dialkylhydrazones to β,γ -unsaturated α -ketoester (**TSII**)^[14] promoted by the same bifunctional thiourea catalyst **4a** (Figure 3).^[15]

Figure 3. Transition states (TS) previously invoked in the literature for catalyst **4a**.

Thus, transition states depicted in the Figure 4 could be envisioned to explain the reactivity and the mode of action of catalyst **4a** in this process. On one hand, the catalyst activates the β,γ -unsaturated α -ketoester **5** and drives the attack of indole **6** over the *re* face of it, in a concomitant coordination. However, we cannot discard both possible coordination modes: monodentate, with one carbonyl group (**TSIII**) or bidentate, with both carbonyl moieties (**TSIV**). Moreover, the OH group in the aminoindanol core of the catalyst would coordinate the indole **6**

to drive the attack of the nucleophile over the electrophile in a preferential attack for the *re* face of the latest. To support our mechanism, *N*-methylindole **6e** was checked with **5d** leading to a racemic mixture (Scheme 2), being in agreement with our proposed mechanism and as previously observed by some of us,^[6b] since the absence of the NH in the indole prevents the crucial interaction between the NH and the OH to drive the approach of both reagents in the **TSIII** and **TSIV**. Interestingly, the low enantiomeric value found with **6b** suggests a possible steric effect between the Me group in the 2 position and the substituent of the α -ketoester in the TS, diffculting the right approach, which will be also in agreement with our tentative proposal. However, additional computational studies are ongoing in our lab in order to confirm these hypotheses.

Figure 4. Possible TS to explain the addition of indole (**6a**) over the β,γ -unsaturated α -ketoester **5**.

Conclusions

In conclusion, we have been able to develop the first thiourea-catalyzed addition reaction of indoles **6a–e** to aliphatic β,γ -unsaturated α -ketoesters **5b–g**. This is the first example where aliphatic derivatives have been focus of an extended study. The simplicity and easily available organocatalyst **4a** makes this approach an interesting alternative to obtain the aliphatic analogues not accessible by other procedures so far, being a complementary strategy to previously reported ones. Final adducts are obtained in good results under mild reaction conditions and they are valuable intermediates for the obtainment of the corresponding α -amino acid or α -hydroxy acid derivatives, as previously demonstrated,^[9,10] which are compounds of biological interest. Computational studies are ongoing in our lab in order to support the proposed activation mode.

Experimental Section

General experimental methods. Purification of reaction products was carried out by flash chromatography using silica gel (0.063–0.200 mm). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. $^1\text{H-NMR}$ spectra were recorded at 300 and 400 MHz; $^{13}\text{C-APT-NMR}$ spectra were recorded at 75 MHz; CDCl_3 as the solvent. Chemical shifts were reported in the δ scale relative to residual CHCl_3 (7.26 ppm) for $^1\text{H-NMR}$ and to the central line of CDCl_3 (77 ppm) for $^{13}\text{C-APT-NMR}$.

Materials. All commercially available solvents and reagents were used as received. The NMR spectra ($^1\text{H-NMR}$ and $^{13}\text{C-APT-NMR}$) for catalyst **4a** are consistent with values previously reported in the literature.^[14] β,γ -Unsaturated α -ketoesters **5a–g** were synthesized following previously reported protocols in the literature and their NMR spectra are consistent with values previously published: **5a**,^[16] **5b**,^[14] **5d**,^[17] **5e**,^[16] and **5g**.^[17]

A. General procedure for the synthesis of β,γ -unsaturated α -ketoesters **5a–g.** To a solution of the Wittig-reagent ethyl 2-oxo-3-(triphenylphosphoranylidene)propanoate (1.13 g, 3.0 mmol) in CH_2Cl_2 (5 mL), the corresponding aldehyde is added (18 mmol). The flask was closed with a stopper and the mixture was stirred at room temperature for 6 days. The solvent was removed under vacuum and the product was isolated by column chromatography (silica gel, hexane/ Et_2O 9:1).

(E)-Ethyl 2-oxohept-3-enoate (5c) Following the general procedure A, compound **5c** was obtained as an orange oil in 41% yield. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.18 (dt, 1H, J = 16.0 Hz, J = 6.8 Hz), 6.64 (dt, 1H, J = 16.0 Hz, J = 1.5 Hz), 4.34 (q, 2H, J = 7.1 Hz), 2.32–2.25 (m, 2H), 1.59–1.49 (m, 2H), 1.37 (t, 3H, J = 7.1 Hz), 0.95 (t, 3H, J = 7.4 Hz). $^{13}\text{C-APT-NMR}$ (75 MHz, CDCl_3) δ 183.5 (1C), 162.4 (1C), 154.9 (1C), 125.2 (1C), 62.3 (1C), 35.0 (1C), 21.0 (1C), 14.0 (1C), 13.6 (1C).

(E)-Ethyl 4-cyclopentyl-2-oxobut-3-enoate (5f) Following the general procedure A, compound **5f** was obtained as an orange oil in 44% yield. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.16 (dd, 1H, J = 15.8 Hz, J = 8.1 Hz), 6.63 (dd, 1H, J = 15.8 Hz, J = 1.1 Hz), 4.34 (q, 2H, J = 7.1 Hz), 2.73–2.63 (m, 1H), 1.92–1.84 (m, 2H), 1.77–1.67 (m, 2H), 1.66–1.60 (m, 2H), 1.49–1.40 (m, 2H), 1.38 (t, 3H, J = 7.1 Hz). $^{13}\text{C-APT-NMR}$ (100 MHz, CDCl_3) δ 183.6 (1C), 162.5 (1C), 159.1 (1C), 123.2 (1C), 62.3 (1C), 43.7 (1C), 32.4 (2C), 25.4 (2C), 14.0 (1C).

B. General experimental procedure for the synthesis of adducts **7a–k.** To a suspension of catalyst **4a** (20 mol%) and β,γ -unsaturated α -ketoester **5a–g** (0.05 mmol) in CHCl_3 (0.25 mL), indole **6a–e** (0.1 mmol) was added and the resulting mixture was stirred at 12 °C for the indicated time. After this time, the reaction was purified by flash chromatography (silica gel, hexane/ EtOAc 8:2).

Ethyl 4-(1*H*-indol-3-yl)-2-oxo-4-phenylbutanoate (7a) Following the general procedure B, compound **7a** was obtained as a yellow liquid after 2 days of reaction in 78% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH 90:10, flow rate 1 mL/min, λ 280.3 nm): τ major = 16.9 min, τ minor = 13.5 min. $[\alpha]_D^{22}$ = -0.6 (c 0.76, CHCl_3 , 40% ee). The NMR spectra ($^1\text{H-NMR}$ and $^{13}\text{C-APT-NMR}$) for compound **7a** are consistent with values previously reported in the literature.^[11d]

Ethyl 4-(1*H*-indol-3-yl)-6-methyl-2-oxoheptanoate (7b) Following the general procedure B, compound **7b** was obtained as a yellow liquid after 4 days of reaction in 71% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH 95:5, flow rate 1 mL/min, λ 280.4 nm): τ major = 15.6 min, τ minor = 13.3 min. $[\alpha]_D^{22}$ = -1.1 (c 0.40, CHCl_3 , 71% ee). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.98 (br s, 1H), 7.68–7.65 (m, 1H), 7.35–7.33 (m, 1H), 7.20–7.08 (m, 2H), 7.00 (d, 1H, J = 2.4 Hz), 4.16–4.10 (m, 2H), 3.68–3.60 (m, 1H), 3.30 (dd, 1H, J = 16.5 Hz, J = 7.8 Hz), 3.15 (dd, 1H, J = 16.5 Hz, J = 7.8 Hz), 1.88–1.78 (m, 1H), 1.55–1.44 (m, 2H), 1.22 (t, 3H, J = 7.1 Hz), 0.91 (d, 3H, J = 6.2 Hz), 0.87 (d, 3H, J = 6.2 Hz). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 194.3 (1C), 161.1 (1C), 136.5 (1C), 126.4 (1C), 122.0 (1C), 121.6 (1C), 119.3 (1C), 119.3 (1C), 118.2 (1C), 111.2 (1C), 62.2 (1C), 46.1 (1C), 44.9 (1C), 30.4 (1C), 25.6 (1C), 23.2 (1C), 21.9 (1C), 13.8 (1C).

Ethyl 4-(1*H*-indol-3-yl)-2-oxoheptanoate (7c) Following the general procedure B, compound **7c** was obtained as a yellow liquid after 4 days

of reaction in 68% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (*n*-hexane/EtOAc 90:10, flow rate 1 mL/min, λ 280.0 nm): τ major = 25.1 min, τ minor = 32.3 min. $[\alpha]_D^{22} = -2.7$ (c 0.46, CHCl₃, 72% ee). ¹H-NMR (300 MHz, CDCl₃) δ 7.98 (br s, 1H), 7.67-7.63 (m, 1H), 7.35-7.32 (m, 1H), 7.21-7.07 (m, 2H), 6.99-6.98 (m, 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 3.62-3.51 (m, 1H), 3.31 (dd, 1H, $J = 16.5$ Hz, $J = 7.6$ Hz), 3.19 (dd, 1H, $J = 16.5$ Hz, $J = 6.8$ Hz), 1.88-1.65 (m, 2H), 1.35-1.25 (m, 2H), 1.23 (t, 3H, $J = 7.1$ Hz), 0.87 (t, 3H, $J = 7.3$ Hz). ¹³C-APT-NMR (75 MHz, CDCl₃) δ 194.3 (1C), 161.1 (1C), 136.4 (1C), 126.5 (1C), 122.0 (1C), 121.4 (1C), 119.3 (1C), 119.3 (1C), 118.3 (1C), 111.2 (1C), 62.2 (1C), 45.6 (1C), 37.9 (1C), 32.1 (1C), 20.7 (1C), 14.0 (1C), 13.8 (1C).

Ethyl 4-(1*H*-indol-3-yl)-5-methyl-2-oxohexanoate (7d) Following the general procedure B, compound **7d** was obtained as a yellow liquid after 4 days of reaction in 67% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (*n*-hexane/EtOAc 90:10, flow rate 1 mL/min, λ 285.2 nm): τ major = 26.0 min, τ minor = 28.5 min. $[\alpha]_D^{22} = -0.4$ (c 1, CHCl₃, 75% ee). ¹H-NMR (300 MHz, CDCl₃) δ 7.98 (br s, 1H), 7.64-7.61 (m, 1H), 7.34-7.31 (m, 1H), 7.19-7.06 (m, 2H), 6.97-6.96 (m, 1H), 4.13-4.01 (m, 2H), 3.44-3.35 (m, 1H), 3.30-3.18 (m, 2H), 2.17-2.04 (m, 1H), 1.16 (t, 3H, $J = 7.1$ Hz), 0.96 (d, 3H, $J = 6.7$ Hz), 0.88 (d, 3H, $J = 6.7$ Hz). ¹³C-APT-NMR (75 MHz, CDCl₃) δ 194.6 (1C), 161.2 (1C), 127.1 (1C), 122.1 (1C), 122.0 (1C), 119.5 (1C), 119.3 (1C), 117.2 (1C), 111.1 (1C), 110.0 (1C), 62.1 (1C), 42.6 (1C), 38.9 (1C), 32.8 (1C), 20.6 (1C), 20.4 (1C), 13.8 (1C).

Ethyl 4-(1*H*-indol-3-yl)-2-oxooctanoate (7e) Following the general procedure B, compound **7e** was obtained as a yellow liquid after 4 days of reaction in 73% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (*n*-hexane/EtOAc 90:10, flow rate 1 mL/min, λ 280.0 nm): τ major = 25.8 min, τ minor = 32.8 min. $[\alpha]_D^{22} = +1.4$ (c 0.38, CHCl₃, 72% ee). ¹H-NMR (300 MHz, CDCl₃) δ 7.97 (br s, 1H), 7.67-7.63 (m, 1H), 7.36-7.32 (m, 1H), 7.21-7.07 (m, 2H), 6.70-6.99 (m, 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 3.59-3.49 (m, 1H), 3.31 (dd, 1H, $J = 16.5$ Hz, $J = 7.5$ Hz), 3.19 (dd, 1H, $J = 16.5$ Hz, $J = 6.8$ Hz), 1.89-1.68 (m, 2H), 1.34-1.20 (m, 4H), 1.22 (t, 3H, $J = 7.1$ Hz), 0.83 (t, 3H, $J = 6.9$ Hz). ¹³C-APT-NMR (75 MHz, CDCl₃) δ 194.3 (1C), 161.2 (1C), 126.5 (1C), 122.0 (1C), 121.7 (1C), 121.4 (1C), 119.3 (1C), 119.3 (1C), 118.4 (1C), 111.2 (1C), 62.2 (1C), 45.7 (1C), 35.4 (1C), 32.4 (1C), 29.7 (1C), 22.6 (1C), 14.0 (1C), 13.8 (1C).

Ethyl 4-cyclopentyl-4-(1*H*-indol-3-yl)-2-oxobutanoate (7f) Following the general procedure B, compound **7f** was obtained as a yellow liquid after 4 days of reaction in 85% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH 95:5, flow rate 1 mL/min, λ 280.5 nm): τ major = 15.1 min, τ minor = 14.0 min. $[\alpha]_D^{22} = -4.8$ (c 0.67, CHCl₃, 76% ee). ¹H-NMR (300 MHz, CDCl₃) δ 7.98 (br s, 1H), 7.68-7.64 (m, 1H), 7.34-7.30 (m, 1H), 7.19-7.07 (m, 2H), 6.98 (d, 1H, $J = 2.4$ Hz), 4.12-3.96 (m, 2H), 3.43-3.32 (m, 2H), 3.28-3.17 (m, 1H), 2.42-2.27 (m, 1H), 1.94-1.83 (m, 1H), 1.73-1.40 (m, 5H), 1.34-1.21 (m, 2H), 1.15 (t, 3H, $J = 7.1$ Hz). ¹³C-APT-NMR (75 MHz, CDCl₃) δ 194.5 (1C), 161.1 (1C), 136.3 (1C), 126.7 (1C), 122.0 (1C), 121.9 (1C), 119.5 (1C), 119.2 (1C), 118.0 (1C), 111.1 (1C), 62.1 (1C), 45.8 (1C), 44.7 (1C), 38.0 (1C), 31.6 (1C), 31.2 (1C), 25.4 (1C), 25.0 (1C), 13.7 (1C).

Ethyl 4-cyclohexyl-4-(1*H*-indol-3-yl)-2-oxobutanoate (7g) Following the general procedure B, compound **7g** was obtained as a yellow liquid after 4 days of reaction in 72% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (*n*-hexane/EtOAc 90:10, flow rate 1 mL/min, λ 280.5 nm): τ major = 22.7 min, τ minor = 25.2 min. $[\alpha]_D^{22} = -0.8$ (c 0.64, CHCl₃, 73% ee). ¹H-NMR (300 MHz, CDCl₃) δ 7.98 (br s, 1H), 7.64-7.60 (m, 1H), 7.34-7.30 (m, 1H), 7.20-7.06 (m, 2H), 6.95-6.94 (m, 1H), 4.11-4.00 (m, 2H), 3.44-3.34 (m,

1H), 3.29-3.26 (m, 2H), 1.86-1.79 (m, 1H), 1.76-1.66 (m, 2H), 1.32-1.19 (m, 2H), 1.15 (t, 3H, $J = 7.1$ Hz), 1.09-0.76 (m, 6H). ¹³C-APT-NMR (75 MHz, CDCl₃) δ 194.7 (1C), 161.2 (1C), 136.2 (1C), 127.1 (1C), 122.1 (1C), 121.9 (1C), 119.6 (1C), 119.3 (1C), 117.2 (1C), 111.1 (1C), 62.1 (1C), 42.7 (1C), 38.1 (2C), 31.3 (1C), 30.8 (1C), 29.7 (1C), 26.5 (1C), 26.4 (1C), 13.8 (1C).

Ethyl 4-(5-methoxy-1*H*-indol-3-yl)-5-methyl-2-oxohexanoate (7h) Following the general procedure B, compound **7h** was obtained as a yellow liquid after 4 days of reaction in 80% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH 95:5, flow rate 1 mL/min, λ 245.4 nm): τ major = 24.5 min, τ minor = 28.1 min. $[\alpha]_D^{28} = +4.6$ (c 0.27, CHCl₃, 74% ee). ¹H-NMR (400 MHz, CDCl₃) δ 7.88 (br s, 1H), 7.21 (dd, 1H, $J = 8.8$ Hz, $J = 0.4$ Hz), 7.05 (d, 1H, $J = 2.4$ Hz), 6.94 (d, 1H, $J = 2.5$ Hz), 6.83 (dd, 1H, $J = 8.8$ Hz, $J = 2.4$ Hz), 4.13-4.04 (m, 2H), 3.87 (s, 3H), 3.39-3.35 (m, 1H), 3.30 (dd, 1H, $J = 21.2$ Hz, $J = 5.6$ Hz), 3.21 (dd, 1H, $J = 15.7$ Hz, $J = 5.2$ Hz), 2.11-2.03 (m, 1H), 1.17 (t, 3H, $J = 7.1$ Hz), 0.96 (d, 3H, $J = 6.7$ Hz), 0.89 (d, 3H, $J = 6.7$ Hz). ¹³C-APT-NMR (100 MHz, CDCl₃) δ 194.6 (1C), 161.2 (1C), 153.8 (1C), 131.4 (1C), 127.6 (1C), 122.9 (1C), 116.9 (1C), 111.9 (1C), 111.7 (1C), 101.6 (1C), 62.2 (1C), 56.0 (1C), 43.5 (1C), 38.7 (1C), 32.8 (1C), 20.6 (1C), 20.3 (1C), 13.8 (1C).

Ethyl 6-methyl-4-(2-methyl-1*H*-indol-3-yl)-2-oxoheptanoate (7i) Following the general procedure B, compound **7i** was obtained as a yellow liquid after 4 days of reaction in 88% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH 95:5, flow rate 1 mL/min, λ 292.3 nm): τ major = 10.9 min, τ minor = 12.7 min. $[\alpha]_D^{27} = -11.9$ (c 0.71, CHCl₃, 50% ee). ¹H-NMR (400 MHz, CDCl₃) δ 7.72 (br s, 1H), 7.56 (d, 1H, $J = 7.2$ Hz), 7.21 (d, 1H, $J = 7.2$ Hz), 7.09-7.01 (m, 2H), 4.05-3.87 (m, 2H), 3.56 (dd, 1H, $J = 16.1$ Hz, $J = 10.4$ Hz), 3.26 (dd, 1H, $J = 16.1$ Hz, $J = 10.4$ Hz), 2.35 (s, 3H), 2.26-2.17 (m, 1H), 1.13 (t, 3H, $J = 7.1$ Hz), 1.09 (d, 3H, $J = 6.6$ Hz), 0.74 (d, 3H, $J = 6.6$ Hz). ¹³C-APT-NMR (100 MHz, CDCl₃) δ 194.9 (1C), 160.8 (1C), 135.4 (1C), 132.1 (1C), 127.0 (1C), 120.7 (1C), 119.2 (1C), 119.0 (1C), 112.2 (1C), 110.3 (1C), 62.2 (1C), 46.6 (1C), 39.8 (1C), 32.4 (1C), 21.5 (1C), 21.3 (1C), 13.7 (1C), 12.1 (1C).

Ethyl 5-methyl-4-(1-methyl-1*H*-indol-3-yl)-2-oxohexanoate (7k) Following the general procedure B, compound **7k** was obtained as a yellow liquid after 4 days of reaction in 90% yield. ¹H-NMR (300 MHz, CDCl₃) δ 7.61 (d, 1H, $J = 7.9$ Hz), 7.27-7.05 (m, 3H), 6.81 (br s, 1H), 4.15-3.99 (m, 2H), 3.72 (s, 3H), 3.43-3.18 (m, 3H), 2.18-2.00 (m, 1H), 1.17 (t, 3H, $J = 7.1$ Hz), 0.96 (d, 3H, $J = 6.7$ Hz), 0.88 (d, 3H, $J = 6.7$ Hz). ¹³C-APT-NMR (75 MHz, CDCl₃) δ 194.6 (1C), 161.3 (1C), 137.0 (1C), 127.6 (1C), 126.9 (1C), 121.4 (1C), 119.65 (1C), 118.7 (1C), 115.5 (1C), 109.1 (1C), 62.1 (1C), 42.8 (1C), 38.8 (1C), 32.9 (1C), 32.7 (1C), 20.6 (1C), 20.4 (1C), 13.8 (1C).

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