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# Asymmetric Organocatalytic Aza-Michael Reactions of Isatin Derivatives

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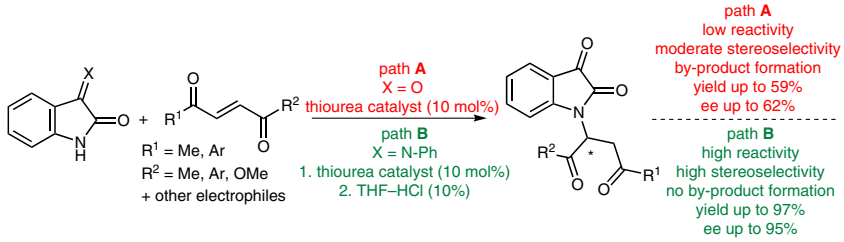


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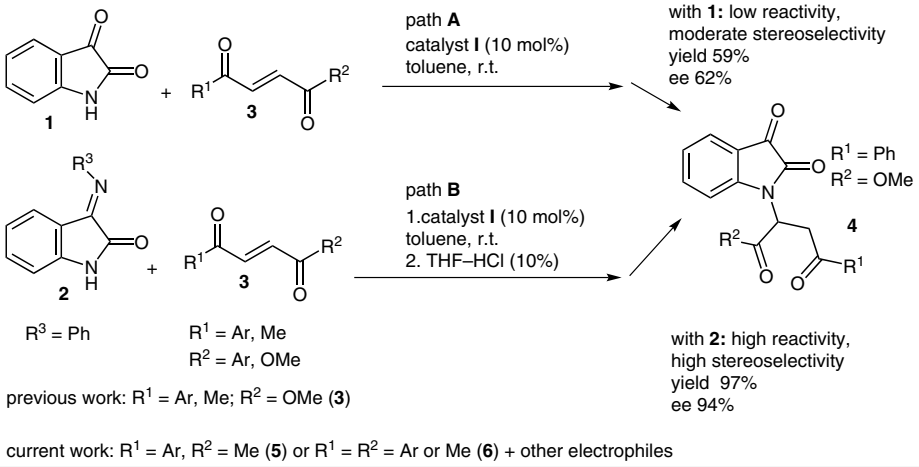
**Abstract** Isatin was activated by derivatization to a Schiff base with aniline and used as an aza-Michael donor in organocatalytic asymmetric reactions with symmetric and nonsymmetric unsaturated 1,4-diketones. After hydrolysis (in situ), the N-substituted isatins were obtained in high yields (up to >95%) with high enantioselectivity (up to 95%).

**Key words** Michael addition, asymmetric catalysis, enantioselectivity, chemoselectivity, imines

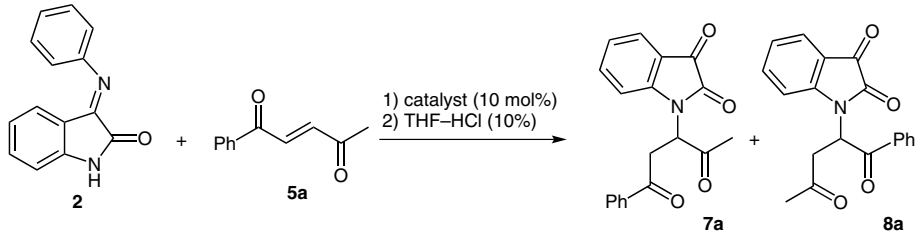
Isatin (**1**) is a well-known natural indole derivative.[1] Because isatin derivatives display a broad spectrum of biological activities,[2] massive efforts have been made to access them via chemical synthesis.[3] The presence of the 1,2-disubstituted aromatic ring, carbonyl group, and γ-lactam moiety make isatin a versatile starting compound for a wide range of chemical transformations[4] including multicomponent reactions[5] and the synthesis of spirocyclic compounds.[6] The nucleophilicity of the nitrogen atom is mainly used for its alkylation,[7] acylation,[8] arylation,[9] or aza-Michael additions.[10] However, not much attention has been paid to the stereochemical aspects, as the obtained products are in most cases achiral or racemic. Medicinal chemistry studies have shown that N-substituted isatins,[11] including chiral ones in a racemic form,[12] possess different pharmaceutical properties. This makes a search for new asymmetric N-derivatization methods of isatin actual. So far, there have only been a few examples, where the N-substitution of isatin has been performed in an asymmetric manner. Shi et al. reported allylic amination of Morita–Baylis–Hillman carbonates with isatin in the presence of cinchona alkaloids.[13] Very recently, enantioselective prolinol-catalyzed N-alkylation of isatin acetals by enals was disclosed by Lu.[14] In our ongoing research on the asymmetric reactions of 1,4-dicarbonyl compounds[15] and oxindole derivatives,[16] we have previously applied the concept of remote activation of the nucleophilicty of isatin for the enantioselective aza-Michael addition.[17] (Scheme 1). It was found that derivatization of isatin (**1**) to Schiff base **2** was the crucial step for obtaining aza-Michael products **4** in high yields with high enantioselectivity (Scheme 1, path **A** vs path **B**), as well as reducing the reaction time and blocking possible by-product formation. The obtained N-alkylated products were easily converted back to isatins by acidic hydrolysis with no loss of yield or enantiomeric excess. The reactivity of the Schiff base strongly depended on the primary amine used. Imine derived from aniline ($R^3$ = Ph) was significantly more efficient than the others. NMR studies revealed strong interactions between isatin Schiff bases **2** and thiourea catalyst **I**, but the results could not explain the activation mechanism. In the current work, we focus on broadening of the scope of aza-Michael reactions with other electrophiles, including nonsymmetric unsaturated 1,4-diketones **5**, symmetric diketones **6**, and other typical Michael acceptors. Computational chemistry methods are used to rationalize this aza-Michael reaction.

In our previous work, keto esters were used as acceptors (Scheme 1, $R^2$ = OMe). Full regioselectivity was obtained and only one isomer derived from the attack on the α-position of the ester carbonyl was found. The transformation of isatin **1** to imine **2** is essential due to the nucleophilicity of the N-atom. Under thiourea catalysis, isatin itself reacts with enolizable carbonyl compounds (such as unsaturated diketones **5**) via aldol condensation at C3.[18] The reaction of imine **2** with nonsymmetric 1,4-diketone **5a** afforded, through an aza-Michael reaction, two regioisomers derived from either attack on the α-position of aliphatic (compound **7a**, major product) or aromatic carbonyl (compound **8a**, minor product) (Table 1).




**Scheme 1** Asymmetric aza-Michael addition of isatin (**1**) and isatin Schiff base **2** to unsaturated 1,4-dicarbonyl compounds

**Table 1** Screening of Catalysts and Reaction Conditions[a]




| Entry | Catalyst | Time (h) | Yield (%)[b] | **7a**/**8a**[c] | **7a** ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **I** | 4 | 91 | 8:1 | 85 (*S*) |
| 2[e] | **I** | 20 | 85 | 6.5:1 | 88 (*S*) |
| 3[f] | **I** | 3.5 | >95 | 5:1 | 87 (*S*) |
| 4[g] | **I** | 20 | >95 | 9.5:1 | 86 (*S*) |
| 5[h] | **I** | 72 | >95 | 12:1 | 92 (*S*) |
| 6 | **II** | 7 | >95 | 6:1 | 83 (*R*) |
| 7 | **III** | 48 | 95 | 6:1 | 86 (*S*) |
| 8 | **IV** | 20 | 95 | 11.5:1 | 80 (*R*) |
| 9 | **V** | 20 | 95 | 3.3:1 | 67 (*R*) |
| 10 | **VI** | 60 | 94 | 2.1:1 | 35 (*R*) |
| 11 | **VII** | 96 | traces | nd | nd |
| 12[i] | **VIII** | 96 | traces | nd | nd |
| 13[i] | **IX** | 96 | traces | nd | nd |

[a] Reaction was conducted in toluene at r.t. (unless otherwise stated).
[b] Isolated yield.
[c] Determined by $^1$H NMR spectroscopy.
[d] The absolute configuration was determined by an X-ray structure analysis of compound **9b** and is presumed to be the same. nd: not determined.
[e] The reaction was performed in THF.
[f] The reaction was performed in 1,2-DCE.
[g] Reaction at 2 °C.
[h] Reaction at –25 °C.
[i] Benzoic acid (10 mol%) was used as a co-catalyst.

We started the optimization of this model reaction by screening the catalyst and solvent (Table 1). Thioureas **I**–**III** (Figure 1) exhibited a similar stereoselectivity pattern in toluene (Table 1, entries 1, 6, 7). The reactions proceeded smoothly, affording the product **7a** in high yield with high enantioselectivity; the ratio of regioisomers varied from 8:1 to 6:1.

Takemoto catalyst **IV** gave the highest regioselectivity, but enantioselectivity was slightly lower (Table 1, entry 8). Pihko's catalysts **V** and **VI**,[19] squaramide **VII**, and catalysts with a primary amino group **VIII** and **IX** were not suitable for the reaction (entries 9–13). Catalyst **I** showed a better cumulative result (higher reactivity, allowing for further improvement of both enantio- and regioselectivity by running the reaction at a lower temperature). By lowering the temperature, the best regio-/enantioselectivity combination was achieved (entry 5), although the reaction became significantly slower. Changing toluene to 1,2-DCE resulted in a slightly faster reaction and better enantioselectivity at the expense of regioselectivity, while THF made the reaction sluggish, along with lowering regioselectivity.

With the optimal conditions in hand (10 mol% of catalyst **I** in toluene), we turned our attention to the scope of the reaction starting with a variety of nonsymmetric methyl aryl diketones **5** (Table 2). Decreasing the reaction temperature allowed us to obtain most of the products in >90% ee and in a high regioisomeric ratio. (As most of the products were obtained with moderate enantioselectivity at r.t., reactions were also conducted at 2 °C or –25 °C. The results obtained at room temperature and a short discussion are presented in a Table, see Supporting Information.) As expected, reaction rates and selectivities strongly depended on the substituent R of the diketone **5**. The major regioisomer was always formed by attack on the α-carbon of methyl ketone moiety. While electronegative or electron-withdrawing groups on the phenyl ring **5d**, **5e**, **5f** (entries 4–6) activated the substrate for the favorable regioisomer **7** formation, the electron-donating methoxy group in **5c** (entry 3) resulted in significantly lower regioselectivity. Replacing the phenyl ring with naphthyl did not change the result noticeably (entries 1 and 2). Diketones with ketones with heteroaromatic substituents **5g**, **5h** were less suitable for the reaction due to moderate enantioselectivity (entries 7, 8), while the reaction with 2-pyrrolyl substituted diketone **5i** afforded a racemic product in very low yield and regioselectivity (entry 9).

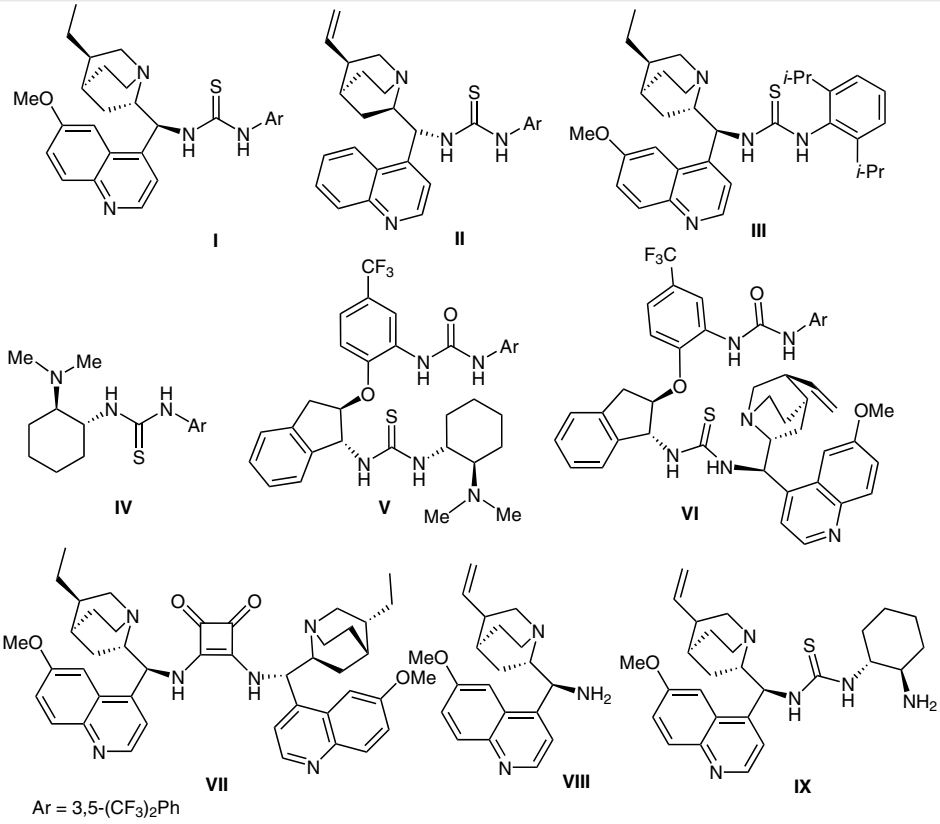
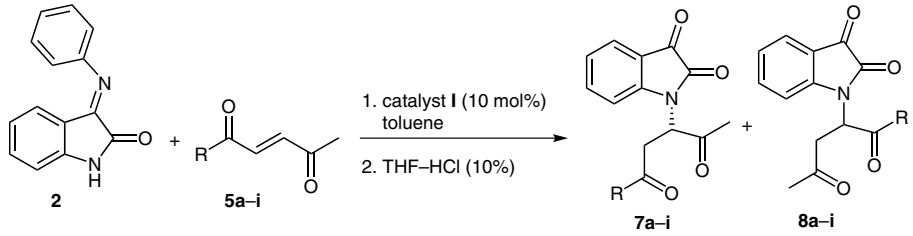



**Figure 1** Catalysts screened

**Table 2** Reactions of Isatin Schiff Base **2** with Unsaturated Nonsymmetric 1,4-Diketones **5a–i**

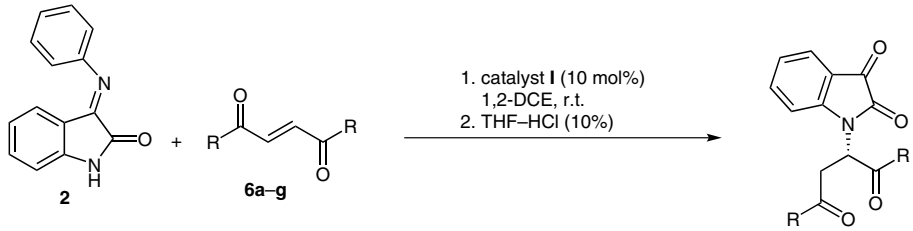



**2** **5a–i** **7a–i** **8a–i**

| Entry | R | Temp (°C) | Time (h) | **7**/**8**[a] | Yield (%)[b] | ee of **7** (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **a**, Ph | –25 | 72 | 12:1 | >95 | 92 |
| 2 | **b**, 2-naphthyl | 2 | 24 | 8.5:1 | >95 | 90 |
| 3 | **c**, 4-MeOC$_6$H$_4$ | 2 | 24 | 4.5:1 | >95 | 93 |
| 4 | **d**, 4-ClC$_6$H$_4$ | –25 | 72 | 15.5:1 | >95 | 90 |
| 5 | **e**, 4-BrC$_6$H$_4$ | –25 | 72 | 15:1 | >95 | 92 |
| 6 | **f**, 4-O$_2$NC$_6$H$_4$ | 2 | 24 | 16.5:1 | 85 | 89 |
| 7 | **g**, 2-thiophenyl | 2 | 72 | 4:1 | 76 | 66 |
| 8 | **h**, 2-furanyl | 2 | 60 | 19.5:1 | >95 | 74 |
| 9 | **i**, 2-pyrrolyl | r.t. | 72 | 4:1 | 10 | *rac* |

[a] Determined by $^1$H NMR spectroscopy.
[b] Isolated yield.
[c] Determined by chiral HPLC.

**Table 3** Reactions of Isatin Schiff Base **2** with Unsaturated Symmetric 1,4-Diketones **6a–g**




**2** **6a–g** **9a–g**

| Entry | R | Time (h) | Yield (%) | ee (%)[a] |
|---|---|---|---|---|
| 1[b] | **a**, Me | 16 | 66 | 40 |
| 2[c] | **a**, Me | 36 | 93 | 83 |
| 3 | **b**, Ph | 2 | >95 | 95 |
| 4[d] | **b**, Ph | 24 | 53 | 44 |
| 5 | **c**, 4-MeC$_6$H$_4$ | 3.5 | >95 | 95 |
| 6 | **d**, 4-MeOC$_6$H$_4$ | 36 | >95 | 84 |
| 7 | **e**, 4-ClC$_6$H$_4$ | 30 | >95 | 87 |
| 8[e] | **f**, 4-BrC$_6$H$_4$ | 228 | 72 | 64 |
| 9 | **g**, 4-O$_2$NC$_6$H$_4$ | 4.5 | 74 | nd[f] |

[a] Determined by chiral HPLC; nd = not determined.
[b] The reaction was performed in toluene.
[c] The reaction was performed in toluene in the presence of 10 mol% of catalyst **IV**.
[d] The reaction was carried out in toluene with isatin (**1**) instead of Schiff base **2**.
[e] The reaction was carried out under more diluted conditions (0.2 M).
[f] Resolution of the enantiomers was not possible.

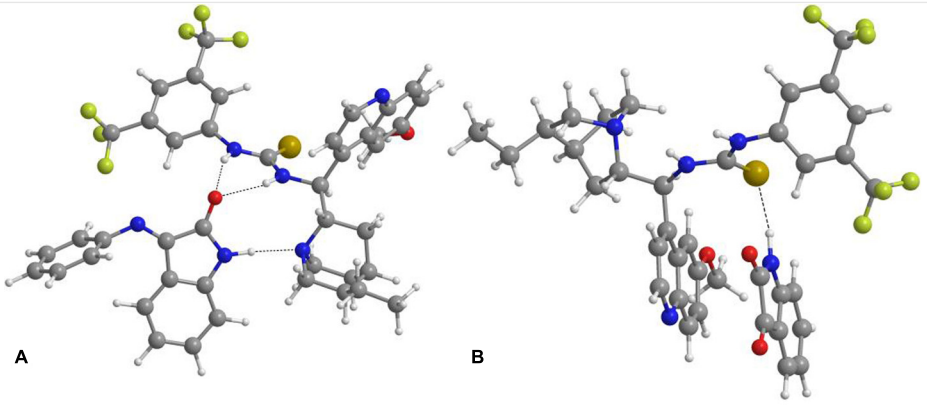
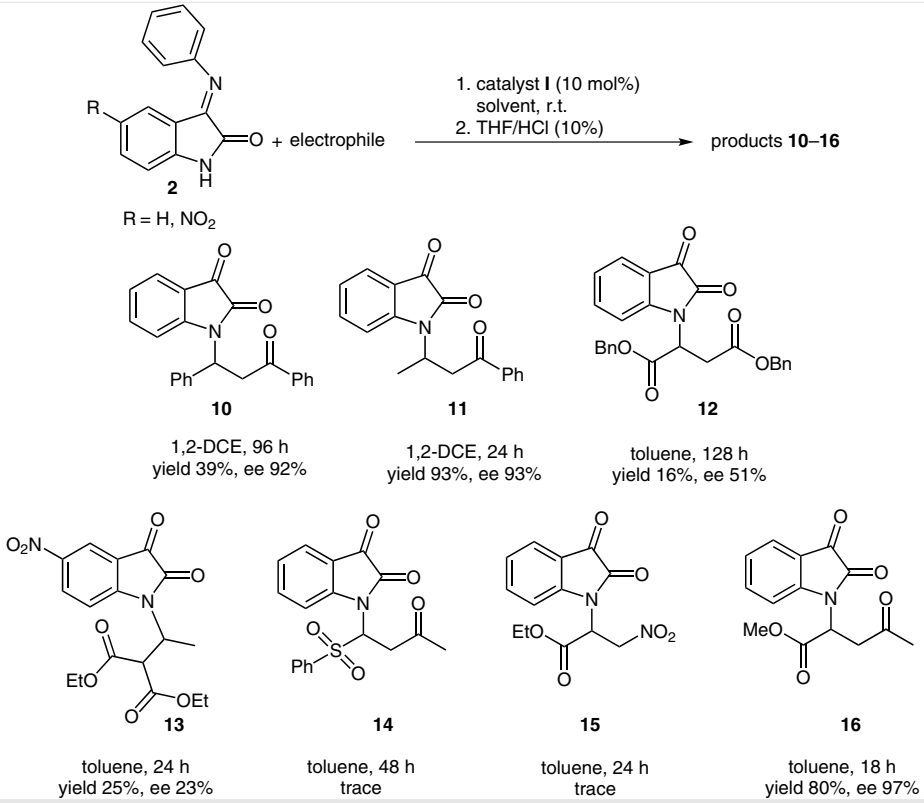



**Figure 2** Two-component complexes between catalyst **I** and imine **2** (**A**) and isatin (**B**)

Next, the reaction with symmetric diketones **6a**–**g** was investigated. As in this case no regioisomers can be formed, 1,2-DCE was the optimal solvent. (A Table comparing the reactions in 1,2-DCE and toluene together with a short discussion is presented in Supporting Information.) The results are shown in Table 3.

Aliphatic diketone **6a** afforded product **9a** in low yield due to the formation of by-products (Table 3, entry 1). Replacing thiourea **I** with Takemoto catalyst **IV** resulted in obtaining a high yield of the product with acceptable enantioselectivity (Table 3, entry 2). Phenyl and tolyl-substituted aromatic diketones **6b** and **6c** reacted smoothly, affording the product in high yields and with excellent enantioselectivities (entries 3, 4). The reaction with a methoxy-substituted inactivated Michael acceptor diketone **6d** was considerably slower, but the product was also obtained in excellent yield and slightly lower enantioselectivity (entry 6). The diketones **6e** and **6f** substituted with 4-$ClC_6H_4$ and 4-$BrC_6H_4$ showed a substantial difference in reactivity: in the case of **6e** the reaction was complete in a reasonable time, while a longer reaction time was needed for the bromophenyl compound **6f**, most probably due to solubility issues (entries 7, 8). Nitro-substituted diketone **6g** reacted smoothly, but we were unable to determine its enantiomeric purity by chiral HPLC. An additional experiment showed that, as in the case of unsaturated 1,4-keto esters, derivatization of isatin (**1**) to a Schiff base **2** was essential for high yield and enantioselectivity (entry 3 vs 4). We next examined the reaction of isatin Schiff base **2** with other typical Michael acceptors (Scheme 2). Reactions with chalcone and its methyl analogue afforded the aza-Michael products **10**, **11** with high enantioselectivities; however, chalcone was less reactive, probably due to sterical hindrance near the stereogenic center. The symmetric unsaturated diester afforded the product **12** in low yield and with moderate enantioselectivity. For the reaction with alkylidenemalonate, a more reactive nitro analogue of Schiff base **2** was needed. Still, the product **13** was obtained in low yield with low enantiomeric purity. In the reactions with unsaturated 1,4-keto sulfone and β-nitro ester, only traces of products **14** and **15** were detected. In our previous work, we had shown that unsaturated keto esters were excellent Michael acceptors affording product **16**. To rationalize the reactivity of imines derived from isatin and the stereochemical outcome, this reaction was investigated by theoretical calculations. Pre-reaction states of imine or isatin with thiourea catalyst **I** were determined by molecular dynamics simulations using an AMBER99 force field. The formation of the hydrogen bonding between the catalyst and imine **2** versus isatin (**1**) was compared. The simulation results revealed that the imine was more involved in the hydrogen bonding network. The prevailing number of hydrogen bonds along the molecular dynamic trajectory for imine ranges from two to three, whereas for isatin this number is one (Table 4). In the case of imine there are two bonds between N–H atoms of the catalyst and the carbonyl group of oxindole ring together with the hydrogen bond between N–H (oxindole ring) and the tertiary amino group in the catalyst. For isatin only one bond is formed in the participation of the sulfur atom of the catalyst and N–H of the imine (Figure 2).

In the pre-reaction state, a well-defined complex with imine was formed whereas the complex with isatin had more conformational diversity. Adding the keto ester, methyl (*E*)-4-oxopent-2-enoate, to those two-component systems changed the hydrogen bondings network substantially. In the case of a three-component system (catalyst **I** + isatin + keto ester), the complex of sulfur hydrogen-bonded with isatin nitrogen disappeared, but very large numbers of different lowly populated hydrogen-bonded complexes appeared making these states very diverse. With imine **2** the lowest energy complexes were nonreactive. However, the complex where the nucleophilicity of the nitrogen atom was increased by a hydrogen bond between the tertiary amino group of the catalyst and between the carbonyl group and N–H atoms was also present (Figure 3).




**Scheme 2** Reactions with other electrophiles

**Table 4** Comparison of the Population of H-Bonds between Catalyst **I** and Imine **2** or Isatin (**1**) During 270 ns of Simulation

| Compound | Probability of number of H-bonds (%) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | >3 | sum |
| imine **2** | 5.90 | 14.66 | 37.57 | 41.87 | 0 | 100 |
| isatin (**1**) | 2.46 | 97.47 | 0.06 | 0 | 0 | 100 |

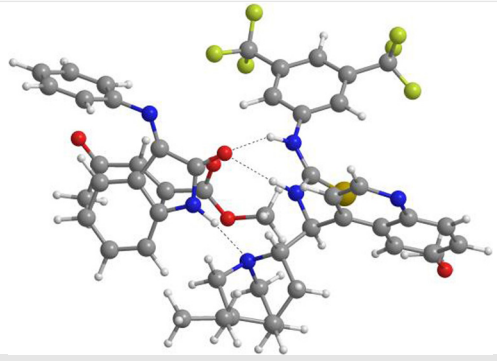


**Figure 3** Three-component complex between catalyst **I**, imine **2** and methyl (*E*)-4-oxopent-2-enoate

In conclusion, we have demonstrated the organocatalytic enantioselective aza-Michael addition of isatin Schiff base **2** to both symmetric and nonsymmetric unsaturated 1,4-diketones and other electrophiles. The activation of isatin by derivatization to imine **2** is essential to reveal its aza-Michael donor properties. The high reactivity of imine **2** has been rationalized by molecular dynamics simulations.

Full assignment of $^{1}H$ and $^{13}C$ chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance 400 MHz instrument. Residual solvent signals were used [$CDCl_3$ δ = 7.26 ($^{1}H$ NMR), 77.16 ($^{13}C$ NMR) or DMSO-$d_6$ δ = 2.54 ($^{1}H$ NMR), 40.45 ($^{13}C$ NMR)] as internal standards, unless otherwise indicated. Standard abbreviations were used to denote the peak multiplicities. High-resolution mass spectra were recorded on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. MS spectra were measured on GC-MS spectrometer on a 70 eV EI. Optical rotations were obtained with an Anton Paar GWB Polarimeter MCP500. Chiral HPLC was performed using Chiralpak AD-H (250 × 4.6 mm), Chiralcel OD-H (250 × 4.6 mm), or Chiralpak AS-H (250 × 4.6 mm) columns. Precoated silica gel (Merck 60 F254) plates were used for TLC. Silica gel was used for column chromatography. The measured melting points are uncorrected. Commercial reagents were used as received. The solvents were freshly distilled using standard methods ($CH_2Cl_2$ and EtOAc over $P_2O_5$; benzene, toluene, and MeOH over Na). Commercial 1,2-DCE used for asymmetric reactions was distilled over $CaH_2$. The reactions were performed under air atmosphere

without additional moisture elimination, unless stated otherwise. Melting points and specific optical rotations for products **7**/**8** are reported for the ones with regioisomeric ratios >10:1.

### Molecular Dynamics Simulations

The force field chosen was AMBER99[20] with a cutoff value of 7.86 Å for the Van der Waals forces; for the long range electrostatics the Particle Mesh Ewald approach (PME)[21] was used. The simulation was run under periodic boundary conditions, and at 298 K temperature and 1.0 atm of pressure. The NVT ensemble was simulated. Multiple time-step was used: 1.25 fs for intramolecular and 2.50 fs for intermolecular forces. After each 10 ps all the coordinates of the complex were saved as a snapshot. These MDS snapshots were prevailingly analyzed with the help of Yasara software; however, part of the trajectory analysis was performed with the VMD molecular visualization and analyze package. All the trajectory snapshots were analyzed in terms of hydrogen bond structure and dihedrical angle values. These values were sorted and the duplicate snapshots were removed from the analysis procedure. In such a way, the population analysis of all the unique structures were performed. In order to mimic the influence of solvent during subsequent MD runs, the simulation cell was 'filled' with toluene solvent in such a way that the solvent density fulfills the density values of 0.87 g/mL. In this way, 478 toluene molecules appear in the corresponding simulation cell. The cell had dimensions of 44 × 44 × 44 Å.

The above prepared complex was allowed to run an MD simulation within the time interval of 2000 ps for preliminary optimization of the solvated structure. After that initial relaxation and optimization step the actual simulation procedure was launched.

### Chiral Catalysts

The catalysts **I**,[22] **II**,[22] **VIII**,[22], **III**,[16a] **IV**,[23] **V**,[19] **VI**,[19] **VII**,[24] and **IX**[25] were prepared by the corresponding literature procedures and the analytical data matched with those previously reported.

### Isatin Schiff Bases

The compounds **2** were prepared by condensation on isatin and aniline in boiling MeOH with AcOH as a catalyst.[17]

### Nonsymmetric Unsaturated 1,4-Diketones; General Procedure

All compounds were prepared by the in situ oxidation/Wittig reaction procedure, based on the method described in the literature.[26] The corresponding ylide (2.5 mmol, 1 equiv) was dissolved in $CH_2Cl_2$ (25 mL, 0.1 M), followed by the addition of 58% $MnO_2$ (2.2 g, 10 equiv) and hydroxyacetone (520 µL, 7.5 mmol, 3 equiv). The reaction mixture was stirred for 24 h at r.t., filtered through Celite, concentrated under reduced pressure, and the residue purified by column chromatography on silica gel using heptane–EtOAc mixtures as eluent.

### (*E*)-1-(1*H*-Pyrrol-2-yl)pent-2-ene-2,4-dione (5i)

Yield: 269 mg (66%); yellow crystalline solid; mp >105 °C (dec.).

IR (KBr): 3271, 1670, 1642, 1592, 1543, 1405, 1253, 1145, 991, 765, 603, 567, 520 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.99 (br s, 1 H), 7.52 (d, *J* = 15.7 Hz, 1 H), 7.19 (s, 1 H), 7.15 (d, *J* = 15.7 Hz, 1 H), 7.11 (s, 1 H), 6.42–6.33 (m, 1 H), 2.42 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 198.2, 177.8, 136.8, 134.2, 132.9, 127.4, 118.7, 111.8, 29.2.

MS (70 eV): *m*/*z* = 163 [$M^+$], 148, 120, 94, 66, 43.

HRMS (ESI-QTOF): *m*/*z* [M + H]$^+$ calcd for $C_9H_9NO_2$: 164.0706; found: 164.0706.

### Symmetric Diketones 6a–g; General Procedure

Diketones **6b**, **6c**, **6e**, and **6f** were prepared by Friedel–Crafts acylation of substituted benzenes with fumaryl chloride.[27] Compounds **6a** and **6d** were prepared by the same principle as the nonsymmetric diketones. Compound **6g** was prepared by a Wittig reaction with the corresponding α-ketoaldehyde.[15a]

### Asymmetric Aza-Michael Reaction; General Procedure

Isatin Schiff base **2** (22.2 mg, 0.1 mmol), the corresponding electrophile (0.2 mmol), and catalyst **I** (6.0 mg, 0.01 mmol) were stirred in toluene or 1,2-DCE (0.3 mL) at the reported temperature for the appropriate time (Tables 2 and 3). In the case of the reactions carried out at 2 or –25 °C, the reaction vessel containing the reagents and the solvent were cooled prior to mixing together. The reactions were followed by TLC ($CH_2Cl_2$–EtOAc, 20:1). The hydrolysis was carried out in situ by adding a mixture of THF and 10% aq HCl (3:1, 1 mL) with vigorous stirring for 15–20 min. The reaction mixture was transferred to separatory funnel, diluted with $H_2O$ (10 mL), and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined extracts were dried ($MgSO_4$), concentrated, and the product was isolated by column chromatography.

The racemic standards were obtained by the same procedure using 1 equiv of $K_2CO_3$ as catalyst. After the completion of the reaction, the mixture was separated from $K_2CO_3$, hydrolyzed, and purified in the same manner.

### (*S*)-1-(1,4-Dioxo-1-phenylpentan-3-yl)indoline-2,3-dione (7a)

Yield: 30.5 mg (95%); orange amorphous solid; $[\alpha]_D^{25}$ –136 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 17.56 min (major isomer), $t_R$ = 12.69 min (minor isomer); enantiomeric ratio 96:4, ee 92%, regioisomeric ratio 12:1.

IR (KBr): 1742, 1683, 1612, 1469, 1358, 754, 690 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.97–7.92 (m, 2 H), 7.68–7.61 (m, 2 H), 7.61–7.55 (m, 1 H), 7.46 (t, *J* = 7.7 Hz, 2 H), 7.21–7.15 (m, 1 H), 7.12 (d, *J* = 8.0 Hz, 1 H), 5.46 (t, *J* = 6.3 Hz, 1 H), 4.13 (dd, *J* = 18.1, 6.4 Hz, 1 H), 3.50 (dd, *J* = 18.1, 6.3 Hz, 1 H), 2.26 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 202.1, 196.2, 182.1, 158.3, 149.9, 138.9, 136.0, 134.0, 128.9, 128.3, 126.0, 124.5, 118.2, 111.2, 56.8, 36.4, 26.9.

MS (70 eV): *m*/*z* = 321 [$M^+$], 279, 250, 174, 159, 146, 119, 105, 92, 77, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{15}NO_4$ + Na: 344.0893; found: 344.0897.

### (*S*)-1-[1-(Naphthalen-2-yl)-1,4-dioxopentan-3-yl]indoline-2,3-dione (7b)

Yield: 37 mg (>95%); orange amorphous solid.

IR (KBr): 2923, 1741, 1678, 1611, 1469, 1358, 1179, 860, 820, 753, 475 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.47 (s, 1 H), 7.96 (dd, *J* = 8.7, 1.7 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.88–7.83 (m, 2 H), 7.69–7.62 (m, 2 H), 7.62–7.57 (m, 1 H), 7.57–7.51 (m, 1 H), 7.21–7.14 (m, 2 H), 5.51 (t, *J* = 6.3 Hz, 1 H), 4.26 (dd, *J* = 18.0, 6.3 Hz, 1 H), 3.64 (dd, *J* = 18.0, 6.4 Hz, 1 H), 2.28 (s, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 202.2, 196.1, 182.1, 158.4, 149.9, 138.9, 135.9, 133.3, 132.5, 130.4, 129.8, 129.0, 128.8, 127.9, 127.1, 126.0, 124.5, 123.6, 118.2, 111.2, 56.9, 36.5, 26.8.

MS (70 eV): *m*/*z* = 371 [M$^+$], 329, 224, 181, 155, 127, 119, 105, 92, 77, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{17}NO_4$ + Na: 394.1050; found: 394.1055.

**(*S*,*E*)-1-(Naphthalen-2-yl)-3-[2-oxo-3-(phenylimino)indolin-1-yl]pentane-1,4-dione (7b imine)**

Obtained by the general procedure without hydrolysis to determine the ee of **7b**; orange amorphous solid.

HPLC: Chiralpak AS-H column; 254 nm, 7:3 hexane–*i*-PrOH, 0.8 mL/min, 35 °C; $t_R$ = 39.12 min (major isomer), $t_R$ = 19.02 min (minor isomer); enantiomeric ratio 95:5.

IR (KBr): 1733, 1678, 1605, 1466, 1359, 1185, 1124, 862, 823, 751, 659 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1 H), 8.00 (dd, *J* = 8.7, 1.6 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.90–7.83 (m, 2 H), 7.63–7.51 (m, 2 H), 7.46–7.39 (m, 3 H), 7.27–7.22 (m, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 7.01–6.95 (m, 2 H), 6.81 (t, *J* = 7.6 Hz, 1 H), 6.69 (d, *J* = 7.7 Hz, 1 H), 5.59 (t, *J* = 5.9 Hz, 1 H), 4.32 (dd, *J* = 17.9, 6.3 Hz, 1 H), 3.68 (dd, *J* = 17.8, 6.2 Hz, 1 H), 2.32 (s, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 202.8, 196.5, 163.3, 153.3, 150.2, 146.3, 135.9, 134.5, 133.5, 132.5, 130.4, 129.8, 129.6, 128.9, 128.7, 127.9, 127.0, 126.7, 125.6, 123.7, 123.4, 117.7, 116.2, 110.5, 56.9, 36.6, 26.8.

MS (70 eV): *m*/*z* = 446 [M$^+$], 375, 355, 263, 222, 194, 155, 127, 77, 43.

HRMS (ESI-QTOF): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{22}N_2O_3$: 447.1703; found: 447.1717.

**(*S*)-1-[1-(4-Methoxyphenyl)-1,4-dioxopentan-3-yl]indoline-2,3-dione (7c)**

Yield: 35 mg (>95%); orange amorphous solid.

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 59.12 min (major isomer), $t_R$ = 23.25 min (minor isomer); enantiomeric ratio 96.5:3.5, regioisomeric ratio 4.5:1.

IR (KBr): 2926, 1742, 1673, 1611, 1469, 1358, 1260, 1172, 1025, 834, 755 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.87 (m, 2 H), 7.66–7.59 (m, 2 H), 7.19–7.10 (m, 2 H), 6.93–6.88 (m, 2 H), 5.43 (t, *J* = 6.3 Hz, 1 H), 4.05 (dd, *J* = 17.9, 6.2 Hz, 1 H), 3.85 (s, 3 H), 3.47 (dd, *J* = 17.9, 6.5 Hz, 1 H), 2.25 (s, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 202.2, 194.6, 182.2, 164.1, 158.3, 150.0, 138.8, 130.6, 129.0, 125.9, 124.4, 118.1, 114.0, 111.2, 56.9, 55.6, 36.0, 26.8.

MS (70 eV): *m*/*z* = 351 [M$^+$], 309, 204, 146, 135, 107, 92, 77, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}NO_5$ + Na: 374.0999; found: 374.1003.

**(*S*)-1-[1-(4-Chlorophenyl)-1,4-dioxopentan-3-yl]indoline-2,3-dione (7d)**

Yield: 35 mg (>95%); orange crystals; mp 149–153 °C; $[\alpha]_D^{25}$ –123 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 27.51 min (major isomer), $t_R$ = 18.88 min (minor isomer); enantiomeric ratio 95:5, ee 90%, regioisomeric ratio 15.5:1.

IR (KBr): 1742, 1683, 1612, 1469, 1358, 1091, 996, 818, 754 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.6 Hz, 2 H), 7.67–7.61 (m, 2 H), 7.42 (d, *J* = 8.6 Hz, 2 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 5.43 (t, *J* = 6.3 Hz, 1 H), 4.09 (dd, *J* = 18.0, 6.5 Hz, 1 H), 3.42 (dd, *J* = 18.0, 6.2 Hz, 1 H), 2.25 (s, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 202.1, 195.1, 182.1, 158.3, 149.8, 140.4, 138.9, 134.3, 129.7, 129.2, 126.1, 124.6, 118.2, 111.1, 56.7, 36.3, 26.8.

MS (70 eV): *m*/*z* = 355 [M$^+$], 313, 284, 208, 193, 139, 119, 111, 92, 75, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{14}ClNO_4$ + Na: 378.0504; found: 378.0508.

**(*S*)-1-[1-(4-Bromophenyl)-1,4-dioxopentan-3-yl]indoline-2,3-dione (7e)**

Yield: 39 mg (>95%); orange crystals; mp 159–161 °C; $[\alpha]_D^{25}$ –108 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 34.11 min (major isomer), $t_R$ = 21.16 min (minor isomer); enantiomeric ratio 96:4, ee 92%, regioisomeric ratio 15:1.

IR (KBr): 1742, 1684, 1612, 1469, 1358, 1178, 1071, 997, 817, 755 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.5 Hz, 2 H), 8.68–8.62 (m, 2 H), 7.60 (d, *J* = 8.5 Hz, 2 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.10 (d, *J* = 7.9 Hz, 1 H), 5.43 (t, *J* = 6.3 Hz, 1 H), 4.09 (dd, *J* = 18.0, 6.5 Hz, 1 H), 3.41 (dd, *J* = 18.0, 6.2 Hz, 1 H), 2.25 (s, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 202.1, 195.3, 182.0, 158.3, 149.8, 138.9, 134.7, 132.2, 129.8, 129.3, 126.1, 124.6, 118.2, 111.1, 56.7, 36.3, 26.8.

MS (70 eV): *m*/*z* = 401, 399 [M$^+$], 359, 357, 330, 328, 254, 252, 239, 237, 211, 209, 185, 183, 157, 155, 147, 119, 92, 76, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{14}BrNO_4$ + Na: 421.9998; found: 421.9999.

**(*S*)-1-[1-(4-Nitrophenyl)-1,4-dioxopentan-3-yl]indoline-2,3-dione (7f)**

Yield: 31 mg (95%); orange crystalline solid; mp 149–152 °C; $[\alpha]_D^{25}$ –96 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 41.01 min (major isomer), $t_R$ = 44.16 min (minor isomer); enantiomeric ratio 94.5:5.5, ee 89%, regioisomeric ratio 16.5:1.

IR (KBr): 1742, 1693, 1612, 1525, 1470, 1347, 1178, 856, 757 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.33–8.27 (m, 2 H), 8.16–8.09 (m, 2 H), 7.71–7.63 (m, *J* = 7.3, 4.1, 1.2 Hz, 2 H), 7.21 (t, *J* = 7.7 Hz, 1 H), 7.09 (d, *J* = 8.3 Hz, 1 H), 5.44 (t, *J* = 6.3 Hz, 1 H), 4.19 (dd, *J* = 18.1, 6.9 Hz, 1 H), 3.43 (dd, *J* = 18.1, 5.9 Hz, 1 H), 2.26 (s, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 202.0, 195.0, 181.8, 158.3, 150.8, 149.6, 140.4, 139.0, 129.5, 126.2, 124.8, 124.1, 118.2, 110.9, 56.7, 36.9, 26.7.

MS (70 eV): *m*/*z* = 366 [M$^+$], 324, 295, 219, 204, 177, 150, 119, 104, 92, 76, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{14}N_2O_6$ + Na: 389.0744; found: 389.0747.

**(*S*)-1-[1,4-Dioxo-1-(thiophen-2-yl)pentan-3-yl]indoline-2,3-dione (7g)**

Yield: 25 mg (76%); orange amorphous solid.

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 17.40 min (major isomer), $t_R$ = 15.35 min (minor isomer); enantiomeric ratio 83:17, regioisomeric ratio 4:1.

IR (KBr): 1741, 1659, 1611, 1525, 1469, 1415, 1358, 1180, 1098, 1054, 753 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.76 (dd, *J* = 3.8, 1.1 Hz, 1 H), 7.67–7.61 (m, 3 H), 7.20–7.15 (m, 1 H), 7.14–7.10 (m, 2 H), 5.37 (t, *J* = 6.4 Hz, 1 H), 4.03 (dd, *J* = 17.7, 6.0 Hz, 1 H), 3.49 (dd, *J* = 17.7, 6.9 Hz, 1 H), 2.25 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 201.9, 189.0, 182.1, 158.3, 149.9, 142.9, 138.9, 134.8, 133.0, 128.5, 126.0, 124.5, 118.2, 111.1, 56.8, 36.9, 26.7.

MS (70 eV): *m*/*z* = 327 [$M^+$], 299, 285, 256, 180, 146, 119, 111, 83.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{13}NO_4S$ + Na: 350.0457; found: 350.0463.

**(*S*)-1-[1-(Furan-2-yl)-1,4-dioxopentan-3-yl]indoline-2,3-dione (7h)**

Yield: 30 mg (>95%); orange amorphous solid; $[\alpha]_D^{25}$ –113 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 16.57 min (major isomer), $t_R$ = 13.78 min (minor isomer); enantiomeric ratio 87:13, ee 74%, regioisomeric ratio 19.5:1.

IR (KBr): 1742, 1672, 1611, 1468, 1415, 1358, 1158, 1018, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.67–7.60 (m, 2 H), 7.58 (dd, *J* = 1.6, 0.6 Hz, 1 H), 7.25–7.22 (m, 1 H), 7.20–7.14 (m, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 6.54 (dd, *J* = 3.6, 1.7 Hz, 1 H), 5.39 (t, *J* = 6.5 Hz, 1 H), 3.96 (dd, *J* = 17.8, 6.3 Hz, 1 H), 3.38 (dd, *J* = 17.8, 6.8 Hz, 1 H), 2.24 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 201.9, 185.0, 182.1, 158.3, 151.9, 149.8, 147.1, 138.9, 126.0, 124.5, 118.3, 112.8, 111.1, 56.4, 36.1, 26.7.

MS (70 eV): *m*/*z* = 311 [$M^+$], 269, 240, 196, 146, 119, 95, 76, 67, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{13}NO_5$ + Na: 334.0686; found: 334.0689.

**(*S*)-1-[1,4-Dioxo-1-(1*H*-pyrrol-2-yl)pentan-3-yl]indoline-2,3-dione (7i)**

Yield: 3 mg (10%); yellow amorphous solid.

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_{R1}$ = 16.75 min, $t_{R2}$ = 21.84 min; enantiomeric ratio ~50:50, regioisomeric ratio 4:1.

IR (KBr): 3307, 1741, 1643, 1612, 1545, 1469, 1406, 1359, 1113, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.28 (br s, 1 H), 7.67–7.59 (m, 2 H), 7.19–7.14 (m, 1 H), 7.05–7.01 (m, 2 H), 6.97–6.93 (m, 1 H), 6.30–6.23 (m, 1 H), 5.42 (dd, *J* = 7.12, 6.13 Hz, 1 H), 3.84 (dd, *J* = 17.1, 5.8 Hz, 1 H), 3.39 (dd, *J* = 17.1, 7.4 Hz, 1 H), 2.25 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 202.3, 185.6, 182.1, 158.3, 149.9, 138.8, 131.1, 126.1, 125.5, 124.5, 118.2, 117.3, 111.4, 111.1, 57.0, 35.3, 26.9.

MS (70 eV): *m*/*z* = 310 [$M^+$], 292, 268, 197, 146, 119, 94, 66, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{14}N_2O_4$ + Na: 333.0846; found: 333.0847.

**(*R*)-1-(2,5-Dioxohexan-3-yl)indoline-2,3-dione (9a)**

Yield: 24 mg (93%); orange crystals; mp 123–125 °C; $[\alpha]_D^{25}$ +129 (*c* 0.25, $CHCl_3$).

HPLC: Chiralcel OD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 12.29 min (major isomer), $t_R$ = 14.39 min (minor isomer); enantiomeric ratio 91.5:8.5, ee 83%.

IR (KBr): 1757, 1736, 1723, 1610, 1472, 1449, 1364, 1193, 1172, 768 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 7.5, 0.8 Hz, 1 H), 7.61 (td, *J* = 7.9, 1.4 Hz, 1 H), 7.18 (td, *J* = 7.6, 0.6 Hz, 1 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 5.24 (t, *J* = 6.7 Hz, 1 H), 3.58 (dd, *J* = 18.0, 7.2 Hz, 1 H), 2.85 (dd, *J* = 18.0, 5.7 Hz, 1 H), 2.24 (s, 3 H), 2.19 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 204.5, 202.2, 182.1, 158.2, 149.7, 138.9, 126.1, 124.6, 118.2, 111.0, 56.5, 40.8, 30.2, 26.7.

MS (70 eV): *m*/*z* = 259 [$M^+$], 217, 188, 175, 146, 119, 90, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{13}NO_4$ + Na: 282.0737; found: 282.0736.

**(*S*)-1-(1,4-Dioxo-1,4-diphenylbutan-2-yl)indoline-2,3-dione (9b)**

Yield: 37 mg (>95%); yellow crystals; mp 74–76 °C; $[\alpha]_D^{25}$ –228 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 20.60 min (major isomer), $t_R$ = 19.11 min (minor isomer); enantiomeric ratio 97.5:2.5, ee 95%.

IR (KBr): 1740, 1682, 1611, 1469, 1449, 1348, 1221, 1179, 1001, 756, 690 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.04–7.93 (m, 4 H), 7.63–7.53 (m, 4 H), 7.51–7.39 (m, 4 H), 7.19 (d, *J* = 8.1 Hz, 1 H), 7.14–7.08 (m, 1 H), 6.55 (dd, *J* = 8.3, 5.0 Hz, 1 H), 4.36 (dd, *J* = 17.7, 8.4 Hz, 1 H), 3.46 (dd, *J* = 17.6, 5.0 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 196.1, 194.6, 181.9, 157.6, 149.5, 138.8, 136.1, 134.4, 134.3, 133.9, 129.2, 128.9, 128.7, 128.3, 125.9, 124.3, 118.2, 111.9, 51.7, 36.6.

MS (70 eV): *m*/*z* = 383 [$M^+$], 355, 278, 236, 208, 147, 119,105, 77, 69.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{17}NO_4$ + Na: 406.1050; found: 406.1053.

**(*S*)-1-[1,4-Dioxo-1,4-di(-*p*-tolyl)butan-2-yl]indoline-2,3-dione (9c)**

Yield: 40 mg (>95%); yellow needles; mp 115–117 °C; $[\alpha]_D^{25}$ –204 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 26.58 min (major isomer); $t_R$ = 33.55 min (minor isomer); enantiomeric ratio 97.5:2.5, ee 95%.

IR (KBr): 2922, 1740, 1679, 1610, 1469, 1348, 1182, 1004, 817, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.2 Hz, 2 H), 7.86 (d, *J* = 8.2 Hz, 2 H), 7.60–7.51 (m, 2 H), 7.25–7.16 (m, 4 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 6.52 (dd, *J* = 8.2, 5.1 Hz, 1 H), 4.30 (dd, *J* = 17.6, 8.3 Hz, 1 H), 3.43 (dd, *J* = 17.6, 5.1 Hz, 1 H), 2.40 (s, 3 H), 2.36 (s, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 195.7, 194.2, 182.1, 157.6, 149.6, 145.4, 144.8, 138.7, 133.7, 131.8, 129.8, 129.5, 128.85, 128.4, 125.8, 124.2, 118.2, 112.0, 51.7, 36.4, 21.84, 21.82.

MS (70 eV): *m*/*z* = 411 [$M^+$], 383, 386, 319, 264, 147, 119, 91, 65, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{21}NO_4$ + Na: 434.1363; found: 434.1361.

**(*S*)-1-[1,4-Bis(4-methoxyphenyl)-1,4-dioxobutan-2-yl]indoline-2,3-dione (9d)**

Yield: 44 mg (>95%); yellow crystals; mp 172–174 °C; $[\alpha]_D^{25}$ –197 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 72.59 min (major isomer), $t_R$ = 93.09 min (minor isomer); enantiomeric ratio 92:8, ee 84%.

IR (KBr): 2932, 1741, 1673, 1600, 1512, 1468, 1348, 1262, 1171, 1028, 837, 757 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.06–7.97 (m, 2 H), 7.99–7.90 (m, 2 H), 7.61–7.49 (m, 2 H), 7.20 (d, *J* = 7.9 Hz, 1 H), 7.10 (t, *J* = 7.8 Hz, 1 H), 6.97–6.84 (m, 4 H), 6.54 (dd, *J* = 8.4, 5.0 Hz, 1 H), 4.29 (dd, *J* = 17.4, 8.5 Hz, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.39 (dd, *J* = 17.4, 5.0 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 194.5, 192.9, 182.2, 164.5, 164.1, 157.6, 149.7, 138.7, 131.3, 130.6, 129.3, 127.2, 125.8, 124.2, 118.2, 114.4, 114.0, 112.3, 55.7, 55.7, 51.4, 36.1.

MS (70 eV): *m*/*z* = 443 [$M^+$], 411, 374, 296, 253, 161, 147, 135, 119, 107, 92, 77, 64, 43.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{21}NO_6$ + Na: 466.1261; found: 466.1264.

**(*S*)-1-[1,4-Bis(4-chlorophenyl)-1,4-dioxobutan-2-yl]indoline-2,3-dione (9e)**

Yield: 44 mg (>95%); yellow crystals; mp 189–191 °C; $[\alpha]_D^{25}$ –171 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AS-H column; 254 nm, 95:5 hexane–*i*-PrOH, 1.0 mL/min, 35 °C; $t_R$ = 89.06 min (major isomer), $t_R$ = 75.87 min (minor isomer); enantiomeric ratio 93.5:6.5, ee 87%.

IR (KBr): 1741, 1685, 1612, 1469, 1357, 1219, 1093, 831, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.97–7.86 (m, 4 H), 7.62–7.55 (m, 2 H), 7.47–7.43 (m, 2 H), 7.40 (d, *J* = 8.6 Hz, 2 H), 7.17–7.10 (m, 2 H), 6.47 (dd, *J* = 8.7, 4.5 Hz, 1 H), 4.34 (dd, *J* = 17.6, 8.8 Hz, 1 H), 3.36 (dd, *J* = 17.6, 4.6 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 194.9, 193.4, 181.7, 157.6, 149.2, 141.1, 140.5, 138.8, 134.3, 132.5, 130.1, 129.7, 129.6, 129.3, 126.1, 124.6, 118.2, 111.8, 51.5, 36.5.

MS (70 eV): *m*/*z* = 451 [$M^+$], 339, 304, 269, 193, 165, 139, 119, 111, 92, 75, 64.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{15}Cl_2NO_4$ + Na: 474.0270; found: 474.1287.

**(*S*)-1-[1,4-Bis(4-bromophenyl)-1,4-dioxobutan-2-yl]indoline-2,3-dione (9f)**

Yield: 39 mg (72%); orange needles; mp 184–186 °C; $[\alpha]_D^{25}$ –112 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 39.27 min (major isomer), $t_R$ = 45.82 min (minor isomer); enantiomeric ratio 82:18, ee 64%.

IR (KBr): 1740, 1682, 1612, 1585, 1469, 1348, 1179, 1071, 1005, 820, 754 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.91–7.76 (m, 4 H), 7.66–7.50 (m, 6 H), 7.20–7.05 (m, 2 H), 6.45 (dd, *J* = 8.7, 4.6 Hz, 1 H), 4.33 (dd, *J* = 17.7, 8.8 Hz, 1 H), 3.35 (dd, *J* = 17.6, 4.6 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 195.1, 193.7, 181.6, 157.6, 149.1, 138.8, 134.7, 132.9, 132.5, 132.3, 130.1, 129.9, 129.8, 129.3, 126.1, 124.6, 118.2, 111.8, 51.5, 36.4.

MS (70 eV): *m*/*z* = 541 [$M^+$], 394, 392, 317, 315, 287, 285, 211, 209, 185, 183, 157, 155, 147, 119, 92, 76, 64.

HRMS (ESI-QTOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{15}Br_2NO_4$: 539.9441; found: 539.9443.

**(*S*)-1-[1,4-Bis(4-nitrophenyl)-1,4-dioxobutan-2-yl]indoline-2,3-dione (9g)**

Yield: 35 mg (74%); yellow crystalline solid; mp 255–258 °C; $[\alpha]_D^{25}$ –105 (*c* 0.125, DMSO).

IR (KBr): 1743, 1689, 1612, 1525, 1468, 1346, 1280, 1108, 1008, 855, 755 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.38–8.33 (m, 2 H), 8.32–8.26 (m, 2 H), 8.19–8.10 (m, 4 H), 7.70–7.59 (m, 2 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 7.9 Hz, 1 H), 6.49 (dd, *J* = 8.7, 4.1 Hz, 1 H), 4.47 (dd, *J* = 17.8, 8.9 Hz, 1 H), 3.40 (dd, *J* = 17.8, 4.3 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 194.6, 193.4, 181.1, 157.6, 151.1, 151.0, 148.6, 140.1, 139.0, 138.8, 129.7, 129.5, 126.5, 125.1, 124.4, 124.3, 118.3, 111.4, 52.0, 37.1.

MS (70 eV): *m*/*z* = 351, 326, 298, 176, 150, 119, 104, 92, 76, 64.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{15}N_3O_8$ + Na: 496.0751; found: 496.0752.

**1-(3-Oxo-1,3-diphenylpropyl)indoline-2,3-dione (10)**

Yield: 23 mg (39%); orange crystals; mp 146–149 °C; $[\alpha]_D^{25}$ +14 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 14.85 min major isomer, $t_R$ = 16.22 min (minor isomer); enantiomeric ratio 96:4, ee 92%.

IR (KBr): 1734, 1679, 1611, 1468, 1350, 1211, 1020, 750, 693 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.01–7.94 (m, 2 H), 7.61–7.49 (m, 5 H), 7.49–7.41 (m, 2 H), 7.41–7.29 (m, 3 H), 7.15–7.06 (m, 2 H), 5.75 (dd, *J* = 9.1, 4.9 Hz, 1 H), 4.76 (dd, *J* = 18.1, 9.2 Hz, 1 H), 3.72 (dd, *J* = 18.1, 4.9 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 196.9, 183.2, 158.8, 151.6, 138.5, 138.4, 136.3, 133.8, 129.3, 128.9, 128.6, 128.4, 127.3, 125.5, 123.8, 117.9, 111.3, 54.0, 41.4.

MS (70 eV): *m*/*z* = 355 [$M^+$], 250, 208, 179, 146, 119, 105, 92, 77.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{17}NO_3$ + Na: 378.1101; found: 378.1104.

**1-(4-Oxo-4-phenylbutan-2-yl)indoline-2,3-dione (11)**

Yield: 27 mg (92%); reddish crystals; mp 116–118 °C; $[\alpha]_D^{25}$ +9 (*c* 0.25, $CHCl_3$).

HPLC: Chiralcel OJ-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 22.00 min (major isomer), $t_R$ = 27.22 min (minor isomer); enantiomeric ratio 96.5:3.5, ee 93%.

IR (KBr): 2980, 1731, 1683, 1613, 1470, 1353, 1219, 1311, 1220, 1003, 755, 691 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.97–7.89 (m, 2 H), 7.62 (td, *J* = 7.9, 1.4 Hz, 1 H), 7.59–7.53 (m, 2 H), 7.44 (t, *J* = 7.7 Hz, 2 H), 7.19 (d, *J* = 8.1 Hz, 1 H), 7.12–7.05 (m, 1 H), 4.81–4.70 (m, 1 H), 4.12 (dd, *J* = 18.0, 7.9 Hz, 1 H), 3.43 (dd, *J* = 18.0, 5.5 Hz, 1 H), 1.61 (d, *J* = 7.0 Hz, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 197.6, 183.5, 158.6, 151.4, 138.5, 136.4, 133.7, 128.9, 128.3, 125.6, 123.5, 117.8, 110.9, 45.9, 41.9, 18.0.

MS (70 eV): *m*/*z* = 293 [$M^+$], 236, 160, 146, 105, 90, 77.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{15}NO_3$ + Na: 316.0944; found: 316.0949.

**Dibenzyl 2-(2,3-Dioxoindolin-1-yl)succinate (12)**

Yield: 7 mg (16%); yellow needles; mp 99–101 °C; $[\alpha]_D^{25}$ –9 (*c* 0.25, $CHCl_3$).

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 27.84 min (major isomer), $t_R$ = 14.63 min (minor isomer); enantiomeric ratio 75.5:24.5, ee 51%.

IR (KBr): 3034, 1739, 1613, 1471, 1361, 1310, 1218, 1169, 910, 753, 698 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.60–7.57 (m, 1 H), 7.48 (td, *J* = 7.9, 1.3 Hz, 1 H), 7.34–7.24 (m, 8 H), 7.24–7.18 (m, 2 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 5.36 (dd, *J* = 8.5, 6.0 Hz, 1 H), 5.18 (d, *J* = 12.2 Hz, 1 H), 5.15 (d, *J* = 12.2 Hz, 1 H), 5.10 (d, *J* = 12.2 Hz, 1 H), 5.07 (d, *J* = 12.2 Hz, 1 H), 3.43 (dd, *J* = 16.9, 6.0 Hz, 1 H), 3.14 (dd, *J* = 16.9, 8.5 Hz, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 182.1, 169.8, 167.8, 158.1, 149.8, 138.5, 135.2, 134.7, 128.8, 128.7 (4C), 128.6, 128.5 (4C), 125.8, 124.1, 118.0, 110.8, 68.4, 67.3, 51.0, 33.9.

MS (70 eV): *m*/*z* = 443 [M$^+$], 352, 280, 266, 236, 172, 146, 117, 107, 91, 77.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{21}NO_6$ + Na: 466.1261; found: 466.1269.

**Diethyl 2-[1-(5-Nitro-2,3-dioxoindolin-1-yl)ethyl]malonate (13)**

Yield: 9 mg (25%); yellow viscous oil.

HPLC: Chiralpak AD-H column; 254 nm, 7:3 hexane–*i*-PrOH, 1 mL/min, 35 °C; $t_R$ = 18.56 min (major isomer), $t_R$ = 34.31 min (minor isomer); enantiomeric ratio 61.5:38.5.

IR (KBr): 2985, 1754, 1615, 1528, 1473, 1343, 1280, 1223, 1020, 839, 748 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 8.8, 2.4 Hz, 1 H), 8.44 (d, *J* = 2.3 Hz, 1 H), 7.32 (d, *J* = 8.9 Hz, 1 H), 4.73 (dq, *J* = 13.7, 6.8 Hz, 1 H), 4.45 (d, *J* = 11.0 Hz, 1 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 4.04 (qq, *J* = 10.8, 7.1 Hz, 2 H), 1.59 (d, *J* = 6.9 Hz, 3 H), 1.32 (t, *J* = 7.1 Hz, 3 H), 1.11 (t, *J* = 7.1 Hz, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 180.9, 167.1, 166.9, 158.1, 155.2, 144.1, 133.6, 121.1, 117.4, 111.7, 62.5, 62.4, 54.2, 49.7, 16.1, 14.2, 14.0.

MS (70 eV): *m*/*z* = 378 [M$^+$], 332, 286, 219, 191, 164, 141, 113, 85, 69.

HRMS (ESI-QTOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{18}N_2O_8$ + Na: 401.0955; found: 401.0956.

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## Supporting Information

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