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Enantioselective *N*-Alkylation of Nitroindoles under Phase-Transfer Catalysis

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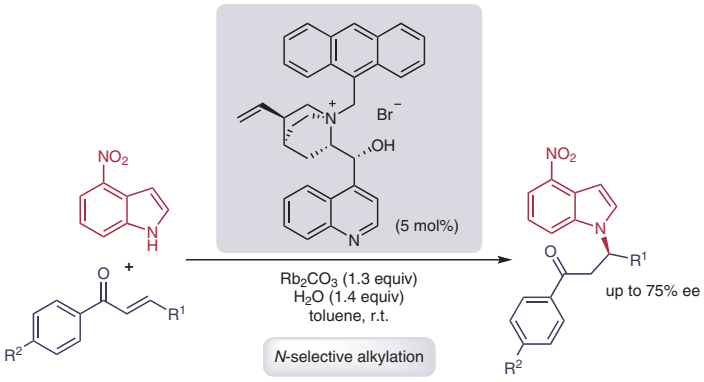

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Abstract An asymmetric phase-transfer-catalyzed *N*-alkylation of substituted indoles with various Michael acceptors was studied. Acidities of nitroindoles were determined in acetonitrile by UV-Vis spectrophotometric titration. There was essentially no correlation between acidity and reactivity in the aza-Michael reaction. The position of the nitro group on the indole ring was essential to control the stereoselectivity of the reaction. Michael adducts were obtained in high yields and moderate enantioselectivities in the reaction between 4-nitroindole and various Michael acceptors in the presence of cinchona alkaloid based phase-transfer catalysts. In addition to outlining the scope and limitations of the method, the geometries of the transition states of the reaction were calculated.

Key words asymmetric catalysis, heterocycles, Michael addition, organocatalysis, phase-transfer catalysis

Indole and its derivatives are very important scaffolds in medicinal chemistry,[1] being among the most prevalent ring system in small molecule drugs.[2] *N*-Substituted indole derivatives are used more seldom but there are still examples of biologically active pharmaceutical compounds containing this structural moiety (Figure 1).[3] The direct functionalization of the indole ring system has been an active area of research for decades.[4] The most widely exploited reaction is an electrophilic aromatic substitution at the C3 position.[5] Recently, methods have been developed for the direct electrophilic reactions at the C2 position via a transition-metal-catalyzed C–H activation.[6] At the same time, the enantioselective *N*-alkylation of indole remains underdeveloped. The aromaticity of the indole ring and, correspondingly, low nucleophilicity of the nitrogen atom make it challenging.

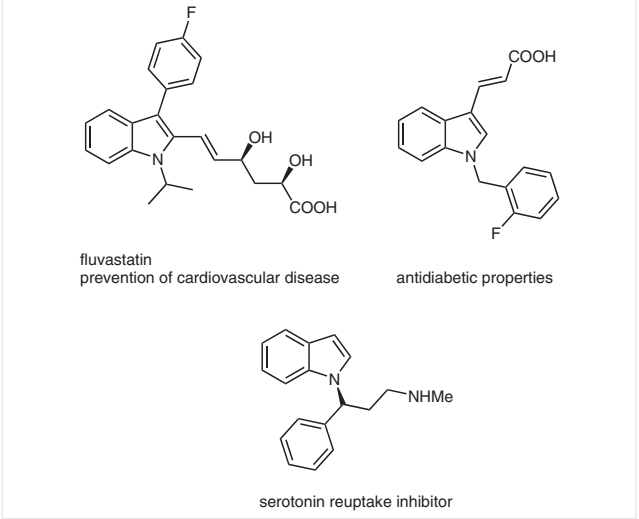

Figure 1 Examples of biologically active *N*-alkylated indoles

Mainly transition-metal-catalyzed reactions have been applied for the enantioselective *N*-addition to indole derivatives.[7] Only limited methodologies have been developed by employing asymmetric organocatalytic strategies for *N*-alkylation. Chiral phosphoric acids were applied as catalysts for the synthesis of *N*-substituted indoles (Scheme 1a).[8] In these examples strong electrophiles are generated under acidic conditions or the simultaneous activation of the electrophile and nucleophile takes place. Alternatively, under basic conditions an intramolecular *N*-alkylation led to the formation of tricyclic products via phase-transfer catalysis (Scheme 1b).[9] The introduction of an electron-withdrawing group reduces the p*Ka* value of the indole and increases the

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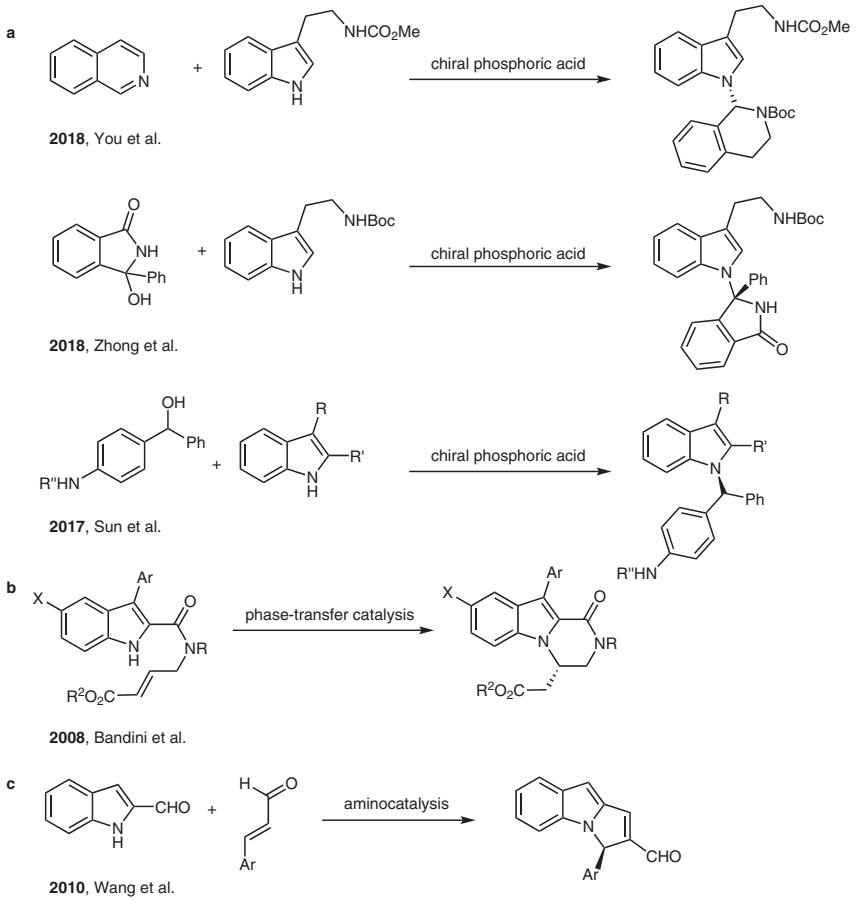


Scheme 1 Organocatalytic enantioselective *N*-alkylation of indole derivatives

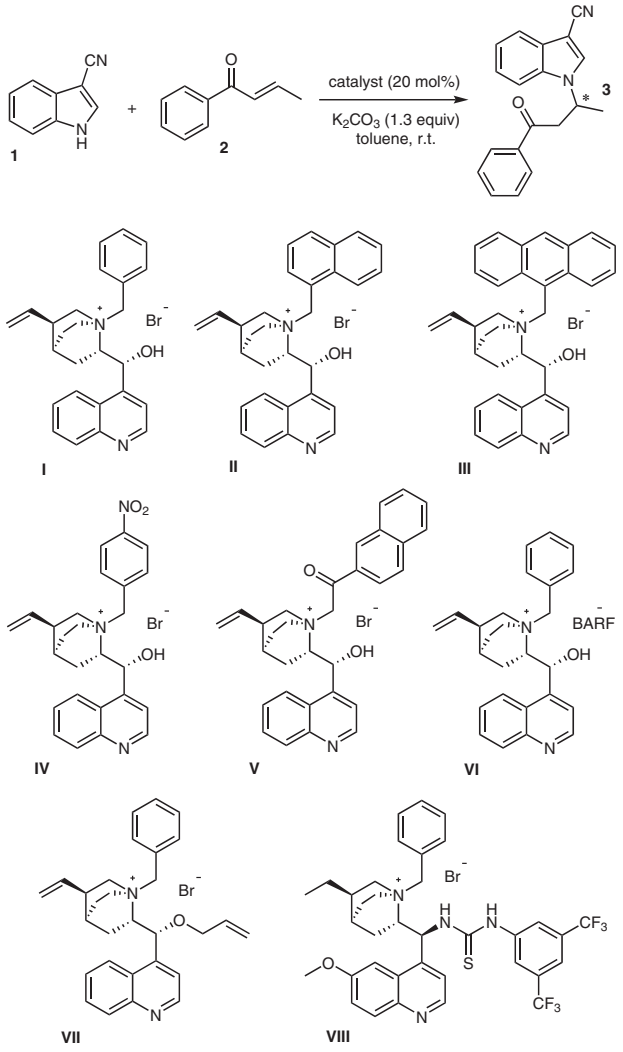
nucleophilicity of the N1 position, enabling an aminocatalytic intramolecular aza-Michael/aldol cascade reaction of 2-formyl-substituted indole, also affording tricyclic products in high enantio- and regioselectivities (Scheme 1c).[10]

In this article, we studied the dependence of the N–H acidity versus the position of the electron-withdrawing group on the indole ring; the synthetic potential of it was further harnessed to access enantiomerically pure indole derivatives via an aza-Michael reaction.[11]

Our initial studies focused on the reaction of 3-cyanoindole (**1**) with *trans*-crotonophenone **2**. An EWG on the third position of the indole ring increases the acidity of the N–H proton and protects the most reactive C3 position. Recently, Yang et al. published a non-asymmetric method consisting of a potassium hydroxide catalyzed intermolecular aza-Michael addition of indole derivatives to aromatic enones.[12] We studied an asymmetric phase-transfer-catalyzed (PTC) version of it. A library of different phase-transfer catalysts based on cinchona alkaloids was screened (Table 1).

The model reaction was performed at room temperature in toluene in the presence of an enantiomerically pure catalyst (20 mol%) and potassium carbonate as a base. First, the steric effect of the substituents of the ammonium salts **I–III** derived from cinchonidine on the reaction was studied. Almost full conversion of the starting compounds **1** and **2** was achieved in the case of benzyl-, naphthyl-, and anthracenyl-substituted catalysts (Table 1, entries 1–3). There was a clear dependence of the steric effect of the catalyst on the enantioselectivity of the reaction. Sterically more demanding catalysts afforded higher enantioselectivities but they remained modest (in the best case 42% ee; entry 3). Catalyst **IV** demonstrated the same conversion and quite similar stereoselectivity as the anthracenyl-substituted catalyst **III** (entry 4). Due to the low solubility of the ammonium salt **V** in toluene, the conversion and ee of product **3** were low (entry 5). The replacement of the bromide anion in catalyst **I** by the tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) anion dramatically affected the reaction rate and enantioselectivity (entry 6). The influence of the hydrogen-bond donor of the catalyst was essential.[13] Protecting the OH group as an allyl ether (catalyst **VII**) provided full conversion of the starting materials but the product was racemic (entry 7). The thiourea derived catalyst **VIII** afforded the opposite enantiomer **3** with low selectivity (entry 8). The obtained results were unsatisfying, and

Table 1 Catalyst Screening for the Reaction between 3-Cyanoindole and *trans*-Crotonophenone[a]



Entry	Catalyst	Time (h)	Conv. (%)[b]	ee (%)[c]
1	**I**	18	98	18
2	**II**	18	99	26
3	**III**	16	83	42
4	**IV**	16	80	36
5	**V**	16	26	4
6	**VI**	18	5	6
7	**VII**	16	99	*rac*
8	**VIII**	20	29	–28

[a] Reaction conditions: **1** (1.2 equiv), **2** (1 equiv), catalyst (20 mol%), base (1.3 equiv), r.t.
[b] Conversion determined by ^{1}H NMR of crude mixture.
[c] Determined by chiral HPLC analysis of the sample obtained by preparative TLC.

therefore a more systematic study of substituted indoles was performed. Nitroindoles were the compounds of choice because of their possible interaction with the phase-transfer catalyst.[14]

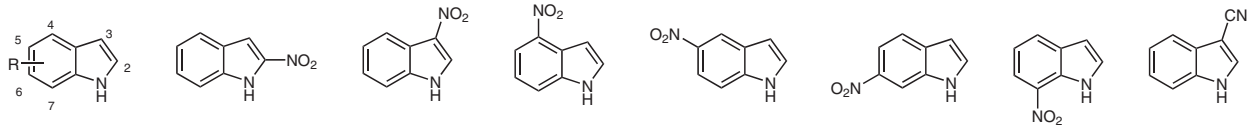
First, the acidities of the nitrosubstituted indoles were determined (Table 2). As expected, nitroindoles and 3-cyanoindole behave in acetonitrile as weak acids, with pK_a values in the range of 22–30, thus being by their acid strength approximately between benzoic acid[15] and phenol.[16] By acid strength, the nitroindoles fall into two distinct groups – the ones with nitro group on the five-membered ring (pK_a between 22 and 24) and the ones with the nitro group on the six-membered ring (pK_a between 27 and 30). The reason is evidently the good match between the electron-withdrawing abilities of the nitro group on the one hand and the vicinity of the nitro group to the acidity center in the five-membered ring, as well as the overall higher electron density in the five-membered ring. The strongest of the nitroindoles – 3-nitroindole – benefits from highly efficient resonance stabilization of the negative charge in the anion via conjugation of the nitro group with the acidity center.

In the following reactions, commercially available 4-nitroindole was used as a model compound. It was found that under similar conditions applied to 3-cyanoindole the reaction with 4-nitroindole in the presence of catalyst **III** was more selective (Table 3, entry 1). The reaction rate was increased when rubidium carbonate was used as a base, affording the *N*-alkylated product in 95% yield within 5 hours without any decrease in enantioselectivity (entry 2, 65% ee). An aqueous solution of rubidium carbonate decreased the rate of the reaction substantially and for the full conversion a reaction time of 24 hours was needed (entry 3). The enantiomeric purity of the product was increased to 74% by lowering the temperature of the reaction to –20 °C (entry 5). Cesium carbonate induced a less selective reaction (entry 6).

During the optimization of the reaction conditions the effect of water on the reaction rate was revealed. Small amounts of water could significantly affect the rate of the reactions catalyzed by the quaternary ammonium salts.[17] The balance between the amount of water and amount of phase-transfer catalyst was screened (for the full optimization process, see the Supporting Information). It was found that both low concentrations and high concentrations of water decreased the reaction rate. With the optimum water concentration the amount of the catalyst **III** was decreased to 5 mol%. Increasing the amount of *trans*-crotonophenone from 1.2 equivalents to 2.1 equivalents afforded the *N*-alkylated 4-nitroindole **5a** in a reasonable time (5 h), high yield (95%), and moderate ee (69%).

Next, the influence of the position of the nitro group on the aza-Michael reaction was studied under the optimal conditions (Table 4). It was found that the most reactive

Table 2 Results of pK_a Measurements in Acetonitrile



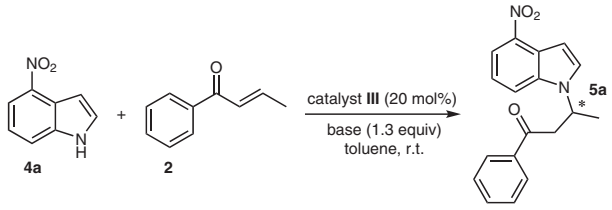
Acid (A)	Reference acid (Ra)	pK_a(Ra)	pK_a[a]	pK_a(A)	Assigned pK_a(A)
2-nitroindole	2-nitrophenol	22.85	–0.80	23.65	23.64
	9-MeO_2C-fluorene	23.53	–0.10	23.63	
3-nitroindole	2-nitrophenol	22.85	0.10	22.75	22.77
	9-MeO_2C-fluorene	23.53	0.74	22.79	
4-nitroindole	(4-MeC_6F_4)(C_6H_5)CHCN	26.96	–0.88	27.84	27.8
	5-nitroindole	28.1	0.28	27.8	
5-nitroindole	(4-MeC_6F_4)(C_6H_5)CHCN	26.96	–1.12	28.08	28.1
6-nitroindole	(4-MeC_6F_4)(C_6H_5)CHCN	26.96	–0.85	27.81	27.7
	4-nitroindole	27.83	0.14	27.69	
7-nitroindole	5-nitroindole	28.1	–1.74	29.8	29.9
	6-nitroindole	27.74	–2.21	29.95	
	9-C_6F_5-fluorene	28.11	1.88	29.99	
3-cyanoindole	(4-MeC_6F_4)(C_6H_5)CHCN	26.96	0.93	26.03	26.0
	(C_6F_5)(C_6H_5)CHCN	26.14	0.18	25.96	

[a] pK_a(Ra) – pK_a(A)

derivatives were 4- and 5-nitroindoles (entries 1 and 3), but the former was more selective (69% and 38% ee, respectively). Also, 3- and 6-nitroindoles were less attractive substrates, affording products in low enantioselectivities (entries 2 and 4). In the case of 2- and 7-nitroindole, no reaction was detected during 24 hours, most probably because of steric reasons (entries 5 and 6). The obtained results show that the position of the nitro group is essential in determining the enantioselectivity and it participates in the transition state. Comparison of Tables 2 and 4 reveals that there is essentially no correlation between acidity and reactivity in the aza-Michael reaction. There is, however, a connection between reactivity and steric hindrance: the least reactive are 2- and 7-nitroindole, where the nitro groups are spatially closest to the acidity center.

The scope of the reaction was studied with the most selective 4-nitroindole **4a** (Scheme 2). Various α,β-unsaturated carbonyl compounds **2a–l**, unsaturated ester **2m**, and nitrostyrene **2n** were used as Michael acceptors. It was found that aromatic and heteroaromatic enones were the most reactive and selective starting compounds, affording products within 5 hours in moderate to high yields and moderate to good enantioselectivities. Neither electron-withdrawing (**4b**), nor electron-donating groups (**4c**) in the phenyl ring influenced the reaction substantially. The heteroaromatic furyl substituent did not affect the reaction enantioselectivity, and product **6d** was obtained in high yield. Steric hindrance in the β-position of the enone decreased the reaction rate, as demonstrated in experiments with the vinyl-substituted enones **2e** and **2f**.

Table 3 Optimization of the Reaction between 4-Nitroindole (**4a**) and *trans*-Crotonophenone (**2**)[a]

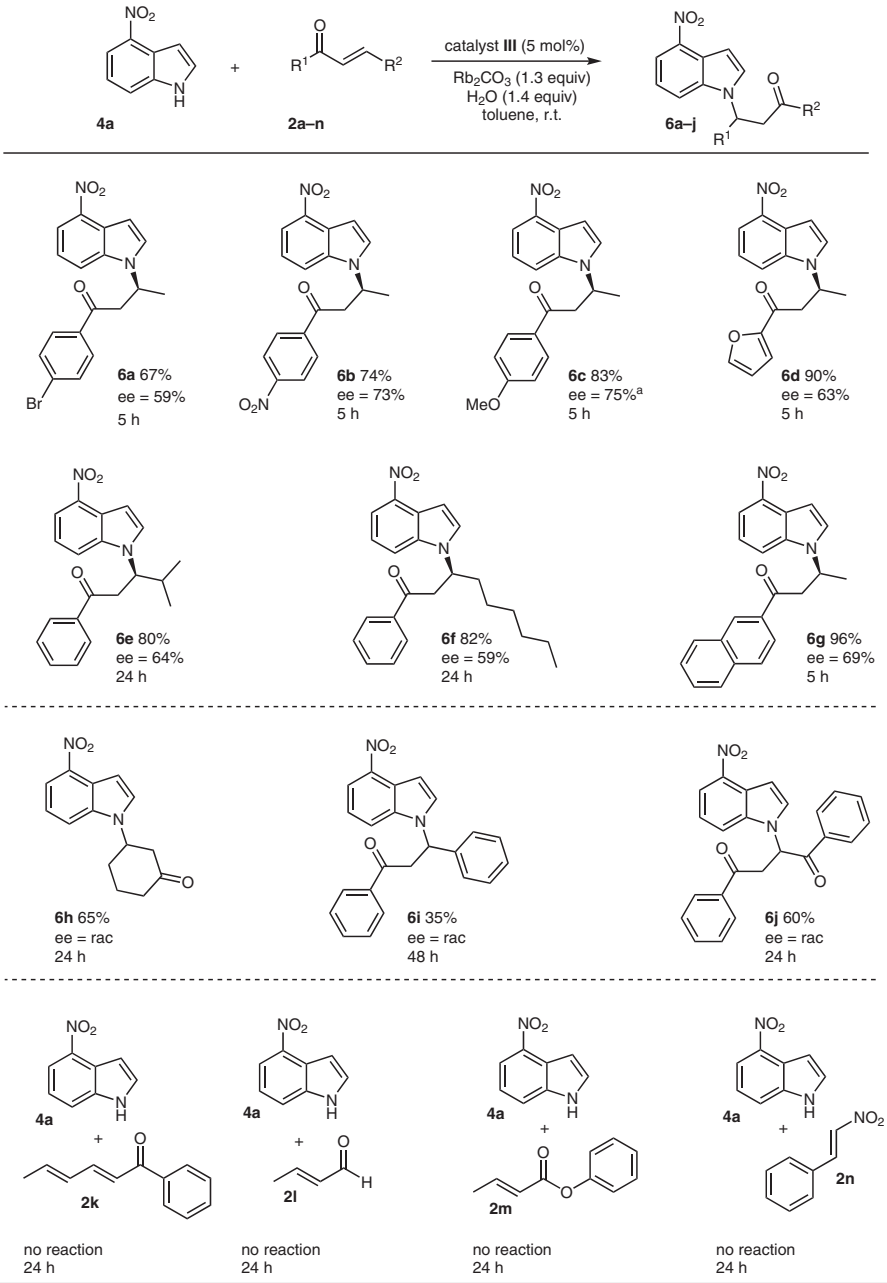


Entry	Base	Time	Yield (%)[b]	ee (%)[c]
1	K_2CO_3	21 h	95	65
2	Rb_2CO_3	5 h	92	65
3	5 M aq Rb_2CO_3	24 h	95	64
4[d]	Rb_2CO_3	24 h	97	70
5[e]	Rb_2CO_3	6 d	97	74
6	Cs_2CO_3	18 h	95	54

[a] Reaction conditions: **4a** (0.1 mmol, 1 equiv), **2** (2.1 equiv), catalyst **III** (20 mol%), Rb_2CO_3 (1.3 equiv), r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Reaction at 5 °C.
[e] Reaction at –20 °C

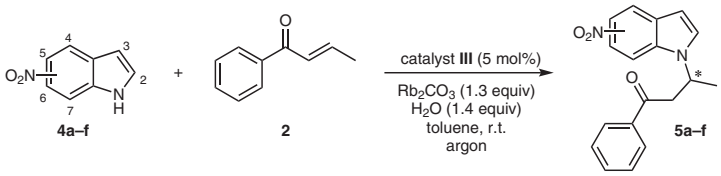
The absolute stereochemistry of compound **6c** was unambiguously assigned by single-crystal X-ray diffraction (Figure 2). The configurations of other compounds in the series were assigned by analogy.

To our disappointment, the reaction had limitations that could be divided into two categories: either the reaction proceeded, but racemic products were formed (**6h**, **6i**, **6j**), or there was no reaction (starting compounds **2k–n**). Sterically more hindered aliphatic cyclic ketone **2h** and *trans*-chalcone **2i** provided racemic products with lower reaction rates compared to the model compound **2a**. It was assumed that the long reaction time gave rise to a nonselective background reaction, leading to racemic products. In the case of the 1,4-diketone **6j**, racemization of the α-position of the carbonyl group through enolization under basic conditions is most probable. The reaction did not proceed



Scheme 2 The reaction scope and limitations. *Reagents and conditions*: **4a** (0.1 mmol, 1 equiv), **2a–n** (2.1 equiv), catalyst **III** (5 mol%), Rb_2CO_3 (1.3 equiv), H_2O (1.4 equiv), under argon atmosphere; all yields are isolated yields; ee values were determined by chiral HPLC analysis; [a] 90% ee was obtained after a single recrystallization.

Table 4 Effect of the Position of the Nitro Group on Nitroindole **4** on the Aza-Michael Reaction[a]



Entry	Product	NO_2 position	Time (h)	Yield (%)[b]	ee (%)[c]
1	**5a**	4	5	92	69
2	**5b**	3	5	65	42
3	**5c**	5	5	95	38
4	**5d**	6	5	82	35
5	**5e**	2	24	nr[d]	–
6	**5f**	7	24	nr[d]	–

[a] Reaction conditions: 0.1 mmol scale, 1 equiv of **4a–f**, 2.1 equiv of **2**, 5 mol% of catalyst **III**, 1.3 equiv of Rb_2CO_3 and 1.4 equiv of H_2O under argon atmosphere.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] nr = no reaction.

with (2*E*,4*E*)-1-phenylhexa-2,4-dien-1-one (**2k**), crotonaldehyde (**2l**), phenyl (*E*)-but-2-enoate (**2m**), and β-nitrostyrene (**2n**).

Generally, aromatic ketones were the best substrates for the *N*-alkylation of nitroindoles. The obtained results suggested the importance of π–π interactions in the transition state. To gain insight into the reaction mechanism, computational studies were conducted based on the density functional M062X/def2SVP method. In order to assess noncovalent interactions, a Natural Bond Orbital (NBO) analysis was performed using the M062X/def2TZVP method (for calculation details and NBO energies, see the Supporting Information). In the ternary complex INT1-S a strong hydrogen bond between the deprotonated N atom of indole **4a** and the hydroxyl group of catalyst **III**, together with the π–π interactions between the quinolone ring of the catalyst **III** and indole **4a**, form (Figure 3A). Distortion of the complex leads to the intermediate (INT2-S) with reorganized geometry: a hydrogen bond forms between the nitro group of indole and the hydroxyl of the catalyst (Figure 3B). The intermediate forms a product via a bond-forming step (TS1) (distance between Michael acceptor and donor site is 2.28

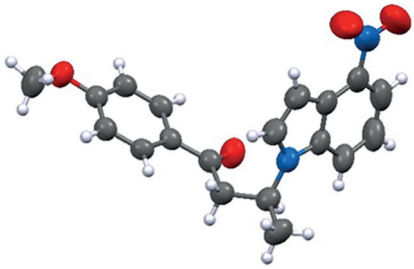


Figure 2 X-ray crystal structure of compound **6c** (CCDC 1923379)

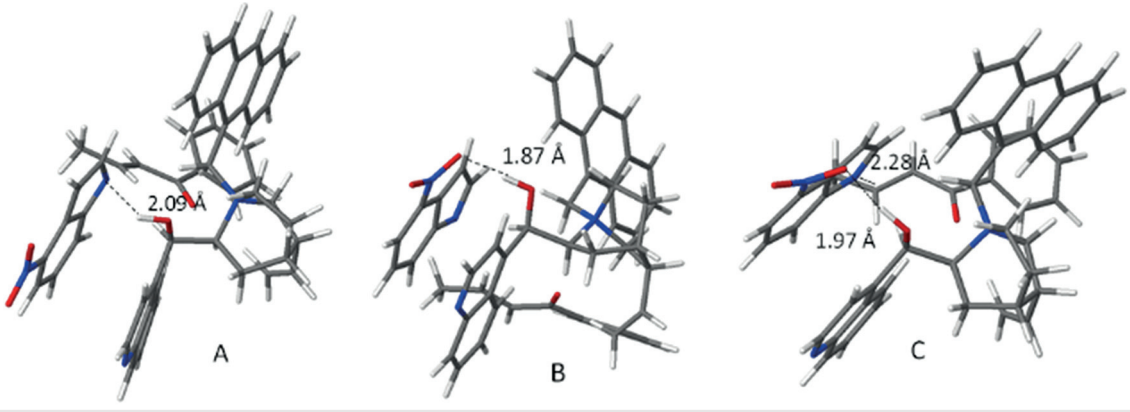


Figure 3 Optimized geometries of intermediates and transition state: A: INT1-S; B: INT2-S; C: TS1-S

Å) (Figure 3C). Throughout the reaction, π–π interactions remain important.

We have revealed here a systematic study of the *N*-alkylation of nitroindoles. It was found that a *Cinchona* alkaloid-derived PTC reaction with various Michael acceptors led exclusively to aza-Michael adducts in high yields and moderate to good enantioselectivities. The acidity of the N–H proton was not the decisive factor in determining the reactivity and selectivity of the reaction. Instead, the position of the nitro group on the indole ring plays a crucial role in the reaction.

All commercially available reagents were used without further purification. All air- or moisture-sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. The reactions were monitored by TLC with silica-gel-coated aluminum plates (Merck 60 F254) and visualized with $KMnO_4$, anisaldehyde, vaniline, or ninhydrine stain. Yields refer to chromatographically purified products. ^{1}H NMR spectra were recorded on a Bruker Avance III instrument at 400 MHz and are reported in ppm (δ) referenced to the residual solvent signal ($CDCl_3$: δ = 7.26; CD_3OD, δ = 3.31). ^{13}C NMR spectra were recorded at 101 MHz and are reported in parts per million (δ) referenced to the residual solvent signal ($CDCl_3$: δ = 77.16; CD_3OD: δ = 49.00). HRMS spectra were recorded with an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrophotometer. Optical rotations were obtained with an Anton Paar GWB Polarimeter MCP500 at 20 °C in $CHCl_3$ and are calibrated with pure solvent as a blank. Chiral HPLC was performed by using Chiralpak AD-H (250 × 4.6 mm), Chiralcel OJ-H (250 × 4.6 mm), or Chiralcel OD-H (250 × 4.6 mm) columns. Column chromatography was performed on a preparative purification system with silica gel Kieselgel 40–63 µm. The measured melting points are uncorrected. All crystalline products are obtained from chloroform. Purchased chemicals and solvents were used as received. DCM was distilled over phosphorus pentoxide. PE has a boiling point of 40–60 °C. The reactions were performed under air without additional moisture elimination unless stated otherwise.

Acidity Measurements

UV-Vis spectrophotometric titration was used to determine the acidity (pK_a values) of the nitroindoles and 3-cyanoindole in acetonitrile. Measurements were carried out in a glovebox, applying a method described earlier.[15] The argon atmosphere (5.0) as the environment for all experiments was kept dry and oxygen-free (both contents below 1 ppm) and only freshly prepared solutions in MeCN (H_2O < 5 ppm) were used. UV-Vis spectra were collected on Agilent Cary 60 and PerkinElmer Lambda 12 spectrophotometers using an external cell compartment inside the glovebox. CF_3SO_2OH and $EtN{=}P_2(dma)_5$ (or *tert*-butyliminotri(pyrrolidino)phosphorane) solutions in MeCN were used as acidic and basic titrants, respectively. In titration experiments the concentration of the indoles and reference acids were in the range of 10^{-5} to 10^{-4} M.

Phase-transfer catalysts **I**–**III**,[18] **VII**,[18] **IV**,[19,20] **V**,[21] **VI**,[22] and **VIII**[23] were prepared by corresponding literature procedures and the

Analytical data matched those in the literature.

Indole derivatives **1**, **4a**, **4c**, **4d**, and **4f** were purchased from Fluorochem Ltd and used as received. 2-Nitroindole (**4e**)[24] and 3-nitroindole (**4b**)[25] were prepared according to literature procedures and the analytical data matched those in the literature.

Synthesis of Unsaturated α,β-Enones 2 and 2a–n

(*E*)-1-Phenylbut-2-en-1-one (2)[26]

To a 1 M solution of phenylmagnesium bromide in THF (25 mL, 25 mmol) in THF (75 mL) crotonaldehyde (2.07 mL, 25 mmol) was added dropwise at 0 °C under argon. The mixture was stirred for 45 min at the same temperature and then quenched with sat. aq NH_4Cl (25 mL). The organic solvent was removed under reduced pressure and aq NH_4Cl (20 mL) was added. The reaction mixture was extracted with EtOAc (5 × 50 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated to dryness under reduced pressure to provide a yellow oil. The Grignard product was dissolved in DCM (40 mL) and MnO_2 (21.7 g, 250 mmol, 10 equiv) was added under vigorous stirring. The reaction mixture was stirred overnight. The mixture was filtered through a pad of Celite, washed with DCM, and purified by column chromatography (silica gel, 2–10% EtOAc–PE).

Yield: 1.988 g (54%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.89 (m, 2 H), 7.58–7.51 (m, 1 H), 7.49–7.43 (m, 2 H), 7.07 (dq, *J* = 15.3, 6.8 Hz, 1 H), 6.91 (dq, *J* = 15.3, 1.6 Hz, 1 H), 2.00 (dd, *J* = 6.8, 1.6 Hz, 3 H).

Analytic data were in agreement with the literature data.

2-En-1-ones 2a,c–f,k by Wittig Reaction; General Procedure

The aldehyde (1.2 equiv) was added to the mixture of phosphonium ylide (1 equiv) in DCM (0.2 M). The reaction was monitored by TLC. Upon completion of the reaction, the DCM was evaporated to give a solid residue that was triturated with hexane. The solid triphenylphosphine oxide was filtered off and the hexane layer was dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The crude mixture was purified by column chromatography (silica gel).

(*E*)-1-(4-Bromophenyl)but-2-en-1-one (2a)

Following the general procedure, starting from 1-(4-bromophenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.75 g, 3.8 mmol) and acetaldehyde (256 µL, 4.56 mmol), the mixture was stirred for 7 d. The title compound was obtained after purification by column chromatography (silica gel, 1–6% EtOAc–PE).

Yield: 611 mg (71%); white crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.75 (m, 2 H), 7.64–7.56 (m, 2 H), 7.08 (dq, *J* = 15.3, 6.9 Hz, 1 H), 6.86 (dq, *J* = 15.3, 1.6 Hz, 1 H), 2.00 (dd, *J* = 6.9, 1.6 Hz, 3 H).

Analytic data were in agreement with the literature data.[27]

(*E*)-1-(4-Methoxyphenyl)but-2-en-1-one (2c)

Following the general procedure starting from 1-(4-metoxyphenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.97 g, 4.8 mmol) and acetaldehyde (326 µL, 5.8 mmol), the mixture was stirred for 7 d. The title compound was obtained after purification by column chromatography (silica gel, 1–10% EtOAc–PE).

Yield: 700 mg (83%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.90 (m, 2 H), 7.06 (dq, *J* = 15.2, 6.7 Hz, 1 H), 6.97–6.89 (m, 3 H), 3.87 (s, 3 H), 1.99 (dd, *J* = 6.8, 1.5 Hz, 3 H).

Analytic data were in agreement with the literature data.[28]

(*E*)-1-(Furan-2-yl)but-2-en-1-one (2d)

Following the general procedure starting from 1-(4-furan-2-yl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.4 g, 3.78 mmol) and acetaldehyde (255 μL, 4.54 mmol), the mixture was stirred for 6 d. The title compound was obtained after purification by column chromatography (silica gel, 2–8% EtOAc–PE).

Yield: 210 mg (41%); white crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.57 (m, 1 H), 7.24–7.22 (m, 1 H), 7.22–7.11 (m, 1 H), 6.82 (dq, *J* = 15.4, 1.7 Hz, 1 H), 6.55 (dd, *J* = 3.5, 1.7 Hz, 1 H), 1.99 (dd, *J* = 6.9, 1.7 Hz, 3 H).

Analytic data were in agreement with the literature data.[28]

(*E*)-4-Methyl-1-phenylpent-2-en-1-one (2e)

Following the general procedure starting from 1-phenyl-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.75 g, 4.6 mmol) and isobutyraldehyde (440 μL, 4.8 mmol, 1.05 equiv), the mixture was stirred for 6 d. The title compound was obtained after purification by column chromatography (silica gel, 2% EtOAc–PE).

Yield: 220 mg (28%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.89 (m, 2 H), 7.59–7.52 (m, 1 H), 7.50–7.42 (m, 2 H), 7.03 (dd, *J* = 15.5, 6.7 Hz, 1 H), 6.82 (dd, *J* = 15.5, 1.4 Hz, 1 H), 2.66–2.51 (m, 1 H), 1.14 (d, *J* = 6.8 Hz, 6 H).

Analytic data were in agreement with the literature data.[29]

(*E*)-1-Phenylnon-2-en-1-one (2f)

Following the general procedure starting from 1-phenyl-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.1 g, 2.9 mmol) and heptanal (494 μL, 3.5 mmol), the mixture was stirred for 5 d. The title compound was obtained after purification by column chromatography (silica gel, 1–6% EtOAc–PE).

Yield: 250 mg (40%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.90 (m, 2 H), 7.59–7.52 (m, 1 H), 7.51–7.42 (m, 2 H), 7.07 (dt, *J* = 15.4, 6.9 Hz, 1 H), 6.87 (dt, *J* = 15.4, 1.4 Hz, 1 H), 2.37–2.27 (m, 2 H), 1.58–1.46 (m, 2 H), 1.42–1.21 (m, 6 H), 0.93–0.84 (m, 3 H).

Analytic data were in agreement with the literature data.[29]

(2*E*,4*E*)-1-Phenylhexa-2,4-dien-1-one (2k)

Following the general procedure starting from 1-phenyl-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.1 g, 2.9 mmol) and (*E*)-but-2-enal (290 μL, 3.5 mmol), the mixture was stirred for 5 d. The title compound was obtained after purification by column chromatography (silica gel, 2–4% EtOAc–PE).

Yield: 250 mg (40%); yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.90 (m, 2 H), 7.57–7.51 (m, 1 H), 7.50–7.36 (m, 3 H), 6.87 (dd, *J* = 15.1, 0.8 Hz, 1 H), 6.40–6.19 (m, 2 H), 1.90 (dd, *J* = 6.1, 1.0 Hz, 3 H).

Analytic data were in agreement with the literature data.[30]

(*E*)-1-(4-Nitrophenyl)but-2-en-1-one (2b)

3-Hydroxy-1-(4-nitrophenyl)butan-1-one

To a dry flask under argon was added diisopropylamine (1.4 mL, 10 mmol) in THF (15 mL). The mixture was cooled to –20 °C and 2.5 M *n*-BuLi in hexane (4 mL, 10 mmol, 1.05 equiv) was added. The mixture was stirred for 30 min, cooled to –78 °C, and *p*-nitroacetophenone (1 equiv) was added. The reaction mixture was stirred for 20 min at –78 °C and acetaldehyde (590 μL, 10.5 mmol, 1.1 equiv) was added. After 1 h the mixture was quenched with sat. aq $NaHCO_3$ and warmed to r.t. The crude mixture was poured into Et_2O and washed with H_2O, 1% aq HCl (2 × 50 mL), sat. aq $NaHCO_3$ (2 × 50 mL), and brine (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude mixture was purified by column chromatography (silica gel, 5–30% EtOAc–PE) providing 3-hydroxy-1-(4-nitrophenyl)butan-1-one; yield: 470 mg (24%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.29 (m, 2 H), 8.14–8.09 (m, 2 H), 4.54–4.37 (m, 1 H), 3.18–3.12 (m, 2 H), 2.98 (s, 1 H, OH), 1.33 (d, *J* = 6.4 Hz, 3 H).

Analytic data were in agreement with the literature data.[31]

2b

3-Hydroxy-1-(4-nitrophenyl)butan-1-one (470 mg, 2.25 mmol) was dissolved in a mixture of DCM (7 mL) and pyridine (1.8 mL) and treated with mesyl chloride (174 μL, 2.25 mmol) under an argon atmosphere for 4 h. H_2O (10 mL) was added and reaction mixture was extracted with DCM (3 × 20 mL). The organic phase was washed with sat. aq $CuSO_4$ (4 × 30 mL) and brine (2 × 30mL), dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The title compound was obtained after purification by column chromatography (silica gel, 2–10% EtOAc–PE).

Yield: 175 mg (41%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.26 (m, 2 H), 8.07–7.99 (m, 2 H), 7.12 (dq, *J* = 15.4, 6.9 Hz, 1 H), 6.87 (dq, *J* = 15.3, 1.7 Hz, 1 H), 2.03 (dd, *J* = 6.9, 1.7 Hz, 3 H).

Analytic data were in agreement with the literature data.[32]

(*E*)-1-(Naphthalen-2-yl)but-2-en-1-one (2g)

3-Hydroxy-1-(2-naphthalenyl)-1-butanone

Diisopropylamine (1.37 mL, 9.8 mmol) was dissolved in THF (18 mL) under argon. The mixture was cooled to –20 °C and 2.5 M *n*-BuLi in hexane (3.92 mL, 9.8 mmol) was added; then the mixture was stirred for 30 min and cooled to –78 °C before 1-(naphthalen-2-yl)ethan-1-one (1.59 g, 9.3 mmol) was added. The mixture was stirred for 20 min at –78 °C and acetaldehyde (570 μL, 10.26 mmol) was added. The mixture was stirred for an additional 1 h and was quenched with sat. aq $NaHCO_3$ and warmed to r.t. The crude mixture was poured into Et_2O, washed with H_2O, 1% aq HCl (2 × 50 mL), sat. aq $NaHCO_3$ (2 × 50 mL), and brine (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude mixture was purified by column chromatography (silica gel, 5–30% EtOAc–PE); this provided 3-hydroxy-1-(2-naphthalenyl)-1-butanone; yield: 1.788 g (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 1.7 Hz, 1 H), 8.11–7.80 (m, 4 H), 7.67–7.52 (m, 2 H), 4.53–4.41 (m, 1 H), 3.41 (d, *J* = 3.0 Hz, 1 H, OH), 3.31 (dd, *J* = 17.6, 2.8 Hz, 1 H), 3.18 (dd, *J* = 17.6, 8.9 Hz, 1 H), 1.35 (d, *J* = 6.4 Hz, 3 H).

Analytic data were in agreement with the literature data.[31]

2g

3-Hydroxy-1-(2-naphthalenyl)-1-butanone (900 mg, 4.2 mmol) was dissolved in pyridine (3.2 mL) and treated with mesyl chloride (325 µL, 4.2 mmol) under argon for 24 h. After H_2O was added to the flask, the mixture was extracted with Et_2O (3 × 50 mL). The organic phase was washed with sat. aq $CuSO_4$ (4 × 30 mL) and brine (2 × 40 mL), dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The crude 4-(naphthalen-2-yl)-4-oxobutan-2-yl methanesulfonate and TEA (608 µL, 4.2 mmol) were mixed in Et_2O (20 mL) overnight. The crude mixture was concentrated and purified by column chromatography (silica gel, 1–8% EtOAc–PE), providing product **2g**.

Yield: 480 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47–8.42 (m, 1 H), 8.03 (dd, *J* = 8.6, 1.8 Hz, 1 H), 8.00–7.94 (m, 1 H), 7.94–7.85 (m, 2 H), 7.63–7.51 (m, 2 H), 7.21–7.02 (m, 2 H), 2.05 (dd, *J* = 6.4, 1.1 Hz, 3 H).

Analytic data were in agreement with the literature data.[33]

Phenyl (*E*)-But-2-enoate (2m)

Compound **2m** was prepared according to a literature procedure.[34]

Yield: 573 mg (35%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.34 (m, 2 H), 7.27–7.07 (m, 4 H), 6.05 (dq, *J* = 15.6, 1.7 Hz, 1 H), 1.96 (dd, *J* = 6.9, 1.7 Hz, 3 H).

***N*-Alkylation of Nitroindoles; General Procedure**

Indole **1** or **4** (0.1 mmol), phase-transfer catalyst **III** (0.005 mmol), and Rb_2CO_3 (0.13 mmol) were loaded in a 1 mL vial. The mixture of compounds was held for 1 h under vacuum. The vial was filled with an argon atmosphere. Toluene (1 mL), ketone **2** (0.21 mmol), and H_2O (0.14 mmol) were added and the reaction mixture was stirred at r.t. for 5 h under argon unless stated otherwise. The progress of the reaction was monitored by TLC and NMR spectroscopy. After completion of the reaction, the reaction mixture was directly purified by column chromatography to afford pure products **3**, **5**, or **6**.

(*S*)-3-(4-Nitro-1*H*-indol-1-yl)-1-phenylbutan-1-one (5a)

The reaction time was 24 h. Title compound **5a** was obtained according to the general procedure from 4-nitroindole (**4a**; 162.2 mg, 1 mmol) and **2** (307 mg, 2.1 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 281 mg (91%); orange amorphous solid; 65% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R = 21.3 (major), t_R = 29.9 (minor)]; $[\alpha]_D^{20}$ –21.4 (*c* 0.033, $CHCl_3$); R_f = 0.4 (PE–EtOAc, 3:1).

IR (KBr): 2979, 1685, 1597, 1511, 1498, 1448, 1361, 1332, 1312, 1268, 755, 735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.91–7.86 (m, 2 H), 7.83 (d, *J* = 8.2 Hz, 1 H), 7.60–7.54 (m, 1 H), 7.51 (d, *J* = 3.3 Hz, 1 H), 7.47–7.41 (m, 2 H), 7.31–7.26 (m, 2 H), 5.42–5.31 (m, 1 H), 3.58 (dd, *J* = 17.3, 5.8 Hz, 1 H), 3.47 (dd, *J* = 17.3, 7.3 Hz, 1 H), 1.70 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.8, 140.6, 137.9, 136.4, 133.9, 128.9 (2 C), 128.6, 128.1 (2 C), 123.1, 120.6, 117.8, 116.6, 101.1, 48.2, 42.7, 20.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1227.

(*S*)-3-(3-Nitro-1*H*-indol-1-yl)-1-phenylbutan-1-one (5b)

Title compound **5b** was obtained according to the general procedure from 3-nitroindole (**4b**; 16.2 mg, 0.1 mmol) and **2** (30.9 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 20 mg (65%); rose amorphous solid; 42% ee [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R = 41.0 (major), t_R = 45.1 (minor)]; $[\alpha]_D^{20}$ –4.7 (*c* 0.034, $CHCl_3$); R_f = 0.4 (PE–EtOAc, 3:1).

IR (KBr): 3128, 1685, 1597, 1525, 1481, 1449, 1379, 1303, 1225, 750, 689 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.26 (m, 2 H), 7.94–7.89 (m, 2 H), 7.63–7.54 (m, 2 H), 7.49–7.44 (m, 2 H), 7.44–7.36 (m, 2 H), 5.42–5.29 (m, 1 H), 3.62 (dd, *J* = 17.6, 5.4 Hz, 1 H), 3.53 (dd, *J* = 17.6, 7.5 Hz, 1 H), 1.73 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.0, 136.1, 135.0, 134.1, 129.5, 129.0 (2 C), 128.1 (2 C), 127.8, 124.7, 124.5, 121.14, 121.12, 111.0, 48.9, 45.2, 21.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1228.

(*S*)-3-(5-Nitro-1*H*-indol-1-yl)-1-phenylbutan-1-one (5c)

Title compound **5c** was obtained according to the general procedure from 5-nitroindole (**4c**; 16.2 mg, 0.1 mmol) and **2** (30.9 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 29.3 mg (95%); orange amorphous solid; 38% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R = 31.8 (minor), t_R = 35.9 (major)]; $[\alpha]_D^{20}$ –76.4 (*c* 0.032, $CHCl_3$); R_f = 0.5 (PE–EtOAc, 3:1).

IR (KBr): 2980, 1685, 1610, 1580, 1470, 1450, 1319, 1219, 1070, 743, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 2.3 Hz, 1 H), 8.12 (dd, *J* = 9.1, 2.3 Hz, 1 H), 7.93–7.84 (m, 2 H), 7.60–7.54 (m, 1 H), 7.51 (d, *J* = 9.2 Hz, 1 H), 7.48–7.38 (m, 3 H), 6.71 (d, *J* = 3.4 Hz, 1 H), 5.39–5.26 (m, 1 H), 3.58 (dd, *J* = 17.3, 6.0 Hz, 1 H), 3.46 (dd, *J* = 17.3, 7.1 Hz, 1 H), 1.69 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.7, 141.7, 138.5, 136.4, 133.8, 128.9 (2 C), 128.1 (2 C), 127.7, 127.4, 118.4, 117.4, 109.8, 105.0, 48.3, 45.5, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1232.

(*S*)-3-(6-Nitro-1*H*-indol-1-yl)-1-phenylbutan-1-one (5d)

Title compound **5d** was obtained according to the general procedure from 6-nitroindole (**4d**; 16.2 mg, 0.1 mmol) and **2** (30.9 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–15% EtOAc–PE).

Yield: 25.3 mg (82%); yellow solid; mp 168–170 °C; 35% ee [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R =16.6 (major), t_R = 22.6 (minor)]; $[\alpha]_D^{20}$ –76.4 (*c* 0.035, $CHCl_3$); R_f = 0.5 (PE–EtOAc, 3:1).

IR (KBr): 2978, 1684, 1580, 1511, 1495, 1462, 1330, 1219, 1070, 777, 730, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50–8.43 (m, 1 H), 8.00 (dd, *J* = 8.7, 2.0 Hz, 1 H), 7.93–7.86 (m, 2 H), 7.63 (d, *J* = 8.7 Hz, 1 H), 7.60–7.49 (m, 2 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 6.62 (d, *J* = 3.2 Hz, 1 H), 5.41–5.29 (m, 1 H), 3.62 (dd, *J* = 17.2, 6.1 Hz, 1 H), 3.50 (dd, *J* = 17.2, 7.1 Hz, 1 H), 1.71 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.5, 143.1, 136.4, 134.2, 133.8, 133.5, 130.5, 128.9 (2 C), 128.1 (2 C), 121.0, 115.2, 107.0, 103.1, 48.6, 45.4, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1226.

(*S*)-1-(4-Bromophenyl)-3-(4-nitro-1*H*-indol-1-yl)butan-1-one (6a)

Title compound **6a** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(4-bromophenyl)but-2-en-1-one (**2a**; 47.3 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2a** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 2–15% EtOAc–PE).

Yield: 25.9 mg (67%); orange amorphous solid; 59% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ =254 nm): t_R =27.2 (major), t_R = 35.2 (minor)]; $[\alpha]_D^{20}$ –25.4 (*c* 0.050, $CHCl_3$); R_f = 0.4 (PE–EtOAc, 10:1).

IR (KBr): 2979, 1686, 1585, 1568, 1511, 1498, 1361, 1331, 1304, 1269, 1105, 790, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.09 (m, 1 H), 7.82 (d, *J* = 8.3 Hz, 1 H), 7.76–7.70 (m, 2 H), 7.60–7.54 (m, 2 H), 7.49 (d, *J* = 3.3 Hz, 1 H), 7.32–7.26 (m, 2 H), 5.40–5.29 (m, 1 H), 3.54 (dd, *J* = 17.3, 5.9 Hz, 1 H), 3.42 (dd, *J* = 17.4, 7.2 Hz, 1 H), 1.69 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.7, 140.5, 137.8, 135.0, 132.1 (2 C), 129.5 (2 C), 129.0, 128.4, 122.5, 120.6, 117.7, 116.5, 102.9, 47.9, 45.5, 21.3

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_2O_3Br$: 387.0339; found: 387.0342.

(*S*)-3-(4-Nitro-1*H*-indol-1-yl)-1-(4-nitrophenyl)butan-1-one (6b)

Title compound **6b** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(4-nitrophenyl)but-2-en-1-one (**2b**; 40.1 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2b** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 3–20% EtOAc–PE).

Yield: 26.1 mg (74%); yellow solid; mp 64–68 °C; 73% ee [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 70:30, flow rate 0.9 mL/min, *T* = 35 °C, λ = 254 nm): t_R =23.2 (minor), t_R = 49.8 (major)]; $[\alpha]_D^{20}$ –40.2 (*c* 0.041, $CHCl_3$); R_f = 0.5 (PE–EtOAc, 3:1).

IR (KBr): 3109, 2929, 1693, 1603, 1524, 1347, 1318, 1269, 790, 786 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30–8.24 (m, 2 H), 8.16–8.09 (m, 1 H), 8.05–8.00 (m, 2 H), 7.85–7.80 (m, 1 H), 7.50 (d, *J* = 3.3 Hz, 1 H), 7.33–7.27 (m, 2 H), 5.45–5.29 (m, 1 H), 3.64 (dd, *J* = 17.6, 6.0 Hz, 1 H), 3.51 (dd, *J* = 17.7, 6.9 Hz, 1 H), 1.73 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.3, 150.7, 140.63, 140.61, 137.8, 129.2 (2 C), 128.4, 124.1 (2 C), 122.6, 120.8, 117.9, 116.5, 103.2, 47.9, 46.2, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_3O_5$: 354.1084; found: 354.109.

(*S*)-1-(4-Methoxyphenyl)-3-(4-nitro-1*H*-indol-1-yl)butan-1-one (6c)

Title compound **6c** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(4-methoxyphenyl)but-2-en-1-one (**2c**; 37 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 3–20% EtOAc–PE).

Yield: 28 mg (83%); yellow crystals; mp 100–104 °C; 75% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 80:20, flow rate 1.0 mL/min, *T* = 35 °C, λ= 254 nm): t_R =15.8 (major), t_R = 23.6 (minor)]; $[\alpha]_D^{20}$ –34.3 (*c* 0.065, $CHCl_3$); R_f = 0.3 (PE–EtOAc, 3:1).

IR (KBr): 2976, 1675, 1600, 1575, 1511, 1456, 1361, 1308, 1266, 1171, 759, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.9 Hz, 1 H), 7.88–7.79 (m, 3 H), 7.49 (d, *J* = 3.3 Hz, 1 H), 7.29–7.23 (m, 2 H), 6.91–6.85 (m, 2 H), 5.39–5.28 (m, 1 H), 3.83 (s, 3 H), 3.49 (dd, *J* = 17.0, 5.8 Hz, 1 H), 3.39 (dd, *J* = 17.0, 7.3 Hz, 1 H), 1.67 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.2, 164.1, 140.5, 137.9, 130.4 (2 C), 129.5, 128.7, 122.6, 120.6, 117.7, 116.7, 114.0 (2 C), 102.8, 55.7, 48.3, 45.3, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_2O_4$: 339.1339; found: 339.1341.

CCDC 1923379 contains the supplementary crystallographic data for **6c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(*S*)-1-(Furan-2-yl)-3-(4-nitro-1*H*-indol-1-yl)butan-1-one (6d)

Title compound **6d** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(furan-2-yl)but-2-en-1-one (**2d**; 28.6 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2d** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 26.8 mg (90%); orange crystals; mp 85–90 °C; 63% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R =19.4 (major), t_R = 26.5 (minor)]; $[\alpha]_D^{20}$ –37.8 (*c* 0.030, $CHCl_3$); R_f = 0.3 (PE–EtOAc, 3:1).

IR (KBr): 3132, 2980, 1672, 1567, 1511, 1499, 1467, 1361, 1332, 1308, 760, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.54–7.43 (m, 2 H), 7.25–7.20 (m, 2 H), 7.09 (d, *J* = 3.6 Hz, 1 H), 6.46 (dd, *J* = 3.6, 1.7 Hz, 1 H), 5.33–5.20 (m, 1 H), 3.41 (dd, *J* = 16.5, 6.4 Hz, 1 H), 3.26 (dd, *J* = 16.5, 7.1 Hz, 1 H), 1.64 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.8, 152.5, 147.0, 140.6, 137.9, 128.5, 122.6, 120.7, 117.82, 117.78, 116.6, 112.8, 103.0, 48.1, 45.5, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_4$: 299.1026; found: 299.1032.

(*R*)-4-Methyl-3-(4-nitro-1*H*-indol-1-yl)-1-phenylpentan-1-one (6e)

The reaction time was 24 h. Title compound **6e** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-4-methyl-1-phenylpent-2-en-1-one (**2e**; 36.6 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 26.9 mg (80%); orange amorphous solid; 64% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_R =17.3 (major), t_R = 20.8 (minor)]; $[\alpha]_D^{20}$ –31.9 (c 0.037, $CHCl_3$); R_f = 0.7 (PE–EtOAc, 3:1).

IR (KBr): 2966, 1686, 1597, 1565, 1512, 1499, 1448, 1361, 1327, 1302, 1273, 758, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.07 (m, 1 H), 7.88 (d, J = 8.2 Hz, 1 H), 7.86–7.79 (m, 2 H), 7.58–7.50 (m, 1 H), 7.45–7.36 (m, 3 H), 7.32–7.23 (m, 2 H), 5.00–4.90 (m, 1 H), 3.67 (dd, J = 17.3, 8.4 Hz, 1 H), 3.55 (dd, J = 17.3, 4.3 Hz, 1 H), 2.38–2.23 (m, 1 H), 1.09 (d, J = 6.6 Hz, 3 H), 0.74 (d, J = 6.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.9, 140.5, 139.1, 136.5, 133.7, 129.2, 128.9 (2 C), 128.1 (2 C), 122.2, 120.6, 117.7, 117.2, 103.0, 58.4, 42.0, 34.2, 20.4, 19.4.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{21}N_2O_3$: 337.1547; found: 337.1543.

(*S*)-3-(4-Nitro-1*H*-indol-1-yl)-1-phenylnonan-1-one (6f)

The reaction time was 24 h. Title compound **6f** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-phenylnon-2-en-1-one (**2f**; 45.4 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 2–15% EtOAc–PE).

Yield: 31.0 mg (82%); orange amorphous solid; 59% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 95:5, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_R =19.4 (major), t_R = 22.4 (minor)]; $[\alpha]_D^{20}$ –12.2 (c 0.064, $CHCl_3$); R_f = 0.6 (PE–EtOAc, 4:1).

IR (KBr): 3106, 2928, 2856, 1685, 1597, 1580, 1361, 1323, 1274, 755, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 8.0, 0.8 Hz, 1 H), 7.89–7.82 (m, 3 H), 7.59–7.51 (m, 1 H), 7.48–7.38 (m, 3 H), 7.32–7.24 (m, 2 H), 5.26–5.15 (m, 1 H), 3.58 (dd, J = 17.3, 6.7 Hz, 1 H), 3.46 (dd, J = 17.3, 6.1 Hz, 1 H), 2.08–1.92 (m, 2 H), 1.35–0.97 (m, 8 H), 0.81 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.1, 140.8, 138.9, 136.6, 134.0, 129.1 (2 C), 129.0, 128.3 (2 C), 122.6, 120.9, 117.9, 117.0, 103.3, 52.8, 45.0, 36.1, 31.8, 29.1, 26.4, 22.8, 14.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_3$: 379.2016; found: 379.2021.

(*S*)-1-(Naphthalen-2-yl)-3-(4-nitro-1*H*-indol-1-yl)butan-1-one (6g)

Title compound **6g** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(naphthalen-2-yl)but-2-en-1-one (**2g**; 41.2 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2g** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 3–20% EtOAc–PE).

Yield: 34.2 mg (96%); orange amorphous solid; 69% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_R =27.8 (major), t_R = 42.4 (minor)]; $[\alpha]_D^{20}$ –87.9 (c 0.032, $CHCl_3$); R_f = 0.5 (PE–EtOAc, 3:1).

IR (KBr): 2979, 1680, 1626, 1565, 1510, 1498, 1469, 1361, 1331, 1302, 1269, 756, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 1.7 Hz, 1 H), 8.12 (dd, J = 8.0, 0.8 Hz, 1 H), 7.97–7.81 (m, 5 H), 7.64–7.52 (m, 3 H), 7.39–7.19 (m, 2 H), 5.47–5.36 (m, 1 H), 3.70 (dd, J = 17.2, 5.8 Hz, 1 H), 3.61 (dd, J = 17.1, 7.2 Hz, 1 H), 1.74 (d, J = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.7, 140.5, 137.9, 135.9, 133.7, 132.5, 130.0, 129.7, 129.0, 128.8, 128.7, 127.9, 127.2, 123.5, 122.7, 120.6, 117.8, 116.7, 102.9, 48.3, 45.8, 21.5.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1390; found: 359.1389.

3-(4-Nitro-1*H*-indol-1-yl)cyclohexan-1-one (6h)

The reaction time was 24 h. Title compound **6h** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and cyclohex-2-en-1-one (**2h**; 20.2 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–30% EtOAc–PE).

Yield: 16.8 mg (65%); yellow amorphous solid; racemic [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_{R1} = 23.2, t_{R2} = 26.8]; R_f = 0.1 (PE–EtOAc, 3:1).

IR (KBr): 2952, 1713, 1512, 1498, 1449, 1362, 1333, 1307, 1284, 792, 757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.0 Hz, 1 H), 7.68 (d, J = 8.2 Hz, 1 H), 7.47 (d, J = 3.3 Hz, 1 H), 7.36–7.27 (m, 2 H), 4.80–4.70 (m, 1 H), 2.99–2.87 (m, 1 H), 2.87–2.74 (m, 1 H), 2.62–2.32 (m, 3 H), 2.30–2.12 (m, 2 H), 1.91–1.76 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.2, 140.8, 137.6, 128.2, 122.8, 120.9, 118.0, 116.0, 103.2, 54.7, 48.4, 40.9, 31.7, 22.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1077; found: 259.1081.

3-(4-Nitro-1*H*-indol-1-yl)-1,3-diphenylpropan-1-one (6i)

The reaction time was 48 h. Title compound **6i** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (2*E*)-1,3-diphenylprop-2-en-1-one (**2i**; 43.7 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2i** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 13.0 mg (35%); yellow solid; mp = 79–83 °C; racemic [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 70:30, flow rate 1.0 mL/min, T = 35 °C, λ = 254 nm): t_{R1} = 15.7, t_{R2} = 33.4]; R_f = 0.3 (PE–EtOAc, 3:1).

IR (KBr): 3063, 1685, 1596, 1580 1521, 1497, 1448, 1361, 1329, 1296, 753, 737, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 8.0, 0.8 Hz, 1 H), 7.98–7.90 (m, 2 H), 7.76 (d, J = 8.2 Hz, 1 H), 7.63–7.56 (m, 1 H), 7.51–7.44 (m, 3 H), 7.36–7.18 (m, 7 H), 6.50–6.43 (m, 1 H), 4.07 (dd, J = 17.4, 7.8 Hz, 1 H), 3.95 (dd, J = 17.4, 6.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.8, 140.6, 139.7, 138.4, 136.3, 134.0, 129.6 (2 C), 129.3 (2 C), 129.0, 128.5, 128.2 (2 C), 126.4 (2 C), 123.0, 121.0, 117.9, 117.1, 103.0, 55.7, 43.9.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_3$: 371.1390; found: 371.1387.

2-(4-Nitro-1*H*-indol-1-yl)-1,4-diphenylbutane-1,4-dione (6j)

The reaction time was 24 h. Title compound **6j** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**2j**; 49.6 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2i** was added before evacuation of the system. The product was isolated by two sequential column chromatography procedures (silica gel; first: 3–20% EtOAc–PE; second: 50% DCM–PE).

Yield: 22.6 mg (60%); yellow amorphous solid; racemic [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 70:30, flow rate 1.0 mL/min, T = 35 °C, λ = 254 nm): t_{R1} = 11.1, t_{R2} = 20.8]; R_f = 0.7 (PE–EtOAc, 3:1).

IR (KBr): 3063, 1680, 1596, 1580, 1516, 1502, 1359, 1332, 1293, 1230, 760, 737, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, J = 8.0, 0.8 Hz, 1 H), 8.00–7.88 (m, 5 H), 7.63–7.57 (m, 1 H), 7.57–7.50 (m, 1 H), 7.50–7.44 (m, 2 H), 7.43 (d, J = 3.3 Hz, 1 H), 7.42–7.34 (m, 3 H), 7.28 (dd, J = 3.4, 0.8 Hz, 1 H), 6.74 (dd, J = 8.1, 5.0 Hz, 1 H), 4.33 (dd, J = 17.8, 8.1 Hz, 1 H), 3.53 (dd, J = 17.8, 5.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.6, 194.2, 140.9, 137.6, 135.9, 134.7, 134.4, 134.1, 130.7, 129.1 (2 C), 129.0 (2 C), 128.6 (2 C), 128.3 (2 C), 123.3, 121.6, 118.2, 116.2, 104.3, 55.9, 40.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{43}H_{19}N_2O_4$: 399.1339; found: 399.1347.

(*S*)-1-(4-Oxo-4-phenylbutan-2-yl)-1*H*-indole-3-carbonitrile (3)

Title compound **3** was obtained according to the general procedure from 3-cyanoindole (**1**; 14.2 mg, 0.1 mmol) and (*E*)-1-phenylbut-2-en-1-one (**2**; 30.9 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 27.4 mg (95%); white solid; mp 59–61 °C; 42% ee [HPLC (Daicel Chiralpak OJ-H, hexane–^{i}PrOH, 80:20, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_R = 41.7 (major), t_R = 46.2 (minor)]; $[\alpha]_D^{20}$ –19.6 (*c* 0.033, $CHCl_3$); R_f = 0.4 (PE–EtOAc, 3:1).

IR (KBr): 3121, 2217, 1685, 1597, 1580, 1530, 1461, 1449, 1361, 1288, 1214, 1184, 744, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.86 (m, 2 H), 7.79–7.71 (m, 2 H), 7.63–7.51 (m, 2 H), 7.49–7.40 (m, 2 H), 7.39–7.26 (m, 2 H), 5.39–5.26 (m, 1 H), 3.58 (dd, J = 17.4, 5.4 Hz, 1 H), 3.47 (dd, J = 17.4, 7.6 Hz, 1 H), 1.71 (d, J = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.4, 136.3, 135.0, 134.0, 132.0, 129.0 (2 C), 128.11 (2 C), 128.06, 124.0, 122.4, 120.2, 116.0, 111.0, 86.6, 48.8, 45.2, 21.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{17}N_2O$: 289.1335; found: 289.1325.

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Supporting Information

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